IARC MONOGRAPHS

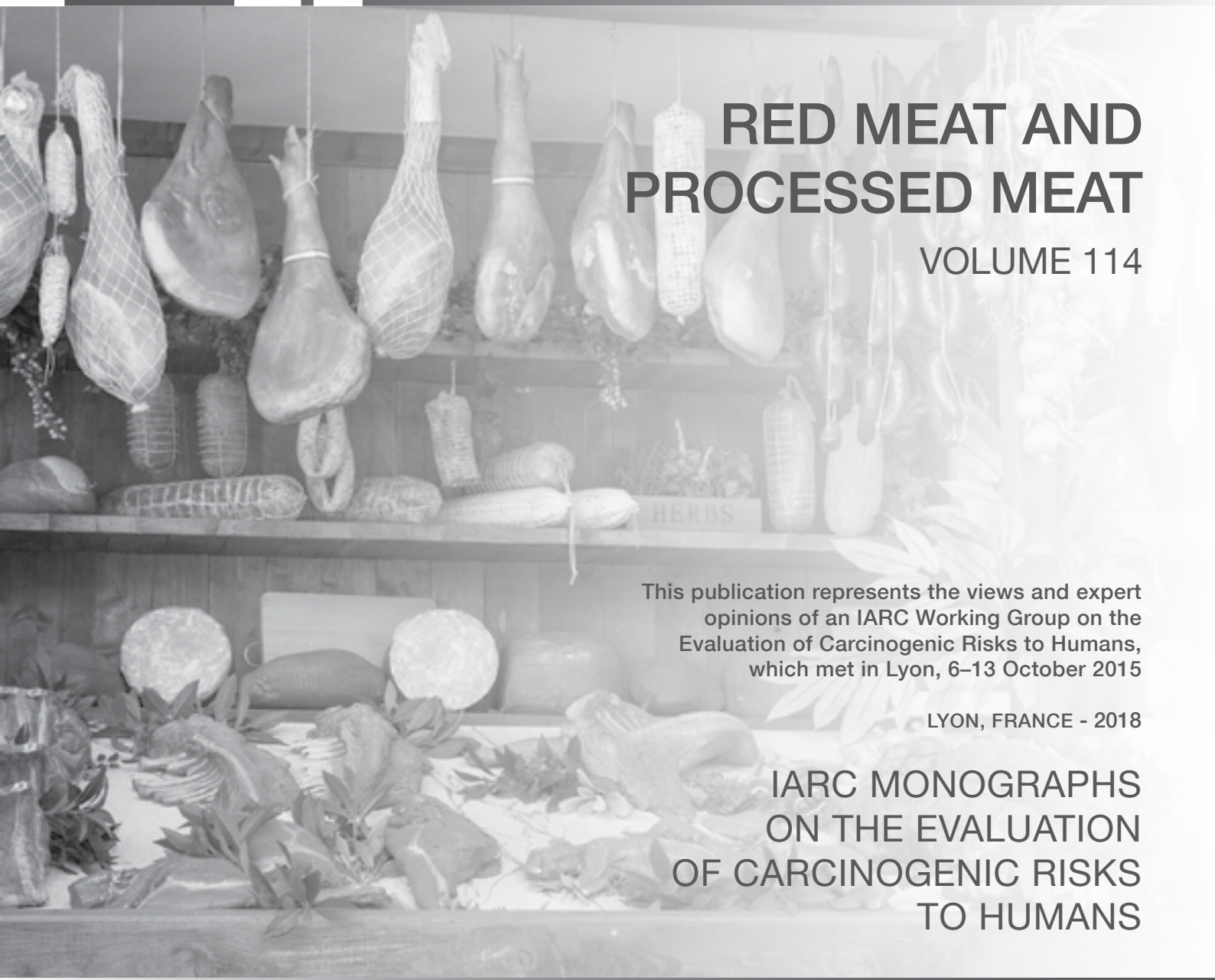
RED MEAT AND PROCESSED MEAT

VOLUME 114

IARC MONOGRAPHS
ON THE EVALUATION
OF CARCINOGENIC RISKS
TO HUMANS

International Agency for Research on Cancer
World Health Organization

IARC MONOGRAPHS



RED MEAT AND PROCESSED MEAT

VOLUME 114

This publication represents the views and expert opinions of an IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, which met in Lyon, 6–13 October 2015

LYON, FRANCE - 2018

IARC MONOGRAPHS ON THE EVALUATION OF CARCINOGENIC RISKS TO HUMANS

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IARC MONOGRAPHS

In 1969, the International Agency for Research on Cancer (IARC) initiated a programme on the evaluation of the carcinogenic risk of chemicals to humans involving the production of critically evaluated monographs on individual chemicals. The programme was subsequently expanded to include evaluations of carcinogenic risks associated with exposures to complex mixtures, lifestyle factors and biological and physical agents, as well as those in specific occupations. The objective of the programme is to elaborate and publish in the form of monographs critical reviews of data on carcinogenicity for agents to which humans are known to be exposed and on specific exposure situations; to evaluate these data in terms of human risk with the help of international working groups of experts in carcinogenesis and related fields; and to indicate where additional research efforts are needed. The lists of IARC evaluations are regularly updated and are available on the Internet at http://monographs.iarc.fr/.

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The IARC Monographs Working Group alone is responsible for the views expressed in this publication.

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CONTENTS

NOTE TO THE READER

The term 'carcinogenic risk' in the *IARC Monographs* series is taken to mean that an agent is capable of causing cancer. The *Monographs* evaluate cancer hazards, despite the historical presence of the word 'risks' in the title.

Inclusion of an agent in the *Monographs* does not imply that it is a carcinogen, only that the published data have been examined. Equally, the fact that an agent has not yet been evaluated in a *Monograph* does not mean that it is not carcinogenic. Similarly, identification of cancer sites with *sufficient evidence* or *limited evidence* in humans should not be viewed as precluding the possibility that an agent may cause cancer at other sites.

The evaluations of carcinogenic risk are made by international working groups of independent scientists and are qualitative in nature. No recommendation is given for regulation or legislation.

Anyone who is aware of published data that may alter the evaluation of the carcinogenic risk of an agent to humans is encouraged to make this information available to the Section of IARC Monographs, International Agency for Research on Cancer, 150 cours Albert Thomas, 69372 Lyon Cedex 08, France, in order that the agent may be considered for re-evaluation by a future Working Group.

Although every effort is made to prepare the *Monographs* as accurately as possible, mistakes may occur. Readers are requested to communicate any errors to the Section of IARC Monographs, so that corrections can be reported in future volumes.

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[7] Dominik Alexander attended as an Observer for the EpidStat Institute, USA. He is the Principal Epidemiologist of the EpidStat Institute, USA; he receives significant financial support from Beef Checkoff for research, consulting, travel and speaking engagements.

[8] Betsy Booren attended as an Observer for the North American Meat Institute, USA. She is employed as Vice President of Scientific Affairs by the North American Meat Institute, and as President by the North American Meat Institute Foundation.

[9] Julien Carretier attended as an Observer for the Centre Léon Bérard, France.

[10] Jason Hlywka attended as an Observer for Kraft Heinz Company. He is is currently employed by the Kraft Heinz Company. He holds significant retirement investments in Kraft Heinz Company and Cargill Inc.

[11] Daniel Kovich attended as an Observer for the National Pork Producers Council, USA. He is Assistant Director of Science and Technology of the National Pork Producers Council.

[12] Hector Lazaneo attended as an Observer for the National Meat Institute (INAC), Uruguay, which has the purpose of promoting, ruling, coordinating and monitoring activities concerning production, transformation, trade, storing and transport of meats.

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[14] Shalene McNeill attended as an Observer for Beef Checkoff, USA.

PREAMBLE

The Preamble to the *IARC Monographs* describes the objective and scope of the programme, the scientific principles and procedures used in developing a Monograph, the types of evidence considered and the scientific criteria that guide the evaluations. The Preamble should be consulted when reading a Monograph or list of evaluations.

A. GENERAL PRINCIPLES AND PROCEDURES

1. Background

Soon after IARC was established in 1965, it received frequent requests for advice on the carcinogenic risk of chemicals, including requests for lists of known and suspected human carcinogens. It was clear that it would not be a simple task to summarize adequately the complexity of the information that was available, and IARC began to consider means of obtaining international expert opinion on this topic. In 1970, the IARC Advisory Committee on Environmental Carcinogenesis recommended '... that a compendium on carcinogenic chemicals be prepared by experts. The biological activity and evaluation of practical importance to public health should be referenced and documented.' The IARC Governing Council adopted a resolution concerning the role of IARC in providing government authorities with expert, independent, scientific opinion on environmental carcinogenesis. As one means to that end, the Governing Council recommended that IARC should prepare monographs on the evaluation of carcinogenic risk of chemicals to man, which became the initial title of the series.

In the succeeding years, the scope of the programme broadened as *Monographs* were developed for groups of related chemicals, complex mixtures, occupational exposures, physical and biological agents and lifestyle factors. In 1988, the phrase 'of chemicals' was dropped from the title, which assumed its present form, *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*.

Through the *Monographs* programme, IARC seeks to identify the causes of human cancer. This is the first step in cancer prevention, which is needed as much today as when IARC was established. The global burden of cancer is high and continues to increase: the annual number of new cases was estimated at 10.1 million in 2000 and is expected to reach 15 million by 2020 (Stewart & Kleihues, 2003). With current trends in demographics and exposure, the cancer burden has been shifting from high-resource countries to low- and medium-resource countries. As a result of *Monographs* evaluations, national health agencies have been able, on scientific grounds, to take measures to reduce human exposure to carcinogens in the workplace and in the environment.

The criteria established in 1971 to evaluate carcinogenic risks to humans were adopted by the Working Groups whose deliberations resulted in the first 16 volumes of the *Monographs* series. Those criteria were subsequently updated by further ad hoc Advisory Groups (IARC, 1977, 1978, 1979, 1982, 1983, 1987, 1988, 1991; Vainio et al., 1992; IARC, 2005, 2006).

The Preamble is primarily a statement of scientific principles, rather than a specification of working procedures. The procedures through which a Working Group implements these principles are not specified in detail. They usually involve operations that have been established as being effective during previous *Monograph* meetings but remain, predominantly, the prerogative of each individual Working Group.

2. Objective and scope

The objective of the programme is to prepare, with the help of international Working Groups of experts, and to publish in the form of *Monographs*, critical reviews and evaluations of evidence on the carcinogenicity of a wide range of human exposures. The *Monographs* represent the first step in carcinogen risk assessment, which involves examination of all relevant information to assess the strength of the available evidence that an agent could alter the age-specific incidence of cancer in humans. The *Monographs* may also indicate where additional research efforts are needed, specifically when data immediately relevant to an evaluation are not available.

In this Preamble, the term 'agent' refers to any entity or circumstance that is subject to evaluation in a *Monograph*. As the scope of the programme has broadened, categories of agents now include specific chemicals, groups of related chemicals, complex mixtures, occupational or environmental exposures, cultural or behavioural practices, biological organisms and physical agents. This list of categories may expand as causation of, and susceptibility to, malignant disease become more fully understood.

A cancer 'hazard' is an agent that is capable of causing cancer under some circumstances, while a cancer 'risk' is an estimate of the carcinogenic effects expected from exposure to a cancer hazard. The *Monographs* are an exercise in evaluating cancer hazards, despite the historical presence of the word 'risks' in the title. The distinction between hazard and risk is important, and the *Monographs* identify cancer hazards even when risks are very low at current exposure levels, because new uses or unforeseen exposures could engender risks that are significantly higher.

In the *Monographs*, an agent is termed 'carcinogenic' if it is capable of increasing the incidence of malignant neoplasms, reducing their latency, or increasing their severity or multiplicity. The induction of benign neoplasms may in some circumstances (see Part B, Section 3a) contribute to the judgement that the agent is carcinogenic. The terms 'neoplasm' and 'tumour' are used interchangeably.

The Preamble continues the previous usage of the phrase 'strength of evidence' as a matter of historical continuity, although it should be understood that *Monographs* evaluations consider studies that support a finding of a cancer hazard as well as studies that do not.

Some epidemiological and experimental studies indicate that different agents may act at different stages in the carcinogenic process, and several different mechanisms may be involved. The aim of the *Monographs* has been, from their inception, to evaluate evidence of carcinogenicity at any stage in the carcinogenesis process, independently of the underlying mechanisms. Information on mechanisms may, however, be used in making the overall evaluation (IARC, 1991; Vainio et al., 1992; IARC, 2005, 2006; see also Part B, Sections 4 and 6). As mechanisms of carcinogenesis are elucidated, IARC convenes international scientific conferences to determine whether a broad-based consensus has emerged

on how specific mechanistic data can be used in an evaluation of human carcinogenicity. The results of such conferences are reported in IARC Scientific Publications, which, as long as they still reflect the current state of scientific knowledge, may guide subsequent Working Groups.

Although the *Monographs* have emphasized hazard identification, important issues may also involve dose–response assessment. In many cases, the same epidemiological and experimental studies used to evaluate a cancer hazard can also be used to estimate a dose–response relationship. A *Monograph* may undertake to estimate dose–response relationships within the range of the available epidemiological data, or it may compare the dose–response information from experimental and epidemiological studies. In some cases, a subsequent publication may be prepared by a separate Working Group with expertise in quantitative dose–response assessment.

The *Monographs* are used by national and international authorities to make risk assessments, formulate decisions concerning preventive measures, provide effective cancer control programmes and decide among alternative options for public health decisions. The evaluations of IARC Working Groups are scientific, qualitative judgements on the evidence for or against carcinogenicity provided by the available data. These evaluations represent only one part of the body of information on which public health decisions may be based. Public health options vary from one situation to another and from country to country and relate to many factors, including different socioeconomic and national priorities. Therefore, no recommendation is given with regard to regulation or legislation, which are the responsibility of individual governments or other international organizations.

3. Selection of agents for review

Agents are selected for review on the basis of two main criteria: (a) there is evidence of human exposure and (b) there is some evidence or suspicion of carcinogenicity. Mixed exposures may occur in occupational and environmental settings and as a result of individual and cultural habits (such as tobacco smoking and dietary practices). Chemical analogues and compounds with biological or physical characteristics similar to those of suspected carcinogens may also be considered, even in the absence of data on a possible carcinogenic effect in humans or experimental animals.

The scientific literature is surveyed for published data relevant to an assessment of carcinogenicity. Ad hoc Advisory Groups convened by IARC in 1984, 1989, 1991, 1993, 1998 and 2003 made recommendations as to which agents should be evaluated in the *Monographs* series. Recent recommendations are available on the *Monographs* programme web site (http://monographs.iarc.fr). IARC may schedule other agents for review as it becomes aware of new scientific information or as national health agencies identify an urgent public health need related to cancer.

As significant new data become available on an agent for which a *Monograph* exists, a re-evaluation may be made at a subsequent meeting, and a new *Monograph* published. In some cases it may be appropriate to review only the data published since a prior evaluation. This can be useful for updating a database, reviewing new data to resolve a previously open question or identifying new tumour sites associated with a carcinogenic agent. Major changes in an evaluation (e.g. a new classification in Group 1 or a determination that a mechanism does not operate in humans, see Part B, Section 6) are more appropriately addressed by a full review.

4. Data for the *Monographs*

Each *Monograph* reviews all pertinent epidemiological studies and cancer bioassays in experimental animals. Those judged inadequate or irrelevant to the evaluation may be cited but not summarized. If a group of similar studies is not reviewed, the reasons are indicated.

Mechanistic and other relevant data are also reviewed. A *Monograph* does not necessarily cite all the mechanistic literature concerning the agent being evaluated (see Part B, Section 4). Only those data considered by the Working Group to be relevant to making the evaluation are included.

With regard to epidemiological studies, cancer bioassays, and mechanistic and other relevant data, only reports that have been published or accepted for publication in the openly available scientific literature are reviewed. The same publication requirement applies to studies originating from IARC, including meta-analyses or pooled analyses commissioned by IARC in advance of a meeting (see Part B, Section 2c). Data from government agency reports that are publicly available are also considered. Exceptionally, doctoral theses and other material that are in their final form and publicly available may be reviewed.

Exposure data and other information on an agent under consideration are also reviewed. In the sections on chemical and physical properties, on analysis, on production and use and on occurrence, published and unpublished sources of information may be considered.

Inclusion of a study does not imply acceptance of the adequacy of the study design or of the analysis and interpretation of the results, and limitations are clearly outlined in square brackets at the end of each study description (see Part B). The reasons for not giving further consideration to an individual study also are indicated in the square brackets.

5. Meeting participants

Five categories of participant can be present at *Monograph* meetings.

(a) The Working Group

The Working Group is responsible for the critical reviews and evaluations that are developed during the meeting. The tasks of Working Group Members are: (i) to ascertain that all appropriate data have been collected; (ii) to select the data relevant for the evaluation on the basis of scientific merit; (iii) to prepare accurate summaries of the data to enable the reader to follow the reasoning of the Working Group; (iv) to evaluate the results of epidemiological and experimental studies on cancer; (v) to evaluate data relevant to the understanding of mechanisms of carcinogenesis; and (vi) to make an overall evaluation of the carcinogenicity of the exposure to humans. Working Group Members generally have published significant research related to the carcinogenicity of the agents being reviewed, and IARC uses literature searches to identify most experts. Working Group Members are selected on the basis of (a) knowledge and experience and (b) absence of real or apparent conflicts of interests. Consideration is also given to demographic diversity and balance of scientific findings and views.

(b) Invited Specialists

Invited Specialists are experts who also have critical knowledge and experience but have a real or apparent conflict of interests. These experts are invited when necessary to assist in the Working Group by contributing their unique knowledge and experience during subgroup and plenary discussions. They may also contribute text on non-influential issues in the section on exposure, such as a general description of data on production and use (see Part B, Section 1). Invited Specialists do not serve as meeting chair

or subgroup chair, draft text that pertains to the description or interpretation of cancer data, or participate in the evaluations.

(c) Representatives of national and international health agencies

Representatives of national and international health agencies often attend meetings because their agencies sponsor the programme or are interested in the subject of a meeting. Representatives do not serve as meeting chair or subgroup chair, draft any part of a *Monograph*, or participate in the evaluations.

(d) Observers with relevant scientific credentials

Observers with relevant scientific credentials may be admitted to a meeting by IARC in limited numbers. Attention will be given to achieving a balance of Observers from constituencies with differing perspectives. They are invited to observe the meeting and should not attempt to influence it. Observers do not serve as meeting chair or subgroup chair, draft any part of a *Monograph*, or participate in the evaluations. At the meeting, the meeting chair and subgroup chairs may grant Observers an opportunity to speak, generally after they have observed a discussion. Observers agree to respect the Guidelines for Observers at *IARC Monographs* meetings (available at http://monographs.iarc.fr).

(e) The IARC Secretariat

The IARC Secretariat consists of scientists who are designated by IARC and who have relevant expertise. They serve as rapporteurs and participate in all discussions. When requested by the meeting chair or subgroup chair, they may also draft text or prepare tables and analyses.

Before an invitation is extended, each potential participant, including the IARC Secretariat, completes the WHO Declaration of Interests to report financial interests, employment and consulting, and individual and institutional research support related to the subject of the meeting. IARC assesses these interests to determine whether there is a conflict that warrants some limitation on participation. The declarations are updated and reviewed again at the opening of the meeting. Interests related to the subject of the meeting are disclosed to the meeting participants and in the published volume (Cogliano et al., 2004).

The names and principal affiliations of participants are available on the *Monographs* programme web site (http://monographs.iarc.fr) approximately two months before each meeting. It is not acceptable for Observers or third parties to contact other participants before a meeting or to lobby them at any time. Meeting participants are asked to report all such contacts to IARC (Cogliano et al., 2005).

All participants are listed, with their principal affiliations, at the beginning of each volume. Each participant who is a Member of a Working Group serves as an individual scientist and not as a representative of any organization, government or industry.

6. Working procedures

A separate Working Group is responsible for developing each volume of *Monographs*. A volume contains one or more *Monographs*, which can cover either a single agent or several related agents. Approximately one year in advance of the meeting of a Working Group, the agents to be reviewed are announced on the *Monographs* programme web site (http://monographs.iarc.fr) and participants are selected by IARC staff in consultation with other experts. Subsequently, relevant biological and epidemiological data are collected by IARC from recognized sources of information on carcinogenesis, including data storage and retrieval systems such as PubMed. Meeting participants who are asked to prepare

preliminary working papers for specific sections are expected to supplement the IARC literature searches with their own searches.

Industrial associations, labour unions and other knowledgeable organizations may be asked to provide input to the sections on production and use, although this involvement is not required as a general rule. Information on production and trade is obtained from governmental, trade and market research publications and, in some cases, by direct contact with industries. Separate production data on some agents may not be available for a variety of reasons (e.g. not collected or made public in all producing countries, production is small). Information on uses may be obtained from published sources but is often complemented by direct contact with manufacturers. Efforts are made to supplement this information with data from other national and international sources.

Six months before the meeting, the material obtained is sent to meeting participants to prepare preliminary working papers. The working papers are compiled by IARC staff and sent, before the meeting, to Working Group Members and Invited Specialists for review.

The Working Group meets at IARC for seven to eight days to discuss and finalize the texts and to formulate the evaluations. The objectives of the meeting are peer review and consensus. During the first few days, four subgroups (covering exposure data, cancer in humans, cancer in experimental animals, and mechanistic and other relevant data) review the working papers, develop a joint subgroup draft and write summaries. Care is taken to ensure that each study summary is written or reviewed by someone not associated with the study being considered. During the last few days, the Working Group meets in plenary session to review the subgroup drafts and develop the evaluations. As a result, the entire volume is the joint product of the Working Group, and there are no individually authored sections.

IARC Working Groups strive to achieve a consensus evaluation. Consensus reflects broad agreement among Working Group Members, but not necessarily unanimity. The chair may elect to poll Working Group Members to determine the diversity of scientific opinion on issues where consensus is not readily apparent.

After the meeting, the master copy is verified by consulting the original literature, edited and prepared for publication. The aim is to publish the volume within six months of the Working Group meeting. A summary of the outcome is available on the *Monographs* programme web site soon after the meeting.

B. SCIENTIFIC REVIEW AND EVALUATION

The available studies are summarized by the Working Group, with particular regard to the qualitative aspects discussed below. In general, numerical findings are indicated as they appear in the original report; units are converted when necessary for easier comparison. The Working Group may conduct additional analyses of the published data and use them in their assessment of the evidence; the results of such supplementary analyses are given in square brackets. When an important aspect of a study that directly impinges on its interpretation should be brought to the attention of the reader, a Working Group comment is given in square brackets.

The scope of the *IARC Monographs* programme has expanded beyond chemicals to include complex mixtures, occupational exposures, physical and biological agents, lifestyle factors and other potentially carcinogenic exposures. Over time, the structure of a *Monograph* has evolved to include the following sections:

Exposure data

Studies of cancer in humans

Studies of cancer in experimental animals

Mechanistic and other relevant data

Summary

Evaluation and rationale

In addition, a section of General Remarks at the front of the volume discusses the reasons the agents were scheduled for evaluation and some key issues the Working Group encountered during the meeting.

This part of the Preamble discusses the types of evidence considered and summarized in each section of a *Monograph*, followed by the scientific criteria that guide the evaluations.

1. Exposure data

Each *Monograph* includes general information on the agent: this information may vary substantially between agents and must be adapted accordingly. Also included is information on production and use (when appropriate), methods of analysis and detection, occurrence, and sources and routes of human occupational and environmental exposures. Depending on the agent, regulations and guidelines for use may be presented.

(a) General information on the agent

For chemical agents, sections on chemical and physical data are included: the Chemical Abstracts Service Registry Number, the latest primary name and the IUPAC systematic name are recorded; other synonyms are given, but the list is not necessarily comprehensive. Information on chemical and physical properties that are relevant to identification, occurrence and biological activity is included. A description of technical products of chemicals includes trade names, relevant specifications and available information on composition and impurities. Some of the trade names given may be those of mixtures in which the agent being evaluated is only one of the ingredients.

For biological agents, taxonomy, structure and biology are described, and the degree of variability is indicated. Mode of replication, life cycle, target cells, persistence, latency, host response and clinical disease other than cancer are also presented.

For physical agents that are forms of radiation, energy and range of the radiation are included. For foreign bodies, fibres and respirable particles, size range and relative dimensions are indicated.

For agents such as mixtures, drugs or lifestyle factors, a description of the agent, including its composition, is given.

Whenever appropriate, other information, such as historical perspectives or the description of an industry or habit, may be included.

(b) Analysis and detection

An overview of methods of analysis and detection of the agent is presented, including their sensitivity, specificity and reproducibility. Methods widely used for regulatory purposes are emphasized. Methods for monitoring human exposure are also given. No critical evaluation or recommendation of any method is meant or implied.

(c) Production and use

The dates of first synthesis and of first commercial production of a chemical, mixture or other agent are provided when available; for agents that do not occur naturally, this information may allow a reasonable estimate to be made of the date before which no human exposure to the agent could have occurred. The dates of first reported occurrence of an exposure are also provided when available. In addition, methods of synthesis used in past and present commercial production and different methods of production,

which may give rise to different impurities, are described.

The countries where companies report production of the agent, and the number of companies in each country, are identified. Available data on production, international trade and uses are obtained for representative regions. It should not, however, be inferred that those areas or nations are necessarily the sole or major sources or users of the agent. Some identified uses may not be current or major applications, and the coverage is not necessarily comprehensive. In the case of drugs, mention of their therapeutic uses does not necessarily represent current practice nor does it imply judgement as to their therapeutic efficacy.

(d) Occurrence and exposure

Information on the occurrence of an agent in the environment is obtained from data derived from the monitoring and surveillance of levels in occupational environments, air, water, soil, plants, foods and animal and human tissues. When available, data on the generation, persistence and bioaccumulation of the agent are also included. Such data may be available from national databases.

Data that indicate the extent of past and present human exposure, the sources of exposure, the people most likely to be exposed and the factors that contribute to the exposure are reported. Information is presented on the range of human exposure, including occupational and environmental exposures. This includes relevant findings from both developed and developing countries. Some of these data are not distributed widely and may be available from government reports and other sources. In the case of mixtures, industries, occupations or processes, information is given about all agents known to be present. For processes, industries and occupations, a historical description is also given, noting variations in chemical composition, physical properties and levels of occupational exposure with date and place. For biological agents, the epidemiology of infection is described.

(e) Regulations and guidelines

Statements concerning regulations and guidelines (e.g. occupational exposure limits, maximal levels permitted in foods and water, pesticide registrations) are included, but they may not reflect the most recent situation, since such limits are continuously reviewed and modified. The absence of information on regulatory status for a country should not be taken to imply that that country does not have regulations with regard to the exposure. For biological agents, legislation and control, including vaccination and therapy, are described.

2. Studies of cancer in humans

This section includes all pertinent epidemiological studies (see Part A, Section 4). Studies of biomarkers are included when they are relevant to an evaluation of carcinogenicity to humans.

(a) Types of study considered

Several types of epidemiological study contribute to the assessment of carcinogenicity in humans — cohort studies, case–control studies, correlation (or ecological) studies and intervention studies. Rarely, results from randomized trials may be available. Case reports and case series of cancer in humans may also be reviewed.

Cohort and case–control studies relate individual exposures under study to the occurrence of cancer in individuals and provide an estimate of effect (such as relative risk) as the main measure of association. Intervention studies may provide strong evidence for making causal inferences, as exemplified by cessation of smoking and the subsequent decrease in risk for lung cancer.

In correlation studies, the units of investigation are usually whole populations (e.g. in

particular geographical areas or at particular times), and cancer frequency is related to a summary measure of the exposure of the population to the agent under study. In correlation studies, individual exposure is not documented, which renders this kind of study more prone to confounding. In some circumstances, however, correlation studies may be more informative than analytical study designs (see, for example, the *Monograph* on arsenic in drinking-water; IARC, 2004).

In some instances, case reports and case series have provided important information about the carcinogenicity of an agent. These types of study generally arise from a suspicion, based on clinical experience, that the concurrence of two events — that is, a particular exposure and occurrence of a cancer — has happened rather more frequently than would be expected by chance. Case reports and case series usually lack complete ascertainment of cases in any population, definition or enumeration of the population at risk and estimation of the expected number of cases in the absence of exposure.

The uncertainties that surround the interpretation of case reports, case series and correlation studies make them inadequate, except in rare instances, to form the sole basis for inferring a causal relationship. When taken together with case–control and cohort studies, however, these types of study may add materially to the judgement that a causal relationship exists.

Epidemiological studies of benign neoplasms, presumed preneoplastic lesions and other end-points thought to be relevant to cancer are also reviewed. They may, in some instances, strengthen inferences drawn from studies of cancer itself.

(b) Quality of studies considered

It is necessary to take into account the possible roles of bias, confounding and chance in the interpretation of epidemiological studies. Bias is the effect of factors in study design or execution that lead erroneously to a stronger or weaker association than in fact exists between an agent and disease. Confounding is a form of bias that occurs when the relationship with disease is made to appear stronger or weaker than it truly is as a result of an association between the apparent causal factor and another factor that is associated with either an increase or decrease in the incidence of the disease. The role of chance is related to biological variability and the influence of sample size on the precision of estimates of effect.

In evaluating the extent to which these factors have been minimized in an individual study, consideration is given to several aspects of design and analysis as described in the report of the study. For example, when suspicion of carcinogenicity arises largely from a single small study, careful consideration is given when interpreting subsequent studies that included these data in an enlarged population. Most of these considerations apply equally to case–control, cohort and correlation studies. Lack of clarity of any of these aspects in the reporting of a study can decrease its credibility and the weight given to it in the final evaluation of the exposure.

First, the study population, disease (or diseases) and exposure should have been well defined by the authors. Cases of disease in the study population should have been identified in a way that was independent of the exposure of interest, and exposure should have been assessed in a way that was not related to disease status.

Second, the authors should have taken into account — in the study design and analysis — other variables that can influence the risk of disease and may have been related to the exposure of interest. Potential confounding by such variables should have been dealt with either in the design of the study, such as by matching, or in the analysis, by statistical adjustment. In cohort studies, comparisons with local rates of disease may or may not be more appropriate than

those with national rates. Internal comparisons of frequency of disease among individuals at different levels of exposure are also desirable in cohort studies, since they minimize the potential for confounding related to the difference in risk factors between an external reference group and the study population.

Third, the authors should have reported the basic data on which the conclusions are founded, even if sophisticated statistical analyses were employed. At the very least, they should have given the numbers of exposed and unexposed cases and controls in a case–control study and the numbers of cases observed and expected in a cohort study. Further tabulations by time since exposure began and other temporal factors are also important. In a cohort study, data on all cancer sites and all causes of death should have been given, to reveal the possibility of reporting bias. In a case–control study, the effects of investigated factors other than the exposure of interest should have been reported.

Finally, the statistical methods used to obtain estimates of relative risk, absolute rates of cancer, confidence intervals and significance tests, and to adjust for confounding should have been clearly stated by the authors. These methods have been reviewed for case–control studies (Breslow & Day, 1980) and for cohort studies (Breslow & Day, 1987).

(c) Meta-analyses and pooled analyses

Independent epidemiological studies of the same agent may lead to results that are difficult to interpret. Combined analyses of data from multiple studies are a means of resolving this ambiguity, and well conducted analyses can be considered. There are two types of combined analysis. The first involves combining summary statistics such as relative risks from individual studies (meta-analysis) and the second involves a pooled analysis of the raw data from the individual studies (pooled analysis) (Greenland, 1998).

The advantages of combined analyses are increased precision due to increased sample size and the opportunity to explore potential confounders, interactions and modifying effects that may explain heterogeneity among studies in more detail. A disadvantage of combined analyses is the possible lack of compatibility of data from various studies due to differences in subject recruitment, procedures of data collection, methods of measurement and effects of unmeasured co-variates that may differ among studies. Despite these limitations, well conducted combined analyses may provide a firmer basis than individual studies for drawing conclusions about the potential carcinogenicity of agents.

IARC may commission a meta-analysis or pooled analysis that is pertinent to a particular *Monograph* (see Part A, Section 4). Additionally, as a means of gaining insight from the results of multiple individual studies, ad hoc calculations that combine data from different studies may be conducted by the Working Group during the course of a *Monograph* meeting. The results of such original calculations, which would be specified in the text by presentation in square brackets, might involve updates of previously conducted analyses that incorporate the results of more recent studies or de-novo analyses. Irrespective of the source of data for the meta-analyses and pooled analyses, it is important that the same criteria for data quality be applied as those that would be applied to individual studies and to ensure also that sources of heterogeneity between studies be taken into account.

(d) Temporal effects

Detailed analyses of both relative and absolute risks in relation to temporal variables, such as age at first exposure, time since first exposure, duration of exposure, cumulative exposure, peak exposure (when appropriate) and

time since cessation of exposure, are reviewed and summarized when available. Analyses of temporal relationships may be useful in making causal inferences. In addition, such analyses may suggest whether a carcinogen acts early or late in the process of carcinogenesis, although, at best, they allow only indirect inferences about mechanisms of carcinogenesis.

(e) Use of biomarkers in epidemiological studies

Biomarkers indicate molecular, cellular or other biological changes and are increasingly used in epidemiological studies for various purposes (IARC, 1991; Vainio et al., 1992; Toniolo et al., 1997; Vineis et al., 1999; Buffler et al., 2004). These may include evidence of exposure, of early effects, of cellular, tissue or organism responses, of individual susceptibility or host responses, and inference of a mechanism (see Part B, Section 4b). This is a rapidly evolving field that encompasses developments in genomics, epigenomics and other emerging technologies.

Molecular epidemiological data that identify associations between genetic polymorphisms and interindividual differences in susceptibility to the agent(s) being evaluated may contribute to the identification of carcinogenic hazards to humans. If the polymorphism has been demonstrated experimentally to modify the functional activity of the gene product in a manner that is consistent with increased susceptibility, these data may be useful in making causal inferences. Similarly, molecular epidemiological studies that measure cell functions, enzymes or metabolites that are thought to be the basis of susceptibility may provide evidence that reinforces biological plausibility. It should be noted, however, that when data on genetic susceptibility originate from multiple comparisons that arise from subgroup analyses, this can generate false-positive results and inconsistencies across studies, and such data therefore require careful evaluation. If the known phenotype of a genetic polymorphism can explain the carcinogenic mechanism of the agent being evaluated, data on this phenotype may be useful in making causal inferences.

(f) Criteria for causality

After the quality of individual epidemiological studies of cancer has been summarized and assessed, a judgement is made concerning the strength of evidence that the agent in question is carcinogenic to humans. In making its judgement, the Working Group considers several criteria for causality (Hill, 1965). A strong association (e.g. a large relative risk) is more likely to indicate causality than a weak association, although it is recognized that estimates of effect of small magnitude do not imply lack of causality and may be important if the disease or exposure is common. Associations that are replicated in several studies of the same design or that use different epidemiological approaches or under different circumstances of exposure are more likely to represent a causal relationship than isolated observations from single studies. If there are inconsistent results among investigations, possible reasons are sought (such as differences in exposure), and results of studies that are judged to be of high quality are given more weight than those of studies that are judged to be methodologically less sound.

If the risk increases with the exposure, this is considered to be a strong indication of causality, although the absence of a graded response is not necessarily evidence against a causal relationship. The demonstration of a decline in risk after cessation of or reduction in exposure in individuals or in whole populations also supports a causal interpretation of the findings.

Several scenarios may increase confidence in a causal relationship. On the one hand, an agent may be specific in causing tumours at one site or of one morphological type. On the other, carcinogenicity may be evident through the causation of

multiple tumour types. Temporality, precision of estimates of effect, biological plausibility and coherence of the overall database are considered. Data on biomarkers may be employed in an assessment of the biological plausibility of epidemiological observations.

Although rarely available, results from randomized trials that show different rates of cancer among exposed and unexposed individuals provide particularly strong evidence for causality.

When several epidemiological studies show little or no indication of an association between an exposure and cancer, a judgement may be made that, in the aggregate, they show evidence of lack of carcinogenicity. Such a judgement requires first that the studies meet, to a sufficient degree, the standards of design and analysis described above. Specifically, the possibility that bias, confounding or misclassification of exposure or outcome could explain the observed results should be considered and excluded with reasonable certainty. In addition, all studies that are judged to be methodologically sound should (a) be consistent with an estimate of effect of unity for any observed level of exposure, (b) when considered together, provide a pooled estimate of relative risk that is at or near to unity, and (c) have a narrow confidence interval, due to sufficient population size. Moreover, no individual study nor the pooled results of all the studies should show any consistent tendency that the relative risk of cancer increases with increasing level of exposure. It is important to note that evidence of lack of carcinogenicity obtained from several epidemiological studies can apply only to the type(s) of cancer studied, to the dose levels reported, and to the intervals between first exposure and disease onset observed in these studies. Experience with human cancer indicates that the period from first exposure to the development of clinical cancer is sometimes longer than 20 years; latent periods substantially shorter than 30 years cannot provide evidence for lack of carcinogenicity.

3. Studies of cancer in experimental animals

All known human carcinogens that have been studied adequately for carcinogenicity in experimental animals have produced positive results in one or more animal species (Wilbourn et al., 1986; Tomatis et al., 1989). For several agents (e.g. aflatoxins, diethylstilbestrol, solar radiation, vinyl chloride), carcinogenicity in experimental animals was established or highly suspected before epidemiological studies confirmed their carcinogenicity in humans (Vainio et al., 1995). Although this association cannot establish that all agents that cause cancer in experimental animals also cause cancer in humans, it is biologically plausible that agents for which there is *sufficient evidence of carcinogenicity* in experimental animals (see Part B, Section 6b) also present a carcinogenic hazard to humans. Accordingly, in the absence of additional scientific information, these agents are considered to pose a carcinogenic hazard to humans. Examples of additional scientific information are data that demonstrate that a given agent causes cancer in animals through a species-specific mechanism that does not operate in humans or data that demonstrate that the mechanism in experimental animals also operates in humans (see Part B, Section 6).

Consideration is given to all available long-term studies of cancer in experimental animals with the agent under review (see Part A, Section 4). In all experimental settings, the nature and extent of impurities or contaminants present in the agent being evaluated are given when available. Animal species, strain (including genetic background where applicable), sex, numbers per group, age at start of treatment, route of exposure, dose levels, duration of exposure, survival and information on tumours (incidence, latency, severity or multiplicity of neoplasms or preneoplastic lesions) are reported. Those studies in experimental animals that are judged to be irrelevant to the evaluation or judged to be inadequate

(e.g. too short a duration, too few animals, poor survival; see below) may be omitted. Guidelines for conducting long-term carcinogenicity experiments have been published (e.g. OECD, 2002).

Other studies considered may include: experiments in which the agent was administered in the presence of factors that modify carcinogenic effects (e.g. initiation–promotion studies, co-carcinogenicity studies and studies in genetically modified animals); studies in which the end-point was not cancer but a defined precancerous lesion; experiments on the carcinogenicity of known metabolites and derivatives; and studies of cancer in non-laboratory animals (e.g. livestock and companion animals) exposed to the agent.

For studies of mixtures, consideration is given to the possibility that changes in the physicochemical properties of the individual substances may occur during collection, storage, extraction, concentration and delivery. Another consideration is that chemical and toxicological interactions of components in a mixture may alter dose–response relationships. The relevance to human exposure of the test mixture administered in the animal experiment is also assessed. This may involve consideration of the following aspects of the mixture tested: (i) physical and chemical characteristics, (ii) identified constituents that may indicate the presence of a class of substances and (iii) the results of genetic toxicity and related tests.

The relevance of results obtained with an agent that is analogous (e.g. similar in structure or of a similar virus genus) to that being evaluated is also considered. Such results may provide biological and mechanistic information that is relevant to the understanding of the process of carcinogenesis in humans and may strengthen the biological plausibility that the agent being evaluated is carcinogenic to humans (see Part B, Section 2f).

(a) Qualitative aspects

An assessment of carcinogenicity involves several considerations of qualitative importance, including (i) the experimental conditions under which the test was performed, including route, schedule and duration of exposure, species, strain (including genetic background where applicable), sex, age and duration of follow-up; (ii) the consistency of the results, for example, across species and target organ(s); (iii) the spectrum of neoplastic response, from preneoplastic lesions and benign tumours to malignant neoplasms; and (iv) the possible role of modifying factors.

Considerations of importance in the interpretation and evaluation of a particular study include: (i) how clearly the agent was defined and, in the case of mixtures, how adequately the sample characterization was reported; (ii) whether the dose was monitored adequately, particularly in inhalation experiments; (iii) whether the doses, duration of treatment and route of exposure were appropriate; (iv) whether the survival of treated animals was similar to that of controls; (v) whether there were adequate numbers of animals per group; (vi) whether both male and female animals were used; (vii) whether animals were allocated randomly to groups; (viii) whether the duration of observation was adequate; and (ix) whether the data were reported and analysed adequately.

When benign tumours (a) occur together with and originate from the same cell type as malignant tumours in an organ or tissue in a particular study and (b) appear to represent a stage in the progression to malignancy, they are usually combined in the assessment of tumour incidence (Huff et al., 1989). The occurrence of lesions presumed to be preneoplastic may in certain instances aid in assessing the biological plausibility of any neoplastic response observed. If an agent induces only benign neoplasms that appear to be end-points that do not readily undergo transition to malignancy, the agent

should nevertheless be suspected of being carcinogenic and requires further investigation.

(b) Quantitative aspects

The probability that tumours will occur may depend on the species, sex, strain, genetic background and age of the animal, and on the dose, route, timing and duration of the exposure. Evidence of an increased incidence of neoplasms with increasing levels of exposure strengthens the inference of a causal association between the exposure and the development of neoplasms.

The form of the dose–response relationship can vary widely, depending on the particular agent under study and the target organ. Mechanisms such as induction of DNA damage or inhibition of repair, altered cell division and cell death rates and changes in intercellular communication are important determinants of dose–response relationships for some carcinogens. Since many chemicals require metabolic activation before being converted to their reactive intermediates, both metabolic and toxicokinetic aspects are important in determining the dose–response pattern. Saturation of steps such as absorption, activation, inactivation and elimination may produce nonlinearity in the dose–response relationship (Hoel et al., 1983; Gart et al., 1986), as could saturation of processes such as DNA repair. The dose–response relationship can also be affected by differences in survival among the treatment groups.

(c) Statistical analyses

Factors considered include the adequacy of the information given for each treatment group: (i) number of animals studied and number examined histologically, (ii) number of animals with a given tumour type and (iii) length of survival. The statistical methods used should be clearly stated and should be the generally accepted techniques refined for this purpose (Peto et al., 1980; Gart et al., 1986; Portier & Bailer, 1989; Bieler & Williams, 1993). The choice of the most appropriate statistical method requires consideration of whether or not there are differences in survival among the treatment groups; for example, reduced survival because of non-tumour-related mortality can preclude the occurrence of tumours later in life. When detailed information on survival is not available, comparisons of the proportions of tumour-bearing animals among the effective number of animals (alive at the time the first tumour was discovered) can be useful when significant differences in survival occur before tumours appear. The lethality of the tumour also requires consideration: for rapidly fatal tumours, the time of death provides an indication of the time of tumour onset and can be assessed using life-table methods; non-fatal or incidental tumours that do not affect survival can be assessed using methods such as the Mantel-Haenzel test for changes in tumour prevalence. Because tumour lethality is often difficult to determine, methods such as the Poly-K test that do not require such information can also be used. When results are available on the number and size of tumours seen in experimental animals (e.g. papillomas on mouse skin, liver tumours observed through nuclear magnetic resonance tomography), other more complicated statistical procedures may be needed (Sherman et al., 1994; Dunson et al., 2003).

Formal statistical methods have been developed to incorporate historical control data into the analysis of data from a given experiment. These methods assign an appropriate weight to historical and concurrent controls on the basis of the extent of between-study and within-study variability: less weight is given to historical controls when they show a high degree of variability, and greater weight when they show little variability. It is generally not appropriate to discount a tumour response that is significantly increased compared with concurrent controls by arguing that it falls within the range of historical controls, particularly

when historical controls show high between-study variability and are, thus, of little relevance to the current experiment. In analysing results for uncommon tumours, however, the analysis may be improved by considering historical control data, particularly when between-study variability is low. Historical controls should be selected to resemble the concurrent controls as closely as possible with respect to species, gender and strain, as well as other factors such as basal diet and general laboratory environment, which may affect tumour-response rates in control animals (Haseman et al., 1984; Fung et al., 1996; Greim et al., 2003).

Although meta-analyses and combined analyses are conducted less frequently for animal experiments than for epidemiological studies due to differences in animal strains, they can be useful aids in interpreting animal data when the experimental protocols are sufficiently similar.

4. Mechanistic and other relevant data

Mechanistic and other relevant data may provide evidence of carcinogenicity and also help in assessing the relevance and importance of findings of cancer in animals and in humans. The nature of the mechanistic and other relevant data depends on the biological activity of the agent being considered. The Working Group considers representative studies to give a concise description of the relevant data and issues that they consider to be important; thus, not every available study is cited. Relevant topics may include toxicokinetics, mechanisms of carcinogenesis, susceptible individuals, populations and life-stages, other relevant data and other adverse effects. When data on biomarkers are informative about the mechanisms of carcinogenesis, they are included in this section.

These topics are not mutually exclusive; thus, the same studies may be discussed in more than one subsection. For example, a mutation in a gene that codes for an enzyme that metabolizes the agent under study could be discussed in the subsections on toxicokinetics, mechanisms and individual susceptibility if it also exists as an inherited polymorphism.

(a) Toxicokinetic data

Toxicokinetics refers to the absorption, distribution, metabolism and elimination of agents in humans, experimental animals and, where relevant, cellular systems. Examples of kinetic factors that may affect dose–response relationships include uptake, deposition, biopersistence and half-life in tissues, protein binding, metabolic activation and detoxification. Studies that indicate the metabolic fate of the agent in humans and in experimental animals are summarized briefly, and comparisons of data from humans and animals are made when possible. Comparative information on the relationship between exposure and the dose that reaches the target site may be important for the extrapolation of hazards between species and in clarifying the role of in-vitro findings.

(b) Data on mechanisms of carcinogenesis

To provide focus, the Working Group attempts to identify the possible mechanisms by which the agent may increase the risk of cancer. For each possible mechanism, a representative selection of key data from humans and experimental systems is summarized. Attention is given to gaps in the data and to data that suggests that more than one mechanism may be operating. The relevance of the mechanism to humans is discussed, in particular, when mechanistic data are derived from experimental model systems. Changes in the affected organs, tissues or cells can be divided into three non-exclusive levels as described below.

(i) Changes in physiology

Physiological changes refer to exposure-related modifications to the physiology and/or response of cells, tissues and organs. Examples of potentially adverse physiological changes include mitogenesis, compensatory cell division, escape from apoptosis and/or senescence, presence of inflammation, hyperplasia, metaplasia and/or preneoplasia, angiogenesis, alterations in cellular adhesion, changes in steroidal hormones and changes in immune surveillance.

(ii) Functional changes at the cellular level

Functional changes refer to exposure-related alterations in the signalling pathways used by cells to manage critical processes that are related to increased risk for cancer. Examples of functional changes include modified activities of enzymes involved in the metabolism of xenobiotics, alterations in the expression of key genes that regulate DNA repair, alterations in cyclin-dependent kinases that govern cell cycle progression, changes in the patterns of post-translational modifications of proteins, changes in regulatory factors that alter apoptotic rates, changes in the secretion of factors related to the stimulation of DNA replication and transcription and changes in gap–junction-mediated intercellular communication.

(iii) Changes at the molecular level

Molecular changes refer to exposure-related changes in key cellular structures at the molecular level, including, in particular, genotoxicity. Examples of molecular changes include formation of DNA adducts and DNA strand breaks, mutations in genes, chromosomal aberrations, aneuploidy and changes in DNA methylation patterns. Greater emphasis is given to irreversible effects.

The use of mechanistic data in the identification of a carcinogenic hazard is specific to the mechanism being addressed and is not readily described for every possible level and mechanism discussed above.

Genotoxicity data are discussed here to illustrate the key issues involved in the evaluation of mechanistic data.

Tests for genetic and related effects are described in view of the relevance of gene mutation and chromosomal aberration/aneuploidy to carcinogenesis (Vainio et al., 1992; McGregor et al., 1999). The adequacy of the reporting of sample characterization is considered and, when necessary, commented upon; with regard to complex mixtures, such comments are similar to those described for animal carcinogenicity tests. The available data are interpreted critically according to the end-points detected, which may include DNA damage, gene mutation, sister chromatid exchange, micronucleus formation, chromosomal aberrations and aneuploidy. The concentrations employed are given, and mention is made of whether the use of an exogenous metabolic system in vitro affected the test result. These data are listed in tabular form by phylogenetic classification.

Positive results in tests using prokaryotes, lower eukaryotes, insects, plants and cultured mammalian cells suggest that genetic and related effects could occur in mammals. Results from such tests may also give information on the types of genetic effect produced and on the involvement of metabolic activation. Some end-points described are clearly genetic in nature (e.g. gene mutations), while others are associated with genetic effects (e.g. unscheduled DNA synthesis). In-vitro tests for tumour promotion, cell transformation and gap–junction intercellular communication may be sensitive to changes that are not necessarily the result of genetic alterations but that may have specific relevance to the process of carcinogenesis. Critical appraisals of these tests have been published (Montesano et al., 1986; McGregor et al., 1999).

Genetic or other activity manifest in humans and experimental mammals is regarded to be of

greater relevance than that in other organisms. The demonstration that an agent can induce gene and chromosomal mutations in mammals in vivo indicates that it may have carcinogenic activity. Negative results in tests for mutagenicity in selected tissues from animals treated in vivo provide less weight, partly because they do not exclude the possibility of an effect in tissues other than those examined. Moreover, negative results in short-term tests with genetic end-points cannot be considered to provide evidence that rules out the carcinogenicity of agents that act through other mechanisms (e.g. receptor-mediated effects, cellular toxicity with regenerative cell division, peroxisome proliferation) (Vainio et al., 1992). Factors that may give misleading results in short-term tests have been discussed in detail elsewhere (Montesano et al., 1986; McGregor et al., 1999).

When there is evidence that an agent acts by a specific mechanism that does not involve genotoxicity (e.g. hormonal dysregulation, immune suppression, and formation of calculi and other deposits that cause chronic irritation), that evidence is presented and reviewed critically in the context of rigorous criteria for the operation of that mechanism in carcinogenesis (e.g. Capen et al., 1999).

For biological agents such as viruses, bacteria and parasites, other data relevant to carcinogenicity may include descriptions of the pathology of infection, integration and expression of viruses, and genetic alterations seen in human tumours. Other observations that might comprise cellular and tissue responses to infection, immune response and the presence of tumour markers are also considered.

For physical agents that are forms of radiation, other data relevant to carcinogenicity may include descriptions of damaging effects at the physiological, cellular and molecular level, as for chemical agents, and descriptions of how these effects occur. 'Physical agents' may also be considered to comprise foreign bodies, such as surgical implants of various kinds, and poorly soluble fibres, dusts and particles of various sizes, the pathogenic effects of which are a result of their physical presence in tissues or body cavities. Other relevant data for such materials may include characterization of cellular, tissue and physiological reactions to these materials and descriptions of pathological conditions other than neoplasia with which they may be associated.

(c) Other data relevant to mechanisms

A description is provided of any structure–activity relationships that may be relevant to an evaluation of the carcinogenicity of an agent, the toxicological implications of the physical and chemical properties, and any other data relevant to the evaluation that are not included elsewhere.

High-output data, such as those derived from gene expression microarrays, and high-throughput data, such as those that result from testing hundreds of agents for a single end-point, pose a unique problem for the use of mechanistic data in the evaluation of a carcinogenic hazard. In the case of high-output data, there is the possibility to overinterpret changes in individual end-points (e.g. changes in expression in one gene) without considering the consistency of that finding in the broader context of the other end-points (e.g. other genes with linked transcriptional control). High-output data can be used in assessing mechanisms, but all end-points measured in a single experiment need to be considered in the proper context. For high-throughput data, where the number of observations far exceeds the number of end-points measured, their utility for identifying common mechanisms across multiple agents is enhanced. These data can be used to identify mechanisms that not only seem plausible, but also have a consistent pattern of carcinogenic response across entire classes of related compounds.

(d) Susceptibility data

Individuals, populations and life-stages may have greater or lesser susceptibility to an agent, based on toxicokinetics, mechanisms of carcinogenesis and other factors. Examples of host and genetic factors that affect individual susceptibility include sex, genetic polymorphisms of genes involved in the metabolism of the agent under evaluation, differences in metabolic capacity due to life-stage or the presence of disease, differences in DNA repair capacity, competition for or alteration of metabolic capacity by medications or other chemical exposures, pre-existing hormonal imbalance that is exacerbated by a chemical exposure, a suppressed immune system, periods of higher-than-usual tissue growth or regeneration and genetic polymorphisms that lead to differences in behaviour (e.g. addiction). Such data can substantially increase the strength of the evidence from epidemiological data and enhance the linkage of in-vivo and in-vitro laboratory studies to humans.

(e) Data on other adverse effects

Data on acute, subchronic and chronic adverse effects relevant to the cancer evaluation are summarized. Adverse effects that confirm distribution and biological effects at the sites of tumour development, or alterations in physiology that could lead to tumour development, are emphasized. Effects on reproduction, embryonic and fetal survival and development are summarized briefly. The adequacy of epidemiological studies of reproductive outcome and genetic and related effects in humans is judged by the same criteria as those applied to epidemiological studies of cancer, but fewer details are given.

5. Summary

This section is a summary of data presented in the preceding sections. Summaries can be found on the *Monographs* programme web site (http://monographs.iarc.fr).

(a) Exposure data

Data are summarized, as appropriate, on the basis of elements such as production, use, occurrence and exposure levels in the workplace and environment and measurements in human tissues and body fluids. Quantitative data and time trends are given to compare exposures in different occupations and environmental settings. Exposure to biological agents is described in terms of transmission, prevalence and persistence of infection.

(b) Cancer in humans

Results of epidemiological studies pertinent to an assessment of human carcinogenicity are summarized. When relevant, case reports and correlation studies are also summarized. The target organ(s) or tissue(s) in which an increase in cancer was observed is identified. Dose–response and other quantitative data may be summarized when available.

(c) Cancer in experimental animals

Data relevant to an evaluation of carcinogenicity in animals are summarized. For each animal species, study design and route of administration, it is stated whether an increased incidence, reduced latency, or increased severity or multiplicity of neoplasms or preneoplastic lesions were observed, and the tumour sites are indicated. If the agent produced tumours after prenatal exposure or in single-dose experiments, this is also mentioned. Negative findings, inverse relationships, dose–response and other quantitative data are also summarized.

(d) Mechanistic and other relevant data

Data relevant to the toxicokinetics (absorption, distribution, metabolism, elimination) and the possible mechanism(s) of carcinogenesis (e.g. genetic toxicity, epigenetic effects) are summarized. In addition, information on susceptible individuals, populations and life-stages is summarized. This section also reports on other toxic effects, including reproductive and developmental effects, as well as additional relevant data that are considered to be important.

6. Evaluation and rationale

Evaluations of the strength of the evidence for carcinogenicity arising from human and experimental animal data are made, using standard terms. The strength of the mechanistic evidence is also characterized.

It is recognized that the criteria for these evaluations, described below, cannot encompass all of the factors that may be relevant to an evaluation of carcinogenicity. In considering all of the relevant scientific data, the Working Group may assign the agent to a higher or lower category than a strict interpretation of these criteria would indicate.

These categories refer only to the strength of the evidence that an exposure is carcinogenic and not to the extent of its carcinogenic activity (potency). A classification may change as new information becomes available.

An evaluation of the degree of evidence is limited to the materials tested, as defined physically, chemically or biologically. When the agents evaluated are considered by the Working Group to be sufficiently closely related, they may be grouped together for the purpose of a single evaluation of the degree of evidence.

(a) Carcinogenicity in humans

The evidence relevant to carcinogenicity from studies in humans is classified into one of the following categories:

***Sufficient evidence of carcinogenicity*:**

The Working Group considers that a causal relationship has been established between exposure to the agent and human cancer. That is, a positive relationship has been observed between the exposure and cancer in studies in which chance, bias and confounding could be ruled out with reasonable confidence. A statement that there is *sufficient evidence* is followed by a separate sentence that identifies the target organ(s) or tissue(s) where an increased risk of cancer was observed in humans. Identification of a specific target organ or tissue does not preclude the possibility that the agent may cause cancer at other sites.

***Limited evidence of carcinogenicity*:**

A positive association has been observed between exposure to the agent and cancer for which a causal interpretation is considered by the Working Group to be credible, but chance, bias or confounding could not be ruled out with reasonable confidence.

***Inadequate evidence of carcinogenicity*:**

The available studies are of insufficient quality, consistency or statistical power to permit a conclusion regarding the presence or absence of a causal association between exposure and cancer, or no data on cancer in humans are available.

***Evidence suggesting lack of carcinogenicity*:**

There are several adequate studies covering the full range of levels of exposure that humans are known to encounter, which are mutually consistent in not showing a positive association between exposure to the agent and any studied cancer at any observed level of exposure. The results from these studies alone or combined should have narrow confidence intervals with an upper limit close to the null value (e.g. a relative

risk of 1.0). Bias and confounding should be ruled out with reasonable confidence, and the studies should have an adequate length of follow-up. A conclusion of *evidence suggesting lack of carcinogenicity* is inevitably limited to the cancer sites, conditions and levels of exposure, and length of observation covered by the available studies. In addition, the possibility of a very small risk at the levels of exposure studied can never be excluded.

In some instances, the above categories may be used to classify the degree of evidence related to carcinogenicity in specific organs or tissues.

When the available epidemiological studies pertain to a mixture, process, occupation or industry, the Working Group seeks to identify the specific agent considered most likely to be responsible for any excess risk. The evaluation is focused as narrowly as the available data on exposure and other aspects permit.

(b) Carcinogenicity in experimental animals

Carcinogenicity in experimental animals can be evaluated using conventional bioassays, bioassays that employ genetically modified animals, and other in-vivo bioassays that focus on one or more of the critical stages of carcinogenesis. In the absence of data from conventional long-term bioassays or from assays with neoplasia as the end-point, consistently positive results in several models that address several stages in the multistage process of carcinogenesis should be considered in evaluating the degree of evidence of carcinogenicity in experimental animals.

The evidence relevant to carcinogenicity in experimental animals is classified into one of the following categories:

***Sufficient evidence of carcinogenicity*:**

The Working Group considers that a causal relationship has been established between the agent and an increased incidence of malignant neoplasms or of an appropriate combination of benign and malignant neoplasms in (a) two or more species of animals or (b) two or more independent studies in one species carried out at different times or in different laboratories or under different protocols. An increased incidence of tumours in both sexes of a single species in a well conducted study, ideally conducted under Good Laboratory Practices, can also provide *sufficient evidence*.

A single study in one species and sex might be considered to provide *sufficient evidence of carcinogenicity* when malignant neoplasms occur to an unusual degree with regard to incidence, site, type of tumour or age at onset, or when there are strong findings of tumours at multiple sites.

***Limited evidence of carcinogenicity*:**

The data suggest a carcinogenic effect but are limited for making a definitive evaluation because, e.g. (a) the evidence of carcinogenicity is restricted to a single experiment; (b) there are unresolved questions regarding the adequacy of the design, conduct or interpretation of the studies; (c) the agent increases the incidence only of benign neoplasms or lesions of uncertain neoplastic potential; or (d) the evidence of carcinogenicity is restricted to studies that demonstrate only promoting activity in a narrow range of tissues or organs.

***Inadequate evidence of carcinogenicity*:**

The studies cannot be interpreted as showing either the presence or absence of a carcinogenic effect because of major qualitative or quantitative limitations, or no data on cancer in experimental animals are available.

***Evidence suggesting lack of carcinogenicity*:**

Adequate studies involving at least two species are available which show that, within the limits of the tests used, the agent is not carcinogenic. A conclusion of *evidence suggesting lack of carcinogenicity* is inevitably limited to the species, tumour sites, age at exposure, and conditions and levels of exposure studied.

(c) Mechanistic and other relevant data

Mechanistic and other evidence judged to be relevant to an evaluation of carcinogenicity and of sufficient importance to affect the overall evaluation is highlighted. This may include data on preneoplastic lesions, tumour pathology, genetic and related effects, structure–activity relationships, metabolism and toxicokinetics, physicochemical parameters and analogous biological agents.

The strength of the evidence that any carcinogenic effect observed is due to a particular mechanism is evaluated, using terms such as 'weak', 'moderate' or 'strong'. The Working Group then assesses whether that particular mechanism is likely to be operative in humans. The strongest indications that a particular mechanism operates in humans derive from data on humans or biological specimens obtained from exposed humans. The data may be considered to be especially relevant if they show that the agent in question has caused changes in exposed humans that are on the causal pathway to carcinogenesis. Such data may, however, never become available, because it is at least conceivable that certain compounds may be kept from human use solely on the basis of evidence of their toxicity and/or carcinogenicity in experimental systems.

The conclusion that a mechanism operates in experimental animals is strengthened by findings of consistent results in different experimental systems, by the demonstration of biological plausibility and by coherence of the overall database. Strong support can be obtained from studies that challenge the hypothesized mechanism experimentally, by demonstrating that the suppression of key mechanistic processes leads to the suppression of tumour development. The Working Group considers whether multiple mechanisms might contribute to tumour development, whether different mechanisms might operate in different dose ranges, whether separate mechanisms might operate in humans and experimental animals and whether a unique mechanism might operate in a susceptible group. The possible contribution of alternative mechanisms must be considered before concluding that tumours observed in experimental animals are not relevant to humans. An uneven level of experimental support for different mechanisms may reflect that disproportionate resources have been focused on investigating a favoured mechanism.

For complex exposures, including occupational and industrial exposures, the chemical composition and the potential contribution of carcinogens known to be present are considered by the Working Group in its overall evaluation of human carcinogenicity. The Working Group also determines the extent to which the materials tested in experimental systems are related to those to which humans are exposed.

(d) Overall evaluation

Finally, the body of evidence is considered as a whole, to reach an overall evaluation of the carcinogenicity of the agent to humans.

An evaluation may be made for a group of agents that have been evaluated by the Working Group. In addition, when supporting data indicate that other related agents, for which there is no direct evidence of their capacity to induce cancer in humans or in animals, may also be carcinogenic, a statement describing the rationale for this conclusion is added to the evaluation narrative; an additional evaluation may be made for this broader group of agents if the strength of the evidence warrants it.

The agent is described according to the wording of one of the following categories, and the designated group is given. The categorization of an agent is a matter of scientific judgement that reflects the strength of the evidence derived from studies in humans and in experimental animals and from mechanistic and other relevant data.

Group 1: The agent is carcinogenic to humans.

This category is used when there is *sufficient evidence of carcinogenicity* in humans. Exceptionally, an agent may be placed in this category when evidence of carcinogenicity in humans is less than *sufficient* but there is *sufficient evidence of carcinogenicity* in experimental animals and strong evidence in exposed humans that the agent acts through a relevant mechanism of carcinogenicity.

Group 2.

This category includes agents for which, at one extreme, the degree of evidence of carcinogenicity in humans is almost *sufficient*, as well as those for which, at the other extreme, there are no human data but for which there is evidence of carcinogenicity in experimental animals. Agents are assigned to either Group 2A (*probably carcinogenic to humans*) or Group 2B (*possibly carcinogenic to humans*) on the basis of epidemiological and experimental evidence of carcinogenicity and mechanistic and other relevant data. The terms *probably carcinogenic* and *possibly carcinogenic* have no quantitative significance and are used simply as descriptors of different levels of evidence of human carcinogenicity, with *probably carcinogenic* signifying a higher level of evidence than *possibly carcinogenic*.

Group 2A: The agent is probably carcinogenic to humans.

This category is used when there is *limited evidence of carcinogenicity* in humans and *sufficient evidence of carcinogenicity* in experimental animals. In some cases, an agent may be classified in this category when there is *inadequate evidence of carcinogenicity* in humans and *sufficient evidence of carcinogenicity* in experimental animals and strong evidence that the carcinogenesis is mediated by a mechanism that also operates in humans. Exceptionally, an agent may be classified in this category solely on the basis of *limited evidence of carcinogenicity* in humans. An agent may be assigned to this category if it clearly belongs, based on mechanistic considerations, to a class of agents for which one or more members have been classified in Group 1 or Group 2A.

Group 2B: The agent is possibly carcinogenic to humans.

This category is used for agents for which there is *limited evidence of carcinogenicity* in humans and less than *sufficient evidence of carcinogenicity* in experimental animals. It may also be used when there is *inadequate evidence of carcinogenicity* in humans but there is *sufficient evidence of carcinogenicity* in experimental animals. In some instances, an agent for which there is *inadequate evidence of carcinogenicity* in humans and less than *sufficient evidence of carcinogenicity* in experimental animals together with supporting evidence from mechanistic and other relevant data may be placed in this group. An agent may be classified in this category solely on the basis of strong evidence from mechanistic and other relevant data.

Group 3: The agent is not classifiable as to its carcinogenicity to humans.

This category is used most commonly for agents for which the evidence of carcinogenicity is *inadequate* in humans and *inadequate* or *limited* in experimental animals.

Exceptionally, agents for which the evidence of carcinogenicity is *inadequate* in humans but *sufficient* in experimental animals may be placed in this category when there is strong evidence that the mechanism of carcinogenicity in experimental animals does not operate in humans.

Agents that do not fall into any other group are also placed in this category.

An evaluation in Group 3 is not a determination of non-carcinogenicity or overall safety. It often means that further research is needed,

especially when exposures are widespread or the cancer data are consistent with differing interpretations.

Group 4: The agent is probably not carcinogenic to humans.

This category is used for agents for which there is *evidence suggesting lack of carcinogenicity* in humans and in experimental animals. In some instances, agents for which there is *inadequate evidence of carcinogenicity* in humans but *evidence suggesting lack of carcinogenicity* in experimental animals, consistently and strongly supported by a broad range of mechanistic and other relevant data, may be classified in this group.

(e) Rationale

The reasoning that the Working Group used to reach its evaluation is presented and discussed. This section integrates the major findings from studies of cancer in humans, studies of cancer in experimental animals, and mechanistic and other relevant data. It includes concise statements of the principal line(s) of argument that emerged, the conclusions of the Working Group on the strength of the evidence for each group of studies, citations to indicate which studies were pivotal to these conclusions, and an explanation of the reasoning of the Working Group in weighing data and making evaluations. When there are significant differences of scientific interpretation among Working Group Members, a brief summary of the alternative interpretations is provided, together with their scientific rationale and an indication of the relative degree of support for each alternative.

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GENERAL REMARKS

This one-hundred-and-fourteenth volume of the *IARC Monographs* presents evaluations of the carcinogenic hazard to humans arising from consumption of red meat and processed meat. Based on the large amount of available literature reporting an elevated risk of cancer of the colorectum associated with the consumption of red meat or processed meat, the Advisory Group to Recommend Priorities for *IARC Monographs* during 2015–2019 recommended that these agents be evaluated with high priority (IARC, 2014; Straif et al., 2014). A summary of the findings of this volume has been published in *The Lancet Oncology* (Bouvard et al., 2015).

Scope of the volume

This volume is concerned with red meat or processed meat as consumed. Occupational exposure to these foods in the course of preparation (e.g. abattoir workers, butchers) was not considered. For red meat, the overwhelming majority of available epidemiological studies were on consumption of cooked meat. For processed meat, certain products are consumed as they are supplied commercially (e.g. ham), while others (e.g. bacon), may be cooked. The carcinogenicity of different methods of cooking meat was also reviewed.

The Working Group evaluated the carcinogenic hazard associated with meat consumption, and did not consider other potential hazards or benefits (e.g. from the nutritional value of meat).

The scientific literature concerning potential carcinogens that may be contained in meat (e.g. haem iron, heterocyclic aromatic amines, *N*-nitroso-compounds, polycyclic aromatic hydrocarbons) is summarized in this Monograph (see Section 4.5); however, the Working Group did not specifically evaluate these agents in relation to meat consumption.

Definitions of "red meat" and "processed meat"

For red meat, the definition (see Section 1) centres on the animal species from which the meat was derived. The handling of the red meat between abattoir and butcher's shop, and subsequent cooking (often involving addition of condiments such as salt and pepper) are not considered in this volume as "processing". Likewise, meat that has simply been refrigerated is not regarded as processed meat.

Processed meat refers to meat that has been transformed through salting, curing, fermentation, smoking, or other processes to enhance flavour or improve preservation (see Section 1).

For most processed meats, the starting material is red meat, which by definition excludes poultry. However, the definition of processed meat does not exclude products that are partly, or even wholly, derived from poultry or meat products other than red meat.

Challenges in evaluation of the epidemiological data

The Working Group considered more than 800 epidemiological studies that investigated the association between cancer (at more than 15 organ sites) and consumption of red meat or processed meat. A major strength of this database is that it comprised large cohorts and well-conducted population-based case–control studies in many countries, on several continents, considering diverse ethnicities, and varied diets. The Working Group faced two major challenges: quality of exposure assessment and exposure quantification; and potential confounding.

The quality of the exposure assessments and quantification mostly depended on the questionnaire used. For the evaluation, the Working Group gave greatest weight to validated questionnaires that contained a clear definition of red meat and processed meat, considered them separately, and provided quantitative dietary data.

With regard to confounding, the Working Group considered the established or putative role of a variety of dietary and lifestyle factors as potential confounders, according to cancer site. For example, total caloric intake is a putative risk factor for cancers at several sites, including the colorectum, and red meat and processed meat are significant contributors to total caloric intake. Other potential confounders include consumption of fruit and vegetables, and alcoholic beverages, tobacco smoking, obesity, physical activity, and diabetes mellitus. An additional complexity to be considered has been the inter-relationships between diet, including meat consumption, overweight/obesity and diabetes mellitus (Wang & Beydoun, 2009; Micha et al., 2012) (see also Section 4.2.5 (b)).

Based on the above considerations, the Working Group established clear inclusion and exclusion criteria for the systematic evaluation of the available studies; these are detailed in Section 2.1.

Heterogeneity among types of red meat and processed meat

Although the Working Group established clear definitions of red meat and processed meat, each term encompasses heterogeneous food products (see Section 1). There are potentially important nutritional differences between different types of red meat. These differences include calorie intake, iron content, and fatty acid composition, and vary according to the age, sex, breed, and diet of the animal from which the meat is derived, as well as the cut of meat. Similarly, the different processing methods that may or may not include use of preservatives (e.g. nitrate/nitrite) result in distinct products. However, the available cancer data do not allow a distinction to be made between different types of red meat or processed meat products.

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1. EXPOSURE DATA

1.1 Identification of the agents

The focus of this *Monograph* is the consumption of red meat and processed meat. These terms are defined below.

1.1.1 Red meat

Red meat refers to fresh unprocessed mammalian muscle meat (e.g. beef, veal, pork, lamb, mutton, horse, or goat meat), which may be minced or frozen, and is usually consumed cooked.

1.1.2 Offal

Mammalian offal refers to the internal organs and entrails of a butchered animal (e.g. scrotum, small intestine, heart, brain, kidney, liver, thymus, pancreas, testicle, tongue, tripe, or stomach) consumed as such. Mammalian offal is considered to be a specific food category in food consumption surveys (FAO, 2015); however, mammalian offal is reported together with red meat in some epidemiological studies.

1.1.3 Processed meat

Processed meat refers to any meat that has been transformed through one or several of the following processes: salting, curing, fermentation, smoking, or other processes to enhance flavour or improve preservation. Most processed meats are made from pork or beef, but may also include other red meats, poultry, offal, or meat by-products such as blood. It is also important to distinguish between industrial processing and household preparations. As there is a huge variety of processed meat products, it is difficult to sort them into categories (Santarelli et al., 2008). However, based on recommendations by the Food and Agriculture Organization of the United Nations (FAO) (Heinz & Hautzinger, 2007), different groups of industrial processed meats can be proposed.

(a) Cured meat pieces

Examples of cured meat include raw beef, raw ham, cooked beef, cooked ham, corned beef, and bacon.

Curing is a process by which the meat is treated with a small amount of salt (sodium chloride, NaCl, with or without potassium chloride, KCl), with or without nitrate or nitrite salts. Curing enhances shelf-life by preserving and preventing the spoilage of meat. Cured meat cuts are made of entire pieces of muscle meat and can be subdivided into two groups: cured raw meats and cured cooked meats (Pearson & Gillett, 1996; Heinz & Hautzinger, 2007; Honikel, 2010). Cured raw meats are consumed uncooked. They do not undergo any heat treatment during production, which involves curing, fermentation, and ripening in controlled conditions to make the meats palatable. For cured cooked meats, the raw muscle meat is always cured and then undergoes treatment to achieve the desired palatability (Heinz & Hautzinger, 2007).

(b) Fresh industrial processed meat products

Examples of fresh industrial processed meat products include sausage and kebab.

These products are mixtures composed of comminuted muscle meat and animal fat in varying proportions. Products are salted only, not cured. Non-meat ingredients are added in smaller quantities for improvement of flavour and binding, or in larger quantities for volume extension (reducing costs). All meat and non-meat ingredients are mixed when raw. If the fresh meat mixture is packed into casings, the product is defined as sausage. Heat treatment is applied immediately before consumption to make the products palatable (Heinz & Hautzinger, 2007). [The Working Group noted that a hamburger is considered as belonging to this category of processed meat when fat, salt, or other additives are added to the hamburger meat, but is considered as red meat when it contains minced beef only.]

(c) Precooked ready-to-eat products

Examples of precooked ready-to-eat products include frankfurter, mortadella, liver sausage, blood sausage, canned corned beef, and liver pâté.

These products are prepared from muscle meat, fat, and other edible meat by-products (blood and liver) or non-meat ingredients. These products are processed raw through comminuting and mixing. Sometimes the raw meat material can be precooked before it is ground or chopped, and other ingredients are added. The resulting mixture is portioned and then submitted to heat treatment to induce protein coagulation. This leads to the typical firm, elastic texture of precooked ready-to-eat products, as well as a desired palatability and a certain degree of bacterial stability (Heinz & Hautzinger, 2007).

(d) Fermented sausages

Examples of fermented sausages include salami, chorizo, pepperoni, and traditional Asian products such as nem.

Fermented sausages are uncooked meat products, and consist of coarse mixtures of lean meats and fatty tissues combined with salt, nitrite (curing agent), sugar, spices, and other non-meat ingredients packed into casings. Their characteristic properties (flavour, firm texture, and red curing colour) originate from the fermentation process. Short or long ripening phases, combined with moisture reduction, are necessary to develop the typical flavour and texture of the final product. The fermented sausages are not subjected to any heat treatment during processing and, in most cases, are distributed and consumed raw (Heinz & Hautzinger, 2007).

(e) Dried meat

Examples of dried meat include dried meat strips or flat pieces.

Drying, or drying in combination with smoking, is practised all over the world and is probably the most ancient method of meat preservation.

Dried meat products result from dehydration or drying of lean meat in natural or artificial conditions (Zukál & Incze, 2010). Pieces of lean meat without adherent fat are cut to a specific uniform shape that permits the gradual and equal drying of whole batches of meat. Salt, nitrite, and sugar may be added to the meat before the drying process. Many of the nutritional properties of meat, particularly the protein content, remain unchanged through drying. Common dried meat products are beef jerky from the USA, biltong from South Africa, and tasajo from South America (Heinz & Hautzinger, 2007).

Meat may be smoked raw or after salting, marinating, cooking, or other treatments. There are many types of smoking, leading to products with very different sensory properties and

shelf-lives. Warm or cold smoking can be used. Warm smoking is carried out at temperatures of 23–45 °C. Cold smoking is carried out at temperatures of 12–25 °C and is used in the manufacturing of raw fermented sausages made from cured meats.

Drying and smoking are used to improve the shelf-life and organoleptic properties of meat products. In developing countries such as Africa, where extending shelf-life is the priority, drying is the most used process. In parallel with simple drying, west Africa has refined the hot smoking process to further improve shelf-life through the preservative and antibacterial effects of smoke substances. To lower the cost of meat products, African countries have also developed traditional products consisting of mixtures of meat and vegetables. Central and southern American countries have adapted European meat processing techniques for local meat products, especially for barbecuing (e.g. chorizo criollo or morcilla) (Heinz & Hautzinger, 2007).

1.2 Meat composition

1.2.1 Red meat

(a) Main components

The animal carcass consists of muscle, connective tissue, fat and bone, and about 75% water, depending on the species, breed, size, and age. For a given species, the muscle is relatively constant in composition (Table 1.1). Red meat contains high biological value proteins and essential micronutrients, including vitamins and minerals (Table 1.2; Williams, 2007). The composition of the meat varies based on the animal species, sex, age, and diet, as well as the climate and activity during its growth (Lorenzo et al., 2010). Total nitrogen, fat, and iron levels increase as the animal approaches maturity. In addition, the ratio of polyunsaturated fatty acids (PUFAs) to saturated fatty acids (SFAs) decreases with the maturity of the animal. The nutritional value of meat is also significantly affected by the livestock production system (Lorenzo et al., 2010, 2014).

(i) Protein

Red meat contains 20–25 g of protein per 100 g. The proteins are highly digestible (94%) and provide all essential amino acids (lysine, threonine, methionine, phenylalanine, tryptophan, leucine, isoleucine, and valine) (Williams, 2007).

(ii) Fat

Red meat is also a source of fatty acids. Fat in red meat is subcutaneous, intramuscular, or intermuscular, and the composition will vary according to the animal's age, sex, breed, and diet, as well as the cut of meat (Wood & Enser, 1997). For example, the amount of fat in raw cattle longissimus muscle can range from 0.59% to 16%, depending on the breed (Barnes et al., 2012). Fat in meat includes SFAs, monounsaturated fatty acids (MUFAs), and PUFAs. The typical fatty acid composition of fat in beef is reported to be 46.5, 48.9, and 4.59 g per 100 g of total fatty acids for SFAs, MUFAs, and PUFAs, respectively. While these proportions are similar in all red meats, exact amounts depend on the type of meat (Givens, 2005). The main SFAs present in red meat are palmitic acid and stearic acid, and the main MUFA is oleic acid. Red meat also contains n-3 PUFAs, such as α-linolenic acid, and n-6 PUFAs, such as linoleic acid. The animal's diet strongly influences PUFA levels in meat. For example, meat from foals raised by extensive production systems on wood pastures has higher levels of n-3 PUFAs than meat from foals fed concentrate (Lorenzo et al., 2010, 2014). The last category of fat found in the red meat of ruminants is conjugated linoleic acids, the levels of which also depend on feeding practices (Wood et al., 1999; Givens, 2005).

Table 1.1 Chemical composition of typical mammalian muscle (red meat) for consumption

Main component	Constituents	Wet weight (%)	
Water		*75.00*	
Protein		*19.00*	
Myofibrillar:		11.50	
	Myosin		5.50
	Actin		2.50
	Connectin		0.90
	Nebulin (N2 line protein)		0.30
	Tropomyosins		0.60
	Troponins, C, I and T		0.60
	α,β,γ Actinins		0.50
	Myomesin (M-line protein) and C proteins		0.20
	Desmin, filamin, F- and I-proteins, etc.		0.40
Sarcoplasmic:		5.50	
	Glyceraldehyde phosphate dehydrogenase		1.20
	Aldolase		0.60
	Creatine kinase		0.50
	Other glycolytic enzymes		2.20
	Myoglobin		0.20
	Haemoglobin and other unspecified extracellular proteins		0.60
Connective tissue and organelles:		2.00	
	Collagen		1.00
	Elastin		0.05
	Mitochondrial etc. (including cytochrome c and insoluble enzymes)		0.95
Lipid		*2.50*	
Neutral lipid; phospholipids; fatty acids; fat-soluble substances			2.50
Carbohydrate		*1.20*	
	Lactic acid		0.90
	Glucose-6-phosphate		0.15
	Glycogen		0.10
	Glucose, traces of other glycolytic intermediates		0.05
Miscellaneous, soluble non-protein substances		*2.30*	
Nitrogenous:		1.65	
	Creatinine		0.55
	Inosine monophosphate		0.30
	Di- and tri-phosphopyridine nucleotides		0.10
	Amino acids		0.35
	Carnosine, anserine		0.35
Inorganic:		0.65	
	Total soluble phosphorus		0.20
	Potassium		0.35
	Sodium		0.05
	Magnesium		0.02
	Calcium, zinc, trace metals		0.03
Vitamins			
Various fat- and water soluble vitamins		Minute	

This table was published in Lawrie's Meat Science 6th edition, Lawrie (1998), Page No. 59, Copyright Elsevier (1998)

Table 1.2 Average nutrient composition (per 100 g) of the lean component of red meat

Nutrient	Beef	Veal	Lamb	Mutton
Moisture (g)	73.1	74.8	72.9	73.2
Protein (g)	23.2	24.8	21.9	21.5
Fat (g)	2.8	1.5	4.7	4.0
Energy (kj)	498	477	546	514
Cholesterol (mg)	50	51	66	66
Thiamin (mg)	0.04	0.06	0.12	0.16
Riboflavin (mg)	0.18	0.20	0.23	0.25
Niacin (mg)	5.0	16.0	5.2	8.0
Vitamin B6 (mg)	0.52	0.8	0.10	0.8
Vitamin B12 (µg)	2.5	1.6	0.96	2.8
Pantothenic acid (mg)	0.35	1.50	0.74	1.33
Vitamin A (µg)	< 5	< 5	8.6	7.8
Beta-carotene (µg)	10	< 5	< 5	< 5
Alpha-tocopherol (mg)	0.63	0.50	0.44	0.20
Sodium (mg)	51	51	69	71
Potassium (mg)	363	362	344	365
Calcium (mg)	4.5	6.5	7.2	6.6
Iron (mg)	1.8	1.1	2.0	3.3
Zinc (mg)	4.6	4.2	4.5	3.9
Magnesium (mg)	25	26	28	28
Phosphorus (mg)	215	260	194	290
Copper (mg)	0.12	0.08	0.12	0.22
Selenium (µg)	17	< 10	14	< 10

Adapted from Williams (2007). *Nutrition & Dietetics*, John Wiley & Sons

(iii) Vitamins

The only natural source of vitamin B12 is in food derived from animal products. Red meat is a rich source of B vitamins such as B6, B12, niacin, and thiamine (Gille & Schmid, 2015). For example, 100 g of lean beef meat will provide 2.5 µg of vitamin B12, corresponding to 79% of the recommended dietary intake for this nutrient. The older the animal, the richer its meat will be in B vitamins (Williams, 2007). Pork contains a high level of thiamine compared with other meats (Bender, 1992). While the concentration of vitamin E in red meat is low, it is higher in fattier cuts of meat. Vitamin A and folate are found at higher levels in liver than in lean muscle meat (Bender, 1992).

(iv) Minerals

Red meat is one of the richest sources of minerals such as iron or zinc, and has a higher mineral bioavailability than plant products (Williams, 2007). For example, 100 g of lean beef meat will provide approximatively 1.8 mg of iron and 4.6 mg of zinc, corresponding to approximately 14% and 42%, respectively, of the recommended dietary intake for these nutrients (Williams, 2007). Red meat is also a good source of selenium. For example, 100 g of lean beef meat will provide about 17 µg of selenium, corresponding to approximately 26% of the recommended dietary intake for this nutrient (Williams, 2007).

(v) Creatine

Creatine levels in skeletal muscle average 350 mg per 100 g of red meat (Purchas & Busboom, 2005; Williams, 2007). Cooking of the muscle meat transforms creatine into creatinine through non-enzymatic conversion. Creatine and creatinine in meat are critical precursors in the formation of heterocyclic aromatic amines (HAAs) (Skog et al., 1998, 2000).

(b) Effect of slaughtering and storage post mortem

Preslaughter handling of the animal can have an impact on the composition and quality of the meat. For example, stressed or fatigued animals have depleted glycogen. Before slaughtering, animals are usually stunned and then exsanguinated. Blood is drained from the carcass, leading to a loss of oxygen and a depletion of adenosine triphosphate, as well as the combination of the proteins actin and myosin to form actinomyosin to cause muscle contraction. After slaughtering, glycogen is converted to lactic acid, and pH levels fall to approximately 5.5 over a period of 24–36 hours and can have an impact on microbial content (Lawrie, 1998; Lawrie & Ledward, 2006).

A major safety concern in meat production and storage is bacterial contamination. Although muscle is usually sterile, bacterial contamination from gastrointestinal contents and butchering instruments is common. Bacterial contamination is minimized by low temperatures, low temperatures and packaging in a controlled atmosphere. Minced and comminuted meats with larger surface areas may be more likely to become contaminated than large cuts of meat (Lawrie, 1998; Lawrie & Ledward, 2006). Physical and chemical methods, such as spray washing with hot water, can be used for microbial decontamination. Water may be chlorinated and combined with weak organic acids, phosphates, hydrogen peroxide, or ozone to improve antimicrobial activities. Improving hygiene levels by means of antibiotics (chlorotetracycline and oxytetracycline) is increasingly discouraged and regulated. Irradiation is permitted in the USA, but it can induce free radical formation (Isam et al., 2007). Freezing of red meat results in little to no loss of nutrients, apart from vitamin E, which is oxidized. Proteins remain unchanged during frozen storage, but fats are susceptible to changes from oxidation. Pork meat, which is richer in unsaturated fatty acids than other red meats, is the most susceptible to these changes. Once meat is defrosted, the juices containing soluble proteins, vitamins, and minerals are lost (Rahman, 2007).

(c) Chemical contaminants and residues

Residues of drugs (e.g. antibiotics and hormones), pesticides, and agricultural chemicals can be found in meat and meat products (e.g. as a result of exposure of the animals to chemicals used on buildings, grazing areas, and crops) (Fig. 1.1; Engel et al., 2015). Additionally, several hundred substances may be used to treat animals, to preserve animal health, and to improve animal production, including antimicrobial agents, anticoccidial agents, anthelmintics, steroids, anti-inflammatory agents, tranquillizers, vasodilators, analgesics, and anaesthetics (FDA, 2005).

(i) Veterinary drugs

Veterinary drugs given to animals are strictly regulated in most developed countries (FDA, 2005), and maximum residue limits (MLRs) have been established for some of these drugs by the Codex Alimentarius.

Antibiotics: In the European Union (EU), the only antibiotics allowed as feed additives are coccidiostats and histomonostats (European Commission, 2003), as other antibiotics, especially if they are also used for humans, could induce antimicrobial resistance in consumers (Chattopadhyay, 2014). Cooking procedures degrade the residues of several antibacterial drugs, depending on the amount of heat

treatment involved, principally cooking time and temperature (Heshmati, 2015).

Hormones: In several countries, such as the USA, the use of hormones, including testosterone propionate, estradiol, estradiol benzoate, and progesterone, and compounds that display a high affinity for human hormone receptors are approved for food animal production. This raises concerns because these hormones, or their biologically active metabolites, may accumulate in edible tissues, potentially exposing consumers (Nachman & Smith, 2015). Cooking reduces, but does not eliminate, the potential for dietary exposure to hormones, such as estradiol, in ground beef (Braekevelt et al., 2011). Table 1.3 lists the amounts of steroid hormones ingested via the diet from hormone-treated or non–hormone-treated animals, and the amounts of these hormones produced daily in the human body. [The Working Group noted that the ingestion of estradiol, progesterone, and testosterone from meat appears to be minor relative to what is biosynthesized in humans (Table 1.3).]

Environmental and phytosanitary contaminants can also occur in meat products.

(ii) Pesticide residues

Pesticide residues used for phytosanitary treatments may be present in meat products. Animals consume plants treated with pesticides or contaminated by persistent pesticides in the environment. However, vegetable consumption remains by far the main dietary source of human exposure to pesticides (Kan & Meijer, 2007).

(iii) Dioxins and dioxin-like products

Dioxins and dioxin-like products are divided into three groups: polychlorinated dibenzodioxins (PCDDs), polychlorinated dibenzofurans (PCDFs), and polychlorinated biphenyls (PCBs) (see Fig. 1.1).

These contaminants, which are mainly produced by industrial processes, are ubiquitous in foods of animal origin, and accumulate in the fatty tissues of animals and humans (Larsen, 2006; IARC, 2012a, 2016). Food, including meat, remains the primary source of human exposure to these contaminants in the general population (IARC, 2012a, 2016).

(iv) Brominated flame retardants

Brominated flame retardants (BFRs) are widely used in plastic materials, textiles, electric and electronic equipment, and of construction materials for livestock buildings. There are five classes of BFRs: polybrominated diphenyl ethers (PBDEs), hexabromocyclododecanes (HBCDs), tetrabromobisphenol A, and other phenols, polybrominated biphenyls (PBBs) (IARC, 2016), and unclassified BFRs (ANSES, 2011, 2012; IARC, 2016). The persistence of BFRs in the environment is a public health concern (AFSSA, 2005; ANSES, 2011; EPA, 2010). The main source of human exposure to BFRs is the consumption of fish and meat products (Lyche et al., 2015). Studies have shown that the cooking process and, to a greater extent, the type of meat item influence levels of PDBEs.

(v) Polycyclic aromatic hydrocarbons

Polycyclic aromatic hydrocarbons (PAHs) can be generated in the environment or during the processing of foods; this is discussed further in Section 1.2.3(a)(iii). PAHs are closely monitored by health agencies in developed countries (IARC 2010a; Schroeder, 2010). Furthermore, PAH levels can increase depending on cooking conditions.

(vi) Heavy metals

Contamination by heavy metals such as cadmium, lead, arsenic, or mercury largely occurs from industrial wastes (IARC, 2012b). Meat consumption is a significant source of human exposure to lead and cadmium (Kan & Meijer, 2007).

Table 1.3 Comparison of the amounts of steroid hormones produced daily in the human body and ingested via the diet from hormone-treated animals

Hormone	Total daily production (μg/day) (JECFA, 2000; EFSA, 2007)	Residue in muscle (μg/kg) (Paris et al., 2006)		Ingested amount via intake of muscle from treated animals[a] (μg/day)
		Non-treated animals	Treated animals	
Estradiol	< 14 (prepubertal boys) 10–24 (prepubertal girls) 27–68 (adult men) 30–470 (adult women)	0.003–0.035	0.011–0.28	0.0033–0.084
Progesterone	150–250 (prepubertal children) 416–750 (adult men, premenopausal women)	0.0–0.9	0.23–0.77	0.069–0.231
Testosterone	30–100 (prepubertal children) 210–480 (adult female) 2100–6900 (adult male)	0.006–0.029	0.031–0.36	0.0093–0.108

[a] Calculated according to an intake of 300 g/day of muscle

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(vii) Mycotoxins

Mycotoxins, metabolites produced by mould, are toxic and may be carcinogenic to animals and humans. Livestock contamination by mycotoxins occurs via their diet, and human exposure results from consumption of contaminated livestock. However, cereals and oil seeds are the main sources of human exposure to mycotoxins (FDA, 2008; Marroquín-Cardona et al., 2014). Mycotoxin residues accumulate in the blood, liver, and kidney, and, to a lesser degree, in muscle-derived meat products (Kan & Meijer, 2007). Mycotoxins, such as aflatoxin, are not destroyed by normal industrial processing or cooking since they are heat-stable (Awadt et al., 2012).

1.2.2 Processed meat

(a) Ingredients

There are three major reasons for processing meat: reduction in microbial contamination, production of attractive products, and reduction of waste by reconstitution of muscle meat scraps or offal. Therefore, along with the main components, which are meat and animal fat, a wide range of non-meat substances are used in processed meat products (Bender, 1992; Heinz & Hautzinger, 2007; Toldrá, 2010; Weiss et al., 2010).

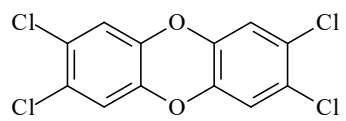
(i) Non-meat ingredients of animal origin

Although not commonly applied, non-meat ingredients of animal origin may be used to improve water binding and prevent fat separation during heat treatment. Some of these ingredients can also be considered as meat extenders. The most commonly used non-meat ingredients of animal origin are milk caseinate; whole milk or non-fat, dried milk; gelatine; blood plasma; eggs; and transglutaminase (Sun & Holley, 2011).

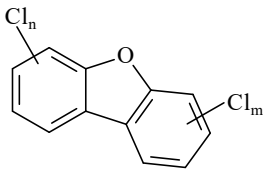
(ii) Ingredients of plant origin

Spices are predominantly functional ingredients, and are used in small quantities to provide or add flavour and taste to meat products. The most commonly used ingredients of plant origin are isolated soy protein (≤ 90% protein) and wheat gluten (≤ 80% protein). The most common ingredients used as fillers (if rich in carbohydrate) or meat extenders (if rich in protein) are soy flour or concentrate, cereal flour or cereals, starches, breadcrumbs, vegetables, and fruits (Asgar et al.,

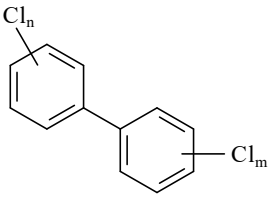
Fig. 1.1 Examples of environmental micropollutants potentially found in red and processed meats



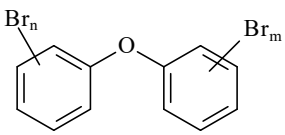
2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD)



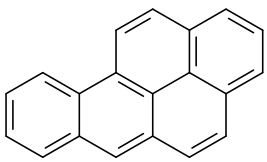
Polychlorinated dibenzofuran (PCDFs)



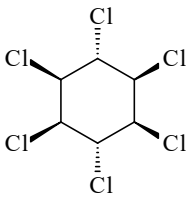
Polychlorinated biphenyls (PCBs)



Polybrominated diphenyl ethers (PBDEs)



Benzo[*a*]pyrene (BaP)



Lindane (pesticide)

Adapted from *Meat Science*, Volume 109, E. Engel, J. Ratel, J. Bouhlel, C. Planche, M. Meurillon, Novel approaches to improving the chemical safety of the meat chain towards toxicants, Pages No. 75–85, Copyright (2015), with permission from Elsevier (Engel et al., 2015)

2010). Several plant derivatives can also be used as fat replacers, antioxidants, or antimicrobials (Hygreeva et al., 2014).

(iii) Chemical substances used as additives

There are a limited number of chemical substances allowed for meat processing, as the substances need to be safe for consumers and improve the quality of the final product. The most commonly used substances are salt (NaCl or NaCl plus KCl) for taste, impact on meat proteins, and shelf-life; nitrate and nitrite for curing, colour, flavour, and shelf-life; ascorbic acid for accelerated curing; phosphates for protein structuring and water binding; chemical preservatives for shelf-life; antioxidants for flavour and shelf-life; monosodium glutamate for enhancement of flavour; and food colourings. Chemical additives have exclusively functional properties. They are used in small amounts, usually below 1%, with nitrate as low as 0.05% and with only salt in the range of 2% (≤ 4% in some fermented dried products) (Heinz & Hautzinger, 2007).

(b) Processing methods

Standard technical processing methods for meat products, such as cutting, comminuting, mixing, tumbling, or stuffing, are an important part of the manufacturing process (Heinz & Hautzinger, 2007). However, as these processes do not influence the formation of potentially carcinogenic process-induced toxicants, they will not be further detailed in this section.

Microbial inactivation can be achieved by "sous vide", a method whereby foods are vacuum-packaged and then slow-cooked (temperature, 55–60 °C), as well as by cooking, canning (temperature, up to 121 °C), irradiation (chilled temperature, 0–4 °C), and high-pressure processing (300–600 MPa). Microbial inactivation can also be achieved by the addition of artificial preservatives such as nitrate or nitrite, weak organic acids, and/or salt or sugar. Canning is probably the most efficient meat preservation method, as it ensures the destruction of pathogens and food spoilage microorganisms, and allows foods to be easily handled and transported (Guerrero Legarreta, 2010).

The most common approaches to retard lipid oxidation, a major limiting factor in the shelf-life of dehydrated muscle tissue, is the addition of antioxidants and the use of appropriate packaging techniques (Rahman, 2007).

Chemical processing methods essentially include curing, smoking, and fermentation.

(i) Curing

Meat curing, in the narrow sense, is the addition of salt (NaCl or NaCl plus KCl), with or without nitrate or nitrite, during the manufacturing of meat products. Nitrate and nitrite are not used as sole curing agents. Each is always applied with salt. In meat products, the concentrations of nitrate and nitrite are usually in the range of 100–200 mg/kg, while salt is 2000 mg/kg or more. Salt lowers the water activity and enhances food safety. Salt also changes the protein structures in meat. Nitrate and nitrite support the safety action of salt, and improve the appearance and flavour. Nitrate must undergo reduction to nitrite to be effective. During the curing process, myoglobin is converted to nitrosomyoglobin, resulting in the characteristic cured meat colour (EFSA, 2003; Honikel, 2008, 2010). Over the past few decades, ascorbic acid or its salt, ascorbate (e.g. isoascorbate or erythorbate), has been used in cured meat batters. Ascorbate reacts with oxygen to form dehydroascorbate, and thus prevents the oxidation of nitrite to nitrate. Ascorbate is also added to reduce the formation of nitrosamines. Ascorbate, together with nitrite and salt, has an effective antimicrobial effect, particularly against *Clostridium botulinum* (Honikel, 2010; Sindelar & Milkowski, 2012). Citric acid or sodium citrate may replace up to half of either form of the ascorbate/erythorbate reductants, but may not be used without the reductants (Sindelar et al., 2010). Nitrite addition is strictly regulated by international standards, and the amount allowed in cured meat is decreasing (see Section 1.5).

(ii) Smoking

Smoking refers to the exposure of meat to the smoke of burning wood (Sikorski & Kalakowski, 2010). Many cured products are also smoked, or contain soluble components of wood smoke, mainly to add flavour and increase shelf-life. Smoking gives meat a brown colour. It changes its flavour and improves its preservation, as smoke contains a wide variety of polyphenolic compounds as well as aldehydes and carboxylic acids, which have antimicrobial properties. Smoking can be done at different temperatures, depending on the end product (Sikorski & Kalakowski, 2010). However, wood pyrolysis may be hazardous, as the process is difficult to control and can lead to the generation of PAHs. Modifications to traditional wood pyrolysis processes are being studied to reduce the production and deposition of PAHs in processed meat (Roseiro et al., 2011; Ledesma et al., 2014). An alternative is to use liquid smoke flavouring solutions produced from different wood products, under specific pyrolysis conditions and as per extraction protocols aimed at strongly reducing the concentration of PAHs (Sikorski & Kalakowski, 2010).

(iii) Fermentation

Fermentation refers to a low-energy, biological acidulation (by cultured or wild microorganisms) and preservation method that results in a distinctive flavour and palatability, colour, and tenderness, as well as in enhanced microbiological safety. Since this process involves microorganisms, it is influenced by many environmental factors, including raw meat quality, sanitation, time, temperature, and humidity, all of which need to be strictly controlled during production. The reduction of pH and the lowering of water activity are microbial hurdles that aid in producing a safe product. Both natural and controlled fermentation processes involve lactic acid bacteria. Fermented sausages often have a long storage life, due to added salt, nitrate, and/or nitrite, and a low pH, due to lactic acid production by bacteria in the early stages of storage and later stages of drying (Ockermann & Basu, 2010).

1.2.3 Changes in meat composition due to cooking methods

Cooking can have a positive and negative impact on food quality. Cooking is important to inactivate pathogenic microorganisms, and improve palatability and digestibility (Santé-Lhoutellier et al., 2008; Bax et al., 2012, 2013).

Generally, cooking reduces, but does not eliminate, meat contaminants such as hormones, antibiotics, chemicals (e.g. PCBs, PCDFs, and PCDDs), or metals (e.g. arsenic, cadmium, mercury, and lead) (Hori et al., 2005; Perelló et al., 2008; Perelló et al., 2010; Braekevelt et al., 2011; Zeitoun & Ahmed, 2011; Heshmati, 2015). Furthermore, cooking can lead to the production of potential carcinogens.

The different cooking methods used to prepare red and processed meat may have varying influences on the production of potential carcinogens (Table 1.4). Cooking methods differ based on cooking temperature, direct or indirect contact with the heating source (flame), and use of fat. The method has an impact on the formation of carcinogenic compounds such as HAAs or PAHs (Skog et al., 1998; Giri et al., 2015). At low temperatures (around 100 °C), steaming, boiling, or stewing generate much lower levels of these carcinogenic compounds. For baking and roasting, temperatures are higher (up to 200 °C), but as there is limited direct contact with a hot surface, the formation of these carcinogenic compounds is also low (Rohrmann et al., 2002). Barbecuing, grilling, and pan-frying expose meat products to high temperatures, and to a hot surface or to direct flame, and thus can produce an appreciable level of these carcinogenic compounds (American Institute for Cancer Research/World Cancer Research Fund, 1997; Sinha et al., 1998a, b).

(a) Red meat

This part of the section focuses on the toxicants found in red meat that are mostly produced by certain heating and cooking conditions.

(i) N-Nitroso compounds

N-Nitroso compounds (NOCs) are mainly formed endogenously in human organisms. No data report their formation in red meat during heat treatment; they are mainly considered processed meat toxicants (see Section 1.2.3(b)(i)).

(ii) Heterocyclic aromatic amines

HAAs are a family of heat-induced food toxicants that were discovered about 30 years ago by Professor Sugimura. Currently, about 25 HAAs have been identified in cooked meat, fish, and poultry products (Sugimura et al., 2004), as well as in cigarette smoke and diesel exhaust (Manabe et al., 1991). HAAs can be divided into two distinct families: aminoimidazoazaarenes and carbolines or pyrolytic HAAs (Fig. 1.2 and Table 1.5). Aminoimidazoazaarenes are formed by Maillard reaction (a chemical reaction between amino acids, creatine/creatinine, and sugars), whereas carbolines and pyrolytic HAAs are formed at

Table 1.4 Definition of cooking methods[a]

Cooking method[b]	Definition
Baked	Cooked by dry heat in an oven, covered or uncovered, no additional fat used for cooking
Barbecued	Cooked on grill bars over burning charcoal, wood or gas
Battered and baked	Covered by batter (flour, milk, and egg mixture) and baked
Battered and fried	Covered by batter (flour, milk, and egg mixture) and fried
Boiled	Cooked in boiling liquid
Breaded and baked	Covered by an outer layer of breadcrumbs and baked
Breaded and fried	Covered by an outer layer of breadcrumbs and fried
Breaded and griddled	Covered by an outer layer of breadcrumbs and griddled
Coated and fried	Covered by an outer layer and fried: includes battered and fried, breaded and fried, in flour and fried
Deep fried	Cooked in hot fat or oil by immersing the food entirely
Fried	Generic descriptor for cooked in heated fat, usually over a direct source of heat
Griddled	Cooked on a heated flat metal surface over a source of direct heat; a little fat or oil may be used to grease the metal surface
Grilled	Cooked rapidly without moisture, on grill bars under or over intense direct heat, no fat used
In flour and fried	Covered by an outer layer of flour and fried
Microwaved	Cooked or reheated in a microwave oven; no fat used
Poached	Cooked by dropping in boiling liquid
Reheated	Made hot; no liquid nor fat is added
Roasted	Cooked by dry heat in an oven or over a fire
Shallow fried	Cooked in a shallow layer of heated fat
Steamed	Cooked by steam, in pressure cooker or cooked suspended above boiling water
Stewed	Cooked by boiling or simmering in liquid contained in an enclosed vessel; the food is cooked over a low heat for a long period of time
Stir fried/sautéed	Cooked by frying food over high heat, by stirring constantly to avoid sticking
Toasted	Cooked with direct heat until the surface of the food is browned

[a] Definitions based on the EPIC Study, Rohrmann et al. (2002)

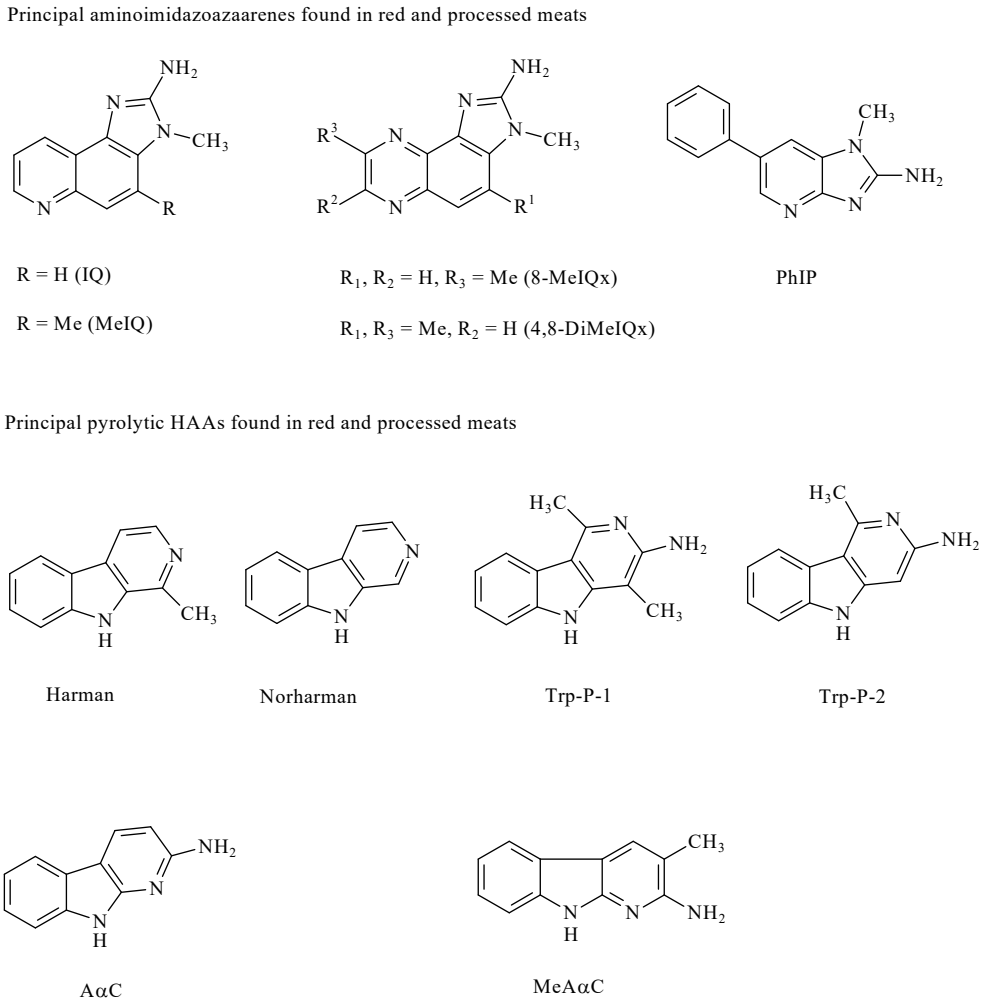
[b] Cooking method is defined as the preparation of meat items just before consumption

Adapted by permission from Macmillan Publishers Ltd: Rohrmann et al. (2002). Cooking of meat and fish in Europe--results from the European Prospective Investigation into Cancer and Nutrition (EPIC). European Journal of Clinical Nutrition, Volume 56, issue 12, pages 1216–1230, copyright (2002)

elevated temperatures (Murkovic, 2004). The main source of human exposure to HAAs is via cooked proteinaceous foods; however, the levels of HAAs are highly dependent on the type of meat, cooking time, and cooking temperature, and generally increase with the level of "doneness" (Skog et al., 2000).

The cooking method also influences HAA formation; it has been shown that high-temperature methods (pan-frying, grilling, and barbecuing) cause the highest HAA concentrations, especially for 2-amino-1-methyl-6-phenylimidazo[4,5-*b*]pyridine (PhIP) (Alaejos & Afonso, 2011). The concentrations of HAAs in different cooked meats are given in Table 1.6. The concentrations of HAAs are highly variable. For a comprehensive review, see Alaejos & Afonso (2011). A series of linear tricyclic ring HAAs containing the 2-amino-1-methylimidazo[4,5-*g*]quinoxaline (IgQx) skeleton are formed in cooked meats at concentrations that are relatively high compared with the concentrations of their angular tricyclic ring isomers or related HAAs (Ni et al., 2008), such as 2-amino-3,8-dimethylimidazo[4,5-*f*] quinoxaline (MeIQx) and PhIP, which are known experimental animal carcinogens and potential human carcinogens (IARC, 1993). The toxicological properties of these recently discovered IgQx

Fig. 1.2 Structures of heterocyclic aromatic amines found in cooked red and/or processed meats



The full chemical names of these compounds are given in Table 1.5
HAA, heterocyclic aromatic amines
Reprinted from *Cancer Science*, Volume 95, Takashi Sugimura, Keiji Wakabayashi, Hitoshi Nakagama, Minako Nagao, Heterocyclic amines: Mutagens/carcinogens produced during cooking of meat and fish, Pages No. 290–299, Copyright (2004), with permission from John Wiley & Sons (Sugimura et al., 2004)

derivatives warrant further investigation and assessment.

Some methods to decrease the levels of HAAs in cooked meats have been described. For example, microwave pretreatment followed by disposal of the resulting liquid before frying of hamburger patties reduces the formation of some aminoimidazoazaarenes (Felton et al., 1992). Various studies have also emphasized the role of added antioxidants with phenolic or polyphenolic moiety in the limitation of HAA formation – via their scavenging capacity for reactive radicals involved in the HAA mechanism of formation (Balogh et al., 2000; Vitaglione & Fogliano, 2004; Gibis & Weiss, 2010, 2012). Other compounds, such as organosulfur compounds, contained in garlic or onion, have also been shown to have an inhibitory effect on HAA formation (Shin et al., 2002).

Table 1.5 Chemical names of heterocyclic aromatic amines potentially found in cooked red and processed meats

Common abbreviation	Full name
IQ	2-amino-3-methylimidazo[4,5-*f*]quinoline
MeIQ	2-amino-3,4-dimethylimidazo[4,5-*f*]quinoline
IQx	2-amino-3-methylimidazo[4,5-*f*]quinoxaline
MeIQx	2-amino-3,8-dimethylimidazo[4,5-*f*]quinoxaline
4,8-DiMeIQx	2-amino-3,4,8-trimethylimidazo[4,5-*f*]quinoxaline
7,8-DiMeIQx	2-amino-3,7,8-trimethylimidazo[4,5-*f*]quinoxaline
4-CH_2OH-8-MeIQx	2-amino-4-hydroxymethyl-3,8-dimethylimidazo[4,5-*f*]quinoxaline
PhIP	2-amino-1-methyl-6-phenylimidazo[4,5-*b*]pyridine
4′-hydroxy-PhIP	2-amino-6-(4-hydroxyphenyl)-1-methylimidazo[4,5-*b*] pyridine
Trp-P-1	3-amino-1,4-dimethyl-5*H*-pyrido[4,3-*b*]indole
Trp-P-2	3-amino-1-methyl-5*H*-pyrido[4,3-*b*]indole
AαC	2-amino-9*H*-pyrido[2,3-*b*]indole
MeAαC	2-amino-3-methyl-9*H*-pyrido[2,3-*b*]indole
Glu-P-1	2-amino-6-methyldipyrido[1,2-*a*:3′2′-*d*]imidazole
Glu-P-2	2-aminodipyridol[1,2-*a*:3′2′-*d*]imidazole
Harman	1-methyl-9*H*-pyrido[3,4-*b*]indole
Norharman	9*H*-pyrido[3,4-*b*]indole
IgQx	2-amino-1-methylimidazo[4,5-*g*]quinoxaline

Note: the chemical structure of some of these compounds is given in Fig. 1.2
Adapted with permission from Sugimura et al. (2004) and Alaejos & Afonso (2011)

(iii) Polycyclic aromatic hydrocarbons

The main source of non-occupational human exposure, for non-smoking individuals, is food consumption (Kazerouni et al., 2001). PAHs can be formed by pyrolysis of organic materials, direct contact of fat with a flame, or incomplete combustion of charcoal, so they are present in grilled meats (Chen & Lin, 1997; Alomirah et al., 2011). More than 30 PAHs have been identified; among them is benzo[*a*]pyrene (BaP), which is classified as a Group 1 human carcinogen (IARC, 2012a). The main PAHs found in processed meats are presented in Fig. 1.3 and Table 1.7. Representative concentrations of PAHs in different processed meat samples are given in Table 1.8.

By avoiding the direct contact of meat with a flame, PAH levels can be lowered. The amount of fat can also influence PAH levels. The more fat that is contained in meat, the more PAHs are produced. This may be related to the pyrolysis of fat, which drips onto the heat source (Mottier et al., 2000).

Heat treatment of red and processed meat can also produce other toxicants, such as acrylamide (Tareke et al., 2002) and *N*-methylacrylamide (Yaylayan et al., 2004).

(iv) Iron

Iron is a trace element essential for human health that can be found in foods of animal and plant origin. In food, iron can be found in two forms: haem iron and non-haem iron. Haem iron, which is more bioavailable than non-haem iron, is only found in animal products (Schonfeldt & Hall, 2011). Haem iron is contained in myoglobin and haemoglobin, whereas non-haem iron is associated with small molecules such as phosphate, ascorbate, or free amino acids to form salts. The amount of iron in meat, and the ratio between haem and non-haem iron, depends on

Table 1.6 Concentrations of heterocyclic aromatic amines in different cooked meats

Cooked meat	Concentrations of HAAs (ng/g)									
	IQ	MeIQ	8-MeIQx	4,8-DiMeIQx	PhIP	Trp-P-1	Trp-P-2	Harman	Norharman	AαC
Minced beef (fried, grilled, and barbecued)	ND–12	ND–8	ND–7	ND–3	ND–34	ND to < 1.45	ND–2	ND–28	ND–30	ND–21
Beef (roasted and oven-broiled)	ND to < 0.2	ND to < 0.2	ND–17.5	ND–3.4	ND–32.4	ND–0.01	ND	ND–240[a]	ND–205[b]	ND–0.11
Beef extract (products commercially cooked)	ND–75	ND–10	ND–38	ND–6	ND–10	ND–13	ND–14	NQ–377	NQ–94	NQ to < 8.1
Lamb (grilled and fried)	< 0.1	< 0.1	ND–3	ND–2	ND–11[b]	ND–1	< 0.3	ND–7	ND–9	ND–0.5
Pork (grilled and fried)	ND–7	ND–11	ND–21	ND–28	ND–32	ND–1	ND–5	ND–25[a]	ND–51[a]	ND–3
Sausage (fried, roasted, and barbecued)	ND–5	ND–2	ND–5	ND–3	ND–6	ND–1	ND–2	ND–3	ND–10	<0.03
Bacon (fried)	ND–11	ND–2	ND–27	ND–9	ND–106[b]	0.6	< 0.29	ND–33	ND–60	NQ to < 0.5
Pan scrapings from different meats	< 2		29–63	4–15	83–144					3–77

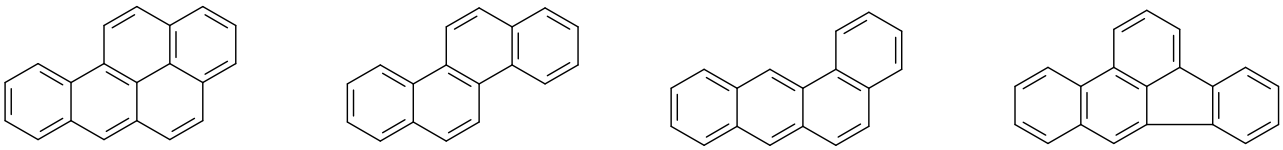
[a] The highest levels of harman and norharman were found in commercially roasted beef (Khan et al., 2008)

[b] A study in the Republic of Korea reported very high concentrations of PhIP (258 ng/g), harman (990 ng/g), and norharman (413 ng/g) in griddled pork loin, and of PhIP (168 ng/g) in griddled bacon (Back et al., 2009)

4,8-DiMeIQx, 2-amino-3,4,8-trimethylimidazo[4,5-*f*]quinoxaline; 8-MeIQx, 2-amino-3,8-dimethylimidazo[4,5-*f*]quinoxaline; A*α*C, 2-amino-9*H*-pyrido[2,3-*b*]indole; HAA, heterocyclic aromatic amines; harman, 1-methyl-9*H*-pyrido[3,4-*b*]indole; IQ, 2-amino-3-methylimidazo[4,5-*f*]quinoline; MeIQ, 2-amino-3,4-dimethylimidazo[4,5-*f*]quinoline; ND, not detected; norharman, 9*H*-pyrido[3,4-*b*]indole; NQ, not quantified; PhIP, 2-amino-1-methyl-6-phenylimidazo[4,5-*b*]pyridine; Trp-P-1, 3-amino-1,4-dimethyl-5*H*-pyrido[4,3-*b*]indole; Trp-P-2, 3-amino-1-methyl-5*H*-pyrido[4,3-*b*]indole

Table compiled using data from the review of Alaejos & Afonso (2011), indicating the lowest and highest values found for the different HAAs in different heat-processed meats

Fig. 1.3 Structures of polycyclic aromatic hydrocarbons found in red and/or processed meats



Benzo[*a*]pyrene | Chrysene | Benz[*a*]anthracene | Benzo[*b*]fluoranthene

the species and the type of muscle (Lombardi-Boccia et al., 2002; Table 1.9). Red meat contains more total iron and haem iron than white meat. Beef, lamb, and horse meat are richer in haem iron and total iron than pork meat. The age of the animal is also important in iron intake, as older animals contain more iron. During cooking, part of haem iron is converted to non-haem iron, depending on the cooking parameters, such as time and temperature (Lombardi-Boccia et al., 2002; Purchas & Busboom, 2005; Purchas et al., 2006).

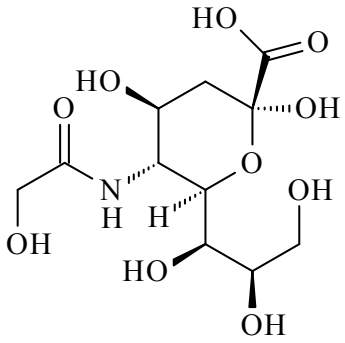
(v) Advanced glycation end products

Advanced glycation end products (AGEPs) are heat-induced food toxicants, which are protein-bound Maillard reaction products. AGEPs constitute a group of heterogeneous moieties produced endogenously from the non-enzymatic glycation of proteins, lipids, and nucleic acids (Krause et al., 2003; Goldberg et al., 2004). They are present in several heated foods, such as canned foods and meat products (Goldberg et al., 2004; Uribarri et al., 2010). The formation of AGEPs is part of the normal metabolism, but if their levels are very high in tissues and in the circulation, they can become pathogenic. Carboxymethyllysine is one of the best-characterized AGEP compounds, and is frequently used as a marker of AGEP formation in food. In meat products, carboxymethyllysine ranges from 0.01 to 6.87 mg per 100 g of food (mean, 0.86), and in meat dishes, it ranges from 0.10 to 42.39 mg per 100 g of food (mean, 2.42) (Hull et al., 2012). AGEP levels depend on red meat composition (Goldberg et al., 2004; Chen & Smith, 2015). Indeed, foods high in protein and lipid content show the highest AGEP levels, probably due to the large quantity of free radicals released via the various lipid peroxidation reactions that catalyse the formation of AGEPs during the cooking of meat products. AGEP formation depends on temperature, method, and duration of heating. The higher the cooking temperature, the more AGEPs are formed in red and processed meat. Different studies have shown that oven-frying produces more AGEPs than deep-frying, and broiling produces more AGEPs than roasting. Boiling produces less AGEPs (Goldberg et al., 2004; Chen & Smith, 2015). Cooking duration seems to be less important than the temperature and method, as shown in Table 1.10.

(vi) N-Glycolylneuraminic acid

Sialic acids are a family of sugars with a nine-carbon sugar acid. *N*-Glycolylneuraminic acid (Neu5Gc) (Fig. 1.4) is one of the most common sialic acids and is found in almost all mammals. Humans are genetically deficient in Neu5Gc production and instead metabolically accumulate it from dietary sources, particularly red meat and milk products. However, metabolically accumulated dietary Neu5Gc results in the production of circulating anti-Neu5Gc antibodies, leading to chronic local inflammation (Hedlund et al., 2008). It has been shown that the amount of Neu5Gc is high in red meats compared with other dietary sources, with beef being the most Neu5Gc-enriched compared with other red meats (Tangvoranuntakul et al., 2003; Samraj et al., 2015; Table 1.11).

Fig. 1.4 Structure of *N*-glycolylneuraminic acid (Neu5Gc)



(b) Processed meat

Processed meat can contain additional toxicants, apart from the heat toxicants described for red meat. The addition of nitrate and nitrite generates NOCs, and smoking can generate PAHs.

(i) N-Nitroso compounds

Processed meat products can be contaminated with NOCs such as *N*-nitrosamines, which result from the reaction between a nitrosating agent, originating from nitrite or smoke, and a secondary amine, derived from protein and lipid degradation (Preussmann & Stewart, 1984; De Mey et al., 2015). *N*-Nitrosamine production is dependent on reaction conditions (e.g. low pH and high temperature), and on meat composition and processing (e.g. ageing, ripening, fermentation, smoking, heat treatment, and storage) (Stadler & Lineback, 2009; Sindelar &Milkowski, 2012; De Mey et al., 2015). NOCs can also be formed endogenously after consumption of red or processed meat (Santarelli et al., 2008).

The most commonly found *N*-nitrosamines in processed meat are *N*-nitrosodimethylamine (NDMA), *N*-nitrosodiethylamine (NDEA), *N*-nitrosopiperidine (NPIP), and *N*-nitrosopyrrolidine (NPYR) (Fig. 1.5; Table 1.12). The concentrations of some of these NOCs in representative processed meats are given in Table 1.13.

A recent study detected *N*-nitrosamines in dry fermented sausages; only NPIP and *N*-nitrosomorpholine (NMOR) were detected in a high number of samples (n = 101; 22% and 28%, respectively). When *N*-nitrosamines were detected, their total amount remained below 5.5 µg/kg, with only one exception at 14 µg/kg (De Mey et al., 2014).

The addition of sodium ascorbate to meat, and to a lesser extent NaCl, was shown to decrease *N*-nitrosamine levels (e.g. NDMA and NDEA) in processed meat. On the contrary, baking processes increased *N*-nitrosamine levels (Rywotycki, 2007). [The Working Group noted that since the levels of nitrate and nitrite allowed in cured products are being lowered in many countries, a decrease in NOC formation is expected compared with previous decades.]

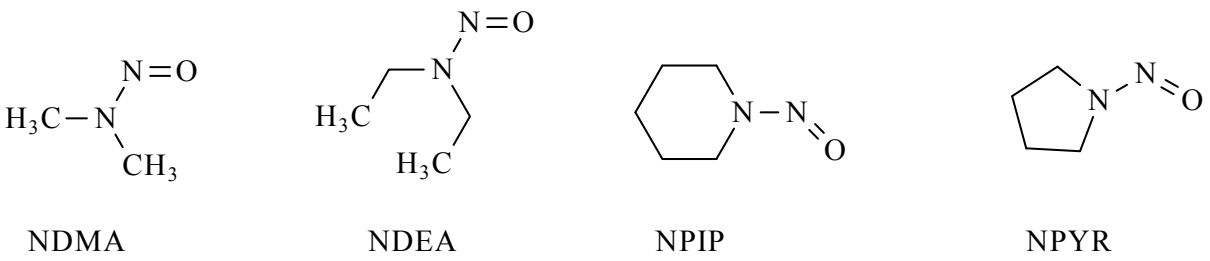
(ii) Polycyclic aromatic hydrocarbons

Traditional commercial smoking techniques, in which smoke from incomplete wood burning comes into direct contact with the product, can lead to significant contamination by PAHs if the process is not adequately monitored. Temperature, time, humidity, type of smoke used, and even the design of the smokehouse are crucial parameters in controlling PAH formation (EFSA, 2008; Roseiro et al., 2011). The concentrations of selected PAHs in different smoked meats are given in Table 1.8.

PAHs have also been found in dry fermented sausages in Portugal. The concentrations of chrysene, benzo[*a*]anthracene, BaP, and benzo[*a*]fluoranthene were 5.1–38.11, 8–32.9, 1.2–6.6, and 0.63–7.4 µg/kg dry matter, respectively (Roseiro et al., 2011).

The use of liquid smoke flavouring might reduce PAH levels in commercially smoked meat products (EFSA, 2008).

Fig. 1.5 Structures of *N*-nitroso compounds commonly found in processed meats



The full chemical names of these compounds are given in Table 1.12

1.3 Exposure via food intake

1.3.1 Data description

Consumption for a given food depends on two parameters: size of the portion and frequency of eating. In addition, the overall dietary pattern is based on types of foods consumed, which depends on socioeconomic factors (e.g. age, ethnicity, geographical origin, religion, level of education, and income). As a result of these difficulties, food consumption can be estimated using two different techniques: per capita studies and individual surveys, which can, respectively, underestimate or overestimate long-term dietary exposures.

Food consumption results can also be generated using household budget surveys, which correspond to per capita estimates at the household level. However, as the data for household budget surveys are weak, they will not be further considered in this *Monograph*.

In epidemiological studies, food frequency questionnaires (FFQs) are typically used for ranking subjects according to food or nutrient intake, rather than for estimating absolute levels of intake (Beaton, 1994; Kushi, 1994; Sempos et al., 1999). These questionnaires are further discussed in Section 1.4.1.

(a) Per capita consumption from economic surveys

The per capita consumption is calculated as follows: national production figures plus imports, minus exports, divided by the total number of individuals in the population. The average values are collected by the Food and Agriculture Organization of the United Nations Statistical Databases (FAOSTAT) (FAO, 2015) on a yearly basis, and may provide a superior estimate of long-term consumption. However, the per capita data underestimate the true consumption of food items, as less than 100% of the population are consumers, and the whole population is used to calculate the data. On the contrary, for food items consumed by 100% of the population, the data correctly account for both the amount consumed and the frequency of consumption. Based on the FAO per capita data, the World Health Organization (WHO) generated the Global Environment Monitoring System (GEMS) cluster diets (WHO, 2015a) using a mathematical technique to group countries with similar dietary patterns (Sy et al., 2013). Consumption values were calculated for each cluster as the average consumption of the food commodity in each country of the cluster. The range of values was therefore narrower than those for FAO national per capita consumption.

Table 1.7 Polycyclic aromatic hydrocarbons cited in this *Monograph*

Common name (name used in this volume)	CAS registry No.
Benz[*a*]anthracene	56-55-3
Benzo[*b*]fluoranthene	205-99-2
Benzo[*j*]fluoranthene	205-82-3
Benzo[*k*]fluoranthene	207-08-9
Benzo[*c*]fluorene	205-12-9
Benzo[*ghi*]perylene	191-24-2
Benzo[*a*]pyrene	50-32-8
Chrysene	218-01-9
Cyclopenta[*cd*]pyrene	27208-37-3
Dibenz[*a,h*]anthracene	53-70-3
Indeno[1,2,3-*cd*]pyrene	193-39-5
Dibenzo[*a,e*]pyrene	192-65-4
Dibenzo[*a,h*]pyrene	189-64-0
Dibenzo[*a,i*]pyrene	189-55-9
Dibenzo[*a,l*]pyrene	191-30-0
Indeno[1,2,3-*cd*]pyrene	193-39-5
5-Methylchrysene	3697-24-3

Note: the chemical structure of some of these compounds is given in Fig. 1.3

(b) Individual food consumption data

Individual food consumption data are generated from surveys based on recall or recording of daily consumption over 1–7 days. This method allows the distribution of consumption across a population and the consumption of high consumers to be estimated. The method overestimates long-term consumption by extrapolating data collected over a short period of time (Tran et al., 2004; IPCS, 2009).

1.3.2 Results

(a) Total meat consumption

For total per capita meat consumption worldwide in 2011, important differences were observed between regions consuming high quantities of meat (i.e. Oceania, 318 g/day; north America, 315 g/day; south America, 215 g/day; Europe, 208 g/day; central America, 148 g/day) and regions consuming low quantities of meat (i.e. Asia, 86 g/day; Africa, 51 g/day) (FAO, 2015).

In the European Prospective Investigation into Cancer and Nutrition (EPIC) study, surveys not representative of the national population were conducted in 10 European countries. Food consumption was estimated based on one 24-hour dietary recall (Linseisen et al., 2002). This study concluded that for total meat, the lowest mean consumption in Europe was observed in Greece (47 g/day for women and 79 g/day for men), and the highest mean consumption was observed in Spain (124 g/day for women and 234 g/day for men) (Linseisen et al., 2002).

According to FAOSTAT, from 2003 to 2011, meat consumption increased in all regions, but most significantly in Asia (16%) and in Africa (20%). These figures were for both red and poultry meats, and for both processed and unprocessed meats (FAO, 2015).

Table 1.8 Concentration levels (µg/kg) of selected polycyclic aromatic hydrocarbon in samples of white, red, and processed meat

PAH	Cooking/ processing method	Beef		Pork		Chicken	
		Range	Mean	Range	Mean	Range	Mean
Benzo[*k*]fluoranthene (BkF)	Smoked	1.03–3.35	2.57	0.65–4.69	2.96	1.13–4.01	3.54
	Grilled	0.35–2.04	1.87	0.22–3.56	1.37	< 0.10–1.95	1.29
	Boiled	< 0.10–1.81	1.09	0.36–1.45	1.01	0.12–1.54	1.19
	Unprocessed	ND	ND	ND	ND	ND	ND
Benzo[*a*]pyrene (BaP)	Smoked	< 0.10–5.43	5.34	0.50–10.02	1.28	< 0.10–5.91	2.91
	Grilled	0.17–2.93	2.74	0.21–5.73	1.75	0.48–3.73	1.82
	Boiled	0.27–1.30	0.87	0.17–1.45	0.94	< 0.10–1.66	0.99
	Unprocessed	1.71–2.42	0.34	ND	ND	ND	ND
Indeno[123-*cd*]pyrene (IP)	Smoked	1.82–27.59	5.10	8.81–31.11	5.29	1.40–7.17	1.39
	Grilled	1.34–8.48	0.62	1.65–8.59	4.01	1.07–3.42	0.61
	Boiled	0.41–1.22	0.54	0.54–1.81	0.97	0.34–1.19	0.45
	Unprocessed	1.32–7.86	3.16	0.27–3.06	1.73	0.21–1.08	0.45
Benzo[*ghi*]perylene (BghiP)	Smoked	< 0.30–2.55	1.42	< 0.30–3.18	1.09	0.88–3.41	2.68
	Grilled	0.61–1.64	1.50	0.78–2.66	1.84	< 0.30–2.56	1.34
	Boiled	0.36–1.19	0.82	< 0.30–1.62	0.93	< 0.30–1.87	1.12
	Unprocessed	ND	ND	ND	ND	ND	ND

Adapted from *Food chemistry*, Volume 156, Olatunji et al. (2014). Determination of polycyclic aromatic hydrocarbons [PAHs] in processed meat products using gas chromatography – Flame ionization detector, Pages No. 296–300, Copyright (2014), with permission from Elsevier

(b) Association between consumption of red meat and consumption of other foods

Food categories are not independent in regard to consumption. In the field of nutrition, nutrient intake is estimated by combining consumption data with food nutrient composition databases. Thereafter, homogeneous subgroups of consumers with comparable nutrient intakes (dietary patterns) are identified by using classical statistical clustering techniques (Pryer et al., 2001; Hu, 2002). The association between food categories can also be observed by using principal component analysis. For example, intake of processed meat was associated with intake of French fries, sweets, cakes, desserts, snacks, and alcoholic beverages (Fung et al., 2003; Dixon et al., 2004; Kesse et al., 2006).

Whereas clustering is based on nutrient intake, it is very difficult to a posteriori identify foods that contribute by a majority to a given dietary pattern. Zetlaoui et al. proposed the use of principal component analysis for food clustering (Zetlaoui et al., 2011). Based on this approach, and its application in the FAO per capita data set (i.e. 415 food products in 179 countries), 30 consumption systems leading to 17 cluster diets have been described (Sy et al., 2013). According to this publication, the consumption of pork meat seemed to be associated with the consumption of barley beer, poultry meat, wheat flour, and refined sugar. The consumption of cattle meat seemed to be associated with cow milk and wheat flour (Sy et al., 2013).

(c) Red meat consumption

According to FAOSTAT in 2011, the cumulated mean per capita consumption of beef, mutton, goat, and pig meat was 30, 60, 130, 140, and 200 g/day, respectively, for Africa, Asia, America, Europe, and Oceania (FAO, 2015). From the WHO/GEMS clusters, the average

Table 1.9 Total iron and percentage of haem iron in raw and cooked meat

Meats	Total iron (mg/100 g)		% Haem iron		% Loss
	Raw	Cooked	Raw	Cooked	
Red meat					
Beef					
Sirloin	2.07	3.59	83	74	11
Fillet	2.35	3.38	90	85	6
Roasted beef	2.04	3.74	87	84	3
Topside	1.93	2.88	87	66	24
Mean	2.09	3.39	87	78	11
Veal					
Fillet	0.85	1.58	84	83	1
Lamb					
Chop	2.23	3.20	75	70	7
Horse					
Fillet	2.21	3.03	79	71	11
Pork					
Loin	0.36	0.46	56	46	18
Chump chop	0.49	0.79	66	69	(+4)
Mean	0.42	0.64	62	61	7
White meat					
Chicken					
Breast	0.40	0.58	30	28	7
Leg (thigh)	0.70	1.34	30	22	27
Leg (lower part)	0.63	1.20	46	35	24
Wing	0.63	0.92	44	25	43
Mean	0.59	1.01	38	28	28
Turkey					
Breast	0.50	0.79	28	27	4
Leg (thigh)	0.99	1.46	50	39	22
Leg (lower part)	0.88	1.51	49	38	22
Mean	0.79	1.25	42	35	18

Adapted from Lombardi-Boccia et al. (2002)

total red meat consumption ranged from 15 to 147 g/day (WHO, 2013).

In a systematic assessment, the Global Burden of Diseases Nutrition and Chronic Diseases Expert Group (NutriCoDE) evaluated the global consumption of key dietary items (foods and nutrients) by region, nation, age, and sex in 1990 and 2010 (Imamura et al., 2015). Consumption data were evaluated from 325 surveys (71.7% nationally representative) covering 88.7% of the global adult population. According to the analysis, the median of mean consumption of red meat worldwide ranged from 23 g/day (2.6–28 g/day) for the first quintile to 84 g/day (71–138 g/day) for the fifth quintile (Imamura et al., 2015).

Individual food consumption surveys provide the distribution of consumption for consumers only (i.e. high percentiles of consumption as well as percentages of consumers by country) (FAO/WHO, 2015; FCID, 2015). Worldwide detailed data on red meat consumption (g/kg bw per day) are presented in Table 1.14 and Table 1.15 for adults and children, respectively.

Table 1.10 Advanced glycation end product content in red meat, processed meat, and chicken[a]

Meat	Cooking/processing method	Advanced glycation end product (kU/110 g)
Beef	Raw	707
	Roast	6 071
	Steak, raw	800
	Steak, broiled	7 479
	Steak, grilled 4 min	7 416
	Steak, microwaved, 6 min	2 687
	Steak, pan fried w/olive oil	10 058
	Steak, strips, 450°F, 15 min	6 851
	Steak, strips, stir fried with 1 T canola oil, 15 min	9 522
	Steak, strips, stir fried without oil, 7 min	6 973
	Stewed	2 443
	Frankfurter, boiled in water, 212° F, 7 min	7 484
	Frankfurter, broiled 450°F, 5 min	11 270
	Ground, 20% fat, pan/cover	5 527
	Hamburger patty, olive oil 180°F, 6 min	2 639
	Meatball, potted (cooked in liquid), 1 h	4 300
	Meatball, w/sauce	2 852
	Meatloaf, crust off, 45 min	1 862
Pork	Bacon, fried 5 min no added oil	91 577
	Bacon, microwaved, 2 slices, 3 min	9 023
	Ham, deli, smoked	2 349
	Liverwurst	633
	Chop, pan fried, 7 min	4 752
	Ribs, roasted	4 430
	Roast (Chinese take-out)	3 544
	Sausage, beef and pork links, pan fried	5 426
	Sausage, Italian, raw	1 861
	Sausage, Italian, barbecued	4 839
	Sausage, pork links, microwaved, 1 min	5 943
Lamb	Leg, raw	826
	Leg, boiled, 30 min	1 218
	Leg, broiled, 450°F, 30 min	2 431
	Leg, microwave, 5 min	1 029
Veal	Stewed	2 858
Chicken	Ground, white meat, raw	877
	Meatball, potted (cooked in liquid) 1 h	1 501
	Potted (cooked in liquid) with onion and water	3 329
	Roasted	6 020
	Skin, back of thigh, roasted then barbecued	18 520

[a] Glycation end product content based on carboxymethyllysine content

Adapted from *Journal of the American Dietetic Association*, Volume 110, issue 6, Jaime Uribarri, Sandra Woodruff, Susan Goodman, Weijing Cai, Xue Chen, Renata Pyzik, Angie Yong, Gary E. Striker, Helen Vlassara, Advanced Glycation End Products in Foods and a Practical Guide to Their Reduction in the Diet, Pages No. 911-916.e12, Copyright (2010), with permission from Elsevier (Uribarri et al., 2010)

Table 1.11 Content of *N*-glycolylneuraminic acid in red or processed meat, raw or cooked under different conditions

Meat	Neu5Gc content (µg/g)
Ground beef	25
Beef steak (raw)	134
Beef steak (baked)	210
Beef steak (boiled)	231
Beef steak (fried)	199
Ground lamb	14
Lamb steak (raw)	57
Lamb steak (baked)	50
Lamb steak (boiled)	47
Lamb steak (fried)	19
Ground pork	19
Pork chop (raw)	25
Pork chop (baked)	40
Pork chop (boiled)	36
Pork chop (fried)	29
Pork bratwurst	11
Pork bacon	7

Neu5Gc, *N*-glycolylneuraminic acid
From Samraj et al. (2015), with permission of the editor

(i) Europe

The European Food Safety Authority (EFSA) collected in a harmonized way the results from national food consumption surveys of more than 20 member states of the EU. The median of mean meat consumption for adults was 35 g/day, ranging from about 10 g/day (Sweden) to 110 g/day (Austria). At the 95th percentile, meat consumption ranged from 20 g/day (Sweden, 21% of consumers) to 237 g/day (Austria, 88% of consumers). Similar results were found for adolescents, both in terms of amount consumed and percentage of the population that are consumers. For infants and toddlers, the median of mean meat consumption was about 50 g/day, ranging from 20 to 80 g/day, and the percentage of consumers ranged from about 5% (the Netherlands) to 100% (Germany). At the 95th percentile, the meat consumption ranged from 40 g/day (the Netherlands) to about 190 g/day (Belgium) (EFSA, 2011).

The EPIC study concluded that red meat consumption ranged from 24 to 57 g/day for women and from 40 to 121 g/day for men based on 24-hour recall (Linseisen et al., 2002).

(ii) Americas

Few representative national surveys were available for the Americas. In the USA (FCID, 2015), the mean consumption of total red meat was 86 g/day for adult consumers and 242 g/day at the 95th percentile for the same population (72% consumers). For children aged between 1 and < 3 years, mean consumption was 31 g/day and 89 g/day at the 95th percentile (62% consumers). For children aged between 3 and 16 years, mean consumption was 60 g/day and 176 g/day at the 95th percentile (71% consumers) (FCID, 2015). Similarly, in Brazil, the mean consumption of beef was 92 g/day for the general population and 232 g/day at the 95th percentile for the same population (69% consumers). No data were available for children in Brazil, and no data were available for other countries in Latin America. However, according to the GEMS Cluster diets, the dietary patterns in this region seemed homogeneous (FAO/WHO, 2015; Table 1.14 and Table 1.15).

(iii) Africa

Data were scarce and incomplete for Africa. Fortunately, individual food consumption surveys were performed for adult women and children in Burkina Faso and Uganda. In these two countries, the percentage of consumers of red meat was less than 5% of the population. However, for these adult consumers, the mean consumption was between 23 and 90 g/day, and consumption at the 95th percentile was between 28 and 147 g/day. For children, the percentage of consumers of red meat was below 4% of this population. Similarly, compared with adults, consumption for child consumers was close to that observed in developed countries, with a mean between 13 and 62 g/day, and a high consumption

Table 1.12 *N*-Nitroso compounds commonly found in processed meat

Common abbreviation	Full name	CAS registry No.
NMDA	*N*-Nitrosodimethylamine	62-75-9
NDEA	*N*-Nitrosodiethylamine	55-18-5
NPIP	*N*-Nitrosopiperidine	100-75-4
NPYR	*N*-Nitrosopyrrolidine	930-55-2
NDBA	*N*-Nitrosodi-*n*-butylamine	924-16-3
–	*N*-Nitrosomethylethylamine	10595-95-6
–	*N*-Nitrosoproline	7519-36-0
–	*N*-Nitrosohydroxyproline	30310-80-6
NMOR	*N*-Nitrosomorpholine	59-89-2

CAS, Chemical Abstracts Service
The chemical structure of some of these compounds is given in Fig. 1.5

at the 95th percentile of between 22 and 69 g/day. It is therefore likely that the difference in the per capita consumption (four to five times lower in Africa than in Europe) was mainly due to a lower number of consumers rather than to large differences in the dietary patterns of consumers (FAO/WHO, 2015; Table 1.14 and Table 1.15).

(iv) Middle East and north Africa

Intake of red meat in countries of the Middle East and north Africa was estimated in 2010 to range from 200 g/week (Afghanistan) to 700 g/week (Algeria and United Arab Emirates) (Afshin et al., 2015).

(v) Asia

Food consumption surveys were available from Bangladesh, China, Japan, the Philippines, the Republic of Korea, and Thailand. In Asia, the main types of red meat consumed were pork and beef (FAO/WHO, 2015). In China, the predominant red meat consumed was pork, with 63% of consumers, a mean consumption of 84 g/day, and consumption at the 95th percentile of 224 g/day for adult consumers only (Table 1.14). Based on three consecutive 24-hour recalls, a prospective study of 5000 adults from 4280 households in nine provinces showed an increase in average consumption of pork of 20% (52 vs 62 g/day per person) from 1989 to 2004 (Zhai et al., 2009). For Chinese children, the mean consumption of pork was 51 g/day, and consumption of pork at the 95th percentile was 142 g/day. Beef was consumed by less than 10% of the Chinese population, with a mean consumption of 46 g/day and consumption at the 95th percentile for consumers of 130 g/day. For children, the mean consumption of beef was 32 g/day, and consumption of beef at the 95th percentile was 85 g/day. These figures were close to those reported in the Americas and Europe (FAO/WHO, 2015; Table 1.15).

Similarly, in the Republic of Korea, the consumption of pork for adults was 76 g/day, and consumption of pork at the 95th percentile was 253 g/day (44% of consumers). For children, the mean consumption of pork was 30 g/day, and consumption of pork at the 95th percentile was 95 g/day. Finally, in the Philippines, for one third of the population, the mean consumption of pork for children was 75 g/day, and consumption of pork at the 95th percentile was 208 g/day (33% of consumers). On the contrary, in Japan, beef and pork were consumed by a wide range of consumers (i.e. 89% and 99% of the population, respectively). The mean consumption and consumption at the 97.5th percentile for consumers only were 53 and 83 g/day, respectively, i.e. about half of the consumption in north

Table 1.13 Major sources of dietary *N*-nitrosamines in processed meats

Processed meat	Concentration of nitrosamines (µg/kg)			
	NDMA	NDEA	NPYR	NPIP
Bacon fried	ND–30	ND–1	ND–200	ND–1
Cured meats	ND–4	ND–4	ND–25	ND–2
Smoked meats	ND–3	ND–7.9	ND–0.1	ND–0.1
Sausages				
Frankfurter	ND–84	–	–	–
Mettwurst	+	+	ND–105	ND–60
Liver sausage	ND–35	ND–25	ND–80	–
Salami	ND–80	–	–	–
Bologna	–	ND–25	ND–105	–

+, detected but not quantitated; –, not reported; ND, not detected; NDMA, *N*-nitrosodimethylamine; NDEA, *N*-nitrosodiethylamine; NPIP, *N*-nitrosopiperidine; NPYR, *N*-nitrosopyrrolidine

From: *Nitrates, nitrites and N-nitrosocompounds: A review of the occurrence in food and diet and the toxicological implications*, R. Walker, Food Additives & Contaminants, 1990, reprinted by permission of Taylor & Francis (Taylor & Francis Ltd, http://www.tandfonline.com) (Walker, 1990)

America or in China. In Thailand, the percentage of pork meat consumers was 89%, with a mean consumption of 23 g/day. In Bangladesh, the percentage of red meat consumers was less than 10%. The mean consumption for consumers was between 10 and 23 g/day, and the consumption at the 95th percentile was between 25 and 77 g/day (FAO/WHO, 2015; Table 1.14 and Table 1.15).

(iv) Oceania

The 2008/09 New Zealand Adult Nutrition Survey (University of Otago and Ministry of Health, 2011) estimated the mean consumption of beef and veal to be 180 g/day, and consumption of beef and veal at the 90th percentile to be 397 g/day for consumers only. The same survey estimated the mean consumption of lamb and mutton to be 137 g/day, and consumption of lamb and mutton at the 90th percentile to be 275 g/day. For these two food categories, the percentage of consumers was 24% for beef and veal meat, and 7% for lamb and goat meat (Parnell et al., 2012). Data on the consumption of pork, as well as the total red meat consumption, were not available for adults. For Australia, data on consumption were only available for children. They showed a mean consumption that for consumers only ranged from 13 to 70 g/day, and a consumption at the 97.5th percentile that ranged from 83 to 257 g/day (FAO/WHO, 2015; Table 1.15).

In summary, for most countries (e.g. Australia, central and southern Europe, China, the Philippines, the Republic of Korea, and the USA), the mean consumption of red meat for consumers only was around 50–100 g/day, and high consumption was around 200–300 g/day. The percentage of meat consumers seemed to be proportional to the income or the level of development. In other words, the distribution of meat consumption was fairly similar among consumers in these countries. Therefore, analysis of per capita data only may give the wrong perception of the levels of consumption. In some countries (e.g. Japan, northern Europe, and Thailand), the consumption of red meat was low, despite a percentage of consumers of about 90%, probably due to substitution with fish and other seafoods. Finally, in less-industrialized countries for which data were available (e.g. Bangladesh, Burkina Faso, and Uganda), the percentage of consumers was below 10%, probably due to the high price of red meat. It should be noted that, in these countries, the mean and high

Table 1.14 Worldwide consumption of red meat in adults

Age class	Country	Survey	Meat type	No. of subjects	No. of consumers	Percentage of consumers	Consumers, Mean (g/bw per day)	Consumers, STD (g/bw per day)	Consumers, P975 (g/bw per day)
Adult women	Bangladesh	Harvest_2007/8	Beef and other bovines meat	474	39	8.23%	0.4	0.3	0.9
Adult women	Bangladesh	Harvest_2007/8	Goat and other caprines	474	9	1.90%	0.5	0.7	2.0
Adults	Belgium	Diet_National_2004	Beef and other bovines meat	1304	449	34.43%	0.9	0.7	2.5
Adults	Belgium	Diet_National_2004	Horse and other equines	1304	16	1.23%	1.1	0.7	2.6
Adults	Belgium	Diet_National_2004	Meat from mammals other than marine mammals, NES	1304	9	0.69%	0.7	0.3	1.1
Adults	Belgium	Diet_National_2004	Pork and other porcines	1304	273	20.94%	0.9	0.5	2.3
Adults	Belgium	Diet_National_2004	Sheep and other ovines	1304	84	6.44%	0.9	0.5	2.1
General population	Brazil	Brazilian Institute of Geography and Statistics	Beef and other bovines meat	34 003	23 320	68.58%	1.4	1.2	4.4
General population	Brazil	Brazilian Institute of Geography and Statistics	Goat and other caprines	34 003	194	0.57%	1.8	1.2	4.8
General population	Brazil	Brazilian Institute of Geography and Statistics	Meat from mammals other than marine mammals, NES	34 003	2071	6.09%	1.0	0.9	3.5
General population	Brazil	Brazilian Institute of Geography and Statistics	Pork and other porcines	34 003	2577	7.58%	1.8	1.7	6.3
General population	Brazil	Brazilian Institute of Geography and Statistics	Sheep and other ovines	34 003	136	0.40%	1.5	1.1	4.8
Adult women	Burkina Faso	Harvest_2010	Beef and other bovines meat	287	7	2.44%	0.4	0.1	0.5
Adult women	Burkina Faso	Harvest_2010	Goat and other caprines	287	7	2.44%	0.7	0.5	1.5
Adult women	Burkina Faso	Harvest_2010	Meat from mammals other than marine mammals, NES	287	3	1.05%	1.7	0.5	2.2

Table 1.14 (continued)

Age class	Country	Survey	Meat type	No. of subjects	No. of consumers	Percentage of consumers	Consumers, Mean (g/bw per day)	Consumers, STD (g/bw per day)	Consumers, P975 (g/bw per day)
Adult women	Burkina Faso	Harvest_2010	Pork and other porcines	287	11	3.83%	0.8	0.5	1.8
Adult women	Burkina Faso	Harvest_2010	Sheep and other ovines	287	4	1.39%	0.9	0.3	1.2
General population	China	2002 China Nutrition and Health Survey	Beef and other bovines meat	65 359	5278	8.08%	0.9	0.9	3.2
General population	China	2002 China Nutrition and Health Survey	Horse and other equines	65 359	66	0.10%	2.1	4.0	10.4
General population	China	2002 China Nutrition and Health Survey	Meat from mammals other than marine mammals, NES	65 359	635	0.97%	1.2	1.2	4.6
General population	China	2002 China Nutrition and Health Survey	Pork and other porcines	65 359	41 283	63.16%	1.6	1.4	5.3
General population	China	2002 China Nutrition and Health Survey	Sheep and other ovines	65 359	3690	5.65%	1.2	1.2	4.3
Adults	Czech Republic	SISP04	Beef and other bovines meat	1666	514	30.85%	0.8	0.6	2.2
Adults	Czech Republic	SISP04	Pork and other porcines	1666	694	41.66%	1.1	0.7	2.9
Adults	Denmark	Danish_Dietary_ Survey	Beef and other bovines meat	2822	2780	98.51%	0.5	0.4	1.4
Adults	Denmark	Danish_Dietary_ Survey	Pork and other porcines	2822	2750	97.45%	0.6	0.5	1.8
Adults	Denmark	Danish_Dietary_ Survey	Sheep and other ovines	2822	187	6.63%	0.4	0.2	1.0
Adults	Finland	FINDIET_2007	Beef and other bovines meat	1575	695	44.13%	0.6	0.5	2.0
Adults	Finland	FINDIET_2007	Pork and other porcines	1575	431	27.37%	0.7	0.6	2.4
Adults	Finland	FINDIET_2007	Sheep and other ovines	1575	62	3.94%	0.6	0.6	1.8
Adults	France	INCA2	Beef and other bovines meat	2276	2002	87.96%	0.7	0.5	1.8
Adults	France	INCA2	Horse and other equines	2276	52	2.28%	0.3	0.2	0.8
Adults	France	INCA2	Meat from mammals other than marine mammals, NES	2276	825	36.25%	0.1	0.2	0.5

Table 1.14 (continued)

Age class	Country	Survey	Meat type	No. of subjects	No. of consumers	Percentage of consumers	Consumers, Mean (g/bw per day)	Consumers, STD (g/bw per day)	Consumers, P975 (g/bw per day)
Adults	France	INCA2	Pork and other porcines	2276	1154	50.70%	0.3	0.3	1.1
Adults	France	INCA2	Sheep and other ovines	2276	627	27.55%	0.2	0.2	0.7
Adults	Hungary	National_Repr_Surv	Beef and other bovines meat	1074	382	35.57%	0.3	0.3	1.1
Adults	Hungary	National_Repr_Surv	Pork and other porcines	1074	860	80.07%	0.9	0.6	2.6
Adults	Hungary	National_Repr_Surv	Sheep and other ovines	1074	8	0.74%	0.5	0.2	0.8
Adults	Ireland	NSIFCS	Beef and other bovines meat	958	761	79.44%	0.7	0.6	2.0
Adults	Ireland	NSIFCS	Pork and other porcines	958	427	44.57%	0.5	0.4	1.5
Adults	Ireland	NSIFCS	Sheep and other ovines	958	361	37.68%	0.4	0.3	1.4
Adults	Italy	INRAN_ SCAI_2005_06	Beef and other bovines meat	2313	1698	73.41%	0.8	0.6	2.3
Adults	Italy	INRAN_ SCAI_2005_06	Goat and other caprines	2313	3	0.13%	0.6	0.2	0.8
Adults	Italy	INRAN_ SCAI_2005_06	Horse and other equines	2313	57	2.46%	0.7	0.4	1.5
Adults	Italy	INRAN_ SCAI_2005_06	Pork and other porcines	2313	735	31.78%	0.6	0.5	1.8
Adults	Italy	INRAN_ SCAI_2005_06	Sheep and other ovines	2313	71	3.07%	0.6	0.8	1.4
General population	Japan	DSFFQ _FI	Beef and other bovines meat	2711	2406	88.75%	0.3	0.3	1.0
General population	Japan	DSFFQ _FI	Meat from mammals other than marine mammals, NES	2711	112	4.13%	0.2	0.1	0.7
General population	Japan	DSFFQ _FI	Pork and other porcines	2711	2691	99.26%	0.6	0.4	1.5
Adults	Latvia	EFSA_TEST	Beef and other bovines meat	1306	66	5.05%	0.8	0.6	2.7
Adults	Latvia	EFSA_TEST	Goat and other caprines	1306	1	0.08%	0.7		0.7
Adults	Latvia	EFSA_TEST	Meat from mammals other than marine mammals, NES	1306	20	1.53%	0.7	0.4	1.7
Adults	Latvia	EFSA_TEST	Pork and other porcines	1306	796	60.95%	1.2	0.9	3.5

Table 1.14 (continued)

Age class	Country	Survey	Meat type	No. of subjects	No. of consumers	Percentage of consumers	Consumers, Mean (g/bw per day)	Consumers, STD (g/bw per day)	Consumers, P975 (g/bw per day)
Adults	Latvia	EFSA_TEST	Sheep and other ovines	1306	5	0.38%	0.8	0.3	1.3
Adults	Netherlands	DNFCS_2003	Beef and other bovines meat	750	180	24.00%	1.0	0.6	2.5
Adults	Netherlands	DNFCS_2003	Horse and other equines	750	2	0.27%	0.2	0.1	0.3
Adults	Netherlands	DNFCS_2003	Pork and other porcines	750	309	41.20%	1.2	0.9	3.8
Adults	Netherlands	DNFCS_2003	Sheep and other ovines	750	30	4.00%	1.2	0.9	4.1
General population	Republic of Korea	KNHNES	Beef and other bovines meat	9391	3141	33.45%	0.9	1.2	4.1
General population	Republic of Korea	KNHNES	Pork and other porcines	9391	4124	43.91%	1.4	1.8	6.3
Adults	Spain	AESAN_FIAB	Beef and other bovines meat	981	680	69.32%	1.1	0.7	2.8
Adults	Spain	AESAN	Beef and other bovines meat	410	176	42.93%	1.2	0.8	3.2
Adults	Spain	AESAN_FIAB	Goat and other caprines	981	3	0.31%	1.1	0.2	1.3
Adults	Spain	AESAN_FIAB	Pork and other porcines	981	366	37.31%	1.0	0.7	3.0
Adults	Spain	AESAN	Pork and other porcines	410	129	31.46%	1.0	0.6	2.4
Adults	Spain	AESAN_FIAB	Sheep and other ovines	981	102	10.40%	1.0	0.5	2.3
Adults	Spain	AESAN	Sheep and other ovines	410	18	4.39%	1.1	0.9	3.8
Adults	Sweden	Riksmaten_1997_98	Beef and other bovines meat	1210	590	48.76%	0.3	0.2	0.9
Adults	Sweden	Riksmaten_1997_98	Horse and other equines	1210	8	0.66%	0.1	0.1	0.5
Adults	Sweden	Riksmaten_1997_98	Pork and other porcines	1210	699	57.77%	0.4	0.2	1.0
Adults	Sweden	Riksmaten_1997_98	Sheep and other ovines	1210	32	2.64%	0.2	0.2	1.0
General population	Thailand	FCDT	Beef and other bovines meat	16 383	7880	48.10%	0.1		
General population	Thailand	FCDT	Pork and other porcines	16 383	14 646	89.40%	0.4		
Adult women	Uganda	Harvest_2007	Beef and other bovines meat	176	8	4.55%	1.2	0.8	2.8
Adult women	Uganda	Harvest_2007	Goat and other caprines	176	2	1.14%	1.2	0.7	1.7
Adults	United Kingdom	NDNS	Beef and other bovines meat	1724	1349	78.25%	0.4	0.3	1.1

Table 1.14 (continued)

Age class	Country	Survey	Meat type	No. of subjects	No. of consumers	Percentage of consumers	Consumers, Mean (g/bw per day)	Consumers, STD (g/bw per day)	Consumers, P975 (g/bw per day)
Adults	United Kingdom	NDNS	Pork and other porcines	1724	535	31.03%	0.3	0.2	0.9
Adults	United Kingdom	NDNS	Sheep and other ovines	1724	434	25.17%	0.3	0.2	0.8
Adults over 16 years	USA	FCID-WWEIA data for years 2005–2010	Total red meat	31 484	23 825	75.67%	1.1		3.06*
General population	USA	FCID-WWEIA data for years 2005–2010	Total red meat	49 343	35 752	72.46%	1.2		3.59*
General population	USA	FCID-WWEIA data for years 2005–2010	Sheep meat	49 343	2518	5.10%	0.1		0.56*
General population	USA	FCID-WWEIA data for years 2005–2010	Goat meat	49 343	35	0.07%	1.9		5.8*
General population	USA	FCID-WWEIA data for years 2005–2010	Pork meat	49 343	26 256	53.21%	0.55		2.04*
General population	USA	FCID-WWEIA data for years 2005–2010	Beef meat	49 343	29 788	60.37%	0.96		3.08*

* 95th percentile

NES, not elsewhere specified

Data on USA from FCID (2015): What We Eat In America – Food Commodity Intake Database 2005–10, United States Environmental Protection Agency – Office of Pesticide Programs © University of Maryland 2012 – 2016. Available from: http://fcid.foodrisk.org/percentiles.php

Data for other countries from FAO/WHO (2015): the FAO/WHO Chronic individual food consumption database – Summary statistics (CIFOCOss), © Copyright World Health Organization (WHO), 2016. All Rights Reserved. Available from: http://www.who.int/foodsafety/databases/en/

Table 1.15 Worldwide consumption of red meat in children

Age class	Country	Survey	Meat type	No. of subjects	No. of consumers	Percentage of consumers	Consumers, mean consumption (g/bw per day)	Consumers, STD (g/bw per day)	Consumers, P975 (g/bw per day)
Adolescents	Belgium	Diet_National_2004	Beef and other bovines meat	584	175	29.97%	1.0	0.7	2.5
Adolescents	Belgium	Diet_National_2004	Horse and other equines	584	6	1.03%	1.3	0.4	1.9
Adolescents	Belgium	Diet_National_2004	Meat from mammals other than marine mammals, NES	584	11	1.88%	0.7	0.4	1.7
Adolescents	Belgium	Diet_National_2004	Pork and other porcines	584	121	20.72%	1.1	0.7	3.1
Adolescents	Belgium	Diet_National_2004	Sheep and other ovines	584	43	7.36%	1.0	0.7	2.8
Adolescents	Cyprus	Childhealth	Beef and other bovines meat	303	18	5.94%	0.6	0.2	0.9
Adolescents	Cyprus	Childhealth	Pork and other porcines	303	154	50.83%	1.1	0.6	2.8
Adolescents	Cyprus	Childhealth	Sheep and other ovines	303	12	3.96%	0.8	0.4	1.8
Adolescents	Czech Republic	SISP04	Beef and other bovines meat	298	97	32.55%	1.2	0.8	3.1
Adolescents	Czech Republic	SISP04	Pork and other porcines	298	125	41.95%	1.4	0.8	3.2
Adolescents	Denmark	Danish Dietary Survey	Beef and other bovines meat	479	478	99.79%	0.7	0.5	2.0
Adolescents	Denmark	Danish_Dietary_ Survey	Pork and other porcines	479	472	98.54%	0.7	0.5	2.0
Adolescents	Denmark	Danish_Dietary_ Survey	Sheep and other ovines	479	21	4.38%	0.5	0.3	1.3
Adolescents	France	INCA2	Beef and other bovines meat	973	912	93.73%	0.9	0.6	2.4
Adolescents	France	INCA2	Horse and other equines	973	21	2.16%	0.5	0.3	1.6
Adolescents	France	INCA2	Meat from mammals other than marine mammals, NES	973	424	43.58%	0.2	0.2	1.0
Adolescents	France	INCA2	Pork and other porcines	973	482	49.54%	0.4	0.3	1.2
Adolescents	France	INCA2	Sheep and other ovines	973	257	26.41%	0.3	0.3	0.8
Adolescents	Italy	INRAN_ SCAI_2005_06	Beef and other bovines meat	247	204	82.59%	1.2	0.9	3.2

Table 1.15 (continued)

Age class	Country	Survey	Meat type	No. of subjects	No. of consumers	Percentage of consumers	Consumers, mean consumption (g/bw per day)	Consumers, STD (g/bw per day)	Consumers, P975 (g/bw per day)
Adolescents	Italy	INRAN_ SCAI_2005_06	Horse and other equines	247	8	3.24%	0.8	0.3	1.4
Adolescents	Italy	INRAN_ SCAI_2005_06	Pork and other porcines	247	81	32.79%	0.8	0.7	2.5
Adolescents	Italy	INRAN_ SCAI_2005_06	Sheep and other ovines	247	2	0.81%	0.7	0.2	0.9
Adolescents	Latvia	EFSA_TEST	Beef and other bovines meat	470	16	3.40%	0.9	0.6	2.3
Adolescents	Latvia	EFSA_TEST	Meat from mammals other than marine mammals, NES	470	4	0.85%	0.5	0.1	0.5
Adolescents	Latvia	EFSA_TEST	Pork and other porcines	470	263	55.96%	1.4	1.1	4.1
Adolescents	Spain	AESAN_FIAB	Beef and other bovines meat	86	62	72.09%	1.4	1.0	4.5
Adolescents	Spain	NUT_INK05	Beef and other bovines meat	651	294	45.16%	1.7	1.1	4.8
Adolescents	Spain	NUT_INK05	Goat and other caprines	651	2	0.31%	1.3	0.5	1.6
Adolescents	Spain	enKid	Horse and other equines	209	2	0.96%	1.0	0.2	1.2
Adolescents	Spain	NUT_INK05	Horse and other equines	651	1	0.15%	1.3		1.3
Adolescents	Spain	enKid	Meat from mammals other than marine mammals, NES	209	69	33.01%	1.5	0.9	3.9
Adolescents	Spain	AESAN_FIAB	Pork and other porcines	86	42	48.84%	1.0	0.6	2.0
Adolescents	Spain	enKid	Pork and other porcines	209	60	28.71%	1.2	0.8	3.3
Adolescents	Spain	NUT_INK05	Pork and other porcines	651	212	32.57%	1.1	0.7	3.3
Adolescents	Spain	AESAN_FIAB	Sheep and other ovines	86	4	4.65%	1.3	0.6	2.0
Adolescents	Spain	enKid	Sheep and other ovines	209	11	5.26%	1.9	2.3	8.5
Adolescents	Spain	NUT_INK05	Sheep and other ovines	651	29	4.45%	1.3	0.7	3.8
Adolescents	Sweden	NFA	Beef and other bovines meat	1018	542	53.24%	0.5	0.4	1.7
Adolescents	Sweden	NFA	Horse and other equines	1018	9	0.88%	0.3	0.3	0.9
Adolescents	Sweden	NFA	Pork and other porcines	1018	286	28.09%	0.8	0.5	2.0
Adolescents	Sweden	NFA	Sheep and other ovines	1018	6	0.59%	0.8	0.8	2.4

Table 1.15 (continued)

Age class	Country	Survey	Meat type	No. of subjects	No. of consumers	Percentage of consumers	Consumers, mean consumption (g/bw per day)	Consumers, STD (g/bw per day)	Consumers, P975 (g/bw per day)
Children	Bangladesh	Harvest_2007/8	Beef and other bovines meat	555	41	7.39%	1.0	0.8	3.0
Children	Bangladesh	Harvest_2007/8	Goat and other caprines	555	12	2.16%	0.9	0.7	2.1
Children	Burkina Faso	Harvest_2010	Beef and other bovines meat	288	7	2.43%	0.9	0.6	1.5
Children	Burkina Faso	Harvest_2010	Goat and other caprines	288	6	2.08%	1.8	1.0	3.3
Children	Burkina Faso	Harvest_2010	Meat from mammals other than marine mammals, NES	288	3	1.04%	4.8	3.6	8.0
Children	Burkina Faso	Harvest_2010	Pork and other porcines	288	10	3.47%	2.2	1.6	5.7
Children	Burkina Faso	Harvest_2010	Sheep and other ovines	288	3	1.04%	1.9	0.9	2.8
Children	China	2002 China Nutrition and Health Survey	Beef and other bovines meat	2784	171	6.14%	2.0	1.7	6.7
Children	China	2002 China Nutrition and Health Survey	Horse and other equines	2784	7	0.25%	7.6	10.4	30.9
Children	China	2002 China Nutrition and Health Survey	Meat from mammals other than marine mammals, NES	2784	27	0.97%	2.6	2.6	10.6
Children	China	2002 China Nutrition and Health Survey	Pork and other porcines	2784	1703	61.17%	3.3	2.7	10.5
Children	China	2002 China Nutrition and Health Survey	Sheep and other ovines	2784	119	4.27%	2.8	2.9	10.3
Children	Japan	DSFFQ _FI	Beef and other bovines meat	71	66	92.96%	0.5	0.4	1.3
Children	Japan	DSFFQ _FI	Meat from mammals other than marine mammals, NES	71	1	1.41%	0.1		
Children	Japan	DSFFQ _FI	Pork and other porcines	71	71	100.00%	1.3	0.8	3.7
Children	Philippines	Harvest_2003	Beef and other bovines meat	1205	61	5.06%	1.3	0.8	2.8

Table 1.15 (continued)

Age class	Country	Survey	Meat type	No. of subjects	No. of consumers	Percentage of consumers	Consumers, mean consumption (g/bw per day)	Consumers, STD (g/bw per day)	Consumers, P975 (g/bw per day)
Children	Philippines	Harvest_2003	Meat from mammals other than marine mammals, NES	1205	22	1.83%	1.4	0.9	3.1
Children	Philippines	Harvest_2003	Pork and other porcines	1205	395	32.78%	1.4	1.5	5.2
Children	Republic of Korea	KNHNES	Beef and other bovines meat	654	255	38.99%	1.1	1.3	4.9
Children	Republic of Korea	KNHNES	Pork and other porcines	654	329	50.31%	1.9	2.0	6.5
Children (2-16 yrs)	Australia	2007 ANCNPAS	Beef and other bovines meat	4487	3898	86.87%	1.8	1.9	6.8
Children (2-16 yrs)	Australia	2007 ANCNPAS	Pork and other porcines	4487	3594	80.10%	0.9	1.2	4.1
Children (2-16 yrs)	Australia	2007 ANCNPAS	Sheep and other ovines	4487	2479	55.25%	0.6	1.1	4.0
Children (2-6 yrs)	Australia	2007 ANCNPAS	Beef and other bovines meat	1463	1226	83.80%	2.3	2.1	8.4
Children (2-6 yrs)	Australia	2007 ANCNPAS	Pork and other porcines	1463	1114	76.14%	1.3	1.4	5.1
Children (2-6 yrs)	Australia	2007 ANCNPAS	Sheep and other ovines	1463	741	50.65%	0.7	1.2	4.4
Infants	Bulgaria	NUTRICHILD	Beef and other bovines meat	860	89	10.35%	2.7	1.6	7.8
Infants	Bulgaria	NUTRICHILD	Pork and other porcines	860	9	1.05%	2.3	2.2	7.3
Infants	Bulgaria	NUTRICHILD	Sheep and other ovines	860	2	0.23%	2.4	1.0	3.1
Infants	Italy	INRAN_ SCAI_2005_06	Beef and other bovines meat	16	1	6.25%	3.8		3.8
Infants	Italy	INRAN_ SCAI_2005_06	Pork and other porcines	16	1	6.25%	1.0		1.0
Infants	Italy	INRAN_ SCAI_2005_06	Sheep and other ovines	16	1	6.25%	1.3		1.3
Other children	Belgium	Regional_Flanders	Meat from mammals other than marine mammals, nes	625	16	2.56%	1.2	0.8	3.3

Table 1.15 (continued)

Age class	Country	Survey	Meat type	No. of subjects	No. of consumers	Percentage of consumers	Consumers, mean consumption (g/bw per day)	Consumers, STD (g/bw per day)	Consumers, P975 (g/bw per day)
Other children	Belgium	Regional_Flanders	Sheep and other ovines	625	10	1.60%	1.4	0.6	2.3
Other children	Belgium	Regional_Flanders	Beef and other bovines meat	625	185	29.60%	1.4	0.8	3.1
Other children	Belgium	Regional_Flanders	Horse and other equines	625	8	1.28%	1.3	0.6	2.2
Other children	Belgium	Regional_Flanders	Pork and other porcines	625	121	19.36%	1.2	0.7	3.1
Other children	Bulgaria	NUTRICHILD	Beef and other bovines meat	433	276	63.74%	2.6	1.8	7.2
Other children	Bulgaria	NUTRICHILD	Pork and other porcines	433	37	8.55%	1.9	1.2	6.2
Other children	Bulgaria	NUTRICHILD	Sheep and other ovines	433	8	1.85%	1.8	1.2	3.2
Other children	Czech Republic	SISP04	Beef and other bovines meat	389	125	32.13%	1.7	1.2	4.5
Other children	Czech Republic	SISP04	Pork and other porcines	389	121	31.11%	2.0	1.3	5.8
Other children	Denmark	Danish_Dietary_Survey	Beef and other bovines meat	490	482	98.37%	0.9	0.6	2.3
Other children	Denmark	Danish_Dietary_Survey	Pork and other porcines	490	480	97.96%	1.1	0.8	3.0
Other children	Denmark	Danish_Dietary_Survey	Sheep and other ovines	490	25	5.10%	0.6	0.3	1.3
Other children	Finland	DIPP	Beef and other bovines meat	933	634	67.95%	1.4	1.1	4.6
Other children	Finland	STRIP	Beef and other bovines meat	250	81	32.40%	0.8	0.6	2.1
Other children	Finland	DIPP	Pork and other porcines	933	373	39.98%	1.0	1.2	3.8
Other children	Finland	STRIP	Pork and other porcines	250	64	25.60%	0.8	0.6	2.4
Other children	Finland	DIPP	Sheep and other ovines	933	23	2.47%	0.6	0.4	1.5

Table 1.15 (continued)

Age class	Country	Survey	Meat type	No. of subjects	No. of consumers	Percentage of consumers	Consumers, mean consumption (g/bw per day)	Consumers, STD (g/bw per day)	Consumers, P975 (g/bw per day)
Other children	Finland	STRIP	Sheep and other ovines	250	4	1.60%	1.0	1.1	2.6
Other children	France	INCA2	Beef and other bovines meat	482	440	91.29%	1.5	1.0	3.9
Other children	France	INCA2	Horse and other equines	482	9	1.87%	0.7	0.2	1.1
Other children	France	INCA2	Meat from mammals other than marine mammals, NES	482	175	36.31%	0.2	0.4	1.7
Other children	France	INCA2	Pork and other porcines	482	227	47.10%	0.7	0.5	1.8
Other children	France	INCA2	Sheep and other ovines	482	130	26.97%	0.4	0.3	1.4
Other children	Greece	Regional_Crete	Beef and other bovines meat	839	24	2.86%	1.3	0.8	3.1
Other children	Greece	Regional_Crete	Goat and other caprines	839	23	2.74%	1.5	0.8	3.5
Other children	Greece	Regional_Crete	Meat from mammals other than marine mammals, NES	839	54	6.44%	1.5	0.9	3.8
Other children	Greece	Regional_Crete	Pork and other porcines	839	288	34.33%	1.7	0.9	3.9
Other children	Greece	Regional_Crete	Sheep and other ovines	839	149	17.76%	1.3	0.7	3.7
Other children	Italy	INRAN_ SCAI_2005_06	Beef and other bovines meat	193	151	78.24%	2.0	1.4	6.0
Other children	Italy	INRAN_ SCAI_2005_06	Horse and other equines	193	1	0.52%	1.7		1.7
Other children	Italy	INRAN_ SCAI_2005_06	Pork and other porcines	193	71	36.79%	1.2	0.9	3.2
Other children	Italy	INRAN_ SCAI_2005_06	Sheep and other ovines	193	4	2.07%	1.0	0.7	1.9
Other children	Latvia	EFSA_TEST	Beef and other bovines meat	189	6	3.17%	1.2	0.3	1.8

Table 1.15 (continued)

Age class	Country	Survey	Meat type	No. of subjects	No. of consumers	Percentage of consumers	Consumers, mean consumption (g/bw per day)	Consumers, STD (g/bw per day)	Consumers, P975 (g/bw per day)
Other children	Latvia	EFSA_TEST	Meat from mammals other than marine mammals, NES	189	2	1.06%	1.4	0.7	1.9
Other children	Latvia	EFSA_TEST	Pork and other porcines	189	105	55.56%	1.6	1.1	4.5
Other children	Netherlands	VCP_kids	Beef and other bovines meat	957	255	26.65%	1.2	1.0	3.4
Other children	Netherlands	VCP_kids	Horse and other equines	957	2	0.21%	0.3	0.1	0.4
Other children	Netherlands	VCP_kids	Pork and other porcines	957	167	17.45%	1.1	0.8	3.0
Other children	Netherlands	VCP_kids	Sheep and other ovines	957	10	1.04%	0.6	0.3	1.3
Other children	Spain	NUT_INK05	Beef and other bovines meat	399	155	38.85%	2.3	1.4	6.1
Other children	Spain	enKid	Horse and other equines	156	1	0.64%	3.9		3.9
Other children	Spain	NUT_INK05	Horse and other equines	399	2	0.50%	3.1	1.3	4.1
Other children	Spain	enKid	Meat from mammals other than marine mammals, NES	156	44	28.21%	2.4	1.4	6.4
Other children	Spain	enKid	Pork and other porcines	156	32	20.51%	1.8	1.0	4.6
Other children	Spain	NUT_INK05	Pork and other porcines	399	124	31.08%	1.5	0.9	3.7
Other children	Spain	enKid	Sheep and other ovines	156	5	3.21%	2.7	1.0	3.8
Other children	Spain	NUT_INK05	Sheep and other ovines	399	12	3.01%	1.9	1.2	4.9
Other children	Sweden	NFA	Beef and other bovines meat	1473	826	56.08%	0.6	0.5	1.9
Other children	Sweden	NFA	Horse and other equines	1473	15	1.02%	0.2	0.2	0.7

Table 1.15 (continued)

Age class	Country	Survey	Meat type	No. of subjects	No. of consumers	Percentage of consumers	Consumers, mean consumption (g/bw per day)	Consumers, STD (g/bw per day)	Consumers, P975 (g/bw per day)
Other children	Sweden	NFA	Pork and other porcines	1473	536	36.39%	0.9	0.7	2.7
Other children	Sweden	NFA	Sheep and other ovines	1473	15	1.02%	0.6	0.4	1.7
Toddlers	Belgium	Regional_Flanders	Beef and other bovines meat	36	12	33.33%	1.4	0.8	3.0
Toddlers	Belgium	Regional_Flanders	Meat from mammals other than marine mammals, NES	36	2	5.56%	1.8	0.7	2.3
Toddlers	Belgium	Regional_Flanders	Horse and other equines	36	1	2.78%	5.0		5.0
Toddlers	Belgium	Regional_Flanders	Pork and other porcines	36	11	30.56%	2.1	2.0	7.3
Toddlers	Bulgaria	NUTRICHILD	Beef and other bovines meat	428	229	53.50%	2.8	2.0	7.5
Toddlers	Bulgaria	NUTRICHILD	Pork and other porcines	428	26	6.07%	1.6	1.2	5.5
Toddlers	Bulgaria	NUTRICHILD	Sheep and other ovines	428	11	2.57%	1.6	1.0	4.0
Toddlers	Finland	DIPP	Beef and other bovines meat	497	406	81.69%	2.0	1.6	6.4
Toddlers	Finland	DIPP	Pork and other porcines	497	326	65.59%	1.4	1.4	4.8
Toddlers	Finland	DIPP	Sheep and other ovines	497	26	5.23%	1.0	0.8	4.5
Toddlers	Italy	INRAN_ SCAI_2005_06	Beef and other bovines meat	36	20	55.56%	2.4	1.6	6.3
Toddlers	Italy	INRAN_ SCAI_2005_06	Pork and other porcines	36	7	19.44%	0.6	0.2	1.1
Toddlers	Italy	INRAN_ SCAI_2005_06	Sheep and other ovines	36	2	5.56%	1.6	0.7	2.1
Toddlers	Netherlands	VCP_kids	Beef and other bovines meat	322	84	26.09%	1.4	1.2	4.8
Toddlers	Netherlands	VCP_kids	Pork and other porcines	322	47	14.60%	1.2	1.1	4.0
Toddlers	Netherlands	VCP_kids	Sheep and other ovines	322	1	0.31%	1.0		1.0
Toddlers	Spain	enKid	Meat from mammals other than marine mammals, NES	17	3	17.65%	3.6	0.5	4.1
Toddlers	Spain	enKid	Sheep and other ovines	17	2	11.76%	1.1	0.5	1.4

Table 1.15 (continued)

Age class	Country	Survey	Meat type	No. of subjects	No. of consumers	Percentage of consumers	Consumers, mean consumption (g/bw per day)	Consumers, STD (g/bw per day)	Consumers, P975 (g/bw per day)
Children (1–3 yrs)	USA	FCID-WWEIA data for years 2005–2010	Total red meat	5,338	2451	45.92%	2.4		7.04
Children (3–16 yrs)	USA	FCID-WWEIA data for years 2005–2010	Total red meat	12521	9605	76.71%	1.7		4.98

NES, not elsewhere specified

Data on USA from FCID (2015): What We Eat In America - Food Commodity Intake Database 2005-10, U.S. Environmental Protection Agency - Office of Pesticide Programs © University of Maryland 2012 – 2016. Available from: http://fcid.foodrisk.org/percentiles.php

Data for other countries from FAO/WHO (2015): the FAO/WHO Chronic individual food consumption database – Summary statistics (CIFOCOss), © Copyright World Health Organization (WHO), 2016. All Rights Reserved. Available from: http://www.who.int/foodsafety/databases/en/

consumption for consumers were up to 90 and 150 g/day, respectively (FAO/WHO, 2015; Table 1.14, Table 1.15).

(d) Offal consumption

The per capita consumption of mammalian offal worldwide was generally lower than 10 g/day per person, except for Australia and European countries, where the highest levels (15 g/day per person) were reported by GEMS clusters diets (WHO, 2013). From National food consumption surveys, high mean consumption for consumers only was reported for a limited proportion of the population. For example, in Brazil, the average consumption of mammalian offal in the general population was 84 g/day per person for 3.5% of consumers (FAO/WHO, 2015). In Germany, the mean consumption of cattle offal for adults was 53 g/day per person for 0.3% of consumers. In China, the consumption of mammalian offal by the general population was 44 g/day per person for 3.5% of consumers. It should be noted that high consumers can eat up to about 260 g/day per person of mammalian offal (Brazil), and in such situations, offal was a likely substitute for other meat products (FAO/WHO, 2015).

(e) Processed meat consumption

The consumption of processed meat is more difficult to estimate than that of red meat, as it is a heterogeneous food group with different definitions across countries. Detailed worldwide data on processed meat consumption (g/kg bw per day) are presented in Table 1.16 and Table 1.17 for adults and children, respectively.

According to the per capita data collected by FAOSTAT, the total processed meat consumption was between 0 and 33 g/day (FAO/WHO, 2015). Based on the GEMS cluster diets, the total processed meat consumption ranged from less than 1 to 18 g/day (WHO, 2013).

In the NutriCoDE study, the median of mean consumption of processed meat ranged from 3.9 g/day (1.8–5.1 g/day) for the first quintile to 34 g/day (26–76 g/day) for the fifth quintile (Imamura et al., 2015).

These levels of consumption of processed meat were consistent with those in Japan, where the percentage of consumers was about 97%, the mean consumption was 14 g/day, and the consumption at the 95th percentile was 34 g/day (FAO/WHO, 2015; Table 1.16). On the contrary, in China, the percentage of consumers of processed meat was about 2–3.8% of the total population; however, for this group, the mean consumption and the consumption at the 95th percentile were 66 and 182 g/day, respectively (FAO/WHO, 2015; Table 1.16). Based on three consecutive 24-hour recalls, a prospective study of 5000 adults from 4280 households in nine provinces showed that the average processed meat consumption increased by three-fold (5 vs 15 g/day per person) from 1989 to 2004 (Zhai et al., 2009).

Intake of processed meat in countries of the Middle East and north Africa was estimated in 2010 to range from 2.5 g/day (Palestine) to 6.7 g/day (United Arab Emirates) (Afshin et al., 2015).

In New Zealand, the mean consumption of sausages and processed meat was 110 g/day for women and 142 g/day for men. At the 90th percentile, the consumption reached 212 g/day for women and 300 g/day for men. In addition, the percentage of consumers older than 15 years was about 16% of the population (Parnell et al., 2012).

In Brazil, the percentage of consumers of processed meat was about 27% of the total population; however, for this group, the mean consumption and the consumption at the 95th percentile were 33 and 94 g/day, respectively (FAO/WHO, 2015; Table 1.16).

In the USA, detailed results were available for processed meat from game, beef, goat, and pork. Interestingly, the percentage of consumers ranged from 0.07% (processed goat meat) to 65% (processed beef meat), but the mean consumption ranged from 42 to 99 g/day, and the consumption

Table 1.16 Worldwide consumption of processed meat in adults

Age class	Country	Survey	Meat type	No. of subjects	No. of consumers	Percentage of consumers	Consumers, mean consumption (g/bw per day)	Consumers, STD (g/bw per day)	Consumers, P975 (g/bw per day)
General population	Brazil	Brazilian Institute of Geography and Statistics	Processed meat and meat products, NES	34 003	334	0.98%	0.6	0.6	2.1
General population	Brazil	Brazilian Institute of Geography and Statistics	Processed meat and meat products, NES	34 003	9047	26.61%	0.5	0.5	1.8
General population	Brazil	Brazilian Institute of Geography and Statistics	Processed meat and meat products, NES	34 003	54	0.16%	1.2	0.8	2.6
General population	Brazil	Brazilian Institute of Geography and Statistics	Processed meat and meat products, NES	34 003	14	0.04%	1.4	0.8	3.6
General population	Brazil	Brazilian Institute of Geography and Statistics	Processed meat and meat products, NES	34 003	8	0.02%	0.5	0.2	0.8
General population	Brazil	Brazilian Institute of Geography and Statistics	Processed meat and meat products, NES	34 003	24	0.07%	0.9	0.7	2.1
General population	China	2002 China Nutrition and Health Survey	Processed meat and meat products, NES	65 359	1430	2.19%	1.2	1.1	4.2
General population	China	2002 China Nutrition and Health Survey	Processed meat and meat products, NES	65 359	2483	3.80%	0.9	1.3	2.7
General population	Japan	DSFFQ _FI	Processed meat and meat products, NES	2711	2642	97.45%	0.3	0.2	0.8
General population	Japan	DSFFQ _FI	Processed meat and meat products, NES	2711	24	0.89%	0.0	0.0	
Adults	Belgium	Diet_National_2004	Processed meat and meat products, NES	1304	956	73.31%	0.8	0.7	2.7
Adults	Czech Republic	SISP04	Processed meat and meat products, NES	1666	1427	85.65%	1.2	1.0	3.9
Adults	Denmark	Danish Dietary Survey	Processed meat and meat products, NES	2822	2800	99.22%	0.4	0.3	1.3
Adults	Finland	FINDIET_2007	Processed meat and meat products, NES	1575	1188	75.43%	0.7	0.7	2.9

Table 1.16 (continued)

Age class	Country	Survey	Meat type	No. of subjects	No. of consumers	Percentage of consumers	Consumers, mean consumption (g/bw per day)	Consumers, STD (g/bw per day)	Consumers, P975 (g/bw per day)
Adults	France	INCA2	Processed meat and meat products, NES	2276	2167	95.21%	0.6	0.4	1.6
Adults	Hungary	National_Repr_Surv	Processed meat and meat products, NES	1074	1003	93.39%	1.1	0.8	3.0
Adults	Ireland	NSIFCS	Processed meat and meat products, NES	958	906	94.57%	0.8	0.6	2.1
Adults	Italy	INRAN_ SCAI_2005_06	Processed meat and meat products, NES	2313	1921	83.05%	0.5	0.4	1.6
Adults	Latvia	EFSA_TEST	Processed meat and meat products, NES	1306	868	66.46%	0.9	0.7	2.8
Adults	Netherlands	DNFCS_2003	Processed meat and meat products, NES	750	618	82.40%	0.7	0.6	2.4
Adults	Spain	AESAN	Processed meat and meat products, NES	410	334	81.46%	0.9	0.7	2.5
Adults	Spain	AESAN_FIAB	Processed meat and meat products, NES	981	908	92.56%	0.8	0.6	2.5
Adults	Sweden	Riksmaten_1997_98	Processed meat and meat products, NES	1210	1147	94.79%	0.7	0.4	1.6
Adults	United Kingdom	NDNS	Processed meat and meat products, NES	1724	1492	86.54%	0.5	0.4	1.4

NES, not elsewhere specified

Data on USA from FCID (2015): What We Eat In America – Food Commodity Intake Database 2005–10, US. Environmental Protection Agency – Office of Pesticide Programs © University of Maryland 2012 – 2016. Available from: http://fcid.foodrisk.org/percentiles.php

Data for other countries from FAO/WHO (2015): the FAO/WHO Chronic individual food consumption database – Summary statistics (CIFOCOss), © Copyright World Health Organization (WHO), 2016. All Rights Reserved. Available from: http://www.who.int/foodsafety/databases/en/

Table 1.17 Worldwide consumption of processed meat in children

Age class	Country	Survey	Meat type	No. of subjects	No. of consumers	Percentage of consumers	Consumers, Mean consumption (g/bw per day)	Consumers, STD (g/bw per day)	Consumers, P975 (g/bw per day)
Adolescents	Belgium	Diet_National_2004	Processed meat and meat products, NES	584	413	70.72%	0.8	0.7	2.7
Adolescents	Cyprus	Child health	Processed meat and meat products, NES	303	183	60.40%	0.4	0.3	1.1
Adolescents	Czech Republic	SISP04	Processed meat and meat products, NES	298	274	91.95%	1.4	1.2	4.6
Adolescents	Denmark	Danish Dietary Survey	Processed meat and meat products, NES	479	477	99.58%	0.6	0.5	2.0
Adolescents	France	INCA2	Processed meat and meat products, NES	973	950	97.64%	0.7	0.5	2.2
Adolescents	Italy	INRAN_ SCAI_2005_06	Processed meat and meat products, NES	247	216	87.45%	0.8	0.6	2.2
Adolescents	Latvia	EFSA_TEST	Processed meat and meat products, NES	470	333	70.85%	1.2	1.0	3.7
Adolescents	Spain	enKid	Processed meat and meat products, NES	209	190	90.91%	1.6	1.3	5.3
Adolescents	Spain	AESAN_FIAB	Processed meat and meat products, NES	86	81	94.19%	1.0	0.7	2.7
Adolescents	Spain	NUT_INK05	Processed meat and meat products, NES	651	574	88.17%	1.1	0.9	3.4
Adolescents	Sweden	NFA	Processed meat and meat products, NES	1018	918	90.18%	1.0	0.8	2.5
Children	China	2002 China Nutrition and Health Survey	Processed meat and meat products, NES	2784	78	2.80%	2.2	1.5	6.8
Children	China	2002 China Nutrition and Health Survey	Processed meat and meat products, NES	2784	78	2.80%	2.2	6.3	8.9
Children	Japan	DSFFQ _FI	Processed meat and meat products, NES	71	71	100.00%	0.8	0.6	2.6
Infants	Bulgaria	NUTRICHILD	Processed meat and meat products, NES	860	33	3.84%	2.1	1.3	6.3
Infants	Italy	INRAN_ SCAI_2005_06	Processed meat and meat products, NES	16	1	6.25%	1.5		1.5

Table 1.17 (continued)

Age class	Country	Survey	Meat type	No. of subjects	No. of consumers	Percentage of consumers	Consumers, Mean consumption (g/bw per day)	Consumers, STD (g/bw per day)	Consumers, P975 (g/bw per day)
Other children	Belgium	Regional Flanders	Processed meat and meat products, NES	625	468	74.88%	1.5	1.3	4.7
Other children	Bulgaria	NUTRICHILD	Processed meat and meat products, NES	433	261	60.28%	1.9	1.6	5.7
Other children	Czech Republic	SISP04	Processed meat and meat products, NES	389	314	80.72%	1.6	1.4	5.5
Other children	Denmark	Danish Dietary Survey	Processed meat and meat products, NES	490	488	99.59%	1.3	0.9	4.0
Other children	Finland	STRIP	Processed meat and meat products, NES	250	218	87.20%	1.3	1.0	3.9
Other children	Finland	DIPP	Processed meat and meat products, NES	933	825	88.42%	1.8	1.6	6.1
Other children	France	INCA2	Processed meat and meat products, NES	482	465	96.47%	1.3	0.9	3.5
Other children	Greece	Regional Crete	Processed meat and meat products, NES	839	327	38.97%	0.5	0.5	1.8
Other children	Italy	INRAN_ SCAI_2005_06	Processed meat and meat products, NES	193	157	81.35%	1.2	1.0	4.0
Other children	Latvia	EFSA_TEST	Processed meat and meat products, NES	189	113	59.79%	1.8	1.6	6.4
Other children	Netherlands	VCP kids	Processed meat and meat products, NES	957	748	78.16%	1.6	1.2	4.5
Other children	Spain	enKid	Processed meat and meat products, NES	156	138	88.46%	2.2	1.5	6.5
Other children	Spain	NUT_INK05	Processed meat and meat products, NES	399	357	89.47%	1.7	1.2	4.5
Other children	Sweden	NFA	Processed meat and meat products, NES	1473	1379	93.62%	1.5	1.1	4.3
Toddlers	Belgium	Regional Flanders	Processed meat and meat products, NES	36	24	66.67%	1.9	1.2	5.7
Toddlers	Bulgaria	NUTRICHILD	Processed meat and meat products, NES	428	164	38.32%	2.0	1.5	5.2

Table 1.17 (continued)

Age class	Country	Survey	Meat type	No. of subjects	No. of consumers	Percentage of consumers	Consumers, Mean consumption (g/bw per day)	Consumers, STD (g/bw per day)	Consumers, P975 (g/bw per day)
Toddlers	Finland	DIPP	Processed meat and meat products, NES	497	142	28.57%	1.5	1.6	5.5
Toddlers	Italy	INRAN_ SCAI_2005_06	Processed meat and meat products, NES	36	22	61.11%	1.6	1.2	5.6
Toddlers	Netherlands	VCP kids	Processed meat and meat products, NES	322	254	78.88%	1.8	1.6	6.5
Toddlers	Spain	enKid	Processed meat and meat products, NES	17	13	76.47%	2.7	1.8	6.9

NES, not elsewhere specified

Data on USA from FCID (2015): What We Eat In America – Food Commodity Intake Database 2005–10, United States Environmental Protection Agency – Office of Pesticide Programs © University of Maryland 2012 – 2016. Available from: http://fcid.foodrisk.org/percentiles.php

Data for other countries from FAO/WHO (2015): the FAO/WHO Chronic individual food consumption database – Summary statistics (CIFOCOss), © Copyright World Health Organization (WHO), 2016. All Rights Reserved. Available from: http://www.who.int/foodsafety/databases/en/

at the 95th percentile ranged from 152 to 309 g/day (FCID, 2015).

In Europe, the mean consumption of processed meat for adults was between about 10 and 80 g/day. The consumption at the 95th percentile was up to 200 g/day (EFSA, 2011). In the EPIC cohort, the lowest consumption of processed meat was found in Greece, with 11 g/day for women and 19 g/day for men. The highest consumption of processed meat was found in Norway for women (48 g/day) and in Germany for men (89 g/day) (Linseisen et al., 2006).

[The Working Group noted that despite the weaknesses of the data set, it seemed that in certain countries the consumption of processed meat is similar to the consumption of red meat for consumers only. However, the percentage of consumers of processed meat seemed to be much smaller, leading to a per capita consumption four to five times lower than that of red meat.]

(f) Dietary exposure to chemicals in meat

(i) Chemicals in the environment

Several chemicals classified as carcinogens by the International Agency for Research on Cancer (IARC) are present in the environment and can contaminate meat through air, water, or animal feed. They can be generated either from industrial activities or from microorganisms (IARC, 2010a, b, 2012a, b, 2016).

Dioxin and dioxin-like compounds: The Joint FAO/WHO Expert Committee on Food Additives (JECFA) assessed dioxins and related compounds in 2002. The dietary exposure estimate, expressed as toxic equivalency factors for PCDDs and PCDFs based on national data, ranged from 33 to 42 pg/kg bw per month and from 81 to 100 pg/kg bw per month at the 50th and 90th percentiles, respectively. For coplanar PCBs, the dietary exposure estimate ranged from 9 to 47 pg/kg bw per month and from 25 to 130 pg/kg bw per month at the 50th and 90th percentiles, respectively. The contribution from meat was estimated to range from 6% in Asia to 23% in north America for PCDDs and PCDFs, and from 4% in Asia to 55% in north America for dioxin-like PCBs (JECFA, 2002).

Brominated flame retardants (BFRs): Food consumption, especially fish and meat product consumption, is a major route of human contamination (Lyche et al., 2015). For example, higher levels of PBDEs in humans were found in studies in the USA where fish were most highly contaminated (median, 616 pg/g), followed by meat (median, 190 pg/g). However, unlike many European countries where fish consumption predominates, dietary intake of PBDEs in the USA is mostly from meat consumption (Schecter et al., 2008).

Heavy metals: The heavy metals cadmium, arsenic, and lead have been classified as carcinogens by IARC (IARC, 2012a). For the EU, the European Food Safety Authority (EFSA) has estimated that average weekly dietary exposure to cadmium was 2.04 µg/kg bw, and at the 95th percentile, weekly dietary exposure to cadmium was 3.66 µg/kg bw. Food consumed in larger quantities had the greatest impact on dietary exposure to cadmium. This was true for the broad food categories of grains and grain products (26.9%). Meat and edible offal were estimated to contribute 7.7% of the total dietary exposure (EFSA, 2012). In 2010, JECFA estimated that for adults, the mean dietary exposure to cadmium was 2.2–12 µg/kg bw per month, and high-level dietary exposure to cadmium was 6.9–12.1 µg/kg bw per month. For children aged 6 months to 12 years, the mean dietary exposure to cadmium was 3.9–20.6 µg/kg bw per month. Meat was not part of the food groups that contributed significantly (40–85%) to the total dietary

exposure to cadmium (i.e. rice, wheat, vegetables, and molluscs) (JECFA, 2013).

Dietary exposure to inorganic arsenic was last evaluated by JECFA in 2011. The occurrence of total arsenic in meat ranged from 0.004 to 0.78 mg/kg, and meat was not a major contributor to dietary exposure to inorganic arsenic (JECFA, 2011).

Lead was last evaluated by JECFA in 2011. Mean dietary exposure to lead ranged from 0.02 to 3 µg/kg bw per day for adults, and from 0.03 to 9 µg/kg bw per day for children. The contribution of meat and meat products, including offal, was estimated to be 9% of the total dietary exposure to lead (JECFA, 2013).

Mycotoxins: EFSA concluded that carry-over of aflatoxin, deoxynivalenol, zearalenone, and fumonisin to products of animal origin was very low (EFSA, 2004a, b, c, 2005c; Kan & Meijer, 2007). Accumulation of ochratoxin A occurred predominantly in the blood, liver, and kidney. Muscle, milk, and eggs contained much lower levels of this mycotoxin (EFSA, 2004d).

(ii) Chemicals from cooking practices

Heterocyclic aromatic amines (HAAs): No international dietary exposure assessment was available for HAAs; however, in the EPIC study, dietary exposure to HAAs was estimated in the Heidelberg cohort (Germany) using a detailed dietary questionnaire that assessed meat consumption, cooking methods, and degree of browning of the respective food items. Results based on total meat consumption (including poultry meat) showed a total median exposure to HAAs of 30.6 ng/day (13–71.3 ng/day) (Rohrmann et al., 2007). Other studies' results showed a significantly lower dietary exposure to HAAs for Europe (6.1 ng/kg bw per day) (Zimmerli et al., 2001) and the USA (11.0–19.9 ng/kg bw per day) (Keating & Bogen, 2004).

Polycyclic aromatic hydrocarbons (PAHs): In 2006, JECFA estimated the dietary exposure to PAHs in 18 countries, including Australia, Brazil, New Zealand, and the United Kingdom. Estimated intake of BaP ranged from < 1 to 2.0 µg/day and from 0.0001 to 0.005 µg/kg bw per day. For the other nine PAHs, intake ranged from less than 1 to ~12 µg/day and from 0.0001 to 0.015 µg/kg bw per day (WHO, 2006). Generally, despite high concentrations of PAHs, meat and barbecued foods were not major contributors to PAH exposure; however, in the USA, grilled and barbecued meat was estimated to contribute to 21% of the intake of BaP (WHO, 2006). Cereals, vegetal oil, animal fat, and vegetal fat contributed up to 60% to the whole food intake of PAHs, as they are major contributors by weight to the total diet (Dennis et al., 1983).

Nitrosamines: The main sources of NOCs in the diet are nitrite-preserved meat products (Tricker, 1997; Haorah et al., 2001). Haorah et al. (2001) reported a mean concentration of 5.5 µmol/kg of NOCs in frankfurters, but only 0.5 µmol/kg of NOCs in fresh meat.

Acrylamide: Acrylamide may occur in meat during cooking (Tareke et al., 2002). However, meat has been estimated to be a minor contributor, between 0.2% and 2% of total dietary intake (WHO, 2006).

1.4 Exposure assessment and biological markers

1.4.1 Questionnaires

A description of the epidemiological studies included in this *Monograph*, in terms of their study design, is provided in Section 2. A review of dietary assessment methodologies used in the epidemiological studies is beyond the scope of this *Monograph* (e.g. Thompson & Subar, 2013).

The majority of the studies used food frequency questionnaires (FFQs) to assess individual meat intake (including red meat and processed meat). FFQs are typically used in epidemiological studies to measure usual dietary intake in individuals for several reasons. First, FFQs are a feasible approach in case–control studies, where usual diet must be ascertained retrospectively (often from the distant past). Second, in large prospective cohort studies, FFQs can be distributed by mail or online to a large number of participants; are self-administered (typically); may be optically scanned, computer-assisted, or web-based; and are analysed using precoded foods/food groups and portion sizes.

The FFQ approach asks respondents to report their usual frequency of consumption for each food from a list of foods during a specific period of time (several months or a year). FFQs are generally used for ranking subjects according to food or nutrient intake, rather than for estimating absolute levels of intake. In addition, they are widely used in case–control and cohort studies to assess an association between dietary intake and disease risk (Kushi, 1994; Beaton, 1994; Sempos et al., 1999).

The ability to quantify total dietary intake depends on the number of food items listed in the FFQ, on the level of detail collected within the questionnaire, on whether portion sizes for the foods/food groups are included, and on the timeframe of intake or reference period used. For red meat and processed meat specifically, the classifications used to define red meat and processed meat as a food category also influence the calculation of total dietary intake (Block et al. 1986; Rimm et al., 1992).

Although food lists included in FFQs vary based on the purpose of the study and the study population, the appropriateness of the food lists is crucial. The full variability of an individual's diet, which includes many foods and mixed dishes, cannot be captured by a finite food list. Ollberding et al. (2012), for example, identified a food list for their FFQ using 3-day measured food records that could capture 85% or more of the intake of key nutrients and also food items traditionally consumed by the populations represented in the Multiethnic Cohort Study.

Many FFQs have been developed and adapted to suit different research questions and populations. In the USA, for example, several questionnaires are commonly used (and are cited in this *Monograph*), including:

Health Habits and History Questionnaire (HHHQ) or Block questionnaire (Block et al., 1986, 1990; Sobell et al., 1989): This is a semiquantitative food frequency questionnaire (SQFFQ) originally developed by the National Cancer Institute (NCI). The SQFFQ collects portion size information; however, portion sizes are specified as standardized portions or by choosing from a range of portions sizes (e.g. small, medium, or large). The original Block FFQ has been modified, and is continually updated by researchers to suit their research questions and populations.

Harvard FFQ or Willett questionnaire (Caan et al., 1998; McCann et al., 1999): This FFQ was developed at Harvard University. Standard portion size defaults are included as part of the food items listed, rather than as a separate listing.

NCI Diet History Questionnaire (DHQ): The DHQ was designed with an emphasis on cognitive ease of use for respondents (Subar et al., 1995, 2001). It is an SQFFQ, which uses an embedded question approach, that was developed by NCI.

Definitions of red meat and processed meat as a food category varied across the studies included in this *Monograph*. Red meat was commonly defined as beef, pork, lamb, or a combination thereof, and processed meat was generally defined as meat made largely from pork, beef, or poultry that undergoes methods of preservation,

such as curing, smoking, or drying (Santarelli et al., 2008). While many studies explicitly defined these classifications (Tiemersma et al., 2002; Ferrucci et al., 2009; Cross et al., 2010), other studies provided either no description or an unclear description of these classifications (Kato et al., 1997; Järvinen et al., 2001). The level of detail collected by the epidemiological studies, in terms of meat intake, varied widely. Most studies reported the association between categories of meat intake labelled "red meat" or "processed meat" and cancer risk; however, several studies reported results for individual red meat items (e.g. beef or pork) (Brink et al., 2005; Norat et al., 2005; Sato et al., 2006; Takachi et al., 2011; Egeberg et al., 2013) and/or processed meat items (e.g., hot dogs or bacon). The studies that included detailed information on the intake of specific processed meat items were superior to those that combined generic items into one food group or one-line items (e.g. "processed meat"), as the amount of nitrate, nitrite, and haem iron in processed foods can vary dramatically.

(a) Portion size

Scientists have used many methods to improve assessment of portion size in the studies included in this report. For example, Pietinen et al. (1999) included a portion size booklet of 122 photographs of foods, each with three to five different portion sizes. In the Canadian National Breast Screening Study (CNBSS), Kabat et al. (2007) also included photographs of portion sizes to improve portion size assessment. In the Finnish Mobile Clinic Health Examination Survey, Järvinen et al. (2001) used plastic food models and real foods to help estimate portion sizes for their interviewer-assisted FFQ. Dixon et al. (2004) also used three-dimensional food models, plastic cups, and spoons to help participants identify usual serving sizes in the Kaiser Permanente Medical Care Program in northern California, USA.

(b) Validation and calibration

The relative validity of an FFQ provides information on how well the instrument is measuring what it is intended to measure. This is completed by comparing intake assessed using an FFQ with intake assessed using a reference method (which is deemed to be superior) in the same individuals (e.g. an interviewer-led dietary history or multiple 24-hour recalls). FFQs may often be validated for their ability to assess total energy intake in comparison with the doubly labelled water technique (Hill & Davies, 2001). The superior method is often prohibitive for use in large epidemiological studies due to participant burden, or overall cost of administering and coding the instrument. Calibration studies are used to calibrate an FFQ to a reference method using a regression model. Many of the studies included in this *Monograph* used various statistical methods, employing measurement error models and energy adjustment to assess the validity of the FFQs and to adjust estimates of the relative risks for disease outcomes (Bingham & Day, 1997; Kipnis et al., 1997; Carroll et al., 1998; Hu et al., 1999). For example, in the National Institutes of Health – American Association of Retired Persons (NIH-AARP) Diet and Health Study, the FFQ used was calibrated against two non-consecutive 24-hour dietary recalls (Cross et al., 2010). In the EPIC study, investigators used a computerized 24-hour dietary recall method to calibrate dietary measurements across countries and to correct for systematic over- or underestimation of dietary intake (Norat et al., 2005; Pala et al., 2009). Tiemersma et al. (2002) validated their short SQFFQ using a dietary history method, which is a robust, interviewer-administered dietary assessment method. Each study included in this *Monograph* was examined to determine whether the FFQ used to assess red meat and processed meat exposure had been validated (see Section 2).

(i) Heterocyclic aromatic amines

Assessment of dietary HAA intake is challenging, as HAA concentrations vary greatly according to cooking technique, temperature, cooking time, and meat type (Sinha et al., 1995; Knize et al., 1998; Sinha et al., 1998a, b). Epidemiological studies have tried to overcome these difficulties using surrogate markers of HAA intake, such as method of cooking, surface browning, total cooking time, and gravy intake.

To estimate the intake of these cooked meat mutagens, a detailed meat-cooking module was developed. The meat-cooking module was a modified version of the 1992, 100-item, self-administered HHHQ to assess usual dietary intake over the past year (Block et al., 1986). An interviewer-administered questionnaire on meat-cooking practices was also used to assess the consumption of 23 meat, poultry, and fish items using a matrix similar to the 100-item HHHQ. The questionnaire collected information on cooking methods; embedded questions assessed how well the meat was cooked. Portion size was estimated as small, medium, or large, relative to the standard portion size indicated for each food listed in the questionnaire and meat-cooking module. A mutagen database, called Computerized Heterocyclic Amines Resource for Research in Epidemiology of Disease (CHARRED), developed by NCI/NIH (NCI, 2017) was used to estimate the intake of mutagenic compounds from cooked meats. The CHARRED database estimates the HAA content of commonly consumed meats, based on detailed information about the meat-cooking methods used and meat-doneness level. The relative validity of this meat-cooking module has been measured using multiple food diaries (three of four non-consecutive day diaries completed over a 3-month period) as the reference method (Cantwell et al., 2004). Dietary intake of the three most abundant HAAs was considered: MeIQx, 2-amino-3,4,8-trimethylimidazo[4,5-*f*] quinoxaline (4,8-DiMeIQx), and PhIP. Crude correlation coefficients of HAA intake, assessed using the FFQ and food diaries, were 0.43 (95% confidence interval, CI, 0.30–0.55) for MeIQx intake and 0.22 (95% CI, 0.07–0.36) for PhIP intake. Deattenuated correlations were 0.60 (95% CI, 0.49–0.69) and 0.36 (95% CI, 0.22–0.49), respectively (Cantwell et al., 2004). This meat-cooking module has been used in the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial (Cross et al., 2005), Nurses' Health Study (NHS) (Wu et al., 2010), Health Professionals Follow-Up Study (HPFS), and other studies (Cantwell et al., 2004).

(ii) Nitrate and nitrite

Dietary assessment of nitrate and nitrite intake was reported by the NIH-AARP Diet and Health Study (Dellavalle et al., 2013). The baseline questionnaire included an FFQ that asked participants about their frequency of consumption and portion sizes of 124 food items over the past 12 months. Intake of each item was assessed using 10 predefined categories, ranging from "never" to "≥ 2 times per day" for foods, "never" to "≥ 6 times per day" for beverages, and three portion size categories. The FFQ was developed and validated by NCI using two 24-hour recalls in a subset of the cohort (Thompson et al., 2008). Concentrations of nitrate and nitrite for each food item were estimated from the existing body of scientific literature, as previously described (Ward et al., 2003, 2006; Kilfoy et al., 2011). Daily intake of nitrate and nitrite was calculated by multiplying the frequency of consumption by the portion size and the nitrate and nitrite content of each food item, and then summing across all food items. Nitrate and nitrite intake from animal sources and plant sources was calculated separately. In addition to examining nitrate and nitrite intake from all animal sources, intake from processed meat sources was examined separately, as were animal sources excluding processed meat (this primarily included intake

from fresh meats, eggs, yogurt, cheese, and other dairy products).

The nitrate and nitrite content of over 3000 foods was determined by conducting a review of the literature, focusing on Canadian and USA foods, and by calculating the means of the published values weighted by the number of samples analysed (Ward et al., 2003, 2006; Kilfoy et al., 2011). The nitrate and nitrite values for foods constituting an FFQ line item were combined by weighting the food-specific values by sex-specific intake amounts from the 1994–1996 Continuing Survey of Food Intakes by Individuals (CSFII) (Subar et al., 2000). For example, the nitrate content of a line item was calculated using the weighted average of the nitrate content of the included foods, where the weights were determined by intake amounts from the CSFII, based on age group and sex. Daily intake of nitrate and nitrite was calculated by multiplying the frequency of consumption of each line item by its nitrate or nitrite content and summing over line items. In addition to calculating nitrate and nitrite intake from all foods, nitrite intake from plant, animal, and processed meat sources was calculated separately.

(c) Heterogeneity across studies

There was substantial heterogeneity across the studies included in this *Monograph* due to a variety of factors, such as different methods of dietary assessment and/or measurement, definitions (e.g. food groups and serving sizes), analytical categorizations (e.g. servings/week and g/day), exposure contrasts (e.g. analytical cut-points and intake level comparisons), and degrees of adjustment for potential confounding factors. Each cohort study included in this *Monograph* is described in Section 2. The strengths and limitations of the questionnaires used in studies included in this *Monograph* are outlined below.

(d) Cohort studies

A major strength of cohort studies in nutritional epidemiology is their ability to demonstrate a temporal relationship between dietary exposure and cancer risk, as all dietary assessments are completed before diagnoses. This limits difficulties with recall bias and reverse causation.

Wei et al. (2004) used a validated, self-administered, 61-item SQFFQ at baseline in 87 733 women from the NHS and a validated, self-administered, 131-item SQFFQ in 46 632 men from the HPFS. The study had several strengths. For example, the FFQs used were extensively validated and tested for reproducibility using data collected from a subgroup of participants who completed two FFQs (1 year apart) and two 1-week diet records (6 months apart during the intervening year). The association between baseline meat intake and cancer risk was assessed in this study, and red meat intake was clearly defined as the consumption of beef, pork, or lamb as a main dish. In addition, in this combined cohort of women and men, risk estimates were adjusted using a multivariate model that included important confounders (age; family history; body mass index, BMI; physical activity; beef, pork, or lamb as a main dish; processed meat; alcohol; calcium; folate; height; smoking pack-years before aged 30 years; history of endoscopy; and sex). A limitation of this study was the quantification of red meat in servings per day only (i.e. not in g/day).

In the Physicians' Health Study (PHS), Chen et al. (1998) used a nested case–control design to assess the relationship between red meat intake and colorectal cancer by *N*-acetyltransferase (NAT) genotype. The study included 212 men who were recruited as part of the Physicians' Health Study and were subsequently diagnosed with colorectal cancer or rectal cancer during 13 years of follow-up and were genotyped via baseline blood sample, along with 221 controls. At baseline, participants completed an abbreviated, self-administered FFQ, which inquired

about usual consumption of red meat (beef, pork, or lamb as a main dish, as a mixed dish or sandwich, and as hot dogs), chicken, and fish. The abbreviated FFQ used in this study was not validated, but an expanded form of this FFQ was validated among other male health professionals. There were some limitations to this study, as the use of an abbreviated FFQ (with fewer food items listed) prevented the adjustment of risk estimates for total energy intake. In addition, dietary intake of processed meat was included with red meat intake, and meat intake was assessed as servings per day only (i.e. not in g/day).

Dietary assessment in the NIH-AARP Diet and Health Study was described in detail by Cross et al. (2010). The study included approximately half a million women and men, each of whom completed a validated, self-administered, 124-item FFQ at baseline. Approximately 6 months later, cancer-free participants were mailed a risk factor questionnaire, which detailed information on meat intake and cooking preferences. Meat cooking method (grilled/barbecued, pan-fried, microwaved, and broiled) and doneness level (well done/very well done and medium/rare) were used in conjunction with the CHARRED database to estimate the intake of several HAAs. The FFQ assessed the usual frequency of consumption and portion size information of foods and drinks over the past 12 months. All types of beef, pork, and lamb were considered red meat, including bacon, beef, cold cuts, ham, hamburger, hot dogs, liver, pork, sausage, and steak. Processed meat included bacon, cold cuts (red and white meat), ham, luncheon meats (red and white meat), poultry sausage, red meat sausage, and standard hot dogs and low-fat hot dogs made from poultry. Meats added to complex food mixtures, such as pizza, chilli, lasagne, and stew, contributed to the relevant meat type. There were many notable strengths to this study. Several of these strengths were related to the FFQ, which not only contained detailed questions pertaining to the components of meat, but also was calibrated within this study population using two non-consecutive 24-hour dietary recalls. However, there was overlap in the definitions of red meat and processed meat, as some processed meat items were classified as red meat.

In the EPIC study (Norat et al., 2005), dietary intake over the 12 months before enrolment was measured by country-specific, validated dietary questionnaires (88–266 food items, depending on the country), which were self-administered in most countries; in Malmö, Sweden, a questionnaire combined with a food record was used. A second dietary measurement was taken from an 8% random sample of the cohort (36 994 participants) using a computerized 24-hour dietary recall method to calibrate dietary measurements across countries and to correct for systematic over- or underestimation of dietary intake. The major strengths of this study were the large variability in dietary intake across the population and the use of a computerized 24-hour dietary recall method to calibrate dietary measurements across countries.

In the Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) Study, researchers used a self-administered, modified dietary history method to capture usual dietary intake 12 months before recruitment. The dietary history method included 276 food items and a portion size booklet of 122 photographs of foods, each with 3–5 different portion sizes. Red meat intake was defined as intake of beef, pork, or lamb (Pietinen et al., 1999). A major strength of this study was the use of a detailed questionnaire.

In the Multiethnic Cohort Study, Ollberding et al. (2012) assessed diet using a validated quantitative FFQ, which included a list of foods identified from 3-day measured food records, to capture 85% or more of the intake of key nutrients and food items traditionally consumed by the populations represented in the cohort. The definition of meat intake was clearly defined as total meat, red meat, and processed meat. Risk

estimates were adjusted for important potential confounders, including energy intake. This study had many strengths, including a large variability in diet due to the inclusion of multiple ethnicities and the use of an extensive dietary questionnaire.

The PLCO Cancer Screening Trial (Ferrucci et al., 2009) used an NCI DHQ to assess usual intake (both frequency and portion size) of 124 food items over the past year. The definition of red meat (g/day) included bacon, beef, cheeseburger, cold cuts, ham, hamburger, hot dogs, liver, pork, sausage, veal, venison, and red meat from mixed dishes. Processed meat included bacon, cold cuts, ham, hot dogs, and sausage. However, a limitation of this study was the clear overlap in the definitions of red meat and processed meat, as some processed meat items were classified as red meat.

Flood et al. (2003) used a 62-item NCI Block FFQ in the Breast Cancer Detection Demonstration Project (BCDDP) to assess red meat intake in the previous year. A limitation of this study was the combined estimate of exposure to meat, which included pork, beef, hamburger, processed meat, and liver, so risk estimates for red meat alone or processed meat alone were not possible. As the cohort was generated based on a screening programme, participants may have changed their dietary habits before baseline, and recorded intake may therefore not have accurately reflected long-term intake.

Singh & Fraser (1998) assessed dietary intake in the Adventists Health Study cohort using a self-administered, mailed, 55-item SQFFQ. The SQFQQ included just six questions regarding red meat intake, defined as current intake of beef or pork. A limitation of this study was the relatively short dietary questionnaire in a low-risk population, with low red meat consumption.

In the New York University Women's Health Study, Kato et al. (1997) assessed red meat intake using a 70-item FFQ, which was slightly modified from the questionnaire designed by Block and coworkers (Block et al., 1986). However, the FFQ was not very extensive, and there were no quantitative data on red meat intake provided. It is also unclear whether intake of red meat included processed meat.

A study by Tiemersma et al. (2002) in the Netherlands examined the association between meat intake and cancer risk using a nested case–control design. A strength of this study was the use of an SQFFQ, which was validated for use through comparison with a dietary history method. A limitation of this study, however, was that a major source of meat in the population (i.e. a mixture of pork and beef) was not captured by the FFQ.

In the Shanghai Women's Health Study, Lee et al. (2009) assessed dietary intake at baseline using a validated quantitative FFQ, which included 19 food items/groups of animal origin. A major strength of this study was that the FFQ was administered by interview.

In the prospective cohort study of 37 112 residents of Melbourne, Australia, English et al. (2004) assessed dietary intake using a 124-item FFQ. They also provided a clear definition of what they included in terms of fresh red meat (veal, beef, lamb, pork, rabbit, or other game). A limitation of this study, however, was that portion size was not measured.

In the Iowa Women's Health Study, (Lee et al., 2005) assessed usual dietary intake over the past year using a validated, 127-item, self-administered SQFFQ virtually identical to the questionnaire used in the 1984 survey of the NHS (Bostick et al., 1994). Red meat was defined as beef, pork, or lamb as a main dish. This study had several strengths, including assessment of reliability and accuracy of the FFQ used, which was comparable to what was observed in the NHS. The extensive FFQ allowed for multivariable adjustment, including age, total energy intake, height, parity, total vitamin E intake, interaction term vitamin E *age, and vitamin A supplement use.

(e) Case–control studies

A description of the case–control studies included in this *Monograph* is provided in Section 2. Case–control studies investigating the association between meat intake and cancer risk are limited, as they assess dietary intake after cancer has been diagnosed, which can lead to recall bias. In addition, patients often change their dietary intake due the presence of a solid tumour to avoid pain or reflux, for example. As a result, investigators usually ask cases included in their studies to recall dietary intake in the period before diagnosis of cancer to capture usual diet before diagnosis. As a result, case–control studies are limited due to the measurement error associated with dietary intake due to memory recall. Tavani et al. (2000), for example, assessed total red meat intake (beef, veal, and pork) per week 2 years before diagnosis, while Chiu et al. (2003) assessed dietary intake 5 years before diagnosis in a case–control study in Shanghai.

In the North Carolina Colon Cancer Study, Butler et al. (2003) assessed usual diet in the year before diagnosis for patients, or the year before the date of selection for controls, using a 150-item FFQ, which was a modified version of the Block questionnaire. However, no information regarding validation was provided. Red meat intake was calculated as the sum of hamburger, steak, pork chop, sausage, and bacon intake.

(f) Conclusion

As outlined in this section, the questionnaires used in the cohort and case–control studies varied in several ways, including in the methods of dietary assessment and/or measurement, the use of validated/calibrated questionnaires, the definitions of meat and processed meat as food groups, the inclusion of serving or portion sizes, the ability to assess intake (i.e. in g/day), and the degree of adjustment for potential confounding factors.

1.4.2 Biological markers

Despite more than 35 years of research, no long-term validated biomarkers of exposure have been employed in molecular epidemiology studies to assess the role of genotoxicants in cooked or processed meat and cancer risk. Additionally, other than HAAs, the biomarkers of PAHs or NOCs are not specific to meat, as they may also measure environmental or endogenous exposure.

[The Working Group noted that short-lived biomarkers, including urinary metabolites and DNA adducts of meat-related genotoxicants, exist; however, they cannot be used as biomarkers of exposure in epidemiological studies, and do not belong in this section (see Section 4 for details).]

The accumulation of PhIP in hair may represent the first long-term biomarker of HAA exposure in cooked meats, although this biomarker is a measure of the unmetabolized chemical and not the biologically effective dose. Harmonization of the method across laboratories is required for validation and implementation in epidemiological studies.

Recent studies of omnivores have used metabolomics to identify constituents of meat in plasma and urine to measure meat consumption. Metabolomics is still a developing technology. It employs liquid chromatography-mass spectrometry (LC-MS)–based methods to identify the constituents or chemicals present in cooked or processed meat, and may provide reliable assessment of dietary habits and patterns of meat consumption in the future.

Data on the most promising biomarkers of exposure for red meat and processed meat consumption in epidemiological studies are summarized in Section 1.4.2(a) and (b).

(a) Hair biomarkers

Gas chromatography-mass spectrometry (GC-MS) with negative ion chemical ionization or liquid chromatography-tandem mass spectrometry (LC-MS/MS) with triple quadrupole-mass spectrometry (TQ-MS) instruments have been employed to measure PhIP in the hair of subjects in European countries (Alexander et al., 2002), Japan (Kobayashi et al., 2005; Kobayashi et al., 2007; Iwasaki et al., 2014), and the USA (Bessette et al., 2009; Turesky et al., 2013). PhIP was identified in the hair of omnivores, but not in the hair of vegetarians (Bessette et al., 2009). The binding of PhIP to hair is strongly driven by melanin content, and binding levels of PhIP in hair should be normalized to melanin content (Bessette et al., 2009; Turesky et al., 2013). Turesky et al. (2013) observed that, after being fed a semicontrolled diet, levels of PhIP in the hair of volunteers increased in an exposure-dependent manner. Levels of PhIP in hair were stable over time, varying in two meat eaters by less than 24% over a 6-month interval (Turesky et al., 2013). In another study, levels of PhIP in the hair of Japanese subjects were correlated with grilled/stir-fried meat intake, but not with grilled/stir-fried fish intake (Kobayashi et al., 2005). Levels of PhIP were further correlated with dietary HAA intake, according to an FFQ (Kobayashi et al., 2007). Since the binding of PhIP to hair is largely influenced by pigmentation, the biomonitoring of PhIP in an older population with predominantly white hair may be difficult. Moreover, because the growth cycles of individual hair follicles are asynchronous across the scalp, hair samples should be consistently collected from the same area of the scalp for comparison of PhIP levels in the hair of individuals (Bessette et al., 2009; Turesky et al., 2013). Despite these limitations, biomonitoring of PhIP levels in hair is the first biomarker for assessing long-term exposure to this cooked meat carcinogen. Other HAAs bind less efficiently to hair, and exposure cannot be assessed with hair (Bessette et al., 2009; Iwasaki et al., 2014).

There are reports on the measurement by GC-NICI/MS of hydroxylated PAHs, including naphthalene and pyrene, in the hair of subjects (Schummer et al., 2009; Appenzeller et al., 2012; Appenzeller & Tsatsakis, 2012). Using hair to assess exposure to PAHs through meat consumption is challenging because of the multiple sources of exposure to PAHs and the low levels of hydroxylated PAHs in hair.

(b) Urinary and plasma biomarkers

Targeted approaches have been used to measure different procarcinogens, their metabolites, and DNA adducts in urine. More recently, untargeted metabolomics approaches have been used to understand dietary patterns of meat consumption, to strengthen self-administered FFQs.

(i) Metabolomics: nutrients and secondary or indirect biomarkers

Plasma and urine from subjects on different diets have been characterized by proton nuclear magnetic resonance, GC-MS, and LC-MS techniques, and hundreds of chemicals have been identified (Puiggròs et al., 2011; Hedrick et al., 2012; Scalbert et al., 2014).

Correlations were observed among chemical biomarkers of red meat, shellfish, fish, other food components, multivitamins, and diets, in plasma (Guertin et al., 2014). Several biomarkers in urine correlated to meat intake included: creatine, creatinine, carnitine, carnosine, ophidine, 1-methylhistidine, and 1-methylhistidine and 3-methylhistidine (Dragsted, 2010; Puiggròs et al., 2011).

In a urinary metabolomic study employing LC-MS, 3-indoleacetyl-glucuronide, a microbiome metabolite of tryptophan, which is found at high concentrations in animal protein, was identified, possibly reflecting differences in the

protein sources between the diets (Andersen et al., 2014). Indole propionate was also identified as a potential biomarker of red meat in plasma (Guertin et al., 2014). Indoles are metabolites of tryptophan that are largely produced by the bacterial flora; however, they are not specific to meat, as they are also found in high amounts in soya and eggs (Guertin et al., 2014).

(ii) Urinary 1-methylhistidine, 3-methylhistidine, creatinine, and taurine

There were marked differences between the proton nuclear magnetic resonance spectra of high–red meat, low–red meat, and vegetarian diets, which included elevated urinary levels of creatinine, taurine, carnitine, trimethylamine-*N*-oxide, and methylhistidine in the high–red meat group. However, the spectral changes differentiating the low–red meat and vegetarian groups were subtle. The urinary metabolite trimethylamine-*N*-oxide, a product formed from carnitine by the bacterial microbiota, was associated with meat intake, but it is also a biomarker of fish intake, and may confound the interpretation of meat consumption patterns (Stella et al., 2006).

In another controlled meat-feeding study, the urinary excretion of creatinine, taurine, 1-methylhistidine, and 3-methylhistidine was investigated in individuals who consumed various amounts of red meat: vegetarian (0 g/day), low red meat (60 g/day), medium red meat (120 g/day), and high red meat (420 g/day) (Cross et al., 2011). All components demonstrated a significant dose–response relationship, increasing as red meat intake increased ($P_{trend} < 0.0001$). There were significant differences in the mean levels of 1-methylhistidine and 3-methylhistidine across the four dietary intake groups ($P < 0.01$ and $P < 0.05$, respectively). However, taurine and creatinine levels in the vegetarian and low–red meat intake groups could not be distinguished ($P = 0.95$ and $P = 0.88$, respectively). 3-Methylhistidine and creatinine are formed during muscle catabolism, thus lack specificity for meat intake. 1-Methylhistidine has also been found in the urine of subjects on a fish diet (Lloyd et al., 2011). Another study reported that the mean urinary levels of 1-methylhistidine and 3-methylhistidine did not differ among 131 colorectal adenoma and control subjects ($P = 0.72$) (Cross et al., 2014). Thus, methylhistidine may not be a good indicator of meat processing conditions, and the levels of methylhistidine present in meat may not correlate to the levels of procarcinogens formed in cooked or processed meat.

To date, there are no chemical markers or metabolites of meat constituents that can provide information on the methods of meat processing and cooking that produce carcinogens.

1.5 Regulations and guidelines

In many countries, the production of red meat and processed meat is subject to stringent regulations. These regulations are primarily intended to prevent infectious diseases and minimize contamination of the meat products. Under the auspices of WHO and FAO, the Codex Alimentarius was established to provide international food standards, guidelines, and codes of practice to protect and promote safety, quality, and fairness in the international food trade (Codex Alimentarius, 2015). The scope of standards issued by the Codex Alimentarius is illustrative of standards and regulatory measures typically issued on a national basis for the maintenance of food safety in relation to meat products (Table 1.18).

An exhaustive list of all regional and national food authorities is not provided here, but a summary of those operating in Europe and the USA is provided.

EFSA (EFSA, 2015) is the EU risk assessment authority for food and feed safety. For red meat and processed meat, relevant EFSA panels or units include animal health and welfare, biological

Table 1.18 Examples of meat-related food safety standards issued by Codex Alimentarius

Reference	Standard	Committee	Last modified
CAC/GL 14-1991	Guide for the Microbiological Quality of Spices and Herbs Used in Processed Meat and Poultry Products	CCPMPP	1991
CAC/GL 78-2011	Guidelines for the Control of *Campylobacter* and *Salmonella* in Chicken Meat	CCFH	2011
CAC/GL 85-2014	Guidelines for the Control of *Taenia saginata* in Meat of Domestic Cattle	CCFH	2014
CAC/GL 86-2015	Guidelines for the Control of *Trichinella* spp. in Meat of Suidae	CCFH	2015
CAC/GL 87-2016	Guidelines for the Control of Nontyphoidal *Salmonella* spp. in Beef and Pork Meat	CCFH	2016
CAC/RCP 58-2005	Code of Hygienic Practice for Meat	CCMPH	2005
CODEX STAN 89-1981	Standard for Luncheon Meat	CCPMPP	2015
CODEX STAN 98-1981	Standard for Cooked Cured Chopped Meat	CCPMPP	2015

CCFH, Codex Committee on Food Hygiene; CCMPH, Codex Committee on Meat Hygiene; CCPMPP, Codex Committee on Processed Meat and Poultry Products
From Codex Alimentarius (2016a)

monitoring, contaminants, and assessment and methodological support.

In the USA, the relevant statutory authority for safety in relation to meat products is the United States Department of Agriculture (Department of Agriculture, 2015). The United States Food and Drug Administration (FDA) is responsible for regulating chemicals authorized in meat. A range of guidance documents and regulations are issued by this administration (FDA, 2015).

1.5.1 Prevention of infectious disease

The broad issues addressed by food safety regulations have been summarized by Henson & Caswell (1999), and include new potential foodborne risks, such as bovine spongiform encephalopathy and genetically modified organisms, as well as recognized risks posed by well-characterized bacteria. The scientific rationale for food safety regulations involves risk assessment, management, and communication.

For meat products, the regulations aim to decrease contamination by microbial pathogens (e.g. *Listeria monocytogenes*, *Escherichia coli*, and *Salmonella*) by minimizing cross-contamination of other foods and water with enteric pathogens of animal origin (Sofos, 2008).

Many countries approach food safety, specifically in relation to meat production, through compliance with hazard analysis and critical control point (HACCP)-based regulations; HACCP is a safety and quality management tool (Hudson et al., 1996).

1.5.2 Prevention of contamination

(a) Red meat

Red meat may contain residues from veterinary drugs. These compounds are generally regulated at the national level, but 67 of them are regulated by international standards (i.e. maximum residue limits, MRLs) established by the Codex Alimentarius (2015). There is currently no international monitoring of the frequency of use of these chemicals.

Red meat is usually free of additives. However, in certain circumstances, colours are used for certification stamps on the surfaces of fresh cuts of meat, and are indicated in the food category system with a notation for "stamping, marking or branding the product" (Codex Alimentarius, 2016a).

Red meat may also contain chemicals present in the environment or used in the production of feed-like pesticide residues. When there is sufficient scientific information available about a chemical, the Joint FAO/WHO Expert Committee defines its acceptable daily intake (ADI), which is the amount of chemical, expressed based on body weight, that can be ingested over a lifetime without appreciable health risks. From the ADI, the Codex Alimentarius Commission establishes an MRL per kilogram of food that is recommended as being legally acceptable. The Codex Alimentarius Commission does not establish an MRL for a chemical if dietary exposure is above the ADI. Furthermore, no MRL is established if a chemical is assessed to be a genotoxic carcinogen in humans (Codex Alimentarius, 2015). MRLs have been established by the Codex Alimentarius for several pesticide residues possibly occurring in meat (Codex Alimentarius, 2016b). Most of these limits were established at the limit of detection of the analytical method.

Other chemical contaminants present in the environment, such as heavy metals or persistent organic pollutants, may also occur in red meat. Some of these contaminants are regulated internationally by the Codex Alimentarius. WHO/GEMS has collected national monitoring data on 145 environmental contaminants (WHO, 2015b). Moreover, the Codex Alimentarius has adopted codes of practice to reduce food and feed contamination by lead (Codex Alimentarius, 2004), by dioxin and dioxin-like PCBs (Codex Alimentarius, 2006), and by PAHs (Codex Alimentarius, 2009).

(b) Processed meat

National regulations are in place for processed meat in many countries around the world, e.g. in the USA (Office of the Federal Register, 2015). In Europe, the European Parliament and the Council of the EU define a "meat product" in Annex I to Regulation (EC) No 853/2004. The annex states that "meat products" means processed products resulting from the processing of meat or from the further processing of such processed products, so that the cut surface shows that the product no longer has the characteristics of fresh meat" (European Commission, 2004).

At the international level, there is currently no active committee of the Codex Alimentarius to deal with meat (abolished in 1971) or processed meat (abolished in 1990), and the international standards for meat products are established by horizontal committees (e.g. committees for food additives, contaminants, or pesticide residues). In addition to the chemicals possibly present in meat in general, processed meat may contain food additives. However, many of these food additives, such as nitrites (80 mg/kg), colouring agents such as erythrosine (30 mg/kg), and antioxidants including butylated hydroxytoluene (100 mg/kg) are regulated by international standards established by the Codex Alimentarius (2016a).

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2. CANCER IN HUMANS

2.1 General issues regarding the epidemiology of cancer and consumption of red meat and processed meat

The association between consumption of red meat or processed meat and cancer risk has been examined in numerous studies. In this section, the Working Group summarized the results of existing studies. For those studies reporting on the same study population and published at different times, the most recent, complete, or informative publication was included when possible.

In reviewing and interpreting the available literature, the Working Group considered the five following criteria: exposure definition; sample size and number of exposed cases; study design; exposure assessment tools; and adjustment for potential confounding factors described below.

2.1.1 Exposure definition

The Working Group placed the greatest emphasis on the studies that reported data separately for unprocessed red meat (i.e. "red meat") or processed meat, and had a clear definition of what questions or types of meats were included in the meat variables. For definitions, please see Section 1 of this *Monograph* and (a) and (b) below. Studies that defined total red meat as including processed meat and studies that reported on "red meat" (unclear whether unprocessed or total red meat) were also included in the Working Group discussion, but were given less weight; the latter studies were given the least weight for many cancers (e.g. cancer of the colorectum).

(a) Red meat

Red meat refers to fresh unprocessed mammalian muscle meat (e.g. beef, veal, pork, lamb, mutton, horse, or goat meat), which may be minced or frozen, and is usually consumed cooked. Studies reporting separate results for individual red meat subtypes (e.g. beef, pork, lamb, etc.) and fresh organ meats (offal) were included as "red meat". Mammalian offal refers to the internal organs and entrails of a butchered animal (scrotum, small intestine, heart, brain, kidney, liver, thymus, pancreas, testicle, tongue, tripe, or stomach) consumed as such. The Working Group considered offal as "red meat".

(b) Processed meat

Processed meat refers to any meat that has been transformed through one or several of the following processes: salting, curing, fermentation, smoking, or other processes to enhance flavour or improve preservation. Most processed meats are made from pork or beef, but may also include other meats such as poultry and/or offal, or meat by-products such as blood. It is also important to distinguish between industrial processing and household preparations.

This *Monograph* excluded results on poultry, fish, and seafood; studies of dietary patterns (i.e. clusters of food items grouped by investigators or by statistical analysis); and results of reported ratios of red to white meat. Studies with unspecified meat intake, studies that reported only combined results for red and white meat, or studies of white meat were excluded for most cancers, or were given less weight in the evaluation than others. In addition, studies that only reported on estimated carcinogens derived from meat, but not on "red meat" or "processed meat" variables were excluded.

2.1.2 Sample size and the number of exposed cases

The sample size and the number of exposed cases can have an impact on statistical power. As there was a large number of informative studies, those with a sample size of fewer than 100 cases were excluded.

2.1.3 Study design

For cohort studies, prospective cohort studies and case–control or case–cohort analyses of such studies were considered. For cancer sites with a large number of informative studies and with low case fatality, studies based on mortality data were excluded or given less weight. These decisions are noted, where relevant, in the sections for each specific cancer site. For case–control studies, the selection of hospital-based versus population-based cases and controls was considered. Greater emphasis was given during the evaluation to studies that used population-based controls, as they were more representative of the underlying population. For hospital-based controls, studies that clearly listed the diseases of the controls were given greater emphasis, as the inclusion of controls with conditions related to risk factors for the disease under study may lead to bias. In particular, if the people selected as controls had conditions that could potentially lead to modifications in their diet, they would be less representative of the underlying population, thus leading to biased estimates.

2.1.4 Exposure assessment tools

Greater emphasis was given to studies that used validated dietary instruments and in-person interviews compared with non-validated dietary instruments and mailed, self-administered questionnaires, respectively. The Working Group assessed whether the questionnaires were validated in the population under study, whether the red or processed meat questions captured most subtypes of red or processed meats consumed in that population, and whether there was detailed assessment of portion size (e.g. use of pictures and models, in addition to frequency of consumption).

2.1.5 Adjustment for potential confounding factors

Studies that appropriately adjusted for confounding factors were given greater weight. Studies with insufficient adjustment were either noted and given less weight, or excluded from the review, depending on the number of studies available for a particular cancer site. For each cancer site, potential confounders for associations with meat intake are listed.

In general, total energy/caloric intake, physical activity, and body mass index (BMI) were considered important confounders; however, several other factors were considered for specific cancer sites (e.g. alcohol for cancer of the colorectum and breast, tobacco smoking for cancer of the lung and colorectum, etc.).

Total caloric intake is a putative risk factor for several cancers, and given that red meat and processed meat are significant contributors to total caloric intake, appropriate consideration of this confounder was important. Similarly, given

the established or putative role of other dietary and lifestyle factors that may be correlated with meat intake, the consideration of these factors as possible confounders was important, depending on the cancer site (e.g. dietary fibre, BMI, and physical activity). In particular, it has been shown that individuals who consume high levels of processed meat often tend to eat less fruits and vegetables, to drink more alcoholic beverages, to smoke more tobacco, to consume more calories and more fat, and to be more obese and less active than those who do not consume processed meat (Fung et al., 2003; Dixon et al., 2004; Kesse et al., 2006; Nkondjock & Ghadirian 2005).

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2.2 Cancer of the colorectum

2.2.1 Cohort studies

This section includes prospective cohort studies and case–control studies nested within prospective studies on the association between red or processed meat intake and risk of cancer of the colorectum. The most recent publication of a cohort study, or the publication with the highest number of cases in the analysis, was included in the review. The results of superseded studies were not detailed.

This evaluation excluded prospective studies with colorectal cancer mortality, rather than incidence, as the end-point, and study results on the association between meat intake and colorectal cancer risk when the definition of meat intake included poultry and/or fish. Studies on dietary patterns and studies with fewer than 100 cases in the analyses were also not included.

The results of the included studies are presented according to the type of meat investigated: red meat (i.e. unprocessed red meat), processed meat, and red meat and processed meat combined. When studies reported on two or more of these types of meat, only the data for red meat and processed meat considered separately were treated in detail. A few studies that reported results only for particular aspects of meat consumption, such as doneness or type of meat, are described in this section, but these studies are not included in the tables. Studies on gene–exposure interactions are described in the section of the corresponding meat type, as are studies on the association between cooking methods or meat doneness levels and colorectal cancer.

As studies with greater precision can be considered more informative, particularly when the strength of the association appears to be weak to moderate, the descriptions of the studies are ordered for each section by the number of cases in the analysis, and tables are ordered chronologically. Other study quality criteria are indicated in the text when relevant. The study results most pertinent to the evaluation are included in the tables. Other findings of interest are briefly described in the text.

(a) Red meat

Fourteen cohort studies and two cohort consortia provided informative data on the association between red meat and risk of colorectal cancer (see Table 2.2.1). A few studies investigated specific types of red meat only. The results of these studies are described at the end of this section.

The New York University Women's Health Study (NYUWHS) enrolled women aged 34–65 years at mammographic screening clinics from 1985 to 1991, and followed them up until 1994 through a combination of direct contact and record linkage to cancer registries. A 70–food item, modified Block questionnaire was used to assess diet. Colorectal cancer risk was not significantly associated with red meat intake. The relative risk (RR) for the highest compared with the lowest quartile was 1.23 (95% confidence interval, CI, 0.68–2.22) (Kato et al., 1997). [The Working Group noted that the amount of red meat intake was not reported in the publication, and the study was small (100 cases in the analysis).]

In a nested case–control study using data from the Monitoring Project on Cardiovascular Disease Risk Factors study in the Netherlands (Tiemersma et al., 2002), 102 incident colorectal cancer cases were identified during 8.5 years of follow-up, and a random sample of 537 controls were matched for sex and age. The odds ratio (OR) for consumption of red meat ≥ 5 times/week compared with ≤ 3 times/week was 1.6 (95% CI, 0.9–2.9). In an analysis stratified by sex, a positive association was observed in men (OR, 2.7; 95% CI, 1.1–6.7; P_{trend} = 0.06), but not in women (OR, 1.2; 95% CI, 0.5–2.8; P_{trend} = 0.64). The same comparison was statistically significant

in men and women combined after the exclusion of participants who were younger than age 50 years at the end of the follow-up (RR, 2.0; 95% CI, 1.1–3.8; highest vs lowest intake). The relationship between red meat and colorectal cancer was not modified by *NAT1*, *NAT2*, and *GSTM1* genotypes. [The Working Group noted that a limited number of cancer cases were included in the study, and the assessment of meat intake was not comprehensive. A major source of meat intake – a mix of minced pork and beef – in the Dutch population was missed by the questionnaire. However, the authors indicated that meat consumption was estimated by the questionnaire, with acceptable reproducibility and validity when compared with a dietary history method (data were not given in the paper).]

A cohort study in Takayama, Japan, included 30 221 subjects aged 35 years or older who completed a general questionnaire and a 169–food item, validated food frequency questionnaire (FFQ) at baseline in 1992. Until 2000, 111 cases of colon cancer in men and 102 cases in women were identified through the medical records of two hospitals in Takayama, accounting for about 90% of the colon cancer cases registered in the city cancer registry (Oba et al., 2006). Red meat intake was unrelated to colon cancer risk. Multivariate-adjusted relative risks for the highest compared with the lowest tertile of intake were 1.03 (95% CI, 0.64–1.66; P_{trend} = 0.86) in men and 0.79 (95% CI, 0.49–1.28; P_{trend} = 0.20) in women. Rectal cancer cases were not included in the analysis. [The Working Group noted that a limited number of cancer cases were included in the study, and meat intake was low compared with meat intake in North American and European cohorts.]

In a 6-year follow-up of a cohort of 32 051 non-Hispanic, White members of the Adventist Health Study (AHS) in California, USA (1976–1982), 157 colon cancer cases were identified (Singh & Fraser, 1998). The participants completed at baseline a semiquantitative, 55–food item dietary questionnaire, in which six questions were on meat intake. Participants who consumed beef or pork ≥ 1 time/week were at increased risk of colon cancer compared with those who did not consume beef or pork (RR, 1.90; 95% CI, 1.16–3.11; P_{trend} = 0.02). White meat intake was also positively associated with colon cancer risk. [The Working Group noted that out of the 157 colon cancer cases identified, 42 cases were vegetarians and 40 cases were occasional meat eaters. The association with red meat remained significant in the analysis stratified by intake of white meat, and the analyses were adjusted for tobacco smoking and physical activity. Given the nature of the study population, and that residual confounding could not be ruled out, other lifestyle differences for low meat eaters and vegetarians could at least partially explain the association observed with both red and white meats. The exclusion of current or past smokers, and alcohol consumers did not substantially alter the association with red meat.]

In the Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) Study, a randomized, double-blind, placebo-controlled trial on the prevention of incidence of lung cancer in Finnish male smokers, 185 colorectal cancer cases were identified during 8 years of follow-up (Pietinen et al., 1999). Usual diet at baseline was assessed using a self-administered questionnaire with 276 items, and total red meat was defined as beef, lamb, and pork and processed meat. Colorectal cancer was not associated with intake of beef, pork, and lamb (i.e. red meat), specifically; the relative risk for the highest compared with the lowest quartile was 0.8 (95% CI, 0.5–1.2; P_{trend} = 0.74) (Pietinen et al., 1999). Intake of fried meats (determined by adding up the frequency of intake of all dishes where the meat was prepared by frying) was not related to colorectal cancer risk (RR, 0.9; 95% CI, 0.6–1.3; for 204 vs 60 times/year). [The Working Group noted that fried meats may have included fried white meats. No other cooking methods

were reported. A main limitation of this study was the low number of cases.]

In the Iowa Women's Health Study (IWHS), a study in postmenopausal women, 212 incident colon cancer cases were identified during 5 years of follow-up. Diet was assessed using a validated, 127–food item semiquantitative food frequency questionnaire (SQFFQ). Total red meat was defined as beef, lamb, or pork, and processed meat. Consumption of total red meat as defined was not associated with colon cancer, nor was consumption of beef, lamb, or pork as a main dish (RR, 1.21; 95% CI, 0.75–1.96; P_{trend} = 0.16; for > 3 vs < 1 serving/week) (Bostick et al., 1994). This lack of association was observed in women with or without a family history of colon cancer in first-degree relatives (Sellers et al., 1998).

Andersen et al. (2009) conducted a case–cohort study nested in the Danish Diet, Cancer and Health cohort study (372 cases, 765 controls), and reported a null association between intake of red meat and colorectal cancer risk. [Estimates were not adjusted for total energy intake, raising concerns about uncontrolled confounding. In addition,the Working Group noted that the study had a short follow-up (5 years), and cases identified in the first years of follow-up were not excluded from the analyses.]

In a case–cohort study in the Danish Diet, Cancer and Health cohort, including 379 colorectal cancer cases and 769 subcohort members, colorectal cancer was not significantly associated, although it was slightly increased, with intake of red meat (RR, 1.03; 95% CI, 0.97–1.09, per 25 g/day) or fried red meat (RR, 1.09; 95% CI, 0.96–1.23, per 25 g/day). A higher risk was observed in people who reported a preference for brown–dark pan-fried meat (any type of meat) compared with light–light brown meat (RR, 1.36; 95% CI, 1.04–1.77). This risk did not differ significantly between *NAT1* or *NAT2* genotype carriers ($P_{interaction}$ > 0.4) (Sørensen et al., 2008). [The Working Group noted that about 18% of the participants in this cohort were also included in the Danish component of the European Prospective Investigation into Cancer and Nutrition (EPIC).]

In another nested case–control study in the same cohort, a statistically significant increase (RR, 3.70; 95% CI, 1.70–8.04) in colorectal cancer risk per 100 g/day of red meat intake was observed among carriers of the homozygous variant *XPC* Lys939Gln, and no association among carriers of the wildtype allele was observed (Hansen et al., 2007). None of the other polymorphisms investigated (*XPA* A23G, *XPD* Lys751Gln, and *XPD* Asp312Asn) were related to colorectal cancer risk. [The Working Group noted that results regarding the association between *XPC* Lys939Gln and red meat intake on colorectal cancer risk might have been a chance finding, as multiple comparisons were made.]

The Shanghai Women's Health Study (SWHS) included 73 224 women aged 40–70 years at recruitment who completed an FFQ by interview at the baseline assessment beginning in 1997. Follow-up was through active surveys and periodic linkage to the Shanghai Cancer Registry. After a mean follow-up of 7.4 years, 394 incident cases of colorectal cancer (236 colon, 158 rectum) were identified (Lee et al., 2009). The risk of colorectal cancer was not related to the amount of red meat intake. The relative risks for the highest compared with the lowest quintile (> 67 g/day and < 24 g/day, respectively) were 0.8 (95% CI, 0.6–1.1; P_{trend} = 0.53) for colorectal cancer, 0.9 (95% CI, 0.6–1.5; P_{trend} = 0.31) for colon cancer, and 0.6 (95% CI, 0.3–1.1; P_{trend} = 0.79) for rectal cancer. When intakes of 90 g/day and 100 g/day were instead used as cut-points in a further analysis, the relative risk estimates for colorectal cancer were 1.29 (95% CI, 0.88–1.89) and 1.67 (95% CI, 1.11–2.52), respectively. [The Working Group noted that the association may not have been detected in the previous analyses due to an overall low level of meat consumption.] In an analysis of cooking methods, the risk of colon cancer was significantly associated with

preparing food by smoking (RR, 1.4; 95% CI, 1.1–1.9; for ever vs never), but not with other cooking methods. [The Working Group noted that the definition of red meat was not given, but appeared to be unprocessed pork, beef, and lamb. Cooking methods were for all animal foods. The range of meat intake was low in the study.]

In the Melbourne Collaborative Cohort Study, the relative risk of colorectal cancer for consuming red meat more than 6.5 times/week compared with < 3 times/week was 1.4 (95% CI, 1.0–1.9; P_{trend} = 0.2; 451 cases). Red meat was defined as veal, beef, lamb, pork, and rabbit or other game. The association was mainly driven by a positive association with rectal cancer (RR for the same comparison, 2.3; 95% CI, 1.2–4.2; P_{trend} = 0.07; 169 cases). The relative risk for colon cancer was 1.1 (95% CI, 0.7–1.6; P_{trend} = 0.9; 283 cases) (English et al., 2004). In analyses with continuous variables for meat consumption, the relative risks for an increase of 1 time/week were 1.0 (95% CI, 0.94–1.07) for the colon and 1.08 (95% CI, 0.99–1.16) for the rectum.

In the Swedish Mammography Cohort (SMC), 733 incident cases of colorectal cancer were identified after completion of a 67-item, self-administered dietary questionnaire at baseline in 1987–1990. Consumption of unprocessed beef and pork was associated with almost a twofold risk of distal colon cancer for ≥ 4 servings/week, whereas there was no apparent association with risk of proximal colon or rectal cancers (Larsson et al., 2005a). The relative risks for consumption of beef and pork ≥ 4 times/week compared with < 2 times/week were 1.22 (95% CI, 0.98–1.53) for colorectal cancer, 1.10 (95% CI, 0.74–1.64) for proximal colon cancer (234 cases), 1.99 (95% CI, 1.26–3.14; P_{trend} = 0.01) for distal colon cancer (155 cases), and 1.08 (95% CI, 0.72–1.62) for rectal cancer (230 cases), respectively. [The Working Group noted that case ascertainment was virtually complete, and the analyses were controlled for main potential confounders.]

Singaporean Chinese aged 45–74 years who resided in government-built housing estates were enrolled in a prospective study in 1993–1998. At baseline, a 165-item quantitative FFQ, developed for and validated in this population, was administered to assess usual diet over the past year. After an average follow-up duration of nearly 10 years, 941 incident colorectal cancer cases were identified through record linkage to the population-based Singapore Cancer Registry (Butler et al., 2008 b). The adjusted hazard ratio (HR) for the highest compared with the lowest quartile of red meat intake was 1.01 (95% CI, 0.82–1.26; P_{trend} = 0.6). [The Working Group noted that the usual diet was mainly composed of mixed dishes. Red meat appeared to be unprocessed, but the definition was not given in the paper. The cut-off points of the quartiles were not given, and the 95th percentile of red meat intake in non-cases was 76 g/day.]

The EPIC study identified 1329 colorectal cancer cases during a mean follow-up of 4.8 years. Red meat included all fresh, minced, and frozen beef, veal, pork, and lamb. In the EPIC study (Norat et al., 2005), the relative risk for colorectal cancer was 1.17 (95% CI, 0.92–1.49; P_{trend} = 0.08) for an intake of red meat > 80 g/day compared with < 10 g/day. A significant association (RR, 1.21; 95% CI, 1.02–1.43, per 100 g/day; P_{trend} = 0.03) was observed when red meat was expressed as a continuous increment. The association with red meat was strengthened, but not significant, after calibration using 24-hour recall data. The calibrated relative risk for colorectal cancer per 100-g increment was 1.49 (95% CI, 0.91–2.43). The associations were similar for cancers of the colon and rectum, and of the proximal and distal colon. Analysis of specific meat types showed significant positive trends for intake of pork (highest vs lowest intake RR, 1.18; 95% CI, 0.95–0.48; P_{trend} = 0.02) and lamb (HR, 1.22; 95% CI, 0.96–1.55; P_{trend} = 0.03), but not for intake of beef/veal (HR, 1.03; 95% CI, 0.86–1.24; P_{trend} = 0.76). When mutually adjusted,

only the trend for pork remained significant. [The Working Group noted that the strengths of the study were that participants were from 10 European countries with different dietary habits, and detailed validated dietary questionnaires were used. Dietary data were also calibrated using 24-hour recall in a subset of the population to partially correct the relative risk estimates for dietary measurement error. This study investigated red meat, processed meat, and specific meat types in relation to colorectal cancer risk. Follow-up was virtually complete, and the analyses were adjusted for main potential confounders. A potential limitation of the study was that different dietary questionnaires were used in the centres; however, the associations were strengthened after calibration of the dietary data, and no heterogeneity across centres was detected.]

The Nurses' Health Study (NHS) and the Health Professionals Follow-Up Study (HPFS) were among the first American cohorts to investigate the association between red and processed meat and colon cancer risk. The NHS included female, married nurses aged 30–55 years, and diet was assessed by a validated, 61-item SQFFQ. Self-reported cases were validated by medical or pathology records. The HPFS included men aged 40–75 years, and diet was assessed by a self-administered FFQ. Both studies had repeated measures of diet during follow-up (NHS, from 1980 to 2010; HPFS, from 1986 to 2010). Early reports from these cohorts, which included a small number of cases, showed significant positive associations between red and processed meat and colon cancer (age- and energy-adjusted) (Willett et al., 1990; Giovannucci et al., 1994). Several papers on the cohorts have since been published (Wei et al., 2004, 2009; Fung et al., 2010; Zhang et al., 2011; Bernstein et al., 2015), generally showing no association between beef, pork, or lamb as a main dish and colorectal cancer risk (Wei et al., 2004; Fung et al., 2010; Bernstein et al., 2015).

In the most recent analysis of the NHS and the HPFS (Bernstein et al., 2015), which included 2731 colorectal cancer cases (1151 proximal colon, 816 distal colon, and 589 rectum), the cumulative average intake of unprocessed red meat was not associated with colorectal cancer risk (RR per 1 serving/day increase, 0.99; 95% CI, 0.87–1.13; P_{trend} = 0.88). The results were similar when analysed in grams of intake. When analysed by tumour location, red meat consumption was inversely associated with risk of distal colon cancer (RR per 1 serving/day increase, 0.75; 95% CI, 0.68–0.82; $P_{trend} < 0.001$); a weak, non-significant positive association was observed with proximal colon cancer (RR, 1.14; 95% CI, 0.92–1.40; P_{trend} = 0.22)., and no association was observed with rectal cancer (RR, 1.14; 95% CI, 0.86–1.51; P = 0.37). The inverse associations with distal colon cancer were primarily seen after adjustment for specific nutrients, including fibre, folate, and calcium in men and calcium in women. [The Working Group noted that the analyses took into account long-term exposure and several potential risk factors simultaneously. Multiple sensitivity and effect modification analyses were conducted, and the results were robust.]

In a previous nested case–control study of 183 colorectal cancer cases and 443 controls enrolled in the NHS, women with the *NAT2* rapid acetylator genotype who consumed > 0.5 servings/day of beef, pork, or lamb as a main dish had an increased risk of colon cancer compared with women who consumed less red meat (OR, 3.01; 95% CI, 1.10–8.18). No association was observed in slow acetylators (multivariate OR, 0.87; 95% CI, 0.35–2.17; $P_{interaction}$ = 0.07) or in all women (OR, 1.21; 95% CI, 0.85–1.72) (Chan et al., 2005). [The Working Group noted that this study was large. Diet was estimated from repeated questionnaires, and there was a detailed selection of potential confounders.]

The Multiethnic Cohort Study identified 3404 incident cases of colorectal cancer up to 2007 among a sample of African Americans,

Japanese Americans, Latinos, native Hawaiians, and Whites aged 45–75 years living in Hawaii and California, USA (Nöthlings et al., 2009; Ollberding et al., 2012). Red meat intake was not associated with colorectal cancer risk. The relative risk for the highest compared with the lowest quintile (34.86 and 4.59 g/1000 kcal, respectively) was 0.98 (95% CI, 0.87–1.10; P_{trend} = 0.58). For all types of meats considered together, the risk did not vary by doneness preference (cooked until dark brown or well done) or cooking method preference (pan-fried, oven-broiled, or grilled/barbecued); data were not reported by the authors. [The Working Group noted that this was a large study that sampled people from different ethnic groups for better generalizability of results. There was a strong attenuation of the effect estimates after multivariable adjustment.]

In a nested case–control in the United Kingdom Dietary Cohort Consortium, based on seven cohort studies in the United Kingdom (Spencer et al., 2010), diet was assessed using 4-, 5-, or 7-day food diaries. Red meat was defined as including beef, pork, lamb, and meat from burgers, and other non-processed meat items made with these meats. Red meat intake was not related to risk of colorectal cancer (579 cases). The relative risk estimate for an increase in intake of 50 g of red meat was 1.01 (95% CI, 0.84–1.22) for colorectal cancer. Similar relative risks were observed for colon and rectal cancers. [The Working Group noted that meat intake was relatively low in the overall consortium, as many participants were either vegetarians or low meat eaters. The use of food diaries may also have led to overestimation of the number of non-consumers of infrequently consumed food items.]

In a pooled analysis of the Genetics and Epidemiology of Colorectal Cancer Consortium (GECCO) and the Colon Cancer Family Registry (CCFR) (Kantor et al., 2014), which included 9160 cases of colorectal cancer and 9280 controls, the pooled relative risk estimate for colorectal cancer for each serving per day increase in intake of red meat was 1.33 (95% CI, 1.23–1.44) for all studies combined. The purpose of the study was to investigate gene–environment interactions, and the estimates of associations reported were controlled only for age, sex, and study centre. In another paper based on the same pooled study, Figueiredo et al. (2014) reported a relative risk of 1.23 (95% CI, 1.12–1.34) for red meat consumption above versus below the median and a relative risk of 1.15 per quartile of intake. In another publication based on GECCO and the CCFR that included data from case–control studies nested in five cohorts, red meat consumption was related to colorectal cancer risk only from retrospective case–control studies. The pooled odds ratio from four retrospective case–control studies was 1.75 (95% CI, 1.55–1.98). The relationship was not modified by NAT2 enzyme activity (based on polymorphism at rs1495741) (Ananthakrishnan et al., 2015). No interaction involving any gene and red meat was detected in a genome-wide diet–gene interaction analysis in GECCO or in a study on colorectal cancer susceptibility loci (Hutter et al., 2012). [The exact definition of red meat was not given in these studies.]

Five additional cohort studies did not investigate the overall association between colorectal cancer risk and red meat consumption, but did evaluate associations with specific red meat items (data not reported in Table).

In a prospective study conducted by the Norwegian National Health Screening Service (143 cases of colon cancer) among Norwegian men and women aged 20–54 years between 1977 and 1983 (Gaard et al., 1996), consumption of meatballs, meat stews, and fried or roasted meats was unrelated to colon cancer risk. [The Working Group noted that the analyses were only for specific red meat types and adjusted only for age.]

In the Women's Health Study (WHS), a randomized trial in the USA of low-dose aspirin and vitamin E in the primary prevention of cancer and cardiovascular disease, diet was assessed at study baseline using a 131-item FFQ that was

previously validated in the NHS. Two hundred and two incident colorectal cancer cases were identified during 8.7 years of follow-up. The definition of red meat included hot dogs, bacon, and other processed meats. Data for consuming unprocessed red meat were limited to beef or lamb as a main dish and were stratified by cooking method. In comparison with beef or lamb cooked rare or medium–rare, the relative risks were 0.73 (95% CI, 0.47–1.11) for medium doneness, 1.02 (95% CI, 0.68–1.52) for medium well-done meat and 0.94 (95% CI, 0.63–1.41) for well-done meat (P_{trend} = 0.83) (Lin et al., 2004). Meat doneness was available only for beef or lamb as a main dish. This study also reported a positive association between white meats and colorectal cancer.]

In a case–cohort analysis including 448 colon and 160 rectal cancer cases and a subcohort of 2948 participants in the Netherlands Cohort Study (NLCS), intake of beef, pork, minced meat, or liver was not significantly associated with colon or rectal cancer risk, although a positive association was suggested for beef and colon cancer (RR for highest vs lowest category of beef intake, 1.28; 95% CI, 0.96–1.72; P_{trend} = 0.06) (Brink et al., 2005). In another analysis (434 colon cancer cases, 154 rectal cancer cases) (Lüchtenborg et al., 2005), beef consumption was associated with an increased risk of colon tumours without a truncating *APC* somatic mutation. The incidence rate ratio for the highest versus the lowest quartile of intake was 1.58 (95% CI, 1.10–2.25; P_{trend} = 0.01). [The Working Group noted that the follow-up period was short, and cases diagnosed in the first years of follow-up were excluded.]

A recent full cohort analysis of the Netherlands Cohort Study – Meat Investigation Cohort (NLCS-MIC), with all individuals reporting to be vegetarian or to consume meat only 1 day/week, was conducted with 20.3 years of follow-up (Gilsing et al., 2015). For red meat, defined as fresh meat without chicken, no clear association was observed with colon or rectal cancer.

In a cohort study in Japan, 47 605 residents aged 40–64 years from the Miyagi Prefecture completed a self-administered, 40-item FFQ in 1990. Four hundred and seventy-four colorectal cancer cases were identified after an average follow-up of 11 years through linkage to the Miyagi Prefectural Cancer Registry. Relative risk estimates for the highest compared with the lowest intake were 0.93 (95% CI, 0.67–1.30; P_{trend} = 0.63) for beef and 1.13 (95% CI, 0.79–1.74; P_{trend} = 0.31) for pork intake. No associations were observed with risk of cancers of the colon, proximal or distal colon, and rectum (Sato et al., 2006). [The Working Group noted that the number of categories in the questionnaire was low, and there was low variability in meat intake. The median intake in the top category was 7.4 g/week for beef and 26.3 g/week for pork (excluding ham and sausage). Beef and pork combined was not investigated.]

In the Japan Public Health Center-based Prospective Study (JPHC Study), men and women completed a self-administered questionnaire in 1995–1999 at age 45–74 years (Takachi et al., 2011), and 1145 cases of colorectal cancer were identified until the end of 2006. The category of red meat was defined as including processed products and chicken liver. In women, a significant association between beef intake and colon cancer was observed (RR for fifth vs first quintile, 1.62; 95% CI, 1.12–2.34; P_{trend} = 0.04), and a non-significant association was observed for pork (RR for fifth vs first quintile, 1.42; 95% CI, 0.99–2.04; P_{trend} = 0.05) (Takachi et al., 2011). No significant association between beef or pork intake and colon or rectal cancer was observed in men. [The Working Group noted that although red and processed meat consumption was lower in this cohort than in cohorts from Western countries, there was a sevenfold difference in the median intakes of the lowest and highest quintiles. Total consumption of red meat was not investigated.]

(b) Processed meat

Associations between colorectal cancer and consumption of processed meat have been examined in 18 informative cohort studies and two pooled analyses (see Table 2.2.2); some of these studies also reported data for red meat.

Intake of processed meat (ham and sausages) was not related to colorectal cancer risk in the NYUWHS (Kato et al., 1997). The relative risk for the highest compared with the lowest quartile was 1.09 (95% CI, 0.59–2.02; P_{trend} = 0.735; 100 cases). [The Working Group noted that this study had a small sample size. The analyses were adjusted only for energy intake, age, place, and education level.]

Colorectal cancer was not associated with intake of processed meat in the ATBC Study in Finnish male smokers (185 cases) (Pietinen et al., 1999). The relative risk for the highest compared with the lowest quartile (medians, 122 g/day and 26 g/day, respectively) was 1.2 (95% CI, 0.7–1.8; P_{trend} = 0.78). [The Working Group noted that a main limitation of this study was the low number of cases.]

In the WHS, processed meat intake was inversely, although not significantly, associated with colorectal cancer in the analysis including 202 cases (Lin et al., 2004). The relative risk for the highest compared with the lowest quintile was 0.85 (95% CI, 0.53–1.35; P_{trend} = 0.25; medians of the quintiles, 0.5 servings/day and 0 servings/day, respectively). Processed meat was defined as hot dogs, bacon, and other processed meats. [The Working Group noted that this study reported an inverse non-significant association between total red meat and colorectal cancer, and positive associations between white meat and colorectal cancer, in contrast with the results of other cohort studies.]

In the IWHS cohort (Bostick et al., 1994), which included 212 cases, the relative risk of colon cancer for consumption of > 3 servings/week of processed meat compared with none was 1.51 (95% CI, 0.72–3.17; P_{trend} = 0.45). In the same cohort, nitrate-treated meats were not related to colon cancer in women with or without a family history of colon cancer in first-degree relatives (Sellers et al., 1998). [The Working Group noted that this study had a small sample size, follow-up was 5 years, and cases identified in the first years of follow-up were not excluded from the analyses.]

In a community-based prospective study in Takayama, Japan, including 213 cases of colorectal cancer, there was a twofold, significant increased risk of colon cancer only in men who consumed a higher intake of processed meats (Oba et al., 2006). The relative risks for the highest compared with the lowest tertile of intake were 1.98 (95% CI, 1.24–3.16; P_{trend} < 0.01) in men and 0.85 (95% CI, 0.50–1.43; P_{trend} = 0.62) in women. Processed meat was defined as ham, sausage, bacon, and yakibuta (Chinese-style roasted pork). The results did not change after the exclusion of cases diagnosed in the first 3 years of follow-up.

Processed meat intake was associated with colorectal cancer in the Melbourne Collaborative Cohort Study (451 cases) (English et al., 2004). The relative risks were 1.5 (95% CI, 1.1–2.0; P_{trend} = 0.01) for the highest compared with the lowest intake and 1.07 (95% CI, 1.01–1.13) for an increase of 1 serving/week. Processed meat intake was more strongly associated with risk of rectal cancer than with risk of colon cancer in a categorical analysis. The relative risks for the highest compared with the lowest quartile were 1.3 (95% CI, 0.9–1.9) for the colon and 2.0 (95% CI, 1.1–3.4) for the rectum. The hazard ratios for each additional serving per week were similar; the hazard ratios were 1.07 (95% CI, 1.00–1.14) and 1.08 (95% CI, 0.99–1.18) for the colon and rectum, respectively (P = 0.8, test of homogeneity of trends).

In the Breast Cancer Detection Demonstration Project (BCDDP) in the USA (467 cases), women completed a 62-item National Cancer Institute (NCI)/Block FFQ. The Block FFQ defined processed meat as bacon, ham, lunchmeat,

hot dogs, and sausage (Flood et al., 2003). The relative risk for the highest compared with the lowest quintile of processed meat intake was 0.97 (95% CI, 0.73–1.28; P_{trend} = 0.35; medians of the quintiles, 22.2 and 0.02 g/1000 kcal, respectively) after adjustment for age, energy, and total meat consumption. The inclusion of several other variables, including smoking, alcohol drinking, and BMI, did not materially change the estimates and were not kept in the final models. [The Working Group noted that colorectal cancer diagnosis was self-reported in most cases. Pathology reports were obtained for 79% of these cases, and the diagnosis confirmed in 94% of them, suggesting that case identification was not an issue.]

In the Miyagi Cohort Study in Japan, processed meat consumption was not related to risk of colorectal cancer (colorectum, colon, proximal colon, and distal colon and rectum); the analysis included 474 incident colorectal cancer cases (Sato et al., 2006). The relative risk for the highest compared with the lowest quartile was 0.91 (95% CI, 0.61–1.35; P_{trend} = 0.99). No associations were observed for cancers of the colon, rectum, or proximal and distal colon. [The Working Group noted that the number of categories in the questionnaires was low, and there was low variability in meat intake due to low frequency of consumption of some meat items.]

In the Danish Diet, Cancer and Health study (18% of the cases were included in the Danish component of the EPIC study), the relative risks per 25 g/day increase in intake of processed meats were 1.03 (95% CI, 0.94–1.13; 644 cases) for the colon and 0.93 (95% CI, 0.81–1.07; 345 cases) for the rectum (Egeberg et al., 2013). No significant associations were observed with intakes of sausages, cold cuts, or liver pâté. In addition, associations were not modified by four polymorphisms (*XPA* A23G, *XPC* Lys939Gln, *XPD* Lys751Gln, and *XPD* Asp312Asn) of enzymes involved in the nucleotide excision repair pathway in a case–control study nested in the cohort (405 colorectal cancer cases, 810 controls) (Hansen et al., 2007). Another analysis of 379 colorectal cancer cases and 769 subcohort members showed no association with consumption of processed meat when stratified by *NAT1* or *NAT2* genotypes (Sørensen et al., 2008).

In the SMC (Larsson et al., 2005a), processed meat intake was not related to risk of colorectal cancer or colorectal cancer subsites. The relative risk estimates for the highest compared with the lowest quartile of intake were 1.07 (95% CI, 0.85–1.33; P_{trend} = 0.23) for the colorectum (733 cases), 1.02 (95% CI, 0.69–1.52; P_{trend} = 0.97) for the proximal colon (234 cases), 1.39 (95% CI, 0.86–2.24; P_{trend} = 0.20) for the distal colon (155 cases), and 0.90 (95% CI, 0.60–1.34; P_{trend} = 0.88) for the rectum (230 cases). [The Working Group noted that the dietary questionnaire had 67 food items. Follow-up was long (13.9 years on average), and changes in dietary habits during follow-up were not taken into account. Case ascertainment was virtually complete, and the analyses were controlled for main potential confounders.]

In the Singapore Chinese Health Study (SCHS) (Butler et al., 2008b), the relative risk for the highest compared with the lowest quartile of processed meat intake was 1.16 (95% CI, 0.95–1.41; 941 incident colorectal cancer cases after an average follow-up of 10 years). Types of processed meats were not defined. [The Working Group noted that the cut-points of the quartiles were not given, and processed meat intake was low (the 95th percentile of processed meat intake in non-cases was 10 g/day).]

In the JPHC Study (Takachi et al., 2011) (1145 cases of cancer of the colorectum), processed meat included ham, sausage or wiener sausage, bacon, and luncheon meat. The relative risks of colon cancer for the highest compared with the lowest quintile were 1.27 (95% CI, 0.95–1.71; P_{trend} = 0.10) in men and 1.19 (95% CI, 0.82–1.74; P_{trend} = 0.64) in women. Similar results were observed for proximal and distal colon cancers. The relative risk for rectal cancer was 0.70 (95% CI, 0.45–1.09; P_{trend} = 0.10) in men and 0.98 (95% CI, 0.53–1.79;

P_{trend} = 1.00) in women. [The Working Group noted that the range of processed meat intake was low. The median intake in the top quintile was 16 g/day in men and 15 g/day in women.]

In the European EPIC study (1329 incident colorectal cancer cases), processed meats included mostly pork and beef preserved by methods other than freezing, such as salting (with and without nitrites), smoking, marinating, air-drying, or heating (i.e. ham, bacon, sausages, blood sausages, meat cuts, liver pâté, salami, bologna, tinned meat, luncheon meat, corned beef, and others). The relative risk of colorectal cancer for an intake of > 80 g/day of processed meat compared with < 10 g/day of processed meat was 1.42 (95% CI, 1.09–1.86; P_{trend} = 0.02) (Norat et al., 2005). The relative risk for an increase in intake of 100 g/day of processed meat was 1.32 (95% CI, 1.07–1.63; P_{trend} = 0.009). This was strengthened to 1.70 (95% CI, 1.05–2.76; P_{trend} = 0.03) after calibration using 24-hour recall data from a subset of the study population. The relative risks for the highest versus the lowest quintile were 1.62 (95% CI, 1.04–2.50), 1.48 (95% CI, 0.87–2.53), and 1.19 (95% CI, 0.70–2.01) for rectal, distal, and proximal colon cancer, respectively. No significant differences across cancer sites were observed ($P_{heterogeneity}$ = 0.87). Intake of ham (RR for highest vs lowest intake, 1.12; 95% CI, 0.90–1.37; P_{trend} = 0.44), bacon (HR, 0.96; 95% CI, 0.79–1.17; P_{trend} = 0.34), and other types of processed meats (HR, 1.05; 95% CI, 0.84–1.32; P_{trend} = 0.22) was not significantly related to colorectal cancer risk. [This was a large study in 10 European countries that used extensive dietary questionnaires. Follow-up is virtually complete, and the analyses were adjusted for main potential confounders.] In a substudy of the EPIC-Norfolk study, higher consumption of processed meat was associated with an increased risk of colorectal cancer harbouring a truncating *APC* mutation and, in particular, rectal tumours with GC→AT transitions compared with colorectal cancer without mutations (OR for increment of 19 g/day, 1.68; 95% CI, 1.03–2.75) (Gay et al., 2012).

A case–cohort analysis of the Netherlands Cohort Study (NLCS) included 1535 incident colorectal cancer cases identified after 9.3 years of follow-up through linkage to the Netherlands Cancer Registry (Balder et al., 2006). The relative risks for processed meats (meat items mostly cured, and sometimes smoked or fermented) and colorectal cancer (RR for highest vs lowest quartile) were 1.18 (95% CI, 0.84–1.64; P_{trend} = 0.25) in men and 1.05 (95% CI, 0.74–1.48; P_{trend} = 0.62) in women. No associations were observed for colon or rectal cancer in men or women. In another analysis in the same cohort, consumption of meat products (same definition as for processed meats) was significantly positively associated with risk of colon tumours with a wildtype *K-ras* gene (RR for highest vs lowest quartile of intake, 1.42; 95% CI, 1.00–2.03; P_{trend} = 0.03) (Brink et al., 2005) and *APC*-positive colon cancer (RR for highest vs lowest quartile of intake, 1.61; 95% CI, 0.96–2.71; P_{trend} = 0.04) (Lüchtenborg et al., 2005), but not with other types of colon or rectal tumours. These analyses included more than 430 colon and 150 rectal cancers occurring during 7.3 years of follow-up, excluding the first 2.3 years, and 2948 subcohort members. An analysis of the MIC embedded within the NLCS, which included individuals reporting to be vegetarian or to consume meat only 1 day/week, was conducted with 20.3 years of follow-up (Gilsing et al., 2015). For processed meat, a statistically significant association with rectal cancer was observed (RR, 1.36 for every 25 g/day of intake; 95% CI, 1.01–1.81; P_{trend} = 0.008). No significant association was observed with colon cancer, although a positive association with distal colon cancer was suggested.

The Cancer Prevention Study II (CPS-II) Nutrition Survey enrolled men and women in the USA who completed a mailed FFQ in 1992–1993 (1667 incident colorectal cancer cases) (Chao et al., 2005). The relative risk for the highest quintile compared with the lowest quintile of processed meat intake was

1.13 (95% CI, 0.91–1.41; P_{trend} = 0.02) in women and men combined. A significant trend was observed in men (P_{trend} = 0.03), but not in women (P_{trend} = 0.48). No significant associations were observed with proximal or distal colon cancer, and rectal cancer, although the relative risk estimates were higher for distal and rectal tumours. When long-term consumption of processed meat was considered, based on consumption reported in 1982 and at baseline in 1992–1993, participants in the highest tertile of consumption had an increased risk of distal colon cancer (RR, 1.50; 95% CI, 1.04–2.17). A non-significant 14% and 21% increased risk of cancers of the proximal colon, and rectosigmoid junction and rectum were observed. [The Working Group noted that the 1982 questionnaire did not assess the number of servings per day, and could not differentiate people who ate multiple servings from those who ate processed meat only once per day. It was also not possible to estimate total energy intake from the 1982 dietary questionnaire.]

In the NHS and the HPFS (Bernstein et al., 2015), using cumulative dietary intake data, the relative risk of colorectal cancer per 1 serving/day increment of processed meat was 1.15 (95% CI, 1.01–1.32; P_{trend} = 0.03), and it was 1.08 (95% CI, 0.98–1.18; P_{trend} = 0.13) when diet, as assessed at baseline, was analysed. Using cumulative dietary intake data, the relative risks were 0.99 (95% CI, 0.79–1.24) for proximal colon cancer (1151 cases), 1.36 (95% CI, 1.09–1.69; P_{trend} = 0.006) for distal colon cancer (817 cases), and 1.18 (95% CI, 0.89–1.57) for rectal cancer (589 cases). [The analyses were extensively adjusted for potential risk factors. The use of repeated questionnaires should have reduced dietary measurement error. Several sensitivity and stratified analyses showed the robustness of the results.] In an earlier nested case–control in the NHS including 197 cases identified by the year 2000 (Tranah et al., 2006), colorectal cancer risk was not related to consumption of > 1 slice/week of processed meat (OR, 1.06; 95% CI, 0.73–1.55), > 2 pieces/week of bacon (OR, 0.94; 95% CI, 0.56–1.58), or > 1 hot dog/week (OR, 1.06; 95% CI, 0.68–1.65). Compared with infrequent consumption of these items, no association with all types of processed meats combined was observed. There was no significant interaction on a multiplicative scale between the *MGMT* genotype and intake of processed meat, bacon, and hot dogs in women.

In the Multiethnic Cohort Study, the relative risk of colorectal cancer (n= 3404 cases) for the highest compared with the lowest quintile of processed meat intake was 1.06 (95% CI, 0.94–1.19; P_{trend} = 0.259) (Ollberding et al., 2012). Relative to the significant association that was observed in models adjusted only for age, ethnicity, and sex (HR, 1.25; 95% CI, 1.12–1.40; $P < 0.001$), this relative risk was attenuated after further adjustment for family history of colorectal cancer, history of colorectal polyps, BMI, pack-years of cigarette smoking, nonsteroidal anti-inflammatory drug use, alcohol consumption, vigorous physical activity, history of diabetes, hormone replacement therapy use (women only), total calories, and dietary fibre, calcium, folate, and vitamin D. [The main strengths of this study were its large size, the ethnic diversity of the study population, and the population-based sampling frame that was used, which allowed for better generalizability of the study results. As indicated in the section on red meats, the Working Group noted that there was a strong attenuation of the association estimates after multivariable adjustment.]

The National Institutes of Health – American Association of Retired Persons (NIH-AARP) Diet and Health Study was based on a cohort of over 500 000 men and women from eight states in the USA, aged 50–71 years at baseline (1995–1996), who completed a validated, 124-item FFQ. In an analysis of 5107 colorectal cancer cases, identified on average during 8.2 years of follow-up (Cross et al., 2007), processed meat consumption was significantly related to colorectal cancer risk. The relative risk for the fifth compared with the first quintile of intake was 1.20 (95% CI, 1.09–1.32;

P_{trend} < 0.001). The relative risks were similar for colon cancer and rectal cancer. Similar results were observed in another study in the same cohort that explored the mechanisms relating colorectal cancer and meat intake (Cross et al., 2010). The overall relative risk for the association between colorectal cancer and processed meat intake was 1.16 (95% CI, 1.01–1.32; P_{trend} = 0.017) for the highest compared with the lowest quintile. For colon and rectal cancer separately, the relative risks for the same comparison were 1.11 (95% CI, 0.95–1.29) and 1.30 (95% CI, 1.00–1.68), respectively. Nitrate and nitrite intake from processed meats was estimated using a database containing measured values of nitrate and nitrite from 10 types of processed meats. The relative risk of colorectal cancer for the highest compared with the lowest quintile of intake of nitrate from processed meat was 1.16 (95% CI, 1.02–1.32; P_{trend} = 0.001; medians of the quintiles, 289.2 µg/1000 kcal per day and 23.9 µg/1000 kcal per day, respectively). The association with nitrite from processed meat did not attain statistical significance (RR for highest vs lowest quintile, 1.11; 95% CI, 0.97–1.25; P_{trend} = 0.055; medians of the quintiles, 194.1 µg/1000 kcal per day and 11.9 µg/1000 kcal per day, respectively). In a lag analysis excluding the first 2 years of follow-up (1941 colorectal cancer cases), the association between processed meat intake and colorectal cancer remained significant (HR, 1.19, 95% CI, 1.02–1.39, P_{trend} = 0.013). Participants in the NIH-AARP study also completed a 37-item FFQ about diet 10 years before baseline. Participants in the highest intake category of processed meat 10 years before baseline had a higher risk of cancer of the colon (RR, 1.30; 95% CI, 1.13–1.51; P_{trend} < 0.01) and rectum (RR, 1.40; 95% CI, 1.09–1.81; P_{trend} = 0.02) than participants in the lower intake category (Ruder et al., 2011). [The Working Group noted that the questionnaire to assess diet 10 years before baseline was not validated, and did not allow for estimation of total energy intake.]

In the United Kingdom Dietary Cohort Consortium (Spencer et al., 2010), processed meat was assessed as ham, bacon, the meat component of sausages, and other items made with processed meat. For a 50 g/day increase in consumption of processed meat, the odds ratio for colorectal cancer was 0.88 (95% CI, 0.68–1.15). The odds ratios for colon and rectal cancer separately were also non-significantly different from unity.

In a pooled analysis of the GECCO study (Kantor et al., 2014), the pooled relative risk of colorectal cancer for each serving per day increase in intake of processed meats was 1.48 (95% CI, 1.30–1.70) for all studies combined. [The main strength of the study was the large number of cases included in the analysis.] In genome-wide diet–gene interaction analyses in GECCO, which included five retrospective case–control studies and five case–control studies nested in prospective studies, there was a positive interaction between rs4143094 (10p14/near *GATA3*) and processed meat consumption (OR, 1.17; 95% CI, 1.11–1.23; *P* = 8.7E–09), which was consistently observed across studies ($P_{heterogeneity}$ = 0.78) (Figueiredo et al., 2014). The risk of colorectal cancer associated with processed meat was increased among individuals with the rs4143094–TG (OR, 1.20; 95% CI, 1.13–1.26) and –TT genotypes (OR, 1.39; 95% CI, 1.22–1.59), and null among those with the –GG genotype (OR, 1.03; 95% CI, 0.98–1.07). In another study in GECCO on gene–environment interactions and colorectal cancer susceptibility loci, no interaction with processed meat was detected (all studies combined) (Hutter et al., 2012).

In the prospective study conducted by the Norwegian National Health Screening Service (Gaard et al., 1996), colon cancer risk was higher in women who consumed fried or poached sausages as their main meal ≥ 5 times/month compared with those who reported a consumption of < 1 time/month (RR, 3.50; 95% CI, 1.02–11.9; P_{trend} = 0.03). Among men, a similar, but not significant, association was observed

(RR, 1.98; 95% CI, 0.70–5.58; P_{trend} = 0.35). [The Working Group noted that only specific types of processed meats were investigated. The analyses were only adjusted for age. The 50 535 participants were relatively young (age, 20–54 years) at recruitment in 1977–1983, and only 143 cases of colon cancer were identified through linkage to the Norwegian Cancer Registry after 11.4 years of follow-up.]

(c) Red meat and processed meat combined

Several studies reported on the risk of colorectal cancer associated with measures of meat consumption, which included processed meats and unprocessed red meats, both red and white meats, or meats without a clear definition. The Working Group considered these data to be less informative than associations with red meat and processed meat considered separately. Key findings from this group of studies are summarized in this section and given in Table 2.2.1.

Several other studies reported data for specific red meat items, such as beef or pork, or for unprocessed red meat or processed meat separately, as well as for a broader category including both types of meats (e.g. Bostick et al., 1994; Pietinen et al., 1999; Lin et al., 2004; Larsson et al., 2005a; Norat et al., 2005; Spencer et al., 2010; Takachi et al., 2011; Ollberding et al., 2012; Bernstein et al., 2015). For these studies, the more informative data for red meat and for processed meat are reviewed in the preceding sections, but data for the combined category are not presented.

In the Finnish Mobile Clinic Health Examination Survey (109 colorectal cancer cases), the relative risks for the highest compared with the lowest quartile of red meat intake were 1.50 (95% CI, 0.77–2.94) for colorectal cancer, 1.34 (95% CI, 0.57–3.15) for colon cancer, and 1.82 (95% CI, 0.60–5.52) for rectal cancer (Järvinen et al., 2001). [The Working Group considered that the category of red meat may have included processed items. In contrast with other studies, there was a significant increase of colorectal cancer in participants consuming poultry compared with non-consumers. An important limitation of the study was the small size.]

In the Physicians' Health Study (PHS) (originally designed as a double-blind trial of aspirin and β-carotene as preventive measures for cardiovascular disease and cancer), diet at enrolment was assessed using an abbreviated FFQ, in which red and processed meat intake included beef, pork, lamb, and hot dogs. A case–control study nested in the PHS cohort (212 colorectal cancer cases) (Chen et al., 1998) found that combined red and processed meat intake was not significantly related to colorectal cancer risk (RR, 1.17; 95% CI, 0.68–2.02; for ≥ 1 vs ≤ 0.5 servings/day). There was no significant interaction with *NAT1*/*NAT2* genotypes (all $P_{interaction}$ > 0.16). [The Working Group noted that the definition of red meat included hot dogs, and analyses were not controlled for total energy intake, BMI, and other important confounders.]

A case–cohort study done within the CLUE II cohort (250 genotyped cases) (Berndt et al., 2006) reported a non-statistically significant positive association between red meat [including processed meat] intake and colorectal cancer risk (RR for highest vs lowest tertile, 1.32; 95% CI, 0.86–2.02), when adjusting for age, sex, and total energy. [The main focus of this paper was to explore gene–environment interactions with nucleotide excision repair genes; therefore, analyses of the main effects of meat were limited.]

A nested case–control study, the EPIC-Norfolk component of EPIC, investigated the effect of the variant genotype *MGMT* Ile143Val on colorectal cancer risk among 273 colorectal cancer cases and 2984 matched controls. The odds ratio was 1.43 (95% CI, 0.82–2.48; $P_{interaction}$ = 0.04) for the variant genotype carriers and red and processed meat intake above the median compared with common genotype carriers and red and processed meat intake below the median (Loh et al., 2010). The polymorphism was not related to colorectal cancer risk. [The Working Group noticed that

red and processed meat intakes were assessed according to baseline 7-day food diary data.]

The Breast Cancer Detection Demonstration Project (BCDDP) (487 colorectal cancer cases) (Flood et al., 2003) reported a relative risk of 1.04 (95% CI, 0.77–1.41) for > 52.2 g/1000 kcal compared with < 6.1 g/1000 kcal (quintiles) of combined red and processed meat intake. [The Working Group noted that the associations became stronger after multiple adjustments.]

In a prospective study based on a trial of screening for breast cancer, the Canadian National Breast Screening Study (CNBSS), participants reported their diet in 1982 using an 86–food item SQFFQ (Kabat et al., 2007). Red meat intake, defined as beef, veal, pork, ham, bacon, and pork-based luncheon meats, was related to an increased risk of rectal cancer, but not colon cancer. For the highest compared with the lowest quintile (> 40.3 and < 14.2 g/day, respectively), the relative risks were 1.12 (95% CI, 0.86–1.46) for colorectal cancer (617 cases), 0.88 (95% CI, 0.64–1.21) for colon cancer (428 cases), and 1.95 (95% CI, 1.21–3.16; $P_{trend} = 0.008$) for rectal cancer (195 cases). No associations were observed with cancers of the proximal and distal colon (data were not shown).

In a study based on the Multiethnic Cohort, no clear evidence was found for an interaction with *NAT2* or *NAT1* acetylator genotypes on the association between colorectal cancer risk and red and processed meat intake, or meat doneness preference in 1009 cases and 1522 controls (Nöthlings et al., 2009).

In the CPS-II Nutrition Survey (1667 colorectal cancer cases) (Chao et al., 2005), red meat was defined as including bacon, sausage, liver, hot dogs, ham, bologna, salami, and lunchmeat, as well as unprocessed beef and pork. The relative risk for colon cancer and red meat (as defined above) consumption assessed at baseline was 1.15 (95% CI, 0.90–1.46; $P_{trend} = 0.04$) in men and women combined. Consumption of these meats was related to an increased risk of cancers of the rectosigmoid junction and rectum (RR, 1.71; 95% CI, 1.15–2.52; $P_{trend} = 0.007$; for highest vs lowest quintile), but not to cancers of the rectosigmoid junction only (numerical data were not shown). [The Working Group noted that an earlier questionnaire used to estimate long-term consumption assessed only frequency of intake; thus, estimation of total energy intake from that questionnaire was not possible.]

The NIH-AARP study defined red meat as beef, pork, and lamb, including bacon, cold cuts, ham, hamburger, hot dogs, liver, sausage, and steak. After an average follow-up of 7 years, 2719 colorectal cancer cases were identified. Red meat and processed meat were related to an increased risk of colon and rectal cancer. The relative risks for the highest compared with the lowest quintile of red and processed meat intake (61.6 and 9.5 g/1000 kcal, respectively) were 1.24 (95% CI, 1.09–1.42; $P_{trend} < 0.001$) for colorectal cancer, 1.21 (95% CI, 1.03–1.41; $P_{trend} < 0.001$) for colon cancer, and 1.35 (95% CI, 1.03–1.76; $P_{trend} = 0.024$) for rectal cancer (Cross et al., 2007, 2010). Significant associations were also observed when intake was analysed on a continuous scale. The relative risks were similar for proximal and distal colon cancer. The findings remained the same after exclusion of the first 2 years of follow-up. Study participants also completed a 37-item FFQ on dietary intake 10 years before baseline (Ruder et al., 2011). Participants in the highest intake category of red and processed meat 10 years before baseline (defined as ground beef, roast beef or steak, cold cuts, bacon or sausage, and hot dogs) had a higher risk of colon cancer (RR, 1.46; 95% CI, 1.26–1.69; $P_{trend} = 0.01$) than participants in the lowest intake category. A significant trend was observed for the rectum (RR, 1.24; 95% CI, 0.97–1.59; $P_{trend} = 0.03$). [The Working Group noticed that the FFQ to assess diet 10 years before baseline was not validated, and did not allow for estimation of total energy intake for adjustment of the analyses.]

(d) Haem iron

Data on the association between colorectal cancer risk and haem iron intake were available from five cohort studies reviewed in this section (Lee et al., 2004; Larsson et al., 2005b; Balder et al., 2006; Kabat et al., 2007; Cross et al., 2010). One study reported a statistically significant positive association with proximal, but not distal colon cancer (Lee et al., 2004), and another found a significant positive association with colon cancer after excluding 2 years of follow-up when registry data were believed to be incomplete (Balder et al., 2006). Relative risks were null or non-significantly increased (range, 0.99–1.31) in three other studies that reported data on colon cancer (Larsson et al., 2005b; Kabat et al., 2007; Cross et al., 2010), rectal cancer (Kabat et al., 2007; Cross et al., 2010), and colorectal cancer overall (Kabat et al., 2007; Cross et al., 2010). [The Working Group noted that the overall evidence on haem iron was limited by the possibility of publication bias and the few databases for estimating haem iron intake from dietary questionnaires.]

2.2.2 Case–control studies

Numerous case–control studies have examined the association between red or processed meat intake and risk of colorectal cancers. This section presents studies by how meat was defined in the following order: red meat and processed meat separately, red meat and processed meat combined, and then red meat, unclear whether fresh or processed.

In reviewing and interpreting the available literature, the Working Group considered for each of these categories the criteria summarized in Section 2.1 and the greatest weight was given to studies that met the following criteria:

- Had an unambiguous definition of red and processed meat (studies that reported data for unprocessed red and/or processed meat separately, and/or listed subtypes of meats included in each meat definition) (see criterion 1 in Section 2.1.1);
- Met the definition of a population-based study, or included hospital-based cases using approaches that ensured a representative sample of the underlying population (e.g. community hospitals that serve specific regions in a country) and population-based controls (see criterion 3 in Section 2.1.3);
- Used a previously validated dietary instrument (see criterion 4 in Section 2.1.4); and
- Considered detailed assessment for potential confounders, in particular total energy intake (see criterion 5 in Section 2.1.5).

The Working Group also considered as informative studies that met these criteria but showed limitations in criteria 3, 4, or 5 summarized above. Sample size was considered for informativeness (see criterion 2 in Section 2.1.2). The main limitations identified by the Working Group are noted between brackets in the description of each paper.

The Working Group gave less weight to other studies that showed important limitations in criterion 3, 4, or 5 above, and/or defined "total red meat" without further clarifying whether processed meat was included.

The Working Group excluded the following papers due to the reasons described below. None of the excluded studies are presented in the tables.

Studies with fewer than 100 cases were excluded because of limited statistical power (e.g. Phillips, 1975; Dales et al., 1979; Pickle et al., 1984; Tajima & Tominaga, 1985; Vlajinac et al., 1987; Wohlleb et al., 1990; Nashar & Almurshed, 2008; Guesmi et al., 2010; Ramzi et al., 2014).

Certain dietary patterns (e.g. traditional "Western-type" diet) are often characterized by a higher intake of red and processed meats, but these patterns also capture other foods that tend to be consumed with a diet high in red and processed meats, such as refined grains and a high intake of sugar. Thus, these studies are not

specific enough to address the role of red meat and processed meats. Therefore, the Working Group also excluded from this review studies that reported on dietary patterns or dietary diversity, or only examined red meat in combination with other foods (e.g. McCann et al., 1994; Slattery et al., 1997, 2003; Rouillier et al., 2005; Satia et al., 2009; De Stefani et al., 2012b; Pou et al., 2012, 2014; Chen et al., 2015). In addition, the Working Group also excluded studies that reported on "meat" variables without a clear definition of what types of meats were included, making it impossible to rule out the inclusion of poultry and/or fish (e.g. Zaridze et al., 1992; Roberts-Thomson et al., 1996; Ping et al., 1998; Welfare et al., 1999; Zhang et al., 2002; Kim et al., 2003; Yeh et al., 2003, 2005; Kuriki et al., 2006; Little et al., 2006; Wakai et al., 2006; Skjelbred et al., 2007; Sriamporn et al., 2007; Jedrychowski et al., 2008; Arafa et al., 2011; Mahfouz et al., 2014; Pimenta et al., 2014), and studies that stated clearly that they had included poultry in their meat definition (e.g. Hu et al., 1991; Fernandez et al., 1996; Kuriki et al., 2005; Ganesh et al., 2009).

The Working Group also excluded studies that did not provide sufficient information to abstract risk estimates for red and processed meat intake per se or within strata defined by genotype (e.g. Gerhardsson de Verdier et al., 1990; Ghadirian et al., 1997; Keku et al., 2003; Forones et al., 2008; da Silva et al., 2011; Gialamas et al., 2011; Silva et al., 2012; Zhivotovskiy et al., 2012; Angstadt et al., 2013; Helmus et al., 2013). Studies were not described if they only reported on estimated amounts of carcinogens derived from meat, and not on meat variables. Of note, studies that reported on the same study population, published at different times, were generally summarized together, if applicable. The most recent, complete, or informative publication was included.

A few studies reported on selected red meat types (e.g. beef), groups of red meat types (e.g. beef/pork), or total processed meats, and presented estimates for total red meat variables, including processed meats. For these studies, the Working Group only summarized the estimates for red meat types and/or processed meat, but not the estimates for the combination of both, as the Working Group did not find these as informative.

Studies that unambiguously defined red meat as unprocessed only, or as unprocessed and processed combined, or did not provide an unambiguous definition and referred to "total red meat", are summarized in Table 2.2.3. Studies that unambiguously defined processed meat are summarized in Table 2.2.4.

(a) Red meat

See Table 2.2.3

(i) Studies considered to be informative

The case–control studies that follow reported results for red meat and were considered informative by the Working Group. These studies were given more weight in the evaluation. The studies are presented in order by sample size, from largest to smallest.

Joshi et al. (2015) (3350 cases, 3504 controls) presented results for colorectal cancer, and for colon and rectal cancer, and for subtypes of colorectal cancer defined by mismatch repair (MMR) proficiency from a population-based study done in Canada and the USA. They reported a non-statistically significant positive association with red meat (Q5 vs Q1 OR, 1.2; 95% CI, 1.0–1.4; P_{trend} = 0.085), with no associations for total beef or pork, and a marginal positive association for organ meats (Q5 vs Q1 OR, 1.2; 95% CI, 1.0–1.4; P_{trend} = 0.058). No differences were observed between colon and rectal cancer, and no other differences were observed between MMR-proficient and MMR-deficient tumours. When cooking methods were considered, stronger, statistically significant associations emerged; a positive association was

observed for pan-fried beef steak (Q4 vs Q1 OR, 1.3; 95% CI, 1.1–1.5; $P_{trend} < 0.001$), which was stronger among MMR-deficient cases. A positive association was also observed with pan-fried hamburgers among MMR-deficient colorectal cancer cases (Q4 vs Q1 OR, 1.5; 95% CI, 1.0–2.1; $P_{trend} < 0.01$). Among oven-broiled meats, a statistically significant positive association was reported for short ribs or spare ribs (Q4 vs Q1 OR, 1.2; 95% CI, 1.0–1.5; $P_{trend} = 0.002$), which was restricted and stronger among MMR-deficient colorectal cancer cases (Q4 vs Q1 OR, 1.9; 95% CI, 1.12–3.00; $P_{trend} = 0.003$). No associations were reported for oven-broiled beef steak or hamburgers, grilled beef steak or short ribs or spare ribs; instead, an inverse association was reported for grilled hamburgers (Q4 vs Q1 OR, 0.8; 95% CI, 0.7–0.9; $P_{trend} = 0.002$). When use of marinades was considered ("Asian-style" vs "Western-style"), there was evidence that the use of "Asian-style" marinades (soy-based) was an effect modifier of the association with red meat, suggesting a stronger and statistically significant association among individuals who reported never using a soy-based marinade with their meats (Q5 vs Q1 OR, 1.3; 95% CI, 1.1.–1.6; $P_{trend} = 0.007$; $P_{interaction} = 0.008$). Overall, it was indicated that, given the many estimates obtained, if a Bonferroni correction was applied for multiple testing, the only statistically significant association would be the association between pan-fried beef steak and colorectal cancer risk, particularly for MMR-deficient tumours. The estimates for three different heterocyclic aromatic amines (HAAs), PhIP, DiMeIQx, and MeIQx were presented, and a positive association with increasing levels of DiMeIQx and MMR-deficient colorectal cancer was reported.

As part of a multicancer, population-based case–control study in Canada, which examined 18 cancer sites, Hu et al. (2007) (1723 cases, 3097 controls) reported that beef, pork, or lamb as a main dish and hamburger intake were positively associated with risk of proximal colon cancers in men only, but not in women. In men, the odds ratios for the highest versus the lowest tertile of intake (servings/week) were 1.5 (95% CI, 1.0–2.4; $P_{trend} = 0.05$) for beef, pork, or lamb as a main dish and 2.1 (95% CI, 1.3–3.5; $P_{trend} = 0.006$) for hamburger. A borderline positive association between hamburger intake in men and distal colon cancers was also observed. The odds ratio for the second tertile versus the lowest tertile was 1.4 (95% CI, 1.0–1.9), and the odds ratio for the highest tertile versus the lowest tertile was 1.4 (95% CI, 0.9–2.0; $P_{trend} = 0.11$).

Kampman et al. (1999) (1542 cases, 1860 controls) conducted a population-based case–control study in the USA, and reported that red meat intake was not associated with colon cancer in men (highest vs lowest intake OR, 0.9; 95% CI, 0.7–1.3) or women (OR, 1.0; 95% CI, 0.7–1.5). In both men and women, higher doneness was not significantly associated with risk of colon cancer (well-done vs rare OR, 1.2; 95% CI, 0.9–1.5). Further, no significant interactions between red meat and the examined *NAT2* and *GSTM1* gene variants were found.

In a companion paper, Slattery et al. (1998) examined associations separately by stage of disease. Some non-significant positive associations between red meat and colon cancer by stage were noted. In men, the odds ratios for > 7.9 oz/week versus ≤ 2.6 oz/week were 1.5 (95% CI, 0.9–2.3) for local, 1.2 (95% CI, 0.8–1.9) for regional, and 0.9 (95% CI, 0.4–1.8) for distant metastasis. In women, the odds ratios for > 5.4 oz/week versus ≤ 1.7 oz/week was 1.2 (95% CI, 0.7–2.1) for local, 1.1 (95% CI, 0.7–1.8) for regional, and 0.5 (95% CI, 0.2–1.2) for distant metastasis. Other papers by Slattery et al. (2000, 2002a, b) examined associations by the molecular characteristics of the tumours and borderline positive associations between red meat intake and colon cancers were observed among cancers with *p53* mutations.

In a related publication (Murtaugh et al., 2004) (952 rectal cancer cases, 1205 controls),

no associations were observed between red meat intake and rectal cancers. The odds ratio for men consuming ≥ 6.1 servings/week versus < 2.9 servings/week was 1.08 (95% CI, 0.77–1.51). The odds ratio for women consuming ≥ 4.2 servings/week versus < 1.9 servings/week was 1.05 (95% CI, 0.72–1.53). A higher intake of well-done red meat was associated with a higher risk of rectal cancers in men compared with rare-done meat (OR, 1.33; 95% CI, 0.98–1.79; P_{trend} = 004). *NAT2*-phenotype and *GSTM1* did not consistently modify the rectal cancer risk associated with red meat intake. Follow-up papers combining the two aforementioned study populations reported no evidence for an interaction between red meat intake, cooking temperatures, use of red meat drippings red meat mutagen index or *CYP1A1* genotype and colorectal cancer . Nonetheless in men carrying the CYP1A1*1 allele, a higher intake of well-done red meat compared with rare-done meat intake was associated with a higher risk of colorectal cancer (OR, 1.37; 95% CI, 1.06–1.77; P_{trend} < 005). (Murtaugh et al., 2005). On the other hand, Murtaugh et al. (2006) found a higher risk of rectal cancer among those with a high intake of red meat and the vitamin D receptor gene FF genotype only. For high versus low intake of red meat for the FF genotype, the odds ratio was 1.45 (95% CI, 0.97–2.19), and for the Ff/ff genotypes combined, the odds ratio was 1.08 (95% CI, 0.74–1.58; $P_{interaction}$ = 0.06 additive, 0.09 multiplicative). [The Working Group noted that, in all these studies, the red meat variable included ham, likely baked ham, which is technically a processed meat.]

In a population-based case–control study in the USA (1192 colorectal cases, 1192 controls), Le Marchand et al. (1997) reported a positive association with beef/veal/lamb that was statistically significant among men (highest vs lowest quartile OR, 2.1; 95% CI, 1.4–3.1; P_{trend} < 0.0001), but not among women (highest vs lowest quartile OR, 1.3; 95% CI, 0.9–2.1; P_{trend} = 0.5). There was no association with pork. The odds ratio for the highest versus the lowest quartile in men was 1.2 (95% CI, 0.8–1.9; P_{trend} = 0.90), and the odds ratio in women was 0.7 (95% CI, 0.4–1.2; P_{trend} = 0.3). [The Working Group noted that the researchers also reported on a total red meat variable with more red meat items, but it also included processed meats. A positive statistically significant association was reported for this variable.]

Miller et al. (2013) (989 cases, 1033 controls) conducted a population-based study in the USA, and reported no association between red meat intake and colorectal cancer, and no differences between colon and rectal cancer. When considering cooking methods, they reported a positive association with pan-fried red meat (Q5 vs Q1 OR, 1.26; 95% CI, 0.93–1.70; P_{trend} = 0.044), but no associations with grilled/barbecued red meat, microwaved/baked red meat, broiled red meat, or red meat cooked rare/medium or well done/charred. A positive association was reported for estimated total PhIP and rectal cancer (Q5 vs Q1 OR, 1.33; 95% CI, 0.88–2.02; P_{trend} = 0.023). [The Working Group noted the somewhat low participation rate in cases and controls (57% cases, 51% controls), which raised concerns about possible bias introduced by the types of individuals who agreed to participate.]

The North Carolina Colon Cancer Study–Phase II, a population-based case–control study conducted in the USA (945 cases, 959 controls) in Whites and African Americans (Williams et al., 2010), reported that red meat was not significantly associated with risk of distal colorectal cancers. The odds ratios for the highest versus the lowest quartile were 0.66 (95% CI, 0.43–1.00; P_{trend} = 0.90) in Whites and 0.64 (95% CI, 0.27–1.50; P_{trend} = 0.94) in African Americans. [The Working Group noted that distal cancers included cancers of the sigmoid, rectosigmoid, and rectum. Controls had a lower response rate compared with cases (56% vs 74%).]

Chiu et al. (2003) reported on a population-based case–control study in Shanghai, China (931 colon cancer cases, 1552 controls).

Positive associations were observed between red meat and risk of colon cancer for both men and women; however, the associations were only statistically significant among men. The odds ratios for the highest versus the lowest quartile of intake (servings/month) were 1.5 (95% CI, 1.0–2.1; $P_{trend} = 0.03$) among men and 1.5 (95% CI, 1.0–2.2; $P_{trend} = 0.08$) among women. [The Working Group noted that a modified version of the validated Block FFQ was used, but no details regarding whether this modified FFQ was validated were provided. In addition, no reference was provided to confirm whether the modified FFQ captured the foods mostly eaten in that area.]

Using data from the Fukuoka Colorectal Cancer Study, Kimura et al. (2007) (840 hospital-based cases, 833 population-based controls) reported no significant associations between intake of beef/pork and colorectal cancer, regardless of the cancer subsite. There were some significant associations for the quintiles, but not for the highest quintile, and overall P_{trend} was not significant. [The Working Group noted that, even though the authors labelled the study as a population-based case–control study, the cases were recruited in hospitals, and the coverage of cases was not reported. The response rate of the controls (60%) was also considerably lower than that of the cases (80%).]

Tuyns et al. (1988) conducted a population-based study in Belgium (818 colorectal cases, 2851 controls). Higher beef consumption was associated with a higher risk of colon cancer (Q4 vs Q1 OR, 2.09; 95% CI, not reported; $P_{trend} < 0.001$), but not rectal cancer (Q4 vs Q1 OR, 0.71; $P_{trend} = 0.14$). Pork intake was not associated with risk of colon or rectal cancers, and a higher pork intake was associated with a lower risk of colon cancer (Q4 vs Q1 OR, 0.39; $P_{trend} < 0.001$). [The lack of adjustment for energy intake was noted as a limitation. A previous report stated that energy intake was similar between cases and controls, suggesting that it may not have been a confounder of meat in this study; however, data were not provided, and there was unclear validation of the questionnaire. The total pork variable included smoked pork.]

In another population-based case–control study by Le Marchand et al. (2001) (727 colorectal cancer cases, 727 controls), no association was observed between red meat intake and colorectal cancer risk when considering men and women combined. However, among participants with the *NAT2* genotype (rapid acetylators) and *CYP1A2* phenotype, an above the median, higher intake of well-done red meat was significantly associated with a higher risk of colorectal cancer (OR, 3.3; 95% CI, 1.3–8.1). In a subsequent paper (Le Marchand et al., 2002b) on the same study population (Le Marchand et al., 2001), associations with "total" red meat [not defined] intake appeared to be restricted to rectal cancer only (highest vs lowest tertile OR, 1.7; 95% CI, 1.0–3.0; $P_{trend} = 0.16$). No association was observed for colon cancer. Positive associations were reported for total HAAs, in particular DiMeIQx and MeIQx. Interactions were also reported, suggesting that smokers who preferred their red meat well done, and had a rapid metabolic phenotype for both NAT2 and CYP1A2 exhibited a risk that was almost nine times higher compared with those with low NAT2 and CYP1A2 activities and who preferred meat rare or medium done. Well-done red meat was not associated with risk among never-smokers or smokers with the slow or intermediate phenotype. A follow-up study on the same study population (Le Marchand et al., 2002a) reported that participants with a high consumption of red meat and the insert polymorphism in CYP2E1 had approximately a twofold increased risk of rectal cancers compared with those with no insert polymorphism who consumed a low intake of red meat (OR, 2.1; 95% CI, 1.2–3.7).

Gerhardsson de Verdier et al. (1991) conducted a population-based case–control in Stockholm, Sweden (559 colorectal cancer

cases, 505 controls). For colon cancer, significant positive associations were observed with boiled beef/pork (OR, 1.8; 95% CI, 1.2-2.6 $P_{trend} = 0.004$), and for all cases with oven-roasted beef/pork (OR,1.8; 95% CI,, 1.1–2.9 $P_{trend} = 0.02$), and boiled beef/pork (OR, 1.9; 95% CI, 1.2–3.0 $P_{trend} = 0.007$). [The Working Group noted that the researchers did not provide an effect estimate for beef/pork without considering the cooking methods. They only asked about beef and pork, so it was unclear whether this was really representative of the subtypes of red meats consumed in that population. Information on validation of the dietary instrument was not provided.]

A hospital-based study done in the United Kingdom (Turner et al., 2004) (484 cases, 738 controls) reported that higher red meat intake was associated with a higher risk of colorectal cancer (highest vs lowest quartile, servings/month, OR, 2.3; 95% CI, 1.6–3.5; $P_{trend} = 0.0001$). A significant interaction between red meat intake and *GSTP1* ($P_{interaction} = 0.02$, after adjustment for potential confounders) and *NQO1* predicted phenotype ($P_{interaction} = 0.01$) on risk of colorectal cancer was reported. The original study (Barrett et al., 2003) reported no significant interaction between *NAT2* genotype and red meat intake. [The Working Group noted that the associations were reported after adjustment for total energy intake; however, lifestyle factors, such as physical activity, alcohol intake, or smoking, were not adjusted for.]

A hospital-based study done in Córdoba, Argentina (Navarro et al., 2003) (287 colorectal cases, 564 controls), reported that beef intake was inversely associated with colorectal cancer, particularly lean beef. The odds ratios for the highest versus the lowest tertile of intake (g/day) were 0.78 (95% CI, 0.51–1.18) for fatty beef and 0.67 (95% CI, 0.40–0.97) for lean beef. Pork (highest versus the lowest tertile) intake was not associated with risk of colorectal cancer (OR, 0.92; 95% CI, 0.62–1.36) (Navarro et al., 2003). A follow-up report on the same study (Navarro et al., 2004) (296 cases, 597 controls) reported that a higher intake of darkly browned red meat was associated with a higher risk of colorectal cancer, particularly for barbecued, iron pan–cooked, and fried red meat, but not roasted red meat. [Limitations noted by the Working Group included lack of report on the time between diagnosis and interview, lack of clarity whether total red meat included processed meat or not, and lack of adjustment for physical activity.]

Kampman et al. (1995) conducted a population-based study in the Netherlands (232 colon cancer cases, 259 controls), and reported no association between unprocessed red meat intake and colon cancer among men, but a positive association among women. For women consuming > 83 g/day versus < 38 g/day, the odds ratio was 2.35 (95% CI, 0.97–5.66; $P_{trend} = 0.04$), and for men consuming > 102 g/day versus < 60 g/day, the odds ratio was 0.89 (95% CI, 0.43–1.81; $P_{interaction}$ by sex = 0.02). The ratio of red meat to vegetables plus fruit was also positively associated with colon cancer in women. For the highest versus the lowest category, in men, the odds ratio was 1.18 (95% CI, 0.57–2.43; $P_{trend} = 0.89$), and in women, the odds ratio was 3.05 (95% CI, 1.39–6.17; $P_{trend} = 0.0006$; $P_{interaction} = 0.0001$). [The Working Group noted that no information was provided about the validity of the FFQ.]

Steinmetz & Potter (1993) conducted a population-based case–control study in Australia (220 colon cases, 438 controls). Red meat intake was positively, but not significantly, associated with risk of colon cancer in both men and women. The odds ratios for the highest versus the lowest quartile were 1.48 (95% CI, 0.73–3.01) in women and 1.59 (95% CI, 0.81–3.13) in men. [The Working Group concluded that a key limitation was the lack of adjustment for energy intake.]

Juarranz Sanz et al. (2004) conducted a population-based study in Madrid, Spain (196 colorectal cases, 196 controls). They reported positive associations with red meat (g/day) (OR

for red meat as a continuous variable, 1.026; 95% CI, 1.010–1.040; P_{trend} = 0.002) and organ meats (also considered as red meat) (OR, 1.122; 95% CI, 1.027–1.232; P_{trend} = 0.015). [The Working Group concluded that the main weakness was the lack of consideration of important confounders, such as total energy intake or BMI, although it was unclear whether the researchers did or did not find evidence of confounding.]

Boutron-Ruault et al. (1999) (171 colorectal cancer cases, 309 population-based controls) conducted a population-based study in France, and reported a non-statistically significant positive association with beef (OR for highest vs lowest quartile, g/day, 1.4; 95% CI, 0.8–2.4; P_{trend} = 0.31) and lamb (OR for high vs low, g/day, 1.3; 95% CI, 0.9–1.9; P = 0.2), and no association with pork (OR for highest vs lowest quartile, g/day, 1.0; 95% CI, 0.7–2.8). A statistically significant positive association was reported for offal (OR, 1.7; 95% CI, 1.1–2.8; P_{trend} = 0.04), which seemed stronger for rectal than colon cancer. [The Working Group noted that there was no consideration of additional potential confounders, such as BMI, alcohol, or smoking status. A difference in the response rates of cases and controls (80% vs 53%) was noted.]

(ii) Studies considered less informative

The following case–control studies that presented results for red meat were considered less informative by the Working Group. The studies are presented in order by sample size, from largest to smallest.

The hospital-based study by Di Maso et al. (2013) (2390 colorectal cases, 4943 controls) that included previous publications from the same group (i.e. Franceschi et al., 1997 and Levi et al., 1999), reported that a higher red meat intake was associated with a higher risk of colon and rectal cancers in men and women. The odds ratios per 50 g/day increase for colon cancer were 1.17 (95% CI, 1.08–1.26) in men and 1.11 (95% CI, 0.98–1.26) in women, and for rectal cancer, the odds ratios were 1.15 (95% CI, 1.02–1.29) in men and 1.32 (95% CI, 1.54–1.29) in women. Associations did not differ by cooking practice, except for rectal cancers, where the strongest associations were seen with fried/pan-fried red meat intake. The odds ratios per 50 g/day increase were 1.24 (95% CI, 1.07–1.45) for roasting/grilling, 1.32 (95% CI, 1.10–1.58) for boiling/stewing, and 1.90 (95% CI, 1.38–2.61) for frying/pan-frying ($P_{heterogeneity}$ = 0.06). [The Working Group concluded that the limitations included lack of adjustment for total caloric intake and physical activity. The researchers also did not assess the quantiles and differences in standard serving sizes between regions, which may have affected the calculated grams of intake per day.]

The hospital-based study by Tavani et al. (2000) (828 colorectal cases, 7990 controls) in Italy reported a positive association between the highest intake of red meat and both colon (highest vs lowest tertile OR, 1.9; 95% CI, 1.5–2.3; P_{trend} <0.01) and rectal cancer (highest vs lowest tertile OR, 1.7; 95% CI, 1.3–2.2; P_{trend} <0.01). [The Working Group concluded that the main weaknesses were lack of validation of the FFQ, which only included 40 food items, and lack of adjustment for total energy, BMI, and physical activity.]

A hospital-based case–control study was conducted in Harbin, China, by Guo et al. (2015) (600 colorectal cases, 600 controls), and reported a positive association between servings of red meat per week and colorectal cancer risk (> 7 vs < 7 servings/week OR, 1.5; 95% CI, 1.1–2.4; P_{trend} = 0.001). No evidence of interaction was observed for two polymorphisms in the *ADIPOQ* gene. [The Working Group concluded that the main weaknesses were lack of consideration of total energy intake and other dietary factors, and lack of information on whether the FFQ was validated.]

Muscat & Wynder (1994) conducted a hospital-based case–control study (511 colorectal cases, 500 controls) in the USA. No associations were observed between beef doneness and risk

of colorectal cancer in men or women. The odds ratios for well-done versus rare beef were 1.15 (95% CI, 0.6–2.4) in men and 1.0 (95% CI, 0.6–1.5) in women. Estimates were only adjusted for matching variables. Results were only presented for beef doneness as exposure. [The Working Group concluded that the limitations included poor focus on red meat, by reporting only on well-done beef, and lack of validation of exposure survey tools.]

Kotake et al. (1995) conducted a hospital-based case–control study in Japan (363 colorectal cases, 363 controls). No significant associations between beef or pork intake and colon and rectal cancer were found. For an intake of > 3–4 times/week versus 1–2/week, the odds ratios for colon cancer were 1.7 (95% CI, 0.85–3.28) for beef and 0.8 (95% CI, 0.50–1.33) for pork, and the odds ratios for rectal cancer were 0.8 (95% CI, 0.38–1.52) for beef and 1.6 (95% CI, 0.95–2.73) for pork. [The Working Group concluded that the limitations were lack of use of quantiles for exposure variables, unclear validation status of the FFQ, lack of adjustment for energy intake, and inclusion of hospital controls with other tumours, including 49 cases with upper gastrointestinal tract cancers.]

A hospital-based study was done in Thailand (Lohsoonthorn & Danvivat, 1995) (279 colorectal cases, 279 controls), and reported null associations with either beef or pork intake. [The Working Group noted that the main weakness of this study was lack of consideration of any potential confounders.]

Freedman et al. (1996) reported on a hospital-based study in New York, USA (163 cases, 326 controls). They reported a positive association with beef (highest vs lowest tertile OR, 2.01; 95% CI, 0.96–4.20; P_{trend} = 0.03). They also subtyped tumours based on p53 expression and reported that the association with beef intake (highest vs lowest) was stronger among tumours that lacked overexpression of p53 (OR, 3.17; 95% CI, 1.83–11.28; P_{trend} = 0.006). The association was very modest and not statistically significant among p53+ tumours. [The Working Group concluded that the limitations of this study were lack of consideration of total energy adjustment, and lack of consideration of other dietary and lifestyle covariates.]

A population-based study in China (Chen et al., 2006) (140 colorectal cases, 343 controls) reported no association between red meat and colon cancer, but a non-significant association with rectal cancer (OR, 1.4; 95% CI, 0.7–2.82). Interactions with *SULT1A1* were also reported, without conclusive results. [The Working Group concluded that the limitations included lack of adjustment for total energy intake and other potential confounders, and unclear definition of red meat.]

A population-based case–control study in southern Italy (Centonze et al., 1994) (119 cases, 119 controls) reported a lack of association between beef intake and colorectal cancer risk; odds ratio for medium (>22 g/day) vs low (~21 g/day) intake of beef was, 0.95; 95% CI, 0.50–1.80. [The Working Group concluded that the use of a validated questionnaire was among the major strengths. The limitations were a small sample size, the fact that the researchers presented results for beef only, and the lack of total caloric intake adjustment.]

The study by Iscovich et al. (1992) (110 colon cancers, 220 controls) in Argentina reported a positive association with red meat intake, which was observed only in the second quartile (Q1 vs Q2 OR, 2.29; 95% CI, 1.03–5.08; Q1 vs Q3 OR, 0.82; 95% CI, 0.39–1.70; Q1 vs Q4, no estimates presented). [The Working Group concluded that the limitations of this study included lack of information about FFQ validation, lack of adjustment for energy intake, and limited distribution of red meat, given the very high consumption of red meat in Argentina, which limited the variability of red meat intake.]

Manousos et al. (1983) conducted a hospital-based case–control study of colorectal cancer

(100 cases, 100 controls) in Greece, and reported positive associations with beef (OR, 1.77) and lamb (OR, 2.61). [The Working Group concluded that the major limitations were lack of consideration of important confounders, such as total energy intake, among others, and small samples size.]

(b) Processed meat

(i) Studies considered informative

The following case–control studies reported results for processed meat separately and were considered informative by the Working Group (see Table 2.2.4). These studies were given more weight in the evaluation. The studies are presented in order by sample size, from largest to smallest. Many of these studies were described in the previous section.

Joshi et al. (2015) (3350 cases, 3504 controls), which was described as an informative study in Section 2.2.2(b), reported a positive association for processed meat (5th Quintile vs 1st quintile OR, 1.2; 95% CI, 1.0–1.4; P_{trend} = 0.054).; a similar positive association was reported for sausage and lunchmeats (Q5 vs Q1 OR, 1.2; 95% CI, 1.0–1.4; P_{trend} = 0.187). Analyses that considered subtypes of colorectal cancer defined by MMR status showed a statistically significant association with sausages and lunchmeats among MMR-proficient cases (Q5 vs Q1 OR, 1.3; 95% CI, 1.0–1.7; P_{trend} = 0.029). When cooking methods were considered, positive associations were noted for pan-fried sausage (4th quartile vs 1st quartile OR, 1.2; 95% CI, 1.0–1.3; P_{trend} = 0.041) and pan-fried spam or ham (Q4 vs Q1 OR, 1.2; 95% CI, 1.0–1.4; P_{trend} = 0.048). The latter seemed restricted and stronger among MMR-proficient cases. No associations were noted for pan-fried bacon and for grilled/barbecued sausages. No differences were noted for colon versus rectal cancers for any of these variables. [The limitations were the same as those described in Section 2.2.2(b).]

Hu et al. (2007) (1723 cases, 3097 controls), described as an informative study in Section 2.2.2(b),reported that processed meat intake was significantly positively associated with both proximal and distal colon cancers in both sexes, with risk estimates ranging between 1.5 and 1.6 for the highest compared with the lowest quartile of intake. Positive associations appeared to be stronger for bacon than for sausage intake, which was not significantly associated with proximal or distal cancers in men or women. For the highest tertile compared with the lowest tertile of bacon intake, the odds ratios for proximal cancer were 1.5 (95% CI, 1.0–2.2; P_{trend} = 0.04) in men and 2.2 (95% CI, 1.4–3.3; P_{trend} = 0.001) in women; andthe odds ratios for distal cancer were 1.4 (95% CI, 1.0–1.9; P_{trend} = 0.05) in men and 1.8 (95% CI, 1.2–2.8; P_{trend} = 0.01) in women. [It was unclear why associations were presented for bacon and sausage, but not for other types of processed meats.] A later published companion paper by the same group using the same study population confirmed their previous findings for processed meat and colon cancer (≥ 5.42 vs ≤ 0.94 servings/week OR, 1.5; 95% CI, 1.2–1.8; P_{trend} < 0.0001) (Hu et al., 2011). This publication also reported results for rectal cancer separately (≥ 5.42 vs ≤ 0.94 servings/week OR, 1.5; 95% CI, 1.2–2.0; P_{trend} = 0.001). [The limitations were the same as those noted for Hu et al. (2007).]

Kampman et al. (1999) (1542 cases, 1860 controls), an informative study described in Section 2.2.2(b), also reported on processed meats. They reported a statistically significant positive association with risk of colon cancers in men who consumed > 3.1 servings/week versus men who consumed ≤ 0.5 servings/week of processed meats (OR, 1.4; 95% CI, 1.0–1.9), but no significant associations were found in women. Moreover, stronger positive associations between processed meats and colon cancer were observed among those with the intermediate or rapid *NAT2* acetylator phenotype (albeit not a statistically significant interaction), while associations

did not appear to differ by *GSTM1* genotype. A follow-up paper by this group (Slattery et al., 2000) reported that, among cases, higher processed meat intake was less likely to be associated with tumours with G→A transitions in the *KRAS* gene (OR, 0.4; 95% CI, 0.2–0.8; P_{trend} = 0.14). In a later publication by the same group focusing on rectal cancer (Murtaugh et al., 2004), processed meat intake was not significantly associated with risk of rectal cancer. For the highest versus the lowest intake, the odds ratios were 1.18 (95% CI, 0.87–1.61) in men and 1.23 (95% CI, 0.84–1.81) in women. [For the limitations, refer to Section 2.2.2(b).]

Le Marchand et al. (1997) (1192 cases, 1192 controls), an informative study described in Section 2.2.2(b),reported positive associations between processed meat intake and colorectal cancer; however, the associations appeared to be restricted to men only (highest vs lowest quartile of intake among men, OR, 2.3; 95% CI, 1.5–3.4; P_{trend} = 0.001; among women, OR, 1.2; 95% CI, 0.8–2.0; P_{trend} = 0.20; $P_{interaction}$ = 0.05). When considering processed meat subtypes, positive associations were reported for beef or pork luncheon meats, salami, sausage, and beef wieners among men only. In contrast, among women, a positive association was observed with spam (highest vs lowest quartile of intake among women OR, 1.8; 95% CI, 1.1–2.9; P_{trend} = 0.02). [The limitations were the same as those described in Section 2.2.2(b).]

Miller et al. (2013) (989 cases, 1033 controls), an informative study described in Section 2.2.2(b),reported a slight positive association between processed red meat and colorectal cancer; however, neither the estimates by intake category nor trend of association werestatistically significant. No differences were observed between colon and rectal cancer or between proximal and distal colon cancer. A statistically significant positive association between estimated levels of total nitrites and proximal cancer (Q5 vs Q1, OR, 1.57; 95% CI, 1.06–2.34; P_{trend} = 0.023) was reported. [For the limitations, refer to Section 2.2.2(b); additionally, processed red meat and processed poultry meat were considered separately and so total processed meat was not reported.]

In the study by Williams et al. (2010) (945 cases, 959 controls), described in Section 2.2.2(b), a positive association between processed meat intake and colon cancer was reported for the third quartile among Whites, but there was no evidence of a linear trend. No significant associations were observed among African Americans. [For the limitations, refer to Section 2.2.2(b).]

Kimura et al. (2007) (840 cases, 833 controls), described in Section 2.2.2(b), reported that processed meat was not associated with colorectal cancer, regardless of the cancer subsite. For Q5 versus Q1, the odds ratios were 1.15 (95% CI, 0.83–1.60) for colorectal cancer, 1.2 (95% CI, 0.72–2.03) for proximal colon cancer, 1.32 (95% CI, 0.82–2.11) for distal colon cancer, and 1.14 (95% CI, 0.73–1.77) for rectal cancer (all $P_{trend} \geq 0.27$). [The Working Group concluded that a limitation was the lack of information on how processed meat was defined.]

A study by Tuyns et al. (1988) (818 cases, 2851 controls), described in Section 2.2.2(b), also reported data on "charcuterie", and reported no association with risk of colon or rectal cancers. [For the limitations, refer to Section 2.2.2(b).]

A study by Gerhardsson de Verdier et al. (1991) (559 cases, 505 controls), described in Section 2.2.2(b), also reported on individual processed meats and considered cooking methods. Significant positive associations were observed between intake of boiled sausage (P_{trend} = 0.04) and risk of colon cancer. Furthermore, positive associations were also found between bacon/smoked ham (P_{trend} = 0.025), oven-roasted sausage (P_{trend} = 0.038), and boiled sausage (P_{trend} < 0.001) and risk of rectal cancer. Associations did not appear to differ consistently by sex or colon subsites. [The Working Group noted that a limitation was the reduced number of processed meat

items, as it was unclear whether the items were representative of the subtypes of processed meats consumed in this population. For other limitations, refer to Section 2.2.2(b).]

The study by Le Marchand et al. (2002a) (521 cases, 639 controls), described in Section 2.2.2(b), also reported that, among participants with a high intake of processed red meat and the *CYP2E1* insert polymorphism, a threefold risk was observed compared with those with low consumption and no insert polymorphism (OR, 3.1; 95% CI, 1.8–5.6; $P_{interaction} = 0.22$).

Squires et al. (2010) (518 cases, 688 controls) conducted a population-based case–control study in Canada. They reported that a higher consumption of pickled meat (food commonly eaten in Newfoundland) was significantly associated with an increased risk of colorectal cancer in both men and women (OR for men, 2.07; 95% CI, 1.37–3.15; OR for women, 2.51; 95% CI, 1.45–4.32).

Rosato et al. (2013) (329 cases, 1361 controls) conducted a hospital-based case–control study of young-onset colorectal cancer (diagnosis ≤ 45 years of age) in Italy. The study included individuals from three previously reported case–control studies on colorectal cancers – Levi et al. (1999), La Vecchia et al. (1991), and Negri et al. (1999). [Participants in these previous studies may have overlapped.] A statistically significant positive association was observed between processed meat intake and colorectal cancer (highest vs lowest tertile OR for processed meat, 1.56; 95% CI, 1.11–2.20; $P_{trend} = 0.008$). [The limitations of this study were lack of definition of meat types included in the processed meat variable, lack of clarity on the overlap with previous studies, and no consideration of alcohol and smoking as potential confounders.]

A study by Navarro et al. (2003) (287 cases, 564 controls), described in Section 2.2.2(b),reported that processed meat was positively associated with risk of colorectal cancer (highest vs lowest tertile OR, 1.47; 95% CI, 1.02–2.15). [For the limitations, refer to Section 2.2.2(b).]

Steinmetz & Potter (1993) (220 cases, 438 controls), described in Section 2.2.2(b), reported that processed meat intake was not associated with risk of colon cancer in either sex. For the highest compared with the lowest quartile, the odds ratios were 0.77 (95% CI, 0.35–1.68) in women and 1.03 (95% CI, 0.55–1.95) in men. [For the limitations, refer to Section 2.2.2(b).]

Juarranz Sanz et al. (2004) (196 cases, 196 controls), described in Section 2.2.2(b), reported positive associations between processed meat intake (12.9 ± 11.4 g/day vs 5.62 ± 7.6 g/day) and colorectal cancer (OR, 1.070; 95% CI, 1.035–1.107; $P_{trend} = 0.001$). [The Working Group noted that processed meat was not clearly defined. For other limitations, refer to Section 2.2.2(b).]

Boutron-Ruault et al. (1999) (171 cases, 309 controls), summarized in Section 2.2.2(b), reported that a higher intake of delicatessen (processed) meat was associated with a higher risk of colorectal cancer (highest vs lowest quartile, g/day, OR, 2.4; 95% CI, 1.3–4.5). [For the limitations, refer to Section 2.2.2(b).]

(ii) Studies considered less informative

The following case–control studies reported results for processed meat separately and were considered less informative by the Working Group. The studies are presented in order by sample size, from largest to smallest.

A hospital-based study was done by Franceschi et al. (1997) (1953 colorectal cancer cases, 4154 controls) in Italy. The study reported no statistically significant associations between processed meat and risk of colorectal cancer. Similarly, no associations were observed for colon or rectal cancer separately. [Processed meat was not defined.]

Macquart-Moulin et al. (1986) (399 colorectal cases, 399 controls) reported no statistically significant associations between a high intake of processed meats and colorectal cancer. [The

Working Group concluded that the main weaknesses of this study were lack of consideration of dietary fibre or total vegetables, and lack of details on the analytical models, such as confidence intervals.]

A hospital-based case–control study was done in Montevideo, Uruguay. De Stefani et al. (2012a) (361 colorectal cases, 2532 controls) reported that a higher intake of processed meat was associated with a higher risk of colon and rectal cancers in both sexes. For the highest tertile compared with the lowest tertile of intake (g/day), the odds ratios for colon cancer were 2.01 (95% CI, 1.07–3.76; P_{trend} = 0.03) in men and 3.53 (95% CI, 1.93–6.46; P_{trend} = 0.0001) in women, and the odds ratios for rectal cancer were 1.76 (95% CI, 1.03–3.01; P_{trend} = 0.03) in men and 3.18 (95% CI, 1.54–6.57; P_{trend} = 0.01) in women. A previous hospital-based study by the same group (De Stefani et al., 1997) (250 colorectal cases, 500 controls) had reported no statistically significant associations between processed meat and colorectal cancer, and no differences by cancer subsite (colon vs rectum) or by sex. [A major limitation of this study was that the control group may have included patients with diseases related to diet, increasing the likelihood of biased results. In addition, in the 1997 study, the researchers did not consider adjusting for energy intake.]

A hospital-based case–control study was done in the canton of Vaud, Switzerland, by Levi et al. (2004) (323 colorectal cases, 611 controls) and later included in the study by Di Maso et al. (2013), although the latter did not report on processed meat. A higher intake of processed meat was associated with a higher risk of colorectal cancer (OR for highest vs lowest category of intake, 2.35; 95% CI, 1.50-4.27; P_{trend} < 0.001).

A population-based case–control study in Majorca, Spain (Benito et al., 1990) (286 cases; 498 controls, which included some hospital-based), reported no significant associations with processed meat intake. [Lack of energy adjustment, lack of detailed analysis, use of a non-validated FFQ, and limited sample size were among the limitations of this study.]

Lohsoonthorn & Danvivat (1995) (279 colorectal cases, 279 controls), described in Section 2.2.2(b), reported positive associations with bacon (>10 vs ≤ 5 times/month OR, 12.49; 95% CI, 1.68–269) and with sausage (>10 vs ≤ 5 times/month OR, 1.26; 95% CI, 0.71–2.25), and a null association with salted beef. [The main weakness of this study was lack of consideration of any potential confounders.]

In a population-based study in France (Faivre et al., 1997) (171 colorectal cases, 309 controls) a positive association was reported between a high intake of processed meat and delicatessen and colorectal cancer risk (OR, 3.0; 95% CI, 2.1–4.8; P_{trend} < 0.001). [The key weaknesses included lack of information regarding how the processed meat estimate was obtained, and lack of consideration of smoking, BMI, dietary fibre, and alcohol.]

A population-based case–control study in Italy (Centonze et al., 1994) (119 cases, 119 controls), previously described in Section 2.2.2(b), reported that processed meat was not associated with colorectal cancer risk (OR for ≥ 3g/day vs < 2g/day processed meat, 1.01; 95% CI, 0.57–1.69). [For the limitations, refer to Section 2.2.2(b).]

Fernandez et al. (1997) (112 cases and 108 controls), based on data from a case–control study in northern Italy, focused on subjects with a family history of cancer and reported that some processed meats were positively associated with colorectal cancer. For the highest versus the lowest tertile, the odds ratios were 2.1 (95% CI, 0.9–4.9; P_{trend} > 0.05) for raw ham, 2.6 (95% CI, 1.0–6.8; P_{trend} > 0.05) for ham, and 1.9 (95% CI, 1.0–3.3; P_{trend} < 0.05) for canned meat. [The limitations of this study were the unclear definition of processed meats, the modest sample size, and the lack of adjustment for energy intake and other potential confounders.]

Iscovich et al. (1992) (110 cases, 220 controls), described in Section 2.2.2(b), reported that processed meat was inversely associated with risk

of colon cancers, regardless of fat content (OR for highest vs lowest, 0.45; 95% CI, 0.23–0.90; P_{trend} = 0.017; for fat with skin; OR, 0.38; 95% CI, 0.19–0.75; for lean processed meat; P_{trend} = 0.002). [For the limitations, refer to Section 2.2.2(b).]

(c) Red meat and processed meat combined

In this subsection, the term "total red meat" as used in many studies refers to "unprocessed and processed red meats combined".

(i) Studies considered informative

The following case–control studies that reported results for red meat and processed meat combined were considered informative by the Working Group. The studies are presented in order by sample size, from largest to smallest.

A population-based colorectal case–control study conducted in Canada (Cotterchio et al., 2008) (1095 cases, 1890 controls) reported a positive association with total red meat (OR for highest vs lowest intake of total red meat, servings/week, 1.67; 95% CI, 1.36–2.05) and well-done total red meat (OR for > 2 servings/week of total well-done red meat vs ≤2 servings/week of rare total red meat, 1.57; 95% CI, 1.27–1.93). Polymorphisms in 15 xenobiotic-metabolizing enzymes (XMEs) were considered, and no statistically significant gene-environment interactions were observed, with two exceptions. In analyses stratified by genotypes, the relative risk of colorectal cancer for > 2 servings/week of "well-done" compared with ≤ 2 servings/week of "rare/regular" red meat was higher in *CYP1B1* wildtype variants compared with other genotypes with increased activity ($P_{interaction}$ = 0.04), and higher in the *SULT1A1* GG genotype compared with AA/GA genotypes ($P_{interaction}$ = 0.03). A follow-up study with a subset of the individuals (Mrkonjic et al., 2009) investigated gene-environment interactions, focusing on two single-nucleotide polymorphisms on the apolipoprotein E (*APOE)* gene and considering tumour subtypes with microsatellite instability (MSI). They reported that *APOE* isoforms might modulate the risk of MSI-high and MSI-low/normal colorectal cancers among high total red meat consumers. [The Working Group concluded that the major limitations of these studies were use of a dietary instrument that was not validated for red meat and lack of energy adjustment.]

Kune et al. (1987) reported on a population-based case–control study conducted in Melbourne, Australia (715 colorectal cases, 727 controls). They reported a positive association between high intake of beef, unprocessed and processed (> 360 g/week), and colorectal cancer risk for men and women combined (OR, 1.75; 95% CI, 1.26–2.44), and a positive association of similar magnitude for the colon and rectum. Results for men showed similar estimates. Estimates for women were not presented. In contrast, for pork, inverse associations were reported with colorectal cancer for men and women combined (OR, 0.55; 95% CI, 0.42–0.73) and similarly by sex and by cancer location (i.e. colon and rectum). [The lack of total energy adjustment and consideration of lifestyle risk factors were noted. The data analysis strategy and presentation were not sufficiently clear, and did not allow for proper interpretation of the findings.]

The North Carolina Colon Cancer Study (Butler et al., 2003), a population-based case–control study in the USA (620 colon cancer cases, 1038 controls), reported a twofold risk of colon cancer for total red meat intake (highest vs lowest intake OR, 2.0; 95% CI, 1.3–3.2). In addition, statistically significant associations between colon cancer risk and pan-fried red meat (OR, 2.0; 95% CI, 1.4–3.0) and well-done red meat (OR, 1.7; 95% CI, 1.2–2.5) were reported. In another paper (Satia-Abouta et al., 2004), differences by ethnic group were examined ("Caucasians" vs African Americans), and it was reported that the positive associations previously reported by Butler et al. (2003) for all individuals combined were no longer observed with ethnic stratification e (e.g. Q4 vs Q1 total red meat among Whites OR, 1.1;

95% CI, 0.7–1.8; P_{trend} = 0.61). Follow-up studies (Butler et al., 2005, 2008a) considered *UGT1A7* and *NAT1* polymorphisms in a subset of cases, and reported no significant gene–environment interactions. In a subset of cases (486 cases), Satia et al. (2005) observed that the positive association between total red meat intake and colon cancers seemed restricted to MSI-high cases (49 cases only), but was not statistically significant, and was null among MSI-low/MSI-stable tumours (total red meat intake T3 vs T1 OR for MSI-high cancers: 1.3; 95% CI, 0.6–3.0; P_{trend} = 0.42; and OR for MSI-low or MSI-stable cancers, 0.9; 95% CI, 0.7–1.3; P_{trend} = 0.90). A subsequent study conducted by Steck et al. (2014) considered gene-environment interactions between total red meat, pan-fried total red meat, and well-done or very well-done total red meat and seven single-nucleotide polymorphisms in five nucleotide excision repair genes (*XPD, XPF, XPG, XPC, RAD23B*). No significant interactions were reported. [Slightly lower response rates were noted for controls compared with cases, although this is not unusual for studies that include minority populations, and the response rates were still within an acceptable range.]

A population-based study of colorectal cancer was done by Joshi et al. (2009) (577 cases, 361 controls) and reported a positive association with total red meat (OR for > 3 vs ≤ 3 servings/week, 1.8; 95% CI, 1.3–2.5; P_{trend} = 0.001), which was restricted to colon cancer cases, and not rectal cases, and a similar association with total red meat cooked using high-temperature methods (pan-frying, broiling, grilling OR, 1.6; 95% CI, 1.1–2.2). No associations were reported for total red meat doneness (on the outside or inside of the meat) and colorectal cancer. Polymorphisms in five genes in the nucleotide excision repair pathway (*ERCC1, XPA, XPC, XPD, XPF, XPG*) and two genes in the MMR pathway (*MLH1, MSH2*) were considered. Overall, results suggested that a high intake of total red meat browned on the outside may increase the risk of colorectal cancer (especially rectal cancer) among carriers of the *XPD* codon 751 Lys/Lys genotype (OR, 3.8; 95% CI, 1.1–13; $P_{interaction}$ = 0.037). Two subsequent studies investigated additional interactions between these meat variables and polymorphisms in the base excision repair pathway (*APEX1, OGG1, PARP, XRCC1*) (Brevik et al., 2010) and carcinogen metabolism enzymes (*CYP1A2, CYP1B1, GSTP1, PTGS2, EPHX, NAT2*) (Wang et al., 2012). They reported a stronger association between a higher intake of total red meat cooked at high temperatures and colorectal cancer among carriers of one or two copies of the *PARP* codon 762 Ala allele (OR, 2.64; 95% CI, 1.54–4.51; $P \leq 0.0001$) than among carriers of two copies of the Val allele (OR, 1.17; 95% CI, 0.76–1.77; $P = 0.484$; $P_{interaction} = 0.012$) (Brevik et al., 2010). They also reported that the *CYP1A2* –154 A > C single-nucleotide polymorphism may modify the association between intake of total red meat cooked using high-temperature methods ($P_{interaction} < 0.001$) and colorectal cancer risk, and the association between total red meat heavily browned on the outside and rectal cancer risk ($P_{interaction} < 0.001$) (Wang et al., 2012). [The Working Group concluded that a limitation of these studies was the use of sibling controls, which may have reduced power to detect associations with red meat variables; however, the use of a case-only design improved power for gene–environment interaction testing. Total energy intake was considered, but was obtained from a separate questionnaire than the ones used for meat assessment; therefore, residual confounding could not be excluded.]

A population-based case–control study of colorectal cancer was conducted in western Australia (Tabatabaei et al., 2011) (567 cases, 713 controls). The study reported that intake of total red meat cooked with different cooking methods (pan-fried, barbecued, stewed) was not significantly associated with risk of colorectal cancer, although a statistically significant inverse association with baked total red meat was observed.

For the highest versus the lowest intake, the odds ratios were 0.8 (95% CI, 0.57–1.13; $P_{trend} = 0.27$) for pan-fried, 0.89 (95% CI, 0.63–1.24; $P_{trend} = 0.17$) for barbecued, 0.73 (95% CI, 0.53–1.01; $P_{trend} = 0.04$) for baked, and 0.95 (95% CI, 0.67–1.33; $P_{trend} = 0.53$) for stewed. Results were not provided for red meat per se, only by cooking method. [The Working Group concluded that the main limitations were the lack of information regarding whether the FFQ was validated and the fact that the researchers inquired about meat intake 10 years before inclusion into the study, which may have increased the likelihood of misclassification of exposures.]

Squires et al. (2010) (518 cases, 686 controls) conducted a study in Newfoundland, Canada, summarized in Section 2.2.2(c), and reported a positive, but non-statistically significant, association between total red meat intake and colorectal cancer among women, but not among men. For the highest compared with the lowest category of intake (servings/day), the odds ratio among men was 0.75 (95% CI, 0.43–1.29), and among women, it was 1.81 (95% CI, 0.94–3.51; no $P_{interaction}$ by sex reported). In addition, a higher intake of well-done red meat was associated with a higher risk of colorectal cancer in women (> 2 servings well done vs < 2 servings rare/regular, OR, 3.1; 95% CI, 1.11–8.69).

Shannon et al. (1996) conducted a population-based study in Seattle, USA (424 colon cases, 414 controls), and reported no statistically significant associations between total red meat intake and colon cancer among women, but did report a statistically non-significant positive association among men (Q4 vs Q1 OR, 1.48; 95% CI, 0.82–2.66; $P_{trend} = 0.53$).

Nowell et al. (2002) conducted a hospital-based case–control study (155 cases, 380 population-based controls) in Arkansas and Tennessee, USA, and reported a positive association with total red meat cooked well/very well done (Q4 vs Q1 OR, 4.36; 95% CI, 2.08–9.60). They also reported a positive association with estimated levels of MeIQx (Q4 vs Q1 OR, 4.09; 95% CI, 1.94–9.08). Estimates for total red meat, without considering the cooking methods, were not provided. [A limitation was the lack of consideration of total energy adjustment, BMI, smoking, alcohol, and dietary fibre. Results reported on only one HAA, even though more exposure estimates were available.]

(ii) Studies considered less informative

The following case–control studies that reported results for red meat and processed meat combined were considered less informative by the Working Group. The studies are presented in order by sample size, from largest to smallest.

A case–control study was done in Scotland by Theodoratou et al. (2008) (1656 hospital-based cases, 2292 population-based controls). A validated FFQ was used to investigate gene–environment interactions between total red meat intake (minced meat, sausages, burgers, beef, pork, lamb, bacon, liver, gammon, liver sausage, liver pâté, haggis, black pudding) and two polymorphisms in the *APC* gene (Asp1822Val and Glu1317Gln). Overall, their findings suggested that, among carriers of the *APC* 1822 variant, diets high in total red meat may increase the risk of colorectal cancer. [No main effects were presented for total red meat.]

Bidoli et al. (1992) conducted a colorectal case–control study in Italy (248 cases, 699 controls), and reported that a higher intake of total red meat was associated with a higher risk of both colon and rectal cancers (highest vs lowest intake, colon cancer OR, 1.6; $P_{trend} = 0.07$; rectal cancer OR, 2.0; $P_{trend} = 0.01$). [Several limitations were noted, including lack of adjustment for caloric intake, use of a non-validated dietary instrument, and recruitment of cases and controls from different hospitals, which introduces potential selection bias.] A companion study (Fernandez et al., 1997), previously described in Section 2.2.2(c), focusing on subjects with a family history of cancer reported

that, among participants with a positive family history, total red meat intake was positively associated with colorectal cancer (highest vs lowest tertile OR, 2.9; 95% CI, 1.4–6.0; $P_{trend} < 0.05$). [For the limitations, refer to Section 2.2.2(c).]

(d) Red meat – unclear if processed meat was included

The following studies were given little weight in the evaluation. The studies are presented in order by sample size, from largest to smallest.

A hospital-based case–control study by La Vecchia et al. (1996) in Italy (1326 colorectal cases, 2024 controls) reported a positive association with both colon and rectal cancer using a dichotomous variable for red meat (high vs low OR for colon cancer, 1.6; 95% CI, 1.3–1.9; OR for rectal cancer, 1.6; 95% CI, 1.3–2.0). [The limitations were the lack of clear definition of red meat, the use of a dichotomous variable, and the potential for partial overlap with studies that followed from this group; specifically, this study recruited from 1985 to 1992, and the follow-up study by Di Maso et al. (2013) was from 1991 to 2009.]

A hospital-based study in France (Pays de la Loire region) (1023 colorectal cancer cases with a family history and young onset, 1121 controls) (Küry et al., 2007) reported that an intake of red meat > 5 times/week was associated with a higher risk of colorectal cancers (OR, 2.81; 95% CI, 1.52–5.21; $P = 0.001$) compared with an intake of red meat < 5 times/week. They also examined gene–environment interactions between red meat intake and polymorphisms in cytochrome P450 genes (*CYP1A2, CYP2E1, CYP1B1, CYP2C9*) and colorectal cancer risk, with evidence of interaction for multiple combinations of polymorphisms; however, confidence intervals among high–red meat eaters were very wide, and no formal test of interaction was provided. [The Working Group concluded that the crude assessment of meat intake based on one question on a questionnaire and lack of detail on which covariates were added to the final model, including total energy intake, were among the limitations of this study.]

Morita et al. (2009) conducted a hospital-based study in Fukuoka, Japan (685 cases, 833 population-based controls), and reported a positive association between red meat and colon cancer, but only among carriers of one or two alleles for the 96-bp insertion for *CYP2E1* ($P_{interaction} = 0.03$). They did not report on the main effects of red meat, only on gene- interaction analyses between meat and these polymorphisms. [The Working Group concluded that the main weakness was the lack of presentation of the main effects of red meat.]

A study conducted in the Liverpool postcode area in the United Kingdom (Evans et al., 2002) (512 cases, 512 population-based controls) reported a positive association between red meat and colorectal cancer (highest vs lowest quartile OR, 1.51; 95% CI, 1.06–2.15). Associations appeared to be stronger for proximal cancers (OR for proximal cancer, 3.32; 95% CI, 1.42–7.73; OR for distal and rectal cancer, 1.38; 95% CI, 0.89–2.12). [The Working Group concluded that the key limitations of this study were lack of consideration of potential confounders, presentation of univariate analyses only, and unclear definition of red meat.]

Three papers on a matched, hospital-based case–control study from China (400 cases, 400 controls) (Hu et al., 2013, 2014, 2015) examined gene–environment interactions between red meat intake and different gene polymorphisms associated with insulin resistance pathways, focusing on adiponectin (*ADIPOQ)* rs2241766, uncoupling protein 2 (*UCP2*) rs659366, and fatty acid binding protein 2 (*FABP2*) rs1799883 (Hu et al., 2013); *ADIPOQ* rs2241766, *ADIPOQ* rs1501299, and calpain 10 (*CAPN-10)* rs3792267 (Hu et al., 2015); and *CAPN-10* SNP43 and SNP19 polymorphisms (Hu et al., 2014). A statistically significant positive association between red meat intake and colorectal cancer risk was observed (high vs low, > 7 vs ≤ 7 times/week, OR, 1.87; 95%

CI, 1.39–2.51) (Hu et al., 2013). [The Working Group concluded that lack of a validated dietary instrument, crude assessment of meat intake, lack of a clear definition of red meat, potential for residual confounding, and especially, lack of adjustment for total energy intake were among the main limitations of the study.]

The study by Rosato et al. (2013) (329 cases, 1361 controls), described in Section 2.2.2(c), also reported on red meat intake. They reported no association between red meat and risk of colorectal cancer (highest vs lowest tertile OR for red meat, 1.07; 95% CI, 0.79–1.64; P_{trend} = 0.63). [No definition was provided for red meat. For additional limitations, refer to Section 2.2.2(c).]

A hospital-based study conducted in Uruguay (De Stefani et al., 1997) (250 colorectal cases, 500 controls) reported positive associations between red meat and colorectal cancer (OR, 2.60; 95% CI, 1.64–4.13), with similar estimates for men and women. Similarly, a positive association was reported for beef (OR, 3.88; 95% CI, 2.34–6.45), but not for lamb. Estimates of HAAs were also provided, showing statistically significant associations with PhIP, MeIQx, and DiMeIQx. [The Working Group concluded that the limitations included concerns about hospital-based controls and lack of adjustment for energy intake.]

A hospital-based case–control study was done in Singapore (Lee et al., 1989) (203 colorectal cancer cases, 425 controls), and reported no statistically significant associations between red meat intake and risk of colorectal, colon, or rectal cancers. For the highest compared with the lowest tertile, the odds ratios were 1.29 (95% CI, 0.84–1.97) for colorectal cancer, 1.41 (95% CI, 0.87–2.31) for colon cancer, and 0.97 (95% CI, 0.48–1.92) for rectal cancer (all $P_{trend} > 0.05$). [The Working Group concluded that no adjustment for total energy intake and other potential confounders were among the limitations.]

A population-based study of colorectal cancer was done by Saebø et al. (2008) (198 cases, 222 controls), and reported a non-significant positive association between red meat and colorectal cancer (T3 vs T1 OR, 1.58; 95% CI, 0.71–3.47). No association was found when the doneness level was considered. Interactions with *CYP1A2* polymorphism were also examined, without conclusive results. [The Working Group concluded that the limitations included unclear details of the questionnaire used; lack of consideration of appropriate confounders, such as total energy intake; and unclear definition of red meat.]

A hospital-based study conducted in Jordan (Abu Mweis et al., 2015) (167 cases, 240 controls) reported a non-statistically significant inverse association between red meat and colorectal cancer risk (OR for ≥ 1 vs < 1 serving/week, 0.64; 95% CI, 0.37–1.11). [The Working Group concluded that the choice of the control population, limited sample size, lack of definition of the red meat variable, and crude categorization of exposure were among the limitations of this study.]

Seow et al. (2002) reported results from a hospital-based colorectal case–control study done in Singapore (121 cases, 222 population-based controls), and reported a positive association between red meat portions per year and colorectal cancer (highest vs first tertile OR, 2.2; 95% CI, 1.1–4.2). They also reported results stratified by total vegetable intake and reported that results for red meat were stronger among individuals with a low intake of vegetables; however, no test of heterogeneity was provided. [The Working Group concluded that the main weaknesses of this study were the limited dietary assessment and lack of proper consideration of total energy intake.]

(e) Cooking practices

Most meat products require cooking for consumption. In spite of this, only a subset of studies distinguished meat types by cooking method and/or doneness level, limiting the evaluation of more specific categories of meat.

When considering red meat, among the studies previously reviewed, there were four studies that reported on cooking practices in relation to colorectal cancer risk (Barrett et al., 2003; Navarro et al., 2004; Miller et al., 2013; Joshi et al., 2015), four studies on colon cancer risk (Gerhardsson de Verdier et al., 1991; Kampman et al., 1999; Miller et al., 2013; Joshi et al., 2015), and four studies on rectal cancer risk (Gerhardsson de Verdier et al., 1991; Murtaugh et al., 2004; Miller et al., 2013; Joshi et al., 2015). For colorectal cancer risk, data were available from two of the largest population-based case–control studies (Joshi et al., 2015; Miller et al., 2013), which reported on a combined total of 4312 cases ascertained from the USA and Canada. These two studies considered separate cooking methods (pan-frying, broiling, grilling/barbecuing), and both reported positive associations with pan-frying; pan-fried beef steak (Q4 vs Q1 OR, 1.3; 95% CI, 1.1–1.5) was reported by Joshi et al. (2015), and pan-fried red meat (Q5 vs Q1 OR, 1.26; 95% CI, 0.93–1.70) was reported by Miller et al. (2013). Overall, of the seven studies that reported on red meat cooking practices and colorectal, colon, or rectal cancer, six reported positive associations with red meat when high-temperature methods and/or doneness levels were considered.

There were additional studies that considered red meat and processed meats combined in relation to colorectal cancer risk (Le Marchand et al., 2002b; Nowell et al., 2002; Cotterchio et al., 2008; Joshi et al., 2009; Squires et al., 2010; Tabatabaei et al., 2011), colon cancer risk (Le Marchand et al., 2002b; Butler et al., 2003; Joshi et al., 2009), and rectal cancer risk (Joshi et al., 2009). Overall, of the seven studies that reported on cooking practices and colorectal cancer, colon cancer, or rectal cancer, five reported associations with high-temperature cooking methods and/or doneness levels. Of these studies, the only one that looked at cooking methods in detail was Butler et al. (2003), which was in agreement with the studies by Joshi et al. (2015) and Miller et al. (2013) previously described for red meat (only), and reported a positive association with pan-fried red meat (OR, 2.0; 95% CI, 1.4–3.0) in addition to well-done red meat (OR, 1.7; 95% CI, 1.2–2.5).

2.2.3 Meta-analyses

High intakes of red meat and processed meats were associated with a moderate, but significant, increase in colorectal cancer risk in several meta-analyses conducted before 2010 (Sandhu et al., 2001; Norat et al., 2002; Larsson et al., 2006; Huxley et al., 2009). The results of more recent meta-analyses of the associations between colorectal cancer and consumption of unprocessed red meat and processed meat, as well as specific meat types, haem iron, and genetic interactions with red and processed meat intake are described here.

In all meta-analyses, similar methods were used to derive summary estimates of dose–response and relative risks for the highest compared with the lowest intake categories. In most analyses, significant associations were observed for all prospective studies combined. However, because the magnitudes of the summary associations were moderate to small, the statistical significance was often lost in subgroup analyses with fewer studies. In addition, some inconsistencies in the results remained unexplained, as the relatively low number of studies in each subgroup did not allow for extensive exploration of all potential sources of heterogeneity.

Chan et al. (2011) summarized the results of prospective studies on red and processed meat and colorectal cancer risk for the World Cancer Research Fund/American Institute of Cancer Research (WCRF/AICR) Continuous Update Project. For red meat, the relative risks for the highest compared with the lowest intake were 1.10 (95% CI, 1.00–1.21; I^2 = 22%; 12 studies) for colorectal cancer, 1.18 (95% CI, 1.04–1.35; I^2 = 0%; 10 studies) for colon cancer, and 1.14 (95% CI,

0.83–1.56; I^2 = 38%; 7 studies) for rectal cancer. Within the colon, the summary risk for increase of cancer was 13% for proximal colon cancer and 57% for distal colon cancer, but the associations were not significant. The relative risk for an increase of 100 g/day of red meat was 1.17 (95% CI, 1.05–1.31; 8 studies) for colorectal cancer, 1.17 (95% CI, 1.02–1.33; 10 studies) for colon cancer, and 1.18 (95% CI, 0.98–1.42; 7 studies) for rectal cancer. For processed meats, the relative risk for the highest compared with the lowest intake was 1.17 (95% CI, 1.09–1.25; I^2 = 6%; 13 studies) for colorectal cancer, 1.19 (95% CI, 1.11–1.29; I^2 = 0%; 11 studies) for colon cancer, and 1.19 (95% CI, 1.02–1.39; I^2 = 20%; 9 studies) for rectal cancer. Within the colon, the summary risk for increase of cancer was 4% for proximal colon cancer and 20% for distal colon cancer, but the associations were not significant (five studies in the analyses). The relative risks for an increase of 50 g/day were 1.18 (95% CI, 1.10–1.28; I^2 = 12%; 9 studies) for colorectal cancer, 1.24 (95% CI, 1.13–1.35; I^2 = 0%; 10 studies) for colon cancer, and 1.12 (95% CI, 0.99–1.28; I^2 = 0%; 8 studies) for rectal cancer.

The most recent, comprehensive meta-analysis of colorectal cancer and meat consumption included data from 27 prospective cohort studies, published in the English language and identified through 2013 (Alexander et al., 2015). Statistical analyses were based on comparisons of the highest intake category with the lowest intake category. Intake levels in these categories varied across studies. Linear dose–response slopes were derived from categorical meta-analyses of two subgroups, based on the units of red meat intake reported by the studies (grams or servings). Random effect models were used. The summary relative risk of colorectal cancer for the highest compared with the lowest intake of red meat and processed meat was 1.11 (95% CI, 1.03–1.19; I^2 = 33.6%; P = 0.014). Heterogeneity was reduced when the analysis was restricted to studies on (unprocessed) red meat. The summary relative risk for those 17 studies was 1.05 (95% CI, 0.98–1.12; I^2 = 8.4%; P = 0.328).

In analyses by cancer site, the association was significant with no heterogeneity for the colon (RR, 1.11; 95% CI, 1.04–1.18; 16 studies), and not significant with high heterogeneity for the rectum (RR, 1.17; 95% CI, 0.99–1.39; I^2 = 51.97%; 13 studies). When the analyses were restricted to studies of (unprocessed) red meat, there was no evidence of heterogeneity across studies (RR, 1.06; 95% CI, 0.97–1.16; 11 studies) for colon cancer and 1.03 (95% CI, 0.88–1.21; 10 studies) for rectal cancer.

Stronger but more heterogeneous associations were observed in studies conducted in North America compared with studies published in other countries. The weakest associations were observed in Asian studies, where meat intake is lower than in North America and Europe.

In the dose–response analysis, the relative risks were 1.02 (95% CI, 1.00–1.14; 10 studies) for 1 serving/day increase, and heterogeneity was moderate to low (I^2 = 26.5%), and 1.05 (95% CI, 0.97–1.13; 13 studies) for each 70 g/day increase.

Alexander et al. (2015) did not investigate processed meats. However, in an earlier meta-analysis, Alexander et al. (2010) reported the relative risks for the highest compared with the lowest intake of processed meat as 1.16 (95% CI, 1.10–1.23; $P_{heterogeneity}$ = 0.556; 20 studies) for any colorectal cancer, 1.19 (95% CI, 1.10–1.28; 12 studies) for colon cancer, and 1.18 (95% CI, 1.03–1.36; 8 studies) for rectal cancer. The relative risk of any colorectal cancer was 1.10 (95% CI, 1.05–1.15; 9 studies) for an increase of 30 g of processed meat intake and 1.03 (95% CI, 1.01–1.05; 6 studies) for each serving per week intake.

[The Working Group noted that there was no significant evidence of publication bias. The pooled analyses of the GECCO study, which included some cohorts included in the meta-analysis, did not find an association between red and processed meats and colorectal cancer. The Danish Diet, Cancer and Health study (Egeberg

et al., 2013), in which red and processed meats were not related to colorectal cancer risk, was published after the preparation of the meta-analysis, and therefore was not included. The Japanese study by Takachi et al. (2011) was included in Alexander et al. (2015), but was published after the end of the search for the meta-analysis by Chan et al. (2011).]

The statistical methods used by Alexander et al. (2015) and Chan et al. (2011) were similar. However, Chan et al. (2011) rescaled times consumed or servings to grams of intake using values reported in the studies, or standard portion sizes of 120 g for red meat and 50 g for processed meat, following the methodology of the WCRF/AICR second expert report. [The Working Group noted that the rescaling may have increased the measurement error of the diet in the rescaled studies, but allowed for the inclusion of all studies in the analyses. Chan et al. (2011) reported that the summary risk estimate in the studies using serving as the intake unit was lower than that in the studies using grams (same finding in Alexander et al. (2010) for processed meats). It is possible that the rescaling of the intake may have attenuated the observed association. Another difference between the meta-analyses is that Chan et al. (2011) grouped the studies according to exposure: red and processed meats, red meats (unprocessed), and processed meats.]

A meta-analysis of six Japanese cohort studies reported no significant associations between total and specific meat types and colorectal cancer risk (Pham et al., 2014). For red meat consumption, the summary relative risk estimates for the highest compared with the lowest intake in the studies were 1.20 (95% CI, 1.00–1.44; 4 cohort studies) for colon cancer and 0.95 (95% CI, 0.71–1.28; 3 studies) for rectal cancer. For processed meats, the summary relative risks for the same comparison were 1.18 (95% CI, 0.92–1.53; 4 studies) for colon cancer and 0.94 (95% CI, 0.72–1.21; 3 studies) for rectal cancer. When the authors combined the results of the cohort studies with those of 13 case–control studies, the summary relative risks for red meat were 1.16 (95% CI, 1.001–1.34) and 1.21 (95% CI, 1.03–1.43) for colorectal and colon cancer, respectively, and those for processed meat consumption were 1.17 (95% CI, 1.02–1.35) and 1.23 (95% CI, 1.03–1.47) for colorectal and colon cancer, respectively.

Another meta-analysis of prospective studies summarized the associations between types of red meats and risk of colorectal cancer (Carr et al., 2016). The meta-analysis included one study from the Netherlands, one from Denmark, two from Japan, and the 10 European cohorts participating in the EPIC study. For the highest compared with the lowest intake of beef, the summary relative risks were 1.11 (95% CI, 1.01–1.22), 1.24 (95% CI, 1.07–1.44), and 0.95 (95% CI, 0.78–1.16) for colorectal, colon, and rectal cancer, respectively. Higher consumption of lamb was also associated with an increased risk of colorectal cancer (RR, 1.24; 95% CI, 1.08–1.44). No association was observed for pork (RR, 1.07; 95% CI, 0.90–1.27).

Qiao & Feng (2013) summarized the results of eight prospective studies on haem iron intake. The summary relative risk of colorectal cancer for the highest versus the lowest intake was 1.14 (95% CI, 1.04–1.24). The observed associations were not significantly modified by cancer site or sex. In the dose–response analyses, the summary relative risk was 1.11 (95% CI, 1.03–1.18) for an increment of haem iron intake of 1 mg/day.

In another meta-analysis, people with the *NAT2* fast acetylator phenotype who consumed a high intake of total meat had a statistically non-significant increased risk of colorectal cancer compared with slow acetylators who consumed a low intake of total meat (4 cohorts; $P_{interaction} = 0.07$) (Andersen et al., 2013). No interaction with the *NAT1* phenotype was observed (cohort studies) on the multiplicative scale.

Table 2.2.1 Cohort studies: consumption of red meat or red meat & processed meat combined and cancer of the colorectum

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Kato et al. (1997) USA 1985–1994 Cohort study	14 727; New York University Women's Health Study (NYUWHS) Exposure assessment method: questionnaire	Colon and rectum	Red meat intake (quartiles)			Total caloric intake, age, a place at enrolment and level of education
			Q1 (lowest quartile)	NR	1.00	
			Q2	NR	1.28 (0.72–2.28)	
			Q3	NR	1.27 (0.71–2.28)	
			Q4 (highest quartile)	NR	1.23 (0.68–2.22)	
			Trend-test *P* value: 0.545			
Chen et al. (1998) USA 1982–1995 Nested case–control study	Cases: 212; Physicians' Health Study (PHS); self-report, medical records, and death certificates Controls: 221; cohort, matched by age and smoking Exposure assessment method: questionnaire; abbreviated FFQ red meat included: beef, pork, or lamb as main dish, in sandwiches or hot dogs	Colon and rectum	Red meat/processed meat (servings/day)			Age, smoking status, BMI, physical activity, alcohol intake
			≤ 0.5	62	1.00	
			> 0.5–1.0	103	0.98 (0.64–1.52)	
			> 1.0	43	1.17 (0.68–2.02)	
			Trend-test *P* value: 0.59			
Singh and Fraser (1998) California, USA Enrolment, 1976–1982; follow-up, 1977–1982 Cohort study	32 051; non-Hispanic, White members of the Adventist Health Study (AHS), California, USA Exposure assessment method: questionnaire; mailed, 55-item SQFFQ; six questions on current consumption of specific meats; red meat included beef and pork	Colon and rectum	Red meat (times/wk)			Age, sex, BMI, physical activity, parental history of colorectal cancer, current smoking, past smoking, alcohol consumption, aspirin use
			Never	42	1.00	
			> 0 to < 1	40	1.40 (0.87–2.25)	
			≥ 1	45	1.90 (1.16 – 3.11)	
			Trend-test *P* value: 0.02			
Pietinen et al. (1999) Finland Enrolment, 1985 and 1988; follow-up to 1995 Cohort study	27 111; male smokers in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) Study Exposure assessment method: questionnaire; self-administered, modified dietary history of usual diet 12 mo prior to baseline (276 food items)	Colon and rectum	Beef, pork, and lamb, quartile median (g/day)			Age, supplement group, years of smoking, BMI, alcohol, education, physical activity, calcium intake
			35	55	1.0	
			52	35	0.6 (0.4–1.1)	
			69	50	0.9 (0.6–1.3)	
			99	45	0.8 (0.5–1.2)	
			Trend-test *P* value: 0.74			

Table 2.2.1 Cohort studies: consumption of red meat or red meat & processed meat combined and cancer of the colorectum

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Järvinen et al. (2001) Finland Enrolment, 1967–1972; follow-up until late 1999 Cohort study	9959; men and women participating in the population-based Finnish Mobile Clinic Health Examination Survey Exposure assessment method: questionnaire; structured questionnaires including more than 100 foods and mixed dishes; food models and real foods used in portion size estimation [red meat may have included processed meat]	Colon and rectum	Red meat/processed meat Quartiles of intake (g/day)			Age; sex; BMI; occupation; smoking; geographical area; total energy intake; consumption of vegetables, fruits, cereals
			< 94 in men and < 61 in women	NR	1.00	
			94–141 in men, 61–92 in women	NR	1.06 (0.67–2.01)	
			142–206 in men, 93–134 in women	NR	1.55 (0.88–2.73)	
			> 206 in men, > 134 in women	NR	1.50 (0.77–2.94)	
		Colon	Quartiles of intake (g/day)			
			< 94 in men, < 61 in women	NR	1.00	
			94–141 in men, 61–92 in women	NR	0.71 (0.33–1.51)	
			142–206 in men, 93–134 in women	NR	1.29 (0.63–2.66)	
			> 206 in men, > 134 in women	NR	1.34 (0.57–3.15)	
		Rectum	Quartiles of intake (g/day)			
			< 94 in men, < 61 in women	NR	1.00	
			94–141 in men, 61–92 in women	NR	2.18 (0.93–5.10)	
			142–206 in men, 93–134 in women	NR	2.11 (0.84–5.28)	
			> 206 in men, > 134 in women	NR	1.82 (0.60–5.52)	

Table 2.2.1 Cohort studies: consumption of red meat or red meat & processed meat combined and cancer of the colorectum

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Tiemersma et al. (2002) The Netherlands 1987–1998 Nested case–control study	Cases: 102; national and regional cancer registries Controls: 537; cohort, frequency-matched by sex, age, and centre Exposure assessment method: questionnaire; short SQFFQ method, validated by a dietary history method; fresh red meat was beef and pork	Colon and rectum	0–3.0 times/wk	22	1.0	Age, sex, centre, total energy intake, alcohol consumption, body height
			3.1–4.5 times/wk	35	1.3 (0.7–2.3)	
			≥ 5.0 times/wk	45	1.6 (0.9–2.9)	
			Trend-test *P* value: 0.1			
			Women:			
			0–3.0 times/wk	15	1.0	
			3.1–4.5 times/wk	18	0.8 (0.4–1.8)	
			≥ 5.0 times/wk	15	1.2 (0.5–2.8)	
			Trend-test *P* value: 0.64			
			Men:			
			0–3.0 times/wk	7	1.0	
			3.1–4.5 times/wk	17	2.7 (1.1–6.9)	
			≥ 5.0 times/wk	30	2.7 (1.1–6.7)	
			Trend-test *P* value: 0.06			
			Slow and normal *NAT1*:			
			0–3.0 times/wk	NR	1.0	
			3.1–4.5 times/wk	NR	1.2 (0.6–2.4)	
			≥ 5.0 times/wk	NR	1.4 (0.7–2.9)	
			Fast *NAT1*: 0–3.0 times/wk	NR	0.7 (0.3–1.9)	
			3.1–4.5 times/wk	NR	0.9 (0.4–2.0)	
			≥ 5.0 times/wk	NR	1.4 (0.6–3.0)	
			Slow and normal *NAT2*:			
			0–3.0 times/wk	NR	1.0	
			3.1–4.5 times/wk	NR	1.0 (0.5–2.2)	
			≥ 5.0 times/wk	NR	1.4 (0.7–2.9)	
			Fast and intermediate *NAT2*:			
			0–3.0 times/wk	NR	0.7 (0.3–1.9)	
			3.1–4.5 times/wk	NR	1.1 (0.5–2.4)	
			≥ 5.0 times/wk	NR	1.4 (0.6–3.1)	

Table 2.2.1 Cohort studies: consumption of red meat or red meat & processed meat combined and cancer of the colorectum

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Tiemersma et al. (2002) The Netherlands 1987–1998 Nested case–control study (cont.)			*GSTM1* genotype present:			
			0–3.0 times/wk	NR	1.0	
			3.1–4.5 times/wk	NR	1.5 (0.6–3.7)	
			≥ 5.0 times/wk	NR	2.0 (0.8–5.0)	
			GSTM1 genotype null:			
			0–3.0 times/wk	NR	1.7 (0.7–4.4)	
			3.1–4.5 times/wk	NR	1.7 (0.7–4.1)	
			≥ 5.0 times/wk	NR	2.2 (0.9–5.2)	
Flood et al. (2003) USA 1987–1998 Cohort study	61 431; Breast Cancer Detection Demonstration Project (BCDDP) Exposure assessment method: questionnaire; 62-item NCI Block FFQ; red meat was pork, beef, hamburger, processed meats, and liver in previous year	Colon and rectum	Red meat/processed meat (quintile median, g/1000 kcal)			Age, total energy intake by multivariate nutrient density method, total meat intake
			6.1	NR	1.00	
			14.6	NR	1.04 (0.79–1.36)	
			22.6	NR	0.95 (0.72–1.26)	
			32.7	NR	0.95 (0.71–1.27)	
			52.2	NR	1.04 (0.77–1.41)	
			Trend-test *P* value: 0.73			
English et al. (2004) Melbourne, Australia 1990–2002 Cohort study	41 528; residents of Melbourne aged 40–69 yr Exposure assessment method: FFQ; red meat was veal, beef, lamb, pork, rabbit, or other game; diet assessed through 121-item FFQ	Colon and rectum	< 3.0 times/wk	66	1.00	Age; sex; country of birth; intake of energy, fat, cereal products
			3.0–4.4 times/wk	123	1.40 (1.10–1.90)	
			4.5–6.4 times/wk	142	1.50 (1.10–2.10)	
			≥ 6.5 times/wk	120	1.40 (1.00–1.90)	
			Trend-test *P* value: 0.2			
			For increase of 1 time/wk	451	1.03 (0.98–1.08)	
			Trend-test *P* value: 0.9			
		Colon	< 3.0 times/wk	NR	1.00	
			3.0–4.4 times/wk	NR	1.20 (0.80–1.70)	
			4.5–6.4 times/wk	NR	1.30 (0.90–1.90)	
			≥ 6.5 times/wk	NR	1.10 (0.70–1.60)	
			Trend-test *P* value: 0.9			

Table 2.2.1 Cohort studies: consumption of red meat or red meat & processed meat combined and cancer of the colorectum

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
English et al. (2004) Melbourne, Australia 1990–2002 Cohort study (cont.)		Colon	For an increase of 1 time/wk	283	1.00 (0.94–1.07)	
		Rectum	< 3.0 times/wk	NR	1.00	
			3.0–4.4 times/wk	NR	2.20 (1.30–4.00)	
			4.5–6.4 times/wk	NR	2.20 (1.20–3.90)	
			≥ 6.5 times/wk	NR	2.30 (1.20–4.20)	
			Trend-test *P* value: 0.07			
			For an increase of 1 time/wk	169	1.08 (0.99–1.16)	
			Trend-test *P* value: 0.07			
Chao et al. (2005) USA 1992–2001 Cohort study	148 610; Cancer Prevention Study II (CPS-II) Nutrition Survey cohort Exposure assessment method: questionnaire; diet assessed through 68-item, modified Block FFQ; red meat included beef, pork, processed meats, and liver	Colon	Red meat/processed meat, quintile median (g/day)			Age; education; BMI; cigarette smoking; recreational physical activity; multivitamin use; aspirin use; intake of beer, wine, liquor, fruits, vegetables, high-fibre grain foods
			Men:			
			100	88	1.00	
			253	121	1.14 (0.86–1.50)	
			398	141	1.16 (0.88–1.53)	
			612	191	1.22 (0.92–1.61)	
			999	125	1.30 (0.93–1.81)	
			Trend-test *P* value: 0.08			
			Red meat/processed meat, quintile median (g/day)			
			Women:			
			43	76	1.00	
			168	154	0.98 (0.74–1.30)	
			278	72	0.94 (0.68–1.31)	
			416	144	0.98 (0.73–1.32)	
			712	86	0.98 (0.68–1.40)	
			Trend-test *P* value: 0.45			

Table 2.2.1 Cohort studies: consumption of red meat or red meat & processed meat combined and cancer of the colorectum

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Chao et al. (2005) USA 1992–2001 Cohort study (cont.)		Colon	Red meat/processed meat Men and women (sex-specific quintiles):			
			Q1	164	1.00	
			Q2	275	1.07 (0.88–1.31)	
			Q3	213	1.07 (0.86–1.31)	
			Q4	335	1.11 (0.91–1.36)	
			Q5	210	1.15 (0.90–1.46)	
			Trend-test *P* value: 0.4			
		Proximal colon	Red meat/processed meat (sex-specific quintiles)			
			Q1	88	1.00	
			Q2	169	1.21 (0.93–1.58)	
			Q3	113	1.08 (0.81–1.44)	
			Q4	182	1.17 (0.89–1.53)	
			Q5	116	1.27 (0.91–1.76)	
			Trend-test *P* value: 0.05			
		Distal colon	Red meat/processed meat (sex-specific quintiles)			
			Q1	69	1.00	
			Q2	76	0.72 (0.52–1.00)	
			Q3	79	0.89 (0.64–1.24)	
			Q4	120	0.87 (0.63–1.21)	
			Q5	64	0.71 (0.47–1.07)	
			Trend-test *P* value: 0.92			
		Rectosigmoid junction and rectum	Red meat/processed meat (sex-specific quintiles)			
			Q1	57	1.00	
			Q2	118	1.43 (1.03–1.96)	
			Q3	85	1.26 (0.89–1.78)	
			Q4	114	1.18 (0.84–1.67)	
			Q5	96	1.71 (1.15–2.52)	
			Trend-test *P* value: 0.007			

Table 2.2.1 Cohort studies: consumption of red meat or red meat & processed meat combined and cancer of the colorectum

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Larsson et al. (2005a) Sweden 1987–2003 Cohort study	61 433; Swedish women aged 40–76 yr Exposure assessment method: questionnaire; 67-item, 6-mo FFQ; red meat included bacon, ham, hot dogs, and lunchmeat; beef and pork as a main dish reported separately	Colon and rectum	Beef and pork (servings/wk), quartiles (quartile median)			Age; BMI; education level; intake of total energy, alcohol, saturated fat, calcium, folate, fruits, vegetables, whole-grain foods
			< 2.0 (1.5)	NR	1.00	
			2.0 to < 3.0 (2.5)	NR	1.13 (0.95–1.36)	
			3.0 to < 4.0 (4.0)	NR	0.90 (0.70–1.17)	
			≥ 4.0 (5.5)	NR	1.22 (0.98–1.53)	
			Trend-test *P* value: 0.32			
		Colon: proximal colon	Beef and pork (servings/wk), quartiles (quartile median)			
			< 2.0 (1.5)	NR	1.00	
			2.0 to < 3.0 (2.5)	NR	0.90 (0.65–1.24)	
			3.0 to < 4.0 (4.0)	NR	0.78 (0.45–1.17)	
			≥ 4.0 (5.5)	NR	1.10 (0.74–1.64)	
			Trend-test *P* value: 0.9			
		Colon: distal colon	Beef and pork (servings/wk), quartiles (quartile median)			
			< 2.0 (1.5)	NR	1.00	
			2.0 to < 3.0 (2.5)	NR	1.26 (0.84–1.90)	
			3.0 to < 4.0 (4.0)	NR	0.98 (0.55–1.75)	
			≥ 4.0 (5.5)	NR	1.99 (1.26–3.14)	
			Trend-test *P* value: 0.01			
		Rectum	Beef and pork (servings/wk), quartiles (quartile median)			
			< 2.0 (1.5)	NR	1.00	
			2.0 to < 3.0 (2.5)	NR	1.18 (0.86–1.62)	
			3.0 to < 4.0 (4.0)	NR	0.87 (0.55–1.37)	
			≥ 4.0 (5.5)	NR	1.08 (0.72–1.62)	
			Trend-test *P* value: 0.98			

Table 2.2.1 Cohort studies: consumption of red meat or red meat & processed meat combined and cancer of the colorectum

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Norat et al. (2005) Europe 1992–2002 Cohort study	478 040; European Prospective Investigation into Cancer and Nutrition (EPIC) study Exposure assessment method: questionnaire; country-specific, validated dietary questionnaires (88–266 items), self-administered in most countries; second 24-h recall measurement from an 8% random sample to calibrate measurements across countries and correct for systematic error	Colon and rectum	Red meat (g/day)			Age, sex, energy from non-fat sources, energy from fat sources, height, weight, occupational physical activity, smoking status, dietary fibre, alcohol intake, stratified by centre
			< 10	132	1.00	
			10–20	138	1.00 (0.78–1.28)	
			20–40	323	1.03 (0.83–1.28)	
			40–80	486	1.16 (0.94–1.43)	
			> 80	250	1.17 (0.92–1.49)	
			Trend-test *P* value: 0.08			
		Colon	Red meat (g/day)			
			< 10	NR	1.00	
			10–20	NR	1.04 (0.77–1.41)	
			20–40	NR	1.02 (0.78–1.32)	
			40–80	NR	1.16 (0.90–1.51)	
			> 80	NR	1.20 (0.88–1.61)	
			Trend-test *P* value: 0.14			
		Colon: right colon	Red meat (g/day)			
			< 10	NR	1.00	
			10–20	NR	1.13 (0.70–1.84)	
			20–40	NR	1.00 (0.65–1.54)	
			40–80	NR	1.36 (0.90–2.07)	
			> 80	NR	1.18 (0.73–1.91)	
			Trend-test *P* value: 0.22			
		Colon: left colon	Red meat (g/day)			
			< 10	NR	1.00	
			10–20	NR	1.07 (0.68–1.68)	
			20–40	NR	1.10 (0.65–1.63)	
			40–80	NR	1.11 (0.75–1.64)	
			> 80	NR	1.24 (0.80–1.94)	
			Trend-test *P* value: 0.38			

Table 2.2.1 Cohort studies: consumption of red meat or red meat & processed meat combined and cancer of the colorectum

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Norat et al. (2005) Europe 1992–2002 Cohort study (cont.)		Rectum	Red meat (g/day)			
			< 10	NR	1.00	
			10–20	NR	0.93 (0.60–1.44)	
			20–40	NR	1.07 (0.74–1.55)	
			40–80	NR	1.16 (0.80–1.66)	
			> 80	NR	1.13 (0.74–1.71)	
			Trend-test *P* value: 0.32			
		Colon and rectum	For an increase of 100 g/day (observed intake)	1329	1.21 (1.02–1.43)	
			Trend-test *P* value: 0.03			
		Colon and rectum	For an increase of 100 g/day (calibrated intake)	1329	1.49 (0.91–2.43)	
			Trend-test *P* value: 0.11			
		Colon	For an increase of 100 g/day (observed intake)	855	1.20 (0.96–1.48)	
			Trend-test *P* value: 0.1			
		Colon	For an increase of 100 g/day (calibrated intake)	855	1.36 (0.74–2.50)	
			Trend-test *P* value: 0.32			
		Rectum	For an increase of 100 g/day (observed intake)	474	1.23 (0.94–1.62)	
			Trend-test *P* value: 0.14			
		Rectum	For an increase of 100 g/day (calibrated intake)	474	1.75 (0.93–3.30)	
			Trend-test *P* value: 0.08			

Table 2.2.1 Cohort studies: consumption of red meat or red meat & processed meat combined and cancer of the colorectum

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Berndt et al. (2006) Maryland, USA 1989–2003 Nested case–control study	Cases: 272; identified via population-based registry from participants in the CLUE II cohort Controls: 2224; 10% age-stratified sample of CLUE II cohort participants without cancer Exposure assessment method: FFQ; validated, administered by mail, and considered frequency and serving size; red meat was hamburgers, cheeseburgers, meatloaf, beef, beef stew, pork, hot dogs, bacon, sausage, ham, bologna, salami, and lunchmeats	Colon and rectum	Red meat/processed meat (g/day) < 44 44 to < 86.3 ≥ 86.3	 NR NR NR	 1.00 1.16 (0.80–1.70) 1.32 (0.86–2.02)	Age, ethnicity, total energy intake
Oba et al. (2006) Takayama, Japan 1992–2000 Cohort study	30 221; community-based cohort of men and women aged ≥ 35 yr in Takayama, Japan Exposure assessment method: questionnaire; self-administered, 169-item, validated SQFFQ; red meat defined as beef and pork	Colon	Men (tertile median, g/day): 18.7 34.4 56.6 Trend-test *P* value: 0.86 Women (tertile median, g/day): 10.7 25.2 42.3 Trend-test *P* value: 0.2	 40 39 32 50 25 27	 1.00 1.14 (0.73–1.77) 1.03 (0.64–1.66) 1.00 0.64 (0.39–1.03) 0.79 (0.49–1.28)	Age, height, BMI, total pack-years of cigarette smoking, alcohol intake, physical activity

Table 2.2.1 Cohort studies: consumption of red meat or red meat & processed meat combined and cancer of the colorectum

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Kabat et al. (2007) Canada 1980–2000 Cohort study	49 654; Canadian National Breast Screening Study (CNBSS) Exposure assessment method: questionnaire; self-administered, 86-item FFQ with 22 meat items and two mixed dishes containing meat; red meat included ham, bacon, and pork-based luncheon meats	Colon and rectum	Red meat, processed meat (g/day)			Age; BMI; menopausal status; oral contraceptive use; hormone replacement use; pack-years of smoking; alcohol intake; education; physical activity; dietary intake of fat, fibre, folic acid, total calories
			< 14.25	NR	1.00	
			14.25 to < 21.02	NR	1.10 (0.85–1.42)	
			21.02 to < 28.74	NR	1.17 (0.90–1.50)	
			28.74–40.30	NR	0.97 (0.74–1.27)	
			≥ 40.30	NR	1.12 (0.86–1.46)	
			Trend-test *P* value: 0.66			
		Colon	Red meat/processed meat (g/day)			
			< 14.25	NR	1.00	
			14.25 to < 21.02	NR	1.06 (0.79–1.42)	
			21.02 to < 28.74	NR	0.97 (0.72–1.32)	
			28.74–40.30	NR	0.84 (0.61–1.15)	
			≥ 40.30	NR	0.88 (0.64–1.21)	
			Trend-test *P* value: 0.16			
		Rectum	Red meat/processed meat (g/day)			
			< 14.25	NR	1.00	
			14.25 to < 21.02	NR	1.25 (0.75–2.08)	
			21.02 to < 28.74	NR	1.79 (1.11–2.88)	
			28.74–40.30	NR	1.42 (0.85–2.35)	
			≥ 40.30	NR	1.95 (1.21–3.16)	
			Trend-test *P* value: 0.008			
Butler et al. (2008b) Singapore, China 1993–2005 Cohort study	61 321; Singaporean Chinese aged 45–74 yr Exposure assessment method: FFQ; validated, 165-item, 12-mo quantitative FFQ	Colon and rectum	Quartile 4 vs quartile 1	NR	1.01 (0.82–1.26)	Age, sex, total energy intake, dialect group, interview year, alcohol intake, BMI, diabetes, education, physical activity, smoking history, first-degree history of colorectal cancer
			Trend-test *P* value: 0.6			

Table 2.2.1 Cohort studies: consumption of red meat or red meat & processed meat combined and cancer of the colorectum

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Sørensen et al. (2008) Denmark Enrolment, 1993–1997; follow-up to 2003 Cohort study	Case–cohort: 379 cases with colorectal cancer and 769 subcohort members; Danish men and women aged 50–64 yr free of cancer Exposure assessment method: questionnaire; FFQ with 192 foods and recipes, 63 meat items and meat dishes, and standard portion sizes; red meat was beef, veal, pork, lamb, and offal	Colon and rectum	Red meat, all (per 25 g/day increase)	105	1.03 (0.97–1.09)	Age; sex; intake of poultry, fish, alcohol, dietary fibre; BMI; HRT; smoking status
			Red meat for different polymorphisms (per 25 g/day increase)			
			NAT1 fast	NR	1.06 (0.97–1.17)	
			NAT1 slow	NR	1.02 (0.95–1.09)	
			NAT2 slow	NR	1.06 (0.97–1.14)	
			NAT2 fast	NR	1.01 (0.93–1.09)	
Andersen et al. (2009) Denmark 1994–1997 Nested case–control study	Cases: 372; case–cohort study within the Danish Diet, Cancer and Health cohort Controls: 765; subcohort members with DNA and questionnaire data available; frequency-matched to cases by sex Exposure assessment method: FFQ; mailed in, validated, 192-item FFQ; red meat was beef, veal, pork, lamb, and offal	Colon and rectum	Red meat (g/day)			Sex, age, tumour localization (proximal or distal colon, rectum, NOS), BMI, alcohol, processed meat, dietary fibre, smoking status, NSAID use, HRT use
			Per 25 g/day	NR	1.02 (0.94–1.12)	
Lee et al. (2009) Shanghai, China Enrolment, 1997–2000; follow-up to December, 2005 Cohort study	73 224; Shanghai Women's Health Study (SWHS), a population-based prospective cohort study of women aged 40–70 yr living in Shanghai, China Exposure assessment method: questionnaire; validated quantitative FFQ (including 19 food items/groups of animal origin)	Colon and rectum	Red meat (g/day), quintiles			Age, education, income, survey season, tea consumption, NSAID use, energy intake, fibre intake
			< 24	108	1.0	
			24–< 36	80	0.9	
			36–< 49	65	0.7	
			49–< 67	79	1.0	
			≥ 67	62	0.8 (0.6–1.1)	
			Trend-test *P* value: 0.53			
		Colon	Red meat (g/day), quintiles			
			< 24	63	1.0	
			24–< 36	49	0.9	
			36–< 49	40	0.8	
			49–< 67	43	0.9	
			≥ 67	41	0.9 (0.6–1.5)	
			Trend-test *P* value: 0.31			

Table 2.2.1 Cohort studies: consumption of red meat or red meat & processed meat combined and cancer of the colorectum

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
		Rectum	Red meat (g/day), quintiles			
			< 24	45	1.0	
			24–< 36	31	0.8	
			36–< 49	25	0.7	
			49–< 67	36	1.0	
			≥ 67	21	0.6 (0.3–1.1)	
			Trend-test *P* value: 0.79			
Cross et al. (2010) USA 1995–2003 Cohort study	300 948; National Institutes of Health – American Association of Retired Persons (NIH-AARP) Diet and Health Study in men and women aged 50–71 yr from six USA states and two metropolitan areas Exposure assessment method: FFQ; 124-item FFQ calibrated against two 24-h dietary recalls; red meat included beef, pork, lamb, bacon, cold cuts, ham, hamburger, hot dogs, liver, and sausage	Colon and rectum	Red meat/processed meat (median, g/1000 kcal)			Sex, BMI, dietary fibre intake, education level, smoking habits, dietary calcium intake, total energy intake, white meat intake
			9.5	451	1.00	
			20.9	484	1.00 (0.87–1.14)	
			30.7	502	0.99 (0.87–1.13)	
			42.1	614	1.18 (1.03–1.34)	
			61.6	668	1.24 (1.09–1.42)	
			Trend-test *P* value: 0.001			
		Colon and rectum	For an increase of 100 g/day	2719	1.23 (1.10–1.36)	
			Trend-test *P* value: 0.001			
		Colon	Red meat/processed meat (median, g/1000 kcal)			
			9.5	340	1.00	
			20.9	345	0.94 (0.81–1.09)	
			30.7	367	0.96 (0.82–1.12)	
			42.1	457	1.16 (1.00–1.36)	
			61.6	486	1.21 (1.03–1.41)	
			Trend-test *P* value: 0.001			
		Colon	For 100 g/day increase	1995	1.20 (1.05–1.36)	
			Trend-test *P* value: 0.024			

Table 2.2.1 Cohort studies: consumption of red meat or red meat & processed meat combined and cancer of the colorectum

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Cross et al. (2010) USA 1995–2003 Cohort study (cont.)		Rectum	Red and processed meat (median, g/1000 kcal)			
			9.5	111	1.00	
			20.9	139	1.18 (0.91–1.52)	
			30.7	135	1.09 (0.84–1.42)	
			42.1	157	1.21 (0.93–1.58)	
			61.6	182	1.35 (1.03–1.76)	
			Trend-test *P* value: 0.024			
		Rectum	For 100 g/day increase	724	1.31 (1.07–1.61)	
			Trend-test *P* value: 0.024			
		Proximal colon	Red and processed meat intake, quintiles			
			Q5 vs Q1	1150	1.15 (0.94–1.41)	
			Trend-test *P* value: 0.024			
		Distal colon	Red and processed meat intake, quintiles			
			Q5 vs Q1	787	1.29 (1.00–1.66)	
			Trend-test *P* value: 0.018			
Ollberding et al. (2012) California or Hawaii, USA 1993–2007 Cohort study	131 763; multiethnic sample of African Americans, Japanese Americans, Latinos, native Hawaiians, and Whites aged 45–75 yr Exposure assessment method: questionnaire; validated quantitative FFQ that captured 85% of the intake of key nutrients	Colon and rectum	Red meat, excluding processed (quintile median, g/1000 kcal per day)			Age, ethnicity, family history of colorectal cancer, history of colorectal polyps, BMI, smoking, NSAID use, alcohol, physical activity, history of diabetes, HRT use (females), total calories, intake of dietary fibre, calcium, folate, vitamin D
			4.59	654	1.00	
			11.13	702	0.99 (0.89–1.11)	
			16.86	712	1.00 (0.90–1.12)	
			23.40	677	0.97 (0.87–1.09)	
			34.86	659	0.98 (0.87–1.10)	
			Trend-test *P* value: 0.58			

Table 2.2.1 Cohort studies: consumption of red meat or red meat & processed meat combined and cancer of the colorectum

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Figueiredo et al. (2014) International – USA, Canada, and Europe NR Pooled case–control study and nested-case-control studies	Cases: 9287; identified from five case–control and five nested case–control studies within prospective cohorts from the Colon Cancer Family Registry (CCFR) and the Genetics and Epidemiology of Colorectal Cancer Consortium (GECCO) Controls: 9117; controls from the same population as cases Exposure assessment method: questionnaire; unclear harmonized red meat variable (in some studies, it included processed meats; in others, it did not)	Colon and rectum	Red meat intake Per quartile of increasing intake (P = 1.63e–18)	NR	1.15	Age at the reference time, sex (when appropriate), centre (when appropriate), total energy consumption (if available), first three principal components from EIGENSTRAT to account for potential population substructure
Ananthakrishnan et al. (2015) USA, Canada, and Australia NR Pooled case–control study and nested case-control studies	Cases: 8290; cases were incident colorectal cancer patients enrolled in the Colon Cancer Family Registry (CCFR) and 10 different studies that were part of the Genetics and Epidemiology of Colorectal Cancer Consortium (GECCO) Controls: 9115; controls were enrolled as part of CCFR and as part of the 10 studies that were part of GECCO Exposure assessment method: questionnaire; red meat and other covariates were harmonized across all the 11 studies; therefore, the definition of red meat was heterogeneous, with some studies including processed meat and others not	Colon and rectum	Red meat/processed meat (servings/day) Q1 Q2 Q3 Q4	 NR NR NR NR	 1.00 1.15 (1.03–1.28) 1.17 (1.05–1.29) 1.29 (1.15–1.44)	Age, sex, study site, smoking status, aspirin use, NSAID use, BMI, dietary calcium, folate, servings of fruits and vegetables

Table 2.2.1 Cohort studies: consumption of red meat or red meat & processed meat combined and cancer of the colorectum

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Bernstein et al. (2015) USA Nurses' Health Study, 1980–2010; Health Professionals Follow-Up Study, 1986– 2010 Cohort study	87 108 women and 47 389 men; Nurses' Health Study (NHS) and Health Professionals Follow-Up Study (HPFS) Exposure assessment method: FFQ; diet from FFQs collected about every 4 yr during follow-up (see Wei et al., 2004)	Colon and rectum	Red meat (1 serving/day)			Age, follow-up, family history, endoscopy, smoking, alcohol drinking, BMI, physical activity, medications and supplements, menopausal status, hormone use, total caloric intake, folate, calcium, vitamin D, fibre intake
			Baseline intake	2731	1.02 (0.94–1.12)	
			Trend-test *P* value: 0.61			
			Red meat (1 serving/day)			
			Cumulative average	2731	0.99 (0.87–1.13)	
			Trend-test *P* value: 0.88			
		Proximal colon	Red meat (1 serving/day)			
			Baseline intake	1151	1.13 (0.99–1.29)	
			Trend-test *P* value: 0.07			
			Red meat (1 serving/day)			
			Cumulative intake	1151	1.14 (0.92–1.40)	
			Trend-test *P* value: 0.22			
		Distal colon	Red meat (1 serving/day)			
			Baseline intake	817	0.88 (0.75–1.05)	
			Trend-test *P* value: 0.16			
			Red meat (1 serving/day)			
			Cumulative intake	817	0.75 (0.68–0.82)	
			Trend-test *P* value: < 0.01			
		Rectum	Processed red meat (1 serving/day)			
			Baseline intake	589	1.05 (0.84–1.32)	
			Trend-test *P* value: 0.64			
			Processed red meat (1 serving/day)			
			Cumulative intake	589	1.14 (0.86–1.51	
			Trend-test *P* value: 0.25			

BMI, body mass index; CI, confidence interval; FFQ, food frequency questionnaire; GWAS, genome-wide association study; h, hour; HRT, hormone replacement therapy; mo, month; NOS, not otherwise specified; NR, not reported; NSAID, nonsteroidal anti-inflammatory drug; SD, standard deviation; SQFFQ, semiquantitative food frequency questionnaire; wk, week; yr, year

Table 2.2.2 Cohort studies on consumption of processed meat and cancer of the colorectum

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Bostick et al. (1994) USA Enrolment,1985; follow-up, 1986–1990 Cohort study	35 216; women aged 55–69 yr, mostly White, in the Iowa Women's Health Study (IWHS) Exposure assessment method: FFQ; 127-item, validated SQFFQ; processed meat was bacon, hot dogs, and other processed meats	Colon	Processed meats (servings/wk)			Age, total energy intake, height, parity, total vitamin E intake, interaction term vitamin E–age, vitamin A supplement
			0	91	1.00	
			0.5	67	1.00 (0.73–1.38)	
			1.0	32	1.07 (0.71–1.61)	
			2.0–3.0	14	0.81 (0.46–1.44)	
			> 3.0	8	1.51 (0.72–3.17)	
			Trend-test *P* value: 0.45			
Kato et al. (1997) USA Enrolment, 1985–1991; follow-up to 1994 Cohort study	14 727; women aged 34–65 yr in the New York University Women's Health Study (NYUWHS) enrolled at mammographic screening clinics in New York and Florida Exposure assessment method: FFQ; 70-item FFQ; processed meats were ham and sausages	Colon and rectum	Ham and sausage intake, quartiles			Total caloric intake, age, place at enrolment and level of education
			Q1 (lowest quartile)	NR	1.00	
			Q2	NR	1.39 (0.81–2.38)	
			Q3	NR	1.38 (0.79–2.42)	
			Q4 (highest quartile)	NR	1.09 (0.59–2.02)	
			Trend-test *P* value: 0.735			
Pietinen et al. (1999) Finland Enrolment, 1985 and 1988; follow-up, 30 April 1995 (average, 8 yr) Cohort study	27 111; male smokers aged 50 and 69 yr in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) Study Exposure assessment method: FFQ; self-administered, modified, 12-mo dietary history method (276 food items); processed meat was mostly sausages	Colon and rectum	Processed meat (g/day)			Age, supplement group, smoking, BMI, alcohol, education, physical activity at work, calcium intake
			26	41	1.00	
			50	58	1.5 (1–2.2)	
			73	44	1.1 (0.7–1.8)	
			122	42	1.2 (0.7–1.8)	
			Trend-test *P* value: 0.78			
Flood et al. (2003) USA 1987–1998 Cohort study	45 496; follow-up of a subset of the women in the Breast Cancer Detection Demonstration Project (BCDDP) Exposure assessment method: FFQ; 62-item Block FFQ with 17 meat items; processed meats were bacon, ham, or other lunchmeats, hot dogs, and sausage	Colon and rectum	Processed meat (quintile median, g/1000 kcal)			Age, total energy intake by multivariate nutrient density method
			Q1 (0.02)	NR	1.00	
			Q2 (2.40)	NR	0.90 (0.68–1.18)	
			Q3 (5.90)	NR	0.83 (0.63–1.11)	
			Q4 (11.00)	NR	1.09 (0.84–1.43)	
			Q5 (22.20)	NR	0.97 (0.73–1.28)	
			Trend-test *P* value: 0.35			

Table 2.2.2 Cohort studies on consumption of processed meat and cancer of the colorectum

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
English et al. (2004) Melbourne, Australia 1990–2002 Cohort study	41 528; residents of Melbourne aged 40–69 yr Exposure assessment method: questionnaire; 121-item FFQ; processed meat was salami, sausages, bacon, ham, corned beef, and luncheon meats	Colon and rectum	Processed meat intake (times/wk)			Age; sex; country of birth; intake of energy, fat, cereal products
			< 1.0	80	1.00	
			1.5–1.9	105	1.30 (1.00–1.70)	
			2.0–3.9	129	1.00 (0.80–1.40)	
			≥ 4.0	137	1.50 (1.10–2.00)	
			Trend-test *P* value: 0.01			
			For an increase of 1 time/wk	451	1.07 (1.02–1.13)	
			Trend-test *P* value: 0.9			
		Colon	Processed meat intake (times/wk)			
			< 1.0	NR	1.00	
			1.5–1.9	NR	1.10 (0.80–1.60)	
			2.0–3.9	NR	0.80 (0.60–1.10)	
			≥ 4.0	NR	1.30 (0.90–1.90)	
			Trend-test *P* value: 0.06			
			For an increase of 1 time/wk	283	1.07 (1.00–1.14)	
		Rectum	Processed meat intake (times/wk)			
			< 1.0	NR	1.00	
			1.5–1.9	NR	1.90 (1.10–3.20)	
			2.0–3.9	NR	1.70 (1.00–2.90)	
			≥ 4.0	NR	2.00 (1.10–3.40)	
			Trend-test *P* value: 0.09			
			For an increase of 1 time/wk	169	1.08 (0.99–1.18)	

Table 2.2.2 Cohort studies on consumption of processed meat and cancer of the colorectum

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Lin et al. (2004) USA 1993–2003 Cohort study	36 976; Women's Health Study (WHS) Exposure assessment method: FFQ; validated, 131-item SQFFQ; correlation ≥ 0.5 for most items	Colon and rectum	Processed meat (median, servings/day)			Age, random treatment assignment, BMI, family history of colorectal cancer, history of colorectal polyps, physical activity, cigarette smoking, alcohol consumption, postmenopausal hormone therapy, total energy intake
			0	51	1.00	
			0.07	45	1.18 (0.79–1.77)	
			0.13	42	1.27 (0.84–1.91)	
			0.21	32	0.95 (0.60–1.49)	
			0.50	32	0.85 (0.53–1.35)	
			Trend-test *P* value: 0.25			
Chao et al. (2005) USA Enrolment, 1992–1993; follow-up to 2001 Cohort study	148 610; adults in the Cancer Prevention Study II (CPS-II) aged 50–74 yr in 21 states Exposure assessment method: FFQ; 68-item, modified Block FFQ; processed meats were bacon, sausage, hot dogs, and ham, bologna, salami, or lunchmeat	Colon	Processed meat (g/wk)			Age; total energy intake; education; BMI; cigarette smoking; recreational physical activity; multivitamin use; aspirin use; intake of beer, wine, liquor, fruits, vegetables, high-fibre grain foods
			Men:			
			0	64	1.00	
			< 60	125	0.75 (0.55–1.02)	
			61–160	225	1.02 (0.76–1.36)	
			161–240	108	1.11 (0.80–1.54)	
			> 240	143	1.11 (0.80–1.54)	
			Trend-test *P* value: 0.03			
			Processed meat (g/wk)			
			Women:			
			0	89	1.00	
			< 30	125	1.11 (0.84–1.46)	
			31–60	96	0.95 (0.71–1.27)	
			61–120	104	0.94 (0.70–1.26)	
			> 120	118	1.16 (0.85–1.57)	
			Trend-test *P* value: 0.48			
			Processed meat, quintiles			
			Men and women:			
			Q1	153	1.00	
			Q2	250	0.90 (0.74–1.11)	
			Q3	321	1.01 (0.83–1.23)	
			Q4	212	1.02 (0.82–1.27)	
			Q5	261	1.13 (0.91–1.41)	
			Trend-test *P* value: 0.02			

Table 2.2.2 Cohort studies on consumption of processed meat and cancer of the colorectum

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Chao et al. (2005) USA Enrolment, 1992–1993; follow-up to 2001 Cohort study (cont.)		Proximal colon	Processed meat, quintiles			
			Men and women:			
			Q1	96	1.00	
			Q2	133	0.79 (0.61–1.03)	
			Q3	174	0.92 (0.71–1.19)	
			Q4	131	1.03 (0.78–1.35)	
			Q5	133	0.97 (0.72–1.29)	
			Trend-test *P* value: 0.17			
		Distal colon	Processed meat, quintiles			
			Men and women:			
			Q1	44	1.00	
			Q2	98	1.19 (0.83–1.70)	
			Q3	111	1.15 (0.80–1.65)	
			Q4	58	0.95 (0.63–1.43)	
			Q5	97	1.39 (0.94–2.05)	
			Trend-test *P* value: 0.11			
		Rectosigmoid and rectum	Processed meat, quintiles			
			Men and women:			
			Q1	50	1.00	
			Q2	106	1.14 (0.81–1.60)	
			Q3	134	1.24 (0.88–1.74)	
			Q4	86	1.31 (0.91–1.88)	
			Q5	94	1.26 (0.86–1.83)	
			Trend-test *P* value: 0.18			

Table 2.2.2 Cohort studies on consumption of processed meat and cancer of the colorectum

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Larsson et al. (2005a) Sweden 1987–2003 Cohort study	61 433; Swedish women aged 40–76 yr Exposure assessment method: FFQ; 67-item, 6-mo FFQ (nine items on red and processed meats); processed meats were bacon, hot dogs, ham, or other lunchmeats and blood pudding	Colon and rectum	Processed meats (g/day), quartiles (quartile median)			Age; BMI; education level; intake of total energy, alcohol, saturated fat, calcium, folate, fruits, vegetables, wholegrain foods
			< 12 (6)	NR	1.00	
			12–21 (16)	NR	0.89 (0.72–1.90)	
			22–31 (26)	NR	1.01 (0.82–1.24)	
			≥ 32 (41)	NR	1.07 (0.85–1.33)	
			Trend-test *P* value: 0.23			
		Proximal colon	Processed meats (g/day), quartiles (quartile median)			
			< 12 (6)	NR	1.00	
			12–21 (16)	NR	0.92 (0.66–1.32)	
			22–31 (26)	NR	0.85 (0.58–1.24)	
			≥ 32 (41)	NR	1.02 (0.69–1.52)	
			Trend-test *P* value: 0.97			
		Distal colon	Processed meats (g/day), quartiles (quartile median)			
			< 12 (6)	NR	1.00	
			12–21 (16)	NR	1.05 (0.67–1.64)	
			22–31 (26)	NR	0.98 (0.61–1.58)	
			≥ 32 (41)	NR	1.39 (0.86–2.24)	
			Trend-test *P* value: 0.2			
		Rectum	Processed meats (g/day), quartiles (quartile median)			
			< 12 (6)	NR	1.00	
			12–21 (16)	NR	0.78 (0.52–1.12)	
			22–31 (26)	NR	1.02 (0.75–1.55)	
			≥ 31 (41)	NR	0.90 (0.60–1.34)	
			Trend-test *P* value: 0.88			

Table 2.2.2 Cohort studies on consumption of processed meat and cancer of the colorectum

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Lüchtenborg et al. (2005) The Netherlands 1989–1994 Nested case–control study	Cases: 588; cases were identified from the subcohort of the Netherlands Cancer Study (NLCS); this was the same population described by Brink et al. (2005); incident cases with colorectal cancer, with available tumour tissue and FFQ data, were included in this study Controls: 2948; subcohort without colorectal cancer at the last follow-up Exposure assessment method: FFQ; self-administered; see description for Goldbohm et al. (1994); meat products were preserved meat, "sandwich fillings"	Colon	Meat products (g/day); *APC*– genotype			Age, sex, family history of colorectal cancer, smoking, BMI, energy intake
			Q1	71	1.00	
			Q2	62	0.90 (0.62–1.30)	
			Q3	71	0.97 (0.68–1.39)	
			Q4	70	1.07 (0.73–1.56)	
			Trend-test *P* value: 0.66			
			Meat products (g/day); *APC*+ genotype			
			Q1	26	1.00	
			Q2	23	0.87 (0.49–1.56)	
			Q3	33	1.15 (0.67–1.97)	
			Q4	45	1.61 (0.96–2.71)	
			Trend-test *P* value: 0.04			
		Rectum	Meat products (g/day); *APC*– genotype			
			Q1	20	1.00	
			Q2	12	0.57 (0.27–1.19)	
			Q3	19	0.85 (0.44–1.65)	
			Q4	22	1.02 (0.52–1.99)	
			Trend-test *P* value: 0.73			
			Meat products (g/day); *APC*+ genotype-			
			Q1	15	1.00	
			Q2	12	0.79 (0.36–1.74)	
			Q3	14	0.89 (0.41–1.92)	
			Q4	16	1.03 (0.47–2.27)	
			Trend-test *P* value: 0.88			

Table 2.2.2 Cohort studies on consumption of processed meat and cancer of the colorectum

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Norat et al. (2005) Europe 1992–2002 Cohort study	478 040; European Prospective Investigation into Cancer and Nutrition (EPIC) study Exposure assessment method: questionnaire; country-specific, validated dietary questionnaires (88–266 items), self-administered in most countries; second 24-h recall measurement from an 8% random sample to calibrate measurements across countries and correct for systematic error	Colon and rectum	Processed meat (g/day)			Age, sex, energy from non-fat sources, energy from fat sources, height, weight, occupational physical activity, smoking status, dietary fibre, alcohol intake, stratified by centre
			<10	232	1.00	
			10–20	256	1.10 (0.91–1.32)	
			20–40	402	1.12 (0.94–1.35)	
			40–80	318	1.14 (0.94–1.40)	
			> 80	121	1.42 (1.09–1.86)	
			Trend-test *P* value: 0.02			
		Colon and rectum	For an increase of 100 g/day (observed intake)	1329	1.32 (1.07–1.63)	
			Trend-test *P* value: 0.009			
		Colon and rectum	For an increase of 100 g/day (calibrated intake)	1329	1.70 (1.05–2.76)	
			Trend-test *P* value: 0.03			
		Colon	Processed meat (g/day)			
			< 10	NR	1.00	
			10–20	NR	1.04 (0.77–1.41)	
			20–40	NR	1.02 (0.78–1.32)	
			40–80	NR	1.16 (0.90–1.51)	
			> 80	NR	1.20 (0.88–1.61)	
			Trend-test *P* value: 0.14			

Table 2.2.2 Cohort studies on consumption of processed meat and cancer of the colorectum

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Norat et al. (2005) Europe 1992–2002 Cohort study (cont.)		Colon	For an increase of 100 g/day (observed intake)	855	1.39 (1.06–1.82)	
			Trend-test *P* value: 0.01			
		Colon	For an increase of 100 g/day (calibrated intake)	855	1.68 (0.87–3.27)	
			Trend-test *P* value: 0.12			
		Proximal colon	Processed meat (g/day)			
			< 10	NR	1.00	
			10–20	NR	1.04 (0.73–1.49)	
			20–40	NR	0.95 (0.67–1.34)	
			40–80	NR	1.17 (0.80–1.70)	
			> 80	NR	1.19 (0.70–2.01)	
			Trend-test *P* value: 0.22			
		Distal colon	Processed meat (g/day)			
			< 10	NR	1.00	
			10–20	NR	1.30 (0.92–1.83)	
			20–40	NR	1.32 (0.94–1.85)	
			40–80	NR	1.45 (1.00–2.11)	
			> 80	NR	1.48 (0.87–2.53)	
			Trend-test *P* value: 0.38			

Table 2.2.2 Cohort studies on consumption of processed meat and cancer of the colorectum

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Norat et al. (2005) Europe 1992–2002 Cohort study (cont.)		Rectum	Processed meat (g/day)			
			< 10	NR	1.00	
			10–20	NR	1.13 (0.81–1.58)	
			20–40	NR	1.27 (0.93–1.74)	
			40–80 g/day	NR	1.05 (0.74–1.50)	
			> 80 g/day	NR	1.62 (1.04–2.50)	
			Trend-test *P* value: 0.2			
		Rectum	For an increase of 100 g/day (observed intake)	474	1.22 (0.87–1.71)	
			Trend-test *P* value: 0.25			
		Rectum	For an increase of 100 g/day (calibrated intake)	474	1.70 (0.83–3.47)	
			Trend-test *P* value: 0.14			
Balder et al. (2006) The Netherlands 1986–1996 Cohort study	152 852 men and women; case–cohort analysis of the Netherlands Cohort Study (NLCS) Exposure assessment method: FFQ; 150-item FFQ for 12 mo before enrolment	Colon and rectum	Processed meat (g/day) Men:			Age, BMI, family history, smoking, alcohol intake, physical activity, vegetable consumption, total energy intake
			0	78	1.00	
			0.1–9.9	277	1.02 (0.74–1.41)	
			10.0–19.9	239	0.98 (0.71–1.36)	
			≥ 20.0	275	1.18 (0.84–1.64)	
			Trend-test *P* value: 0.25			
			Processed meat (g/day) Women:			
			0	87	1.00	
			0.1–9.9	295	1.04 (0.78–1.39)	
			10.0–19.9	169	1.13 (0.82–1.55)	
			≥ 20.0	115	1.05 (0.74–1.48)	
			Trend-test *P* value: 0.62			

Table 2.2.2 Cohort studies on consumption of processed meat and cancer of the colorectum

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Oba et al. (2006) Takayama, Japan 1992–2000 Cohort study	30221; community-based cohort with 13 894 men and 16 327 women in Takayama, Japan, aged 35 yr or older Exposure assessment method: FFQ; validated, self-administered, 169-item SQFFQ; processed meats were ham, sausage, bacon, and yakibuta (Chinese-style roasted pork)	Colon	Processed meat (tertile mean, g/day)			Age, height, BMI, total pack-years of cigarette smoking, alcohol intake, physical activity
			Men:			
			3.9	33	1.00	
			9.3	34	1.25 (0.75–1.95)	
			20.3	44	1.98 (1.24–3.16)	
			Trend-test *P* value: < 0.01			
			Processed meat (tertile mean, g/day)			
			Women:			
			3.0	42	1.00	
			7.3	37	1.13 (0.72–1.75)	
			16.3	23	0.85 (0.50–1.43)	
			Trend-test *P* value: 0.62			
Sato et al. (2006) Japan Enrolment, 1990; 11-yr follow-up to 2001 Cohort study	47 605; men and women aged 40–64 yr who were residents in Miyagi Prefecture Exposure assessment method: questionnaire; 40-item FFQ with five meat items; processed meat was ham or sausages	Colon and rectum	Median (g/day)			Sex; age; smoking status; alcohol consumption; BMI; education; family history of cancer; time spent walking; consumption of fat, calcium, dietary fibre; total energy intake
			0	75	1.00	
			1.1	118	0.98 (0.74–1.31)	
			4.5	128	1.02 (0.77–1.36)	
			15.8	37	0.91 (0.61–1.35)	
			Trend-test *P* value: 0.99			
		Colon	Median (g/day)			
			0	49	1.00	
			1.1	78	1.00 (0.70–1.42)	
			4.5	70	0.86 (0.60–1.25)	
			15.8	20	0.75 (0.45–1.27)	
			Trend-test *P* value: 0.25			
		Proximal colon	Median (g/day)			
			0	23	1.00	
			1.1	47	1.28 (0.78–2.11)	
			4.5	34	0.86 (0.50–1.46)	
			15.8	9	0.69 (0.32–1.51)	
			Trend-test *P* value: 0.2			

Table 2.2.2 Cohort studies on consumption of processed meat and cancer of the colorectum

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Sato et al. (2006) Japan Enrolment, 1990; 11-yr follow-up to 2001 Cohort study (cont.)		Distal colon	Median (g/day)			
			0	21	1.00	
			1.1	22	0.86 (0.36–1.20)	
			4.5	26	0.79 (0.44–1.41)	
			15.8	7	0.65 (0.28–1.55)	
			Trend-test *P* value: 0.5			
		Rectum	Median (g/day)			
			0	22	1.00	
			1.1	57	0.87 (0.53–1.42)	
			4.5	62	0.90 (0.55–1.47)	
			15.8	16	0.97 (0.51–1.86)	
			Trend-test *P* value: 0.92			
Butler et al. (2008b) Singapore 1993–2005 Cohort study	61 321; Singaporean Chinese aged 45–74 yr Exposure assessment method: questionnaire; validated, 165-item, 12-mo quantitative FFQ	Colon and rectum	Quartile 4 vs quartile 1	NR	1.16 (0.95–1.41)	Age, sex, total energy intake, dialect group, interview year, alcohol intake, BMI, diabetes, education, physical activity, smoking history, first-degree history of colorectal cancer
			Trend-test *P* value: 0.1			
			Per 25 g/day	NR	1.00 (0.85–1.19)	
Cross et al. (2010) USA Enrolment, 1995–1996; follow-up until end of 2003 Cohort study	300 948; prospective cohort of men and women aged 50–71 yr in the National Institutes of Health – American Association of Retired Persons (NIH-AARP) Diet and Health Study Exposure assessment method: questionnaire; 124-item FFQ calibrated within the study population against two non-consecutive 24-h dietary recalls; processed meats were red and white meats	Colon and rectum	Processed meat (quintile median, g/1000 kcal)			Sex, education, BMI, smoking, total energy intake, dietary calcium, non-processed meat intake
			1.6	440	1.00	
			4.3	496	1.04 (0.91–1.18)	
			7.4	538	1.07 (0.94–1.23)	
			12.1	612	1.16 (1.02–1.32)	
			22.3	633	1.16 (1.01–1.32)	
			Trend-test *P* value: 0.017			
		Colon and rectum	For an increase of 100 g/day	2719	1.19 (0.96–1.48)	
			Trend-test *P* value: 0.001			

Table 2.2.2 Cohort studies on consumption of processed meat and cancer of the colorectum

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Cross et al. (2010) USA Enrolment, 1995–1996; follow-up until end of 2003 Cohort study (cont.)		Colon	Processed meat (quintile median, g/1000 kcal)			
			1.6	334	1.00	
			4.3	357	0.98 (0.84–1.14)	
			7.4	393	1.03 (0.89–1.20)	
			12.1	453	1.14 (0.98–1.32)	
			22.3	458	1.11 (0.95–1.29)	
			Trend-test *P* value: 0.057			
			For an increase of 100 g/day	1995	1.13 (0.88–1.45)	
			Trend-test *P* value: 0.001			
		Rectum	Processed meat (quintile median, g/1000 kcal)			
			1.6	106	1.00	
			4.3	139	1.22 (0.94–1.58)	
			7.4	145	1.20 (0.93–1.56)	
			12.1	159	1.24 (0.95–1.61)	
			22.3	175	1.30 (1.00–1.68)	
			Trend-test *P* value: 0.145			
			For an increase of 100 g/day	724	1.38 (0.93–2.05)	
			Trend-test *P* value: 0.001			

Table 2.2.2 Cohort studies on consumption of processed meat and cancer of the colorectum

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Takachi et al. (2011) Japan Follow-up, from 1995–1999 to December 2006 Cohort study	80 658; Japanese in the Japan Public Health Center-based Prospective Study (JPHC Study) Cohorts I and II, registered in 11 public health centre areas, who responded to a self-administered, 5-yr follow-up questionnaire at ages 45–74 yr Exposure assessment method: questionnaire; validated, self-administered, 138-item FFQ including 16 meat items Processed meat included ham, sausages, bacon, and luncheon meat	Colon	Processed meat (quintile median, g/day); in men			Age; area; BMI; smoking status; alcohol consumption; physical activity; medication use for diabetes; history of diabetes; screening examinations; intake of energy, calcium, vitamin D, vitamin B6, folate, dietary fibre, dried and salted fish
			0.2	106	1.00	
			1.9	106	1.11 (0.85–1.46)	
			3.9	81	0.91 (0.68–1.22)	
			7.3	89	1.05 (0.79–1.41)	
			16.0	99	1.27 (0.95–1.71)	
			Trend-test *P* value: 0.1			
		Proximal colon	Processed meat (quintile median, g/day); in men			
			0.2	36	1.00	
			1.9	51	1.60 (1.04–2.46)	
			3.9	37	1.20 (0.75–1.91)	
			7.3	39	1.31 (0.82–2.08)	
			16.0	37	1.38 (0.85–2.25)	
			Trend-test *P* value: 0.54			
		Distal colon	Processed meat (quintile median, g/day); in men			
			0.2	64	1.00	
			1.9	53	0.92 (0.64–1.33)	
			3.9	39	0.73 (0.49–1.10)	
			7.3	46	0.93 (0.63–1.38)	
			16.0	55	1.19 (0.80–1.77)	
			Trend-test *P* value: 0.19			
		Rectum	Processed meat (quintile median, g/day); in men			
			0.2	66	1.00	
			1.9	49	0.84 (0.58–1.21)	
			3.9	35	0.64 (0.42–0.97)	
			7.3	48	0.91 (0.62–1.33)	
			16.0	35	0.70 (0.45–1.09)	
			Trend-test *P* value: 0.25			

Table 2.2.2 Cohort studies on consumption of processed meat and cancer of the colorectum

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Takachi et al. (2011) Japan Follow-up, from 1995–1999 to December 2006 Cohort study (cont.)		Colon	Processed meat (quintile median, g/day); in women			
			0.4	61	1.00	
			2.2	69	1.26 (0.89–1.79)	
			4.3	60	1.10 (0.76–1.58)	
			7.6	58	1.12 (0.77–1.62)	
			15.0	59	1.19 (0.82–1.74)	
			Trend-test *P* value: 0.64			
		Proximal colon	Processed meat (quintile median, g/day); in women			
			0.4	31	1.00	
			2.2	42	1.51 (0.95–2.42)	
			4.3	37	1.33 (0.82–2.16)	
			7.6	38	1.42 (0.87–2.31)	
			15.0	31	1.23 (0.73–2.07)	
			Trend-test *P* value: 0.87			
		Distal colon	Processed meat (quintile median, g/day); in women			
			0.4	26	1.00	
			2.2	23	0.98 (0.55–1.73)	
			4.3	19	0.79 (0.43–1.44)	
			7.6	18	0.77 (0.42–1.44)	
			15.0	24	1.03 (0.57–1.87)	
			Trend-test *P* value: 0.88			
		Rectum	Processed meat (quintile median, g/day); in women			
			0.4	27	1.00	
			2.2	27	1.09 (0.64–1.87)	
			4.3	21	0.85 (0.47–1.52)	
			7.6	27	1.19 (0.68–2.08)	
			15.0	22	0.98 (0.53–1.79)	
			Trend-test *P* value: 1.00			

Table 2.2.2 Cohort studies on consumption of processed meat and cancer of the colorectum

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Ollberding et al. (2012) California and Hawaii, USA 1993–2007 Cohort study	15 717; multiethnic sample of African Americans, Japanese Americans, Latinos, native Hawaiians, and Whites aged 45–75 yr Exposure assessment method: FFQ; validated quantitative FFQ	Colon and rectum	Processed meat (quintile median, g/1000kcal per day)			Age, ethnicity, family history of colorectal cancer, history of colorectal polyps, BMI, smoking, NSAID use, alcohol, physical activity, history of diabetes, HRT use (females), total calories, intake of dietary fibre, calcium, folate, vitamin D
			1.70	599	1.00	
			4.48	626	0.98 (0.87–1.09)	
			7.28	706	1.04 (0.93–1.16)	
			10.86	704	1.00 (0.90–1.13)	
			17.98	769	1.06 (0.94–1.19)	
			Trend-test *P* value: 0.259			
Egeberg et al. (2013) Denmark 1993–2009 Cohort study	53 988; Danish men and women aged 50–64 yr free of cancer Exposure assessment method: FFQ; 192-item FFQ with 63 meat items and meat dishes, including specific processed meat products, mainly from pork; standard portion sizes	Colon	Processed meat (g/day)			Age, sex, waist circumference, schooling, smoking status, HRT use, sports activities, alcohol abstainer, alcohol intake, NSAID use, dietary fibre intake, total energy intake
			≤ 16	172	1.00	
			> 16 to ≤ 27	160	0.96 (0.77–1.20)	
			> 27 to ≤ 42	145	0.96 (0.75–1.22)	
			> 42	167	1.02 (0.78–1.34)	
			Continuous per 25 g/day	644	1.03 (0.94–1.13)	
			Trend-test *P* value: 0.53			
		Rectum	Processed meat (g/day)			
			< 16	75	1.00	
			> 16 to ≤ 27	96	1.21 (0.89–1.65)	
			> 27 to ≤ 42	93	1.18 (0.84–1.64)	
			> 42	81	0.88 (0.60–1.30)	
			Continuous, per 100 g/day	345	0.93 (0.81–1.07)	
			Trend-test *P* value: 0.32			

Table 2.2.2 Cohort studies on consumption of processed meat and cancer of the colorectum

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Bernstein et al. (2015) USA Nurses' Health Study, 1980–2010; Health Professionals Follow-Up Study, 1986–2010 Cohort study	87 108 women and 47 389 men; Nurses' Health Study (NHS) and Health Professionals Follow-Up Study (HPFS) Exposure assessment method: FFQ; diet from FFQs collected about every 4 yr during follow-up (see Wei et al, 2004)	Colon and rectum	Processed red meat (1 serving/day)			Age, follow-up, family history, endoscopy, smoking, alcohol drinking, BMI, physical activity, medications and supplements, menopausal status, hormone use, total caloric intake, folate, calcium, vitamin D, fibre
			Baseline intake	2731	1.08 (0.98–1.18)	
			Trend-test *P* value: 0.13			
			Processed red meat (1 serving/day)			
			Cumulative average	2731	1.15 (1.01–1.32)	
			Trend-test *P* value: 0.03			
		Proximal colon	Processed red meat (1 serving/day)			
			Baseline intake	1151	0.98 (0.84–1.15)	
			Trend-test *P* value: 0.82			
			Processed red meat (1 serving/day)			
			Cumulative intake	1151	0.99 (0.79–1.24)	
			Trend-test *P* value: 0.93			
		Distal colon	Processed red meat (1 serving/day)			
			Baseline intake	817	1.23 (1.05–1.44)	
			Trend-test *P* value: 0.009			
			Processed red meat (1 serving/day)			
			Cumulative intake	817	1.36 (1.09–1.69)	
			Trend-test *P* value: 0.006			

Table 2.2.2 Cohort studies on consumption of processed meat and cancer of the colorectum

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Bernstein et al. (2015) USA Nurses' Health Study, 1980–2010; Health Professionals Follow-Up Study, 1986–2010 Cohort study (cont.)		Rectum	Processed red meat (1 serving/day) Baseline intake Trend-test *P* value: 0.64 Processed red meat (1 serving/day) Cumulative intake Trend-test *P* value: 0.25	589 589 	1.05 (0.86–1.3) 1.18 (0.89–1.57) 	

BMI, body mass index; CI, confidence interval; FFQ, food frequency questionnaire; h, hour; HRT, hormone replacement therapy; mo, month; NOS, not otherwise specified; NR, not reported; NSAID, nonsteroidal anti-inflammatory drug; OR, odds ratio; SQFFQ, semiquantitative food frequency questionnaire; wk, week; yr, year

Table 2.2.3 Case–control studies on consumption of red meat and cancer of the colorectum

Reference, location, enrolment	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Manousos et al. (1983) Athens, Greece 1974–1980	Cases: 100; hospital-based incident colorectal cancer cases Controls: 100; hospital-based patients seen at an orthopaedic clinic, matched to cases by age and sex Exposure assessment method: questionnaire; frequency questionnaire with 80 items, administered in person; individual red meats only were beef and lamb	Colon and rectum	Increase from 1 to 2 times/wk			Age, sex, vegetables
			Beef meat	NR	1.77	
			Lamb meat	NR	2.61	
Kune et al. (1987) Melbourne, Australia 1980–1981	Cases: 715; population-based cases Controls: 727; population-based controls matched to cases by age and sex Exposure assessment method: questionnaire; validated questionnaire with 300 items, administered in person; individual red meats were beef (steak, roast beef, ground beef, beef casserole, corned beef, beef sausages, canned beef meals) and pork (pork chops, roast pork, ham, bacon, pork sausages)	Colon and rectum	Beef (g/wk), men and women:			Age, sex, fibre, cruciferous vegetables, dietary vitamin C, pork, fish, other meat, fat, milk, supplements
			< 360	130	1.00	
			> 360	258	1.75 (1.26-2.44)	
		Colon	Beef (g/wk), men:			
			< 360	NR	1.00	
			> 360	NR	1.58	
		Rectum	Beef (g/wk), men:			
			< 360	NR	1.00	
			> 360	NR	1.88	
		Colon and rectum	Pork (g/wk), men and women:			
			≤ 58	370	1.00	
			> 58	332	0.55 (0.42–0.73)	
			Pork (g/wk), women:			
			≤ 58	212	1.00	
			> 58	115	0.52	
			Pork (g/wk), men:			
			≤ 58	159	1.00	
			> 58	217	0.59	
		Colon	Pork (g/wk), men:			
			≤ 58	NR	1.00	
			> 58	NR	0.73	
			Pork (g/wk), women:			
			≤ 58	159	1.00	
			> 58	217	0.62	

Table 2.2.3 Case–control studies on consumption of red meat and cancer of the colorectum

Reference, location, enrolment	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Kune et al. (1987) Melbourne, Australia 1980–1981 (cont.)		Rectum	Pork (g/wk), men:			
			≤ 58	159	1.00	
			> 58	217	0.47	
			Pork (g/wk), women:			
			≤ 58	159	1.00	
			> 58	217	0.39	
		Colon and rectum	Beef (g/wk), men:			
			Q1 (≤ 250)	74	1.00	
			Q2 (> 250–360)	56	0.80	
			Q3: (> 260–500)	84	1.54	
			Q4 (> 500–720)	75	1.24	
			Q5: (> 720)	99	2.14	
		Colon and rectum	Pork (g/wk), men:			
			Q1 (≤ 15)	95	1.00	
			Q2 (> 15–58)	63	0.55	
			Q3 (> 58–106)	79	0.64	
			Q4 (> 106–174)	63	0.65	
			Q5 (> 174)	75	0.59	
		Colon and rectum	Pork (g/wk), women:			
			Q1 (≤ 0)	73	1.00	
			Q2 (> 0–27)	77	1.16	
			Q3 (> 27–58)	62	0.68	
			Q4 (> 58–114)	65	0.64	
			Q5 (> 114)	50	0.38	

Table 2.2.3 Case–control studies on consumption of red meat and cancer of the colorectum

Reference, location, enrolment	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Tuyns et al. (1988) Belgium 1978–1982	Cases: 818; population-based cases, identified through treatment centres Controls: 2851; population-based Exposure assessment method: questionnaire; validated, administered in person, and captured frequency and serving size; individual red meat was beef (veal, lean beef, half-fat beef, and fat beef) or pork (lean and half-fat pork, fat pork, and smoked pork)	Colon	Beef consumption (g/wk)			Age (10-yr age groups), sex, province
			0	NR	1.00	
			>0– 226	NR	1.76	
			> 227 to ≤ 360	NR	1.60	
			> 361 to ≤ 538	NR	2.09	
			Trend-test *P* value: < 0.0001			
		Colon	Pork consumption (g/wk), quartiles			
			Level 1	NR	1.00	
			≤ 200	NR	0.85	
			> 200 to ≤ 330	NR	0.58	
			> 330 to ≤ 509	NR	0.39	
			Trend-test *P* value: < 0.0001			
		Rectum	Beef consumption (g/wk), quartiles			
			Level 1	NR	1.00	
			≤ 226	NR	1.20	
			> 227 to ≤ 360	NR	1.21	
			> 361 to ≤ 538	NR	0.71	
			Trend-test *P* value: 0.14			
		Rectum	Pork consumption (g/wk), quartiles			
			Level 1	NR	1.00	
			≤ 200	NR	0.89	
			> 200 to ≤ 330	NR	0.75	
			> 330 to ≤ 509	NR	0.70	
			Trend-test *P* value: 0.016			

Table 2.2.3 Case–control studies on consumption of red meat and cancer of the colorectum

Reference, location, enrolment	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Lee et al. (1989) Singapore 1985–1987	Cases: 203; hospital-based colorectal cases, identified at Singapore General Hospital Controls: 425; hospital-based, identified from eye and orthopaedic wards in the same hospital as cases; frequency-matched by age and sex; GI disease excluded Exposure assessment method: questionnaire; validated, administered in person, and included 116 items; red meat was pork, beef, and mutton; unclear if red meat included processed meat	Colon and rectum	Total red meat intake (g/day), tertiles			Age, sex, dialect group, occupational group
			T1	NR	1.00	
			T2	NR	1.18 (0.77–1.81)	
			T3	NR	1.29 (0.84–1.97)	
			Trend-test: *P* value: NS			
		Rectum	Total red meat intake (g/day), tertiles			
			T1	NR	1.00	
			T2	NR	1.43 (0.75–2.74)	
			T3	NR	0.97 (0.48–1.92)	
			Trend-test *P* value: NS			
		Colon	Total red meat intake (g/day), tertiles			
			T1	NR	1.00	
			T2	NR	1.01 (0.60–1.70)	
			T3	NR	1.41 (0.87–2.31)	
			Trend-test *P* value: NS			
Gerhardsson de Verdier et al. (1991) Stockholm, Sweden 1986–1988	Cases: 559; population-based colorectal cases, identified through local hospitals and regional cancer registry Controls: 505; population-based, frequency-matched to cases by age and sex Exposure assessment method: questionnaire; unclear validation, self-administered, and included 55 items; red meat was beef and pork; assessed cooking methods	Colon	Red meat intake (Tertile 3 vs T1, i.e. > 1 time/wk vs more seldom)			Year of birth,sex, fat intake
			Beef/pork, fried	193	1.1 (0.7–1.8)	
			Trend-test *P* value: 0.353			
			Beef/pork, oven-roasted	57	1.2 (0.8–1.8)	
			Trend-test *P* value: 0.428			
			Beef/pork, boiled	104	1.8 (1.2–2.6)	
			Trend-test *P* value: 0.004			
		Rectum	Red meat intake (> 1 time/wk vs more seldom)			
			Beef/pork, fried	124	1.6 (0.9–3.0)	
			Trend-test *P* value: 0.073			
			Beef/pork, oven-roasted	47	1.8 (1.1–2.9)	
			Trend-test *P* value: 0.019			
			Beef/pork, boiled	69	1.9 (1.2–3.0)	
			Trend-test *P* value: 0.007			

Table 2.2.3 Case–control studies on consumption of red meat and cancer of the colorectum

Reference, location, enrolment	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Bidoli et al. (1992) Province of Pordenone, Italy 1986–NR (possibly 1992)	Cases: 248; hospital-based Controls: 699; hospital-based, excluded patients with cancer, digestive-tract disorders, or any condition related to alcohol or tobacco consumption Exposure assessment method: questionnaire; not validated and administered in person; total red meat was beef and pork from all sources; assessed frequency	Colon	Total red meat consumption (frequency)			Age, sex, social status
			T1	35	1.0	
			T2	48	1.5	
			T3	40	1.6	
			Trend-test *P* value: 0.07			
		Rectum	Total red meat consumption (frequency)			
			T1	35	1.0	
			T2	50	1.5	
			T3	40	2.0	
			Trend-test *P* value: 0.01			
Iscovich et al. (1992) La Plata, Argentina 1985–1986	Cases: 110; hospital-based, identified through local hospitals Controls: 220; population-based, identified from neighbourhoods of cases and matched to cases by sex; controls with conditions that may have affected diet were excluded Exposure assessment method: questionnaire; unclear validation, administered in person, and included 140 items; red meat was beef, veal, pork, horse, red wild meat, goat, and hare	Colon	Red meat intake, quartiles			Matching variables
			Q1	NR	1.00	
			Q2	NR	2.29 (1.03–5.08)	
			Q3	NR	0.82 (0.39–1.70)	
			Q4	NR	NR	
			Trend-test *P* value: 0.076			
Steinmetz and Potter (1993) Adelaide, Australia 1979–1980	Cases: 220; population-based colon cases, identified via the South Australian Cancer Registry Controls: 438; population-based; two controls per case selected via the electoral roll; individually matched to cases by age and sex Exposure assessment method: questionnaire; validated, included 141 items, and self-administered; red meat was hamburger (with bread roll), grilled steak, fried steak, grilled pork chop, fried pork chop, grilled lamb chop, fried lamb chop, roast pork, roast beef, veal, crumbed veal (schnitzel), mince, and roast lamb	Colon	Red meat intake (servings/wk), quartiles			Age at first live birth, Quetelet index, alcohol intake, the matching variable age
			Women:			
			Q1 (≤ 3.4)	NR	1.00	
			Q2 (3.5–5.0)	NR	1.44 (0.70–2.93)	
			Q3 (5.1–7.1)	NR	1.15 (0.57–2.32)	
			Q4 (≥ 7.2)	NR	1.48 (0.73–3.01)	
			Red meat intake (servings/wk), quartiles			Occupation, Quetelet index, alcohol intake, the matching variable age
			Men:			
			Q1 (≤ 3.9)	NR	1.00	
			Q2 (4.0–5.5)	NR	1.80 (0.92–3.52)	
			Q3 (5.6–8.2	NR	1.64 (0.82–3.27)	
			Q4 (≥ 8.3)	NR	1.59 (0.81–3.13)	

Table 2.2.3 Case–control studies on consumption of red meat and cancer of the colorectum

Reference, location, enrolment	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Centonze et al. (1994) Southern Italy 1987–1989	Cases: 119; population-based colorectal cases, identified from a population-based cancer registry Controls: 119; population-based, matched to cases by age, sex, and general practitioner Exposure assessment method: questionnaire; unclear validation, administered by in-person interview, and included 70 food items; red meat was beef, reported on individually	Colon and rectum	Beef intake (g/day) Low: 21 Medium (≥ 22)	 92 27	 1.00 0.95 (0.50–1.80)	Age , sex, level of education, smoking status, modifications of diet over the past 10 yr
Muscat and Wynder (1994) USA 1989–1992	Cases: 511; hospital-based cases Controls: 500; hospital-based patients with disease unrelated to dietary fat or fibre intake; frequency-matched to cases by sex, race, hospital, and age Exposure assessment method: questionnaire; administered in person; red meat was beef, steaks, roasts, or hamburgers; assessed doneness level	Colon and rectum	Beef doneness, men: Rare Medium Well done Beef doneness, women: Rare Medium Well done	 82 133 54 83 89 35	 1.00 1.00 1.15 (0.6–2.4) 1.00 0.95 (0.6–1.5) 1.00	Matching factors of sex, race, hospital, age, time of the case interview

Table 2.2.3 Case–control studies on consumption of red meat and cancer of the colorectum

Reference, location, enrolment	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Kampman et al. (1995) The Netherlands 1989–1993	Cases: 232; population-based colon cases, identified from hospitals using a cancer registry Controls: 259; population-based, identified through rosters of general practitioners of participating cases; frequency-matched to cases by age, sex, and degree of urbanization Exposure assessment method: questionnaire; unclear validation, administered in person, included 289 items, and considered frequency and serving size; red meat was unprocessed red meat; no further details provided	Colon	Red meat intake (g/day), women:			Age, urbanization level, total energy intake, alcohol intake, family history of colon cancer, cholecystectomy
			< 38	12	1.00	
			38–59	25	1.82 (0.75–4.46)	
			60–83	36	2.71 (1.15–6.38)	
			> 83	29	2.35 (0.97–5.66)	
			Trend-test *P* value: 0.04			
			Red meat intake (g/day), men:			
			< 60	33	1.00	
			60–83	35	0.80 (0.39–1.61)	
			84–102	24	0.57 (0.27–1.30)	
			> 102	38	0.89 (0.43–1.81)	
			Trend-test *P* value: 0.62			
			Ratio of red meat: vegetables + fruit, men:			
			< 0.14	32	1.00	
			0.14–0.22	33	1.04 (0.51–2.13)	
			0.22–0.33	24	0.79 (0.38–1.64)	
			> 0.33	40	1.18 (0.57–2.43)	
			Trend-test *P* value: 0.69			
			Ratio of red meat: vegetables + fruit, women:			
			< 0.09	16	1.00	
			0.09–0.13	11	0.81 (0.30–2.17)	
			0.13–0.20	26	1.53 (0.67–3.51)	
			> 0.20	48	3.05 (1.39–6.17)	
			Trend-test *P* value: 0.0006			
Kotake et al. (1995) Japan 1992–1994	Cases: 363; hospital-based colorectal cases Controls: 363; hospital-based, individually matched to cases by sex and age group Exposure assessment method: questionnaire; unknown validation and administration; exposure definition for red meat was beef and pork, examined separately	Colon	Beef or pork intake (> 3–4 times/wk vs 1–2 times/wk)			Matching variables (other variables not reported)
			Beef	NR	1.70 (0.85–3.28)	
			Pork	NR	0.80 (0.50–1.33)	
		Rectum	Beef or pork intake (> 3–4 times/wk vs 1–2 times/wk)			
			Beef	NR	0.80 (0.38–1.52)	
			Pork	NR	1.60 (0.95–2.73)	

Table 2.2.3 Case–control studies on consumption of red meat and cancer of the colorectum

Reference, location, enrolment	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Lohsoonthorn and Danvivat (1995) Bangkok, Thailand NR	Cases: 279; hospital-based colorectal cases Controls: 279; hospital-based, individually matched to cases by sex, age, admission period, hospital; included cancer patients with cancer in other organs Exposure assessment method: questionnaire; unclear validation and number of items asked; assessed frequency only; red meat (individual types only) was beef and pork	Colon and rectum	Beef consumption (times/mo)			None
			< 5	180	1.00	
			6– ≥ 10	99	1.00 (0.70–1.44)	
			Trend-test *P* value: 0.95			
			Pork consumption (times/mo)			
			< 5	29	1.00	
			6– ≥ 10	250	1.00 (0.56–1.78)	
			Trend-test *P* value: 0.95			
Freedman et al. (1996) New York, USA 1982–1992	Cases: 163; hospital-based Controls: 326; hospital-based, frequency-matched to cases by age and sex (2:1 ratio); 21.5% had non-malignant GI diseases Exposure assessment method: questionnaire; unclear validation, self-administered, and included 66 items; beef was hamburger, steak, roast, and stew; assessed frequency	Colon and rectum	Beef intake (times/mo)			Age, sex
			≤ 1	37	1.00	
			1–4	109	1.61 (1.03–2.52)	
			5–7	17	2.01 (0.96–4.20)	
			Trend-test *P* value: 0.03			
			Beef intake (times/mo); *p53*+ genotype			
			≤ 1	22	1.00	
			1–4	45	1.12 (0.63–1.98)	
			5–7	6	1.25 (0.45–3.49)	
			Trend-test *P* value: 0.63			
			Beef intake (times/mo)); *p53*– genotype			
			≤ 1	15	1.00	
			1–4	64	2.35 (1.26–4.39)	
			5–7	11	3.17 (1.83–11.28)	
			Trend-test *P* value: 0.006			
La Vecchia et al. (1996) Northern Italy 1985–1992	Cases: 1326; hospital-based colorectal cases Controls: 2024; hospital-based, identified from same hospitals as cases for non-cancer, non-GI conditions Exposure assessment method: questionnaire; unclear validation, administered by in-person interview, and assessed frequency only; red meat was not defined	Colon	Red meat intake (portions/wk)			Age, sex, total caloric intake, β-carotene, vitamin C intake, meal frequency/day, major seasoning fat score, family history of colorectal cancer
			≥4 vs <4	NR	1.6 (1.3–1.9)	
		Rectum	Red meat intake (portions/wk)			
			≥4 vs <4	NR	1.6 (1.3–2)	

Table 2.2.3 Case–control studies on consumption of red meat and cancer of the colorectum

Reference, location, enrolment	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Shannon et al. (1996) Seattle, USA 1985–1989	Cases: 424; population-based colon cancer cases, identified through the SEER Seattle–Puget Sound Registry Controls: 414; population-based controls, identified through random digit dialling; matched to cases by age, sex, and county of residence Exposure assessment method: questionnaire; validated, included 71 items, administered in person, and assessed frequency and portion sizes; total red meat was casserole dishes, beef, ham, lamb, veal, pork and beef roasts, hamburger, ribs, pot roast, bacon, liver, organ meats, wieners, sausages, and luncheon meats	Colon	Total red meat (servings/day), women:			Age, total energy intake
			Q1 (0–0.49)	46	1.00	
			Q2 (> 0.49–0.79)	44	0.90 (0.50–1.64)	
			Q3 (> 0.79–1.20)	49	1.03 (0.55–1.90)	
			Q4 (> 1.20)	47	0.72 (0.37–1.38)	
			Trend-test *P* value: 0.41			
			Total red meat (servings/day), men:			
			Q1 (0–0.78)	49	1.00	
			Q2 (> 0.78–1.20)	51	1.00 (0.58–1.74)	
			Q3 (> 1.20–1.70)	60	1.05 (0.61–1.83)	
			Q4 (> 1.70)	78	1.48 (0.82–2.66)	
			Trend-test *P* value: 0.53			
De Stefani et al. (1997) Montevideo, Uruguay 1993–1995	Cases: 250; hospital-based colorectal cases Controls: 500; hospital-based, identified at same hospitals as the cases and afflicted with a variety of disorders unrelated to tobacco smoking, alcohol, or diet Exposure assessment method: questionnaire; unclear validation, administered in person, and included 60 items; unclear what was included in red meat; assessed cooking methods and HAAS estimates	Colon and rectum	Red meat, quartiles			Age, residence, education, family history of colon cancer in a first-degree relative, BMI, vegetable and dessert intake
			Q1	NR	1.00	
			Q2	NR	1.22 (0.76 –1.94)	
			Q3	NR	1.44 (0.90–2.29)	
			Q4	NR	2.60 (1.64–4.13)	
			Trend-test *P* value: <0.001			
			Beef, tertiles			
			T1	NR	1.00	
			T2	NR	1.66 (1.16–2.38)	
			T3	NR	3.88 (2.34–6.45)	
			Trend-test *P* value: <0.001			
			Lamb, tertiles			
			T1	NR	1.00	
			T2	NR	1.15 (0.78–1.68)	
			T3	NR	1.46 (0.97–2.19)	
			Trend-test *P* value: 0.07			

Table 2.2.3 Case–control studies on consumption of red meat and cancer of the colorectum

Reference, location, enrolment	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
De Stefani et al. (1997) Montevideo, Uruguay 1993–1995 (cont.)			IQ intake estimates, quartiles			
			Q1	NR	1.00	
			Q2	NR	1.63 (1.02–2.62)	
			Q3	NR	2.30 (1.43 –3.72)	
			Q4	NR	3.08 (1.87 –5.07)	
			Trend-test *P* value: <0.001			
			MeIQx intake estimates, quartiles			
			Q1	NR	1.00	
			Q2	NR	1.21 (0.74–1.98)	
			Q3	NR	2.30 (1.44 –3.68)	
			Q4	NR	3.23 (2.02 –5.16)	
			Trend-test *P* value: <0.001			
			PhiP intake estimates, quartiles			
			Q1	NR	1.00	
			Q2	NR	1.43 (0.89 –2.29)	
			Q3	NR	2.12 (1.32 –3.41)	
			Q4	NR	3.01 (1.87 –4.83)	
			Trend-test *P* value: <0.001			
Fernandez et al. (1997) Province of Pordenone, Italy 1985–1992	Cases: 112; cases with a family history of colorectal cancer; see Bidoli et al. (1992) Controls: 108; controls with a family history of colorectal cancer; see Bidoli et al. (1992) Exposure assessment method: questionnaire; see Bidoli et al. (1992)	Colon and rectum	Total red meat intake, tertiles			Sex, age, area of residence
			T1	NR	1.0	
			T2	NR	0.9 (0.5–1.7)	
			T3	NR	2.9 (1.4–6.0)	
			Trend-test *P* value: <0.05			

Table 2.2.3 Case–control studies on consumption of red meat and cancer of the colorectum

Reference, location, enrolment	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Le Marchand et al. (1997) Hawaii, USA 1987–1991	Cases: 1192; population-based cases, identified through the Hawaii Tumor Registry; cases included Japanese, Caucasian (White), Filipino, Hawaiian, and Chinese patients Controls: 1192; population-based, identified through the Hawaii State Department of Health; individually matched to each case by sex, race, and age Exposure assessment method: questionnaire; validated, administered in person, and included 280 items; red meat was beef, pork, and lamb	Colon and rectum	Total beef, veal, and lamb; quartiles			Age; family history of colorectal cancer; alcoholic drinks per wk; pack-years; lifetime recreational activity; BMI 5 yr ago; caloric, dietary fibre, calcium intakes
			Men:			
			Q1	NR	1.0	
			Q2	NR	1.3	
			Q3	NR	1.3	
			Q4	NR	2.1 (1.4–3.1)	
			Trend-test *P* value <0.0001			
			Total beef, veal, and lamb; quartiles			
			Women:			
			Q1	NR	1.0	
			Q2	NR	1.4	
			Q3	NR	0.8	
			Q4	NR	1.3 (0.9–2.1)	
			Trend-test *P* value: 0.5			
Boutron-Ruault et al. (1999) Burgundy, France 1985–1990	Cases: 171; population-based, identified from GI and surgery departments, in conjunction with the registry of digestive cancers Controls: 309; population-based, identified through a census list; frequency-matched to cases by age and sex Exposure assessment method: questionnaire; validated and administered in person; red meat was beef, pork, and lamb, reported individually	Colon and rectum	Beef intake (g/day), quartiles			Age, sex, caloric intake, sex-specific cut-offs for quartiless
			Q1	NR	1.0	
			Q2	NR	1.5 (0.9–2.6)	
			Q3	NR	1.7 (0.9–2.9)	
			Q4	NR	1.4 (0.8–2.4)	
			Trend-test *P* value: 0.31			
			Pork intake (g/day), quartiles			
			Q1	NR	1.0	
			Q2	NR	1.0 (0.6–1.7)	
			Q3	NR	1.5 (0.9–2.5)	
			Q4	NR	1.0 (0.6–2.8)	
			Trend-test *P* value: 0.61			
			Lamb intake			
			None	NR	1.0	
			Any	NR	1.3 (0.9–1.9)	
			Trend-test *P* value: 0.20			

Table 2.2.3 Case–control studies on consumption of red meat and cancer of the colorectum

Reference, location, enrolment	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Kampman et al. (1999) California, Utah, and Minnesota, USA 1991–1994	Cases: 1542; cases identified through the Kaiser Permanente Medical Care Program of Northern California, Utah, and metropolitan twin cities area in Minnesota Controls: 1860; population-based, frequency-matched to cases by sex and age; identified using membership lists of the Kaiser Permanente Medical Care Program, random digit dialling, drivers' licence and identification lists, and Health Care Financing Administration forms Exposure assessment method: questionnaire; validated, administered by in-person interview, and included > 800 items; red meat was ground beef, hamburger, ground beef casseroles, hamburger helper, pot roast, steak, and ham; assessed cooking methods and mutagen index	Colon	Red meat, including ham (servings/wk), men			Age at diagnosis (cases) or selection (controls), BMI, lifetime physical activity, total energy intake, usual number of cigarettes smoked per day, intake of dietary fibre
			≤ 2.2	NR	1.0	
			2.3–3.7	NR	0.8 (0.6–1.0)	
			3.8–5.6	NR	1.1 (0.8–1.0)	
			5.7–8.8	NR	1.0 (0.7–1.4)	
			> 8.8	NR	0.9 (0.7–1.3)	
			Red meat, including ham (servings/wk), women			
			≤ 1.5	NR	1.0	
			1.6–2.5	NR	1.1 (0.8–1.5)	
			2.6–4.0	NR	1.3 (0.9–1.8)	
			4.1–6.2	NR	1.3 (0.9–1.8)	
			> 6.2	NR	1.0 (0.7–1.5)	
Tavani et al. (2000) Milan, Italy 1983–1991	Cases: 828; hospital-based colorectal cases Controls: 7990; hospital-based, admitted to the same network of hospitals as the cancer cases for acute non-neoplastic conditions, but excluded conditions that may have affected diet Exposure assessment method: questionnaire; non-validated but reproducible, 40 items, administered in person; red meat was beef, veal, and pork	Colon	Red meat (servings/wk)			Age, year of recruitment, sex, education, tobacco smoking, alcohol, fats in seasoning, fruits, vegetables
			≤ 3	206	1.0	
			>3 – ≤6	228	1.1 (0.9–1.3)	
			> 6	394	1.9 (1.5–2.3)	
			Per increment of 1 serving/day	828	1.5 (1.1–2.0)	
			Trend-test *P* value ≤ 0.01			
		Rectum	Red meat (servings/wk)			
			≤ 3	123	1.0	
			>3 – ≤6	150	1.1 (0.9–1.5)	
			> 6	225	1.7 (1.3–2.2)	
			Per increment of 1 serving/day	498	1.7 (1.2–2.4)	
			Trend-test *P* value ≤0.01			

Table 2.2.3 Case–control studies on consumption of red meat and cancer of the colorectum

Reference, location, enrolment	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Le Marchand et al. (2001) Hawaii, USA 1994–1998	Cases: 727; population-based colorectal cases, identified through the Hawaii Tumor Registry; cases included Japanese, Caucasians, and native Hawaiians Controls: 727; population-based, selected through the Hawaii State Department of Health and the Health Care Financing Administration; individually matched to cases by sex, ethnicity, and age Exposure assessment method: questionnaire; validated, administered in person, and included 280 items; red meat was beef and pork; considered cooking methods, and interactions with *NAT2* and *CYP1A2* phenotypes, and *NAT* genotype	Colon and rectum	Red meat intake (g/day) in all interviewed participants (768 cases, 768 controls)			Pack-years of cigarette smoking; lifetime recreational physical activity; lifetime aspirin use; BMI 5 yr ago; years of schooling; intakes of non-starch polysaccharides from vegetables and calcium from foods and supplements; the matching variables age, sex, ethnicity
			≤ 18.9	162	1.0	
			19.0–37.4	170	1.0 (0.7–1.4)	
			37.5–68.5	209	1.1 (0.8–1.5)	
			> 68.6	186	1.0 (0.7–1.4)	
			Trend-test *P* value: 0.98			
			Red meat intake (g/day) in all phenotyped participants (349 cases, 467 controls)			
			≤ 18.9	68	1.0	
			19.0–37.4	74	1.0 (0.7–1.6)	
			37.5–68.5	108	1.2 (0.8–1.9)	
			> 68.6	99	1.0 (0.6–1.5)	
			Trend-test *P* value: 0.86			
			Red meat preference in all interviewed participants			
			Did not eat/rare/ medium–rare	328	1.0	
			Medium	188	1.0 (0.7–0.9)	
			Well done/very well done	211	1.2 (0.9–1.5)	
			Trend-test *P* value: 0.29			
			Red meat preference in all phenotyped participants			
			Did not eat/rare/ medium–rare	158	1.0	
			Medium	92	0.8 (0.6–1.1)	
			Well done/very well done	99	1.1 (0.8–1.6)	
			Trend-test *P* value: 0.73			

Table 2.2.3 Case–control studies on consumption of red meat and cancer of the colorectum

Reference, location, enrolment	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Le Marchand et al. (2001) Hawaii, USA 1994–1998 (cont.)		Colon and rectum	Three-way interaction for *NAT2* genotype, *CYP1A2* phenotype, and red meat preference (well-done vs medium-rare red meat)			Age; sex; ethnicity; pack-years of cigarette smoking; number of cigarettes, cigars, pipes smoked during the 2 wk preceding the caffeine test; lifetime recreational physical activity; lifetime aspirin use; BMI 5 yr ago; yrs of schooling; intakes of non-starch polysaccharides from vegetables and calcium from foods and supplements
			NAT2 genotype (slow/intermediate); *CYP1A2* (≤ median)	31	1.2 (0.7–2.3)	
			NAT2 genotype (rapid); *CYP1A2* (≤ median)	19	1.0 (0.5–1.9)	
			NAT2 genotype (slow/intermediate); *CYP1A2* (> median)	28	1.0 (0.6–1.9)	
			NAT2 genotype (rapid); *CYP1A2* (> median)	21	3.3 (1.3–8.1)	
			P value for interaction = 0.12			
Evans et al. (2002) Liverpool, United Kingdom NR	Cases: 512; population-based colorectal cases, identified from the Merseyside and Cheshire Cancer Registry Controls: 512; population-based, identified from general primary care practice lists; matched by age, sex, postal code, and primary care practitioner Exposure assessment method: questionnaire; validated, administered by telephone interview, and included160 items; red meat was not defined; frequency and portion size were assessed	Colon and rectum	Red meat (servings/day)			Only presented univariate odds ratios in tables
			Q1: 0-3	NR	1.00	
			Q2: > 3-5	NR	0.96 (0.65–1.42)	
			Q3: > 5-6	NR	1.03 (0.64–1.66)	
			Q4: > 6- 22	NR	1.51 (1.06–2.15)	
		Proximal colon	Red meat (servings/day)			
			Q1: 0-3	NR	1.00	
			Q2: > 3-5	NR	0.91 (0.39–2.09)	
			Q3: > 5-6	NR	1.30 (0.47–3.62)	
			Q4: > 6- 22	NR	3.32 (1.42–7.73	
		Distal colon + rectum	Red meat (servings/day)			
			Q1: 0-3	NR	1.00	
			Q2: > 3-5	NR	1.02 (0.65–1.59)	
			Q3: > 5-6	NR	0.97 (0.62–1.52)	
			Q4: > 6- 22	NR	1.38 (0.89–2.12)	

Table 2.2.3 Case–control studies on consumption of red meat and cancer of the colorectum

Reference, location, enrolment	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Le Marchand et al. (2002b) Hawaii, USA 1994–1998	Cases: 727; see Le Marchand et al. (2001) Controls: 727; see Le Marchand et al. (2001) Exposure assessment method: other; see Le Marchand et al. (2001)	Colon	Red meat intake, tertiles			Pack-years of cigarette smoking, physical activity, aspirin use, BMI, education, non-starch polysaccharides from vegetables, total calcium, and the matching variables age and sex
			T1	NR	1.0	
			T2	NR	0.9 (0.6–1.3)	
			T3	NR	1.0 (0.7–1.5)	
			Trend-test *P* value: 0.8			
		Rectum	Red meat intake, tertiles			
			T1	NR	1.0	
			T2	NR	1.9 (1.1–3.3)	
			T3	NR	1.7 (1.0–3.0)	
			Trend-test *P* value: 0.16			
		Colon	Red meat preference			
			Rare	NR	1.0	
			Medium	NR	0.8 (0.6–1.1)	
			Well done	NR	1.0 (0.7–1.3)	
			Trend-test *P* value: 0.62			
		Rectum	Red meat preference			
			Rare	NR	1.0	
			Medium	NR	1.1 (0.7–1.7)	
			Well done	NR	1.5 (0.9–2.4)	
			Trend-test *P* value: 0.11			

Table 2.2.3 Case–control studies on consumption of red meat and cancer of the colorectum

Reference, location, enrolment	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
		Colon	Highest vs lowest tertile of HAAs from red meat			Pack-years of cigarette smoking; physical activity; aspirin use; BMI; education; non-starch polysaccharides from vegetables and total calcium; PhIP, MeIQx, and DiMeIQx models for rectal cancer were further adjusted for intake of other HAAs; the matching variables age, sex, ethnicity
			PhIP	NR	1.0 (0.6–1.6)	
			MeIQx	NR	1.0 (0.6–1.1)	
			DiMeIQx	NR	1.1 (0.7–1.7)	
			Total HAAs	NR	1.0 (0.6–1.6)	
		Rectum	Highest vs lowest tertile of HAAs from red meat			
			PhIP	NR	1.7 (0.3–3.8)	
			MeIQx	NR	3.1 (1.3–7.7)	
			Trend-test *P* value:0.01			
			DiMeIQx	NR	2.7 (1.1–6.3)	
			Total HAAs	NR	2.2 (1.0–4.7)	
Nowell et al. (2002) Arkansas and Tennessee, USA 1993–1999	Cases: 157; hospital-based Controls: 380; population-based, identified from Arkansas drivers' licence records; matched to cases by ethnicity, age, and county of residence Exposure assessment method: questionnaire; validated and administered in person; total red meat was burgers, steak, pork chops, bacon, and sausage; cooking methods were assessed using the CHARRED database to estimate HAAs	Colon and rectum	Total red meat cooked well/very well done (g/day)			Age, ethnicity, sex
			Q1	25	1.00	
			Q2	34	1.91 (0.85–4.41)	
			Q3	42	2.42 (1.11–5.47)	
			Q4	54	4.36 (2.08–9.60)	
			MeIQx (ng/day)			
			Q1	29	1.00	
			Q2	32	1.75 (0.78–4.05)	
			Q3	40	2.87 (1.32–6.52)	
			Q4	53	4.09 (1.94–9.08)	
Seow et al. (2002) Singapore 1999–2000	Cases: 121; hospital-based colorectal cases Controls: 222; population-based controls, identified using random sampling from electoral records Exposure assessment method: questionnaire; red meat was pork, beef, lamb, and mutton; unclear if red meat included processed meat	Colon and rectum	Red meat (portions/yr)			Age, family history of colorectal cancer, sex, smoking, education, physical exercise
			< 39	20	1.0	
			39 to < 117	34	1.1 (0.5–2.2)	
			≥ 117	66	2.2 (1.1–4.2)	
			Trend-test Pvalue <0.05			

Table 2.2.3 Case–control studies on consumption of red meat and cancer of the colorectum

Reference, location, enrolment	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Butler et al. (2003) North Carolina, USA 1996–2000	Cases: 620; population-based colon cancer cases, identified through the North Carolina Central Cancer Registry; included White and African American cases Controls: 1038; population-based, identified through the Division of Motor Vehicles; frequency-matched to cases by race, age, and sex Exposure assessment method: questionnaire; unclear validation, administered in person, and included 150 items; red meat was hamburger, steak, pork chop, sausage, and bacon; cooking methods were assessed and HAAs estimated using the CHARRED database	Colon	Total red meat (g/day)			Age, race, sex, energy-adjusted fat intake, energy intake, fibre intake, total meat intake, offsets
			≤ 11.8	97	1.0	
			11.9–22.4	90	0.9 (0.6–1.3)	
			22.5–33.6	99	1.0 (0.7–1.5)	
			33.7–51.8	138	1.5 (1.0–2.2)	
			≥ 51.8	196	2.0 (1.3–3.2)	
			Total red meat intake by doneness (g/day), highest vs lowest intake category (number of cases)			
			Rare/medium done (> 22.7 vs 0)	93	1.2 (0.9–1.7)	
			Well/very well done (> 42.7 vs ≤ 5.9)	192	1.7 (1.2–2.5)	
			Baked (> 7.7 vs 0)	44	1.1 (0.7–1.7)	
			Pan-fried (> 25.2 vs 0)	199	2.0 (1.4–3.0)	
			Broiled (> 16.5 vs 0)	68	1.3 (0.9–1.9)	
			Grilled/barbecued (22.7 vs 0)	97	0.9 (0.6–1.3)	
Chiu et al. (2003) Shanghai, China 1990–1993	Cases: 931; population-based, identified through the Shanghai Cancer Registry Controls: 1552; population-based, frequency-matched to cases by age and sex Exposure assessment method: questionnaire; administered in person, included 86 items, and asked frequency and servings; red meat was pork, organ meats, beef, and mutton	Colon	Red meat (servings/mo of food group)			Age, total energy, education, BMI, income, occupational physical activity
			Men:			
			Q1	NR	1.0	
			Q2	NR	1.2 (0.8–1.6)	
			Q3	NR	1.3 (0.9–1.8)	
			Q4	NR	1.5 (1.0–2.1)	
			Trend-test *P* value: 0.03			
			Red meat (servings/mo of food group)			
			Women:			
			Q1	NR	1.0	
			Q2	NR	1.3 (0.9–1.8)	
			Q3	NR	1.0 (0.7–1.4)	
			Q4	NR	1.5 (1.0–2.2)	
			Trend-test *P* value: 0.08			

Table 2.2.3 Case–control studies on consumption of red meat and cancer of the colorectum

Reference, location, enrolment	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Navarro et al. (2003) Córdoba, Argentina 1993–1998	Cases: 287; hospital-based colorectal cases, identified at hospitals in Córdoba Controls: 564; hospital-based control residents, identified at the same hospitals for acute non-neoplastic conditions unrelated to digestive tract diseases or long-term modifications Exposure assessment method: questionnaire; validated, administered in person, and evaluated frequency and portion size; individual red meats included fatty and lean beef, pork, and bovine viscera; unclear if total red meat included processed meats	Colon and rectum	Fatty beef intake (median, g/day) T1 T2 (37.3) T3 (76.71) Lean beef intake (median, g/day) T1 T2 (53.13) T3 (95.94) Pork intake (median, g/day) T1 T2 (0.05) T3 (2.02)	 NR NR NR NR NR NR NR NR NR	 1.00 0.80 (0.55–1.18) 0.78 (0.51–1.18) 1.00 0.64 (0.43–0.94) 0.67 (0.40–0.97) 1.00 0.98 (0.67–1.43) 0.92 (0.62–1.36)	Sex, age, BMI, social status, total energy intake, total lipids, proteins, glucids, and soluble and insoluble fibres
Juarranz Sanz et al. (2004) Madrid, Spain 1997–1998	Cases: 196; population-based colorectal cases, identified through a cancer registry Controls: 196; population-based, identified through health care rosters from the same districts of the identified cases; individually matched to cases by age, sex, and geographical region Exposure assessment method: questionnaire; validated, included 72 items, administered by phone, and asked about frequency and portion size; red meat was beef, pork, and lamb	Colon and rectum	Continuous variables (g/day) Red meat Trend-test *P* value: 0.002 Continuous variables (g/day) Organ meat Trend-test *P* value: 0.015	 NR NR 	 1.026 (1.010–1.040) 1.122 (1.027–1.232) 	Olives, processed meat, organ meat, cherries/strawberries, oranges, raw tomatoes, yogurt, fresh juice

Table 2.2.3 Case–control studies on consumption of red meat and cancer of the colorectum

Reference, location, enrolment	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Murtaugh et al. (2004) California and Utah, USA 1997–2001	Cases: 952; population-based rectal cancer cases, identified through a cancer registry and online pathology reports from the Kaiser Permanente Northern California Cancer Registry Controls: 1205; controls were randomly selected from membership lists, social security lists, drivers' licence lists; frequency-matched to cases by sex and 5-y age groups Exposure assessment method: questionnaire; validated, administered in person, and included > 800 items; red meat included ground beef, hamburger, ground beef casseroles, hamburger helper, pot roast, steak, and ham; cooking methods were assessed, and interactions with *NAT2* phenotype and *GSTM1* genotypes were assessed	Rectum	Red meat (servings/wk)			
			Men:			
			< 2.9	156	1.00	
			≥ 2.9 to < 6.1	188	1.10 (0.82–1.48)	
			≥ 6.1	212	1.08 (0.77–1.51)	
			Red meat (servings/wk)			
			Women:			
			< 1.9	112	1.00	
			≥ 1.9 to < 4.2	114	0.93 (0.65–1.31)	
			≥ 4.2	163	1.05 (0.72–1.53)	
			Red meat (servings/wk) by *NAT2* phenotype			
			Men: slow acetylator			
			< 2.9	NR	1.00	
			3.0–6.1r	NR	1.20 (0.77–1.87)	
			> 6.1	NR	0.92 (0.58–0.92)	
			Men: rapid or intermediate acetylator			
			< 2.9	NR	1.16 (0.73–1.84)	
			3.0–6.1	NR	0.86 (0.55–1.34)	
			> 6.1	NR	0.96 (0.57–1.60)	
			Red meat (servings/wk by *NAT2* phenotype)			
			Women: slow acetylator			
			< 1.9	NR	1.00	
			2.0–4.2	NR	0.55 (0.32–0.96)	
			> 4.2	NR	0.70 (0.40–1.23)	
			Women: rapid or intermediate acetylator			
			< 1.9	NR	0.53 (0.30–0.93)	
			2.0–4.2	NR	0.66 (0.38–1.16)	
			> 4.2	NR	0.76 (0.42–1.36)	
			P value for interaction on additive scale = significant			

Table 2.2.3 Case–control studies on consumption of red meat and cancer of the colorectum

Reference, location, enrolment	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Murtaugh et al. (2004) California and Utah, USA 1997–2001 (cont.)			Highest vs lowest category			
			Men:			
			Red meat (≥ 6.1 vs < 2.9 servings/wk)	212	1.08 (0.77–1.51)	
			Use of red meat drippings (> 52 vs never frequency/yr)	135	1.03 (0.76–1.39)	
			Doneness of red meat (well done vs rare)	187	1.33 (0.98–1.79)	
			Red meat mutagen index (> 468 vs ≤ 104;	175	1.39 (1.00–1.94)	
			Trend-test *P* value for mutagen index: <0.05			
			Highest vs lowest category			Age, BMI, energy intake, dietary fibre, calcium, lifetime physical activity, usual number of cigarettes smoked
			Women:			
			Red meat (≥ 4.2 vs < 1.9 servings/wk)	163	1.05 (0.72–1.53)	
			Use of red meat drippings (> 52 vs never frequency/yr;	97	0.72 (0.51–1.01)	
			Trend-test *P* value: <0.05			
			Doneness of red meat (well done vs rare)	165	1.05 (0.74–1.50)	
			Red meat mutagen index (≥ 624 vs ≤ 104)	72	0.88 (0.57–1.35)	
			Use of red meat drippings (frequency/yr) by *NAT2* phenotype			
			Men: slow acetylator			
			Never	NR	1.00	
			1–52	NR	0.70 (0.47–1.05)	
			> 52	NR	1.12 (0.72–1.75)	
			Men: rapid or intermediate acetylator			
			Never	NR	1.00 (0.68–1.47)	
			1–52	NR	0.70 (0.46–1.07)	
			> 52	NR	0.93 (0.58–1.47)	

Table 2.2.3 Case–control studies on consumption of red meat and cancer of the colorectum

Reference, location, enrolment	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Murtaugh et al. (2004) California and Utah, USA 1997–2001 (cont.)			Use of red meat drippings (frequency/yr) by *NAT2* phenotype			
			Women: slow acetylator			
			Never,	NR	1.00	
			1–52	NR	0.50 (0.30–0.84)	
			> 52	NR	0.40 (0.23–0.68)	
			Women: rapid or intermediate acetylator			
			Never	NR	0.60 (0.37–0.95)	
			1–52	NR	0.52 (0.31–0.85)	
			> 52	NR	0.62 (0.36–1.05)	
			P value for interaction on multiplicative scale < 0.05			
Navarro et al. (2004) Córdoba, Argentina 1994–2000	Cases: 296; hospital-based colorectal cases, identified at hospitals in Córdoba Controls: 597; hospital-based control residents, identified at the same hospitals for acute non-neoplastic conditions unrelated to digestive tract diseases or long-term modifications Exposure assessment method: questionnaire; validated, administered in person, and evaluated frequency and portion size; individual red meats included fatty and lean beef, pork, and bovine viscera; unclear if total red meat included processed meats	Colon and rectum	Red meat intake (g/day), darkly browned vs no preference			Sex, age, BMI, smoking habit, socioeconomic status
			Barbecued red meat	176	2.85 (1.97–4.10)	
			Trend-test *P* value: <0.05			
			Roasted red meat	110	1.08 (0.76–1.54)	
			Pan–cooked red meat	167	2.44 (1.71–3.47)	
			Trend-test *P* value: <0.05			
			Fried red meat	145	1.74 (1.23–2.45)	
			Trend-test *P* value: <0.05			

Table 2.2.3 Case–control studies on consumption of red meat and cancer of the colorectum

Reference, location, enrolment	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Satia-Abouta et al. (2004) North Carolina, USA 1996–2000	Cases: 613; Controls: 996 see Butler et al. (2003); Exposure assessment method: questionnaire; see Butler et al. (2003); red meat was hamburger, cheeseburger, beef (roast, steak, sandwiches), beef stew, pot pie, liver (including chicken liver), pork, beef, veal, lamb, roast beef, meatloaf, pork roast, tacos or burritos, spaghetti meat sauce, hot dogs, bacon, ham, sausage, bologna, and lunchmeats	Colon	Total red meat intake (frequency/wk), quartiles; Caucasians			Potential confounders examined included age, sex, education, BMI, smoking history, physical activity, family history of colon cancer, NSAID use, fat, carbohydrates, dietary fibre, vitamin C, vitamin E, β-carotene, calcium, folate, fruits, vegetables; covariables ≥ 10% change in parameter coefficient included in model
			Q1	60	1.0	
			Q2	68	1.0 (0.7–1.6)	
			Q3	89	1.2 (0.8–1.9)	
			Q4	120	1.1 (0.7–1.8)	
			Trend-test *P* value: 0.61			
			Total red meat intake (frequency/wk), quartiles; African Americans			
			Q1	60	1.0	
			Q2	68	0.7 (0.4–1.1)	
			Q3	89	0.8 (0.5–1.4)	
			Q4	120	0.7 (0.4–1.3)	
			Trend-test *P* value: 0.61			
Barrett et al. (2003) Dundee, Perth, Leeds, and York, United Kingdom 1997–2001	Cases: 484; hospital-based, identified from hospitals in Dundee, Perth, Leeds, and York, United Kingdom Controls: 738; hospital-based, identified from the practice lists of the cases' general practitioners; matched to cases by age and sex Exposure assessment method: questionnaire; validated, administered in person, and included 132 items; red meat was beef (roast, steak, mince, stew or casserole), beef burgers, pork (roast, chops, stew, or slices), and lamb (roast, chops, or stew)	Colon and rectum	Red meat (servings/mo, quartiles) by *NAT2* genotype			Smoking status; BMI at age 40 yr; the main effects of fruits, vegetables, red meat, and the polymorphism of interest, plus the fruit–vegetable interaction, and the interaction between the polymorphism and the dietary factor of interest
			Men:			
			Slow acetylators			
			Q1	NR	1.00	
			Q2	NR	0.85 (0.42–1.74)	
			Q3	NR	1.22 (0.63–2.37)	
			Q4	NR	1.49 (0.77–2.90)	
			Fast acetylators			
			Q1	NR	1.00	
			Q2	NR	1.57 (0.71–3.44)	
			Q3	NR	1.73 (0.83–3.63)	
			Q4	NR	1.65 (0.77–3.55)	
			P value for interaction: 0.46			

Table 2.2.3 Case–control studies on consumption of red meat and cancer of the colorectum

Reference, location, enrolment	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Barrett et al. (2003) Dundee, Perth, Leeds, and York, United Kingdom 1997–2001 (cont.)			Red meat (servings/mo, quartiles) by *NAT2* genotype			
			Women:			
			Slow acetylators			
			Q1	NR	1.00	
			Q2	NR	1.16 (0.55–2.42)	
			Q3	NR	1.02 (0.46–2.27)	
			Q4	NR	2.14 (0.99–4.66)	
			Fast acetylators			
			Q1	NR	1.00	
			Q2	NR	0.93 (0.30–2.87)	
			Q3	NR	2.22 (0.73–6.78)	
			Q4	NR	2.81 (1.00–7.89)	
			P value for interaction: 0.35			
Turner et al. (2004) Dundee, Perth, Leeds, and York, United Kingdom 1997–2001	Cases: 484; hospital-based, identified from hospitals in Dundee, Perth, Leeds, and York, United Kingdom Controls: 738; hospital-based, identified from the practice lists of the cases' general practitioners; matched to cases by age and sex Exposure assessment method: questionnaire; validated, administered in person, and included 132 items; red meat was beef (roast, steak, mince, stew, or casserole), beef burgers, pork (roast, chops, stew, or slices), and lamb (roast, chops, or stew)	Colon and rectum	Red meat (servings/mo), quartiles			The matching variables age, sex, energy intake
			Q1 (≤ 6)	88	1.0	
			Q2 (> 6 to ≤ 14)	87	1.0 (0.7–1.7)	
			Q3 (> 14 to ≤ 19)	146	1.7 (1.2–2.6)	
			Q4 (> 19)	153	2.3 (1.6–3.5)	
			Trend-test *P* value: 0.0001			
			Red meat (highest vs lowest intake by *GSTP1* Ile105Val			Smoking status; BMI at age 40 yr; the main effects of fruits, vegetables, red meat, and the polymorphism of interest, plus the fruit–vegetable interaction, and the interaction between the polymorphism and the dietary factor of interest
			Homozygous rare variant	103	1.0 (0.4–2.1)	
			Heterozygous	401	1.9 (1.3–2.8)	
			Homozygous common variant	367	2.3 (1.5–3.5)	
			Trend-test *P* value: 0.02			
			Red meat (highest vs lowest intake) by *NQO1*			
			Deficient	48	0.3 (0.1–1.0)	
			Intermediate	307	2.7 (1.7–4.3)	
			Fast	516	1.8 (1.2–2.5)	
			Trend-test *P* value: 0.04			

Table 2.2.3 Case–control studies on consumption of red meat and cancer of the colorectum

Reference, location, enrolment	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Murtaugh et al. (2005) California and Utah, USA Colon, 1991–1994; rectum, 1997–2002	Cases: 2298; Controls: 2749; Exposure assessment method: questionnaire; see Murtaugh et al. (2004) and Kampman et al. (1999); interactions with *CYP1A1* and *GSTM1* genotypes were assessed	Colon and rectum	Highest vs lowest category for *CYP1A1*1* allele			Age, BMI, energy intake, dietary fibre, calcium, lifetime physical activity, usual number of cigarettes smoked
			Men:			
			Red meat (> 6.1 vs ≤ 3.1 servings/wk)	NR	0.95 (0.73–1.25)	
			Use of red meat drippings, (> 36 vs never frequency/yr)	NR	0.90 (0.72–1.12)	
			Doneness of red meat (well done vs rare)	NR	1.37 (1.06–1.77)	
			Red meat mutagen index (> 468 vs ≤ 104)	NR	1.05 (0.79–1.39)	
			Highest vs lowest category for *CYP1A1*1* allele			
			Women:			
			Red meat (> 4.2 vs < 1.9 servings/wk)	NR	1.05 (0.77–1.43)	
			Use of red meat drippings (> 36 vs never frequency/yr)	NR	0.72 (0.55–0.93)	
			Doneness of red meat (well done vs rare)	NR	0.90 (0.67–1.19)	
			Red meat mutagen index (> 624 vs ≤ 104)	NR	0.68 (0.47–0.99)	
			Highest vs lowest category for *CYP1A1* any *2 variant			
			Men:			
			Red meat (> 6.1 vs ≤ 3.1 servings/wk)	NR	0.87 (0.61–1.25)	
			Use of red meat drippings (> 36 vs never frequency/yr)	NR	0.84 (0.61–1.16)	
			Doneness of red meat (well done vs rare)	NR	1.22 (0.87–1.70)	
			Red meat mutagen index (> 468 vs ≤ 104)	NR	0.86 (0.58–1.27)	

Table 2.2.3 Case–control studies on consumption of red meat and cancer of the colorectum

Reference, location, enrolment	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Murtaugh et al. (2005) California and Utah, USA Colon, 1991–1994; rectum, 1997–2002 (cont.)			Highest vs lowest category for *CYP1A1* any *2 variant			
			Women:			
			Red meat (> 4.2 vs < 1.9 servings/wk)	NR	1.24 (0.82–1.88)	
			Use of red meat drippings (> 36 vs never frequency/yr)	NR	0.79 (0.53–1.17)	
			Doneness of red meat (well done vs rare)	NR	1.05 (0.72–1.53)	
			Red meat mutagen index (> 624 vs ≤ 104)	NR	0.77 (0.44–1.33)	
Chen et al. (2006) China 1990–2002	Cases: 140; population-based colorectal cases Controls: 343; population-based Exposure assessment method: questionnaire; unclear validation, administered in person, and assessed portion size and frequency; red meat was pork, beef, and lamb; assessed genotypes in *SULT1A1*	Rectum	Red meat (kg/yr)			Age, sex, smoking, colorectal cancer history
			≤ 5	17	1.00	
			> 5	40	0.85 (0.40–1.80)	
		Colon	Red meat (kg/yr)			
			≤ 5	13	1.00	
			> 5	70	1.40 (0.70–2.82)	
Hu et al. (2007) Canada 1994–1997	Cases: 1723; cases identified via the National Enhanced Cancer Surveillance System (NECSS), including the provinces of British Columbia, Alberta, Saskatchewan, Manitoba, Ontario, Prince Edward Island, Nova Scotia, and Newfoundland Controls: 3097; population-based controls from each province, frequency-matched to cases by age and sex Exposure assessment method: questionnaire; validated FFQ with 70 items, administered by mail; red meat was beef, pork, or lamb; also reported on hamburger	Proximal colon	Beef, pork, and lamb intake as main dish (servings/wk), tertiles			10-yr age group, province, BMI (< 25.0, 25.0–29.9, ≥ 30.0), strenuous activity (h/mo), total energy intake.
			Men:			
			T1	141	1.0	
			T2	175	1.2 (0.9–1.6)	
			T3	58	1.5 (1.0–2.4)	
			Trend-test *P* value: 0.05			
			Hamburger intake (servings/wk), tertiles			
			Men:			
			T1	50	1.0	
			T2	257	2.3 (1.5–3.4)	
			T3	71	2.1 (1.3–3.5)	
			Trend-test *P* value: 0.006			

Table 2.2.3 Case–control studies on consumption of red meat and cancer of the colorectum

Reference, location, enrolment	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Hu et al. (2007) Canada 1994–1997 (cont.)		Proximal colon	Beef, pork, and lamb intake as main dish (servings/wk), tertiles			
			Women:			
			T1	180	1.0	
			T2	130	1.1 (0.8–1.5)	
			T3	36	1.1 (0.7–1.8)	
			Trend-test *P* value: 0.45			
			Hamburger intake (servings/wk), tertiles			
			Women:			
			T1	61	1.0	
			T2	236	1.2 (0.8–1.6)	
			T3	44	1.2 (0.7–1.9)	
			Trend-test *P* value: 0.47			
		Distal colon	Beef, pork, and lamb intake as main dish (servings/wk), tertiles			
			Men:			
			T1	235	1.0	
			T2	241	0.9 (0.7–1.2)	
			T3	86	1.1 (0.8–1.6)	
			Trend-test *P* value: 0.94			
		Distal colon	Hamburger intake (servings/wk), tertiles			
			Men:			
			T1	91	1.0	
			T2	362	1.4 (1.0–1.9)	
			T3	110	1.4 (0.9–2.0)	
			Trend-test *P* value: 0.11			
		Distal colon	Beef, pork, and lamb intake as main dish (servings/wk), tertiles			
			Women:			
			T1	191	1.0	
			T2	163	1.3 (1.0–1.7)	
			T3	52	1.2 (0.8–1.9)	
			Trend-test *P* value: 0.16			

Table 2.2.3 Case–control studies on consumption of red meat and cancer of the colorectum

Reference, location, enrolment	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Hu et al. (2007) Canada 1994–1997 (cont.)		Distal colon	Hamburger intake (servings/wk), tertiles			
			Women:			
			T1	76	1.0	
			T2	273	1.2 (0.8–1.7)	
			T3	57	1.2 (0.7–2.0)	
			Trend-test *P* value: 0.42			
Kimura et al. (2007) Fukuoka, Japan 2000–2003	Cases: 840; hospital-based cases admitted to hospitals in Fukuoka and three adjacent areas Controls: 833; population-based controls from 15 different areas, sampled based on frequency of age and sex of cases Exposure assessment method: questionnaire; validated, administered in person, and included 148 items; reported on beef and pork combined	Colon and rectum	Beef/pork, likely fresh meat (quintile median, g/day)			Age, sex, residential area, BMI 10 yr before, parental colorectal cancer, smoking, alcohol use, type of job, leisure-time physical activity, dietary calcium, dietary fibre
			Q1 (14.2)	142	1.00	
			Q2 (27.3)	188	1.35 (0.98–1.85)	
			Q3 (37.4)	161	1.28 (0.92–1.79)	
			Q4 (48.6)	140	0.03 (0.73–1.44)	
			Q5 (70.1)	151	1.13 (0.80–1.61)	
			Trend-test *P* value: 0.94			
		Proximal colon	Beef/pork (g/day), quintiles			
			Q1	23	1.00	
			Q2	48	2.21 (1.26–3.88)	
			Q3	41	2.00 (1.12–3.58)	
			Q4	35	1.67 (0.91–3.06)	
			Q5	30	1.44 (0.76–2.71)	
			Trend-test *P* value: 0.64			
		Distal colon	Beef/pork (g/day), quintiles			
			Q1	54	1.00	
			Q2	65	1.24 (0.80–1.94)	
			Q3	46	0.94 (0.58–1.52)	
			Q4	41	0.80 (0.49–1.31)	
			Q5	56	1.23 (0.75–2.00)	
			Trend-test *P* value: 0.97			

Table 2.2.3 Case–control studies on consumption of red meat and cancer of the colorectum

Reference, location, enrolment	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Kimura et al. (2007) Fukuoka, Japan 2000–2003 (cont.)		Rectum	Beef/pork (g/day), quintiles			
			Q1	63	1.00	
			Q2	73	1.18 (0.78–1.79)	
			Q3	70	1.18 (0.77–1.81)	
			Q4	57	0.88 (0.56–1.38)	
			Q5	64	1.01 (0.64–1.60)	
			Trend-test *P* value: 0.64			
Küry et al. (2007) Pays de la Loire region, France 2002–2006	Cases: 1023; hospital-based colorectal cases with a family history of colorectal cancer, diagnosed at an age < 40 yr Controls: 1121; hospital-based, identified from health examination centres or the University Hospital of Nantes; matched to cases by sex, age, and geography Exposure assessment method: questionnaire; unclear validation and administered in person; red meat was beef and lamb; assessed genotypes in *CYP1A2*, *CYP2E1*, *CYP1B1*, and *CYP2C9*	Colon and rectum	Red meat intake (times/wk)			The matching variables age, sex, residence
			1– 4	NR	1.00	
			≥ 5	NR	2.81 (1.52–5.21)	
			Trend-test *P* value: 0.001			
Cotterchio et al. (2008) Ontario, Canada 1997–2000	Cases: 1095; population-based colorectal cases, identified through the Ontario Cancer Registry; familial cases were included Controls: 1890; population-based, identified through random digit dialling Exposure assessment method: questionnaire; not validated and self-administered; total red meat was beef, steak, hamburger, prime rib, ribs, beef hot dogs, beef-based processed meat, veal, pork, bacon, pork sausage, ham, lamb, and venison; assessed frequency only, cooking methods, and polymorphisms in 15 xenobiotic-metabolizing enzymes (CYPs, GSTs, UGTs, SULT, NATs, mEH, AHR), *CYP2C9*, and *NAT2*	Colon and rectum	Total red meat (servings/wk)			Age
			0–2.0	307	1.00	
			2.1–3.0	224	1.37 (1.10–1.70)	
			3.1–5.0	265	1.45 (1.18–1.78)	
			> 5.0	276	1.67 (1.36–2.05)	
			Total red meat doneness (servings/wk)			
			≤ 2 “rare/regular”	234	1.00	
			≤ 2 “well done”	278	1.23 (0.99–1.53)	
			> 2 “rare/regular”	211	1.24 (0.98–1.56)	
			> 2 “well done”	321	1.57 (1.27–1.93)	

Table 2.2.3 Case–control studies on consumption of red meat and cancer of the colorectum

Reference, location, enrolment	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Cotterchio et al. (2008) Ontario, Canada 1997–2000 (cont.)			Total red meat doneness (servings/wk) *CYP1B1* combined variance (derived)			
			Wildtype (> 2 "well done" vs ≤ 2 "rare/ regular")	NR	4.09 (2.17–7.71)	
			Increased activity (> 2 "well done" vs ≤ 2 "rare/regular")	NR	1.52 (1.15–2.01)	
			P value for interaction = 0.04			
			Total red meat doneness (servings/wk) *SULT1A1*–638			
			GG (> 2 "well done" vs ≤ 2 "rare/regular")	NR	2.43 (1.66–3.57)	
			AA/GA (> 2 "well done" vs ≤ 2 "rare/ regular")	NR	1.39 (0.99–1.95)	
			P value for interaction = 0.03			
Saebø et al. (2008) Norway NR	Cases: 198; population-based colorectal cases, identified through a screening study Controls: 222; population-based, identified through a screening study and determined to be polyp-free by flexible sigmoidoscopy Exposure assessment method: questionnaire; unclear validation; red meat was not defined; assessed polymorphism in *CYP1A2*	Colon and rectum	Total red meat (g/day)			Age, sex, ever-smoking
			≤ 22.5	74	1.00	
			> 22.5 to ≤ 45.0	48	1.07 (0.54–2.14)	
			> 45.0	23	1.58 (0.71–3.47)	
			Doneness level			
			Rare/medium	45	1.00	
			Well done	73	0.69 (0.36–1.32)	

Table 2.2.3 Case–control studies on consumption of red meat and cancer of the colorectum

Reference, location, enrolment	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Joshi et al. (2009) USA 1997–2002	Cases: 577; population-based colorectal cases, identified through cancer registries from California, North Carolina, Arizona, Minnesota, New Hampshire, and Colorado Controls: 361; unaffected siblings of cases who were older than cases Exposure assessment method: questionnaire; not validated and assessed frequency and cooking methods; total red meat was beef, steak, hamburger, prime rib, ribs, veal, lamb, bacon, pork, pork in sausages, or venison	Colon and rectum	Total red meat (servings/wk)			None
			≤ 3	131	1.00	
			> 3	177	1.8 (1.3–2.5)	
			Trend-test *P* value: 0.001			
		Colon	Total red meat (servings/wk)			
			≤ 3	79	1.00	
			> 3	106	1.8 (1.1–2.8)	
			Trend-test *P* value: 0.019			
		Rectum	Total red meat (servings/wk)			
			≤ 3	40	1.00	
			> 3	44	1.3 (0.6–2.5)	
			Trend-test *P* value: 0.517			
		Colon and rectum	Doneness of total red meat (estimated from outside colour).)			
			Light or medium browned	214	1.00	
			Heavily browned	94	1.1 (0.8–1.6)	
			Trend-test *P* value: 0.559			
			Test of heterogeneity, colon vs rectum ($P = 0.613$)			
		Colon and rectum	Doneness of red meat (estimated from insidecolour)			
			Red or pink	153	1.00	
			Brown	155	1.2 (0.8–1.6)	
			Trend-test *P* value: 0.362			
			Test of heterogeneity, colon vs rectum ($P = 0.351$)			
		Rectum	Doneness of red meat (estimated from outside colour); among carriers of XPD Lys751Lys			
			Light or medium browned	22	1.00	
			Heavily browned	13	3.8 (1.1–13.)	
			Trend-test *P* value = 0.037			

Table 2.2.3 Case–control studies on consumption of red meat and cancer of the colorectum

Reference, location, enrolment	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Morita et al. (2009) Fukuoka, Japan 2000–2003	Cases: 685; hospital-based colorectal cases Controls: 833; population-based Exposure assessment method: questionnaire; validated, administered by in-person interview, and included 148 items; red meat was beef and pork	Colon	Red meat intake (median, g/2000 kcal per day); among carriers of 0 alleles for *CYP2E1* 96-bp insertion			Sex, age, area, cigarette smoking, BMI, type of job, physical activity, parental colorectal cancer
			21	88	1.00	
			38	73	0.79 (0.52–1.18)	
			63	63	0.75 (0.48–1.16)	
			Trend-test *P* value: 0.18			
			Red meat intake (median, g/2000 kcal per day); among carriers of 1 or 2 alleles for *CYP2E1* 96-bp insertion			
			21	46	1.00	
			38	56	1.44 (0.85–2.42)	
			63	55	1.42 (0.82–2.43)	
			Trend-test *P* value: 0.21			
			P value for interaction = 0.03–			
Squires et al. (2010) Newfoundland and Labrador, Canada 1999–2003	Cases: 518; population-based colorectal cases, identified through a cancer registry Controls: 686; population-based, identified through random digit dialling; frequency-matched to cases by age and sex Exposure assessment method: questionnaire; unclear validation of local foods, administered by mail, and included 169 items. Total red meat was beef, steak, hamburger, prime rib, ribs, beef hot dogs, beef-based processed meat, veal, pork, bacon, pork sausage, ham, lamb, and venison; assessed cooking methods	Colon and rectum	Total red meat intake (servings/day)			Age; BMI; smoking status; level of education; intake of vegetables, fruits, folic acid, cholesterol, dietary fibre, saturated fat, alcohol; caloric intake; level of physical activity; NSAID use; presence of inflammatory bowel disease
			Men:			
			≤ 2	125	1.00	
			> 2 to ≤ 3	74	0.96 (0.59–1.57)	
			> 3 to ≤ 5	49	0.95 (0.56–1.59)	
			> 5	53	0.75 (0.43–1.29)	
			Total red meat intake (servings/day)			
			Women:			
			≤ 2	81	1.00	
			> 2 to ≤ 3	41	1.14 (0.61–2.11)	
			> 3 to ≤ 5	40	1.46 (0.73–2.93)	
			> 5	39	1.81 (0.94–3.51)	
			Red meat doneness (servings/day)			
			Women:			
			≤ 2 “rare/regular”	17	1.00	
			≤ 2 “well-done”	106	1.94 (0.81–4.62)	
			> 2 “rare/regular”	10	3.95 (1.02–15.25)	
			> 2 “well-done”	32	3.1 (1.11–8.69)	

Table 2.2.3 Case–control studies on consumption of red meat and cancer of the colorectum

Reference, location, enrolment	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Squires et al. (2010) Newfoundland and Labrador, Canada 1999–2003 (cont.)			Red meat doneness (servings/day)			
			Men:			
			≤ 2 "rare/regular"	71	1.00	
			≤ 2 "well-done"	132	1.23 (0.76–2.00)	
			> 2 "rare/regular"	18	1.42 (0.61-3.33)	
			> 2 "well-done"	42	1.44 (0.76-2.72)	
Williams et al. (2010) North Carolina, USA 2001–2006	Cases: 945; population-based distal colorectal cancer cases, identified through the North Carolina Central Cancer Registry; African Americans were oversampled Controls: 959; population-based, selected from the North Carolina Department of Motor Vehicles or Centers for Medicare and Medicaid Services Exposure assessment method: questionnaire; validated, administered in person, and included portion size and frequency; red meat was veal, lamb, beef steaks, beef roast, beef mixtures, burgers, ham (not luncheon meat), pork, and ribs	Distal colorectum	Red meat (quartile median, g/day) in Whites			Age, sex, education, BMI, family history, NSAID use, physical activity, calcium, fibre, total energy intake
			Q1 (16.2)	149	1.00	
			Q2 (32.9)	186	1.09 (0.78–1.52)	
			Q3 (53.6)	199	1.05 (0.74–1.49)	
			Q4 (94.8)	186	0.66 (0.43–1.00)	
			Trend-test *P* value: 0.90			
			Red meat (quartile median, g/day) in African Americans			
			Q1 (12.7)	58	1.00	
			Q2 (27.8)	39	0.54 (0.27–1.09)	
			Q3 (45.5)	65	0.83 (0.42–1.63)	
			Q4 (108.6)	63	0.64 (0.27–1.50)	
			Trend-test *P* value: 0.94			
Tabatabaei et al. (2011) Australia 2005–2007	Cases: 567; population-based colorectal cases, identified through the Western Australian Cancer Registry Controls: 713; population-based, identified from electoral rolls; frequency-matched to cases by age and sex Exposure assessment method: questionnaire; unclear validation, administered by mail, and included 74 items; total red meat included hamburger/cheeseburger, beef/veal, lamb/mutton, pork chops/ham steaks, bacon, and sausages; assessed cooking methods	Colon and rectum	Total red meat intake (highest vs lowest quartile, servings/wk) by cooking method			BMI, physical activity at ages 35–50 yr, smoking habits, alcohol consumption, fruit and vegetable consumption, supplemental vitamin intake, total energy, fat and fibre consumption, the matching variables age and sex
			Pan-fried	NR	0.80 (0.57–1.13)	
			Trend-test *P* value: 0.27			
			Barbecued	NR	0.89 (0.63–1.24)	
			Trend-test *P* value: 0.17			
			Baked	NR	0.73 (0.53–1.01)	
			Trend-test *P* value: 0.04			
			Stewed	NR	0.95 (0.67–1.33)	
			Trend-test *P* value: 0.53			

Table 2.2.3 Case–control studies on consumption of red meat and cancer of the colorectum

Reference, location, enrolment	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Di Maso et al. (2013) Italy and Switzerland 1991–2009	Cases: 2390; hospital-based colorectal cases, identified from hospitals as part of a network of case–control studies Controls: 4943; hospital-based, identified through the same network of hospitals as cases; frequency-matched to cases for variables not specified Exposure assessment method: questionnaire; validated, administered in person, included 77 items, and assessed frequency and serving size; red meat was beef, veal, pork, horse meat, and half of the first course, including meat sauce (e.g. lasagne, pasta/rice with bologna sauce); assessed cooking methods	Colon	Red meat intake (g/day) in men			Age, sex, education, BMI, tobacco use, alcohol drinking, vegetable consumption, fruit consumption, study centre
			< 60	446	1.00	
			60–89	443	1.19 (1.02–1.38)	
			≥ 90	554	1.22 (1.05–1.41)	
			Per 50 g/day increase	NR	1.17 (1.08–1.26)	
			Trend-test *P* value: 0.02			
		Rectum	< 60	268	1.00	
			60–89	279	1.25 (1.04–1.51)	
			≥ 90	380	1.35 (1.12–1.62)	
			Per 50 g/day increase	NR	1.22 (1.11–1.33)	
			Trend-test *P* value< 0.01			
		Rectum	For every 50 g/day increase in red meat by cooking practice			
			Roasting/ grilling	NR	1.24 (1.07–1.45)	
			Boiling/stewing	NR	1.32 (1.10–1.58)	
			Frying/ pan-frying	NR	1.90 (1.38–2.61)	
Hu et al. (2013) Sichuan, China 2010–2012	Cases: 400; hospital-based cases from the Sichuan Cancer Hospital Controls: 400; hospital-based, identified among individuals who underwent routine medical examinations at a health centre; individually matched by sex and age Exposure assessment method: questionnaire; unclear validation; red meat was beef, pork, and lamb; assessed frequency; genotypes for *ADIPOQ*, *UCP2*, and *FABP2* were assessed	Colon and rectum	Red meat (times/wk)			Family per capita annual income, family history of colorectal cancer, sitting (h/day), BMI, smoking habit, alcohol-drinking habit, tea-drinking habit
			≤ 7	144	1.00	
			> 7	256	1.87 (1.39–2.51)	
			Trend-test *P* value< 0.001			

Table 2.2.3 Case–control studies on consumption of red meat and cancer of the colorectum

Reference, location, enrolment	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Miller et al. (2013) Pennsylvania, USA 2007–2011	Cases: 989; incident cases, identified through the Pennsylvania State Cancer Registry Controls: 1033; identified through random digit dialling; frequency-matched to cases by age, sex, and race Exposure assessment method: questionnaire; validated, in-person FFQ with 137 items; meat-cooking module was used with the CHARRED database to estimate carcinogens; red meat was beef and pork (hamburger, roast beef, pot roast, roast pork, steak, pork chops, pork or beef spare ribs, liver, meat added to mixed dishes)	Colon and rectum	Red meat intake (g/1000 kcal)			Age, sex, BMI, past NSAID use, total energy, total fruits and vegetables, total poultry
			Q1 (< 8.7)	184	1.00	
			Q2 (8.7–14.5)	217	1.24 (0.92–1.67)	
			Q3 (14.6–22.6)	184	1.05 (0.78–1.43)	
			Q4 (22.7–35.6)	231	1.38 (1.03–1.86)	
			Q5 (> 35.6)	173	1.02 (0.75–1.40)	
			Trend-test *P* value: 0.975			
		Colon	Red meat intake (g/1000 kcal)			
			Q1 (< 8.7)	139	1.00	
			Q2 (8.7–14.5)	146	1.12 (0.81–1.55)	
			Q3 (14.6–22.6)	127	1.00 (0.72–1.40)	
			Q4 (22.7–35.6)	162	1.34 (0.97–1.86)	
			Q5 (> 35.6)	119	1.00 (0.71–1.40)	
			Trend-test *P* value: 0.865			
		Rectum	Red meat intake (g/1000 kcal)			
			Q1 (< 8.7)	42	1.00	
			Q2 (8.7–14.5)	71	1.72 (1.10–2.68)	
			Q3 (14.6–22.6)	55	1.28 (0.81–2.03)	
			Q4 (22.7–35.6)	67	1.61 (1.02–2.52)	
			Q5 (> 35.6)	54	1.21 (0.76–1.94)	
			Trend-test *P* value: 0.997			
		Colon and rectum	Total DiMeIQx (ng/1000 kcal)			Age, sex, BMI, past NSAID use, total energy, total fruits and vegetables
			Q1 (< 0.23)	181	1.00	
			Q2 (0.23–0.67)	185	1.04 (0.77–1.40)	
			Q3 (0.68–1.23)	203	1.09 (0.81–1.47)	
			Q4 (1.24–2.20)	183	1.03 (0.77–1.39)	
			Q5 (> 2.20)	237	1.36 (1.02–1.82)	
			Trend-test *P* value: 0.027			

Table 2.2.3 Case–control studies on consumption of red meat and cancer of the colorectum

Reference, location, enrolment	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Miller et al. (2013) Pennsylvania, USA 2007–2011 (cont.)		Colon and rectum	Total MeIQx (ng/1000 kcal)			
			Q1 (< 4.2)	194	1.00	
			Q2 (4.2–8.3)	170	0.90 (0.67–1.22)	
			Q3 (8.4–14.2)	185	0.96 (0.71–1.29)	
			Q4 (14.3–23.8)	197	1.05 (0.78–1.41)	
			Q5 (> 23.8)	243	1.22 (0.91–1.64)	
			Trend-test *P* value: 0.047			
			Total PhIP (ng/1000 kcal)			
			Q1 (< 7.2)	223	1.00	
			Q2 (7.2–17.4)	207	0.97 (0.73–1.29)	
			Q3 (17.4–33.7)	186	0.87 (0.65–1.16)	
			Q4 (33.8–68.3)	190	0.98 (0.73–1.31)	
			Q5 (> 68.3)	183	1.06 (0.79–1.43)	
			Trend-test *P* value: 0.439			
			Total BaP (ng/1000 kcal)			
			Q1 (< 0.32)	264	1.00	
			Q2 (0.32–2.20)	219	0.95 (0.72–1.25)	
			Q3 (2.30–6.60)	152	0.69 (0.52–0.93)	
			Q4 (6.70–19.00)	184	0.92 (0.69–1.23)	
			Q5 (> 19.00)	170	0.90 (0.67–1.21)	
			Trend-test *P* value: 0.906			
			Grilled/barbecued red meat (g/1000 kcal)			Age, sex, BMI, past NSAID use, total energy, total fruits and vegetables, total poultry
			T1 (0)	285	1.00	
			T2 (0.01–4.35)	352	0.84 (0.66–1.06)	
			T3 (> 4.36)	352	0.94 (0.74–1.20)	
			Trend-test *P* value: 0.808			
			Pan-fried red meat (g/1000 kcal)			
			Q1 (< 0.36)	178	1.00	
			Q2 (0.36–1.39)	181	0.97 (0.71–1.31)	
			Q3 (1.40–3.33)	183	0.99 (0.73–1.34)	
			Q4 (3.34–6.79)	188	0.93 (0.69–1.26)	
			Q5 (> 6.79)	259	1.26 (0.93–1.70)	
			Trend-test *P* value: 0.044			

Table 2.2.3 Case–control studies on consumption of red meat and cancer of the colorectum

Reference, location, enrolment	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Miller et al. (2013) Pennsylvania, USA 2007–2011 (cont.)		Colon and rectum	Microwaved/baked red meat (g/1000 kcal)			
			Q1 (< 4.65)	213	1.00	
			Q2 (4.65–7.56)	194	0.89 (0.67–1.20)	
			Q3 (7.57–11.40)	196	0.93 (0.69–1.24)	
			Q4 (11.50–18.60)	204	0.97 (0.72–1.30)	
			Q5 (> 18.60)	182	0.87 (0.65–1.17)	
			Trend-test *P* value: 0.533			
			Broiled red meat (g/1000 kcal)			
			No consumption	727	1.00	
			Ever	262	0.99 (0.8–1.22)	
			Trend-test *P* value: 0.891			
			Red meat, rare/medium (g/1000 kcal)			
			T1 (0)	279	1.00	
			T2 (0.01–4.08)	362	0.94 (0.75–1.90)	
			T3 (> 4.08)	348	0.99 (0.79–1.26)	
			Trend-test *P* value: 0.844			
			Well-done/charred red meat (g/1000 kcal)			
			Q1 (< 0.89)	210	1.00	
			Q2 (0.89–2.41)	176	0.77 (0.57–1.03)	
			Q3 (2.42–4.70)	197	0.92 (0.69–1.24)	
			Q4 (4.71–8.96)	204	1.01 (0.75–1.35)	
			Q5 (> 8.96)	202	0.87 (0.64–1.16)	
			Trend-test *P* value: 0.857			
Rosato et al. (2013) Italy and Switzerland 1985–2009	Cases: 329; hospital-based cases with young-onset colorectal cancer (< 45 yr) Controls: 1361; hospital-based, identified from the same hospitals as cases; conditions unrelated to colorectal cancer risk factors or dietary modifications Exposure assessment method: questionnaire; validated and administered in person; red meat was not defined, and unclear if it included processed meat	Colon and rectum	Red meat intake			Age, sex, centre, study, year of interview, education, family history, alcohol, energy intake
			Low	101	1.00	
			Medium	88	0.93 (0.67–1.29)	
			High	140	1.07 (0.79–1.47)	
			Trend-test *P* value: 0.57			

Table 2.2.3 Case–control studies on consumption of red meat and cancer of the colorectum

Reference, location, enrolment	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Abu Mweis et al. (2015) Jordan 2010–2012	Cases: 167; hospital-based colorectal cases recruited from five major Jordanian hospitals Controls: 240; hospital-based, identified from hospital personnel, outpatients, visitors, and accompanying individuals; matched by age, sex, occupation, and marital status Exposure assessment method: questionnaire; validated, administered in person, and included 109 items; red meat was not defined	Colon and rectum	Red meat intake (serving/wk) < 1 ≥ 1	 103 51	 1.00 0.64 (0.37–1.11)	Age, sex, total energy, metabolic equivalent, smoking, education level, marital status, work, income, family history of colorectal cancer
Guo et al. (2015) Harbin, China 2008–2013	Cases: 600; hospital-based colorectal cases Controls: 600; hospital-based, identified at the community health centre and individually matched to cases by age and sex Exposure assessment method: questionnaire; non-validated and administered in person; red meat was pork, beef, and lamb; unclear if processed meat was included	Colon and rectum	Red meat (times/wk) ≤ 7 > 7 Trend-test *P* value: 0.001	 NR NR	 1.00 1.54 (1.114–2.424)	BMI, family income, drinking, smoking, regular tea drinking, daily sedentary time, family history of cancer

Table 2.2.3 Case–control studies on consumption of red meat and cancer of the colorectum

Reference, location, enrolment	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Joshi et al. (2015) USA and Canada 1997–2002	Cases: 3350; population-based, identified through cancer registries in Ontario, Canada; Hawaii, California, Arizona, North Carolina, New Hampshire, Colorado, Minnesota, USA; cases with familial cases included Controls: 3504; cancer-free siblings of the cases (n = 1759), unaffected spouses of the cases (n = 138), and population-based controls (n = 1607) Exposure assessment method: questionnaire; validated, administered by mail, included 200 items, included portion size and frequency of intake, and used the CHARRED database to estimate carcinogens; red meat was beef, pork, veal, lamb, and game; cooking methods were considered	Colon and rectum	Red meat (g/1000 kcal per day)			Age, BMI, sex, race, saturated fat, dietary fibre, centre, vegetables, physical activity, total caloric intake
			Q1 (0–10.81)	633	1.0	
			Q2 (10.81–16.04)	644	1.0 (0.9–1.2)	
			Q3 (16.04–21.11)	707	1.2 (1.0–1.4)	
			Q4: 21.12–28.19	680	1.2 (1.0–1.4)	
			Q5 (28.19–102.43)	686	1.2 (1.0–1.4)	
			Trend-test P value: 0.085			
		Colon	Red meat (g/1000 kcal per day)			
			Q1 (0–10.81)	396	1.0	
			Q2 (10.81–16.04)	380	1.1 (0.9–1.3)	
			Q3 (16.04–21.11)	429	1.2 (1.0–1.5)	
			Q4 (21.12–28.19)	396	1.2 (1.0–1.4)	
			Q5 (28.19–102.43)	391	1.2 (0.9–1.4)	
			Trend-test P value: 0.152			
		Rectum	Red meat (g/1000 kcal per day)			
			Q1 (0–10.81)	171	1.0	
			Q2 (10.81–16.04)	152	0.8 (0.6–1.0)	
			Q3 (16.04–21.11)	201	1.0 (0.8–1.3)	
			Q4 (21.12–28.19)	179	0.8 (0.7–1.1)	
			Q5 (28.19–102.43)	173	0.8 (0.6–1.0)	
			Trend-test P value: 0.104			
		Colon and rectum	Beef (g/1000 kcal per day)			
			Q1 (0–7.69)	687	1.0	
			Q2 (7.70–11.49)	652	1.0 (0.9–1.2)	
			Q3 (11.49–15.08)	654	1.0 (0.9–1.2)	
			Q4 (12.09–20.06)	672	1.1 (0.9–1.3)	
			Q5 (20.08–83.77)	685	1.1 (0.9–1.3)	
			Trend-test P value: 0.289			

Table 2.2.3 Case–control studies on consumption of red meat and cancer of the colorectum

Reference, location, enrolment	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Joshi et al. (2015) USA and Canada 1997–2002 (cont.)		Colon	Beef (g/1000 kcal per day)			
			Q1 (0–7.69)	426	1.0	
			Q2 (7.70–11.49)	377	9.0 (0.8–1.1)	
			Q3 (11.49–15.08)	396	1.0 (0.8–1.2)	
			Q4 (12.09–20.06)	400	1.1 (0.9–1.3)	
			Q5 (20.08–83.77)	383	1.0 (0.8–1.2)	
			Trend-test *P* value: 0.593			
		Rectum	Beef (g/1000 kcal per day)			
			Q1 (0–7.69)	155	1.0	
			Q2 (7.70–11.49)	185	1.2 (0.9–1.5)	
			Q3 (11.49–15.08)	174	1.1 (0.8–1.4)	
			Q4 (12.09–20.06)	184	1.1 (0.9–1.6)	
			Q5 (20.08–83.77)	209	1.2 (0.9–1.6)	
			Trend-test *P* value: 0.252			
			Test of heterogeneity, colon vs rectum ($P = 0.292$)			
		Colon and rectum	Pork (g/1000 kcal per day)			
			Q1 (0–1.32)	617	1.0	
			Q2 (1.32–3.01)	641	1.0 (0.9–1.2)	
			Q3 (3.01–4.84)	660	1.1 (0.9–1.2)	
			Q4 (4.85–7.44)	743	1.2 (1.0–1.4)	
			Q5 (7.44–49.62)	689	1.1 (1.0–1.3)	
			Trend-test *P* value: 0.069			

Table 2.2.3 Case–control studies on consumption of red meat and cancer of the colorectum

Reference, location, enrolment	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Joshi et al. (2015) USA and Canada 1997–2002 (cont.)		Colon	Pork (g/1000 kcal per day)			
			Q1 (0–1.32)	383	1.0	
			Q2 (1.32–3.01)	388	1.0 (0.8–1.2)	
			Q3 (3.01–4.84)	383	1.0 (0.9–1.2)	
			Q4 (4.85–7.44)	440	1.2 (1.0–1.4)	
			Q5 (7.44–49.62)	398	1.1 (0.9–1.3)	
			Trend-test *P* value: 0.224			
		Rectum	Pork (g/1000 kcal per day)			
			Q1 (0–1.32)	154	1.0	
			Q2 (1.32–3.01)	163	1.0 (0.8–1.3)	
			Q3 (3.01–4.84)	178	1.1 (0.8–1.3)	
			Q4 (4.85–7.44)	207	1.2 (0.9–1.5)	
			Q5 (7.44–49.62)	205	1.1 (0.9–1.5)	
			Trend-test *P* value: 0.133			
		Colon and rectum	Organ meats (g/1000 kcal per day)			
			Q1 (0–0)	884	1.0	
			Q2 0–0)	282	1.2 (1.0–1.4)	
			Q3 (0–0)	650	1.1 (1–1.3)	
			Q4 (0–0.02)	755	1.0 (0.9–1.2)	
			Q5 (0.02–0.64)	779	1.2 (1.0–1.4)	
			Trend-test *P* value: 0.058			
		Colon and rectum	Pan-fried beef steak (g/1000 kcal per day)			
			Q1 (0–0)	1692	1.0	
			Q2 (0.01–0.02)	506	1.0 (0.8–1.1)	
			Q3 (0.02–0.04)	511	1.0 (0.9–1.2)	
			Q4 (0.04–0.99)	619	1.3 (1.1–1.5)	
			Trend-test *P* value: <0.001			

Table 2.2.3 Case–control studies on consumption of red meat and cancer of the colorectum

Reference, location, enrolment	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Joshi et al. (2015) USA and Canada 1997–2002 (cont.)		Colon and rectum	Pan-fried beef steak(g/1000 kcal per day); MMR proficient			
			Q1	469	1.0	
			Q2	129	0.9 (0.7–1.1)	
			Q3	119	0.9 (0.7–1.1)	
			Q4	155	1.0 (1.0–1.5)	
			Trend-test *P* value:0.098			
			Pan-fried beef steak(g/1000 kcal per day); MMR deficient			
			Q1	121	1.0	
			Q2	33	1.0 (0.7–1.5)	
			Q3	35	1.1 (0.8–1.7)	
			Q4	54	1.7 (1.2–2.4)	
			Trend-test *P* value:0.002			
			Test of heterogenicity MMR-deficient vs MMR-proficient (*P*=0.059)			
			Pan-fried hamburger (g/1000 kcal per day)			
			Q1 (0–0)	1297	1.0	
			Q2 (0.01–0.02)	627	0.9 (0.8–1.1)	
			Q3 (0.02–0.05)	707	1.0 (0.9–1.2)	
			Q4 (0.05–0.99)	697	1.1 (0.9–1.2)	
			Trend-test *P* value: 0.209			
			Pan-fried hamburger (g/1000 kcal per day); MMR-proficient			
			Q1 (0–0)	381	1.0	
			Q2 (0.01–0.02)	164	0.8 (0.7–1.0)	
			Q3 (0.02–0.05)	178	1.0 (0.8–1.2)	
			Q4 (0.05–1.37)	150	0.9 (0.7–1.1)	
			Trend-test *P* value: 0.516			

Table 2.2.3 Case–control studies on consumption of red meat and cancer of the colorectum

Reference, location, enrolment	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Joshi et al. (2015) USA and Canada 1997–2002 (cont.)		Colon and rectum	Pan-fried hamburger (g/1000 kcal per day); MMR-deficient			
			Q1 (0–0)	89	1.0	
			Q2 (0.01–0.02)	34	0.8 (0.5–1.2)	
			Q3 (0.02–0.05)	56	1.3 (0.9–1.9)	
			Q4 (0.05–0.99)	63	1.5 (1.0–2.1)	
			Trend-test *P* value: 0.01			
			Test of heterogeneity, MMR-deficient vs MMR-proficient ($P = 0.026$)			
			Oven-broiled beef steak (g/1000 kcal per day)			
			Q1 (0–0)	2145	1.0	
			Q2 (0.01–0.02)	399	1.0 (0.8–1.2)	
			Q3 (0.02–0.04)	397	1.1 (0.9–1.3)	
			Q4 (0.04–1.37)	346	0.9 (0.8–1.1)	
			Trend-test *P* value: 0.742			
			Oven-broiled hamburger (g/1000 kcal per day)			
			Q1 (0–0)	2506	1.0	
			Q2 (0.01–0.02)	241	0.8 (0.7–1.0)	
			Q3 (0.02–0.04)	279	1.0 (0.8–1.2)	
			Q4 (0.04–0.99)	283	1.0 (0.9–1.2)	
			Trend-test *P* value: 0.989			
			Oven-broiled short ribs or spare ribs (g/1000 kcal per day)			
			Q1 (0–0)	2389	1.0	
			Q2 (0.01–0.02)	319	1.2 (1.0–1.5)	
			Q3 (0.02–0.03)	299	1.3 (1.1–1.6)	
			Q4 (0.03–0.99)	306	1.2 (1.0–1.5)	
			Trend-test *P* value: 0.002			

Table 2.2.3 Case–control studies on consumption of red meat and cancer of the colorectum

Reference, location, enrolment	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Joshi et al. (2015) USA and Canada 1997–2002 (cont.)		Colon and rectum	Oven-broiled short ribs or spare ribs (g/1000 kcal per day); MMR-proficient			
			Q1 (0–0)	656	1.0	
			Q2 (0.01–0.02)	91	1.3 (1.0–1.7)	
			Q3 (0.02–0.04)	64	1.1 (0.8–1.5)	
			Q4 (0.04–0.99)	58	1.0 (0.8–1.4)	
			Trend-test *P* value: 0.415			
			Oven-broiled short ribs or spare ribs (g/1000 kcal per day); MMR-deficient			
			Q1 (0–0)	178	1.0	
			Q2 (0.01–0.02)	15	0.9 (0.5–1.5)	
			Q3 (0.02–0.04)	21	1.5 (0.9–2.4)	
			Q4 (0.04–0.99)	26	1.9 (1.2–3.0)	
			Trend-test *P* value: 0.003			
			Test of heterogeneity, MMR-proficient vs MMR-deficient ($P = 0.052$)			
			Grilled beef steak (g/1000 kcal per day)			
			Q1 (0–0)	1314	1.0	
			Q2 (0.01–0.02)	726	0.9 (0.8–1.1)	
			Q3 (0.02–0.04)	677	1.0 (0.8–1.1)	
			Q4 (0.04–0.99)	582	0.9 (0.8–1.0)	
			Trend-test *P* value: 0.212			

Table 2.2.3 Case–control studies on consumption of red meat and cancer of the colorectum

Reference, location, enrolment	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Joshi et al. (2015) USA and Canada 1997–2002 (cont.)		Colon and rectum	Grilled hamburger (g/1000 kcal per day)			
			Q1 (0–0)	1401	1.0	
			Q2 (0.01–0.02)	690	0.9 (0.7–1.0)	
			Q3 (0.02–0.05)	686	0.9 (0.8–1.1)	
			Q4 (0.05–0.99)	542	0.8 (0.7–0.9)	
			Trend-test *P* value: 0.002			
			Grilled short ribs or spare ribs (g/1000 kcal per day)			
			Q1 (0–0)	2239	1.0	
			Q2 (0.01–0.02)	360	0.9 (0.8–1.1)	
			Q3 (0.02–0.03)	344	1.1 (0.9–1.3)	
			Q4 (0.03–0.99)	361	1.1 (0.9–1.3)	
			Trend-test *P* value: 0.166			

AHR, aryl hydrocarbon receptor; BaP, benzo[*a*]pyrene; BMI, body mass index; CHARRED, Computerized Heterocyclic Amines Resource for Research in Epidemiology of Disease; CI, confidence interval; CYP, cytochrome P450; DiMeIQx, 2-amino-3,4,8-trimethylimidazo[4,5-*f*]quinoxaline; FFQ, food frequency questionnaire; GI, gastrointestinal; GST, glutathione S-transferase; h, hour; HAA, heterocyclic aromatic amine; HRT, hormone replacement therapy; kg, kilogram; mEH, microsomal epoxide hydrolase; MeIQx, 2-amino-3,8-dimethylimidazo[4,5-*f*]quinoxaline; min, minute; MMR, mismatch repair; mo, month; NAT, *N*-acetyltransferase; NOS, not otherwise specified; NR, not reported; NS, not significant; NSAID, nonsteroidal anti-inflammatory drug; PhIP, 2-amino-1-methyl-6-phenylimidazo[4,5-*b*]pyridine; SEER, Surveillance, Epidemiology, and End Results; SULT, sulfotransferase; UGT, UDP glucuronosyltransferase; wk, week; yr, year

Table 2.2.4 Case–control studies on consumption of processed meat and cancer of the colorectum

Reference, location, enrolment	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Macquart-Moulin et al. (1986) Marseille, France 1979–1984	Cases: 399; hospital-based colorectal cases Controls: 399; hospital-based, identified from centres treating injuries or trauma; no GI disease, no alcohol-related diseases, and matched to cases by sex and age Exposure assessment method: questionnaire; unknown validation, administered in person, included 158 items, and considered frequency and portion size; processed meat was ham, salami, sausages, and pâté	Colon and rectum	Processed meats (percentiles)			Age, sex, weight, total calories
			Q1	112	1.00	
			Q2 (25th)	109	1.31	
			Q3 (50th)	90	0.88	
			Q4 (75th)	88	0.89	
			Trend-test *P* value: 0.22			
Tuyns et al. (1988) Belgium 1978–1982	Cases: 818; population-based cases, identified through treatment centres Controls: 2851; population-based Exposure assessment method: questionnaire; validated, administered in person, and captured frequency and serving size; processed meat was "charcuterie"	Colon	"Charcuterie" (g/wk)			Age, sex, province
			0	NR	1.00	
			>0-50	NR	1.16	
			>50-125	NR	0.83	
			>125	NR	0.90	
			Trend-test *P* value: 0.26			
		Rectum	"Charcuterie" (g/wk)			
			0	NR	1.00	
			>0-50	NR	1.38	
			>50-125	NR	0.94	
			>125	NR	0.98	
			Trend-test *P* value: 0.63			
Benito et al. (1990) Majorca, Spain 1984–1988	Cases: 286; population-based colorectal cases in a case–control study Controls: 498; population-based, identified from the electoral census and frequency-matched to cases by age and sex; hospital-based, selected from ophthalmology and orthopaedic clinics from hospitals where the majority of cases were identified; Exposure assessment method: questionnaire; not validated, included 99 items, and administered in person; exposure definition was processed meat including all types of cured meat and meats processed with other animal products, such as blood and fats	Colon and rectum	Processed meat (intake per mo), quartiles			Age, sex, weight 10 yr before interview
			Q1	22	1.00	
			Q2	89	1.35	
			Q3	94	1.42	
			Q4	81	1.36	
			Trend-test *P* value= 0.4			

Table 2.2.4 Case–control studies on consumption of processed meat and cancer of the colorectum

Reference, location, enrolment	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Gerhardsson de Verdier et al. (1991) Stockholm, Sweden 1986–1988	Cases: 559; population-based colorectal cases, identified through local hospitals and a regional cancer registry Controls: 505; population-based, frequency-matched to cases by age and sex Exposure assessment method: questionnaire; unclear validation, self-administered, and included 55 items; processed meat was bacon/smoked ham and sausage assessed separately; assessed cooking methods	Colon	Processed meat intake (Tertile 3 vs T1, i.e. > 1 time/wk vs more seldom)			Year of birth, sex, fat intake
			Bacon/smoked ham	84	1.3 (0.8–1.9)	
			Trend-test *P* value = 0.34			
			Sausage, fried	90	1.0 (0.6–1.4)	
			Trend-test *P* value = 0.91:			
			Sausage, oven-roasted	12	1.2 (0.5–2.8)	
			Trend-test *P* value = 0.36			
			Sausage, boiled	57	1.4 (0.9–2.2)	
			Trend-test *P* value = 0.04			
		Rectum	Processed meat intake (> 1 time/wk vs more seldom)			
			Bacon/smoked ham	53	1.7 (1.1–2.8)	
			Trend-test *P* value = 0.025			
			Sausage, fried	71	1.5 (0.9–2.4)	
			Trend-test *P* value = 0.093			
			Sausage, oven-roasted	13	2.1 (0.9–4.9)	
			Trend-test *P* value = 0.038			
			Sausage, boiled	53	3.0 (1.8–4.9)	
			Trend-test *P* value: <0.001			
Iscovich et al. (1992) La Plata, Argentina 1985–1986	Cases: 110; hospital-based, identified through local hospitals Controls: 220; population-based, identified from neighbourhoods of cases and matched to cases by sex; controls with conditions that may have affected diet were excluded Exposure assessment method: questionnaire; unclear validation, administered in person, and included 140 items; processed meat was sausage, mortadella, salami (with skin), ham, and cooked skinless meat	Colon	Processed meat intake (fat with skin), quartiles			Matching variables
			Q1	NR	1.00	
			Q2	NR	0.76 (0.38–1.52)	
			Q3	NR	0.63 (0.28–1.41)	
			Q4	NR	0.45 (0.23–0.90)	
			Trend-test *P* value: 0.017			
			Processed meat intake (lean), quartiles			
			Q1	NR	1.00	
			Q2	NR	0.73 (0.36–1.49)	
			Q3	NR	0.50 (0.20–1.24)	
			Q4	NR	0.38 (0.19–0.75)	
			Trend-test *P* value: 0.002			

Table 2.2.4 Case–control studies on consumption of processed meat and cancer of the colorectum

Reference, location, enrolment	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Steinmetz and Potter (1993) Adelaide, Australia 1979–1980	Cases: 220; population-based colon cases, identified via the South Australian Cancer Registry Controls: 438; population-based; two controls per case selected via the electoral roll and individually matched to cases by age and sex Exposure assessment method: questionnaire; validated, self-administered, and included 141 items; processed meat was grilled bacon, fried bacon, grilled pork sausage, fried pork sausage, grilled beef sausage, fried beef sausage, sausage roll, cold meat (e.g. ham, "fritz"), and spicy meat (e.g. salami)	Colon	Processed meat intake (servings/wk), quartiles Women: Q1 (≥ 1.4) Q2 (1.5–2.8) Q3 (2.9–4.3) Q4 (≥ 4.3) Processed meat intake (servings/wk), quartiles Men: Q1 (≤ 2.2) Q2 (2.3–4.3) Q3 (4.4–7.6) Q4 (≥ 7.7)	 NR NR NR NR NR NR NR NR	 1.00 0.54 (0.25–1.23) 0.81 (0.37–1.77) 0.77 (0.35–1.68) 1.00 0.69 (0.35–1.37) 0.68 (0.35–1.34) 1.03 (0.55–1.95)	Age at first live birth, Quetelet index, alcohol intake, the matching variable age Occupation, Quetelet index, alcohol intake for males, the matching variable age
Centonze et al. (1994) Southern Italy 1987–1989	Cases: 119; population-based colorectal cases, identified from a population-based cancer registry Controls: 119; population-based, matched to cases by age, sex, and general practitioner Exposure assessment method: questionnaire; unclear validation, administered by in-person interview, and included 70 food items; processed meat was sausage, ham, and tinned meat	Colon and rectum	Processed meat (g/day) <2 ≥3	 66 53	 1.00 1.01 (0.57–1.69)	Age, sex, level of education, smoking status, modifications of diet in the past 10 yr
Lohsoonthorn and Danvivat (1995) Bangkok, Thailand NR	Cases: 279; hospital-based colorectal cases Controls: 279; hospital-based, individually matched to cases by sex, age, admission period, and hospital; included cancer patients with cancer in other organs Exposure assessment method: questionnaire; unclear validation and number of items asked; assessed frequency only; processed meat (individual types only) was bacon, salted beef, and sausage	Colon and rectum	Bacon consumption (times/mo) < 5 6– ≥ 10 Trend-test *P* value: 0.82 Salted beef consumption (times/mo) < 5 6– ≥ 10 Trend-test *P* value: 0.93 Sausage consumption (times/mo) < 5 6– ≥ 10 Trend-test *P* value: 0.79	 267 12 184 95 247 32 	 1.00 12.49 (1.68–269) 1.00 0.97 (0.67–1.39) 1.00 1.26 (0.71–2.25) 	Not specified

Table 2.2.4 Case–control studies on consumption of processed meat and cancer of the colorectum

Reference, location, enrolment	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
De Stefani et al. (1997) Montevideo, Uruguay 1993–1995	Cases: 250; hospital-based colorectal cases Controls: 500; hospital-based, identified at the same hospitals as the cases and had a variety of disorders unrelated to tobacco smoking, alcohol, or diet Exposure assessment method: questionnaire; unclear validation, administered in person, and included 60 items; unclear what was included in processed meat; assessed cooking methods	Colon and rectum	Processed meat, quartiles			Age, residence, education, family history of colon cancer in a first-degree relative, BMI, vegetable and dessert intake
			Men:			
			Q1	NR	1.00	
			Q2	NR	1.19 (0.65–2.15)	
			Q3	NR	0.70 (0.39–1.25)	
			Q4	NR	0.75 (0.40–1.37)	
			Trend-test *P* value: 0.17			
			Processed meat, quartiles			
			Women:			
			Q1	NR	1.00	
			Q2	NR	0.81 (0.39–1.65)	
			Q3	NR	0.93 (0.44–1.95)	
			Q4	NR	1.35 (0.65–2.82)	
			Trend-test *P* value: 0.37			
		Colon	Processed meat, quartiles			
			Men:			
			Q1	NR	1.00	
			Q2	NR	1.68 (0.77–3.66)	
			Q3	NR	1.09 (0.50–2.39)	
			Q4	NR	1.21 (0.55–2.66)	
			Trend-test *P* value: 0.99			
			Processed meat, quartiles			
			Women:			
			Q1	NR	1.00	
			Q2	NR	0.64 (0.27–1.49)	
			Q3	NR	0.87 (0.37–2.03)	
			Q4	NR	1.37 (0.59–3.19)	
			Trend-test *P* value: 0.36			

Table 2.2.4 Case–control studies on consumption of processed meat and cancer of the colorectum

Reference, location, enrolment	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
De Stefani et al. (1997) Montevideo, Uruguay 1993–1995 (cont.)		Rectum	Processed meat, quartiles			
			Men:			
			Q1	NR	1.00	
			Q2	NR	0.98 (0.47–2.04)	
			Q3	NR	0.51 (0.24–1.09)	
			Q4	NR	0.54 (0.25–1.17)	
			Trend-test *P* value: 0.04			
			Processed meat, quartiles			
			Women:			
			Q1	NR	1.00	
			Q2	NR	1.10 (0.36–3.33)	
			Q3	NR	0.90 (0.26–3.09)	
			Q4	NR	1.19 (0.36–3.92)	
			Trend-test *P* value: 0.85			
Faivre et al. (1997) Burgundy, France 1985–1990	Cases: 171; population-based colorectal cases, identified through a registry Controls: 309; population-based; no more information was provided Exposure assessment method: questionnaire; validated, administered in person, included 39 items, and queried frequency and portion sizes; no details were provided for processed meat and delicatessen; pâtés and meat spreads were included	Colon and rectum	Processed meat and delicatessen			Age, sex, caloric intake
			NR	NR	3.0 (2.1–4.8)	
			Trend-test *P* value: <0.001			
Fernandez et al. (1997) Province of Pordenone, Italy 1985–1992	Cases: 112; cases with a family history of colorectal cancer; Controls: 108 controls; controls with a family history of colorectal cancer; Exposure assessment method: questionnaire; data on salami/sausage, raw ham and ham intake	Colon and rectum	Processed meat intake (highest vs lowest tertile, times/wk)			Age, sex, area of residence
			Raw ham	NR	2.1 (0.9–4.9)	
			Trend-test *P* value: < 0.05			
			Ham	NR	2.6 (1.0–6.8)	
			Trend-test *P* value: < 0.05			
			Canned meat	NR	1.9 (1.0–3.3)	
			Trend-test *P* value: <0.05			

Table 2.2.4 Case–control studies on consumption of processed meat and cancer of the colorectum

Reference, location, enrolment	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Franceschi et al. (1997) Italy 1992–1996	Cases: 1953; hospital-based colorectal cases, identified at multiple sites Controls: 4154; hospital-based, identified in the same catchment areas of cases; included acute non-neoplastic, non-gynaecological conditions unrelated to hormonal or digestive tract diseases or to long-term modifications of diet Exposure assessment method: questionnaire; validated, administered in person, and included 79 items; processed meat was not defined	Colon and rectum	Processed intake (servings/wk), quintiles			Age, sex, centre, education, physical activity, total energy intake
			Q1	NR	1.00	
			Q2	NR	1.21 (1.03–1.42)	
			Q3	NR	1.06 (0.89–1.26)	
			Q4	NR	1.24 (1.02–1.49)	
			Q5	NR	1.02 (0.84–1.24)	
			Trend-test *P* value: 0.13			
		Colon	Processed meat intake			
			Increase of 1 serving/day	NR	1.08 (0.87–1.36)	
		Rectum	Processed meat intake			
			Increase of 1 serving/day	NR	0.78 (0.57–1.06)	
		Colon and rectum	Processed meat intake			
			Increase of 1 serving/day	NR	0.97 (0.79–1.18)	
Norat et alt al. (1997) Hawaii, USA 1987–1991	Cases: 1192; population-based cases, identified through the Hawaii Tumor Registry; cases included Japanese, Caucasian (White), Filipino, Hawaiian, and Chinese patients Controls: 1192; population-based, identified through the Hawaii State Department of Health and individually matched to each case by sex, ethnicity, and age Exposure assessment method: questionnaire; validated, administered in person, and included 280 items; processed meat was luncheon meat, salami, wieners, sausage, spam, and bacon	Colon and rectum	Processed meat intake, quartiles			Age; family history of colorectal cancer; alcoholic drinks per wk; pack-years; lifetime recreational activity; BMI 5 yr ago; caloric, dietary fibre, calcium intakes
			Men:			
			Q1	NR	1.0	
			Q2	NR	1.7	
			Q3	NR	2.2	
			Q4	NR	2.3 (1.5–3.4)	
			Trend-test *P* value: 0.001			
			Processed meat intake, quartiles			
			Women: Q1	NR	1.0	
			Q2	NR	0.8	
			Q3	NR	1.1	
			Q4	NR	1.2 (0.8–2.0)	
			Trend-test *P* value: 0.2			

Table 2.2.4 Case–control studies on consumption of processed meat and cancer of the colorectum

Reference, location, enrolment	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Boutron-Ruault et al. (1999) Burgundy, France 1985–1990	Cases: 171; population-based, identified from GI and surgery departments in conjunction with a registry of digestive cancers Controls: 309; population-based, identified from a census list and frequency-matched to cases by age and sex Exposure assessment method: questionnaire; validated and administered in person; processed meat was "delicatessen"	Colon and rectum	Intake of delicatessen (g/day), quartiles Q1 Q2 Q3 Q4 Trend-test *P* value: 0.01	 NR NR NR NR	 1.0 1.6 (0.9–2.9) 1.2 (0.6–2.2) 2.4 (1.3–4.5)	Age, sex, caloric intake
Kampman et al. (1999) California, Utah, and Minnesota, USA 1991–1994	Cases: 1542; cases identified through the Kaiser Permanente Medical Care Program of Northern California, Utah, and metropolitan twin cities area in Minnesota Controls: 1860; population-based, frequency-matched to cases by sex and age; identified using membership lists of the Kaiser Permanente Medical Care Program, random digit dialling, drivers' licence and identification lists, and Health Care Financing Administration forms Exposure assessment method: questionnaire; exposure definition, validated, in-person interview, and > 800 items; processed meat was bacon, sausages, and cold cuts; assessed cooking methods and mutagen index	Colon	Processed meat (servings/wk) Men: ≤ 0.5 0.6–1.0 1.1–1.8 1.9–3.1 > 3.1 Processed meat (servings/wk) Women: ≤ 0.2 0.3–0.5 0.6–0.9 1.0–1.7 > 1.7	 NR NR NR NR NR NR NR NR NR	 1.0 1.1 (0.8–1.6) 1.2 (0.9–1.8) 1.3 (1.0–1.8) 1.4 (1.0–1.9) 1.0 1.3 (1.0–1.9) 1.2 (0.9–1.7) 1.3 (0.9–1.8) 1.1 (0.8–1.6)	Age at diagnosis (cases) or selection (controls), BMI, lifetime physical activity, total energy intake, usual number of cigarettes smoked per day, intake of dietary fibre
Navarro et al. (2003) Córdoba, Argentina 1993–1998	Cases: 287 colorectal cancer cases (163 men, 124 women); hospital-based colorectal cases identified at hospitals in Córdoba Controls: 564 (309 men, 255 women); hospital-based control residents identified at the same hospitals for acute non-neoplastic conditions unrelated to digestive tract diseases or long-term modifications Exposure assessment method: questionnaire; validated, administered in person, and evaluated frequency and portion size; processed meats were cold cuts (ham, bologna, salami, cured meat of pork, etc.) and sausages	Colon and rectum	Processed meat ("cold cuts/sausages", g/day) T1 T2 (median intake, 7.39 g/day) T3 (median intake, 16.52 g/day)	 NR NR NR	 1.00 1.07 (0.72–1.59) 1.47 (1.02–2.15)	Sex, age, BMI, social status, energy, total lipids, proteins, carbohydrates, soluble and insoluble fibre intake

Table 2.2.4 Case–control studies on consumption of processed meat and cancer of the colorectum

Reference, location, enrolment	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Juarranz-Sanz et al. (2004) Madrid, Spain 1997–1998	Cases: 196; population-based colorectal cases, identified through a cancer registry Controls: 196; population-based, identified through a health care roster from the same districts of the identified cases; individually matched to cases by age, sex, and geographical region Exposure assessment method: questionnaire; validated, included 72 items, administered by phone, and asked about frequency and portion size; processed meats were not defined	Colon and rectum	Processed meats (g/day), continuous variables Processed meat Trend-test *P* value: 0.001	NR	1.070 (1.035–1.107)	Olives, red meat, organ meat, cherries/ strawberries, oranges, raw tomatoes, yogurt, fresh juice
Levi et al. (2004) Canton of Vaud, Switzerland 1992– 2002	Cases: 323; hospital-based colorectal cancer cases Controls: 611; hospital-based, identified at same hospitals of cases, with conditions unrelated to smoking or alcohol and long-term modification of diet Exposure assessment method: questionnaire; validated, administered in person, and included 79 items; processed meat was raw ham, boiled ham, salami, and sausages	Colon and rectum	Processed meat intake (servings/wk), quartiles < 0.8 0.8–1.5 1.6–3.9 > 4.0 Trend-test *P* value: < 0.001	 36 46 111 130	 1.00 1.03 (0.61–1.75) 1.82 (1.12–2.95) 2.53 (1.50–4.27)	Education, tobacco smoking, alcohol drinking, total energy intake, fruit and vegetable intake, BMI, physical activity
Murtaugh et al. (2004) California and Utah, USA 1997–2001	Cases: 952; population-based rectal cancer cases, identified through a cancer registry and online pathology reports from the Kaiser Permanente Northern California Cancer Registry Controls: 1205; controls were randomly selected from membership lists, social security lists, drivers' licence lists; frequency-matched to cases by sex and 5-y age groups Exposure assessment method: Questionnaire; validated, administered in person, and included >800 items; processed meat was bacon, sausages, and cold cuts; cooking methods were assessed, and interactions with *NAT2* phenotype and *GSTM1* genotypes were assessed	Rectum	Processed meat (servings/wk), men: < 0.6 ≥ 0.6 to < 1.6 ≥ 1.6 Trend-test *P* value: < 0.05 Processed meat (servings/wk), women: < 0.2 ≥ 0.2 to < 0.9 ≥ 0.9 Trend-test *P* value: < 0.05	 172 149 235 87 140 162	 1.00 0.95 (0.71–1.28) 18 (0.87–1.61) 1.00 1.21 (0.85–1.72) 1.23 (0.84–1.81)	Age, BMI, energy intake, dietary fibre, calcium, lifetime physical activity, usual number of cigarettes smoked

Table 2.2.4 Case–control studies on consumption of processed meat and cancer of the colorectum

Reference, location, enrolment	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Hu et al. (2007) Canada 1994–1997	Cases: 1723; identified via the National Enhanced Cancer Surveillance System (NECSS), including the provinces of British Columbia, Alberta, Saskatchewan, Manitoba, Nova Scotia, Newfoundland, Ontario, Prince Edward Island Controls: 3097; population-based controls from each province, frequency-matched to cases by age and sex Exposure assessment method: questionnaire; validated FFQ with 70 items, administered by mail; processed meat was hot dogs, lunch meat, smoked meat, bacon, and sausage	Proximal colon	Processed meat intake (servings/wk), quartiles; men			10-yr age group, province, BMI, strenuous activity, total energy intake
			Q1	68	1.0	
			Q2	92	1.4 (0.9–2.0)	
			Q3	121	1.9 (1.3–2.7)	
			Q4	99	1.6 (1.0–2.4)	
			Trend-test *P* value: 0.01			
			Processed meat intake (servings/wk), quartiles; women			
			Q1	70	1.0	
			Q2	108	1.3 (0.9–1.9)	
			Q3	68	1.2 (0.8–1.8)	
			Q4	105	1.5 (1.0–2.3)	
			Trend-test *P* value: 0.06			
		Distal colon	Processed meat intake (servings/wk), quartiles; men:			
			Q1	112	1.0	
			Q2	130	1.4 (0.9–2.0	
			Q3	177	1.9 (1.3–2.7)	
			Q4	159	1.6 (1.0–2.4)	
			Trend-test *P* value: 0.01			
			Processed meat intake (servings/wk), quartiles; women:			
			Q1	80	1.0	
			Q2	126	1.5 (1.0–2.3)	
			Q3	98	1.8 (1.2–2.7)	
			Q4	110	1.5 (1.0–2.2)	
			Trend-test *P* value: 0.08			
		Proximal colon	Bacon intake (highest vs lowest tertile, servings/wk); men:			
			T1	95	1.0	
			T2	190	1.5 (1.1–2.1)	
			T3	56	1.5 (1.0–2.2)	
			Trend-test *P* value: 0.04			

Table 2.2.4 Case–control studies on consumption of processed meat and cancer of the colorectum

Reference, location, enrolment	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Hu et al. (2007) Canada 1994–1997 (cont.)		Proximal colon	Bacon intake (highest vs lowest tertile, servings/wk); women:			
			T1	NR	1.0	
			T2	NR	1.3 (1.0–1.8)	
			T3	NR	2.2 (1.4–3.3)	
			Trend-test *P* value: 0.001			
		Distal colon	Bacon intake (highest vs lowest tertile, servings/wk); men:			
			T1	NR	1.0	
			T2	NR	1.3 (1.0–1.6)	
			T3	NR	1.4 (1.0–1.9)	
			Trend-test *P* value: 0.05			
			Bacon intake (highest vs lowest tertile, servings/wk); women:			
			T1	NR	1.0	
			T2	NR	(0.9–1.6)	
			T3	NR	(1.2–2.8)	
			Trend-test *P* value: 0.01			
Kimura et al. (2007) Fukuoka, Japan 2000–2003	Cases: 840; hospital-based, cases admitted to hospitals in Fukuoka and three adjacent areas Controls: 833; population-based controls from 15 different areas, sampled based on frequency of age and sex of cases Exposure assessment method: questionnaire; validated, administered in person, and included 148 items; definition of processed meat was not provided	Colon and rectum	Processed meat quintiles (median, g/day)			Age, sex, residential area, BMI, smoking, alcohol use, type of job, leisure-time physical activity, dietary calcium, dietary fibre
			Q1 (0.4)	152	1.00	
			Q2 (2.5)	149	1.03 (0.74–1.43)	
			Q3 (4.9)	160	1.09 (0.79–1.52)	
			Q4 (8.2)	151	1.07 (0.77–1.49)	
			Q5 (14.9)	170	1.15 (0.83–1.60)	
			Trend-test *P* value: 0.40			
		Proximal colon	Processed meat (g/day), quintiles			
			Q1	40	1.00	
			Q2	27	0.82 (0.47–1.44)	
			Q3	35	1.12 (0.65–1.92)	
			Q4	33	1.04 (0.60–1.80)	
			Q5	42	1.20 (0.72–2.03)	
			Trend-test *P* value: 0.33			

Table 2.2.4 Case–control studies on consumption of processed meat and cancer of the colorectum

Reference, location, enrolment	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Kimura et al. (2007) Fukuoka, Japan 2000–2003 (cont.)		Distal colon	Processed meat (g/day), quintiles			
			Q1	48	1.00	
			Q2	49	1.10 (0.68–1.78)	
			Q3	57	1.30 (0.81–2.08)	
			Q4	49	1.15 (0.71–1.86)	
			Q5	59	1.32 (0.82–2.11)	
			Trend-test *P* value: 0.27			
		Rectum	Processed meat (g/day), quintiles			
			Q1	59	1.00	
			Q2	70	1.20 (0.78–1.84)	
			Q3	64	1.08 (0.69–1.67)	
			Q4	68	1.21 (0.78–1.87)	
			Q5	66	1.14 (0.73–1.77)	
			Trend-test *P* value: 0.61			
Squires et al. (2010) Newfoundland and Labrador, Canada 1999–2003	Cases: 518; population-based colorectal cases, identified through a cancer registry Controls: 686; population-based, identified through random digit dialling; frequency-matched to cases by age and sex Exposure assessment method: questionnaire; unclear validation of local foods, administered by mail, and included 169 items. Pickled meat was meats preserved in brine solution (e.g. trimmed navel beef, cured pork riblets); assessed cooking methods	Colon and rectum	Pickled meat (g/day), tertiles, men:			Age; BMI; smoking status; level of education; intake of vegetables, fruits, folic acid, cholesterol, dietary fibre, saturated fat, alcohol; caloric intake; level of physical activity; NSAID use; presence of inflammatory bowel disease
			T1 (< 1)	139	1.00	
			T2 (1–3)	37	1.64 (0.89–3.02)	
			T3 (> 3)	132	2.07 (1.37–3.15)	
			Pickled meat (g/day), tertiles, women:			
			T1 (< 1)	96	1.00	
			T2 (1–3)	24	1.03 (0.49–2.17)	
			T3 (> 3)	90	2.51 (1.45–4.32)	

Table 2.2.4 Case–control studies on consumption of processed meat and cancer of the colorectum

Reference, location, enrolment	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Williams et al. (2010) North Carolina, USA 2001–2006	Cases: 945; population-based distal colorectal cancer cases, identified through the North Carolina Central Cancer Registry; African Americans were oversampled Controls: 959; population-based, selected from the North Carolina Department of Motor Vehicles or Centers for Medicare and Medicaid Services Exposure assessment method: questionnaire; validated, administered in person, and included portion size and frequency; processed meat was sausage, bacon, hot dogs, and all cold cuts (i.e. luncheon meats made from beef, veal, ham, pork, chicken, and turkey)	Distal colon and rectum	Processed meat (quartile median, g/day) in Caucasians			Age, sex, education, BMI, family history, NSAID use, physical activity, calcium, fibre, total energy
			Q1 (3.4)	131	1.00	
			Q2 (9.6)	178	1.15 (0.82–1.62)	
			Q3 (19.1)	208	1.43 (1.02–2.02)	
			Q4 (37.7)	203	1.16 (0.80–1.68)	
			Trend-test *P* value: 0.57			
			Processed meat (quartile median, g/day) in African Americans			
			Q1 (12.2)	44	1.00	
			Q2 (12.2)	85	1.47 (0.76–2.85)	
			Q3 (24.9)	42	0.54 (0.24–1.18)	
			Q4 (42.7)	54	0.86 (0.38–1.96)	
			Trend-test *P* value: 0.94			
De Stefani et al. (2012a) Montevideo, Uruguay 1996–2004	Cases: 361; hospital-based colorectal cases; patients with low socioeconomic status Controls: 2532; Hospital-based from the same hospitals as cases, with conditions unrelated to smoking and drinking Exposure assessment method: questionnaire; not validated, included 64 items, and administered in person; processed meat was bacon, sausage, mortadella, salami, saucisson, hot dog, ham, and air-dried and salted lamb	Colon	Processed meat (g/day), tertiles, men:			Age; residence; BMI; smoking status; smoking cessation; number of cigarettes smoked per day among current smokers; alcohol drinking; mate consumption; total energy, total vegetables and fruits, total white meat, red meat intakes
			≤ 11.4	NR	1.00	
			11.5–28.2	NR	1.76 (0.94–3.28)	
			≥ 28.3	NR	2.01 (1.07–3.76)	
			Trend-test *P* value: 0.03			
			Processed meat (g/day), tertiles, women:			
			≤ 11.4	NR	1.00	
			11.5–28.2	NR	2.25 (1.19–4.23)	
			≥ 28.3	NR	3.53 (1.93–6.46)	
			Trend-test *P* value: <0.0001			
		Rectum	Processed meat (g/day), tertiles, men:			
			≤ 11.4	NR	1.00	
			11.5–28.2	NR	1.47 (0.85–2.54)	
			≥28.3	NR	1.76 (1.03–3.01)	
			Trend-test *P* value: 0.03			
			Processed meat (g/day), tertiles, women:			
			≤ 11.4	NR	1.00	
			11.5–28.2	NR	2.44 (1.17–5.09)	
			≥ 28.3	NR	3.18 (1.54–6.57)	
			Trend-test *P* value: 0.001			

Table 2.2.4 Case–control studies on consumption of processed meat and cancer of the colorectum

Reference, location, enrolment	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Miller et al. (2013) Pennsylvania, USA 2007–2011	Cases: 989; incident cases, identified through the Pennsylvania State Cancer Registry Controls: 1033; identified through random digit dialling; frequency-matched to cases by age, sex, and ethnicity Exposure assessment method: questionnaire; validated, in-person FFQ with 137 items; meat-cooking module was used with the CHARRED database to estimate carcinogens; processed red meat was bacon, sausage, cold cuts, beef jerky, corned beef, hot dogs, ham, and processed meats added to mixed dishes [There were no data for processed meat including processed poultry.]	Colon and rectum	Processed red meat intake (g/1000 kcal)			Age, sex, BMI, past NSAID use, total energy, total fruits and vegetables, total poultry
			Q1 (< 2.8)	170	1.00	
			Q2 (2.8–5.5)	181	0.99 (0.73–1.34)	
			Q3 (5.6–9.4)	195	1.09 (0.81–1.49)	
			Q4 (9.5–17.6)	218	1.18 (0.87–1.61)	
			Q5 (> 17.6)	225	1.18 (0.87–1.62)	
			Trend-test *P* value: 0.223			
		Colon	Processed red meat intake (g/1000 kcal)			
			Q1 (< 2.8)	125	1.00	
			Q2 (2.8–5.5)	120	0.91 (0.65–1.28)	
			Q3 (5.6–9.4)	142	1.13 (0.81–1.57)	
			Q4 (9.5–17.6)	149	1.15 (0.82–1.61)	
			Q5 (> 17.6)	157	1.21 (0.86–1.70)	
			Trend-test *P* value: 0.157			
		Rectum	Processed red meat intake (g/1000 kcal)			
			Q1 (< 2.8)	42	1.00	
			Q2 (2.8–5.5)	59	1.28 (0.81–2.01)	
			Q3 (5.6–9.4)	53	1.12 (0.70–1.79)	
			Q4 (9.5–17.6)	68	1.35 (0.86–2.13)	
			Q5 (> 17.6)	67	1.22 (0.77–1.95)	
			Trend-test *P* value: 0.613			
		Proximal colon	Total nitrites plus nitrates (µg/1000 kcal)			
			Q1 (< 114.6)	77	1.00	
			Q2 (114.6–197.0)	75	1.05 (0.71–1.56)	
			Q3 (197.1–310.2)	86	1.25 (0.85–1.86)	
			Q4 (310.3–496.6)	76	1.06 (0.71–1.58)	
			Q5 (> 496.6)	102	1.57 (1.06–2.34)	
			Trend-test *P* value: 0.023			

Table 2.2.4 Case–control studies on consumption of processed meat and cancer of the colorectum

Reference, location, enrolment	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Rosato et al. (2013) Italy and Switzerland 1985–2009	Cases: 329; hospital-based cases with young-onset colorectal cancer (< 45 yr) Controls: 1361; hospital-based, identified from the same hospitals as cases; conditions unrelated to colorectal cancer risk factors or dietary modifications Exposure assessment method: questionnaire; validated and administered in person; processed meat was not defined	Colon and rectum: young-onset colorectal cancer	Processed meat Low Medium High Trend-test *P* value: 0.008	 69 115 145	 1.00 1.18 (0.84–1.65) 1.56 (1.11–2.20)	Age, sex, centre, study, year of interview, education, family history, alcohol, energy intake
Joshi et al. (2015) USA and Canada 1997–2002	Cases: 3350; population-based, identified through cancer registries in Ontario, Canada; Hawaii, California, Arizona, North Carolina, New Hampshire, Colorado, Minnesota, USA; cases with familial cases included Controls: 3504; cancer-free siblings of the cases (*n* = 1759), unaffected spouses of the cases (*n* = 138), and population-based controls (*n* = 1607) Exposure assessment method: questionnaire; validated, administered by mail, included 200 items, included portion size and frequency of intake, and used the CHARRED database to estimate carcinogens; considered cooking methods Processed meat was reported as total processed meat (including processed red meat and poultry)	Colon and rectum	Processed meat (g/1000 kcal per day) Q1 (0–4.43) Q2 (4.43–7.35) Q3 (7.36–10.62) Q4 (10.63–15.29) Q5 (15.29–152.04) Trend-test *P* value: 0.054 Sausages and lunchmeats (g/1000 kcal per day) Q1 (0–0.08) Q2 (0.08–0.14) Q3 (0.14–0.22) Q4 (0.22–0.32) Q5 (0.32–3.86) Trend-test *P* value: 0.187 Sausages and lunchmeats (g/1000 kcal per day); MMR-proficient Q1 (0–0.08) Q2 (0.08–0.14) Q3 (0.14–0.22) Q4 (0.22–0.32) Q5 (0.32–3.86) Trend-test *P* value: 0.029	 593 643 640 654 820 582 657 706 654 751 138 148 194 179 217 	 1.0 1.1 (0.9–1.2) 1.0 (0.9–1.2) 1.0 (0.8–1.2) 1.2 (1.0–1.4) 1.0 1.1 (0.9–1.3) 1.2 (1.0–1.4) 1.0 (0.9–1.2) 1.2 (1.0–1.4) 1.0 1.0 (0.7–1.3) 1.2 (1.0–1.6) 1.1 (0.8–1.4) 1.3 (1.0–1.7) 	Age, BMI, sex, ethnicity, saturated fat, dietary fibre, centre, vegetables, physical activity, total caloric intake

Table 2.2.4 Case–control studies on consumption of processed meat and cancer of the colorectum

Reference, location, enrolment	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Joshi et al. (2015) USA and Canada 1997–2002 (cont.)		Colon and rectum	Sausages and lunchmeats (g/1000 kcal per day); MMR-deficient			
			Q1 (0–0.08)	44	1.0	
			Q2 (0.08–0.14)	58	1.3 (0.8–1.9)	
			Q3 (0.14–0.22)	56	1.2 (0.8–1.9)	
			Q4 (0.22–0.32)	40	0.9 (0.6–1.4)	
			Q5 (0.32–3.86)	45	1.0 (0.6–1.6)	
			Trend-test *P* value: 0.408			
			Test of heterogeneity, MMR-proficient vs MMR-deficient ($P = 0.069$)			
			Pan-fried sausage (g/1000 kcal per day)			
			Q1 (0–0)	1271	1.0	
			Q2 (0.01–0.02)	643	1.1 (1.0–1.3)	
			Q3 (0.020–0.04)	619	1.1 (0.9–1.2)	
			Q4 (0.04–1.32)	781	1.2 (1.0–1.3)	
			Trend-test *P* value: 0.041			
		Colon	Pan-fried sausage (g/1000 kcal per day)			
			Q1 (0–0)	789	1.0	
			Q2 (0.01–0.02)	371	1.1 (0.9–1.3)	
			Q3 (0.20–0.04)	356	1.0 (0.8–1.2)	
			Q4 (0.04–1.32)	456	1.1 (0.9–1.3)	
			Trend-test *P* value: 0.371			
		Rectum	Pan-fried sausage (g/1000 kcal per day)			
			Q1 (0–0)	302	1.0	
			Q2 (0.01–0.02)	204	1.3 (1.1–1.6)	
			Q3 (0.20–0.04)	177	1.2 (1.0–1.5)	
			Q4 (0.04–1.32)	213	1.4 (1.1–1.7)	
			Trend-test *P* value: 0.004			
			Test of heterogeneity, colon vs rectum ($P = 0.053$)			

Table 2.2.4 Case–control studies on consumption of processed meat and cancer of the colorectum

Reference, location, enrolment	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Joshi et al. (2015) USA and Canada 1997–2002 (cont.)		Colon and rectum	Pan-fried spam or ham (g/1000 kcal per day)			
			Q1 (0–0)	2097	1.0	
			Q2 (0.01–0.02)	395	1.0 (0.9–1.2)	
			Q3 (0.20–0.04)	403	1.1 (0.9–1.3)	
			Q4 (0.04–0.99)	425	1.2 (1.0–1.4)	
			Trend-test *P* value: 0.048			
			Pan-fried spam or ham (g/1000 kcal per day); MMR-proficient			
			Q1 (0–0)	524	1.0	
			Q2 (0.01–0.02)	106	1.3 (1.0–1.7)	
			Q3 (0.20–0.04)	110	1.4 (1.1–1.8)	
			Q4 (0.04–0.99)	128	1.6 (1.2–2.0)	
			Trend-test *P* value: <0.001			
			Pan-fried spam or ham (g/1000 kcal per day); MMR-deficient			
			Q1 (0–0)	173	1.0	
			Q2 (0.01–0.02)	18	0.6 (0.4–1.0)	
			Q3 (0.20–0.04)	30	1.1 (0.7–1.6)	
			Q4 (0.04–0.99)	19	0.8 (0.5–1.3)	
			Trend-test *P* value: 0.461			
			Test of heterogeneity, MMR-proficient vs MMR-deficient ($P = 0.026$)			

Table 2.2.4 Case–control studies on consumption of processed meat and cancer of the colorectum

Reference, location, enrolment	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Joshi et al. (2015) USA and Canada 1997–2002 (cont.)		Colon and rectum	Pan-fried bacon (g/1000 kcal per day)			
			Q1 (0–0)	1094	1.0	
			Q2 (0.01–0.03)	664	1.0 (0.8–1.1)	
			Q3 (0.03–0.05)	720	1.0 (0.9–1.2)	
			Q4 (0.05–1.43)	841	1.0 (0.9–1.2)	
			Trend-test *P* value: 0.61			
			Grilled sausage (g/1000 kcal per day)			
			Q1 (0–0)	2222	1.0	
			Q2 (0.01–0.02)	410	1.1 (0.9–1.3)	
			Q3 (0.02–0.03)	327	0.9 (0.8–1.1)	
			Q4 (0.03–0.99)	357	1.0 (0.9–1.2)	
			Trend-test *P* value: 0.903			

BaP, benzo[*a*]pyrene; BMI, body mass index; CHARRED, Computerized Heterocyclic Amines Resource for Research in Epidemiology of Disease; CI, confidence interval; FFQ, food frequency questionnaire; GI, gastrointestinal; h, hour; HAA, heterocyclic aromatic amine; ICD, International Classification of Diseases; MMR, mismatch repair; mo, month; NR, not reported; NSAID, nonsteroidal anti-inflammatory drug; OR, odds ratio; wk, week; yr, year

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2.3 Cancer of the stomach

The Working Group focused their review on studies that clearly defined red meat or processed meat (see Section 1 and Section 2.1). Studies were excluded if: (1) risk estimates were presented for total meat (red and processed meat combined) intake; (2) the type of meat was not defined or included white meat; (3) fewer than 100 cases were reported, due to the limited statistical power, as a large database of high-quality studies were available; (4) a more recent report from the same study was available; (5) risk estimates, adjusted for important confounders, were not available (crude estimates were not considered to be informative); (6) dietary patterns were the focus; and (7) outcomes were assessed using mortality data.

Several cohort and case–control studies, conducted in areas all over the world, have reported on the association between red and processed meat intake and cancer of the stomach. Important confounders for the assessment of this association are age, tobacco smoking, socioeconomic status (or education), and energy intake. Infection with *Helicobacter pylori* is a risk factor for cancer of the stomach, although its role in the association between intake of red or processed meat and cancer of the stomach is unclear. Salt intake may also be a confounder, as there is evidence that it increases the risk of cancer of the stomach, and it is also present in preserved or salted (processed) meat; however, it is difficult to distinguish the effect of salt from that of preserved meat.

2.3.1 Cohort studies

(a) Red meat

See Table 2.3.1 (web only; available at: http://publications.iarc.fr/564)

Of the publications on cohort studies that reported on the association between red meat and gastric cancer in the USA, Europe, Japan, and China, positive associations were reported in two studies: the EPIC cohort, which followed up 521 457 participants (González et al., 2006), and a case–control study of 226 gastric non-cardia cancer (GNCA) cases and 451 controls nested within the Shanghai Men's Health Study (SMHS) cohort (Epplein et al., 2014). [The Working Group noted that the strengths of the EPIC study (González et al., 2006) were its large size and analysis by subsite, histological type, and *H. pylori* infection. For the study nested within the Shanghai cohort (Epplein et al., 2014), the Working Group noted that this population had over 90% prevalence of CagA-positive *H. pylori* infection. In addition, socioeconomic status (or education) was not included as a covariate, and the items included in red meat were not detailed.]

Several other studies reported no association, or relative risks greater than one, but with wide confidence intervals that included the null value, between red meat consumption and gastric cancer. These studies included a cohort of 13 250 people older than 15 years from the Fukuoka Prefecture in Japan (Ngoan et al., 2002); a population-based cohort of 61 433 Swedish women (Larsson et al., 2006); the Japan Collaborative Cohort Study for Evaluation of Cancer (JACC Study), which included 42 513 men and 57 777 women (Iso et al., 2007); the NIH-AARP study cohort of 494 979 individuals Cross et al. (2011); and a cohort of 120 852 men and women in the NLCS (Keszei et al., 2012). [The Working Group noted that processed meat was included in the definition of red meat in the NIH-AARP study.]

(b) Processed meat

See Table 2.3.2

Studies investigating the association between consumption of total processed meat, specific processed meat are presented below. Of the reviewed papers, we excluded papers reporting fewer than 100 cases (e.g. Kneller et al., 1991; Knekt et al., 1999; Khan et al., 2004). Studies focusing on dietary pattern (e.g. Pham et al., 2010), studies

from mortality data (e.g. McCullough et al., 2001, Ngoan et al.., 2002; Tokui et al., 2005; Iso et al., 2007), studies that were overlapping or updated (Cross et al., 2007) were excluded. Finally, seven studies were included.

Among 7990 American men of Japanese ancestry in a cohort study in which 150 cases of gastric cancer were observed, Nomura et al. (1990) reported an age-adjusted relative risk of 1.3 (95% CI, 0.9–2.0) for the highest versus the lowest frequency of intake of ham and sausage. [The Working Group noted that only age was adjusted. Smoking status was related to gastric cancer, but was not adjusted for. No subsite analysis was conducted.]

In a cohort of 11 907 randomly selected Japanese residents of Hawaii, USA, with an average follow-up period of 14.8 years, 108 observed cases of gastric cancer (44 women, 64 men) were identified, and no association was observed between processed meat consumption and incidence of gastric cancer (Galanis et al., 1998). The adjusted odds ratios for the highest frequency compared with the lowest frequency of consumption were 1.0 (95% CI, 0.5–1.9; 20 exposed cases) and 1.2 (95% CI, 0.6–2.4; 15 exposed cases) for men and women, respectively. [The Working Group noted that the case number was small, especially for women. An FFQ was used with only 13 items. No subsite analysis was conducted.]

González et al. (2006) examined the association between processed meat consumption and risk of gastric cancer in the EPIC study. The adjusted hazard ratio for the association with processed meat intake (highest vs lowest quintile) was 1.62 (95% CI, 1.08–2.41; P_{trend} = 0.02), which was more apparent in non-cardia cancer (HR, 1.92; 95% CI, 1.11–3.33; P_{trend} = 0.01) than in cardia cancer (HR, 1.14; 95% CI, 0.52–2.49; P_{trend} = 0.91). No difference was seen by histological type. When *H. pylori* infection was considered in the case–control data set nested in the present study, *H. pylori* antibody status did not appear to modify the association. [The Working Group noted that it was defined that white meat was not included. The population size was large, and detailed information on subsite, histological type, and *H. pylori* was available.]

In a population-based cohort of 61 433 Swedish women, Larsson et al. (2006) found a positive association between long-term processed meat consumption (using two surveys 10 years apart) and gastric cancer risk. During 18 years of follow-up, 156 incident cases of gastric cancer were diagnosed. The multivariate-adjusted hazard ratio for the highest versus the lowest serving per week of total processed meat was 1.66 (95% CI, 1.13–2.45; 67 exposed cases). [The Working Group noted that using a survey from two time points enabled the effect of long-term exposure to be seen. The number of cases was small. No subsite analysis was conducted.]

In the NIH-American Association of Retired Persons (NIH-AARP Diet and Health Study cohort of 494 979 individuals, aged 50–71 years, Cross et al. (2011) investigated intake of processed meat and meat cooking by-products with accrued 454 gastric cardia cancers (GCAs) and 501 GNCAs. After adjusting for important confounders, no association was observed between processed meat consumption and GCA and GNCA. For the highest versus the lowest quintile, the hazard ratios were 0.82 (95% CI, 0.59–1.14; P_{trend} = 0.285) and 1.09 (95% CI, 0.81–1.48; P_{trend} = 0.329), respectively. Nitrate and nitrite were not associated with gastric cancer. [The Working Group noted that this was a large study with a large number of cases, both for GCA and GNCA.]

In the Netherlands Cohort Study (NLCS), Keszei et al. (2012) reported on the association between intake of processed meat and gastric cancer risk in both men and women, after adjusting for important confounders. The case–cohort study consisted of 120 852 men and women, and after 16.3 years of follow-up, 163 GCAs and 489 GNCAs were observed. The

definition of processed meat included all meat items that had undergone some form of preservation, including cold cuts, croquettes, and all types of sausages. For the highest compared with the lowest category, the relative risks of intake of processed meat for GCA and GNCA were 1.49 (95% CI, 0.81–2.75; P_{trend} = 0.34; 32 exposed cases) and 1.19 (95% CI, 0.78–1.79; P_{trend} = 0.36; 77 exposed cases), respectively, in men. [The Working Group noted that the number of cases for gastric cancer of the cardia was small. A detailed FFQ with 150 items was used.]

Epplein et al. (2014) investigated the interaction between preserved meat, comprising intake of smoked meat, salted meat, and "Chinese" sausage, and *H. pylori* infection among 226 GNCA cases and 451 controls nested within the Shanghai Men's Health Study (SMHS prospective cohort. Overall, after adjusting for important confounders, including age, education, smoking, and total energy, preserved meat intake was not associated with gastric cancer. For the highest compared with the lowest category of intake, the relative risk of preserved meat was 1.01 (95% CI, 0.66–1.55; P_{trend} = 0.99). An effect modification by *H. pylori* was not apparent ($P_{interaction}$ = 0.09). [The Working Group noted that information on *H. pylori* infection was available. This was a study in a population with over 90% prevalence of CagA-positive *H. pylori* infection. Socioeconomic status or education was not adjusted for. Processed meat intake was low in the study population.]

2.3.2 Case–control studies

(a) Red meat

See Table 2.3.3 (web only; available at: http://publications.iarc.fr/564)

The Working Group reviewed 20 reports from case–control studies of gastric cancer reporting on the association with consumption of red meat (La Vecchia et al., 1987; Kono et al., 1988; Ward et al., 1997; De Stefani et al., 1998; Ji et al., 1998; Tavani et al., 2000; Palli et al., 2001; Takezaki et al., 2001; Chen et al., 2002; Huang et al., 2004; Lissowska et al., 2004; Wu et al., 2007; Hu et al., 2008; Navarro Silvera et al., 2008; Pourfarzi et al., 2009; Gao et al., 2011; Wang et al., 2012, 2014; Ward et al., 2012; Zamani et al., 2013). Although odds ratios greater than one were reported in all but three studies (Kono et al., 1988; Ji et al., 1998; Huang et al., 2004), the studies had several methodological limitations, including low precision power resulting from a small number of cases, use of an FFQ that may not have been validated, lack of adjustment for important confounders (e.g. smoking, total energy intake), inclusion of processed meat in the definition of red meat, and issues with the selection of hospital-based controls. Few studies reported analyses by subsite. The Working Group put more emphasis on two well-designed population-based case–control studies from the USA (Wu et al., 2007) and Canada (Hu et al., 2008) that used validated FFQs and adjusted for important confounders.

(b) Processed meat

The Working Group reviewed several case–control studies of gastric cancer that reported on the association with consumption of processed meat. Few studies were hospital-based (Lee et al., 1990; Boeing et al., 1991b; De Stefani et al., 1998, 2012; Huang et al., 2004), and the majority were population-based (Risch et al., 1985; La Vecchia et al., 1987; Sanchez-Diez et al., 1992; Ward & López-Carrillo, 1999; Palli et al., 2001; Takezaki et al., 2001; Chen et al., 2002; Nomura et al., 2003; Lissowska et al., 2004; Wu et al., 2007; Navarro Silvera et al., 2008; Pourfarzi et al., 2009; Hu et al., 2011; Ward et al., 2012).

(i) Hospital-based case–control studies

See Table 2.3.4

Several hospital-based case–control studies of gastric cancer were conducted in Taipei, Taiwan, China (Lee et al., 1990), Germany (Boeing et al., 1991a, b), Uruguay (De Stefani et al., 1998, 2012), and Japan (Huang et al., 2004). All but two

studies (Huang et al., 2004; De Stefani et al., 1998) reported increased risks of gastric cancer associated with processed meat consumption in multivariable models. The possibility of selection bias (due to the selection of hospital-based controls that may have been admitted for conditions leading to modifications in diet), recall bias, and confounding (due to inadequate adjustment for potential confounding variables) could not be ruled out.

(ii) Population-based case–control studies

See Table 2.3.5

Several population-based case–control studies of gastric cancer that reported on processed meat consumption were identified from Canada (Risch et al., 1985; Hu et al., 2011), Italy (La Vecchia et al., 1987; Palli et al., 2001), Poland (Boeing et al., 1991a; Lissowska et al., 2004), Spain (Sanchez-Diez et al., 1992), Mexico (Ward & López-Carrillo, 1999), China (Takezaki et al., 2001), the Islamic Republic of Iran (Pourfarzi et al., 2009), and the USA, specifically Nebraska (Chen et al., 2002; Ward et al., 1997, 2012), Hawaii (Nomura et al., 2003), Los Angeles (Wu et al., 2007), Connecticut, New Jersey, and western Washington state (Navarro Silvera et al., 2008).

Nearly all the studies reported odds ratios above one, although chance, bias, and confounding could not be ruled out as possible explanations for the observed excesses due to study limitations, including inadequate adjustment for potential confounders (e.g. tobacco smoking, total energy intake), recall bias, and information bias (e.g. large amount of information obtained from proxy respondents).

However, no association between processed meat and gastric cancer was reported in a population-based case–control study from 1988 to 1994 in Nebraska, USA (Ward et al., 2012): the multivariate odds ratio for the highest versus the lowest quartile of processed meat consumption was 0.97 (95% CI, 0.51–1.85; P_{trend} = 0.87; 46 exposed cases). Although, in a previous study, Ward et al. (1997) reported a positive association between processed meat and gastric cancer based on servings per day (P_{trend} = 0.06). The 2012 publication conducted a more accurate analysis, estimating grams per day and considering adequate confounding factors. [The Working Group noted that the response rate was high. No subsite analysis was conducted.]

2.3.3 Meta-analyses

(a) Red meat

Among the meta-analyses published on gastric cancer and meat consumption, Song et al. (2014) was the most recent and comprehensive, including 18 studies (4 cohort studies, 14 case–control studies) and 1 228 327 subjects, published between 1997 and 2013. Two case–control studies, Wang et al. (2012) and Navarro Silvera et al. (2008) were not included in the meta-analysis. [Therefore, the Working Group did not place great weight on the meta-analysis.] In the meta-analysis, high–red meat intake was found to be associated with an increased risk of gastric cancer. The summary relative risk of gastric cancer for the highest compared with the lowest categories was 1.37 (95% CI, 1.18–1.59; $P_{heterogeneity}$ < 0.001; I^2 = 67.6%). A significant association was also observed with population-based case–control studies (RR, 1.58; 95% CI, 1.22–2.06; $P_{heterogeneity}$ < 0.001; I^2 = 73.0%) and hospital-based case–control studies (RR, 1.63; 95% CI, 1.38–1.92; $P_{heterogeneity}$ = 0.284; I^2 = 19.1%), but not with cohort studies (RR, 1.00; 95% CI, 0.83–1.20; $P_{heterogeneity}$ = 0.158; I^2 = 33.9%). A significant association was also shown in the subgroup analysis by geographical area (Asia, Europe), publication year (≥ 2000), sample size (< 1000, ≥ 1000), and study quality score. The dose–response analysis revealed that gastric cancer was associated with a 17% increased risk per 100 g/day increment of red meat intake (RR, 1.17; 95% CI, 1.05–1.32). [The Working Group noted that the dose–response

analysis did not distinguish between cohort and case–control studies.]

(b) Processed meat

The most recent and comprehensive meta-analysis on the association between processed meat and gastric cancer was reported by Larsson et al. (2006). The meta-analysis included seven prospective cohort studies and 14 case–control studies. The summary relative risks of gastric cancer for the highest compared with the lowest categories of red meat intake were 1.24 (95% CI, 0.98–1.56; $P_{\text{heterogeneity}} = 0.04$) for cohort studies and 1.63 (95% CI, 1.31–2.01; $P_{\text{heterogeneity}} = 0.06$) for case–control studies. In an exposure–response analysis, the meta-relative risks for gastric cancer were 1.15 (95% CI, 1.04–1.27) for cohort studies and 1.38 (95% CI, 1.19–1.60) for case–control studies per 30 g/day increment of processed meat intake. An elevated risk was also observed for the highest compared with the lowest categories of intake of specific items of processed meat. For bacon, the relative risks were 1.38 (1.12–1.71) for cohort studies and 1.37 (1.06–1.78) for case–control studies, and for sausage, the relative risks were 1.26 (0.92–1.72) for cohort studies and 1.49 (1.09–2.03) for case–control studies. [The Working Group noted that one case–control study in Paraguay (Rolón et al., 1995) was not included. Specific items of processed meat such as ham, bacon, or sausage were analysed separately from processed meat.]

Table 2.3.2 Cohort studies on consumption of processed meat and cancer of the stomach

Reference, location, enrolment/follow-up period, study design	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Nomura et al. (1990) Hawaii, USA 1965–October 1986 Cohort study	7990; men of Japanese ancestry, born between 1919–1990, residing on the Hawaiian island of Oahu Exposure assessment method: questionnaire; FFQ for food and 24-h dietary recall for nutrients	Stomach	Risk by frequency for ham, bacon, and sausage			Age
			≤ 1 time/wk	71	1.0	
			2–4 times/wk	43	1.0 (0.7–1.4)	
			≥ 5 times/wk	36	1.3 (0.9–2.0)	
Galanis et al. (1998) Hawaii, USA (Japanese residents) 1975–1994 Cohort study	11 907 (5610 men, 6297 women); randomly selected Japanese residents of Hawaii Exposure assessment method: questionnaire; FFQ	Stomach	Risk by frequency for processed meats			Age, years of education, Japanese place of birth, sex
			Men and women:			
			None	34	1.0	
			1–2 times/wk	39	0.9 (0.6–1.4)	
			≥ 3 times/wk	35	1.0 (0.6–1.7)	
			Trend-test *P* value: 0.37			
		Stomach	Risk by frequency for processed meats			Age, years of education, Japanese place of birth, cigarette smoking, alcohol intake status
			Men:			
			None	18	1.0	
			1–2 times/wk	26	1.1 (0.6–2.0)	
			≥ 3 times/wk	20	1.0 (0.5–1.9)	
			Trend-test *P* value: 0.58			
		Stomach	Risk by frequency for processed meats			Age, years of education, Japanese place of birth
			Women:			
			None	16	1.0	
			1–2 times/wk	13	0.7 (0.3–1.4)	
			≥ 3 times/wk	15	1.2 (0.6–2.4)	
			Trend-test *P* value: 0.77			

Table 2.3.2 Cohort studies on consumption of processed meat and cancer of the stomach

Reference, location, enrolment/follow-up period, study design	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
González et al. (2006) Ten European countries: Denmark (Aarhus, Copenhagen), France, Germany (Heidelberg, Potsdam), Greece, Italy (Florence, Turin, Varese, Naples, Ragusa), the Netherlands (Bilthoven, Utrecht), Norway, Spain (Granada, Murcia, Asturias, Navarre, San Sebastián), Sweden (Malmö, Umeå), and the United Kingdom (Norfolk, Oxford) 1992–1999/2002 (depending on the study centre) Cohort study	521 457; aged 35–70 yr, usually from the general population Exposure assessment method: questionnaire; FFQ	Stomach	Processed meat (quartiles)			Centre and age at EPIC study entry, and adjusted by sex, height, weight, education level, tobacco smoking, cigarette smoking intensity, work and leisure physical activity, alcohol intake, energy intake, vegetable intake, citrus fruit intake, and non-citrus fruit intake; red meat, poultry, and processed meat intakes were mutually adjusted
			Q1	NR	1.00	
			Q2	NR	1.10 (0.76–1.58)	
			Q3	NR	1.16 (0.79–1.69)	
			Q4	NR	1.62 (1.08–2.41)	
			Continuous, observed	NR	1.18 (0.97–1.43)	
			Continuous, calibrated	NR	1.64 (1.07–2.51)	
			Trend-test *P* value: 0.02			
		Stomach/cardia adenocarcinoma	Processed meat(quartiles)			
			Q1	NR	1.00	
			Q2	NR	1.19 (0.61–2.34)	
			Q3	NR	1.04 (0.51–2.12)	
			Q4	NR	1.14 (0.52–2.49)	
			Continuous, observed	NR	0.89 (0.59–1.34)	
			Continuous, calibrated	NR	0.76 (0.29–1.96)	
			Trend-test *P* value: 0.91			
		Stomach/ non-cardia adenocarcinoma	Processed meat (quartiles)			
			Q1	NR	1.00	
			Q2	NR	1.02 (0.60–1.71)	
			Q3	NR	1.02 (0.59–1.77)	
			Q4	NR	1.92 (1.11–3.33)	
			Continuous, observed	NR	1.36 (1.06–1.74)	
			Continuous, calibrated	NR	2.45 (1.43–4.21)	
			Trend-test *P* value: 0.01			

Table 2.3.2 Cohort studies on consumption of processed meat and cancer of the stomach

Reference, location, enrolment/follow-up period, study design	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
González et al. (2006) (cont.)		Stomach/ adenocarcinoma	Processed meat (nested case–control study)			
			H. pylori antibody status: Negative	40	0.45 (0.05–4.01)	
			Positive	201	2.00 (1.06–3.79)	
			Trend-test *P* value: 0.48			
		Stomach/cardia adenocarcinoma	Processed meat (nested case–control study)			
			H. pylori antibody status: Negative	22	0.86 (0.03–27.0)	
			Positive	47	1.62 (0.47–5.55)	
			Trend-test *P* value: 0.42			
		Stomach/ non-cardia adenocarcinoma	Processed meat (nested case–control study)			
			H. pylori antibody status: Negative	12	0.002 (0.001–62.6)	
			Positive	113	2.67 (1.20–5.93)	
			Trend-test *P* value: 0.25			
Larsson et al. (2006) Uppsala and Västmanland counties, central Sweden Recruitment, 1987–1990; end of follow-up, 2004 Cohort study	61 433; women born in 1914 and 1948 Exposure assessment method: questionnaire; FFQ, age-specific portion sizes (mean of weighed and recorded food data of 213 random samples unpublished)	Stomach	Processed meat (servings/wk)			Age, education, BMI, energy, alcohol, fruits, vegetables
			< 1.5	51	1.00	
			1.5–2.9	38	1.46 (0.95–2.25)	
			≥ 3.0	67	1.66 (1.13–2.45)	
			Trend-test *P* value: 0.01			
		Stomach	Bacon or side pork (servings/wk)			
			0	52	1.00	
			0.1–0.4	66	1.27 (0.88–1.85)	
			≥ 0.5	38	1.55 (1.00–2.41)	
			Trend-test *P* value: 0.05			
		Stomach	Sausage or hot dogs (servings/wk)			
			< 0.4	24	1.00	
			0.4–0.9	55	1.44 (0.89–2.35)	
			≥ 1.0	77	1.50 (0.93–2.41)	
			Trend-test *P* value: 0.13			
		Stomach	Ham or salami (servings/wk)			
			< 0.4	45	1.00	
			0.4–1.4	46	0.97 (0.65–1.51)	
			≥ 1.5	65	1.48 (0.99–2.22)	
			Trend-test *P* value: 0.03			

Table 2.3.2 Cohort studies on consumption of processed meat and cancer of the stomach

Reference, location, enrolment/follow-up period, study design	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Cross et al. (2011) California, Florida, Louisiana, New Jersey, North Carolina, Pennsylvania, and two metropolitan areas (Atlanta, Georgia, and Detroit, Michigan), USA End of 2006 Cohort study	494 979; men and women aged 50–71 yr; enrolled in 1995–1996. The following individuals were excluded: duplicates and participants who died or moved before the baseline questionnaire was received or withdrew from the study, who did not return the baseline questionnaire, whose baseline questionnaire was filled in by someone else on their behalf, who had prevalent cancer according to the cancer registry or self-report, and who had extreme daily total energy intake Exposure assessment method: questionnaire; dietary intake of various food items was assessed through a 124-item FFQ (usual frequency of consumption and portion size information of foods over the previous 12 mo). Portion sizes and daily nutrient intakes were calculated from the 1994–1996 USA Department of Agriculture's Continuing Survey of Food Intakes by Individuals. "Processed meat" was bacon, red meat sausage, poultry sausage, luncheon meats (red and white meat), cold cuts (red and white meat), ham, regular hot dogs, and low-fat hot dogs made from poultry; meat added to complex food mixtures, such as pizza, chilli, lasagne, and stew, contributed to the relevant meat type	Stomach/cardia adenocarcinoma	Processed meat (quintile median, µg/1000 kcal)			Age, sex, BMI, education, ethnicity, tobacco smoking, alcohol drinking, usual physical activity at work, vigorous physical activity, daily intake of fruits, daily intake of vegetables, daily intake of saturated fat, daily intake of calories
			Q1 (1.7)	68	1.00	
			Q2 (4.5)	78	0.89 (0.64–1.24)	
			Q3 (7.8)	93	0.91 (0.66–1.26)	
			Q4 (12.6)	108	0.92 (0.67–1.28)	
			Q5 (23.2)	107	0.82 (0.59–1.14)	
			All processed meats, continuous (per 10 g/1000 kcal)	NR	1.00 (0.92–1.09)	
			Trend-test *P* value: 0.285			
		Stomach/ non-cardia adenocarcinoma	Processed meat (quintile median, µg/1000 kcal)			
			Q1 (1.7)	93	1.00	
			Q2 (4.5)	81	0.87 (0.64–1.18)	
			Q3 (7.8)	105	1.10 (0.82–1.47)	
			Q4 (12.6)	105	1.04 (0.77–1.41)	
			Q5 (23.2)	117	1.09 (0.81–1.48)	
			All processed meats, continuous (per 10 g/1000 kcal)	NR	1.02 (0.94–1.11)	
			Trend-test *P* value: 0.329			

Table 2.3.2 Cohort studies on consumption of processed meat and cancer of the stomach

Reference, location, enrolment/follow-up period, study design	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Cross et al. (2011) California, Florida, Louisiana, New Jersey, North Carolina, Pennsylvania, and two metropolitan areas (Atlanta, Georgia, and Detroit, Michigan), USA End of 2006 Cohort study	303 156; men and women aged 5–71 yr; enrolled in 1995–1996. The following individuals were excluded: duplicates and participants who died or moved before the risk factor questionnaire was received or withdrew from the study, who did not return the risk factor questionnaire, whose risk factor questionnaire was filled in by someone else on their behalf, who had prevalent cancer according to the cancer registry or self-report, and who had extreme daily total energy intake Exposure assessment method: questionnaire; dietary intake of various food items was assessed through a 124-item FFQ (usual frequency of consumption and portion size information of foods over the previous 12 mo). Portion sizes and daily nutrient intakes were calculated from the 1994-1996 USA Department of Agriculture's Continuing Survey of Food Intakes by Individuals. A risk factor questionnaire sent 6 mo later elicited detailed information on meat intake and cooking preferences. Nitrate and nitrite intake from processed meat was estimated using a database of measured values from 10 types of processed meats, which represented 90% of processed meats consumed in the USA	Stomach/ stomach cardia adenocarcinoma	Nitrate (quintile median, µg/1000 kcal)			Age, sex, BMI, education, ethnicity, tobacco smoking, alcohol drinking, usual physical activity at work, vigorous physical activity, daily intake of fruits, daily intake of vegetables, daily intake of saturated fat, daily intake of calories
			Q1 (24.9)	39	1.00	
			Q2 (66.9)	57	1.17 (0.77–1.77)	
			Q3 (112.7)	36	0.64 (0.40–1.02)	
			Q4 (174.5	61	0.94 (0.61–1.45)	
			Q5 (298.0)	62	0.81 (0.52–1.25)	
			All nitrates, continuous (per 100 µg/1000 kcal)	NR	0.99 (0.90–1.09)	
			Trend-test *P* value: 0.259			
		Stomach/cardia adenocarcinoma	Nitrite (quintile median, µg/1000 kcal)			
			Q1 (12.1)	44	1.00	
			Q2 (34.6)	40	0.72 (0.47–1.11)	
			Q3 (61.4)	55	0.88 (0.58–1.32)	
			Q4 (102.9)	61	0.87 (0.58–1.31)	
			Q5 (199.2)	55	0.71 (0.47–1.08)	
			All nitrites, continuous (per 100 µg/1000 kcal)	NR	0.89 (0.77–1.03)	
			Trend-test *P* value: 0.25			
		Stomach/ non-cardia adenocarcinoma	Nitrate (quintile median, µg/1000 kcal)			
			Q1 (24.2)	50	1.00	
			Q2 (66.9)	48	0.90 (0.60–1.35)	
			Q3 (112.7)	50	0.89 (0.59–1.33)	
			Q4 (174.5)	56	0.91 (0.61–1.37)	
			Q5 (298.0)	73	1.04 (0.69–1.55)	
			All nitrates, continuous (per 100 µg/1000 kcal)	NR	1.01 (0.92–1.10)	
			Trend-test *P* value: 0.578			

Table 2.3.2 Cohort studies on consumption of processed meat and cancer of the stomach

Reference, location, enrolment/follow-up period, study design	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Cross et al. (2011) (cont.)		Stomach/ non-cardia adenocarcinoma	Nitrite (quintile median, µg/1000 kcal)			
			Q1 (12.1)	54	1.00	
			Q2 (34.6)	44	0.77 (0.51–1.15)	
			Q3 (61.4)	48	0.79 (0.53–1.18)	
			Q4 (102.9)	67	1.04 (0.71–1.52)	
			Q5 (199.2)	64	0.93 (0.63–1.37)	
			All nitrite, continuous (per 100 µg/1000 kcal)	NR	1.02 (0.91–1.15)	
			Trend-test *P* value: 0.615			
Keszei et al. (2012) The Netherlands 1986–2002 Cohort study	120 852 individuals were recruited, and finally, 3923 sub-cohort members were used in the analysis (case–cohort design); the sample was selected from 204 municipal population registries throughout the Netherlands by sex-stratified random sampling Exposure assessment method: questionnaire; FFQ	Stomach/cardia adenocarcinoma	Processed meat intake			Age, smoking status, years of cigarette smoking, number of cigarettes smoked per day, total energy intake, BMI, alcohol intake, vegetable intake), fruit intake, levels of education, non-occupational physical activity
			Men:			
			Q1	23	1.00	
			Q2	34	1.51 (0.86–2.64)	
			Q3	21	0.89 (0.47–1.68)	
			Q4	29	1.26 (0.71–2.24)	
			Q5	32	1.49 (0.81–2.75)	
			Continuous (50 g/day increment)	139	1.15 (0.71–1.86)	
			Trend-test *P* value: 0.34			
		Stomach/ non-cardia adenocarcinoma	Processed meat intake (quintiles)			
			Men:			
			Q1	62	1.00	
			Q2	65	1.05 (0.71–1.56)	
			Q3	59	0.96 (0.64–1.44)	
			Q4	66	1.09 (0.73–1.63)	
			Q5	77	1.19 (0.78–1.79)	
			Trend-test *P* value: 0.36			

Table 2.3.2 Cohort studies on consumption of processed meat and cancer of the stomach

Reference, location, enrolment/follow-up period, study design	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Keszei et al. (2012) The Netherlands 1986–2002 Cohort study (cont.)		Stomach/cardia adenocarcinoma	Processed meat intake			
			Women:			
			T1	7	1.00	
			T2	8	1.19 (0.41–3.44)	
			T3	9	1.12 (0.36–3.47)	
			Continuous (50 g/day increment)	24	0.70 (0.14–3.47)	
			Trend-test *P* value: 0.89			
		Stomach/ non-cardia adenocarcinoma	Processed meat intake (tertiles)			
			Women:			
			T1	51	1.00	
			T2	56	1.21 (0.81–1.81)	
			T3	53	1.11 (0.73–1.70)	
			Trend-test *P* value: 0.7			
Epplein et al. (2014) Shanghai, China Recruitment, 2002–2006; follow-up, 2009 Nested case–control study	Cases: 226 incident cases; permanent residents of urban Shanghai Controls: 451; permanent residents of urban Shanghai Exposure assessment method: questionnaire; validated FFQ; frequency of intake and not amount; preserved meat was smoked meat, salted meat, and Chinese sausage	Stomach/ non-cardia adenocarcinoma	Processed meat intake (times/mo), tertiles			Age, smoking, history of gastritis, regular aspirin use, total energy intake, high-risk *H. pylori* infection
			T1 (≤ 0.20)	71	1.00	
			T2 (0.21–1.42)	81	1.13 (0.74–1.72)	
			T3 (1.42)	74	1.01 (0.66–1.55)	
			Trend-test *P* value: 0.99			
		Stomach/ non-cardia adenocarcinoma	Processed meat intake (times/mo) in low risk residents (0–4 seropositive results to 6 *H. pylori* proteins), tertiles			
			T1	37	1.00	
			T2	29	0.96 (0.53–1.72)	
			T3	20	0.79 (0.41–1.51)	
			Trend-test *P* value: 0.49			
		Stomach/ non-cardia adenocarcinoma	Processed meat intake (times/mo) in high risk residents (seropositive results to 6 *H. pylori* proteins), tertiles			
			T1	34	1.00	
			T2	52	1.42 (0.80–2.52)	
			T3	54	1.34 (0.76–2.36)	
			Trend-test *P* value: 0.09			

BMI, body mass index; CI, confidence interval; EPIC, European Prospective Investigation into Cancer and Nutrition; FFQ, food frequency questionnaire; h, hour; ICD, International Classification of Diseases; mo, month; NR, not reported; wk, week; yr, year

Table 2.3.4 Case–control studies (hospital-based) on consumption of processed meat and cancer of the stomach

Reference, location, enrolment/follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Lee et al. (1990) Taipei City, Taiwan, China NA	Cases: 210; serial patients with stomach cancer from four major teaching hospitals in Taipei City Controls: 810; hospital controls, group-matched to cases by hospital, age, and sex, were recruited from among ophthalmic patients in study hospitals Exposure assessment method: questionnaire	Stomach	Salted meat consumption, before age 20			
			< 1 meal/mo	129	1.00	
			2–5 meals/mo	50	1.24	
			≥ 6 meals/mo	31	2.90	
			Salted meat consumption, between ages 20 and 39			
			< 1 meal/mo	137	1.00	
			2–5 meals/mo	55	1.26	
			≥ 6 meals/mo	18	3.26	
			Cured meat consumption, before age 20			
			< 1 meal/mo	31	1.00	
			2–5 meals/mo	156	1.61	
			≥ 6 meals/mo	23	1.72	
			Cured meat consumption, between ages 20 and 39			
			< 1 meal/mo	23	1.00	
			2–5 meals/mo	146	2.04	
			≥ 6 meals/mo	41	2.31	
			Salted meat consumption (frequency/mo)			Adjusted for only risk factors significantly associated with stomach cancer in univariate analysis
			< 1 meal/mo	266	1.00	
			2–5 meals/mo	105	1.48	
			≥ 6 meals/mo	49	3.18	
Boeing et al. (1991b) Germany 1985–1988	Cases: 143; the local coordinators identified all patients younger than 80 yr with histologically confirmed incident stomach cancer admitted to hospitals, and organized interviews in the hospitals, which were conducted by trained interviewers	Stomach	Processed meat, tertile 1 (lowest)	NR	1.00	Adjusted for age, sex, hospital, raw vegetables, citrus fruit, cheese, wholemeal bread
			Processed meat, tertile 2	NR	1.37 (0.82–2.31)	
			Processed meat, tertile 3 (highest)	NR	2.21 (1.32–3.71)	
			χ^2 for trend = 9.46	NR	–	

Table 2.3.4 Case–control studies (hospital-based) on consumption of processed meat and cancer of the stomach

Reference, location, enrolment/follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Boeing et al. (1991b) Germany 1985–1988 (cont.)	Controls: 579; one group of controls consisted of patients from the hospitals, usually two controls of the same sex for each case and of comparable age; patients with a history of chronic atrophic gastritis or intestinal metaplasia were not considered to be eligible as controls; another type of control group consisted of visitors to the hospitals, who were approached directly by the interviewers during their temporary stay at the hospital; the interviewers were advised to keep their selection of visitor controls within age limits similar to those of the cases Exposure assessment method: questionnaire		Smoking of meat at home, no	68	1.00	Adjusted for age, sex, hospital
			Smoking of meat at home, yes (other wood)	57	0.88 (0.59–1.34)	
			Smoking of meat at home, yes (specifying spruce)	18	3.19 (1.50–6.75)	
			Nitrate (quintiles)			Age, sex, hospital, vitamin C, carotene, calcium
			Q1	NR	1.00	
			Q2	NR	0.93 (0.53–1.64)	
			Q3	NR	0.61 (0.32–1.19)	
			Q4	NR	0.61 (0.30–1.27)	
			Q5	NR	1.26 (0.59–2.70)	

Table 2.3.4 Case–control studies (hospital-based) on consumption of processed meat and cancer of the stomach

Reference, location, enrolment/follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Boeing et al. (1991a) Poland (nine university hospitals) 1986–1990	Cases: 741 (including 374 carcinoma intestinalis and 259 carcinoma of the diffuse-type cases); consecutive incident cases of gastric cancer (adenocarcinoma), histologically confirmed (histological diagnosis from the surgical excision or, if the patient was not operable, endoscopy-based diagnosis using the obtained biopsy material) Controls: 741; hospital-based controls admitted to the hospital surgical wards for other reasons, matched to the cases by sex and age (≥ 5 yr) Exposure assessment method: questionnaire; dietary intake measured by an FFQ including 43 single-food items; frequency was estimated on a scale of six categories (ranging from "never" to "everyday"), but "no efforts were made to quantify food consumption"; tertiles based on the distribution of frequency categories among the controls were used in the analysis; "processed meat" was estimated by the items "sausages" and "ham of good quality"	Stomach/ adenocarcinoma (all)	Sausages			Age, sex, occupation, education, residency, fruit and vegetable score, non-white bread, cheese score
			Tertile 1 (low)	388	1.00	
			Tertile 2	266	1.20 (0.95–1.51)	
			Tertile 3 (high)	87	1.55 (1.07–2.26)	
			Trend-test *P* value: 0.01			
		Stomach/ adenocarcinoma (intestinal type)	Sausages			
			Tertile 1 (low)	NR	1.00	
			Tertile 2	NR	1.09 (0.79–1.52)	
			Tertile 3 (high)	NR	1.74 (1.00–3.01)	
			Trend-test *P* value: 0.09			
		Stomach/ adenocarcinoma (diffuse type)	Sausages			
			Tertile 1 (low)	NR	1.00	
			Tertile 2	NR	1.19 (0.79–1.79)	
			Tertile 3 (high)	NR	1.63 (0.85–3.15)	
			Trend-test *P* value: 0.13			
		Stomach/ adenocarcinoma (all)	Ham			
			Tertile 1 (low)	313	1.00	
			Tertile 2	268	0.89	
			Tertile 3 (high)	160	0.87	
			Trend-test *P* value: 0.29			

Table 2.3.4 Case–control studies (hospital-based) on consumption of processed meat and cancer of the stomach

Reference, location, enrolment/follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
De Stefani et al. (1998) Montevideo, Uruguay 1993–1996	Cases: 340; all newly diagnosed and microscopically confirmed patients with gastric cancer admitted to the four major hospitals in Montevideo Controls: 698; all controls were selected from the same hospitals and in the same period as the cases; controls were aged 25–84 yr, free of conditions related to digestive tract or nutritional disorders, and free of conditions related to tobacco and alcohol consumption Exposure assessment method: questionnaire	Stomach	Nitrite Processed meat	NR NR	0.53 (0.42–0.67) 0.96 (0.79–1.17)	Age, sex, residence, urban/rural status, tobacco duration, total alcohol consumption, mate drinking; red meat, barbecued meat, salted meat, processed meat, vegetables, and fruits were also included in the model

Table 2.3.4 Case–control studies (hospital-based) on consumption of processed meat and cancer of the stomach

Reference, location, enrolment/follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Huang et al. (2004) Nagoya, Japan 1988–1998	Cases: 1988; of a total of 80 420 first-visit outpatients who visited the Aichi Cancer Center Hospital between January 1988 and June 1998; 8057 outpatients were excluded due to interviewer absence, inadmissible age (younger than 18 yr), or visit for a consultation; the questionnaire was finally administered to 72 363 subjects; among them, 71 277 (98.5%) completed the questionnaire adequately; after linkage between questionnaire data and medical data, 9032 subjects (12.7%) were excluded, as the cancer history of at least one of their parents or siblings was unknown Controls: 50 706; first-visit non-cancer subjects were regarded as the referent group Exposure assessment method: questionnaire; FFQ	Stomach	Risk by frequency for sausage			Age, sex
			≥ 3 times/wk vs < 3 times/wk, without gastric cancer family history	NR	1.03 (0.86–1.22)	
			≥ 3 times/wk vs < 3 times/wk, with gastric cancer family history	NR	0.87 (0.61–1.26)	

Table 2.3.4 Case–control studies (hospital-based) on consumption of processed meat and cancer of the stomach

Reference, location, enrolment/follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
De Stefani et al. (2012) Uruguay 1996–2004	Cases: 234 274; incident cases of stomach cancer (n = 274) diagnosed in the four major hospitals in Montevideo and microscopically confirmed (C15) Controls: 2532; hospital-based controls (from the same hospitals) with conditions unrelated to tobacco smoking and alcohol drinking Exposure assessment method: questionnaire; dietary intake measured by an FFQ including 64 food items (quantities recorded as servings/wk) and tested for reproducibility with good results; "processed meat" was bacon, sausage, mortadella, salami, saucisson, hot dog, ham, and air-dried and salted lamb; intakes were energy-adjusted by the residual method	Stomach	Processed meat by type *Men*			Age, residence, BMI, smoking status, smoking cessation, number of cigarettes smoked per day among current smokers, alcohol drinking, mate consumption, total energy intake, total vegetable and fruit intake, total white meat and red meat intake.
			Bacon	NR	0.64 (0.49–0.83)	
			Sausage	NR	1.02 (0.86–1.21)	
			Mortadella	NR	0.99 (0.87–1.14)	
			Salami	NR	0.99 (0.86–1.15)	
			Saucisson	NR	1.22 (1.03–1.44)	
			Hot dog	NR	1.49 (1.30–1.70)	
			Ham	NR	0.96 (0.81–1.14)	
			Salted meat	NR	1.02 (0.87–1.19)	
			Processed meat by type *Women*			
			Bacon	NR	0.72 (0.46–1.13)	
			Sausage	NR	1.16 (0.88–1.53)	
			Mortadella	NR	1.25 (1.01–1.56)	
			Salami	NR	0.76 (0.58–0.99)	
			Saucisson	NR	1.48 (1.07–2.04)	
			Hot dog	NR	1.50 (1.23–1.83)	
			Ham	NR	1.24 (1.03–1.44)	
			Salted meat	NR	0.62 (0.36–1.07)	
			Processed meat *Men*			
			T1 (< 11.4 g/day)	NR	1.00	
			T2 (11.5–28.2 g/day)	NR	1.60 (1.02–2.49)	
			T3 (≥ 28.3 g/day)	NR	1.93 (1.25–2.98)	
			Trend-test P value: 0.003			
			Processed meat *Women*			
			T1 (< 11.4 g/day)	NR	1.00	
			T2 (11.5–28.2 g/day)	NR	3.07 (1.58–5.98)	
			T3 (≥ 28.3 g/day)	NR	4.51 (2.34–8.70)	
			Trend-test P value: 0.0001			

BMI, body mass index; CI, confidence intervals; FFQ, food frequency questionnaire; mo, month; NA, not available; NR, not reported

Table 2.3.5 Case–control studies (population-based) on consumption of processed meat and cancer of the stomach

Reference, location, enrolment/follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Risch et al. (1985) Toronto, Winnipeg, and St John's, Canada 1979–1982	Cases: 246; aged 35–79 yr with newly diagnosed gastric cancer; all cases were histologically verified Controls: 246; randomly selected population controls; individually matched by age, sex, and area of residence Exposure assessment method: questionnaire	Stomach	Smoked meats (per 100 g/day increase)	246	2.22 (1.19–4.15)	Total food consumption and ethnicity
			Nitrite (1 mg/day)	246	1.71 (1.24–2.37)	
			Nitrate (100 g/day)	246	0.66 (0.54–0.81)	
			Dimethylnitrosamine (10 μg/day)	246	0.94 (0.14–6.13)	
			Smoked meats (per 100 g/day increase)	246	3.92 (1.76–8.75)	Matched by age, sex, area of residence, and adjusted for total food consumption, ethnicity, and consumption of grains, chocolate, fibrous foods, eggs, and public water supply

Table 2.3.5 Case–control studies (population-based) on consumption of processed meat and cancer of the stomach

Reference, location, enrolment/follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
La Vecchia et al. (1987) Greater Milan area, Italy January 1985–June 1986	Cases: 206; incident cases of histologically confirmed gastric cancer diagnosed within the year preceding the interview and admitted to the National Cancer Institute, to several university clinics (chiefly surgery), and to the Ospedale Maggiore in Milan Controls: 474; hospital-based controls who were admitted to the Ospedale Maggiore in Milan and to several university clinics; patients admitted for malignant disorders, any disease of the digestive tract, or any condition related to consumption of alcohol or tobacco that might have resulted in modification of the diet were excluded Exposure assessment method: questionnaire; dietary intake was based on an FFQ including 29 food items; individuals were asked to indicate the frequency of consumption of these items per week before the onset of the disease that led to hospital admission and to recall any major change in frequency of intake of the same foods during the 10-yr period preceding the diagnosis; items related to processed meat were "raw ham", "ham", "salami and other sausages", and "canned meat"	Stomach	Raw ham intake (frequency)			Age, sex
			Low	75	1.00	
			Intermediate	37	0.62	
			High	94	1.04	
			Salami and other sausages intake (frequency)			
			Low	114	1.00	
			Intermediate	31	0.56	
			High	61	1.27	
			Canned meat intake (frequency)			
			Low	187	1.00	
			Intermediate	15	0.95	
			High	4	0.77	

Table 2.3.5 Case–control studies (population-based) on consumption of processed meat and cancer of the stomach

Reference, location, enrolment/follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Sanchez-Diez et al. (1992) Province of León, Spain 1975–1986	Cases: 109; total cases diagnosed between 1975 and 1986 at a specific study site Controls: 123; all people born locally or who had been living in the area for the past 10 yr; one control was randomly selected and matched by year of birth, sex, and municipality of residence Exposure assessment method: questionnaire	Stomach	Homemade sausages, not consumed	13	1.00	Matched by year of birth, sex, municipality of residence
			Homemade sausages, daily consumption	42	3.34 (1.51–7.37)	
			Smoked sausages, not consumed	9	1.00	
			Smoked sausages, daily consumption	40	3.55 (1.59–7.94)	
Ward & López-Carrillo (1999) Mexico City, Mexico 1989–1990	Cases: 220; 267 newly diagnosed cases of gastric cancer in patients aged 20 yr and older were identified between 1989 and 1990 at 15 metropolitan area hospitals in Mexico City; these cases represented approximately 80% of those reported to the Mexican Cancer Registry in the same period; 22 (8.2%) of the identified cases were unavailable for interview; a further 20 cases (7.5%) were excluded because the pathology material could not be obtained, and five cases (1.9%) were excluded because their tumours were not adenocarcinomas of the stomach Controls: 752; controls were an age-stratified random sample of Mexico City metropolitan area residents selected from the 1986–1987 household sampling frame of the Mexican National Survey for Health and Nutrition Exposure assessment method: questionnaire	Stomach/ adenocarcinoma	Processed meat intake (times/wk)			Age, sex, total calories, chilli pepper consumption, added salt, history of peptic ulcer, cigarette smoking, socioeconomic status
			< 1	25	1.0	
			1–2	67	2.0 (1.0–3.8)	
			3–5	68	2.8 (1.4–5.7)	
			≥ 6	60	3.2 (1.5–6.6)	
			Trend-test *P* value: 0.002			
		Stomach/ adenocarcinoma (intestinal)	Processed meat intake (times/wk)			
			< 1	NR	1.0	
			1–2	NR	2.2 (0.9–5.2)	
			3–5	NR	2.6 (1.0–6.4)	
			≥ 6	NR	2.6 (1.0–7.0)	
		Stomach/ adenocarcinoma (diffuse)	Processed meat intake (times/wk)			
			< 1	NR	1.0	
			1–2	NR	1.1 (0.5–2.8)	
			3–5	NR	1.8 (0.7–4.6)	
			≥ 6	NR	2.2 (0.8–6.0)	

Table 2.3.5 Case–control studies (population-based) on consumption of processed meat and cancer of the stomach

Reference, location, enrolment/follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Palli et al. (2001) Florence, Italy 1985–1987	Cases: 382; all gastric cancer cases were histologically confirmed and originally classified according to the Lauren classification by review of all available surgical pathology specimens Controls: 561; computerized lists of residents were used to identify a random sample of eligible population controls Exposure assessment method: questionnaire	Stomach	Cured and canned meat intake, MSI+ Tertile 1 Tertile 2 Tertile 3 Trend-test *P* value: 0.1 Cured and canned meat intake, MSI– Tertile 1 Tertile 2 Tertile 3 Trend-test *P* value: 0.05	 NR NR NR NR NR NR	 1.0 1.0 (0.5–2.4) 1.0 (0.4–2.6) 1.0 1.2 (0.6–2.3) 1.9 (1.0–3.7)	Adjusted for non-dietary variables (age, sex, social class, family history of gastric cancer, area of residence, BMI), total energy, consumption tertiles of each food of interest (reference, lowest tertile)
Takezaki et al. (2001) Pizhou, Jiangsu Province, China 1996 (1995 for controls)–2000	Cases: 187 stomach cancer; incident cases of histopathologically confirmed cases of stomach cancer who visited the Pizhou City Municipal Hospital Controls: 333; healthy residents of Pizhou, matched to cases by sex, ethnicity, and age (≤ 2 yr); controls came from three different sources: individuals from a population-based ecological study conducted in 1995–1996; individuals selected between 1995 and 1998 in the general population; individuals selected between 1998 and 2000 Exposure assessment method: questionnaire; food consumption frequency was measured at the time of the interview and 10 yr previously; among the available items, only "salted meat" could be used to estimate "processed meat" consumption; previously used in a case–control and ecological study	Stomach	Salted meat, < 1 time/mo Salted meat, 1–3 times/mo Salted meat, ≥ 1 time/wk Trend-test *P* value: 0.001	NR NR NR	1.00 3.82 (2.24–6.50) 2.36 (1.08–5.15)	Age, sex, smoking, drinking

Table 2.3.5 Case–control studies (population-based) on consumption of processed meat and cancer of the stomach

Reference, location, enrolment/follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Chen et al. (2002) Eastern Nebraska, USA 1 July 1988–31 June 1993	Cases: 124 (distal stomach); incident, histologically confirmed cases of stomach adenocarcinoma, identified from the Nebraska Cancer Registry or 14 participating hospitals covering > 90% of the study population Controls: 449; population-based controls selected from the control group of a previous case–control study conducted in 1986–1987 in the same base population; frequency-matched to the whole distribution of cases by age, sex, and vital status Exposure assessment method: questionnaire; dietary assessment was based on a modified version of the short HHHQ, with the addition of several food items (e.g. for processed meat); subjects were asked to recall frequency of consumption of 54 dietary items before 1985; "processed meat" was bacon; sausage, including breakfast sausage; processed or smoked ham bought from the store; meat that was cured or smoked at home; sandwich meats, such as bologna or salami; and hot dogs	Stomach/distal adenocarcinoma	Processed meat (times/day), quartiles			Age, sex, energy intake, respondent type, BMI, alcohol use, tobacco use, education, family history, vitamin supplement use
			Q1	NR	1.00	
			Q2	NR	1.70 (0.77–3.70)	
			Q3	NR	1.20 (0.55–2.70)	
			Q4	NR	1.70 (0.72–3.90)	

Table 2.3.5 Case–control studies (population-based) on consumption of processed meat and cancer of the stomach

Reference, location, enrolment/follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Nomura et al. (2003) Hawaii, USA 1993–1999	Cases: 658; from eight major hospitals on the Hawaiian Islands and identified by the rapid reporting system of the Hawaii Tumor Registry Controls: 446; controls identified from lists of Oahu residents interviewed by the Health Surveillance Program, which identifies a 1% representative random sample of all households in the state Exposure assessment method: questionnaire	Stomach	Processed meat *Men* T1 T2 T3 Trend-test *P* value: 0.19 Processed meat, Tertiles *Women* T1 T2 T3 Trend-test *P* value: 0.43 Bacon, Tertiles *Men* T1 T2 T3 Trend-test *P* value: 0.36 Bacon *Women* T1 T2 T3 Trend-test *P* value: 0.4	 NR NR NR NR NR NR NR NR NR NR NR NR	 1.0 1.8 (1.0–3.3) 1.7 (0.9–3.3) 1.0 0.6 (0.3–1.3) 0.7 (0.3–1.5) 1.0 1.3 (0.7–2.2) 1.3 (0.7–2.4) 1.0 0.6 (0.3–1.3) 1.1 (0.5–2.3)	Age, ethnicity, smoking, education, history of gastric ulcer, NSAID use, family history of gastric cancer, total calories, intake of other foods and food groups
Lissowska et al. (2004) Warsaw, Poland 1994–1996	Cases: 274; cases consisted of Warsaw residents newly diagnosed with stomach cancer; identified by collaborating physicians in each of the 22 hospitals Controls: 463; controls randomly selected from the general population in Warsaw Exposure assessment method: questionnaire	Stomach	Sausages ,Quartiles (frequency/wk) Q1 Q2 Q3 Q4 Trend-test *P* value: 0.81	 NR NR NR NR	 1.00 1.13 (0.74–1.71) 0.75 (0.48–1.17) 1.23 (0.79–1.93)	Age, sex, education, smoking, calories from food

Table 2.3.5 Case–control studies (population-based) on consumption of processed meat and cancer of the stomach

Reference, location, enrolment/follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Wu et al. (2007) Los Angeles, USA 1992–1997	Cases: 829; all incident cancers were identified by the Los Angeles Cancer Surveillance Program, a population-based tumour registry Controls: 1308; control subjects were individually matched to interviewed case patients by sex, race, and date of birth (± 5 yr) in the neighbourhoods Exposure assessment method: questionnaire	Stomach/cardia adenocarcinoma	Processed meat, quartiles (g/day)			Age, sex, race, birthplace, education, smoking, BMI (kg/m^2), reflux, use of vitamins, total calories
			Q1	NR	1.00	
			Q2	NR	0.84 (0.60–1.30)	
			Q3	NR	0.76 (0.50–1.20)	
			Q4	NR	0.89 (0.60–1.40)	
			Trend-test *P* value: 0.57			
		Stomach/distal adenocarcinoma	Processed meat, quartiles (g/day)			
			Q1	NR	1.00	
			Q2	NR	1.54 (1.10–2.20)	
			Q3	NR	1.22 (0.80–1.80)	
			Q4	NR	1.65 (1.10–2.50)	
			Trend-test *P* value: 0.049			
		Stomach/cardia adenocarcinoma	Processed meat among subjects infected with *H. pylori*, quartiles of intake (g/day)			
			Q1	NR	1.00	
			Q2	NR	1.16 (0.60–2.40)	
			Q3	NR	0.40 (0.20–0.96)	
			Q4	NR	0.57 (0.20–1.30)	
			Trend-test *P* value: 0.08			
		Stomach/distal adenocarcinoma	Processed meat among subjects infected with *H. pylori*, quartiles of intake (g/day)			
			Q1	NR	1.00	
			Q2	NR	2.46 (1.10–5.20)	
			Q3	NR	1.40 (0.60–3.10)	
			Q4	NR	1.97 (0.90–4.50)	
			Trend-test *P* value: 0.3			

Table 2.3.5 Case–control studies (population-based) on consumption of processed meat and cancer of the stomach

Reference, location, enrolment/follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Navarro Silvera et al. (2008) Connecticut, New Jersey and western Washington, USA 1993–early 1995	Cases: 607; incident cases of stomach adenocarcinoma (255 cardia cases, 352 non-cardia cases); this population was part of a larger population of cases also containing cases of cardia and non-cardia gastric adenocarcinoma; gastric cardia adenocarcinoma were considered as the "target cases", whereas non-cardia gastric adenocarcinoma cases were considered as the "comparison case group", which was frequency-matched to the "target group"	Stomach/cardia adenocarcinoma Stomach/ non-cardia adenocarcinoma	High-nitrite meats, for an increase in intake of 1 serving/day High-nitrite meats, for an increase in intake of 1 serving/day	NR NR NR NR	1.19 (0.74–1.91) 1.88 (1.24–2.84)	Sex; site; age, "race"; proxy status; income; education; usual BMI; cigarettes per day; consumption of beer, wine, and liquor each; energy intake

Table 2.3.5 Case–control studies (population-based) on consumption of processed meat and cancer of the stomach

Reference, location, enrolment/follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Navarro Silvera et al. (2008) Connecticut, New Jersey and western Washington, USA 1993–early 1995 (cont.)	Controls: 687; population-based controls frequency-matched to the expected distribution of the "target cases" by 5-yr age group, sex (in New Jersey and Washington state), "race" (in New Jersey), and study site; controls aged 30–64 yr were identified by the random digit dialling method, and controls aged 65–79 yr were identified by Health Care Financing Administration rosters Exposure assessment method: questionnaire; an expanded version of an FFQ developed and validated by investigators at the Fred Hutchinson Cancer Research Center was used to assess usual food consumption in the period 3–5 yr before diagnosis (cases) or interview (controls); processed meat was defined as " high-nitrite meats", including smoked turkey lunchmeat; cured, smoked ham lunchmeat; bologna; salami; hot dogs; sausage, not including breakfast sausage; bacon; and breakfast sausage					

Table 2.3.5 Case–control studies (population-based) on consumption of processed meat and cancer of the stomach

Reference, location, enrolment/follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Pourfarzi et al. (2009) Ardabil Province, Iran 2004–2005	Cases: 217; identified from the Ardabil Cancer Registry; cases were eligible if they were in people who had been Ardabil residents for at least 5 yr before diagnosis, were aged older than 18 yr, had not had previous gastric surgery, and had a positive histopathological report of gastric carcinoma; in addition to the cases routinely reported to the cancer registry, active surveillance for gastric cancer was conducted by the cancer registry through all hospitals and clinics, particularly those of three gastroenterologists, to maximize the completeness of case ascertainment Controls: 394; two controls were sought for each case and frequency-matched to the case group by age (5 yr) and sex; controls had to satisfy the same residency and age criteria as cases, and were randomly selected from the community using a computer-based sampling frame that had been created for the annual household survey by the health department; this database was used to select random households, which were then visited by health professionals seeking eligible individuals; if such a person was not available or did not satisfy the inclusion criteria, the immediate neighbour to the right-hand side was visited Exposure assessment method: questionnaire	Stomach	Smoked meats, ≥ 1 time/mo Smoked meats, never Processed meats, ≥ 1 time/mo Processed meats, never	20 189 23 188	0.91 (0.40–2.09) 1.00 1.14 (0.55–2.37) 1.00	Sex, age group, education, family history of gastric cancer, citrus fruits, garlic, onion, red meat, fish, dairy products, strength and warmth of tea, preference for salt intake, *H. pylori*

Table 2.3.5 Case–control studies (population-based) on consumption of processed meat and cancer of the stomach

Reference, location, enrolment/follow-up period	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Hu et al. (2011) Canada 1994–1997	Cases: 1182; this study involved histologically confirmed cancer cases Controls: 5039; individuals without cancer were selected from a random sample of the population within each province, with an age and sex distribution similar to that of all cancer cases Exposure assessment method: questionnaire	Stomach	Processed meat (servings/wk) ≤ 0.94 0.95–2.41 2.42–5.41 ≥ 5.42 Trend-test *P* value: 0.0001	 NR NR NR NR	 1.0 1.2 (1.0–1.6) 1.3 (1.0–1.7) 1.7 (1.3–2.2)	Age, province, education, BMI, alcohol drinking, smoking, vegetable and fruit intake, total energy
Ward et al. (2012) USA (66 counties in eastern Nebraska) 1 July 1988–30 June 1993	Cases: 154 for stomach; incident cases of adenocarcinoma of the stomach, identified from the Nebraska Cancer Registry and confirmed by histological review Controls: 449; controls randomly selected from a previous population-based case–control study in the same geographical region; matched by race, age, sex, and vital status Exposure assessment method: questionnaire; dietary information was obtained using a short version of the HHHQ; "processed meat" was bacon, sausage, luncheon meats, hot dogs, ham, and home-cured meat	Stomach	Processed meat Q1 (≤ 16.1 g/day) Q2 (16.2–29.6 g/day) Q3 (29.7–52.3 g/day) Q4 (> 52.3 g/day) OR (per 10 g/day) Trend-test *P* value: 0.87	 30 38 40 46 NR	 1.00 0.81 (0.45–1.46) 1.17 (0.66–2.10) 0.97 (0.51–1.85) 1.03 (0.97–1.10)	Age, sex, smoking status,, education, vitamin C, fibre, carbohydrates, total calories

BMI, body mass index; CI, confidence intervals; FFQ, food frequency questionnaire; *H. pylori*, *Helicobacter pylori*; HHHQ, Health Habits and History Questionnaire; mo, month; MSI, microsatellite instability; NR, not reported; OR, odds ratio

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2.4 Cancer of the pancreas

2.4.1 Cohort studies

Cohort studies on cancer of the pancreas have been conducted in North America, Europe, and Asia. Considering the high mortality rate for cancer of the pancreas, both studies of incidence and mortality were included in the review. Studies investigating the association between consumption of red meat or specific red meats, such as beef, pork, or other meats, are reviewed first, followed by studies on consumption of processed meat or specific processed meat items, such as ham or bacon. Findings for red meat and processed meat combined are presented only when a study did not present data for either type of meat separately.

For studies reporting on more than one type of meat, the descriptive details are given in the section the first time the study is cited, while only the key results are provided for subsequent citations. The Working Group's comments, if any, on the study's strengths and limitations are also presented only the first time a study is cited, unless different issues were noted in each analysis. Studies that did not adjust for important potential confounders for pancreatic cancer, including age, smoking, BMI, and energy intake, are noted.

After reviewing all of the available studies, the Working Group excluded the following groups of publications from further consideration: studies reporting fewer than 100 cases (e.g. Zheng et al., 1993), due to their limited statistical power; studies reporting risk estimates that were not specific for red meat intake (e.g. Yun et al., 2008; Berjia et al., 2014; Hirayama, 1990); and reports on study populations that were included in or updated by subsequent reports (e.g. Khan et al., 2004; Cross et al., 2007; Iso et al., 2007).

(a) Red meat

See Table 2.4.1

In the Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) Study cohort in Finland (Stolzenberg-Solomon et al., 2002), 27 111 male smokers aged 50–69 years were followed from 1985 to 1997, and 163 developed pancreatic cancer. The median value of red meat intake was 128.7 g/day for non-cases. The adjusted hazard ratio for the highest quintile versus the lowest quintile of consumption was 0.95 (95% CI, 0.58–1.56; P_{trend} = 0.71). Beef and pork also did not show any association. [The Working Group noted that the definition of red meat was not reported. Subjects were male smokers with largely atypical diets, so generalizability of the results was limited.]

In the Nurses' Health Study (NHS), 178 pancreatic cancer cases were observed over 18 years of follow-up in 88 802 women (Michaud et al., 2003). Diet was assessed by questionnaire four times during follow-up. The definition of red meat included processed meat, so those results are not reported here. For the highest versus the lowest quintile of consumption of beef, pork, or lamb as a main dish, the multivariate hazard ratio was 0.75 (95% CI, 0.41–1.40). Updating the dietary exposures reportedly produced similar results, but data were not shown. [The Working Group noted that the sample size was small.]

Nöthlings et al. (2005) observed positive associations between red meat, beef, and pork consumption and pancreatic cancer incidence in 190 545 men from the Multiethnic Cohort Study in Hawaii and California, USA. During 7 years of follow-up, 482 incident pancreatic cancers occurred. For the highest compared with the lowest quintiles, after adjusting for important confounders, the multivariate relative risks for intakes of red meat, beef, and pork were 1.45 (95% CI, 1.19–1.76; $P_{trend} < 0.01$), 1.21 (95% CI, 0.99–1.47; P_{trend} = 0.03), and 1.53 (95% CI, 1.25–1.87; $P_{trend} < 0.01$), respectively. [The Working Group noted that the sample size was large, and the cohort included considerable dietary heterogeneity due to the multi-ethnic background. There was no adjustment for BMI.]

In a population-based cohort of 61 433 Swedish women recruited for mammography screening, Larsson et al. (2006) reported a positive association between long-term red meat consumption, measured by two surveys 10 years apart, and pancreatic cancer risk. During follow-up from 1987 to 2004, 172 incident cases of pancreatic cancer were observed. After adjusting for important confounders, the multivariate hazard ratio for the highest versus the lowest number of servings per week of red meat was 1.73 (95% CI, 0.99–2.98). A dose–response relationship was observed (P_{trend} = 0.01). [The Working Group noted that using surveys from two time points enabled the effect of long-term exposure to be seen. The cohort was restricted to women. The sample size was small.]

In the Japan Collaborative Cohort (JACC) Study, Lin et al. (2006) evaluated the relationship between dietary factors, including meat, and risk of pancreatic cancer death; 46 465 men and 64 327 women aged 40–79 years were followed up, and 300 deaths from pancreatic cancer were recognized. After adjustment, the multivariate relative risks for the highest compared with the lowest category of intake of beef were 2.3 (95% CI, 0.83–6.39; P_{trend} = 0.33; 4 observed deaths) for men and 0.98 (95% CI, 0.14–7.11; P_{trend} = 0.74; 1 observed death) for women. The corresponding results for pork were 1.63 (95% CI, 0.62–4.26; P_{trend} = 0.34; 5 observed deaths) for men and 1.71 (95% CI, 0.71–4.09; P_{trend} = 0.35; 6 observed deaths) for women. [The Working Group noted that, while the total number of deaths was not small, the number of observed deaths among the highest category of intake was small. BMI and total energy were not adjusted.]

In a case–cohort analysis of the Netherlands Cohort Study (NLCS), Heinen et al. (2009) observed no association between intake of red meat or individual red meat items and pancreatic cancer risk. The study consisted of 120 852 men and women, and 350 pancreatic cancer cases, identified during 13 years of follow-up. Meat consumption was assessed using a validated FFQ with 150 items. For the highest compared with the lowest quintile, after adjusting for important confounders, the multivariate relative risks for intakes of red meat, beef, pork, and minced meat were 0.75 (95% CI, 0.52–1.09; P_{trend} = 0.23), 1.20 (95% CI, 0.84–1.72; P_{trend} = 0.61), 0.75 (95% CI, 0.52–1.08; P_{trend} = 0.27), and 0.78 (95% CI, 0.54–1.10; P_{trend} = 0.16), respectively. The corresponding value for intake of liver, categorized into two groups, was 1.05 (95% CI, 0.83–1.33). [The Working Group noted that red meat was clearly defined as not including processed meat. BMI was not adjusted.]

In the Iowa Women's Health Study (IWHS), Inoue-Choi et al. (2011) assessed multiple aspects of dietary intake among 34 642 postmenopausal women. A total of 256 pancreatic cancer cases during the period from 1986 to 2007 were included in the analysis. No statistically significant associations were observed between intake of red meat and pancreatic cancer (HR, 0.97; 95% CI, 0.65–1.44; for the highest vs lowest consumption category; P_{trend} = 0.79). [The Working Group noted that the definition of red meat was not reported. The follow-up was nearly complete. BMI and energy were not adjusted.]

Among the 62 581 subjects randomized to screening in the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial in the USA (Anderson et al., 2012), 248 cases of exocrine pancreatic cancer were identified during follow-up from 1993 to 2007. The multivariate hazard ratios for the highest versus the lowest quintile of intake of red meat by doneness preference were 0.84 (95% CI, 0.55–1.29; P_{trend} = 0.36) for rare to medium well done and 1.60 (95% CI, 1.01–2.54; P_{trend} = 0.04) for well to very well done. When quintiles 1–4 were combined, the corresponding values for the highest quintile of "red barbecued meat" [definition not reported] were 0.79 (95% CI, 0.55–1.13; 39 exposed cases) for rare to medium well done and 1.35 (95% CI, 1.00–1.83; 56 exposed cases) for well to very well

done. Pancreatic cancer was significantly associated with consumption of fried (HR, 1.74; 95% CI, 1.05–2.90) and grilled or barbecued pork chops (HR, 1.80; 95% CI, 1.04–3.13), but not with any other cooking method or preference of doneness for pork chops, hamburger, or steak. [The Working Group noted that BMI was not adjusted. The definitions of red meat and barbecued meat were not reported.]

Rohrmann et al. (2013) examined the association between meat consumption and risk of pancreatic cancer in the European Prospective Investigation into Cancer and Nutrition (EPIC) study. A total of 477 202 EPIC participants from 10 European countries recruited between 1992 and 2000 were included in the analysis. Eight hundred and sixty-five non-endocrine pancreatic cancer cases were observed during follow-up to 2008. After adjusting for important confounders, no significant association between consumption of red meat and pancreatic cancer was observed; the multivariate relative risk for the fourth compared with the first quantile of intake was 1.07 (95% CI, 0.83–1.38). [The Working Group took note of the large international study encompassing diverse diets.]

(b) Processed meat

See Table 2.4.2 (web only; available at: http://publications.iarc.fr/564)

In the ATBC Study cohort (Stolzenberg-Solomon et al., 2002), the median value of processed meat intake was 61.2 g/day. After adjusting for important confounders, no association was observed for processed meat (highest vs lowest quintile multivariate HR,1.04; 95% CI, 0.66–1.65).

In the NHS, the adjusted hazard ratio for the highest versus the lowest quintile of processed meat consumption was 1.28 (95% CI, 0.86–1.92; $P_{trend} = 0.10$) (Michaud et al., 2003) Analyses using dietary exposures updated during follow-up produced similar results. [The Working Group noted that repeated surveys enabled changes in diet to be considered, and exposure updates did not alter the results. BMI was not adjusted.]

Nöthlings et al. (2005) observed a positive association between processed meat consumption and pancreatic cancer incidence in the Multiethnic Cohort Study. For the highest compared with the lowest quintile, after adjusting for important confounders, the multivariate relative risk for intake of processed meat was 1.68 (95% CI, 1.35–2.07; $P_{trend} < 0.01$).

In a population-based cohort of 61 433 Swedish women, Larsson et al. (2006) found no association between pancreatic cancer risk and processed meat consumption at baseline or in the long term, measured using two surveys 10 years apart. For long-term processed meat consumption, the multivariate hazard ratio for the highest versus the lowest number of servings per week was 0.94 (95% CI, 0.61–1.44; $P_{trend} = 0.70$). Results for baseline consumption were similar. [The Working Group noted that using surveys from two time points enabled the effect of long-term exposure to be seen. The cohort was restricted to women.]

In the JACC Study (Lin et al., 2006), for the highest compared with the lowest category, the multivariate relative risks for intakes of ham and sausage were 1.82 (95% CI, 0.62–4.26; $P_{trend} = 0.34$; 7 observed deaths) for men and 0.93 (95% CI, 0.29–2.99; $P_{trend} = 0.63$; 3 observed deaths) for women.

In the NLCS (Heinen et al., 2009), for the highest compared with the lowest category of processed meat intake, the multivariate relative risk was 0.93 (95% CI, 0.65–1.35; $P_{trend} = 0.97$; 70 exposed cases). [A detailed validated FFQ with 150 items was used.] Among subjects randomized to screening in the PLCO trial in the USA (Anderson et al., 2012), the multivariate hazard ratio for the highest versus the lowest tertile of bacon/sausage consumption by doneness preference was 0.99 (95% CI, 0.73–1.35) for crisp or charred compared with cooked to a lesser degree of doneness. [The Working Group noted that

BMI was not adjusted. Information on cooking method preferences was available.]

In the EPIC study, Rohrmann et al. (2013) did not find a significant relation between consumption of processed meat and pancreatic cancer (multivariate RR per 50 g/day increase, 0.93; 95% CI, 0.71–1.23).

During follow-up of the NIH-AARP cohort, until 2006, where 2193 pancreatic cancer cases were identified, Jiao et al. (2015) investigated the joint associations between pancreatic cancer and processed meat consumption and intake of advanced glycation end products (AGEPs). The multivariate hazard ratio for the highest compared with the lowest quintile of processed meat consumption was 1.03 (95% CI, 0.92–1.37; P_{trend} = 0.28). Further adjustment for AGEPs did not alter the results.

(c) Red meat and processed meat combined

Coughlin et al. (2000), in a cohort of 483 109 men and 619 199 women from the Cancer Prevention Study (CPS) II (CPS-II), confirmed 3751 pancreatic cancer deaths during follow-up from 1982 to 1996. The red meat variable used in the analysis included processed meat items. The multivariate-adjusted hazard ratios for the highest versus the lowest quintile for this variable were 1.1 (95% CI, 0.9–1.2) in men and 0.9 (95% CI, 0.8–1.0) in women. [The Working Group noted that this was a large study with a low percentage of men and women lost to follow-up. Red meat and processed meat were combined.]

Based on a follow-up of the NIH-AARP study cohort from 1995 to 2000 with 836 cases, Stolzenberg-Solomon et al. (2007) reported a statistically significant association between pancreatic cancer risk and red meat consumption for men (adjusted HR, 1.42; 95% CI, 1.05–1.91; highest vs lowest category of consumption), but not for women (HR, 0.69 ; 95% CI, 0.83–1.35) or for both sexes combined (HR, 1.06; 95% CI, 0.83–1.35). [The Working Group noted that the red meat variable included processed items.]

Jiao et al. (2015) investigated the risk of pancreatic cancer associated with red meat consumption and intake of AGEPs in the same cohort. For the highest compared with the lowest quintile of intake among men, the multivariate hazard ratios for red meat and red meat cooked at a high temperature were 1.35 (95% CI, 1.07–1.70; P_{trend} = 0.05) and 1.18 (95% CI, 0.89–1.56; P_{trend} = 0.01), respectively. The hazard ratios were attenuated and no longer significant after further adjustment for AGEPs. Data on the association between meat consumption and pancreatic cancer risk were not reported for women. [The Working Group noted that this was a large study, but the definition of red meat may have included processed meat items, as per the report based on follow-up through 2000.]

2.4.2 Case–control studies

Case–control studies on cancer of the pancreas have been conducted in North America, Europe, and Asia. Considering the high mortality rate for cancer of the pancreas, both studies of incidence and mortality data were included in the review. The studies were considered based on the quality of reporting of the type of meat, study design issues (e.g. population- vs hospital-based design), sample size, and exposure assessment, including validation of dietary questionnaires and inclusion of relevant confounders. Studies that did not adjust for important potential confounders (see Section 2.4.1) are noted.

As for cohort studies, case–control studies that investigated the association with consumption of total red meat or specific red meats are presented first, followed by studies that investigated the association with consumption of processed meat. Study details and Working Group comments are provided only the first time a study is cited, unless important differences were noted.

After reviewing all of the available studies, studies with fewer than 100 cases (e.g. Kadlubar

et al., 2009; Luckett et al., 2012), papers reporting only dietary patterns (e.g. Bosetti et al., 2013; Chan et al., 2013) or preserved processed items including eggs (e.g. Ji et al., 1995), and overlapping studies of the same population (e.g. Hu et al., 2011) were excluded from further consideration. Studies that did not report pertinent odds ratios (e.g. Li et al., 2007) were excluded when only crude odds ratios could be calculated from the data presented.

(a) Red meat

See Table 2.4.3

Lyon et al. (1993) reported the results of a population-based case–control study of cancer of the exocrine pancreas conducted from 1984 to 1987 in Utah, USA; 149 cases of pancreatic cancer were identified from the Utah Cancer Registry, and 363 controls were identified by random digit dialling or health insurance records of those older than 65 years. Dietary intake data were collected from a 32-item FFQ administered to proxy respondents for cases and controls. Red meat was defined as beef and pork. The multivariate odds ratios for the highest versus the lowest level of red meat consumption were 1.41 (95% CI, 0.72–2.75; P_{trend} = 0.30) in men and 1.44 (95% CI, 0.65–3.20; P_{trend} = 0.45) in women. [The Working Group noted that the study was small, and BMI and energy were not adjusted.]

Ji et al. (1995) reported findings for red meat consumption in a population-based case–control study conducted from 1990 to 1993 in Shanghai, China. Pancreatic cancer cases (n = 451) were identified by a rapid reporting system. Controls (n = 1552) were selected Shanghai residents, frequency-matched to cases by sex and age. Interviews with next of kin were conducted for 38% of cases and 10% of controls. Usual meat intake over the previous 5 years was ascertained from an 86-item questionnaire. The multivariate odds ratios for the highest versus the lowest quartile of red meat consumption were 0.73 (95% CI, 0.47–1.12; P_{trend} = 0.24) in men and 1.24 (95% CI, 0.73–2.13; P_{trend} = 0.86) in women. [The Working Group noted that processed meat was not included. This study was large, but a substantial number of case and control interviews were performed with next of kin. BMI and energy were not adjusted. No validation data for FFQ were reported.]

In a population-based case–control study, conducted from 1995 to 1999 in California, USA, Chan et al. (2007), reported the results of red meat consumption. Dietary intake of red meat was collected from a validated, 131-item SQFFQ. Cases were 532 pancreatic cancer patients from the Northern California Cancer Center. Controls were 1701 area residents identified by random digit dialling, and frequency-matched to cases by sex and age. Compared with a frequency of < 1 time/month, the multivariate odds ratios for ≥ 2 times/week frequency of beef or lamb intake as a main dish and pork intake as a main dish were 2.2 (95% CI, 1.0–4.5; 14 exposed cases) and 0.6 (95% CI, 0.3–1.1; P_{trend} = 0.2; 11 exposed cases), respectively. Results for total red meats, including processed red meats, were also reported. [The Working Group noted that the study design was sound.]

Hu et al. (2008) reported the results of a population-based case–control study of pancreatic cancer conducted from 1994 to 1997 in eight Canadian provinces. Dietary intake of red meat was collected from a mailed, validated questionnaire with 69 items. Cases were 628 individuals identified from provincial cancer registries. Controls were 5039 individuals selected from a random sample within the provinces. The multivariate odds ratio for the highest versus the lowest quartile of frequency of red meat consumption was 1.1 (95% CI, 0.9–1.5; P_{trend} = 0.31). [The Working Group noted that the sample size was large, and a validated FFQ was used.]

In a population-based case–control study, Anderson et al. (2009) reported the results of red meat consumption from 2003 to 2007 in Canada. Dietary intake of red meat was collected

from a mailed FFQ. Cases were 422 pancreatic cancer patients identified by the Ontario Cancer Registry. Controls were 312 subjects recruited through random digit dialling. The age-adjusted odds ratio for > 3 servings/week versus ≤ 1 serving/week of red meat consumption was 1.49 (95% CI, 0.98–2.28). Adjusting for other factors, such as smoking and education, did not alter the results. [The Working Group noted that the exact definition of red meat was not reported. This study was large, but the questionnaire was not validated. BMI and energy were not adjusted.]

Tavani et al. (2000), using data from a hospital-based case–control study of several cancers in northern Italy in 1983–1996, reported results for red meat consumption and pancreatic cancer. Cases were 362 hospital patients younger than 75 years with confirmed pancreatic cancer. Controls were 7990 patients younger than 75 years admitted to the same network of hospitals as the cancer cases for acute non-cancer conditions. Dietary intake of red meat over the previous 2 years was collected by FFQ, which defined red meat as beef, veal, or pork, excluding processed items. The multivariate odds ratio for the highest (≥ 7 times/week) versus the lowest (≤ 3 times/week) level of red meat consumption was 1.6 (95% CI, 1.2–2.1). [The participation of cases and controls was similar and almost complete. The questionnaire was not tested for validity, but reproducibility was reported to be satisfactory. BMI and energy were not adjusted.] Similar findings were reported in an earlier paper based on the same study (Soler et al., 1998), which also provided data for liver consumption (OR, 1.43; 95% CI, 1.01–1.99). [The Working Group noted that the study population appeared to overlap with those studied by Soler et al. (1998), Tavani et al. (2000), Polesel et al. (2010), and Di Maso et al. (2013).]

Polesel et al. (2010) reported the results of a hospital-based case–control study of pancreatic cancer conducted from 1991 to 2008 in northern Italy. [The study population appeared to overlap with that studied by Tavani et al. (2000).] Cases were 326 men and women with incident pancreatic cancer. Controls were 652 hospital patients admitted for acute conditions. Dietary intake of red meat was collected from a validated questionnaire with 78 items. Cooking methods were assessed for all meats combined. After adjusting for important potential confounders, the multivariate odds ratio for the highest versus the lowest quintile of red meat consumption was 1.99 (95% CI, 1.18–3.36). Data were also reported for pork and processed meat combined (multivariate OR, 1.25; 95% CI, 0.85–1.84; $P_{trend} = 0.27$). [The definition of red meat was not reported. and data were not reported for pork and processed meat separately. The Working Group judged the data on cooking methods to be uninformative, as they were reported only for all meats combined. The response rate was high for both cases and controls.]

Di Maso et al. (2013) also reported results of a hospital-based case–control study that partially overlapped with that of Tavani et al. (2000). Red meat was defined as including beef, veal, pork, horse meat, and meat sauces. The multivariate odds ratio for pancreatic cancer was 1.51 (95% CI, 1.25–1.82) per 50 g/day increment. Associations with red meat cooked in different ways were also examined, with no significant heterogeneity identified between meats cooked by roasting/grilling, boiling/stewing, and frying/pan-frying. [The Working Group noted that the results of later, overlapping studies were similar to those reported by Tavani et al. (2000), and the Tavani et al. study had a large number of cases and controls, and the definition of red meat was clearly described and did not include processed meat.]

(b) Processed meat

See Table 2.4.4 (web only; available at: http://publications.iarc.fr/564)

Lyon et al. (1993), in a population-based case–control study of cancer of the exocrine pancreas

in Utah, USA (previously described in Section 2.4.2(a)), assessed dietary intake of nitrated meats (bacon, sausages, and hot dogs) with a standardized questionnaire. The multivariate odds ratios for the highest versus the lowest level of nitrated meat consumption were 2.77 (95% CI, 1.34–5.72; $P_{trend} < 0.001$) in men and 1.08 (95% CI, 0.48–2.42; $P_{trend} = 0.15$) in women.

In a population-based case–control study in Japan from 1987 to 1992, Ohba et al. (1996) reported on the association with ham and sausage consumption. Cases were 141 pancreatic cancer patients identified from hospitals. Controls were 282 subjects randomly selected from telephone books. Dietary data were collected from an FFQ, which was administered in person to cases and by mail to controls. Only the univariate odds ratio was reported for consumption of ham/sausage > 3 times/week (OR, 0.89; 95% CI, 0.44–1.77). [The Working Group noted that this study had several limitations: sample size was small, data collection methods were different for cases and controls; questionnaire was not validated, and only univariate analysis was conducted for processed meats.]

In a population-based case–control study in California, USA (Chan et al., 2007) (as previously described in Section 2.4.2(a)), the multivariate odds ratios for intake ≥ 2 times/week versus < 1 time/month of sausage, kielbasa, salami, bologna, other processed meat sandwiches, beef or pork hot dogs were 1.8 (95% CI, 1.3–2.6) and 1.9 (95% CI, 1.3–3.0), respectively. For intake of bacon ≥ 4 times/week, the odds ratio was 1.9 (95% CI, 1.0–3.5), and for intake of beef or pork hot dogs ≥ 1 time/week, the odds ratio was 1.1 (95% CI, 0.8–1.4; $P_{trend} = 0.9$).

In a population-based case–control study of pancreatic cancer in eight Canadian provinces [previously described in Section 2.4.2(a)], Hu et al. (2008) reported that the multivariate odds ratio for the highest versus the lowest level of processed meat consumption was 1.4 (95% CI, 1.0–1.9; $P_{trend} = 0.01$).

In a hospital-based case–control study, Mizuno et al. (1992) reported the results of ham/sausage consumption and pancreatic cancer incidence from 1989 to 1990 in seven cooperating hospitals in Japan. Cases were 124 pancreatic cancer patients identified in seven cooperating hospitals in Japan. Controls were 124 sex- and age-matched patients with non-cancer conditions. Information was collected by questionnaire, but details were not reported. The sex- and age-adjusted odds ratio for consuming ham/sausage ≥ 3 times/week was 1.05 (95% CI, 0.54–2.04). [The Working Group noted that this study was small. Details of dietary assessment were not reported, and only age and sex were adjusted.]

A hospital-based case–control study in northern Italy by Soler et al. (1998), partially overlapping with studies by Tavani et al. (2000), Polesel et al. (2010), and Di Maso et al. (2013), reported a multivariate odds ratio for the highest versus the lowest frequency of ham and sausage consumption of 1.64 (95% CI, 1.24–2.18). [The Working Group took note of the high participation of cases and controls. BMI and energy were not adjusted.]

(c) Red meat and processed meat combined

Anderson et al. (2002) reported the results of a population-based case–control study of pancreatic cancer conducted from 1994 to 1998 in the upper Midwestern USA. Cases were 193 (approximately 30% participation rate) patients recruited from hospitals. Controls were 674 (59% response rate) subjects selected from drivers' licence lists or USA Health Care Financing Administration records. Dietary intake of red meat was collected from in-person interviews using an FFQ. After adjusting for potential confounders, the multivariate odds ratios for the highest versus the lowest quintile of consumption for red and processed meat combined were 2.2 (95% CI, 1.4–3.4) for grilled or barbecued meats, 1.4 (95% CI, 0.7–2.6) for fried meats, and 0.7 (95% CI, 0.4–1.2) for

broiled meats. [The Working Group noted that red meat and processed meat were combined. Detailed information on the cooking methods was available. This study had limited power, and BMI and energy were not adjusted.]

2.4.3 Meta-analyses

Associations between pancreatic cancer and consumption of red meat and processed meat were estimated in two meta-analyses published in 2012: Larsson & Wolk (2012), focused on prospective studies, and Paluszkiewicz et al. (2012), considered both cohort and case–control studies.

Larsson & Wolk (2012), in a meta-analysis based on 11 prospective studies with 6643 cases identified through PubMed and Embase searches through November 2011, reported on red and processed meat consumption. An increase in red meat consumption of 120 g/day was associated with a meta-relative risk of 1.13 (95% CI, 0.93–1.39; $P_{\text{heterogeneity}} < 0.001$; 11 studies). For processed meat, the relative risk for a 50 g/day increase in consumption was 1.19 (95% CI, 1.04–1.36; $P_{\text{heterogeneity}} = 0.46$; 7 studies). [The Working Group noted that there were no studies missing. Studies considering specific items of red or processed meat were also included. No evidence of publication bias was found.]

Paluszkiewicz et al. (2012) included cohort studies and case–control studies identified through MEDLINE, PubMed, Cochrane Library, Embase, CANCERLIT, Scopus, and Google Scholar through 2010. Six cohort studies and four case–control studies provided data for red meat. For the highest versus the lowest category of red meat intake, a statistically significant increased risk was observed for case–control studies (OR, 1.48; 95% CI, 1.25–1.76; $P_{\text{heterogeneity}} = 0.7716$), but not for cohort studies (RR, 1.14; 95% CI, 0.94–1.38; $P_{\text{heterogeneity}} = 0.004$). Analyses for processed meat were not reported. [The Working Group noted that several electronic databases were searched for relevant studies. Study quality was assessed, but how quality scores were used in the analysis was not reported. No analyses of sensitivity or publication bias were reported.]

Two large prospective studies were published since these meta-analyses, both showing no association overall between red or processed meat consumption and pancreatic cancer risk (Rohrmann et al., 2013; Jiao et al., 2015). However, results in Jiao et al. (2015) were positive for red meat before adjusting for AGEP consumption.

Table 2.4.1 Cohort studies on consumption of red meat and cancer of the pancreas

Reference, location, enrolment/follow-up period,	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Coughlin et al. (2000) USA 1982–1996	483 109 men and 619 199 women; American Cancer Society volunteers Exposure assessment method: questionnaire; four-page, self-administered questionnaire; total red meat included beef, pork, ham, hamburgers, liver, sausages, bacon, and smoked meats	Pancreas	Red meat, quartiles Men: Q1 Q2 Q3 Q4 Red meat, quartiles Women: Q1 Q2 Q3 Q4	 454 425 461 447 421 458 314 345	 1.0 1.1 (0.9–1.2) 1.1 (0.9–1.2) 1.1 (0.9–1.2) 1.0 1.0 (0.9–1.1) 0.9 (0.7–1.0) 0.9 (0.8–1.0)	Age, race, education, family history of pancreatic cancer, history of gallstones, BMI, smoking, alcohol, citrus fruits and juices, vegetables, history of diabetes mellitus
Stolzenberg-Solomon et al. (2002) Finland 1985–1997	27 111; male smokers aged 50–69 yr Exposure assessment method: questionnaire; 200-item dietary history questionnaire	Pancreas	Red meat (g/day) ≤ 93.0 > 93.0 to ≤ 117.3 > 117.3 to ≤ 141.6 > 141.6 to ≤ 175.6 ≥ 175.6 Trend-test *P* value: 0.71 Beef (g/day) ≤ 10.8 > 10.8 to ≤ 17.5 > 17.5 to ≤ 25.1 > 25.1 to ≤ 36.8 ≥ 36.8 Trend-test *P* value: 0.28 Pork (g/day) ≤ 25.2 > 25.2 to ≤ 33.1 > 33.1 to ≤ 41.2 > 41.2 to ≤ 52.5 ≥ 52.5 Trend-test *P* value: 0.96	 NR NR NR NR NR NR NR NR NR NR NR NR NR NR NR	 1.00 0.88 (0.54–1.44) 0.84 (0.51–1.39) 1.28 (0.81–2.01) 0.95 (0.58–1.56) 1.00 1.09 (0.66–1.81) 1.11 (0.67–1.83) 1.19 (0.73–1.96) 1.30 (0.79–2.12) 1.00 1.00 (0.61–1.61) 0.99 (0.61–1.60) 0.94 (0.57–1.53) 1.01 (0.62–1.64)	Age, smoking, total energy

Table 2.4.1 Cohort studies on consumption of red meat and cancer of the pancreas

Reference, location, enrolment/follow-up period,	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Michaud et al. (2003) USA 1980–1998	88 802; female registered nurses aged 30–55 yr from the USA Exposure assessment method: questionnaire; validated FFQ, assessed dietary intake in 1980, 1984, 1986, and 1990 using an SQFFQ (61 items in 1980, 131 items other years)	Pancreas	Beef, pork, or lamb as main dish (frequency)			Smoking, BMI, diabetes, total energy intake, physical activity, height, menopausal status
			Baseline consumption: < 3 times/mo	29	1.00	
			1 time/wk	60	0.97 (0.62–1.51)	
			2–4 times/wk	67	0.89 (0.56–1.42)	
			≥ 5 times/wk	22	0.75 (0.41–1.40)	
			Trend-test *P* value: 0.33			
			Beef, pork, or lamb as sandwich or mixed dish (frequency)			
			Baseline consumption: < 3 times/mo	21	1.00	
			1 time/wk	57	1.13 (0.68–1.86)	
			2–4 times/wk	55	0.91 (0.55–1.52)	
			≥ 5 times/week	45	0.95 (0.55–1.62)	
			Trend-test *P* value: 0.60			
Nöthlings et al. (2005) USA 1993–2001	190 545; African American, Latino, Japanese American, native Hawaiian, and Caucasian residents of Hawaii and California, aged 45–75 yr Exposure assessment method: questionnaire; quantitative FFQ	Pancreas	Red meat (quintile median, g/1000 kcal per day)			Sex, time in study, age at cohort entry, ethnicity, history of diabetes mellitus, familial history of pancreatic cancer, smoking status, energy intake
			4.5	86	1.00	
			11.0	95	1.06 (0.87–1.29)	
			16.8	113	1.27 (1.05–1.54)	
			23.4	83	1.03 (0.84–1.26)	
			35.0	105	1.45 (1.19–1.76)	
			Trend-test *P* value: 0.01			
			Beef (quintile median, g/1000 kcal per day)			
			3.1	93	1.00	
			7.7	103	1.01 (0.84–1.22)	
			11.8	103	1.08 (0.89–1.30)	
			16.7	89	1.02 (0.84–1.24)	
			25.9	94	1.21 (0.99–1.47)	
			Trend-test *P* value: 0.03			

Table 2.4.1 Cohort studies on consumption of red meat and cancer of the pancreas

Reference, location, enrolment/follow-up period,	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Nöthlings et al. (2005) USA 1993–2001 (cont.)			Pork (quintile median, g/1000 kcal per day)			
			0.4	75	1.00	
			1.8	87	1.14 (0.93–1.40)	
			3.5	95	1.12 (0.91–1.39)	
			5.7	112	1.44 (1.18–1.76)	
			9.7	113	1.53 (1.25–1.87)	
			Trend-test *P* value: 0.01			
Larsson et al. (2006) Sweden 1987–2004	61 433; women born between 1914 and 1948 and residing in Uppsala and Västmanland counties, central Sweden Exposure assessment method: questionnaire; 67- and 96-item FFQ; "red meat" was minced meat (hamburgers, meatballs, meatloaf, etc.); casserole with beef, pork, or veal; and whole beef (steaks, roasts, etc.)	Pancreas	Red meat (servings/wk)			Age, BMI, smoking, alcohol intake, education, total energy intake, folate, processed meat, poultry, eggs
			Baseline consumption: < 1.5	38	1.00	
			1.5 to < 2.5	32	1.15 (0.70–1.89)	
			2.5 to < 4.0	76	1.30 (0.85–2.00)	
			≥ 4.0	26	1.33 (0.77–2.31)	
			Trend-test *P* value: 0.07			
			Red meat (servings/wk)			
			Updated average consumption: < 1.5	31	1.00	
			1.5 to < 2.5	42	1.62 (1.00–2.64)	
			2.5 to < 4.0	70	1.34 (0.85–2.13)	
			≥ 4.0	29	1.73 (0.99–2.98)	
			Trend-test *P* value: 0.01			
Lin et al. (2006) Japan 1988–1999	110 792 (46 465 men, 64 327 women); Japanese residing in 45 areas throughout Japan Exposure assessment method: questionnaire; 33-item FFQ	Pancreas	Beef (frequency)			Age, area, pack-years of smoking
			Men: 0–2 times/mo	65	1.00	
			1–4 times/wk	25	0.60 (0.37–0.99)	
			Almost every day	4	2.30 (0.83–6.39)	
			Trend-test *P* value: 0.33			

Table 2.4.1 Cohort studies on consumption of red meat and cancer of the pancreas

Reference, location, enrolment/follow-up period,	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Lin et al. (2006) Japan 1988–1999 (cont.)			Beef (frequency)			
			Women: 0–2 times/mo	61	1.00	
			1–4 times/wk	35	1.10 (0.69–1.74)	
			Almost every day	1	0.98 (0.14–7.11)	
			Trend-test *P* value: 0.74			
			Pork (frequency)			
			Men: 0–2 times/mo	34	1.00	
			1–4 times/wk	67	1.15 (0.74–1.80)	
			Almost every day	5	1.63 (0.62–4.26)	
			Trend-test *P* value: 0.34			
			Pork (frequency)			
			Women: 0–2 times/mo	39	1.00	
			1–4 times/wk	71	1.11 (0.69–1.67)	
			Almost every day	6	1.71 (0.71–4.09)	
			Trend-test *P* value: 0.35			
Stolzenberg-Solomon et al. (2007) USA 1995–2000	537 302; National Institutes of Health – American Association of Retired Persons (NIH-AARP) Diet and Health Study Exposure assessment method: questionnaire	Pancreas	Red meat consumption (highest vs lowest category)			Smoking, energy-adjusted saturated fat
			Men	147	1.42 (1.05–1.91)	
			Women	47	0.69 (0.45–1.05)	

Table 2.4.1 Cohort studies on consumption of red meat and cancer of the pancreas

Reference, location, enrolment/follow-up period,	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Heinen et al. (2009) The Netherlands 1986–1999	120 852; men and women aged 55–69 yr at enrolment Exposure assessment method: questionnaire; 150-item FFQ	Pancreas	Red meat, quintiles			Sex, age, energy intake, smoking, alcohol, diabetes, hypertension, vegetable and fruit intake
			Q1	70	1.00	
			Q2	69	0.98 (0.69–1.39)	
			Q3	67	0.93 (0.65–1.34)	
			Q4	84	1.14 (0.80–1.61)	
			Q5	60	0.75 (0.52–1.09)	
			Trend-test *P* value: 0.23			
			Beef, quintiles			
			Q1	65	1.00	
			Q2	75	1.16 (0.81–1.66)	
			Q3	70	0.99 (0.69–1.42)	
			Q4	56	0.81 (0.56–1.18)	
			Q5	84	1.20 (0.84–1.72)	
			Trend-test *P* value: 0.61			
			Pork, quintiles			
			Q1	76	1.00	
			Q2	64	0.85 (0.60–1.22)	
			Q3	70	0.89 (0.63–1.26)	
			Q4	80	1.01 (0.72–1.43)	
			Q5	60	0.75 (0.52–1.08)	
			Trend-test *P* value: 0.27			
			Minced meat, quintiles			
			Q1	75	1.00	
			Q2	65	0.79 (0.56–1.13)	
			Q3	84	1.02 (0.73–1.43)	
			Q4	61	0.75 (0.52–1.07)	
			Q5	65	0.78 (0.54–1.10)	
			Trend-test *P* value: 0.16			
			Liver (g/day)			
			> 0	130	1.05 (0.83–1.33)	

Table 2.4.1 Cohort studies on consumption of red meat and cancer of the pancreas

Reference, location, enrolment/follow-up period,	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Inoue-Choi et al. (2011) Iowa, USA 1986–2007	34 642; postmenopausal women aged 55 to 69 yr Exposure assessment method: questionnaire; FFQ	Pancreas	Red meat (mean, servings/wk)			Age, race, education, alcohol intake, smoking, physical activity
			2.0	54	1.00	
			3.5	43	0.85 (0.57–1.28)	
			5.0	52	0.99 (0.67–1.47)	
			7.0	55	1.06 (0.72–1.55)	
			9.0	52	0.97 (0.65–1.44)	
			Trend-test *P* value: 0.79			
Anderson et al. (2012) USA 1993–2007	62,581; women and men aged 55–74 yr Exposure assessment method: FFQ (170 questions)	Pancreas	Red meat, rare to medium well done			Age, sex, education, diabetes, dietary fat intake, cigarette smoking history, race
			Q1	53	1.00	
			Q2	57	1.11 (0.76–1.63)	
			Q3	43	0.81 (0.54–1.21)	
			Q4	50	0.91 (0.61–1.34)	
			Q5	45	0.84 (0.55–1.29)	
			Trend-test *P* value: 0.364			
			Red meat, well to very well done			
			Q1	39	1.00	
			Q2	58	1.52 (1.01–2.29)	
			Q3	47	1.25 (0.81–1.92)	
			Q4	49	1.37 (0.88–2.12)	
			Q5	55	1.60 (1.01–2.54)	
			Trend-test *P* value: 0.039			
			Red barbecued meat, rare to medium well done			
			Q1–Q4	209	1.00	
			Q5	39	0.79 (0.55–1.13)	
			Red barbecued meat, well to very well done			
			Q1–Q4	192	1.00	
			Q5	56	1.35 (1.00–1.83)	
			Pork chops, cooking method			
			Do not eat	19	1.00	
			Baked	67	1.44 (0.86–2.40)	
			Oven-broiled	31	1.78 (1.00–3.17)	
			Pan-fried	86	1.74 (1.05–2.90)	
			Grilled or barbecued	42	1.80 (1.04–3.13)	

Table 2.4.1 Cohort studies on consumption of red meat and cancer of the pancreas

Reference, location, enrolment/follow-up period,	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Anderson et al. (2012) USA 1993–2007 (cont.)			Hamburger, cooking method			
			Do not eat	11	1.00	
			Oven-broiled	23	1.11 (0.54–2.30)	
			Pan-fried	75	1.32 (0.69–2.51)	
			Grilled or barbecued	133	1.43 (0.77–2.67)	
			Steak, cooking method			
			Do not eat	20	1.00	
			Oven-broiled	76	1.15 (0.70–1.89)	
			Pan-fried	32	1.10 (0.62–1.94)	
			Grilled or barbecued	119	0.93 (0.57–1.50)	
			Hamburger, doneness preference			
			Do not eat	10	1.00	
			Rare or medium rare	26	1.40 (0.67–2.93)	
			Medium	38	0.88 (0.43–1.78)	
			Medium well done	60	1.04 (0.53–2.06)	
			Well done	99	1.32 (0.68–2.55)	
			Very well done	15	1.39 (0.62–3.11)	
			Steak, doneness preference			
			Do not eat	13	1.00	
			Rare or medium rare	72	1.43 (0.79–2.61)	
			Medium	55	0.99 (0.54–1.83)	
			Medium well done	61	1.16 (0.64–2.13)	
			Well done	35	1.19 (0.62–2.26)	
			Very well done	12	1.68 (0.76–3.70)	
Rohrmann et al. (2013) Europe 1992–2008	477 202; European Prospective Investigation into Cancer and Nutrition (EPIC) participants from 10 European countries Exposure assessment method: questionnaire	Pancreas	Red meat intake (g/day)			Area, sex, age, height, weight, physical activity index, smoking, education, history of diabetes mellitus, total energy
			0 to < 20	176	1.00	
			20 to < 40	215	1.01 (0.82–1.24)	
			40 to < 80	291	0.99 (0.80–1.22)	
			≥ 80	183	1.07 (0.83–1.38)	
			Per 50 g observed	865	1.05 (0.94–1.17)	
			Per 50 g calibrated	865	1.03 (0.93–1.14)	

Table 2.4.1 Cohort studies on consumption of red meat and cancer of the pancreas

Reference, location, enrolment/follow-up period,	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Rohrmann et al. (2013) Europe 1992–2008 (cont.)			Red meat intake (g/day)			
			Men: 0 to < 20	58	1.00	
			20 to < 40	84	1.01 (0.71–1.43)	
			40 to < 80	134	0.95 (0.67–1.35)	
			≥ 80	120	0.94 (0.63–1.40)	
			Trend-test *P* value: 0.53			
			Red meat intake (g/day)			
			Women: 0 to < 20	118	1.00	
			20 to < 40	131	1.01 (0.78–1.31)	
			40 to < 80	157	1.00 (0.76–1.32)	
			≥ 80	63	1.23 (0.87–1.75)	
Jiao et al. (2015) USA 1995–2006	567 169; members of the National Institutes of Health – American Association of Retired Persons (NIH-AARP) aged 50–71 yr, in six states Exposure assessment method: questionnaire; 124-item, 12-mo FFQ	Pancreas	Red meat intake (g/1000 kcal)			Age, race, education, diabetes, smoking status, first-degree family history of cancer, BMI, alcohol consumption, carbohydrate intake, saturated fat
			Men: 0–30.2	242	1.00	
			30.3–51.8	268	1.19 (0.99–1.42)	
			51.9–76.6	282	1.09 (0.90–1.32)	
			76.7–115.5	302	1.17 (0.95–1.43)	
			115.6–972.8	313	1.35 (1.07–0.70)	
			Trend-test *P* value: 0.05			
			Red meat cooked at high temperatures (g/1000 kcal)			
			Men: 0–9.2	245	1.00	
			9.3–18.0	255	0.87 (0.69–1.10)	
			18.1–29.7	294	1.23 (0.98–1.54)	
			29.8–49.2	300	1.01 (0.78–1.30)	
			49.3–693.7	313	1.18 (0.89–1.56)	
			Trend-test *P* value: 0.01			

BMI, body mass index; CVI, confidence interval; FFQ, food frequency questionnaire; mo, month; NR, not reported; SQFFQ, semi-quantitative food frequency questionnaire; wk, week; yr, year

Table 2.4.3 Case–control studies on consumption of red meat and cancer of the pancreas

Reference, location, enrolment	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/deaths	Risk estimate (95% CI)	Covariates controlled
Lyon et al. (1993) Utah, USA 1984–1987	Cases: 149; Utah Cancer Registry Controls: 363; random digit dialling and health care financing records Exposure assessment method: questionnaire; 32-item FFQ; red meat included beef and pork	Pancreas	Red meat Men: Low	30	1.00	Age, smoking, consumption of coffee and alcohol
			Medium	16	0.64 (0.30–1.37)	
			High	41	1.41 (0.72–2.75)	
			Trend-test *P* value: 0.3			
			Red meat Women: Low	16	1.00	
			Medium	23	1.05 (0.47–2.34)	
			High	21	1.44 (0.65–3.20)	
			Trend-test *P* value: 0.45			
Ji et al. (1995) Shanghai, China 1990–1993	Cases: 451; rapid reporting system; residents in Shanghai aged 30–74 yr Controls: 1552; Shanghai general population, frequency-matched by age and sex Exposure assessment method: questionnaire; 86-item FFQ; no validation data were reported	Pancreas	Red meat (servings/mo) Men: ≤ 13.7	NR	1.00	Age. income, smoking, green tea drinking (females only), response status
			13.8–22.5	NR	0.64 (0.42–0.99)	
			22.6–37.7	NR	0.76 (0.50–1.15)	
			≥ 37.8	NR	0.73 (0.47–1.12)	
			Trend-test *P* value: 0.24			
			Red meat (servings/mo) Women: ≤ 10.7	NR	1.00	
			10.7–19.8	NR	1.34 (0.81–2.21)	
			19.9–33.1	NR	0.83 (0.47–1.43)	
			≥ 33.0	NR	1.24 (0.73–2.13)	
			Trend-test *P* value: 0.86			

Table 2.4.3 Case–control studies on consumption of red meat and cancer of the pancreas

Reference, location, enrolment	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/deaths	Risk estimate (95% CI)	Covariates controlled
Tavani et al. (2000) Italy 1983–1996	Cases: 362; patients at several hospitals aged < 75 yr Controls: 7990; patients aged < 75 yr in the same network of hospitals for acute non-cancer conditions Exposure assessment method: questionnaire; FFQ with approximately 40 foods; red meat defined as beef, veal, and pork, excluding canned and preserved	Pancreas	Red meat consumption (median, times/wk) 3 5 7 Trend-test *P* value: ≤ 0.01	 115 120 127	 1.0 1.2 (0.9–1.6) 1.6 (1.2–2.1)	Age; year of recruitment; sex; education; smoking habits; alcohol, fat, fruit, and vegetable intakes
Anderson et al. (2002) USA 1994–1998	Cases: 193; incident cases aged ≥ 20 yr from area hospitals and clinics Controls: 674; aged ≥ 20 yr from drivers' licence and health care financing records; matched by age, sex, and race Exposure assessment method: questionnaire; in-person FFQ; "red meat" included bacon, sausage, and ham	Pancreas	Grilled/barbecued red meat (g/day) 0 0.9–3.5 3.7–10.7 10.8–88.0 Trend-test *P* value: < .001 Fried red meat (g/day) 0–1.1 1.2–4.6 4.7–11.5 11.7–24.1 24.2–192.6 Trend-test *P* value: 0.90 Broiled red meat (g/day) 0–0.49 0.50–4.90 5.00–11.70 12.00–171.10 Trend-test *P* value: 0,08	 77 14 36 66 25 26 55 44 43 102 31 28 32	 1.0 1.4 (0.7–2.7) 1.2 (0.7–1.9) 2.2 (1.4–3.4) 1.0 1.1 (0.6–2.0) 1.9 (1.1–3.3) 1.6 (0.9–2.8) 1.4 (0.7–2.6) 1.0 0.9 (0.5–1.4) 0.7 (0.4–1.1) 0.7 (0.4–1.2)	Age, sex, smoking, education, race, diabetes, red meat cooked by other methods

Table 2.4.3 Case–control studies on consumption of red meat and cancer of the pancreas

Reference, location, enrolment	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/deaths	Risk estimate (95% CI)	Covariates controlled
Chan et al. (2007) USA 1995–1999	Cases: 532; from Northern California Cancer Center and aged 21–85 yr Controls: 1701; general population, identified by random digit dialling; matched by age and sex Exposure assessment method: questionnaire; validated, 131-item FFQ; red meat included bacon and other processed meats	Pancreas	Beef or lamb as main dish (frequency)			Age, sex, energy intake, BMI, race, education, smoking, diabetes
			< 1 time/mo	107	1.0	
			1–3 times/mo	175	1.2 (0.9–1.6)	
			1 time/wk	127	1.1 (0.8–1.5)	
			2–4 times/wk	102	1.4 (1.0–2.0)	
			≥ 5 times/wk	14	2.2 (1.0–4.5)	
			Trend-test *P* value: 0.03			
			Pork as main dish (frequency)			
			< 1 time/mo	132	1.0	
			1–3 times/mo	113	0.9 (0.7–1.2)	
			1 time/wk	57	0.9 (0.6–1.4)	
			≥ 2 times/wk	11	0.6 (0.3–1.1)	
			Trend-test *P* value: 0.2			
			Hamburger (frequency)			
			< 1 time/mo	230	1.0	
			1–3 times/mo	134	1.1 (0.8–1.4)	
			1 time/wk	92	1.3 (1.0–1.7)	
			≥ 2 times/wk	70	1.7 (1.2–2.4)	
			Trend-test *P* value: 0.005			
Hu et al. (2008) Canada 1994–1997	Cases: 628; aged 20–76 yr from provincial cancer registries Controls: 5039; random sample within provinces, frequency-matched by age and sex Exposure assessment method: questionnaire; Block FFQ, short version (69 items)	Pancreas	Red meat (servings/wk)			Age, province, education, BMI, sex, alcohol use, smoking, total vegetable and fruit intake, total energy intake
			Q1	NR	1.0	
			Q2	NR	1.2 (0.9–1.5)	
			Q3	NR	1.3 (1.0–1.7)	
			Q4	NR	1.1 (0.9–1.5)	
			Trend-test *P* value: 0.31			

Table 2.4.3 Case–control studies on consumption of red meat and cancer of the pancreas

Reference, location, enrolment	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/deaths	Risk estimate (95% CI)	Covariates controlled
Anderson et al. (2009) Canada 2003–2007	Cases: 422; Ontario Cancer Registry Controls: 312; random digit dialling Exposure assessment method: questionnaire; mailed questionnaire, but a full FFQ was not administered; validity was not reported	Pancreas	Red meat (servings/wk) ≤ 1 2–3 > 3	 99 151 131	 1.00 1.16 (0.78–1.72) 1.49 (0.98–2.28)	Age
Polesel et al. (2010) Italy 1991–2008	Cases: 326; incident cases admitted to major general hospitals Controls: 652; hospital patients with various acute conditions, matched by study centre, sex, and age Exposure assessment method: questionnaire; 78-item FFQ on average weekly consumption in the past 2 yr; meat-cooking methods assessed, but definition of red meat was not specified	Pancreas	Red meat (median, servings/wk) 1.00 2.25 3.25 4.25 6.25 Trend-test *P* value: 0.01 Pork and processed meat (median, servings/wk) 1.50 3.00 5.00 Trend-test *P* value: 0.27	 43 51 51 84 97 89 115 122	 1.00 1.26 (0.75–2.12) 1.69 (0.98–2.91) 1.79 (1.09–2.96) 1.99 (1.18–3.36) 1.00 1.18 (0.81–1.73) 1.25 (0.85–1.84)	Year of interview, education, tobacco smoking, alcohol drinking, self-reported history of diabetes, BMI, total energy, study centre, age, sex
Di Maso et al. (2013) Italy, Switzerland 1991–2009	Cases: 326; incident cases from major hospitals Controls: 652; patients in the same hospitals with acute conditions Exposure assessment method: questionnaire; validated FFQ; red meat included beef, veal, pork, horse meat, and meat sauces	Pancreas	Red meat intake (g/day) < 60 60–89 ≥ 90 Increase of 50 g/day Trend-test *P* value: < 0.01	 96 96 134 326	 1.00 1.42 (0.98–2.07) 2.18 (1.51–3.16) 1.51 (1.25–1.82)	Study centre, age, sex, education, year, BMI, tobacco, alcohol, fruit and vegetable consumption

BMI, body mass index; CI, confidence interval; FFQ, food frequency questionnaire; mo, month; NR, not reported; wk, week; yr, year

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2.5 Cancer of the prostate

2.5.1 Cohort studies

See Table 2.5.1 (red meat) and Table 2.5.2 (processed meat, web only; available at: http://publications.iarc.fr/564)

The quality of the studies was evaluated based on sample size, quality of reporting of the type of meat, consideration of relevant confounders, study design issues (e.g. population- vs hospital-based design, response rates), and exposure assessment, including validation of dietary questionnaires. The Working Group considered total energy intake, BMI, and race as important potential confounders. Cancer of the prostate poses a special problem compared with other sites because there is a broad range of clinical behaviours, and the classification is not uniform across studies (e.g. grade, stage, Gleason score, or other definitions of clinical aggressiveness). In addition, the widespread use of prostate-specific antigen (PSA) testing, which may be associated with dietary habits, further complicates the interpretation of epidemiological findings.

More than 20 cohort studies have reported on the intake of red meat or processed meat and the incidence or mortality (when incident cases were also considered) from prostate cancer, spanning from 1984 to 2011. The Americas, Asia, and Europe were represented, with studies from Japan, Norway, the Netherlands, the United Kingdom, and the USA.

The most informative cohorts were published by Schuurman et al. (1999), Michaud et al. (2001), Cross et al. (2005) (PLCO randomized trial), Rodriguez et al. (2006), Park et al. (2007), Allen et al. (2008), Koutros et al. (2008), Agalliu et al. (2011), and Major et al. (2011), and several of these studies were included in a pooled analysis of 15 prospective cohort studies (Wu et al., 2016).

Studies with fewer than 100 exposed cases are not described further in the text or tables (e.g. Gann et al., 1994; Giovannucci et al., 1993; Loh et al., 2010; Phillips & Snowdon, 1983; Richman et al., 2011; Rohrmann et al., 2007; Sander et al., 2011; Snowdon et al., 1984; Veierød et al., 1997; Wu et al., 2006).

(a) Pooling Project of Prospective Studies of Diet and Cancer

The Pooling Project of Prospective Studies of Diet and Cancer (DCPP) (Wu et al., 2016) pooled data from 15 of the prospective cohorts conducted globally (Ahn et al., 2008; Neuhouser et al., 2007; Rohrmann et al., 2007; Rodriguez et al., 2006; Larsson et al., 2009; Allen et al., 2008; Michaud et al., 2001; Kurahashi et al., 2008; Muller et al., 2009; Park et al., 2007; Schuurman et al., 1999; Sinha et al., 2009; Kristal et al., 2010; Cross et al., 2005). The individual studies included in the DCPP are not described in detail in the text and tables because the analysis was superseded by Wu et al. (2016).

Among over 700 000 men, 52 683 incident cases of prostate cancer, including 4924 advanced cases, were identified. Methods of ascertainment of meat intake and outcome measures were harmonized across cohorts (all dietary instruments were validated). Median intakes of red meat ranged from 10.3 g/day in a Japanese cohort to 109 g/day in a Melbourne cohort.

A modest positive association was found between the highest category of red meat consumption and prostate tumours identified as advanced stage at diagnosis (RR, 1.19; 95% CI, 1.01–1.40; P_{trend} = 0.07; $P_{heterogeneity}$ = 0.47). For processed meat, the corresponding relative risk was 1.17 (95% CI, 0.99–1.39; P_{trend} = 0.10; $P_{heterogeneity}$ = 0.94). Positive associations between red meat, and inverse associations between poultry intake, and advanced cancers were limited to North American studies.

(b) Studies not included in the pooling project

Among a cohort of farmers in the Agricultural Health Study in the USA involved in pesticide application, Koutros et al. (2008)

reported on the 668 prostate cancer cases that were identified, including 140 with advanced-stage prostate cancer. The response rate was low (about 50%). Slight increases in incident prostate cancer risk were noticed with quintiles of red meat intake, with no dose–response relationship (P_{trend} = 0.76). Doneness was associated with risk. For the second tertile of intake of well-done meat (median, 40.6 g/day), the relative risk was 1.12 (95% CI, 0.92–1.37), and for the third tertile of intake of well-done meat (median, 80.3 g/day), it was 1.26 (95% CI, 1.02–1.54; P_{trend} = 0.03). When this was limited to advanced cases, the relative risk for the second versus the first tertile (40.6 vs 18.0 g/day) was 1.63 (95% CI, 1.06–2.52), and for the third tertile versus the first tertile (median, 80.3 g/day), it was 1.97 (95% CI, 1.26–3.08; P_{trend} = 0.004). [Red meat was not clearly defined; doneness was for total meat.]

Major et al. (2011) conducted a study on African Americans within the NIH-AARP study. Levels of HAAs and polycyclic aromatic hydrocarbons (PAHs) from meats were ascertained by linking data to the NCI Computerized Heterocyclic Amines Resource for Research in Epidemiology of Disease (CHARRED) database. Haem iron intake was estimated. No association between incident prostate cancer and red meat intake was found, except for red meat cooked at high temperatures: the relative risk for the second (median, 11.40 g per 1000 kcal) versus the first tertile (3.49 g per 1000 kcal) was 1.18 (95% CI, 1.0–1.38), and for the third tertile (median, 24.74 g per 1000 kcal), it was 1.22 (95% CI, 1.03–1.44). The relative risk of the estimated exposure to the mutagen DiMeIQx for the second tertile (median, 0.93 ng per 1000 kcal) was 1.15 (95% CI, 0.93–1.42), and for the third tertile, it was 1.3 (95% CI, 1.05–1.61; P_{trend} = 0.02). No associations were observed with intake of other HAAs. The results for processed meat were inconclusive. [The Working Group noted that red meat included all types of beef and pork.]

Agalliu et al. (2011) described a nested case–cohort study in a Canadian cohort, with 702 cases and 1979 controls (subcohort), who were alumni of the University of Alberta. Elevated relative risks were reported for red meat, but none reached statistical significance, except Q5 (median, 3.1 oz [~87.8 g/day]) vs Q1 (median, 0.7 oz [~19.8 g/day]); the relative risk was 1.44 (95% CI, 1.06–1.95). There was no dose–response relationship. [The Working Group noted that red meat was not defined.]

2.5.2 Case–control studies

See Table 2.5.3 (red meat) and Table 2.5.4 (processed meat, web only; available at: http://publications.iarc.fr/564)

More than 20 case–control studies were considered, six with a population-based design. The Working Group considered first the population-based studies that tended to be more informative, given the uncertainty in the choice of hospital controls, who were affected by diseases that could have possibly had an impact on dietary habits. Studies with fewer than 100 cases were excluded (see details below).

(a) Population-based studies

Slattery et al. (1990) was not considered here because meat intake was considered together with estimated intake of saturated fats. Studies by Nowell et al. (2004) and Ukoli et al. (2009) were excluded because numbers were small, or dietary assessment was limited.

Norrish et al. (1999) conducted a population-based study in New Zealand that included 317 cases and 480 controls randomly selected from electoral rolls. They used a 107-item FFQ. An association was found with intake of browned beef steaks. The odds ratios were 1.36 (95% CI, 0.84–2.18) for medium/lightly browned and 1.68 (95% CI, 1.02–2.77) for well browned. Similar, but not statistically significant, associations were found in advanced cases. The researchers also

looked separately at other types of red meats, including pork, lamb, and minced beefand, processed meats including sausage, and bacon, with null results.

Wright et al. (2011) conducted a population-based study that included 1754 cases and 1645 controls identified by random digit dialling. Response rates were high (78%) in cases and lower (67%) in controls. Detailed clinical data were obtained for the cases. Disease aggressiveness was based on a composite variable incorporating Gleason score stage and PSA, where more aggressive cases were defined by a Gleason score of ≥ 7, non-localized stage, or PSA > 20 ng/mL at the time of diagnosis. A positive association was found with increasing servings per day (1 serving/day) of red meat. The odds ratios were 1.21 (95% CI, 0.97–1.51) for 0.59–1.09 servings/day and 1.43 (95% CI, 1.11–1.84) for > 1.09 servings/day. [The definition of red meat was unclear.] Similar associations were found among less and more aggressive cancer cases.

Joshi et al. (2012) conducted a study in the USA, with 717 localized and 1140 advanced incident cases, in a multiethnic population. Controls were selected with a "neighbourhood walking algorithm" or randomly from a health care financing organization. [The degree of selection bias with this type of procedure was uncertain, as selection was conditioned by local characteristics, such as the social structure of the neighbourhood and the nature of the financing organization.] The response rate was not given. Accurate dietary histories were collected with a modified version of the Block FFQ. No association with red meat intake was found, except when hamburgers cooked at high temperatures were considered, and only among advanced cases. The odds ratios were 1.3 (95% CI, 1.0–1.6) for low frequency (< 4.4 g/1000 kcal) versus never, 1.4 (95% CI, 1.0–1.8) for medium frequency (≥ 4.4 to < 7.9 g/1000 kcal), and 1.7 (95% CI, 1.3–2.2) for high frequency (≥ 7.9 g/1000 kcal). Associations were particularly strong for pan-fried red meat; subgroup analyses and multiple comparisons were considered. Previously, John et al. (2011) had reported on the San Francisco Bay Area portion of this study (John et al., 2011). In that study, advanced prostate cancer cases showed an association with increasing tertiles of total red meat intake versus no intake. The odds ratios were 1.1 (95% CI, 0.68–1.79), 1.65 (95% CI, 1.02–2.65), and 1.53 (95% CI, 0.93–2.49; P_{trend} = 0.02). Similar associations with advanced cases were found for hamburgers, steaks, and processed meat. The odds ratios for processed meat (increasing tertiles versus no intake) were 1.25 (95% CI, 0.85–1.83), 1.15 (95% CI, 0.77–1.71), and 1.57 (95% CI, 1.04–2.36), again with no clear dose–response. This study also examined cooking methods and meat mutagens.

(b) Hospital-based studies

The following hospital-based studies were given less weight for different reasons: Bashir et al. (2014), as no details given on the choice of controls; Li et al. (2014), as no response rates and limited exposure assessment; Mahmood et al. (2012), as no details on exposure assessment and no response rates; Punnen et al. (2011), as no response rates, no adjustment for total energy intake, and only cases with Gleason ≥ 7 included; Rodrigues et al. (2011), as no response rates and no adjustment for energy intake; Román et al. (2014), as no response rates and source of controls not identified; Rosato et al. (2014), as no response rates and results not given for meat as such; Salem et al. (2011), as diagnoses in controls not specified and poor dietary history; Sonoda et al. (2004), as no response rates and limited adjustment for confounders; Subahir et al. (2009), as diseases of controls not specified and no response rates; Sung et al. (1999), as no response rates, unclear adjustment for confounders, and limited dietary history; Walker et al. (2005), as no response rates for controls and only dietary patterns examined; and De Stefani et al. (1995), as the distinction between red and white meat was unclear. These

studies are not further described in the text and tables.

Deneo-Pellegrini et al. (1999) described a study in Uruguay with cancer-free controls, with small numbers. For red meat and for processed meat, the slightly elevated odds ratios were not statistically significant. An update of the same study was published by the same authors with similar results (Deneo-Pellegrini et al. (2012).

Aune et al. (2009) conducted a hospital-based study on multiple cancers in Uruguay, with 345 histologically confirmed cases. A 64-item FFQ validated was used. An association was found with red meat. The odds ratio for the second (150 to < 250 g/day) versus the first (0 to < 150 g/day) tertile was 1.56 (95% CI, 1.15–2.13), and the odds ratio for the third (250–600 g/day) versus the first tertile was 1.87 (95% CI, 1.08–3.21; P_{trend} = 0.001). No association was found with processed meat. [The Working Group noted that the results were adjusted for energy intake, BMI, and numerous other risk factors.]

Among those given less priority, Punnen et al. (2011) is worth mentioning because of the relatively large size of the study (466 cases). They found an association with an increasing intake of grilled beef. The odds ratios were 1.5 (95% CI, 1.03–2.19) for low intake versus none, 1.69 (95% CI, 1.19–2.38) for medium intake versus none, and 1.61 (95% CI, 1.13–2.28) (P_{trend} = 0.004) for high intake versus none. The odds ratios with increasing intake of grilled hamburgers versus no intake were 1.41 (95% CI, 0.99–2.01), 1.58 (95% CI, 1.11–2.24), and 1.86, (95% CI, 1.28–2.71; P_{trend} = 0.001).

Di Maso et al. (2013) published results based on data from a large hospital-based study in Italy (1294 cases, non-neoplastic controls). They reported slightly elevated odds ratios for red meat, which were not statistically significant.

(c) Other studies

Amin et al. (2008), in Canada, recruited 1356 subjects with increased PSA undergoing a prostate biopsy, comparing those with a cancer diagnosis with the others. All men were asked to respond to a self-administered, validated FFQ (included only 12 food groups) before the procedure; the procedure was a biopsy administered after a rising serum PSA level or a suspicious digital rectal examination. Increased odds ratios with intake of red meat (including ham and sausages) were found, with an apparent dose–response relationship across quintiles. The odds ratio for Q4 (5 servings/week) versus Q1 (1 serving/week) was 2.31 (95% CI, 1.32–2.46), and for Q5 (data missing or unavailable) versus Q1, it was 2.91 (95% CI, 1.56–4.87; P_{trend} = 0.027). [The Working Group noted that there was apparently a low response rate among controls. This study was of interest because both cases and controls had high PSA. That is, screening was not a source of confounding, the FFQ was administered when PSA was measured, and the identification of cases occurred after, so recall bias could be reasonably ruled out. Red meat included ham and sausages and so corresponded to red meat and processed meat combined.]

Table 2.5.1 Cohort studies on consumption of red meat and cancer of the prostate

Reference, location, enrolment/follow-up period, study design	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Koutros et al. (2008) USA Recruitment, 1993–1997 Cohort study	23 080 men, 197 017 person-years, 668 prostate cancer cases (140 advanced); Agricultural Health Study included 57 311 licenced pesticide applicators from Iowa and North Carolina; 23 080 available for analysis Exposure assessment method: questionnaire; frequency of intake of hamburgers, beef steaks, chicken, pork chops/ham steaks, and bacon/sausage in the last 12 mo; doneness of total meat and cooking methods [red meat was not clearly defined]	Prostate: incident cases	Red meat (median, g/day)			Age, state of residence, race, smoking, family history of prostate cancer
			Q1 (23.2)	145	1.00	
			Q2 (42.5)	143	1.28 (1.15–1.62)	
			Q3 (60.9)	121	1.15 (0.90–1.48)	
			Q4 (81.6)	109	1.16 (0.90–1.50)	
			Q5 (122.3)	95	1.11 (0.84–1.46)	
			Trend-test *P* value: 0.76			
		Prostate: incident cases	Doneness level, well- and very well-done total meat (median, g/day)			
			T1 (18.0)	187	1.00	
			T2 (40.6)	212	1.12 (0.92–1.37)	
			T3 (80.3)	214	1.26 (1.02–1.54)	
			Trend-test *P* value: 0.03			
		Prostate: (aggressive/ advanced)	Doneness level, very well-done total meat (median, g/day)			
			T1 (18.0)	35	1.00	
			T2 (40.6)	51	1.63 (1.06–2.52)	
			T3 (80.3)	54	1.97 (1.26–3.08)	
			Trend-test *P* value: 0.004			
		Prostate: incident cases	Doneness level, rare or medium total meat (median, g/day)			
			T1 (0)	239	1.00	
			T2 (18.0)	205	1.06 (0.87–1.29)	
			T3 (63.0)	169	1.04 (0.84–1.29)	
			Trend-test *P* value: 0.8			

Table 2.5.1 Cohort studies on consumption of red meat and cancer of the prostate

Reference, location, enrolment/follow-up period, study design	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Agalliu et al. (2011) Canada 1995–1998 Cohort study	702 cases and 1979 controls (subcohort); prospective cohort of 73 909 men and women, mainly alumni of the University of Alberta, (34 291 men) Exposure assessment method: questionnaire; 166 food items and validated; red meat was not defined	Prostate	Quintiles of red meat intake [median, g/day]			Age, race, BMI, physical activity, education
			Q1 [19.8]	108	1.00	
			Q2 [36. 8]	124	1.10 (0.80–1.50)	
			Q3 [48.2]	151	1.33 (0.98–1.80)	
			Q4 [62.3]	128	1.18 (0.87–1.61)	
			Q5 [87.8]	150	1.44 (1.06–1.95)	
			Trend-test *P* value: 0.04			
		Prostate (aggressive/ advanced)	Quintiles of red meat intake [median, g/day]			
			Q1 [19.8]	28	1.00	
			Q2 [36.8]	40	1.44 (0.85–2.43)	
			Q3 [48.2]	37	1.30 (0.76–2.23)	
			Q4 [62.3]	32	1.17 (0.67–2.03)	
			Q5 [87.8]	36	1.38 (0.80–2.39)	
			Trend-test *P* value: 0.10			
Major et al. (2011) USA Enrolment, 1995–1996 Cohort study	Prospective cohort of 7949 men; from National Institutes of Health – American Association of Retired Persons (NIH-AARP) Diet and Health Study; men and women aged 50–57 yr; 556 401 people, including 9304 African American men (after exclusions, 7949) Exposure assessment method: questionnaire; 124-item FFQ on previous 12 mo; "red meat" included all types of beef and pork	Prostate	Quintiles of red meat (median intake, g/1000 kcal)			Age, BMI, smoking, education, marital status, alcohol consumption, health status, family history of prostate cancer, family history of diabetes, fruit intake
			Q1 (8.42)	244	1.00	
			Q2 (19.35)	225	0.99 (0.82–1.19)	
			Q3 (29.17)	226	1.05 (0.87–1.26)	
			Q4 (40.32)	213	1.01 (0.83–1.24)	
			Q5 (60.92)	181	0.92 (0.75–1.14)	
			Trend-test *P* value: 0.48			
		Prostate	Tertiles of red meat cooked at high temperatures (median intake, g/1000 kcal)			
			T1 (3.49)	365	1.00	
			T2 (11.40)	373	1.18 (1.00–1.38)	
			T3 (24.74)	351	1.22 (1.03–1.44)	
			Trend-test *P* value: 0.04			

Table 2.5.1 Cohort studies on consumption of red meat and cancer of the prostate

Reference, location, enrolment/follow-up period, study design	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/ deaths	Risk estimate (95% CI)	Covariates controlled
Major et al. (2011) USA Enrolment, 1995–1996 Cohort study (cont.)		Prostate	Tertiles of red meat cooked at low temperatures (median intake, g/1000 kcal)			
			T1 (6.63)	405	1.00	
			T2 (15.36)	368	0.91 (0.78–1.06)	
			T3 (29.06)	316	0.84 (0.71–0.99)	
			Trend-test *P* value: 0.05			
		Prostate: advanced cases	Tertiles of red meat cooked at high temperatures (median intake, g/1000 kcal)			
			T1 (3.49)	34	1.00	
			T2 (11.40)	35	1.23 (0.74–2.06)	
			T3 (24.74)	39	1.44 (0.83–2.47)	
			Trend-test *P* value: 0.20			
Wu et al. (2016) International pooled cohort consortium 1985–2009 Cohort study	842 149 men; consortium of 15 cohort studies (52 683 incident prostate cancer cases, including 4924 advanced cases) Exposure assessment method: questionnaire	Prostate (aggressive/ advanced)	Quintiles of red meat intake (g/day)			Marital status, race, education, BMI, height, alcohol intake, total energy intake, smoking status, family history of prostate cancer, physical activity, history of diabetes, multivitamin use
			Q1 (< 20)	NR	1.00	
			Q2 (20 to < 40)	NR	1.02 (0.89–1.16)	
			Q3 (40 to < 60)	NR	1.11 (0.96–1.27)	
			Q4 (60 to < 100)	NR	1.05 (0.91–1.21)	
			Q5 (≥ 100)	NR	1.19 (1.01–1.40)	
			Trend-test *P* value: 0.07			

BMI, body mass index; FFQ, food frequency questionnaire; mo, month; NR, not reported; yr, year

Table 2.5.3 Case–control studies on consumption of red meat and cancer of the prostate

Reference, location, enrolment	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/deaths	Risk estimate (95% CI)	Covariates controlled
Deneo-Pellegrini et al. (1999) Uruguay 1994–1997	Cases: 175; localized cancers, 25%; regional cancers, 72%; disseminated cancers, 3% Controls: 233; hospital patients with conditions unrelated to diet, mainly mild surgical conditions, and no cancers Exposure assessment method: questionnaire; 64 food items; red meat was beef and lamb	Prostate	Red meat, quartiles Q1 Q2 Q3 Q4 Trend-test *P* value: 0.17	 32 61 36 46	 1.0 1.5 (0.9–2.7) 1.7 (0.9–3.3) 1.7 (0.8–3.4)	Age, residence, urban/rural, education, family history, BMI, energy intake
Norrish et al. (1999) New Zealand 1996–1997	Cases: 317; population-based, histologically confirmed cases Controls: 480; controls were randomly selected from electoral rolls and matched by age Exposure assessment method: questionnaire; self-administered, 107-item FFQ	Prostate Prostate: advanced cases	Beef steak doneness Medium or lightly browned vs never eaten Well done or well browned vs never eaten Trend-test *P* value: 0.03 Beef steak doneness Medium or lightly browned vs never eaten Well done or well browned vs never eaten Trend-test *P* value: 0.16	 163 123 NR NR	 1.36 (0.84–2.18) 1.68 (1.02–2.77) 1.38 (0.78–2.42) 1.56 (0.86–2.81)	Age, socioeconomic status, total NSAIDs, total energy intake
Amin et al. (2008) Canada 2003–2006	Cases: 386 men; cohort of 1356 subjects with increased PSA who underwent prostate biopsy; cases were those with cancer at biopsy Controls: 268 men; controls had high PSA, but non-malignant lesions at biopsy Exposure assessment method: questionnaire; self-administered FFQ with 12 food groups; repeated questionnaires among 50 subjects to validate the FFQ and exclude recall bias	Prostate	Red meat, ham, and sausages; quintiles Q1 Q2 Q3 Q4 Q5 Trend-test *P* value: 0.027	 NR NR NR NR NR	 1.00 1.55 (0.85–1.69) 1.97 (0.74–2.73) 2.31 (1.32–2.46) 2.91 (1.56–4.87)	Age, ethnicity, education, family history, smoking, alcohol, sexually transmitted infection, cystitis

Table 2.5.3 Case–control studies on consumption of red meat and cancer of the prostate

Reference, location, enrolment	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/deaths	Risk estimate (95% CI)	Covariates controlled
Aune et al. (2009) Uruguay 1996–2004	Cases: 345; recruited in four major hospitals in Montevideo Controls: 2032; controls had non-neoplastic diseases not related to smoking or drinking, and no recent changes in dietary habits Exposure assessment method: questionnaire; 64 food items; FFQ tested for reproducibility (correlation coefficient between two assessments was 0.77 for red meat); red meat was defined as fresh meat, including lamb and beef	Prostate	Red meat (g/day), tertiles T1 (0 to < 150) T2 (150 to < 250) T3 (250–600) Trend-test *P* value: 0.001	 125 179 41	 1.00 1.56 (1.15–2.13) 1.87 (1.08–3.21)	Residence; age; education; income; interviewer; smoking; alcohol; intake of grains and fatty foods, fruits and vegetables; energy intake; BMI; other dietary habits
John et al. (2011) USA 1997–2000	Cases: 726; population-based, aged 40–70 yr; non-Hispanic, whites and African Americans; SEER codes 41–85 Controls: 527; controls identified with random digit dialling and randomly selected from the rosters of beneficiaries of the Health Care Financing Administration; frequency-matched by age and ethnicity Exposure assessment method: questionnaire; 74-item food questionnaire; red meat was all types of beef and pork	Prostate: advanced cases	Hamburgers (g/1000 kcal per day), tertiles No red meat consumed T1 T2 T3 Trend-test *P* value: 0.005	 42 144 150 195	 1.00 1.21 (0.75–1.95) 1.33 (0.82–2.14) 1.79 (1.10–2.92)	Age, race, socioeconomic status, family history, BMI, calorie intake, fat, fruits, vegetables
		Prostate: advanced cases	Red meat (g/1000kcal per day), tertiles No red meat consumed T1 T2 T3 Trend-test *P* value: 0.02	 42 128 190 171	 1.00 1.10 (0.68–1.79) 1.65 (1.02–2.65) 1.53 (0.93–2.49)	
		Prostate: localized cases	Red meat (g/1000kcal per day), tertiles No red meat consumed T1 T2 T3 Trend-test *P* value: 0.62	 58 156 157 156	 1.00 0.71 (0.39–1.27) 1.12 (0.63–2.01) 0.91 (0.49–1.69)	

Table 2.5.3 Case–control studies on consumption of red meat and cancer of the prostate

Reference, location, enrolment	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/deaths	Risk estimate (95% CI)	Covariates controlled
Punnen et al. (2011) USA 2001–2004	Cases: 466; hospital-based. incident histologically confirmed cases; only aggressive cases (Gleason score ≥ 7) Controls: 511; controls were men older than 50 yr undergoing medical examination, with PSA < 4; frequency-matched by age, ethnicity, and medical centre Exposure assessment method: questionnaire; SQFFQ; estimation of exposure to mutagens	Prostate	Grilled beef intake			Age, ethnicity, medical centre, family history, smoking, BMI, prior history of PSA testing, education level, n-3 fatty acid intake
			Low intake vs none	85	1.50 (1.03–2.19)	
			Medium vs none	124	1.69 (1.19–2.38)	
			High vs none	129	1.61 (1.13–2.28)	
			Trend-test *P* value: 0.004			
			Grilled hamburger intake			
			Low vs none	106	1.41 (0.99–2.01)	
			Medium vs none	126	1.58 (1.11–2.24)	
			High vs none	120	1.86 (1.28–2.71)	
			Trend-test *P* value: 0.001			
Wright et al. (2011) USA 1993–1996	Cases: 1754; population-based study; cases identified from the SEER Registries Controls: 1645; population controls identified by random digit telephone dialling and matched by age Exposure assessment method: questionnaire; self-administered FFQ on usual dietary intake during 3–5 yr before the reference date; [red meat not clearly defined]	Prostate	Red meat (servings/day)			Age, PSA screening history, BMI, total caloric intake
			≤ 0.58	NR	1.00	
			0.59–1.09	NR	1.21 (0.97–1.51)	
			> 1.09	NR	1.43 (1.11–1.84)	
			Trend-test *P* value: <0.01			
		Prostate: less aggressive cancer	Red meat (servings/day)			
			≤ 0.58	NR	1.00	
			0.59–1.09	NR	1.11 (0.87–1.42)	
			> 1.09	NR	1.38 (1.05–1.82)	
			Trend-test *P* value: 0.02			
		Prostate: more aggressive cancer	Red meat (servings/day)			
			≤ 0.58	NR	1.00	
			0.59–1.09	NR	1.43 (1.06–1.96)	
			> 1.09	NR	1.55 (1.10–2.20)	
			Trend-test *P* value: 0.01			

Table 2.5.3 Case–control studies on consumption of red meat and cancer of the prostate

Reference, location, enrolment	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/deaths	Risk estimate (95% CI)	Covariates controlled
Deneo-Pellegrini et al. (2012) Uruguay 1996–2004	Cases: 326; hospital-based study; localized cancers, 25%; regional cancers, 72%; and disseminated cancers, 3% Controls: 652; hospital controls; conditions not related to smoking, drinking and no recent dietary changes (minor surgical conditions); matched 2:1 on age and residence Exposure assessment method: questionnaire; 64 food items; red meat was beef and lamb	Prostate	T1 T2 T3 Trend-test *P* value: 0.17	95 119 112	1.00 1.28 (0.90–1.81) 1.28 (0.90–1.82)	Age, residence, urban/rural, BMI, education, family history, energy intake, other types of meats
Joshi et al. (2012) USA 1997–1998	Cases: 717 localized, 1140 advanced; multiethnic, population-based; incident cases identified through cancer registries Controls: 1096; controls selected with neighbourhood walk algorithm or randomly selected from the Health Care Financing Administration Exposure assessment method: questionnaire; red meat was all types of beef and pork, hamburgers, and steak	Prostate: advanced cases	High-temperature cooked hamburger (g/1000 kcal/day) Never/rarely (0) Low (> 0 to < 4.4) Medium (≥ 4.4 to < 7.9) High (> 7.9) Trend-test *P* value: < 0.001	 501 310 145 183	 1.0 1.3 (1.0–1.6) 1.4 (1.0–1.8) 1.7 (1.3–2.2)	Age, BMI, caloric intakes, family history, fat intake, alcohol, smoking, fruit intake, vegetable intake
		Prostate: advanced cases	Red meat (g/1000 kcal per day), quintiles Q1 (≥ 0 to < 4.6) Q2 (≥ 4.6 to < 8.9) Q3 (≥ 8.9 to < 14.4) Q4 (≥ 14.4 to < 23.3) Q5 (≥ 23.3) Trend-test *P* value: 0.667	 209 200 250 257 223	 1.0 0.9 (0.7–1.2) 1.2 (0.9–1.5) 1.1 (0.8–1.5) 1.0 (0.8–1.4)	

Table 2.5.3 Case–control studies on consumption of red meat and cancer of the prostate

Reference, location, enrolment	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/deaths	Risk estimate (95% CI)	Covariates controlled
Joshi et al. (2012) USA 1997–1998 (cont.)		Prostate: localized cases	Red meat (g/1000 kcal per day), quintiles			
			Q1 (≥ 0 to < 4.6)	124	1.0	
			Q2 (≥ 4.6 to < 8.9)	142	1.2 (0.8–1.6)	
			Q3 (≥ 8.9 to < 14.4)	140	1.1 (0.8–1.5)	
			Q4 (≥ 14.4 to < 23.3)	141	1.0 (0.7–1.4)	
			Q5 (≥ 23.3)	168	1.1 (0.8–1.6)	
			Trend-test *P* value: 0.822			
		Prostate: advanced cases	High-temperature cooked red meat (g/1000 kcal per day)			
			Never/rarely (0)	133	1.0	
			Low (> 0 to < 9.4)	457	1.1 (0.9–1.5)	
			Medium (≥ 9.4 to < 16.9)	274	1.4 (1.0–1.9)	
			High (≥ 16.9)	275	1.4 (1.0–1.9)	
			Trend-test *P* value: 0.026			
		Prostate: advanced cases	Well-done red meat (g/1000 kcal per day)			
			Never/rarely (0)	392	1.0	
			Low (> 0 to < 6.1)	355	1.2 (0.9–1.4)	
			Medium (≥ 6.1 to < 11.0)	161	1.1 (0.8–1.4)	
			High (≥ 11.0)	231	1.4 (1.1–1.8)	
			Trend-test *P* value: 0.013			
		Prostate: advanced cases	Pan-fried red meat (g/1000 kcal per day)			
			Never/rarely (0)	538	1.0	
			Low (> 0.0 to < 5.0)	297	1.2 (1.0–1.5)	
			Medium (≥ 5.0 to < 9.8)	137	1.2 (0.9–1.6)	
			High (≥ 9.8)	167	1.3 (1.0–1.8)	
			Trend-test *P* value: 0.035			

Table 2.5.3 Case–control studies on consumption of red meat and cancer of the prostate

Reference, location, enrolment	Population size, description, exposure assessment method	Organ site	Exposure category or level	Exposed cases/deaths	Risk estimate (95% CI)	Covariates controlled
Di Maso et al. (2013) Italy and Switzerland 1991–2002	Cases: 1294; hospitalized incident cases Controls: 11 656; hospital controls; non-neoplastic conditions unrelated to alcohol, diet, and tobacco; frequency-matched to cases Exposure assessment method: questionnaire; red meat was beef, veal, pork, horse meat, and half of the first course, including meat sauce (e.g. lasagne, pasta/rice with bologna sauce)	Prostate	Red meat (g/day) 60–89 vs < 60 ≥ 90 vs < 60 Trend-test *P* value: 0.14	 385 453	 1.17 (0.96–1.42) 1.15 (0.96–1.39)	Centre, age, education, BMI, smoking, alcohol, vegetable intake, fruit intake
		Prostate	Increase of 50 g/day	NR	1.07 (0.97–1.18)	

BMI, body mass index; FFQ, food frequency questionnaire; NR, not reported; NSAID, nonsteroidal anti-inflammatory drug; PSA, prostate-specific antigen; SEER, Surveillance, Epidemiology, and End Results; SQFFQ, semi-quantitative food frequency questionnaire; yr, year

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2.6 Cancer of the breast

2.6.1 Cohort studies

More details of the cohort studies can be found in Table 2.6.1 and Table 2.6.2 (web only; available at: http://publications.iarc.fr/564).

Intake of red and processed meat was evaluated in relation to cancer of the breast in cohort studies conducted in the USA, Canada, the Netherlands, the United Kingdom, Sweden, Denmark, and France, as well as in the EPIC study, which included multiple European countries, and in a cohort consortium of eight studies in North America and Europe. Important potential confounders for breast cancer included age, alcohol intake, reproductive factors (such as age at menarche, parity, age at first birth, use of oral contraceptives, age at menopause), use of postmenopausal hormones among postmenopausal women, family history of breast cancer, obesity, and energy intake. Studies that did not adjust for these covariates are noted. Recent publications with more reliable exposure assessment, more adequate adjustment for potential confounders, and longer follow-up time were included in the evaluation.

Studies were considered uninformative and not included in the evaluation if they assessed meat intake without specifying the types of meats included (e.g. Mills et al., 1988; van den Brandt et al., 1990; Vatten et al., 1990; Knekt et al., 1994; Gaard et al., 1995). In addition, studies that evaluated breast cancer in relation to dietary patterns, rather than the consumption of red or processed meat (e.g. Männistö et al., 2005; Cottet et al., 2009; Butler et al., 2010; Couto et al., 2013), or had a low number of cases (Byrne et al., 1996) were excluded from further review.

Mills et al., (1989) evaluated individual red meat items, "beef index", and breast cancer in a low-risk cohort of 20 341 Californian, Seventh-Day Adventist women aged 25–99 years. The beef index was the sum of intake from individual red meat items, including beef hamburger, beef steak, and other beef/veal. During a mean follow-up of 6 years (1976–1982), 215 primary breast cancer cases were histologically verified. The relative risk for the top (≥ 1 time/week) versus the bottom (never) category of the beef index was 1.05 (95% CI, 0.75–1.47). Intake of red meat (i.e. beef hamburger, beef steak, and other beef/veal) was not associated with breast cancer. [Alcohol and caloric intake were not adjusted for in statistical analyses. This study was part of the Pooling Project of Prospective Studies by Missmer et al., (2002). A smaller number of cases were included in the pooling project (160 cases).]

Toniolo et al. (1994) conducted a nested case–control study of 180 breast cancer cases and 829 controls from the first 6 years of follow-up (median follow-up time, 22.2 months) in the New York University Women's Health Study (NYUWHS) cohort. The study originally included 14 291 women aged 35–65 years enrolled between 1985 and 1991. Diet was assessed with a 71–food item, validated Block FFQ. The relative risk for the top versus the bottom quintile of meat intake was 1.87 (95% CI, 1.09–3.21; P_{trend} = 0.01). [The Working Group noted the relatively small sample size. In addition, the study did not specify red meat. Meat included beef, veal, lamb, or pork preparations or processed luncheon meats (ham, cold cuts, turkey rolls), that is, unprocessed and processed red meat and processed white meat. Alcohol intake was not adjusted for. This study was part of the Pooling Project of Prospective Studies by Missmer et al. (2002). A larger number of cases were included in the pooling project (385 cases).]

The Iowa Women's Health Study (IWHS) cohort included 41 836 postmenopausal (age, 55–69 years) women. Five nested case–control studies of the cohort were included (Zheng et al., 1998; Zheng et al., 1999; Deitz et al., 2000; Zheng et al., 2001; Zheng et al., 2002). These studies are described in more detail below.

Zheng et al. (1998) conducted a nested case–control study of 273 cases and 657 controls nested within the IWHS. All eligible subjects were asked to complete a self-administered FFQ on meat intake habits during the reference year. The questionnaire included questions on usual intake and preparation of 15 meats. A doneness score was also calculated to describe the eating preferences of the participants based on their responses to colour photographs. The study found a positive dose–response relationship between doneness of red and processed meat and breast cancer risk. The odds ratios for very well-done meat versus rare or medium-done meat were 1.54 (95% CI, 0.96–2.47) for hamburger, 2.21 (95% CI, 1.30–3.77) for beef steak, and 1.64 (95% CI, 0.92–2.93) for bacon. Women who consumed these three meats consistently very well done had an odds ratio of 4.62 (95% CI, 1.36–15.70; P_{trend} = 0.001) compared with women who consumed the meats rare or medium done. In addition, compared with women in the lowest tertile of intake of these three types of meats with a doneness level of rare/medium, those who were in the top tertile of intake with a doneness level of consistently very well done had an odds ratio of 3.01 (95% CI, 1.47–6.17). [The Working Group noted that there was a statistically significant positive association between intake of red meat and risk of breast cancer (P_{trend} = 0.02), with a 78% elevated risk observed for the highest versus the lowest tertile of intake group; however, red meat included processed meat. Reproductive factors and alcohol intake were not adjusted for in statistical analyses. This study was part of the Pooling Project of Prospective Studies by Missmer et al. (2002). A much larger number of cases were included in the pooling project (1130 cases).]

Deitz et al. (2000) used a subset of the nested case–control study data from the IWHS (174 cases, 387 controls) with DNA samples, and evaluated doneness score and red meat [which included processed meat] intake and breast cancer by *NAT2* polymorphism. Polymorphisms in the *NAT2* gene may result in a rapid, intermediate, and slow acetylation phenotype. The study found that a higher intake of red meat was suggestively positively associated with breast cancer among women with the *NAT2* rapid/intermediate type (OR, 1.7; 95% CI, 0.9–3.4; for the highest vs lowest tertile of intake), but not associated with breast cancer among those with the *NAT2* slow type (OR, 0.9; 95% CI, 0.5–1.7; for the same comparison). However, the *P* value for interaction by *NAT2* genotype was not significant (*P* = 0.91). For the association between doneness score and breast cancer, there was a borderline significant interaction by *NAT2* genotype (*P* = 0.06). Compared with women who reported consuming hamburger, beef steak, and bacon rare/medium (doneness score, 3/4), those who reported consuming these meats very well done (doneness score, 9) had odds ratios of 3.9 (95% CI, 0.8–18.9; P_{trend} = 0.22) for the *NAT2* slow genotype and 7.6 (95% CI, 1.1–50.4; P_{trend} = 0.003) for the *NAT2* rapid/intermediate type. [The Working Group noted that the sample size was much more limited than the original study by Zheng et al. (1999) because a large number of the subjects had buccal cell samples instead of blood samples, and *NAT2* amplification was successful only in 9% (79/878) of buccal cell DNA samples. Sample size was too small to evaluate the interaction with genetic polymorphisms. Only age was adjusted for. Red meat included processed meat.]

A similar study using a subset of the nested case–control study data from the IWHS was conducted to evaluate the association between doneness of red meat and breast cancer risk stratified by *SULT1A1* polymorphism (Zheng et al., 2001). The study included 156 cases and 332 controls, with blood samples. The association between doneness of red meat [which included processed meat] and breast cancer appeared to differ by the polymorphism, although the *P* value for interaction was not significant (*P* = 0.40). Compared with participants consuming rare/medium-

done red meat, those who consistently consumed well-done red meat had relative risks of 3.6 (95% CI, 1.4–9.3; P_{trend} = 0.01) for the *SULT1A1* Arg/Arg genotype, 1.8 (95% CI, 0.9–3.8; P_{trend} = 0.10) for the Arg/His genotype, and 1.0 (95% CI, 0.3–3.7; P_{trend} = 0.98) for the His/His genotype. [The Working Group noted that the sample size was too small to evaluate the interaction with genetic polymorphisms, and most of the categories had fewer than 20 cases. Age, waist:hip ratio, and number of live births were adjusted for. Red meat included processed meat.]

Zheng et al. (2002) also evaluated a similar interaction between meat doneness level and breast cancer risk by *GSTM1* and *GSTT1* polymorphisms in a nested case–control study in the IWHS (202 cases, 481 controls; with blood samples and genotyping for *GSTM1*). The association between doneness of red meat and breast cancer did not vary by *GSTT1* genotype. However, there was a significant interaction by *GSTM1* genotype ($P_{interaction}$ = 0.04). Compared with women who consumed rare/medium-done meat and had the *GSTM1* genotype, those who consistently consumed well- or very well-done meat and had the *GSTM1* null genotype had a relative risk of 2.5 (95% CI, 1.3–4.5). [The Working Group noted that the sample size was too small to evaluate the interaction with genetic polymorphisms. Age, waist: hip ratio, number of live births, and family history were adjusted for. Red meat included processed meat.]

Voorrips et al. (2002) evaluated red meat and processed meat intake and breast cancer in the Netherlands Cohort Study on Diet and Cancer (NLCS), among a cohort of 62 573 women aged 55–69 years. Diet was assessed with a validated FFQ with 150 food items. Red meat, which was presented as "fresh meat", included beef and pork, and did not include processed meat. Subjects were classified into quintiles or categories of consumption (g/day), based on the distribution in the control group of 1598 women. During a mean follow-up of 6 years, 941 breast cancer cases were documented. The relative risk for the top (median, 145 g/day) versus the bottom (median, 45 g/day) quintile of red meat intake was 0.98 (95% CI, 0.73–1.33) for breast cancer. The relative risk for the top (median, 13 g/day) versus the bottom (median, 0 g/day) category of processed meat intake was 0.93 (95% CI, 0.67–1.29) for breast cancer. Intake of beef and pork was also not associated with breast cancer. [The Working Group noted that assessment and adjustment of information on postmenopausal hormone use was not mentioned. This study was part of the Pooling Project of Prospective Studies by Missmer et al. (2002). Almost the same number of cases was included in the pooling project (937 cases).]

Missmer et al. (2002) conducted a pooled analysis of eight prospective cohort studies (Adventist Health Study (AHS); Canadian National Breast Screening Study (CNBSS); IWHS; NLCS; New York State Cohort, (NYSC); New-York University Women's Health Study (NYUWHS); Nurses' Health Study (NHS); and Sweden Mammography Cohort (SMC)) from North America and western Europe, which used validated FFQs. A total of 7379 breast cancer cases diagnosed during up to 15 years of follow-up were included. Pooled multivariate-adjusted relative risks for an increase of 100 g/day in red meat intake were 0.98 (95% CI, 0.93–1.04) in all women, 0.97 (95% CI, 0.79–1.20) in premenopausal women, and 0.97 (95% CI, 0.91–1.03) in postmenopausal women. None of the red meat items, including ground beef, organ products or processed meats, bacon products, sausage products, and hot dogs, were associated with breast cancer risk. [The Working Group noted that red meat included both fresh and processed red meat, blood pudding, liver, and kidney.]

Holmes et al. (2003) evaluated red meat and processed meat intake and breast cancer among 88 647 women included in the NHS. Diet was assessed using a 61–food item FFQ at baseline and a 116–food item FFQ since 1984. Both FFQs were validated. FFQs were sent to the women

multiple times during follow-up. Red meats included hamburger, beef/pork/lamb as a main dish, beef/pork/lamb in sandwiches or mixed dishes, hot dogs, bacon, and other processed meats. Between 1980 and 1998, 4107 cases of invasive breast cancer were identified. There was no association between intake of red meat or processed meat and breast cancer. The relative risk for the top (≥ 1.32 servings/day) versus the bottom (≤ 0.55 servings/day) quintile of red meat intake was 0.94 (95% CI, 0.84–1.05). The relative risk for the top (≥ 0.46 servings/day) versus the bottom (≤ 0.10 servings/day) quintile of processed meat intake was 0.94 (95% CI, 0.85–1.05). The associations were similar by menopausal status. [The study was limited by the definition of red meat, which included processed meat. Fung et al. (2005) evaluated the same cohort, with a shorter follow-up period (1984–2000) and a smaller number of cases (3026 cases), and was not considered. Similarly, Wu et al. (2010) evaluated the consumption of mutagens from meats cooked at a high temperature in an NHS subcohort, with a shorter follow-up period (1996–2006) and fewer cases (2317 cases), and was not considered. The NHS was part of the Pooling Project of Prospective Studies by Missmer et al. 2002. A smaller number of cases were included in the pooling project (2661 cases).]

van der Hel et al. (2004) evaluated red meat and processed meat intake in relation to breast cancer in a nested case–control study of 229 cases (average age, 48 years) and 264 controls, with blood samples, nested within a Dutch prospective study. Controls were frequency-matched by age, town, and menopausal status. Meat consumption was recorded at baseline with the use of a validated, self-administered FFQ. Red meat intake in grams per day was calculated by adding up intakes of beef and pork. There was no association between red meat or processed meat intake and breast cancer risk. Compared with women who had a red meat intake of < 30 g/day, women who were in the high-intake category of ≥ 45 g/day had an odds ratio of 1.32 (95% CI, 0.84–2.08). Compared with women with a processed meat intake of < 20 g/day, those who were in the high-intake category of ≥ 35 g/day had an odds ratio of 1.08 (95% CI, 0.60–1.70). When polymorphisms related to metabolism of HAAs, including *NAT1, NAT2, GSTM1, GSTT1*, were evaluated, there was a positive association with *GSTM1* null genotype. When the association with red meat intake was stratified by *GSTM1* polymorphism, no interaction was observed. [The Working Group noted that the sample size was too limited to evaluate the interaction with genetic polymorphisms. Family history of breast cancer and postmenopausal hormone use were not adjusted for in the multivariate analysis.]

Kabat et al., (2007) evaluated red meat and haem iron intake and breast cancer in the CNBSS, a randomized controlled trial of screening for breast cancer involving women aged 40–59 years. Diet was assessed with a validated FFQ with 86 food items. During a mean follow-up of 16.4 years, 2491 breast cancer cases (1171 premenopausal cases, 993 postmenopausal cases) were included. The relative risk for the top (≥ 40.30 g/day) versus the bottom (< 14.25 g/day) quintile of red meat intake was 0.98 (95% CI, 0.86–1.12) for breast cancer. The relative risk for the top (> 2.95 mg/day) versus the bottom (< 1.58 mg/day) quintile of haem iron intake was 1.03 (95% CI, 0.90–1.18) for breast cancer. The results were similar by menopausal status. [The Working Group noted that red meat was not defined. Although this study was part of the Pooling Project of Prospective Studies by Missmer et al. (2002), which evaluated red meat intake, only 419 breast cancer cases, with a shorter follow-up period (5 years), were included in the pooling project.]

Taylor et al. (2007) evaluated red meat and processed meat intake and breast cancer in the United Kingdom Women's Cohort Study (UKWCS) in 678 cases (283 premenopausal cases, 395 postmenopausal cases). Diet was assessed

between 1995 and 1998 using a 217-item, postal FFQ developed from that of the EPIC study. Red meat consisted of beef, pork, lamb, and other red meats included in mixed dishes, such as meat lasagne, moussaka, ravioli, and filled pasta with sauce. Processed meat consisted of bacon, ham, corned beef, spam, luncheon meats, sausages, pies, pasties, sausage rolls, liver pâté, salami, and meat pizza. Higher intakes of both red meat and processed meat were associated with an elevated risk of breast cancer. Compared with non-consumers, those who were in the high-intake category had a hazard ratio of 1.41 (95% CI, 1.11–1.81) for red meat (> 57 g/day) and 1.39 (95% CI, 1.09–1.78) for processed meat (> 20 g/day). When the association was evaluated by menopausal status, the hazard ratios for the highest versus the lowest quartile of intake were 1.32 (95% CI, 0.93–1.88; 61 cases) among premenopausal women and 1.56 (95% CI, 1.09–2.23; 106 cases) among postmenopausal women for red meat. [The Working Group noted that family history of breast cancer and alcohol intake were not adjusted for.]

Egeberg et al. (2008) conducted a nested case–control study among 24 697 postmenopausal women included in the Diet, Cancer and Health cohort study (1993–2000) in Denmark. The study included 378 breast cancer cases and 378 matched controls. Meat consumption was estimated from a 192-item, validated FFQ, completed at baseline, covering the participants' habitual diet during the preceding 12 months. Intake of red meat in grams per day was calculated by adding up intakes of beef, veal, pork, lamb, and offal. [Intake of processed meat included processed fish, and was not reviewed.] Compared with women whose red meat intake was < 50 g/day, those who consumed > 80 g/day had a relative risk of 1.65 (95% CI, 1.09–2.50; $P_{trend} = 0.03$). The associations were also stratified by *NAT1* and *NAT2* polymorphisms. There was no significant interaction by *NAT1* polymorphism, but there was a significant interaction by *NAT2* polymorphism for red meat intake ($P_{interaction} = 0.04$). The relative risks per 25 g/day increase in red meat intake were 1.37 (95% CI, 1.07–1.76) for the *NAT2* intermediate/fast acetylator phenotype and 1.00 (95% CI, 0.85–1.18) for the *NAT2* slow acetylator phenotype. [The Working Group noted that sample size was limited in some of the stratified analyses by *NAT* polymorphisms. Caloric intake and family history of breast cancer were not adjusted for in the multivariate analysis.]

Kabat et al. (2009) evaluated the association between red meat intake and meat preparation in relation to breast cancer among postmenopausal women only in the NIH-AARP study. Diet was assessed with the NCI Diet History Questionnaire (DHQ), a self-administered, validated FFQ with 124 food items. [Red meat included many types of processed meats, and data are not reported here.] Processed meat included bacon, red meat sausage, poultry sausage, luncheon meats (red and white meat), cold cuts (red and white meat), ham, regular hot dogs, and low-fat hot dogs made from poultry. During a follow-up of 8 years, 3818 breast cancer cases were documented. Processed meat was not associated with breast cancer risk. The relative risk for the top (> 12.5 g/1000 kcal) versus the bottom (≤ 2.2 g/1000 kcal) quintile of processed meat intake was 1.0 (95% CI, 0.90–1.12) for breast cancer. Cooking methods (grilled or barbecued meat, pan-fried meat, oven-broiled meat, sautéed meat, baked meat, or microwaved meat) and meat doneness levels (rare/medium-done cooked meat or well/very well-done cooked meat) were not associated with breast cancer risk. [The Working Group noted that an earlier publication of the NIH-AARP cohort that had a shorter follow-up and inferior adjustment for potential confounders of breast cancer (Cross et al., 2007) was not considered. Evaluation of cooking methods and doneness levels included poultry.]

Larsson et al. (2009) evaluated red meat intake and breast cancer in the SMC, which was established in 1987–1990 in central Sweden. Diet was assessed with a 67– and 96–food item FFQ at baseline and in 1997, respectively. During a mean follow-up of 17.4 years, 2952 breast cancer cases were ascertained. For overall breast cancer, the relative risks for the top (≥ 98 g/day) versus the bottom (< 46 g/day) quintile of intake were 0.98 (95% CI, 0.86–1.12) for red meat, 1.08 (95% CI, 0.96–1.22) for processed meat, 1.10 (95% CI, 0.90–1.34) for estrogen receptor (ER)+/progesterone receptor (PR)+ tumours, 0.86 (95% CI, 0.60–1.23) for ER+/PR– tumours, and 1.12 (95% CI, 0.70–1.79) for ER–/PR– tumours. [The Working Group noted that red meat included all fresh and minced pork, beef, and veal. Processed meats included ham, bacon, sausages, salami, processed meat cuts, liver pâté, and blood sausages. This study was part of the Pooling Project of Prospective Studies by Missmer et al. (2002). However, a much smaller number of cases were included in the pooling project (1320 cases).]

Ferrucci et al., (2009) evaluated red meat and processed meat intake and cooking methods and doneness levels, and breast cancer risk in the Prostate, Lung, Colorectal and Ovarian (PLCO) trial, a multicentre, randomized controlled trial in women aged 55–74 years who were recruited in 1993–2001. Diet was assessed with by the NCI Diet history Questionnaire (DHQ), a self-administered, validated FFQ with 124 food items. During a mean follow-up of 5.5 years, 1205 breast cancer cases were documented. [Red meat included processed meat, and data are not reported here.] Processed meat included bacon, cold cuts, hams, hot dogs, and sausage. The hazard ratio for the top (> 11.6 g/1000 kcal; median, 16.9 g/1000 kcal) versus the bottom (≤ 2.4 g/1000 kcal; median, 1.4 g/1000 kcal) quintile of processed meat intake was 1.12 (95% CI, 0.92–1.36; P_{trend} = 0.22). Intake of steak, hamburger, sausage, bacon, and pork chops was not associated with breast cancer. The hazard ratios for the top versus the bottom quintile were 1.03 (95% CI, 0.84–1.27) for pan-fried meat, 1.10 (95% CI, 0.90–1.34) for grilled meat, 1.09 (95% CI, 0.90–1.32) for well/very well-done meat, and 1.20 (95% CI, 0.99–1.45) for grilled/pan-fried well/very well-done meat. [The Working Group noted that red meat included processed meat.]

Pala et al. (2009) evaluated the association between red meat and processed meat and breast cancer in the EPIC study. Information on diet was collected from 319 826 women aged 20–70 years in 1992–2003. Diet was assessed by using country-specific (Italy and Sweden centre-specific) validated FFQs designed to capture habitual consumption of food over the preceding year. Red meat consisted of fresh, minced, and frozen beef, veal, pork, and lamb. Processed meats were mostly pork and beef preserved by methods other than freezing, such as salting, smoking, marinating, air-drying, or heating, and included ham, bacon, sausages, blood sausages, liver pâté, salami, mortadella, tinned meat, and others. A total of 7119 invasive breast cancer cases were documented during a median of 8.8 years of follow-up. A higher intake of processed meat, but not red meat, was associated with a modest elevated risk of breast cancer. The hazard ratio for the highest (median, 84.6 g/day) compared with the lowest (median, 1.4 g/day) quintile of red meat consumption was 1.06 (95% CI, 0.98–1.14; P_{trend} = 0.19). The hazard ratio for the highest (median, 56.5 g/day) compared with the lowest (median, 1.7 g/day) quintile of processed meat consumption was 1.10 (95% CI, 1.00–1.20; P_{trend} = 0.07). The positive association was limited to postmenopausal breast cancer (3673 postmenopausal cases vs 1699 premenopausal cases). The corresponding hazard ratios were 1.13 (95% CI, 1.00–1.28; P_{trend} = 0.06) for postmenopausal women and 0.99 (95% CI, 0.82–1.19; P_{trend} = 0.72) for premenopausal women. [The Working Group noted that family history of breast cancer was not adjusted for.]

Loh et al. (2010) evaluated the association between red and processed meat intake and breast cancer stratified by *MGMT* Ile143Val polymorphism in the EPIC-Norfolk study in 276 cases and 1498 controls. There was no significant interaction with the polymorphism. [The Working Group noted that the sample size was too small to evaluate the interaction with genetic polymorphisms.]

Lee et al. (2013) conducted a nested case–control study within the NHS to evaluate the interaction between red meat intake and *NAT2* acetylator genotype and cytochrome P450 1A2–164 A/C (*CYP1A2*) polymorphism. The study included 579 cases and 981 matched controls. There was no interaction between *NAT2* acetylator genotype or *CYP1A2* polymorphism and red meat intake in relation to breast cancer. [The Working Group noted that the study was limited by the definition of red meat, which included processed meat. Holmes et al. (2003) evaluated red meat intake in the same cohort.]

Genkinger et al. (2013) evaluated breast cancer among African American women from the Black Women's Health Study (BWHS). The study included a total of 1268 cases, among 52 062 women, identified during 12 years of follow-up. Diet during the past year was estimated from a 68-item, modified Block FFQ completed at baseline in 1995. In 2001, a modified version of the 1995 FFQ, which asked about 85 food items, was administered to collect updated dietary information. The 1995 FFQ ascertained the intake of 13 meat items; the 2001 FFQ asked about 15 meat items. Intakes of red meat or processed meat were not associated with breast cancer. Compared with women with a red meat intake of < 100 g/week, those who consumed ≥ 400 g/week had a relative risk of 1.02 (95% CI, 0.83–1.24; P_{trend} = 0.83). Compared with women with a processed meat intake of < 100 g/week, those who consumed ≥ 200 g/week had a relative risk of 0.99 (95% CI, 0.82–1.20; P_{trend} = 0.96). The associations were similar by menopausal status. [The Working Group noted that information on the definitions of red meat and processed meat, and validation of the FFQs was not provided.]

The study by Pouchieu et al. (2014) was based on the SU.VI.MAX, a randomized, double-blind, placebo-controlled trial of a combination of low-dose antioxidants (ascorbic acid, vitamin E, β-carotene, selenium, and zinc), conducted from 1994 to 2002. The study included 190 cases, among 4684 women aged 35–60 years at baseline, identified during a median of 11.3 years of follow-up (1994–2007). Participants completed a dietary record every 2 months, in which they declared all foods and beverages consumed during periods of 24 hours. These dietary records were randomly distributed between week and weekend days, and over seasons to take into account intra-individual variability. Dietary records from the first 2 years of follow-up were used in the study. Portion sizes were assessed using a validated picture booklet, and the amounts consumed from composite dishes were estimated using French recipes validated by food and nutrition professionals. Red meat consisted of fresh, minced, and frozen beef, veal, pork, and lamb. Processed meats were mostly pork and beef preserved by methods other than freezing, such as salting, smoking, marinating, air-drying, or heating, and included ham, bacon, sausages, blood sausages, liver pâté, salami, mortadella, tinned meat, and others. There was no association between baseline intake of either red meat or processed meat and breast cancer in the whole population. The relative risks for the top versus the bottom quartile of intake were 1.19 (95% CI, 0.79–1.80; P_{trend} = 0.3) for red meat (< 24.9 vs > 63.7 g/day) and 1.45 (95% CI, 0.92–2.27; P_{trend} = 0.03) for processed meat (< 16.4 vs > 43.5 g/day). However, processed meat intake was positively associated with breast cancer risk in the placebo group, but not in the treatment group. The relative risks for the highest compared with the lowest quartile of processed meat consumption were 2.46 (95% CI, 1.28–4.72; P_{trend} = 0.001) in the placebo group and 0.86

(95% CI, 0.45–1.63; P_{trend} = 0.7) in the antioxidant-supplemented group ($P_{interaction}$ = 0.06). [The Working Group took note of the relatively small number of cases. No information was provided on the number of cases in each red meat intake category. Adjustment of lipid intake would be an overadjustment. Some reproductive factors were not adjusted for.]

Farvid et al. (2014) also evaluated early-adulthood total red meat intake and breast cancer in the NHS II. The study included 2830 cases, among 88 803 premenopausal women aged 26–45 years, identified during 20 years of follow-up. Diet was assessed by validated FFQ, with approximately 130 food items. The study found that a higher total red meat (i.e red meat and processed read meat) intake was associated with an elevated risk of breast cancer. The relative risk for the top (median, 1.50 servings/day) versus the bottom (median, 0.14 servings/day) quintile of intake was 1.22 (95% CI, 1.06–1.40; P_{trend} = 0.01). The association was similar by menopausal status, but not statistically significant. [The Working Group noted that the study was limited by the definition of red meat, which included processed meat. Earlier studies of the cohort by Cho et al. (2003) and Cho et al. (2006) were not evaluated.]

Farvid et al. (2015) also evaluated the association between adolescent total red meat intake and breast cancer risk in the NHS II. A subcohort of 44 231 women aged 33–52 years, who filled in a special 124-item FFQ about diet during high school, were followed up for 13 years, and 1132 breast cancer cases were documented. Total red meat intake included unprocessed red meat (hamburger, beef, lamb, pork, and meatloaf) and processed red meat items (hot dog, bacon, and other processed meats such as sausage, salami, and bologna). There was a positive association between adolescent total red meat intake and premenopausal breast cancer. The relative risk for the top (median, 2.43 servings/day) versus the bottom (median, 0.7 servings/day) quintile of total red meat intake was 1.43 (95% CI, 1.05–1.94; P_{trend} = 0.007). The positive association was similar, but significant only for processed meat (RR, 1.29; 95% CI, 0.98–1.70; P_{trend} = 0.02) when intakes of red meat and processed meat were evaluated separately. The association with premenopausal breast cancer was stronger among those with ER+/PR+ breast cancer than among those with ER–/PR– breast cancer; the relative risks per 1 serving/day of total red meat were 1.23 (95% CI, 1.06–1.44) for ER+/PR+ breast cancer and 1.18 (95% CI, 0.87–1.60) for ER–/PR– breast cancer. Haem iron intake was not associated with breast cancer risk. [The Working Group noted that the relative risks for breast cancer by quintile of processed meat and red meat intake in premenopausal, postmenopausal, and all women were reported in tables. A limitation was that the adolescent dietary intake was reported when women were 33–52 years of age. An earlier study by Linos et al. (2008) was not evaluated.]

2.6.2 Case–control studies

Case–control studies on the association between breast cancer and consumption of red meat (see Table 2.6.3, web only) or processed meat (see Table 2.6.4, web only) have been conducted in North America, Latin America, Europe, North Africa, and Asia (these tables are available online at: http://publications.iarc.fr/564). These studies are organized according to the definition of red meat or processed meat, and within these categories, by publication year and study design. Important potential confounders for breast cancer include age, alcohol intake, reproductive factors, use of postmenopausal hormones among postmenopausal women, family history of breast cancer, obesity, and energy intake. Studies that did not adjust for these covariates are noted. In addition, studies with low participation rates (< 50%) in cases or controls, or with large differences in the participation rates of cases and controls are noted because this may have led to selection bias.

Studies that met several exclusion criteria were considered to be uninformative for this evaluation and were not considered further. Studies that evaluated meat intake without providing data specifically for red meat or processed meat were excluded (e.g. Hirayama, 1978; Kinlen, 1982; Talamini et al., 1984; Kato et al., 1992; Malik et al., 1993; Holmberg et al., 1994; Trichopoulou et al., 1995; Núñez et al., 1996; Potischman et al., 1998; Han et al., 2004; Lee et al., 2004; Ko et al., 2013; Bessaoud et al., 2008; Dos Santos Silva et al., 2002; La Vecchia et al., 1987). Similarly, studies that evaluated breast cancer in relation to dietary patterns instead of evaluating red or processed meat were excluded (e.g. Cui et al., 2007; Wu et al., 2009; Cade et al., 2010; Cho et al., 2010; Ronco et al., 2010; Buck et al., 2011; Zhang et al., 2011; Bessaoud et al., 2012; Jordan et al., 2013; Mourouti et al., 2014; Pou et al., 2014). Other reasons for exclusion were small sample size (about < 100 breast cancer cases) (e.g. Phillips, 1975; Kikuchi et al., 1990; Ingram et al., 1991; Morales Suárez-Varela et al., 1998; Delfino et al., 2000; Lima et al., 2008; Di Pietro et al., 2007; Landa et al., 1994), and the availability of updated or more complete data from the same population (Lee et al., 1991; Levi et al., 1993; Ronco et al., 1996; Favero et al., 1998).

(a) Red meat and/or processed meat

(i) Population-based studies

Lubin et al. (1981) conducted a study in Canada with 577 cases and 826 controls. The study evaluated intake of beef and pork. Women who consumed beef daily had a relative risk of 1.53 (95% CI, 1.1–2.1) compared with women who consumed beef < 3 times/week in the age-adjusted analysis. Similarly, compared with women who consumed pork ≤ 1 day/month, those who consumed it ≥ 1 time/week had a relative risk of 2.16 (95% CI, 1.6–2.9) in the age-adjusted analysis. [The Working Group noted that the response rate was much lower among controls. The FFQ was not validated. Only age was adjusted for in statistical analyses.]

Hislop et al. (1986) evaluated intake of beef and pork and breast cancer in British Columbia, Canada. A total of 846 cases (74% participation rate) and 862 controls (79% participation rate) were included. Eligible cases included women younger than 70 years who were registered in the British Columbia Cancer Registry during 1980–1982. A pool of controls, frequency-matched on age, was created from the neighbours or acquaintances of the cases. Diet was assessed with a mailed, self-administered questionnaire for four different age periods. Compared with a beef intake of less than once daily, those who consumed beef daily had an odds ratio of 1.47 (95% CI, 1.12–1.92). Compared with a pork intake of less than once weekly, those who consumed pork weekly had an odds ratio of 1.13 (95% CI, 0.92–1.39). [The Working Group noted that diet was not assessed with a validated and standardized assessment tool. Odds ratios were adjusted for age only. The evaluation of intake was dichotomous only.]

Toniolo et al. (1989) evaluated intake of cured meat [i.e. processed meat] and offal and breast cancer in Italy. A total of 250 cases (91% participation rate) and 499 controls (86% participation rate) were included. Women younger than 75 years who resided in the province of Vercelli were included. Cases were women with microscopically confirmed invasive breast cancer who were free of local or distant metastases, except in the regional lymph nodes. Controls were female residents who were frequency-matched to the cases within 10-year age strata in an approximately 2:1 ratio. Diet was assessed with a dietary history method. The relative risk for the top versus the bottom intake of cured meat [i.e. processed meat] was 1.3. [The Working Group noted that diet was assessed with a validated assessment tool. Odds ratios were adjusted for age and caloric intake only, and 95% confidence intervals were not provided.]

Matos et al. (1991) conducted a population-based study in Argentina that included 196 cases recruited in 1979–1981 and 205 controls selected from friends and sanguineous family members of the cases. The study evaluated beef consumption based on cooking methods (barbecued, deep-fried, baked, boiled, stewed). None of the associations were significant. [The Working Group noted that the study had a modest sample size, and did not report the response rate among controls. The FFQ was not validated. Only age, age at first birth, and years of schooling were adjusted for in the statistical analysis. The consumption of beef was adjusted for other meat items, and the way of cooking for the other ways of cooking.]

Ambrosone et al. (1998) conducted a population-based case–control study of diet and breast cancer in New York, USA, with 740 cases and 810 controls. Controls younger than 65 years were randomly selected from the New York State Motor Vehicle Registry, and those 65 years and over were identified from Health Care Financing Administration lists. Of the premenopausal women contacted, 66% of eligible cases and 62% of eligible controls participated, and of the postmenopausal women contacted, 54% of cases and 44% of controls participated. An FFQ with the usual portion sizes of over 300 foods was administered to assess usual intake 2 years before the interview. Processed meat included ham, hot dogs, sausages, bacon, and cold cuts. The study found that intake of beef or pork was not associated with breast cancer risk in either premenopausal or postmenopausal women. Processed meat intake was non-significantly associated with premenopausal breast cancer; intake of > 48 g/day compared with < 14 g/day was associated with an odds ratio of 1.4 (95% CI, 0.9–2.3; $P_{trend} = 0.09$). [The Working Group noted the low response rate, especially among controls, which might have led to selection bias. There was no description of validation of the FFQ. Caloric intake was not adjusted for.]

Hermann et al. (2002) evaluated diet and breast cancer among women up to 50 years of age [thus, probably almost all of them were premenopausal women] in Germany (355 cases, 838 controls). Cases were women with a diagnosis of incident in situ or invasive breast cancer (35% participation rate). Controls were matched by exact age and study region, and were selected from a random list of residents provided by the population registries (37% participation rate). Diet was assessed with a 176-item FFQ similar to the FFQ used in the German part of the EPIC study, which was validated in other populations. The study found that the highest quartile of intake of red meat (≥ 65 g/day) was associated with an increased risk of breast cancer of up to 85% (OR, 1.85; 95% CI, 1.23–2.78; $P_{trend} = 0.016$) compared with the lowest quartile of intake (1–21 g/day). The odds ratios for the highest intake categories (≥ 33 g/day for beef, ≥ 39 g/day for pork, and ≥ 73 g/day for processed meat) were 1.58 (95% CI, 1.06–2.36; $P_{trend} = 0.04$), 1.47 (95% CI, 0.98–2.21; $P_{trend} = 0.07$), and 1.29 (95% CI, 0.86–1.95; $P_{trend} = 0.17$) for beef, pork, and processed meat, respectively. [The Working Group noted the modest sample size, and the median time between diagnosis of breast cancer and FFQ administration was 209 days for the cases, which led to a low response rate. This study overlapped with Brandt et al. (2004).]

Using essentially the same data set, Brandt et al. (2004) evaluated the association with breast cancer risk, stratified by the allelic length of the epidermal growth factor receptor (*EGFR*) gene CA simple sequence repeat. The sample size was further reduced to 311 cases and 689 controls, after excluding those with no genetic data. The positive association between red meat intake and breast cancer appeared to be limited to those with the long/long allele of *EGFR* (OR for red meat intake of ≥ 65 vs < 22 g/day, 10.68; 95% CI, 1.57–72.58; $P_{trend} = 0.03$) and those with the short/short allele of *EGFR* (OR for the same comparison, 1.86; 95% CI, 1.06–3.27; $P_{trend} = 0.02$), but

was not shown among those with the short/long allele of *EGFR*. Processed meat was not evaluated. [The Working Group noted that the sample size for the evaluation of the long/long allele of *EGFR* was limited, with six cases in the reference category. Caloric intake was not adjusted for. The data set was also used in (Hermann et al., 2002).]

Steck et al. (2007) evaluated the lifetime intakes of grilled or barbecued and smoked meats [i.e. processed meats] among 1508 cases and 1556 controls in a population-based case–control study in Long Island, New York, USA. Cases (82% eligible) were identified through the pathology/cytology records of 33 institutions, and lived in Nassau County and Suffolk County. Controls (63% eligible) were identified using random digit dialling and Centers for Medicare & Medicaid Services rosters. Meat intake was assessed as part of an in-home questionnaire administered by a trained interviewer. The consumption patterns of four categories of grilled/barbecued and smoked meats over each decade of life since the teenage years were examined. The participants also completed a Block FFQ, which included approximately 100 food items, that assessed diet in the previous year. The associations were evaluated by menopausal status. In postmenopausal women, compared with those who consumed grilled/barbecued red meat (beef, pork, and lamb) ≤ 630 times over their lifetime, those who consumed grilled/barbecued red meat ≥ 2163 times over their lifetime had an odds ratio of 1.32 (95% CI, 1.01–1.72; $P_{trend} = 0.10$). Compared with those who consumed smoked ham, pork, and lamb [i.e. processed meat] ≤ 810 times over their lifetime, those who consumed smoked ham, pork, and lamb ≥ 2278 times over their lifetime had an odds ratio of 1.30 (95% CI, 0.99–1.69; $P_{trend} = 0.22$). However, there was no association among premenopausal women, probably because the sample size was much smaller among premenopausal women. [The Working Group noted that the much lower response rate in controls was a limitation that might have led to selection bias. In addition, although energy intake was adjusted for, only a limited number of breast cancer risk factors were adjusted for.]

Fu et al. (2011) used the Nashville Breast Health Study (the USA). The study included 2386 (62% response rate) newly diagnosed primary breast cancer (invasive ductal or ductal carcinoma in situ) cases between the ages of 25 and 75 years. The majority of the participants were residents of the Nashville metropolitan area. The study included 1703 controls (71% response rate), which had virtually identical criteria to the cases. Of the controls, 87% were identified by random digit dialling households, and the remaining controls were mostly identified among women who received a screening mammography with a normal finding. Interviewer-administered telephone interviews were used to obtained information on usual intake frequency, portion size, cooking method, and doneness of 11 meats in the previous year before the interviews (for controls) or cancer diagnosis (for cases). All participants who completed questions on food doneness had a photograph booklet in front of them during the telephone interview. Red meat included hamburgers, cheeseburgers, beef patties, beef steaks, pork chops, ham steaks, and ribs (short ribs or spare ribs). Processed meat included bacon, sausage, and hot dogs/frankfurters. Compared with those in the lowest quartile of intake, those in the highest quartile of intake had odds ratios of 1.7 (95% CI, 1.3–2.4; $P_{trend} < 0.001$) for red meat and 1.7 (95% CI, 1.2–2.3; $P_{trend} < 0.001$) for well-done red meat among postmenopausal women. Corresponding odds ratios were 1.3 (95% CI, 0.9–2.0; $P_{trend} = 0.031$) for red meat and 1.5 (95% CI, 1.1–2.2; $P_{trend} = 0.017$) for well-done red meat among premenopausal women. The results for individual processed meat items, but not for total processed meats, were presented. Compared with those in the lowest quartile of intake, those in the highest quartile of intake had odds ratios of 1.2 (95% CI, 1.0–1.4; $P_{trend} = 0.006$) for bacon, 1.0 (95% CI, 0.7–1.3; $P_{trend} = 0.612$) for sausage,

and 1.0 (95% CI, 0.8–1.3; P_{trend} = 0.633) for hot dogs/frankfurters. [The Working Group noted that the FFQ was not validated and that red meat included some processed meat (e.g. ham).]

Chandran et al. (2013), in the USA, evaluated ethnic disparities with red and processed meat intake and breast cancer in African Americans (803 cases, 889 controls) and Caucasians (755 cases, 701 controls). Controls were identified by random digit dialling of residential telephone and cell phone numbers. Diet was assessed with an FFQ with approximately 125 food items, which was validated in other USA populations. Processed meat included lunchmeats, as well as bacon, sausages, bratwursts, chorizo, salami, and hot dogs. For Caucasian women, the odds ratios for the top versus the bottom quartile of intake were 1.48 (95% CI, 1.07–2.04; P_{trend} = 0.07) for processed meat (> 15.19 vs ≤ 2.35 g/1000 kcal per day) and 1.40 (95% CI, 1.01–1.94; P_{trend} = 0.29) for red meat (> 24.70 vs ≤ 4.14 g/1000 kcal per day). For African American women, the odds ratios for the top versus the bottom quartile of intake were 1.21 (95% CI, 0.89–1.64; P_{trend} = 0.18) for processed meat (> 15.19 vs ≤ 2.35 g/1000 kcal per day) and 0.84 (95% CI, 0.61–1.14; P_{trend} = 0.28) for red meat (> 24.70 vs ≤ 4.14 g/1000 kcal per day). The results supported an association between red meat or processed meat consumption and increased breast cancer risk in Caucasian women. However, in African American women, only processed meat consumption was positively associated with breast cancer. [The Working Group concluded that the strengths of the study included the large sample of African American women, and evaluation by menopausal status and hormone receptor status. In addition, an extensive list of covariates was adjusted for. Limitations included the much lower response rate in controls, which may have led to selection bias and limited statistical power in some subgroup analyses. In addition, alcohol intake was not adjusted for in statistical analyses.]

Mourouti et al. (2015) evaluated red meat and processed meat in 250 cases and 250 controls from Greece. Breast cancer patients that visited the pathology–oncology clinics of five major general hospitals in Athens, Greece, were recruited as cases (average age, 56 years). Controls were selected from the same catchment area, and had a participation rate of 88%. Diet was assessed with a validated SQFFQ with 86 questions. Red meat included beef, lamb, veal, and pork. Processed meat included cured and smoked meats, ham, bacon, sausages, and salami. The study found a positive association with processed meat intake, but not with red meat intake. Compared with non-consumers, women who consumed processed meat 1–2 times/week and women who consumed processed meat ≥ 6 times/week had odds ratios of 2.65 (95% CI, 1.36–5.14) and 2.81 (95% CI, 1.13–6.96), respectively ($P < 0.05$). Compared with women who consumed red meat ≤ 1 time/week, those who consumed red meat 8–10 times/week had an odds ratio of 0.99 (95% CI, 0.31–3.12). [The Working Group noted that the study had a modest sample size, but did not adjust for caloric intake, alcohol intake, and reproductive factors.]

(ii) Hospital-based studies

Richardson et al. (1991) conducted a hospital-based case–control study in southern France that included 409 cases and 515 controls. Cases were women between 28 and 66 years of age with histologically confirmed primary carcinoma of the breast. Controls were women of the same age group who were admitted for the first time to a nearby hospital or hospitalized for general surgery in a large clinic. Among the 932 people interviewed, all cases joined, but eight controls refused to join the study. A dietary history questionnaire of similar design to the one described in Block (1982) with 55 food items was used to assess diet. The study found a non-significant positive association between processed pork meat intake and breast cancer (OR, 1.4;

95% CI, 0.9–2.0; intake of > 87.5 vs ≤ 25 g/week). [The Working Group noted that no description was provided whether the dietary history questionnaire was validated. Information on caloric intake was not available for adjustment in statistical analyses.]

Franceschi et al. (1995) conducted a hospital-based case–control study in Italy in 1991–1994. The study included 2569 cases and 2588 controls. Cases were women with first histologically confirmed cancer of the breast, diagnosed no later than 1 year before the interview, and with no previous diagnoses of cancer at other sites. Controls were patients with no history of cancer admitted to major teaching and general hospitals in the same catchment area of the cases for acute non-neoplastic, non-gynaecological conditions, unrelated to hormonal or digestive tract diseases, or to long-term modifications of diet. Diet was measured with a 79–food item, validated FFQ. Red meat included steak, roast beef, lean ground beef, boiled beef, beef or veal stew, wiener schnitzel, liver, and pasta with meat sauce and with meat filling. Pork and processed meats included pork chop, prosciutto, ham, salami, and sausages. Compared with those in the lowest quintile of red meat intake (≤ 2.0 servings/week), participants in the highest quintile of red meat intake (> 5.3 servings/week) had an odds ratio of 1.09 (95% CI, 0.90–1.31). Compared with those in the lowest quintile of pork and processed meat intake (≤ 1.0 servings/week), participants in the highest quintile of pork and processed meat intake (> 4.5 servings/week) had an odds ratio of 1.09 (95% CI, 0.89–1.33). The participation rate of cases and controls was > 95%. In addition, a limited number of breast cancer risk factors (age and parity) were adjusted for. This study was included in a later analysis of case–control studies conducted in Italy and Switzerland (Di Maso et al. 2013). [The Working Group noted that, in this study, pork (i.e. red meat) was included in processed meat, and red meat did not include pork.]

Tavani et al. (2000) conducted a large hospital-based study of red meat intake and multiple cancer sites in Italy that included 3412 breast cancer cases. Controls (n = 7990) were selected among those who were admitted to the same network of hospitals as the cases. Controls with a wide spectrum of acute non-neoplastic conditions were accrued. A structured questionnaire asked about the frequency of intake of approximately 40 foods and total red meat consumption per week. Red meat included beef, veal, and pork, and excluded canned and preserved meat. Compared with those who consumed ≤ 3 portions/week of red meat, women who consumed > 6 portions/week of red meat had an odds ratio of 1.2 (95% CI, 1.1–1.4). [The Working Group noted that the participation rate of cases and controls was > 95%. The questionnaire asking about food intake was not validated. Processed meat was not evaluated separately. Caloric intake was not adjusted for in statistical analyses.]

Di Maso et al. (2013) evaluated data with information on cooking practices from a network of case–control studies conducted in Italy and Switzerland between 1991 and 2009. Multiple cancer sites were evaluated in relation to red meat intake and intake by cooking method (roasting/grilling, boiling/stewing, frying/pan-frying). For breast cancer analysis, 3034 cases and 11 656 controls were included. Trained personnel administered a structured questionnaire to cases and controls during hospitalization. Subjects' usual diet in the 2 years before diagnosis (or hospital admission for controls) was investigated using an FFQ that included specific food items on weekly consumption of red meat according to different cooking methods (i.e. boiling/stewing, roasting/grilling, or frying/pan-frying). Serving size was defined as an average serving in the Italian diet. Red meat included beef, veal, pork, horse meat, and half of the first course, including meat sauce (e.g. lasagne, pasta/rice with bologna sauce), and did not include processed meat. The

FFQ was tested for validity. Compared with those who consumed < 60 g/day of red meat, those who consumed ≥ 90 g/day of red meat had an odds ratio of 1.18 (95% CI, 1.04–1.33; P_{trend} < 0.01). The odds ratios per 50 g/day increase in red meat intake were 1.14 (95% CI, 1.02–1.28) for pre- and perimenopausal women and 1.10 (95% CI, 1.01–1.19) for postmenopausal women ($P_{interaction}$ = 0.55). Among the cooking methods, roasting/grilling conferred the highest risk (OR, 1.20; 95% CI, 1.08–1.34) for an increase of 50 g/day of red meat. [The Working Group noted that the study included Franceschi et al. (1995), previously reported in this section.]

(b) Red meat and processed meat combined or not clearly defined

(i) Population-based studies

Ewertz and Gill (1990) evaluated intake of individual red meat items and breast cancer in Denmark. A total of 1474 cases (88% participation rate) and 1322 age-matched controls (79% participation rate) were included. Cases were recruited from the Danish Cancer Registry and the nationwide clinical trial of the Danish Breast Cancer Cooperative Group (DBCG). Controls were an age-stratified random sample of the general female population, selected from the central population register. Diet was assessed with an FFQ with 21 food items. Intake of lean pork, medium-fat pork, fatty pork, and liver was evaluated. The relative risk for the top versus the bottom quartile of intake of medium-fat pork was 1.34 (95% CI, 1.05–1.71). No other items were significantly related to breast cancer. [The Working Group noted that diet was assessed 1 year after the diagnosis among cases. Information on validation of the FFQ was not provided. Odds ratios were adjusted for age at diagnosis and place of residence only.]

Goodman et al. (1992) evaluated bacon, sausage, liver and pork, and other meats, including spam, luncheon meats, beef, and lamb, but not red meat or processed meat intake in 272 postmenopausal breast cancer cases and 296 controls in Hawaii, USA. The study selected 43 different food items that largely contribute to the intake of fat and animal protein in Japanese and Caucasian women. A dose–response relation with breast cancer risk and sausage intake was suggested (P_{trend} < 0.01). The odds ratio for high (> 60 g/week) versus low (none) sausage intake was 1.7 (95% CI, 1.2–2.4). [The Working Group noted the modest sample size. In addition, there was no separate evaluation of red meat or processed meat. Caloric intake was not adjusted for. Age, ethnicity, age at first birth, and age at menopause were adjusted for, but other breast cancer risk factors were not adjusted for.]

Witte et al. (1997) conducted a family-matched case–control study including cases from a multicentre genetic epidemiology study of breast cancer conducted in the USA and Canada in 1989. Survivors of bilateral premenopausal breast cancer with at least one sister who was alive in 1989 were included, and one or more of the sisters served as controls. A total of 140 cases and 222 unaffected sisters of the cases were included. Cases and controls were mailed a 61-item SQFFQ to assess diet a median time of > 13 years after diagnosis. Red meat was not positively associated with breast cancer risk (OR, 0.6; 95% CI, 0.3–1.3) for the highest versus the lowest quartile (14.1 vs 4.5 servings/week) of intake. [The Working Group noted that the sample size was small. Red meat was not defined.]

Männistö et al. (1999) evaluated intake of beef and pork [i.e. red meat] and breast cancer in Finland. The subjects were participants in the Kuopio Breast Cancer Study who lived in the catchment area of the Kuopio University Hospital in 1990–1995. A total of 310 cases aged 25–75 years (81% participation rate), and 454 controls (72% participation rate) from the Finnish National Population Register and 506 controls (92% participation rate) who were referred to the same examinations as the cases

and subsequently found healthy were included. Diet was assessed with a validated FFQ with 110 food items. Among premenopausal women, the odds ratios for the top versus the bottom quintile (> 77 vs < 37 g/day) of intake of beef and pork [red meat] were 0.6 (95% CI, 0.3–1.4) versus population controls and 0.5 (95% CI, 0.3–1.2) versus referral controls. Among postmenopausal women (top vs bottom quintile, > 68 vs < 29 g/day), the corresponding odds ratios were 0.9 (95% CI, 0.5–1.7) and 1.0 (95% CI, 0.5–2.0). [The Working Group noted that caloric intake was not adjusted for in statistical analyses.]

Shannon et al. (2003) conducted a population-based case–control study of diet and postmenopausal breast cancer in western Washington, USA, with 441 cases and 370 controls. Diet was assessed by FFQ with 95 food items. The study found that red meat was, but processed meat was not, associated with an elevated breast cancer risk. The odds ratio for the top quartile (> 0.82 servings/day) compared with the bottom quartile (≤ 0.29 servings/day) of intake was 2.03 (95% CI, 1.28–3.22; $P_{trend} = 0.002$) for red meat intake. [The Working Group noted that red meat and processed meat were not defined. The response rate was low, especially among controls (50%). In addition, the FFQ might not have been validated because there was no description of validation.]

Shannon et al. (2005) evaluated intake of red meat and processed meat and breast cancer in China. The study was nested within a randomized trial of breast self-examination. A total of 378 cases (85% participation rate) and 1070 age- and menstrual status–matched controls (64–82% participation rate) were included. Diet was assessed with an interviewer-administered FFQ with 115 food items. Red meat included beef, pork, pork chops, spare ribs, pig trotters, ham, pork liver, beef, other red meats, organ meat (except liver), and lamb or mutton. The odds ratio for the top (≥ 6.1 servings/week) versus the bottom (≤ 3.0 servings/week) quartile of red meat intake was 1.24 (95% CI, 0.77–1.99). The odds ratio for the top (≥ 2 servings/month) versus the bottom (≤ 0.5 servings/month) quartile of cured meat intake was 1.2 (95% CI, 0.82–1.74). Red meat or cured meat [i.e. processed meat] intake was not associated with breast cancer risk. [The Working Group noted that, although the study was based on a prospective clinical trial study, there was no follow-up of participants after dietary assessment, which was based on the status of the cases and controls, and for cases, was conducted before biopsy, and thus, was considered as a case–control study. The statistical analysis was adjusted for age, total energy intake, and breastfeeding only. Red meat included ham, which is a processed meat.]

Mignone et al. (2009) used data from the Collaborative Breast Cancer Study (CBCS) in the USA. The study included 2686 cases and 3508 community controls. Recent incident invasive breast cancer cases were identified through their respective state cancer registries. Community controls were selected at random (within age strata) from lists of licenced drivers and Medicare beneficiaries with no history of breast cancer. Detailed questions on red meat consumption and cooking practices in the recent past (approximately 5 years before diagnosis in the cases or a comparable time referent in the controls) were collected. Women were asked to report on the degree of doneness for red meat. Compared with women who consumed red meat < 2 servings/week, those who consumed ≥ 5 servings/week had an odds ratio of 0.98 (95% CI, 0.81–1.18) in the multivariate analysis among all women. Corresponding odds ratios were 0.82 (95% CI, 0.60–1.13) among premenopausal women and 1.02 (95% CI, 0.80–1.31) among postmenopausal women. [The Working Group noted that the study did not appear to utilize the full FFQ. Red meat was not clearly defined, but presumably did not include processed meat because processed meat items were not described

as assessed. Caloric intake was not adjusted for in the multivariate analysis.]

Rabstein et al. (2010) in Germany included 1020 cases and 1047 population-based controls. Women with a histopathologically confirmed breast cancer diagnosis within 6 months before enrolment were included (88% response rate). Current residence in the study region, age not more than 80 years, and Caucasians were selected. Controls were frequency-matched to cases by year of birth in 5-year classes with the same inclusion criteria as cases. The study evaluated red meat intake and breast cancer by hormone receptor status and *NAT2* polymorphism. Regular (> 1 time/week) consumption of red meat was associated with an elevated risk of breast cancer compared with rare (< 1 time/month) consumption (OR, 1.59, 95% CI, 1.11–1.99). The positive association was similar by hormone receptor status; the corresponding odds ratios were 1.33 (95% CI, 0.95–1.87) for ER+ cases (n = 601), 1.71 (95% CI, 0.95–3.09) for ER– cases (n = 169), 1.42 (95% CI, 1.00–2.00) for PR+ cases (n = 569), and 1.43 (95% CI, 0.85–2.41) for PR– cases (n = 195). The association was also similar by *NAT2* acetylation status ($P_{interaction}$ = 0.16); the corresponding odds ratios were 1.71 (95% CI, 1.15–2.55) for slow acetylators (n = 569) and 1.73 (95% CI, 1.15–2.61) for fast acetylators (n = 439). [The Working Group concluded that the study lacked information on the dietary assessment, the validation study of the dietary assessment tool, and the definition of red meat.]

The population-based Shanghai Breast Cancer Study was analysed by Dai et al. (2002), Kallianpur et al. (2008), and Bao et al. (2012). The study consisted of a phase 1 (1996–1998) and phase 2 (2002–2004). Cases were identified through the rapid case ascertainment system of the Shanghai Cancer Registry and were permanent residents of urban Shanghai (age, 25–70 years); 1602 eligible breast cancer cases were identified during phase 1, and 2388 cases were identified during phase 2 (86% participant rate). Controls were randomly selected from women in the Shanghai Resident Registry and frequency-matched to cases by age in 5-year intervals (78% participation rate). Diet was measured with a validated, 76–food item FFQ that included 19 animal foods.

Dai et al. (2002) published the association between red meat intake and breast cancer using phase 1 subjects (1459 cases, 1556 controls). Red meat included pork, beef, and lamb. Red meat intake and breast cancer risk were evaluated and stratified by the deep-frying cooking method (never, ever, well done). The positive association between red meat intake and breast cancer appeared to be stronger in those who used ever or well-done deep-frying cooking method than in those who never used this cooking method. After adjusting for total energy and other potential confounders, the odds ratios for > 87 g/day of red meat compared with < 29 g/day of red meat were 1.49 (95% CI, 1.04–2.15) for never-users of the deep-frying cooking method, 1.78 (95% CI, 1.24–2.55) for ever-users of the deep-fried cooking method, and 1.92 (95% CI, 1.30–2.83) for well-done users of the deep-frying cooking method. [The Working Group noted that no information was provided on whether red meat included processed meat. Alcohol intake was not adjusted for in statistical analyses.]

Bao et al. (2012) used subjects from phases 1 and 2 of the Shanghai Breast Cancer Study (3443 cases, 3474 controls). Red meat was positively associated with breast cancer. Compared with women who consumed ≤ 26 g/day of red meat, those who consumed ≥ 82 g/day of red meat had an odds ratio of 1.45 (95% CI, 1.22–1.72; P_{trend} < 0.0001). Corresponding odds ratios were 1.51 (1.20–1.90) for ER+/PR+, 1.55 (1.16–2.07) for ER–/PR–, 1.81 (95% CI, 1.15–2.84) for ER+/PR–, and 1.29 (95% CI, 0.81–2.03) ER–/PR+ breast cancers (for ER+/PR+ and ER–/PR– , $P_{heterogeneity}$ = 0.57). [The Working Group noted that no information was provided on whether red meat included processed meat.]

Kallianpur et al. (2008) evaluated iron intake in the phase 1 and 2 population (3452 cases, 3474 controls). After adjusting for known risk factors, including total energy intake, animal-derived (largely haem) iron intake was positively associated with breast cancer risk ($P_{trend} < 0.01$). The odds ratio for the top versus the bottom quartile of intake was 1.50 (95% CI, 1.19–1.88). The association was similar by menopausal status. [The Working Group noted that no information was provided on whether red meat included processed meat. Alcohol intake was not adjusted for in statistical analyses.]

(ii) Hospital-based studies

Lee et al. (1992) conducted a study among Singapore Chinese women, comprising 200 cases (93% response rate) and 420 hospital-based controls (94% response rate). Diet was assessed by interview using a 90–food item FFQ. Red meat intake was associated with breast cancer in premenopausal women (109 cases), but not in postmenopausal women (91 cases). The odds ratios for the highest versus the lowest tertile of red meat intake (≥ 48.6 vs < 22.0 g/day) was 2.6 (95% CI, 1.3–4.9) in premenopausal women and 1.2 (95% CI, 0.6–2.4) in postmenopausal women. [The Working Group noted that red meat intake was mostly pork, but also included beef and mutton; it was not specified whether processed meat was excluded. The study had a modest sample size. The FFQ was not validated in this population.]

De Stefani et al. (1997) conducted a hospital-based case–control study in Uruguay in 1994–1996 that included 352 breast cancer cases (96% participation) and 382 controls (98% participation). The study used an FFQ with 64 items that was not validated. The study found an increased risk of breast cancer was associated with a higher beef intake and lamb intake. The odds ratios were 3.84 (95% CI, 2.09–7.05) for beef and 2.38 (95% CI, 1.27–4.47) for lamb for the top versus the bottom quartile of intake (≥ 365 vs ≤ 154 servings/year) and for the third versus the first tertile of intake (< 12 vs > 53 servings/year), respectively. The results were not similar by menopausal status since P_{trend} was significant only among postmenopausal women. Processed meat was not associated with breast cancer risk. [The Working Group noted that this was a hospital-based study with a small sample size. The FFQ was not validated. Adjustment of fat intake in the multivariate analysis would have been an overadjustment. Red meat included processed meat, so data are not presented here.]

A hospital-based case–control study of breast cancer was conducted in Guangdong, China, with 438 cases (96% response rate) and 438 controls (98% response rate) by Zhang et al. (2009). Diet was assessed with an 81–food item, validated FFQ. Processed meat included sausage, ham, bacon, and hot dog. The odds ratio for the highest quartile of intake was 1.44 (95% CI, 0.97–2.15; $P_{trend} = 0.07$) for processed meat. [The Working Group took note of the high participation rate. Alcohol intake was not adjusted for in statistical analyses. Red meat included processed meat, so data are not given here.]

Kruk (2007), in Poland, evaluated 858 cases and 1085 controls aged 28–78 years, and evaluated the association between red meat intake and breast cancer. Cases were identified from the Szczecin Regional Cancer Registry and were diagnosed with histologically confirmed invasive cancer. Controls were frequency-matched by age (5-year age group) and place of residence. Most controls (853) were selected among patients admitted to ambulatories in the same area as the cases to control for health. The remaining 232 controls were selected from hospital patients. Diet was assessed by FFQ, which was modified from the Block (the USA) and Franceschi (Italy) FFQs to include 18 main, Polish-specific food groups. Kruk & Marchlewicz (2013) described that red meat included pork, beef, or lamb that was broiled, fried, or canned. The study presented the results by menopausal status (310

premenopausal, 548 postmenopausal cases). The positive association between red meat intake and breast cancer risk was significant in premenopausal women and was suggestive, but not significant, among postmenopausal women. The odds ratios comparing those who consumed 0 servings/week of red meat with those who consumed ≥ 5 servings/week of red meat were 2.96 (95% CI, 1.49–5.91; P_{trend} = 0.009) among premenopausal women and 1.51 (95% CI, 0.89–2.57; P_{trend} = 0.65) among postmenopausal women. [The Working Group noted that the study had low response rates among cases. The FFQ was not validated. Caloric intake was not adjusted for. Kruk & Marchlewicz used the same data set and stratified the association by physical activity level. Red meat included processed meat.]

Kruk & Marchlewicz (2013) used the same data set as Kruk (2007), and evaluated the association between red meat and processed meat intake and breast cancer stratified by lifetime physical activity. A positive association between processed meat intake and breast cancer was only significant among those with low lifetime physical activity. The odds ratio comparing those who consumed ≤ 2 servings/week of processed meat with those who consumed ≥ 7 servings/week of processed meat was 1.78 (95% CI, 1.04–3.59) among women with < 105 metabolic equivalent hours per week of physical activity. Separate results were not presented by menopausal status. [The Working Group noted that the study had low response rates among cases. The FFQ was not validated. Caloric intake was not adjusted for. It was unclear whether the reported data were the result of a true effect modification by physical activity because the statistically significant subgroup had the largest sample size, and the *P* value for interaction was not calculated. Red meat included canned red meat (i.e. processed meat), so data are not reported here.]

Ronco et al. (2012) conducted a hospital-based case–control study (253 cases, 497 controls) and evaluated multiple risk factors for premenopausal breast cancer in Uruguay. Red meat included beef, barbecue, and milanesas (a typical form of fried meat in Uruguay). The study found that a high consumption of red meat, which was based on two food items, was associated with a higher risk of breast cancer (OR, 2.2; 95% CI, 1.35–3.60). [The Working Group concluded that the limitations were that this was a hospital-based study with a relatively small sample size. In addition, the study used a limited and non-validated FFQ, had no category cut-points for red meat intake, and made no adjustment for caloric intake in statistical analyses.]

Laamiri et al. (2014) reported that both red meat and processed meat intake were strongly positively associated with breast cancer among 400 cases and 400 controls from Morocco. Cases were recruited from the National Institute of Oncology. Controls were recruited at the institute after they had undergone a mammography that showed no signs of breast cancer. Diet was measured by FFQ. The odds ratios were 4.61 [95% CI, 2.26–9.44] for red meat intake and 9.78 [95% CI, 4.73–20.24] for processed meat intake. [The Working Group concluded that the study lacked information on response rates, details of items collected in the FFQ, validation study of the dietary assessment tool, and definition of red meat and processed meat, as well as the increment unit for the odds ratios, which appeared to treat red meat and processed meat as continuous variables. The study also did not adjust for alcohol intake, caloric intake, and reproductive factors.]

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2.7 Cancer of the lung

The quality of the available studies on the association between cancer of the lung and consumption of red and processed meat was evaluated based on sample size, quality of reporting of the type of meat, inclusion of relevant confounders, study design issues (e.g. population- vs hospital-based design, response rates), and exposure assessment, including validation of dietary questionnaires. Adequate control for potential confounding by energy intake and smoking (including details on smoking history, given the strength of the association with cancer of the lung) was considered as key in the evaluation of the association between cancer of the lung and red and processed meat consumption. Studies that did not distinguish clearly between red and white meat were excluded from review, unless otherwise noted. Additional criteria are listed below for case–control studies.

2.7.1 Cohort studies

See Table 2.7.1 and Table 2.7.2 (web only; available at: http://publications.iarc.fr/564)

Six cohort studies were considered informative with respect to the association between cancer of the lung and meat intake. Unlike for other cancer sites, such as the colorectum, there were fewer studies available for the review of cancer of the lung. Therefore, the Working Group included most studies of lung cancer and red or processed meat, with exceptions as noted. The Working Group included one study investigating mortality; given the short survival of lung cancer patients, mortality is a reasonable surrogate for incidence. Balder et al. (2005) was excluded because it referred to a mixed category of "pork, processed meat, and potatoes". The study by Knekt et al. (1994) was excluded because it only reported results for fried meat (did not specify if red or white).

Breslow et al. (2000) studied 20 195 individuals with dietary data from the 1987 National Health Interview Survey, who were then linked to the National Death Index. Baseline diet was assessed with a 59-item FFQ. Food groups, including total meat/poultry/fish, red meats, and processed meats, were analysed after adjustment for age, sex, BMI, smoking, and other variables, but not total energy. There were 158 deaths from lung cancer. Red meat intake was associated with lung cancer mortality. The relative risk was 1.6 (95% CI, 1.0–2.6; P_{trend} = 0.014) for the highest (6.6 servings/week) versus the lowest (0–2.3 servings/week) quartile. No association was found with processed meat (P_{trend} = 0.721). [The Working Group noted that this was a small study based on mortality, with a limited FFQ and no adjustment for total energy.]

Tasevska et al. (2009) studied 278 380 men and 189 596 women from the National Institutes of Health-AARP Diet and Health (NHI-AARP) study. Diet was assessed with a 124-item FFQ. Meat-cooking modalities were investigated, and the CHARRED database was used to estimate the intake of HAAs, benzo[*a*]pyrene (BaP), and haem iron. A high intake of red meat was associated with an increased risk of lung cancer in both men (HR, 1.22; 95% CI, 1.09–1.38; P_{trend} = 0.005) and women (HR, 1.13; 95% CI, 0.97–1.32; P_{trend} = 0.05) for the highest compared with the lowest category of intake. A high intake of processed meat increased the risk only in men (HR, 1.23; 95% CI, 1.10–1.37; P_{trend} = 0.003). In an analysis stratified by smoking status, never-smoking men and women had increased risks with red meat consumption that were not statistically significant. The hazard ratios for the 90th versus the 10th percentile were 1.19 (95% CI, 0.69–2.06; P_{trend} = 0.52) in men and 1.21 (95% CI, 0.76–1.94; P = 0.44) in women for red meat. The relative risk for the highest versus the lowest tertile of intake of well/very well-done meat was 1.20 (95% CI, 1.07–1.35; P_{trend} = 0.002), and for intake of MeIQx, it was 1.20 (95% CI, 1.04–1.38;

P_{trend} = 0.04) in men. Haem iron intake for the highest compared with the lowest quintile was associated with an increased risk of lung carcinoma in both men (HR, 1.25; 95% CI, 1.07–1.45; P_{trend} = 0.02) and women (HR, 1.18; 95% CI, 0.99–1.42; P_{trend} = 0.002).

Linseisen et al. (2011) used the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort, with 1822 incident lung cancers, exposure assessment based on a validated FFQ and 24-hour recall, and statistical analyses including adjustment for several smoking variables. With a continuous model, they found a statistically non-significant increase in risk of lung cancer. The relative risks were 1.06 (95% CI, 0.89–1.27) per 50 g increment of red meat and 1.13 (95% CI, 0.95–1.34) for the same amount of processed meat. Some subcohorts included health-conscious or vegetarian subjects [very large size].

Tasevska et al. (2011) used the Prostate, Lung, Colorectal and Ovarian (PLCO) cohort in which lung cancer screening was offered. There were 454 lung cancer cases in men and 328 in women. No information was given on response rates and losses to follow-up. No association was found with red meat or processed meat intake in men in multivariable modelling. Women showed slightly elevated relative risks with increasing quintiles of red meat intake (from ≤ 14.6 to > 42.5 g/1000 kcal): 1.33 (95% CI, 0.91–1.94), 1.60 (95% CI, 1.10–2.33), 1.24 (95% CI, 0.84–1.85), 1.30 (95% CI, 0.87–1.95), with no dose–response (P_{trend} = 0.65; adjusted for total energy intake and several other confounders, including smoking). [The Working Group noted that the study included both screened and non-screened arms, and the authors reported that associations were similar. There was accurate adjustment for smoking variables.]

Gnagnarella et al. (2013) invited asymptomatic volunteers aged 50 years or older who were current smokers or recent quitters, and had smoked at least 20 pack-years, to undergo annual screening with computed tomography. They assessed participants' diet at baseline using a self-administered FFQ that included 188 food items and beverages. During a mean screening period of 5.7 years, 178 of 4336 participants were diagnosed with lung cancer. In the multivariable analysis, red meat consumption was associated with an increased risk of lung cancer [HR for quartile 4 vs quartile 1, 1.73; 95% CI, 1.15–2.61; P_{trend} = 0.003]. [The Working Group noted that this was a relatively small study of heavy smokers.]

Butler et al. (2013) published a study based on data from a prospective cohort study among Chinese in Singapore that included 1004 lung cancer cases. A 165-item FFQ was used. The relative risk for fried meat was 1.13 (95% CI, 0.98–1.31) for the second tertile and 1.09 (95% CI, 0.94–1.27) for the third tertile of intake, but it was not specified whether fried meat was red or white. The corresponding relative risks for adenocarcinomas were 1.31 (95% CI, 1.03–1.68) and 1.36 (95% CI, 1.06–1.74). Risk estimates for fried pork consumption separately showed no clear association. [The Working Group concluded that a limitation was that the fried meat definition included both white and red meat. The strengths were that the study used a validated FFQ, had a large sample size, and adequately controlled for smoking, with 70% of the cohort being non-smokers.]

2.7.2 Case–control studies

See Table 2.7.3 and Table 2.7.4 (web only; available at: http://publications.iarc.fr/564)

The Working Group identified 21 case–control studies on the association between lung cancer and red and processed meat consumption from the USA, Uruguay, Europe, China, and China, Hong Kong Special Administrative Region, India, Canada, Singapore, Pakistan, and Brazil. When there were multiple publications from the same study, only the most recent one was included. Most of these studies were not

originally designed to assess meat consumption, and most of the available papers reported positive associations. The potential for reporting bias (i.e. reporting only statistically significant associations among the many associations that were investigated), therefore, needed to be considered in the evaluation of these findings.

The Working Group subsequently excluded eight case–control studies (most hospital-based) because the type of meat (red or white) was not specified (Suzuki et al., 1994; Phukan et al., 2014), the methods of control selection were unclear (Kubík et al., 2001; Shen et al., 2008; Chiu et al., 2010), the response rates were not given (Dosil-Díaz et al., 2007), or the information on adjustment for confounders was inadequate (Ganesh et al., 2011; Luqman et al., 2014). Brennan et al. (2000) was included, in spite of the lack of distinction between white and red meat, because it was one of the few studies to report estimates for non-smokers only.

Goodman et al. (1992) conducted a population-based study in Hawaii, USA, among 326 cases of histologically confirmed lung cancer and 865 controls. Exposure assessment was good, with an FFQ with 130 items. Results were inconsistent, with an increased risk for sausages, luncheon meat, and bacon in men (weaker and not statistically significant in women) and lack of association for red meat. A strong interaction was found with smoking, with odds ratios rising up to 11.8 (95% CI, 2.3–61.6) for smokers with > 70 pack-years of cigarettes consuming more than the median intake of sausages (men only for squamous cell carcinoma). There was also a statistically significant association with estimated nitrosamine intake. [The Working Group noted that the method of selection of controls changed during the conduction of the study. Strong odds ratios were based on the subgroup analysis.]

The study by Swanson et al. (1992) from China was based on a case–control design nested within an occupational population (a mining company) and a population-based study in a city. The response rate was very high. The accuracy of cancer ascertainment was uncertain, although the authors stated that it was based on pathological examinations. No association with meat intake (almost exclusively pork) was found. [The Working Group noted that there was a very small number of non-smoking cases.]

Sankaranarayanan et al. (1994) conducted a hospital-based study in India, based on 387 cases. Controls were relatives of patients or bystanders. Forty-five items were included in the dietary questionnaire. Strong but statistically unstable associations were reported for beef, with no dose–response. [The Working Group noted that the number of meat eaters in this study was small.]

Sinha et al. (1998) reported on a population-based study from the USA that included 593 cases and 628 controls, drawn from the drivers' licences or health care financing rosters. [The selection of controls was unclear, particularly oversampling of smokers.] A 110-item Health Habits and History Questionnaire (HHHQ) with 15 items related to red meat was used to assess exposure. Information on cooking methods and doneness levels was also obtained. Only women were included. There were statistically significant increases in risk with 10 g/day increments in the consumption of all red meat, well-done red meat, and fried red meat. When comparing the 90th and 10th percentiles, lung cancer risk increased for all red meat (OR, 1.8; 95% CI, 1.2–2.7), for well-done red meat (OR, 1.5; 95% CI, 1.1–2.1), and for fried red meat (OR, 1.5; 95% CI, 1.1–2.0).

Brennan et al. (2000) conducted a multicentre, hospital-based case–control study in non-smokers (defined as having smoked < 400 cigarettes in a lifetime) in Europe with a large samples size (506 cases, 1045 controls); diseases in controls were not specified. There was no association with meat intake, except in small cell carcinomas. Odds ratios were 1.2 (95% CI, 0.3–4.5) and 1.6 (95% CI, 1.1–2.2)

in increasing tertiles (weekly/several times and weekly/daily vs never, respectively). [The Working Group noted that the study was informative because it provided data on non-smokers. However, no distinction between white and red meat was made, and no adjustment for second-hand smoke was made.]

Alavanja et al. (2001) conducted a population-based study in the USA, with 360 cases identified through the Surveillance, Epidemiology, and End Results (SEER) Program and 574 controls sampled from drivers' licences and Medicare rosters (females only). A 70-item FFQ (NCI Block questionnaire) was used. Red meat was defined as hamburger, beef burritos, beef stew, pot pie, meatloaf, beef (fat unspecified), pork (fat unspecified), ham, lunchmeats, bacon, liver, sausage, or hot dogs. [The response rate, particularly in controls, was low.] The researchers found an association with increasing levels of red meat intake. Odds ratios were 1.7 (95% CI, 0.9–3.3) for 3.5–5.5 times/week, 2.0 (95% CI, 1.4–4.0) for 5.6–7.6 times/week, 2.5 (95% CI, 1.2–5.2) for 7.7–9.8 times/week, and 3.3 (95% CI, 1.7–7.6) for > 9.8 times/week (P_{trend} = 0.005). In addition, effect modification by histological type and smoking was considered. The odds ratios for red meat consumption were similar among adenocarcinoma cases (OR, 3.0; 95% CI, 1.1–7.9) and non-adenocarcinoma cases (OR, 3.2; 95% CI, 1.3–8.3), and among lifetime non-smokers and ex-smokers (OR, 2.8; 95% CI, 1.4–5.4) and current smokers (OR, 4.9; 95% CI, 1.1–22.3). [Red meat included processed meat.]

Hu et al. (2002) published the results of a population-based study in Canada in which controls were drawn from an insurance plan or random digit dialling. Only women who never smoked were included. A 70-item FFQ based on the NCI Block questionnaire was used. Overall, 161 cases and 483 controls were included, with a 1:3 case–control ratio. Modest associations were found with red meat (OR, 0.8 for second quartile, 2–3 servings/week; OR, 1.4. for third quartile, 3.1–5 servings/week; OR, 1.4 for fourth quartile, > 5 servings/week; none statistically significant). An increase in risk for processed red meat and bacon was not statistically significant, except for smoked meat (third tertile vs first tertile OR, 2.1; 95% CI, 1.1–4.0). Never-smokers were examined separately with the following results: for red meat, in increasing quartiles of servings/week, OR were 0.8 (95% CI, 0.4–1.5), 1.4 (95% CI, 0.7–2.6), and 1.4 (95% CI, 0.7–2.8), and for smoked meat, in increasing tertiles, 1.3 (95% CI, 0.8–2.3) and 2.1 (95% CI, 1.1–4.0). [The Working Group noted that the study size was small.]

Zatloukal et al. (2003) published the results of a study in the Czech Republic using spouses, relatives, and friends of hospital patients as controls. They found an association between lung cancer and increasing tertiles of intake of red meat, but only for histologies other than adenocarcinoma. The odds ratios were 1.54 (95% CI, 0.89–2.67) for weekly consumption and 1.81 (95% CI, 1.04–3.8) for daily consumption (P_{trend} = 0.04) [subgroup analysis noted].

Kubík et al. (2004) published the results of a hospital-based study in the Czech Republic among non-smoking women only (130 cases; 1022 controls were spouses, friends, or relatives of hospital patients). [Only nine food items were included in the dietary questionnaire.] They found an association with red meat (≥ 1 time/day to ≥ 1 time/week vs ≤ 1 time/week to > 1 time/month ; OR, 2.2; 95% CI, 1.07–4.51).

Lam et al. (2009) published a well-designed population-based study in Italy, with high response rates (87% cases, 72% controls) and large numbers (1903 cases, 2073 controls). Exposure assessment included a 58-item FFQ, with estimation of exposure to mutagens and detailed information on cooking practices. The researchers found increased odds ratios with increasing tertiles of red meat intake, 1.3 (95% CI, 1.1–1.6) and 1.8 (95% CI, 1.5–2.2). The odds ratios with increasing tertiles of processed meat intake were 1.3 (95% CI, 1.1–1.5) and 1.7 (95%

CI, 1.4–2.1). The odds ratios for estimated intake of the mutagen PhIP were 1.1 (95% CI, 0.9–1.4) and 1.5 (95% CI, 1.2–1.8). Never-smokers were examined separately. For red meat, the odds ratios with increasing tertiles were 1.1 (95% CI, 0.7–2.0) for the second tertile and 2.4 (95% CI, 1.4–4.0) for the third tertile for red meat (P_{trend} = 0.001), and 1.5 (95% CI, 0.9–2.6) and 2.5 (95% CI, 1.5–4.2) for processed meat (P = 0.001). [The Working Group noted that adjustment for smoking was accurate and detailed.]

Concerning hospital-based studies, Aune et al. (2009) from Uruguay reported associations with the highest compared with the lowest quartile of intake of red meat (OR, 2.17; 95% CI, 1.52–3.10) and processed meat (OR, 1.7; 95% CI, 1.28–2.25). They also looked at beef and lamb separately, and associations were similar. Twin papers from Uruguay were published by De Stefani et al. (2009) and Deneo-Pellegrini et al. (2015). The first differed because exposure assessment was broader with estimation of exposure to mutagens, and the second was restricted to squamous cell carcinoma in men. In addition to finding results that were very similar to Aune et al. (2009), De Stefani et al. (2009) reported results for exposure to PhIP, assessed through a database compiled from the literature (Jakszyn et al., 2004). In increasing tertiles of exposure, the odds ratios for PhIP were 1.12 (95% CI, 0.80–1.56), 1.48 (95% CI, 1.05–2.07), and 2.16 (95% CI, 1.48–3.15). Deneo-Pellegrini et al. (2015) reported on squamous cell lung cancer, and the odds ratios were 1.82 (95% CI, 1.13–2.91) and 1.09 (95% CI, 0.73–1.64) for the highest versus the lowest tertiles of intake of red meat and processed meat, respectively.

Lim et al. (2011) published the results of a hospital-based study in Singapore (399 cases, 815 controls) with high response rates (81% cases, 85% controls), but only 18 meat-related items were included in the FFQ. There was no significant association with total meat, pork, or processed meat intake. However, there was a significant association with high-bacon consumption (OR, 1.51; 95% CI, 1.06–2.16).

2.7.3 Meta-analyses

Two meta-analyses of the association between lung cancer and consumption of red or processed meat were identified. Yang et al. (2012) included 23 case–control and 11 cohort studies identified via MEDLINE, Embase, and the Web of Science through 2011. The meta-relative risk for the highest compared with the lowest category of intake was significantly greater than unity for red meat (RR, 1.34; 95% CI, 1.18–1.52), but not for processed meat intake (RR, 1.06; 95% CI, 0.90–1.25). The association with red meat was observed in never-smokers (RR, 1.66; 95% CI, 1.31–2.11), and was robust in sensitivity analyses that took into account the study type and quality. In general, results for processed meat were weak or inconsistent. All estimates (including those for red meat) showed high heterogeneity, with highly significant P values ($P < 0.001$) and high I^2 levels. There was no evidence of publication bias.

The second meta-analysis was an extension of the previous one, and aimed to explore the dose–response relationships in more detail (Xue et al., 2014). Dose–response data were available from 11 studies for red meat and 11 studies for processed meat. The meta-relative risks were 1.35 (95% CI, 1.25–1.46) for red meat (per 120 g increment) and 1.20 (95% CI, 1.11–1.29) for processed meat (per 50 g increment). In general, estimates varied considerably by study design. In cohort studies, the relative risks for red meat and processed meat were 1.21 (95% CI, 1.14–1.28; $P_{heterogeneity}$ = 0.7) and 1.09 (95% CI, 0.99–1.19; $P_{heterogeneity}$ = 0.1), respectively, with higher estimates in case–control studies. In case–control studies and other subgroup analyses by region and sex, P values for heterogeneity were highly significant.

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2.8 Cancer of the oesophagus

The Working Group focused their review on studies that clearly defined red meat or processed meat (see Section 1 and Section 2). Studies were excluded if: (1) risk estimates were presented for total meat (red and processed meat combined) intake; (2) the type of meat was not defined or included white meat; (3) fewer than 100 cases were reported, due to the limited statistical power, as a large database of high-quality studies were available; (4) a more recent report from the same study was available; (5) risk estimates, adjusted for important confounders, were not available (crude estimates were not considered to be informative); (6) dietary patterns were the focus; (7) outcome was assessed using mortality data; and (8) the analysis and results were reported for cancers of the upper aerodigestive tract as a group.

Important covariates for the association between red meat and cancer of the oesophagus include age, tobacco smoking, alcohol drinking (squamous cell carcinoma), BMI (adenocarcinoma), and energy intake.

2.8.1 Cohort studies

(a) Red meat

See Table 2.8.1 (web only; available at: http://publications.iarc.fr/564)

Conflicting results were reported in the three cohort studies that reported on the association between red meat consumption and oesophageal cancer reviewed by the Working Group. No association was observed between consumption of red meat and oesophageal cancer among women enrolled in the NLCS (Keszei et al., 2012), or among participants in the EPIC study (Jakszyn et al., 2013). Increased risks were observed among the NIH-AARP study cohort (Cross et al., 2011) and among men enrolled in the NLCS (Keszei et al., 2012). The NIH-AARP study also reported positive associations between haem iron intake and risk of oesophageal adenocarcinoma (EAC). [The Working Group noted that, in the EPIC study, processed meat was not included in the definition of red meat, but the sample size was limited (137 cases), and the analyses did not adjust for alcohol. A strength of the NLCS was that a detailed questionnaire with 150 items was used; however, the sample size was limited (107 oesophageal squamous cell carcinomas, ESCCs; 145 EACs). The Working Group also noted that, although the NIH-AARP study cohort was large with a large number of cases (215 ESCCs, 630 EACs), and the study investigated the intake of meat-cooking by-products and haem iron intake, the interpretation of results was hampered because processed meat was included in the definition of red meat.]

(b) Processed meat

See Table 2.8.2 (web only; available at: http://publications.iarc.fr/564)

The Working Group reviewed three studies that investigated the association between consumption of processed meat and oesophageal cancer. One report from Cross et al. (2007) was updated and, therefore, not included. Studies based on mortality data were excluded (e.g. Iso et al., 2007). The Working Group noted when important risk factors for oesophageal cancer, such as tobacco and alcohol consumption, were not adjusted for in the analyses.

In the NIH-AARP study cohort, Cross et al. (2011) reported hazard ratios for the highest versus the lowest quintile of processed meat intake, adjusted for important confounders, of 1.32 (95% CI, 0.83–2.10; P_{trend} = 0.085; 60 exposed cases) for ESCC and 1.08 (95% CI, 0.81–1.43; P_{trend} = 0.262; 181 exposed cases) for EAC. [The Working Group noted that this was a large study with a large number of cases, especially for EAC.]

In the NLCS, Keszei et al. (2012) reported adjusted relative risks for oesophageal cancer for the highest compared with the lowest category of processed meat intake of 3.47 (95% CI, 1.21–9.94; P_{trend} = 0.04; 16 exposed cases) for ESCC and

0.94 (95% CI, 0.46–1.89; P_{trend} = 0.84; 24 exposed cases) for EAC in men. Corresponding relative risks in women were below one. [The Working Group noted that a detailed questionnaire with 150 items was used. The sample size was limited.]

Within the EPIC cohort, Jakszyn et al. (2013) reported a positive association between consumption of processed meat and EAC, after adjusting for important confounders (highest vs lowest tertile HR, 2.27; 95% CI, 1.33–3.89; P_{trend} = 0.004; 62 exposed cases). [The Working Group noted that this was a large study with a large number of cases, especially for EAC. Processed meat did not include white meat. Alcohol was not adjusted for.]

2.8.2 Case–control studies

(a) Red meat

See Table 2.8.3 (web only; available at: http://publications.iarc.fr/564)

The Working Group reviewed 20 case–control studies, both hospital-based and population-based, that investigated the association between oesophageal cancer and consumption of red meat. The studies were conducted in North America, South America, Europe, Asia, and Africa (Yu et al., 1988; Rogers et al., 1993; Castelletto et al., 1994; Brown et al., 1995, 1998; Rolón et al., 1995; Bosetti et al., 2000; Levi et al., 2000; Chen et al., 2002; Xibib et al., 2003; Wang et al., 2007; Wu et al., 2007; Navarro Silvera et al., 2008; Sapkota et al., 2008; Gao et al., 2011; O'Doherty et al., 2011; Wu et al., 2011; Ward et al., 2012; Di Maso et al., 2013; De Stefani et al., 2014a; Matejcic et al., 2015). All but seven studies were population-based. Two studies reported risk estimates less than or equal to one (Rogers et al., 1993; Sapkota et al., 2008), while most of the studies reported an increased risk of oesophageal cancer was associated with red meat intake, after adjusting for important confounding factors (Yu et al., 1988; Castelletto et al., 1994; Brown et al., 1995, 1998; Rolón et al., 1995; Bosetti et al., 2000; Levi et al., 2000; Chen et al., 2002; Xibib et al., 2003; Wang et al., 2007; Wu et al., 2007; Navarro Silvera et al., 2008; Gao et al., 2011; Wu et al., 2011; O'Doherty et al., 2011; Ward et al., 2012; Di Maso et al., 2013; De Stefani et al., 2014a; Matejcic et al., 2015).

(b) Processed meat

See Table 2.8.4 (web only; available at: http://publications.iarc.fr/564)

About 15 case–control studies that investigated the association between consumption of processed meat and oesophageal cancer, conducted in different areas of the world (the USA, South America, Europe, and Asia), were included in the evaluation by the Working Group (Yu et al., 1988; Brown et al., 1995, 1998; De Stefani et al., 2014b; Bosetti et al., 2000; Takezaki et al., 2001; Hung et al., 2004; Levi et al., 2004; Yang et al., 2005; Wu et al., 2007; Navarro Silvera et al., 2008; Sapkota et al., 2008; Chen et al., 2009; O'Doherty et al., 2011; Song et al., 2012; Ward et al., 2012; Lin et al., 2015). The quality of the studies was considered, based on the reporting of the type of meat; study design issues (e.g. population-based vs hospital-based design); sample size; exposure assessment, including validation of dietary questionnaires; and inclusion of relevant confounders. Important covariates for oesophageal cancer include age, tobacco smoking, alcohol drinking, BMI (adenocarcinoma), and energy intake. Nine studies were population-based (Yu et al., 1988; Brown et al., 1995, 1998; Takezaki et al., 2001; Wu et al., 2007; Navarro Silvera et al., 2008 ; O'Doherty et al., 2011 ; Song et al., 2012; Ward et al., 2012; Lin et al., 2015), two of which adjusted for *Helicobacter pylori* (Wu et al., 2007; O'Doherty et al., 2011.

2.8.3 Meta-analyses

Among the five meta-analyses on red and processed meat published recently (Choi et al., 2013; Huang et al., 2013; Qu et al., 2013; Salehi

et al., 2013; Zhu et al., 2014), Qu et al. (2013) considered ESCC, whereas Huang et al. (2013) considered EAC only. Choi et al. (2013) considered both types, but studies without information on the histological type were not included. Salehi et al. (2013) considered all oesophageal cancers, but studies reporting only one type of red meat, such as beef, pork etc., were included in the meta-analyses by Qu et al. (2013) and Choi et al. (2013). The results of the two most recent and comprehensive meta-analyses are summarized below. [The Working Group did not place emphasis on the results of the meta-analyses due to their significant limitations.]

Zhu et al. (2014) was the most recent and comprehensive meta-analysis. The meta-analysis included all types of oesophageal cancers: ESCC and EAC, and total oesophageal cancers. The meta-analysis included three cohort studies and 12 case–control studies; however, two reports, one for EAC (Brown et al., 1995) and the other for ESCC (Brown et al., 1998), on a population-based case–control study conducted in the USA were not included. The summary relative risks of oesophageal cancer for the highest compared with the lowest categories were 1.55 (95% CI, 1.22–1.96; $P_{heterogeneity} < 0.001$; $I^2 = 63.6\%$) for red meat and 1.33 (95% CI, 1.04–1.69; $P_{heterogeneity} < 0.001$; $I^2 = 61.5\%$) for processed meat. A statistically significant association was also observed for case–control studies (OR, 1.78 and 1.39, respectively), but not for cohort studies (RR, 1.22 and 1.25, respectively). When stratified by histological type, an association was observed between ESCC and red meat, and EAC and processed meat; the summary estimates were calculated as OR, 1.86 (95% CI, 1.31–2.66) and 1.23 (95% CI, 1.01–1.50), respectively. [The Working Group noted that this review included all types of oesophageal cancers. The interpretation of this analysis was limited by the fact that two reports were missing, and papers reporting on only one type of red meat, such as beef or pork, were not included.]

Qu et al. (2013) presented a comprehensive meta-analysis that considered study design, and further analysed dose–response and linearity. A total of two cohort studies and 19 case–control studies with 6499 oesophageal cancer cases were included in the meta-analysis. The summary relative risks of oesophageal cancer for the highest compared with the lowest categories were 1.57 (95% CI, 1.26–1.95; $P_{heterogeneity} = 0.003$) for red meat intake and 1.55 (95% CI, 1.22–1.97; $P_{heterogeneity} = 0.029$) for processed meat intake. These results were consistent with those of the dose–response analyses. Stratified analysis by histological type, study design, number of cases (< 200 vs ≥ 200), and adjustment of covariates did not reveal any differences, although the summary relative risks in the population-based case–control studies and the European studies were not statistically significant. [This review did not include studies reporting on EAC; however, studies reporting on only one item of red meat were included.]

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2.9 Other cancers

The Working Group focused their review on studies that clearly defined red meat or processed meat (see Section 1). Studies were excluded if: (1) risk estimates were presented for total meat (red and processed meat combined) intake; (2) the type of meat was not defined; (3) fewer than 100 cases were reported, due to the limited statistical power; (4) a more recent report from the same study was available; (5) risk estimates, adjusted for important confounders, were not available (crude estimates were not considered to be informative); (6) dietary patterns were the focus; and (7) outcomes were assessed using mortality data.

The tables for this section are available online at: http://publications.iarc.fr/564.

2.9.1 Non-Hodgkin lymphoma

For studies on non-Hodgkin lymphoma, apart from the criteria previously mentioned for all cancers, the studies were also evaluated carefully in regard to the main confounders, including age, sex, and energy intake. Some studies additionally adjusted for occupational exposures (if available) or excluded participants with HIV infection, namely in case–control studies. The Working Group noted when studies did not meet the criteria.

(a) Cohort studies

Five cohort studies reported on red meat consumption and risk of non-Hodgkin lymphoma, and four of these studies reported on processed meat consumption separately. Data on red meat and processed meat intake combined were not reported here.

(i) Red meat

See Table 2.9.1 (web only; available at: http://publications.iarc.fr/566)

The IWHS was a prospective cohort study that included 35 156 women aged 55–69 years at baseline in 1986 and who were followed up for 7 years (Chiu et al., 1996). A total of 104 incident cases of non-Hodgkin lymphoma were identified during the course of follow-up that also had usable dietary data. A 126-item, validated SQFFQ was used to estimate, among others, red meat and processed meat intake. [In this study, the red meat group included bacon, hot dogs, processed meat, liver, beef stew, hamburger, and beef as a main dish, which corresponded to red meat and processed meat combined. In addition, pork and lamb were not explicitly specified.] None of the separate meat components of the red meat group were significantly associated with non-Hodgkin lymphoma, except for the consumption of hamburger. The fully adjusted relative risk for the highest tertile (> 4 servings/month of hamburger) compared with the lowest tertile (< 4 servings/month of hamburger) of consumption amounted to 2.35 (95% CI, 1.23–4.48; $P_{trend} = 0.02$).

In 1992, after the cases had already been identified, an additional questionnaire, returned by 79% of the participants (64% of incident cases), was used to collect information about doneness levels of red meat, and specified beef, pork, and lamb as examples of red meat. The results for doneness of red meat revealed an inverse association with consumption of well-done red meat versus rare to medium–rare (RR, 0.47; 95% CI, 0.22–0.99; $P_{trend} = 0.09$). [The Working Group concluded that the inverse association with well-done red meat needed to be interpreted with caution because of potential information bias, since the information was collected later during follow-up, when cases had already occurred, and there were very few cases in the reference category ($n = 11$).]

The association between red and processed meat and risk of non-Hodgkin lymphoma ($n = 199$) in 88 410 women after 14 years of follow-up was investigated in the NHS (Zhang et al., 1999). Consumption of beef, pork, or lamb as a main dish was significantly associated with

an increased risk of non-Hodgkin lymphoma. The adjusted relative risk for the highest compared with the lowest quintile of intake was 2.2 (95% CI, 1.1–4.4; P_{trend} = 0.002). Analyses according to cooking methods showed a significant association between consumption of broiled beef, pork, or lamb as a main dish and non-Hodgkin lymphoma (consumption of 2–4 times/week vs < 1 time/month RR, 1.8; 95% CI, 1.0–3.3), although the *P* value for trend was not significant (*P* = 0.09). There was an elevated, but non-significant, association with barbecued beef, pork, or lamb consumed ≥ 1 time/week compared with barbecued beef, pork, or lamb consumed < 1 time/month (RR, 1.5; 95% CI, 0.9–2.4; P_{trend} = 0.13). [The Working Group noted that this was a large study that showed an association with consumption of red meat.]

The association between red and processed meat intake and risk of chronic lymphocytic leukaemia (CLL) and small lymphocytic lymphoma (SLL) was investigated in a pooled analysis of two prospective cohort studies: the NIH-AARP study and the PLCO trial. The analysis was restricted to Caucasians, and excluded outliers of energy intake (top and bottom 1%) and BMI (< 18.5 or > 50 kg/m^2). Among 525 982 participants from both cohorts, 1129 incident CLL/SLL cases were identified after 11.2 years of follow-up. Red meat consumption (age-, sex-, and BMI-adjusted HR, 0.90; 95% CI, 0.76–1.08) was not associated with risk of CLL/SLL for the highest compared with the lowest quartile of intake (Tsai et al., 2010). [The Working Group noted that this was a large study. There was no adjustment for energy intake, but BMI was adjusted for.]

In the EPIC study (Rohrmann et al., 2011), 410 411 participants were followed up for a median of 8.5 years, resulting in the identification of 1267 non-Hodgkin lymphoma cases classified according to the International Classification of Diseases for Oncology, Second Edition (ICD-O-2) and reclassified according to the Third Edition (ICD-O-3). Diet was assessed over the previous 12 months with validated questionnaires that covered meals or food groups, and individual average portions or standard portions. Red meat included beef, pork, and mutton/lamb. Red meat consumption was neither associated with non-Hodgkin lymphoma nor with any of the subtypes (the latter results were not shown). The multivariate-adjusted hazard ratio for the highest quintile of red meat consumption (≥ 80 g/day) compared with the lowest quintile (< 20 g/day) was 1.01 (95% CI, 0.82–1.26; P_{trend} = 0.55). [The Working Group noted that this was an important study because it was large and had a wide range of intake.]

The NIH-AARP study was a large prospective cohort study conducted in six different states and two metropolitan areas in the USA (Daniel et al., 2012a). The cohort included 492 186 individuals aged 50–71 years who were followed up for a mean of 9 years, resulting in the identification of 3611 incident cases of non-Hodgkin lymphoma (ICD-O-3). Usual dietary intake over the past year was assessed using a 124-item, validated FFQ. Red meat consumption was not associated with non-Hodgkin lymphoma or with any of the subtypes. The adjusted relative risk was 0.93 (95% CI, 0.83–1.05; P_{trend} = 0.27) for the highest quintile of red meat consumption (median, 48.1 g/1000 kcal) compared with the lowest quintile of red meat consumption (median, 6.8 g/1000 kcal). Doneness of meat was estimated for a subcohort, and extra analyses with these exposures did not reveal any association between doneness of meat and risk of non-Hodgkin lymphoma. Estimates of meat-cooking mutagens (from CHARRED) and meat-related compounds (i.e. haem iron and nitrate and nitrite) were also assessed, and none were found to be associated with non-Hodgkin lymphoma. [The Working Group concluded that this was a very informative study because of the large power, the well-described and seemingly comprehensive definition of the outcome and the exposures, and the ability to distinguish

between subtypes, sex, and other potential effect modifiers.]

(ii) Processed meat

See Table 2.9.2 (web only; available at: http://publications.iarc.fr/564)

In the IWHS, previously described (Chiu et al., 1996), processed meat was not defined further. Processed meat consumption was not associated with risk of non-Hodgkin lymphoma. The age- and energy-adjusted relative risk for the highest tertile (> 6 servings/month) of consumption of processed meat compared with the lowest tertile (< 4 servings/month) of consumption of processed meat was 1.11 (95% CI, 0.68–1.79; P_{trend} = 0.67). [The Working Group noted that it was difficult to draw conclusions based on the comparison of > 6 to < 4 servings/month; however, this could have been a typing error in the publication. The lack of definition of the processed meat group was a potential limitation of this study. In addition, the range of intake was very narrow, and the intake was low overall. Therefore, the results on processed meat consumption from this study should be regarded cautiously.]

In the pooled-analysis study described above, processed meat consumption (HR, 0.88; CI, 0.74–1.05) was not associated with risk of CLL/SLL, when comparing the highest with the lowest quartile of intake (Tsai et al., 2010).

In the EPIC study, previously described (Rohrmann et al., 2011), processed meat included all meat products, including ham, bacon, different types of sausages, canned/smoked/dried meat, pâté, hamburger, and meatballs. Processed meat consumption was not associated with non-Hodgkin lymphoma, yet a significant positive association with B-cell chronic lymphocytic leukaemia (BCLL) was observed. The multivariate-adjusted hazard ratio for the highest quintile (≥ 80 g/day) compared with the lowest quintile (< 20 g/day) of processed meat consumption was 1.06 (95% CI, 0.82–1.37; P_{trend} = 0.82) for non-Hodgkin lymphoma. A significant positive association was only observed for BCLL (HR for highest vs lowest quintile of intake, 2.19; 95% CI, 1.27–3.77; P_{trend} = 0.01). The results for the other subgroups were not reported because of the small number of exposed cases or non-significant associations. [The association observed for the BCLL subgroup may have been a chance finding amidst the many associations that were tested in this study. The Working Group concluded that this was an important study because it was large with a wide range of intake.]

In the NIH-AARP study, previously described (Daniel et al., 2012a). Processed meat consumption was not associated with non-Hodgkin lymphoma or with any of the subtypes (results for the latter not provided in this summary). The multivariate-adjusted relative risk of non-Hodgkin lymphoma for the highest quintile of processed meat consumption (median, 23.6 g/1000 kcal) compared with the lowest quintile of processed meat consumption (median, 2.2 g/1000 kcal) was 0.99 (95% CI, 0.89–1.11; P_{trend} = 0.45). The adjusted relative risk was 1.07 (95% CI, 0.95–1.20; P_{trend} = 0.91) for the highest quintile of red processed meat consumption (median, 19.9 g/1000 kcal) compared with the lowest quintile of red processed meat consumption (median, 1.4 g/1000 kcal). [The Working Group concluded that this was a very informative study because of the large power, the well-described and seemingly comprehensive definition of the outcome and the exposures, and the ability to distinguish between subtypes, sex, and other potential effect modifiers.]

(b) Case–control studies

Four population-based case–control studies and four hospital-based case–control studies reported on the association between red meat consumption and/or processed meat consumption and non-Hodgkin lymphoma.

(i) Red meat

See Table 2.9.3 (web only; available at: http://publications.iarc.fr/564)

Cross et al. (2006) conducted a population-based case–control study in four areas of the USA covered by NCI-sponsored SEER registries. A total of 458 (87% response rate) newly diagnosed, histologically confirmed non-Hodgkin lymphoma patients without HIV infection and 383 (90% response rate) controls matched by age (5 years), centre, ethnicity, and sex participated. There was no significant association between red meat intake and risk of non-Hodgkin lymphoma. Red meat consumption was assessed using a 117-item, self-administered FFQ (which was based on the 1995 revision of the Block questionnaire) covering usual diet over the past 12 months. [The definition of red meat was not specifically mentioned, but since the different cooking methods and doneness levels specified the following meats, they were potentially included in the red meat definition: hamburger, steak, pork chops, bacon, and sausage; therefore, red meat may have partially included some processed meats.] Based on cooking levels and doneness levels of the meats, several HAA intakes were estimated, but are not reported in this *Monograph*. The multivariate-adjusted odds ratio for the highest quartile compared with the lowest quartile of red meat intake was 1.10 (95% CI, 0.67–1.81; P_{trend} = 0.87). There was also no association with red meat intake according to different cooking methods (i.e. red meat with known cooking methods, either barbecued, pan-fried, or broiled) and doneness levels of red meat (rare, rare/medium, medium, or well-done red meat). [The Working Group noted that this study had very high response rates for cases and controls.]

A population-based case–control study was carried out in Canada (1994–1997). The study included a large group of histologically confirmed cases of cancer, among which 1666 were non-Hodgkin lymphomas, and 5039 were controls (Hu et al., 2008). A short version of the Block FFQ was used. The FFQ contained 69 items and ascertained usual dietary intake 2 years earlier. Red meat intake included intake from beef, pork, or lamb as a main dish; beef, pork, or lamb as a mixed dish (stew or casserole, pasta dish); and hamburger. Red meat intake was not associated with risk of non-Hodgkin lymphoma. The multivariate-adjusted odds ratio for the highest quartile of intake (≥ 5.1 servings/week) compared with the lowest quartile of intake (≤ 2 servings/week) of red meat was 1.1 (95% CI, 0.9–1.3; P_{trend} = 0.60). [The main strength of this study was that it was a large case–control study, but no details were provided on the number of cases per exposure category.] An earlier report of the previous study (Purdue et al., 2004), based on nearly the same data, reported essentially the same results (not presented in the table).

In a population-based case–control study in the USA (1999–2002), among 336 newly diagnosed, histologically confirmed non-Hodgkin lymphoma patients and 460 controls, red meat intake was significantly associated with non-Hodgkin lymphoma (Aschebrook-Kilfoy et al., 2012). A validated, 117-item FFQ (a modified Block questionnaire, HHHQ) was used. Red meat consisted of beef (hamburger/cheeseburger patties, roast beef/sandwiches, beef stew/pot pie, steak, tacos/burritos), pork (pork chops, roast), and liver. Additional analyses were conducted for meat-related carcinogens, estimated with the CHARRED database. The multivariate-adjusted odds ratio, additionally adjusted for white and processed meat intake, was 1.5 (95% CI, 1.1–2.2; P_{trend} = 0.01) for the highest tertile (≥ 61.8 g/1000 kcal) compared with the lowest tertile (< 41.2 g/1000 kcal) of intake. The associations were most pronounced for diffuse large B-cell lymphoma (DLBCL) and follicular lymphoma, and the association with DLBCL was especially evident with hamburger patties. [The Working Group noted that, although no associations

were observed for other disease subgroups, there were too few cases in these subgroups to draw conclusions.]

A hospital-based case–control study was conducted in north-eastern and southern Italy (1999–2002). The study included 190 incident, histologically confirmed non-Hodgkin lymphoma patients (excluding HIV-infected patients) and 484 controls (Talamini et al., 2006a). The cases were between 18 and 84 years of age, and were admitted to the major reference hospitals of the areas for surveillance. The controls were of the same age range and were admitted for a wide spectrum of acute conditions to the same network of hospitals. A validated, 63-item FFQ that covered the 2 years before diagnosis or hospital admission was used to estimate exposure. Red meat consumption was calculated from weekly serving sizes of beef, veal, pork, liver, pasta/rice with meat sauce, and lasagne/cannelloni. Red meat consumption was not associated with non-Hodgkin lymphoma. The multivariate-adjusted odds ratio for non-Hodgkin lymphoma was 0.93 (95% CI, 0.56–1.55; P_{trend} = 0.65) for the highest (> 3.25 servings/week) compared with the lowest (≤ 1.6 servings/week) quartile of red meat intake. An earlier hospital-based case–control study was also conducted in northern Italy (1983–1996) among 200 histologically confirmed non-Hodgkin lymphoma patients (< 5% non-response rate for cases and controls) [no mention of exclusion of HIV-infected individuals] (Tavani et al., 2000). The control group comprised 7990 patients younger than 75 years admitted to the same network of hospitals as the cancer cases for a wide spectrum of acute non-neoplastic conditions. Red meat was defined as beef, veal, and pork. Lamb, horse, goat, and offal were not included in the questionnaire. Canned meat and preserved meat were excluded. The information was collected through a 40-item FFQ that was not validated, but it did show a correlation of 0.61 for reproducibility of meat intake. It was estimated that a portion of red meat in Italy was between 100 and 150 g. There was also no evidence from this study of an association between red meat intake and non-Hodgkin lymphoma. The multivariate-adjusted odds ratio for the highest (≥ 7 portions/week) compared with the lowest tertile (≤ 3 portions/week) of intake of red meat was 1.2 (95% CI, 0.8–1.7). The adjusted odds ratio associated with an increase in intake of red meat of 1 average portion/day was 1.2 (95% CI, 0.9–1.7). [The Working Group noted that adjustment for energy intake was possible only for gastrointestinal cancers in this study.]

A hospital-based case–control study was conducted in Uruguay between 1996 and 2004. The study included 369 non-Hodgkin lymphoma cases and 3606 controls (De Stefani et al., 2013). All incident and microscopically confirmed non-Hodgkin lymphoma cases that occurred in the Cancer Institute of Uruguay were considered eligible for the study and were defined according to the WHO guidelines (Feller & Diebold, 2004). Controls were identified through the same institute. All interviews were conducted shortly after admittance, and an FFQ was used to assess exposure [validity not specified]. Red meat was defined as beef or lamb, and reported as servings per year. Red meat consumption was not associated with non-Hodgkin lymphoma. The odds ratio for the highest compared with the lowest tertile of red meat consumption was 1.25 (95% CI, 0.92–1.69; P_{trend} = 0.14). [The Working Group noted that there was no mention of exclusion of patients with HIV. It was also unclear what time period the FFQ referred to, and there was no mention of its validity. In addition, the unit of measurement for the exposure (i.e. servings/year) was unusual. The definition of red meat did not include pork.]

An earlier hospital-based case–control study was conducted in Uruguay (1988–1995). The study included 160 incident cases of non-Hodgkin lymphoma (92% response rate) [no mention of exclusion of HIV-infected

individuals] and 163 hospital-based controls matched by age (in 10-year age groups), sex, and residence and urban/rural status (De Stefani et al., 1998). Dietary intake was assessed through a food frequency form used by interviewers. [There was no mention of the period of intake that was covered.] Red meat was defined as beef and lamb. In this study, a significant association between red meat intake and non-Hodgkin lymphoma was reported for men, but the association was not significant for women. The odds ratio for non-Hodgkin lymphoma for the highest tertile (≥ 12.7 servings/week) compared with the lowest tertile (≤ 7.7 servings/week) of red meat intake was 2.53 (95% CI, 1.01–6.34; P_{trend} = 0.04) for men and 2.45 (95% CI, 0.88–6.82; P_{trend} = 0.08) for women (≥ 9.3 vs ≤ 6.0 servings/week, respectively). [The Working Group noted that results on specific types of red meats and cooking methods were provided, but only for certain subgroups, not all (only beef, and only barbecued and salted meat). Therefore, these risk estimates are not displayed further, neither in the text nor in the table, to avoid reporting bias.]

A hospital-based case–control study was conducted in India (1997–1999) in 390 men with microscopically confirmed non-Hodgkin lymphoma and 1383 controls with no evidence of disease (microscopically confirmed cancer-free) selected from the comprehensive cancer centre (Balasubramaniam et al., 2013). Red meat was defined as mutton, liver, pork, brain, etc. and based on interviews using a structured questionnaire on food items and frequency per week, covering a period of 1 year before the interview. Red meat consumption was strongly associated with non-Hodgkin lymphoma. The adjusted odds ratio for red meat consumption compared with no red meat consumption [dichotomous variable] was 7.3 (95% CI, 2.2–24.6). [The Working Group noted that the number of exposed cases was not provided for subgroups of red meat consumers. In addition, it is unknown whether the odds ratio was also adjusted for age and energy intake. It is also unclear whether only newly diagnosed non-Hodgkin lymphoma patients were included or whether patients living with the diagnosis for some time already were included. There was also no mention of whether HIV-infected cases were excluded. Although this was a study in India with a large number of vegetarians, only a dichotomous variable of red meat intake was provided (yes/no), and it is plausible that there was some residual confounding.]

(ii) Processed meat

See Table 2.9.4 (web only; available at: http://publications.iarc.fr/564)

In the population-based case–control study in the USA conducted by Cross et al. (2006), described earlier in the red meat subsection, processed meat included bacon, sausage, ham, hot dogs, liver, and luncheon meats. There was no significant association between processed meat intake and risk of non-Hodgkin lymphoma. The adjusted odds ratio for the highest quartile compared with the lowest quartile of processed meat intake was 1.18 (95% CI, 0.74–1.89; P_{trend} = 0.94).

In the population-based case–control study that was conducted in Canada (1994–1997), previously described in Section 2.9.1(b)(i) (Hu et al., 2008), processed meat intake included hot dogs, smoked meat, or corned beef; bacon and sausage. Processed meat consumption was not associated with non-Hodgkin lymphoma. The odds ratio for the highest quartile (≥ 5.42 servings/week) compared with the lowest quartile (≤ 0.94 servings/week) of intake of processed meat was 1.2 (95% CI, 0.9–1.4; P_{trend} = 0.15). The analysis was adjusted for age (10-year age group), province, education, BMI, sex, alcohol use, pack-years of smoking, total vegetable and fruit intake, and total energy intake. [The main strength of this study was that it was a large case–control study, but little detail was provided on the number of cases per exposure category.] An earlier publication on almost the same data as those in this

case–control study reported a positive association with processed beef/pork/lamb, defined as hot dogs, luncheon meats (salami, bologna; 1 piece or slice), smoked meat or corned beef (1 piece or slice), and bacon (1 slice), which could have been defined as processed red meat (Purdue et al., 2004). The Working Group decided to evaluate only the most recent publication as the results were contradictory.

In the population-based case–control study that was conducted in eastern Nebraska, USA (1999–2002), described in Section 2.9.1(b)(i) (Aschebrook-Kilfoy et al., 2012), processed meat intake was not associated with non-Hodgkin lymphoma. The multivariate-adjusted odds ratio was 1.3 (95% CI, 0.9–1.9; P_{trend} = 0.2) for the highest tertile of intake (≥ 13.1 g/1000 kcal) compared with the lowest tertile of intake (< 6.2 g/1000 kcal). An earlier population-based case–control study was conducted, in part by the same group, in eastern Nebraska, USA. The study included 385 histologically confirmed non-Hodgkin lymphoma cases diagnosed between 1983 and 1986 and 1432 controls (Ward et al., 1994). Controls were frequency-matched by ethnicity, sex, vital status, and age (5-year age groups). Interviews were conducted with the cases (60%) and controls (56%) themselves, and for the remaining, with the next of kin (when cases had died). Interviews included questions about the frequency of consumption of 30 food items, including meat. Processed meat was defined as bacon/sausage and processed ham/hot dogs. Processed meat intake was not associated with non-Hodgkin lymphoma. For men, the age-adjusted odds ratio was 0.6 (95% CI, 0.4–1.1) for those who consumed processed meat > 6 times/week compared with those who consumed processed meat < 2 times/week. For women, the age-adjusted odds ratio was 1.2 (95% CI, 0.7–2.1) for those who consumed processed meat > 4 times/week compared with those who consumed processed meat < 2 times/week. The odds ratio did not change materially after additional adjustment for non-Hodgkin lymphoma risk factors in this study (i.e. ever-use of herbicides; ever-use of the herbicide 2,4-dichlorophenoxyacetic acid; use of organophosphate insecticides; family history of lymphatic or haematopoietic cancer; ever-use of permanent hair dye, women only; and type of respondent, subject/next of kin). [The Working Group concluded that a limitation of this study was that a relatively large part of the population was not directly interviewed, but the lifestyle information was obtained through interviews with the next of kin (40% of cases, 44% of controls). Finally, the multivariate adjustment did not include energy intake.]

In the hospital-based case–control study in Uruguay between 1996 and 2004 including 369 non-Hodgkin lymphoma cases and 3606 controls, previously described in Section 2.9.1(b)(i), consumption of processed meat was defined as servings per year of bacon, sausage, blood pudding, mortadella, salami, saucisson, hot dog, and ham (De Stefani et al., 2013). The odds ratio for the highest compared with the lowest tertile of processed meat consumption was 0.95 (95% CI, 0.72–1.25; P_{trend} = 0.86). There was a positive association between salted meat (which was part of processed meat) intake and non-Hodgkin lymphoma. The odds ratio for the highest tertile versus the lowest tertile of salted meat intake was 2.29 (95% CI, 1.62–3.22; P_{trend} < 0.0001). [A limitation was that it was unclear which time period the FFQ referred to, and there was no mention of its validity. In addition, the unit of measurement for the exposure (i.e. servings/year) was strange.] An earlier hospital-based case–control study was also conducted by this group in Uruguay (1988–1995) and described previously. Processed meat included salami, saucisson, ham, and mortadella (De Stefani et al., 1998). There was no significant dose–response association between processed meat consumption and non-Hodgkin lymphoma for either men or women. The odds ratios for the highest versus the lowest tertile of processed meat intake were 1.03 (95% CI,

0.43–2.42; P_{trend} = 0.92) for men and 1.90 (95% CI, 0.66–5.45; P_{trend} = 0.09) for women. There was a positive association between non-Hodgkin lymphoma and salted meat intake among men, but not among women. The odds ratio for the highest (≥ 1.1 servings/week) versus the lowest (never) tertile of salted meat intake among men was 4.96 (95% CI, 1.39–17.7; P_{trend} = 0.01).

A hospital-based case–control study was conducted in the USA (2002–2008) in 603 pathologically confirmed, incident cases of non-Hodgkin lymphoma (excluding those with HIV infection) and 1007 frequency-matched controls (matched by 5-year age group, sex, and geographical location of residence) (Charbonneau et al., 2013). A 103–food item, validated, self-administered FFQ (based on the 1995 revised Block questionnaire) was used. The definition of processed meat included hot dogs, ham, bologna, and lunchmeats. The multivariate-adjusted odds ratio for the highest compared with the lowest quartile of consumption (> 6 vs ≤ 0.9 servings/month, respectively) was 1.37 (95% CI, 1.02–1.83; P_{trend} = 0.03). Although the associations between processed meat consumption and follicular lymphoma, CLL/SLL, and DLBCL were all in the same direction and of the same magnitude as the association with non-Hodgkin lymphoma overall, none reached statistical significance.

(c) Meta-analyses

A recent meta-analysis of all cohort and case–control studies reporting on the relationship between red meat and/or processed meat consumption and non-Hodgkin lymphoma was conducted by Fallahzadeh et al. (2014). Although significant positive summary estimates were provided for both red meat consumption and processed meat consumption, and some disease subgroups, caution is warranted when interpreting these results. First, not all studies were included; six case–control studies were missing (Ward et al., 1994; De Stefani et al., 1998; Tavani et al., 2000; Hu et al., 2008, 2011; Balasubramaniam et al., 2013; Charbonneau et al., 2013), and one cohort study was missing (Chiu et al., 1996). In addition, one cohort study that was included was not eligible because there was no mention of red and processed meat consumption specifically (Erber et al., 2009), as the paper dealt with dietary patterns. The exposure categories were not comparable across studies. Therefore, this meta-analysis was not used to evaluate the evidence in regard to non-Hodgkin lymphoma.

2.9.2 Cancer of the liver (hepatocellular carcinoma)

(a) Cohort studies

(i) Red meat

See Table 2.9.1 (web only; available at: http://publications.iarc.fr/564)

Two informative prospective cohort studies reported on red and/or processed meat consumption and risk of cancer of the liver (hepatocellular carcinoma).

In the EPIC study, a large prospective cohort study in 10 European countries, red meat consumption was investigated in association with hepatocellular carcinoma (Fedirko et al., 2013). The cohort included 477 206 participants who were followed up for a mean of 11.4 years, resulting in the identification of 191 hepatocellular carcinoma cases, classified according to ICD-10. Diet was assessed over the previous 12 months with validated questionnaires on meals or food groups, and individual average portions or standard portions. Red meat included all fresh, minced, and frozen beef, veal, pork, mutton, lamb, horse, and goat. Red meat consumption was not associated with risk of hepatocellular carcinoma. The multivariate-adjusted hazard ratio for the highest quartile (> 63.4 g/day) compared with the lowest quartile (0–16.6 g/day) of red meat consumption was 1.25 (95% CI, 0.68–2.27; P_{trend} = 0.950). Additional adjustment

for hepatitis B and C infection was made possible through a nested case–control study, which also did not show an association between red meat and risk of hepatocellular carcinoma. [The Working Group noted that this was an important study because it was large with a wide range of intake.]

(ii) Processed meat

See Table 2.9.2 (web only; available at: http://publications.iarc.fr/564)

In the NIH-AARP study, previously described, processed meat consumption was also investigated in relation to risk of liver cancer incidence (Cross et al., 2007). Processed meat was defined as bacon, red meat sausage, poultry sausage, luncheon meats (red and white meat), cold cuts (red and white meat), ham, regular hot dogs, and low-fat hot dogs made from poultry. Processed meat consumption was not associated with risk of liver cancer incidence. The multivariate-adjusted relative risk of liver cancer for the highest quintile of processed meat consumption (median, 22.6 g/1000 kcal) compared with the lowest quintile of processed meat consumption (median, 1.6 g/1000 kcal) was 1.09 (95% CI, 0.77–1.53; P_{trend} = 0.82) (Freedman et al., 2010). [The Working Group noted that hepatitis B and C virus infection status was not likely to be an important confounder in these analyses.]

In the EPIC study, previously described, processed meat included mostly pork and beef preserved by methods other than freezing, such as salting, smoking, marinating, air-drying, and heating (Fedirko et al., 2013). Processed meat included ham, bacon, sausages, salami, bologna, and corned beef, for example. Processed meat consumption was not associated with hepato-energy-cellular carcinoma. The multivariable energy-adjusted hazard ratio for the highest quartile (> 44.4 g/day) compared with the lowest quartile (0–11.4 g/day) of processed meat consumption was 0.90 (95% CI, 0.52–1.55; P_{trend} = 0.414). Additional adjustment for hepatitis B and C infection was made possible through a nested case–control study, which did not show an association between processed meat and hepatocellular carcinoma risk. [The Working Group noted that this was an important study because it was large with a wide range of intake.]

(b) Case–control studies

(i) Red meat

See Table 2.9.3 (web only; available at: http://publications.iarc.fr/564)

A hospital-based case–control study conducted in Italy (1999–2002) reported on the association between red meat consumption and hepatocellular carcinoma (Talamini et al., 2006b). The study included 185 incident cases and 412 controls. The controls were from the same hospitals and were matched to cases by age, sex, and study centre. An interview-based, validated FFQ covering the 2 years before diagnosis or hospital admission, and including 63 foods, food groups, or recipes was used. Red meat consumption was calculated from weekly serving sizes of beef, veal, pork, liver, pasta/rice with meat sauce, and lasagne/cannelloni. Red meat consumption was not significantly associated with risk of hepatocellular carcinoma. The multivariate-adjusted odds ratio for the highest (> 3.00 servings/week) compared with the lowest (< 1.50 servings/week) energy-adjusted quartile of red meat intake was 2.07 (95% CI, 0.88–4.82), and there was no linear trend (P_{trend} = 0.23). Adjustment included energy intake and the hepatitis virus. An earlier hospital-based case–control study was conducted in northern Italy (1983–1996) among 428 patients with histologically confirmed liver cancer (> 95% response rate) (Tavani et al., 2000). The control group comprised 7990 patients younger than 75 years admitted to the same network of hospitals as the cancer cases for a wide spectrum of acute non-neoplastic conditions. Red meat was defined as beef, veal, and pork. Lamb, horse, goat, and offal were not included in the questionnaire.

The associations were adjusted for age, year of recruitment, sex, education, smoking habits, and alcohol, fat, and fruit and vegetable intakes. There was no evidence of an association between red meat intake and liver cancer. The adjusted odds ratio for the highest tertile (≥ 7 times/week) compared with the lowest tertile (≤ 3 times/week) of intake was 0.8 (95% CI, 0.6–1.1). The adjusted odds ratio associated with an increase in intake of 1 average serving/day of red meat was 0.9 (95% CI, 0.7–1.1).

(ii) Processed meat

See Table 2.9.4 (web only; available at: http://publications.iarc.fr/564)

A hospital-based case–control study was conducted in Italy between 1999 and 2002 (Talamini et al., 2006b). The study included 185 incident cases. Of the cases, 78.2% were histologically or cytologically confirmed, and the remaining were diagnosed based on ultrasound, tomography, and elevated α-fetoprotein levels. The 412 controls were from the same hospitals, but excluded those in which hospital admission was related to alcohol and tobacco use or hepatitis viruses, or excluded those hospitalized for chronic diseases that might have led to substantial lifestyle modifications. The controls were matched to cases by age, sex, and study centre. An interview-based, validated FFQ covering the 2 years before diagnosis or hospital admission, and including 63 foods, food groups, or recipes was used. The processed meat and pork food group included pork, beef, veal, prosciutto, ham, salami, and sausages. Processed meat and pork consumption was not associated with hepatocellular carcinoma. The adjusted odds ratio for the highest (> 3.00 servings/week) compared with the lowest (< 1.25 servings/week) energy-adjusted quartile of processed/pork meat intake was 0.83 (95% CI, 0.40–1.70; P_{trend} = 0.86). Adjustment included energy intake and the hepatitis virus.

(c) Meta-analyses

A systematic literature review and meta-analysis published in 2014 (Luo et al., 2014) concluded that red meat consumption and processed meat consumption were not associated with hepatocellular carcinoma. [The studies were not restricted to those that were able to account for hepatitis B or C infection or to those that were able to adjust for potential confounders, such as alcohol consumption.] For red meat consumption, separate analyses by study type showed a null association for case–control studies (pooled RR, 0.97; 95% CI, 0.71–1.32; for the highest compared with the lowest pooled exposure groups) and a significant positive association for cohort studies (pooled RR, 1.43; 95% CI, 1.08–1.90; for the highest compared with the lowest pooled exposure groups). The more recent studies also tended to show a positive association compared with the older studies. A difference between study types was not reported for processed meat consumption, probably due to the small number of studies. [The Working Group noted that the comparison groups of meat consumption that were pooled across the studies varied substantially, which made it difficult to draw definite conclusions.]

2.9.3 Cancers of the gallbladder and biliary tract

(a) Cohort studies

No cohort studies were available to the Working Group.

(b) Case–control studies

See Table 2.9.3 (web only; available at: http://publications.iarc.fr/564)

One case–control study that investigated the association between red meat consumption and cancer of the gallbladder was found eligible by the Working Group. No studies looking into the consumption of processed meat in relation to cancer of the gallbladder were identified.

A hospital-based case–control study was conducted in northern Italy (1983–1996) among 60 patients with histologically confirmed gallbladder cancer (< 5% non-response) (Tavani et al., 2000). The control group comprised 7990 patients younger than 75 years admitted to the same network of hospitals as the cancer cases for a wide spectrum of acute non-neoplastic conditions. Dietary information was collected through a 40-item FFQ that was not validated, but showed a correlation of 0.61 for reproducibility of meat intake. Red meat was defined as beef, veal, and pork. Lamb, horse, goat, and offal were not included in the questionnaire. It was estimated that a serving of red meat in Italy was between 100 and 150 g. The associations were adjusted for age, year of recruitment, sex, education, smoking habits, and alcohol, fat, and fruit and vegetable intakes [BMI was not adjusted for]. There was no evidence of an association between red meat intake and gallbladder cancer. The adjusted odds ratio for the highest tertile (≥ 7 times/week) compared with the lowest tertile (≤ 3 times/week) of intake was 0.7 (95% CI, 0.3–1.4). The adjusted odds ratio associated with an increase in intake of 1 average serving/day of red meat was 0.6 (95% CI, 0.3–1.2).

2.9.4 Cancer of the testis

(a) Cohort studies

No cohort studies were available to the Working Group.

(b) Case–control studies

See Table 2.9.3 and Table 2.9.4 (web only; available at: http://publications.iarc.fr/564)

One case–control study that investigated the association between consumption of red meat and processed meat and cancer of the testis was found eligible by the Working Group.

A population-based case–control study was conducted in Canada (1994–1997) among 686 histologically confirmed cases and 5039 controls (Hu et al., 2008). The odds ratio for testicular cancer for the highest quartile of intake (≥ 6.1 servings/week) compared with the lowest quartile of intake (≤ 2 servings/week) of red meat was 1.1 (95% CI, 0.8–1.6; P_{trend} = 0.87). The analysis was adjusted for age (10-year age group), province, education, BMI, sex, alcohol use, pack-years of smoking, total vegetable and fruit intake, and total energy intake. The results for processed meat were based on the same numbers as those reported in two papers by Hu et al. (2008, 2011). Processed meat intake included intake from hot dogs, smoked meat, or corned beef; bacon and sausage. Processed meat consumption was significantly associated with an increased risk of testicular cancer. The multivariate-adjusted odds ratio for the highest quartile of intake (≥ 6.95 servings/week) compared with the lowest quartile of intake (≤ 1.41 servings/week) of processed meat was 1.5 (95% CI, 1.2–2.2; P_{trend} = 0.01). [The Working Group concluded that the main strength of this study was that it was a large case–control study, but little detail was provided on the number of cases per exposure category.]

2.9.5 Cancer of the kidney

(a) Cohort studies

See Table 2.9.1 and Table 2.9.2 (web only; available at: http://publications.iarc.fr/564)

There were three publications on red meat and processed meat consumption and risk of cancer of the kidney (renal cell carcinoma, RCC) based on prospectively collected large data sets: results from a pooled study of 13 prospective cohorts (Lee et al., 2008), results from the NIH-AARP study (Daniel et al., 2012b), and results from the EPIC study, which included 10 cohorts (Rohrmann et al., 2015). The studied populations were from North America, Europe, and Australia. The cohort study of Seventh-Day Adventists in California, USA, by Fraser et al. (1990) had only 14 RCC cases, and was not considered in this review. Only one study analysed

separately histological subtypes of RCC: clear cell and papillary RCC (Daniel et al., 2012b). All three publications from the prospective studies, based on 691–1814 incident cases of RCC, were informative.

A pooled analysis of 13 prospective studies (Lee et al., 2008) included 530 469 women and 244 483 men from the USA and Canada (nine cohorts), Europe (three cohorts), and Australia (one cohort) who were followed up for 7–20 years. The study was based on 1478 incident cases of RCC (709 in women, 769 in men). All cohorts used validated FFQs, and harmonized exposure and outcome data. Consumption of red meat (beef, pork, lamb, liver, and veal) was not associated with risk of RCC (P_{trend} = 0.93), and there was no heterogeneity between studies (between studies $P_{heterogeneity}$ = 0.75). However, there was a suggestion of heterogeneity of results observed for women and men (between studies $P_{heterogeneity}$ due to sex = 0.06); the relative risks for 80 g/day versus 20–60 g/day were 1.20 (95% CI, 0.93–1.55) for women and 0.88 (95% CI, 0.72–1.07) for men. Processed meat (sausage, bacon, hot dog, ham, and luncheon meat) was not associated with the risk (P_{trend} = 0.31), and there was no heterogeneity of results observed (between studies Pheterogeneity = 0.96; between studies $P_{heterogeneity}$ due to sex = 0.40). [The Working Group noted that all 13 cohorts used validated FFQs. The models were adjusted for age, total energy intake, BMI, pack-years of smoking, history of hypertension, fruit and vegetable intake, alcohol, and reproductive factors in women. The potential interaction with sex for red meat should be noted.]

The largest prospective study of RCC was based on the NIH-AARP study (Daniel et al., 2012b). The study included 176 179 men and 125 983 women who filled in a validated, 124-item FFQ and a second questionnaire (risk factor questionnaire) that included a validated meat-cooking (pan-fried, grilled or barbecued, oven-broiled, sautéed, baked, or microwaved) module at baseline (1995–1996). Over 9 years (mean) of follow-up, 1814 cases of RCC were diagnosed (including 498 clear cell and 115 papillary adenocarcinomas). There was no association between red meat (P_{trend} = 0.99) or processed red meat (P_{trend} = 0.16) and total RCC. A significant association was observed between red meat and an increased risk of papillary RCC (Q5 vs Q1 HR, 1.79; 95% CI, 0.94–3.42; P_{trend} = 0.008) and between processed meat and clear cell RCC (P_{trend} = 0.04). Haem iron intake was associated with a tendency towards an increased risk of RCC (HR, 1.15; 95% CI, 0.94–1.40; P_{trend} = 0.03; for quintile 5 vs quintile 1) and a 2.4-fold risk of papillary RCC (P_{trend} = 0.003). [Of note, the previously described study by Daniel et al. (2012b) with 1814 RCC cases was an extended update of the published report on RCC in the NIH-AARP cohort by Cross et al. (2007), which was based on 1363 cases diagnosed during up to 8.2 years of follow-up. Models were adjusted for age, education, BMI, total energy intake, smoking status, physical activity, family history of cancer, ethnicity, marital status, fruit and vegetable intake, and alcohol intake. Red and processed red meat were mutually adjusted, and adjusted for poultry and fish intake. Results were not modified by sex.]

Rohrmann et al. (2015) presented results from the EPIC cohorts, which included 335 014 women and 142 217 men from 10 European countries who were recruited between 1992 and 2000, and followed up to December 2008. Among the women and men, 691 incident RCC cases were identified. Meat consumption was assessed at baseline using validated, country-specific FFQs. In women, a high intake of red meat, which included beef, pork, mutton/lamb, horse, goat, and processed red meat, which included ham, bacon, sausages, and a small part of minced meat that had been bought as a ready-to-eat-product, had a significantly increased risk of RCC. The hazard ratios per 50 g/day of intake were 1.36 (95% CI, 1.14–1.62) for red meat and 1.78 (95% CI,

1.05–3.03) for processed red meat. No association was observed in men. After multivariate adjustment, a statistically significant interaction was observed between red meat consumption and sex ($P_{interaction}$ = 0.002), and a weaker interaction was observed for processed meat ($P_{interaction}$ = 0.06). Furthermore, for processed meat, the association with RCC incidence was prominent in premenopausal women and was lacking in postmenopausal women ($P_{interaction}$ = 0.02). [The Working Group noted that all 10 cohorts used validated FFQs. The models were adjusted for age, centre, education, BMI, total energy intake, smoking status and duration, history of hypertension, fruit intake, vegetable intake, and alcohol intake. The potential interaction with sex for red meat should be noted.]

(b) Case–control studies

See Table 2.9.3 and Table 2.9.4 (web only; available at: http://publications.iarc.fr/564)

Four population-based case–control studies (one in the USA, one in Canada, one in Europe, and one in Australia) and four hospital-based case–control studies (one in central Europe, one in Italy, and two in Uruguay) of RCC were eligible based on the criteria defined in the introduction of Section 2.9.

(i) Population-based

Wolk et al. (1996) reported results of a multicentre, population-based case–control study performed in Australia, Denmark, Sweden, and the USA. The study included 1185 incident, histologically confirmed RCC cases (698 men, 487 women) and 1526 controls frequency-matched to cases by sex and age (response rates were not reported). No association was observed with red meat or processed meat consumption; for both, the P_{trends} were not significant. However, a statistically significant association was observed with fried meat (OR, 1.44; 95% CI, 1.15–1.79; for fried/sautéed vs baked/roasted) and degree of "doneness" (for well done/charred/burnt vs rare + medium–rare OR, 1.24; 95% CI, 0.99–1.59; P_{trend} = 0.05). [The Working Group noted that specific definitions of red meat and processed meat were not presented. The limits/median values of intake amounts/frequencies were also not reported.]

Yuan et al. (1998) performed a population-based case–control study between 1986 and 1994 in a non-Asian population in Los Angeles, USA. The study included 1204 histologically confirmed RCC cases (70% diagnosed) and 1204 neighbourhood controls matched by sex, age (≤ 5 years), and ethnicity (69% first-eligible residents, and 19% second-eligible and 12% third-eligible controls). No association with processed meat (fried bacon/ham, salami/pastrami/corned beef, bologna, hot dogs/Polish sausage, and other luncheon meats) was observed (P_{trend} = 0.57). [The Working Group noted that a specific definition of processed meat was presented. There was a large number of cases and an acceptable response rate. The model was adjusted for BMI and smoking, but not for energy intake.]

Hu et al. (2008) studied 1345 RCC cases (727 men, 618 women) diagnosed between 1994 and 1997 in eight provinces in Canada. RCC was one of 19 cancer types studied (56.3% response rate for all ascertained cancers and 69.7% response rate for all contacted cancers), and 5039 controls (62.1% response rate and 66.8% response rate, respectively) were randomly selected within the age and sex groups of the population. A self-administered, 69-item FFQ was used (modified version of the validated Block questionnaire), and diet 2 years before the study was assessed. Among the 1345 renal cell cancer patients, the mean (SD) intake of red meat was 4.7 (4.8) servings/week, and the mean (SD) intake of processed meat was 4.7 (7.7) servings/week. Red meat (beef, pork, or lamb as a main dish or as a mixed dish, and hamburger) was not associated with an increased risk of RCC (P_{trend} = 0.21). Processed meat (hot dogs, smoked meat, corned beef; bacon and sausage) was associated with a statistically

significant increased risk of RCC (Q4 vs Q1 OR, 1.3; 1.1–1.6; P_{trend} = 0.02). [The Working Group noted that specific definitions of red meat and processed red meat were presented. The response rate was relatively low, and there was a large number of cases. Models were adjusted for energy intake, BMI, smoking, alcohol, fruit and vegetables, and other variables.]

Grieb et al. (2009) studied 335 RCC cases (69% response rate) and 337 population-based controls (42% response rate). Controls were frequency-matched to cases by sex, age (≤ 5 years), and ethnicity. A validated, 70-item Block FFQ was used. Consumption of red meat (beef steaks, pot roasts, and ground meat) was associated with a significantly increased risk of RCC among all subjects (OR, 4.43; 95% CI, 2.02–9.75; P_{trend} < 0.001) for ≥ 5 times/week versus < 1 time/week and among women (OR, 3.04; 95% CI, 1.60–5.79; P_{trend} < 0.001) for ≥ 3 times/week versus < 1 time/week. A significant RCC risk was also observed among women who consumed bacon and breakfast sausages (i.e. processed meat) ≥ 3 times/week versus < 1 time/week (OR, 1.87; 95% CI, 0.88–3.96; P_{trend} = 0.03). [The Working Group noted that a specific definition of red meat was presented. The number of cases was limited, and there was a low response rate among controls. The model was adjusted for BMI and smoking, but not for energy intake.]

(ii) Hospital-based

A multicentre study (Hsu et al., 2007) was performed in eastern and central European countries (in the Russian Federation, Romania, Poland, and the Czech Republic). The study included 1065 incident RCC cases (622 men, 443 women; 90–98.6% response rates across study centres) and 1509 hospital-based controls (90.3–96.1% response rates). Controls were hospitalized for conditions unrelated to smoking or genitourinary disorders, and were frequency-matched by age. A 23-item FFQ was used. A high consumption of red meat (beef, pork, lamb) was associated with an increased risk (OR, 2.01; 95% CI, 1.02–3.99; P_{trend} < 0.01), but consumption of processed meat (ham, salami, sausages) was not associated with an increased risk (OR, 1.03; 95% CI, 0.71–1.51). [The Working Group noted that specific definitions of red meat and processed meat were presented. A short FFQ with 23 food items was validated during the pilot stage, and response rates were high in cases and controls. Models were adjusted for age, BMI, smoking, alcohol, vegetables, and other variables, but not for energy intake.]

Bravi et al. (2007) reported results from a case–control study in northern, central, and southern Italy that was performed in 1992–2004. The study included 767 incident, histologically confirmed RCC cases (494 men, 273 women; > 95% response rate) and 1534 controls (matched 1:2). Controls were admitted to the same hospitals for acute non-neoplastic conditions not related to long-term diet modifications. An interviewer-administered FFQ included 78 foods and beverages. Red meat consumption was not associated with an increased risk (P_{trend} = 0.17). Processed meat was associated with a decreased risk (OR, 0.64; 95% CI, 0.45–0.90; P_{trend} = 0.006). [Specific definitions of red meat and processed meat were not presented. The 78-item FFQ was validated, and there were high response rates in cases and controls. Models were adjusted for period of interview, years of education, age, BMI, smoking, alcohol, family history of kidney cancer, and energy intake.] The study by Tavani et al. (2000), which was performed earlier (1983–1996) in the same study area of northern Italy, and included 190 kidney cancer cases and 7990 controls, did not demonstrate any association between consumption of red meat and risk of kidney cancer (P_{trend} = 0.55).

Aune et al. (2009) reported the results of a multisite cancer case–control study performed in 1996–2004 in Uruguay. The study included 114 RCC cases (94.5% response rate for all cancer sites) and 2032 hospital controls (96% response

rate). A high intake of red meat was associated with RCC risk. For T3 (≥ 250 g/day; 18 cases) versus T1 (< 150 g/day; 53 cases), the odds ratio was 2.72 (95% CI, 1.22–6.07; P_{trend} = 0.06). There was no association with processed meat (P_{trend} = 0.52).

Data from essentially the same study (114 RCC cases, 2532 controls) were analysed separately for men and women by De Stefani et al. (2012). There was a suggestion of an increased risk with processed meat intake among women (for T3 vs T1 OR, 2.15; 95% CI, 0.90–5.13; P_{trend} = 0.07), but not among men (P_{trend} = 0.51). Mean consumption of processed meat was 25.3 g/day in men and 33.9 g/day in women. [The Working Group noted that specific definitions of red meat and processed meat were not presented. The FFQ was not validated. There was a high response rate, but a limited number of cases. The model was adjusted for BMI, smoking, fruit and vegetables, other dietary factors, and energy intake.]

(c) Meta-analyses

The results from a meta-analysis by Alexander & Cushing (2009) of total red meat (not considered here) and processed meat consumption and RCC risk were based on 16 prospective studies (three individual cohorts and one pooled analysis of 13 cohorts) and seven case–control studies. Meta-analysis of processed meat consumption based on the cohorts (n = 3) showed a statistically significant increased risk of RCC with high intake ($RR_{summary}$ for high vs low intake, 1.19; 95% CI, 1.03–1.37; $P_{heterogeneity}$ = 0.984). The summary relative risk of seven case–control studies did not show an increased risk with processed meat consumption (highest vs lowest category $RR_{summary}$, 1.01; 95% CI, 0.83–1.23; $P_{heterogeneity}$= 0.028).

The results from two large cohorts (NIH-AARP and EPIC) (Daniel et al., 2012b; Rohrmann et al., 2015) were published after the meta-analysis. [The Working Group noted that some studies suggested that a positive association may be present in women only and may be confined to papillary adenocarcinoma only. Meat-cooking methods may also be associated with an increased RCC risk. However, these hypotheses were tested in very few/single studies, and the evidence was very limited.]

2.9.6 Cancer of the bladder

(a) Cohort studies

See Table 2.9.1 and Table 2.9.2 (web only; available at: http://publications.iarc.fr/564)

Five cohort studies were published on incidence of cancer of the bladder in relation to red meat and processed meat consumption. Two were performed in Europe (one in Sweden and the other was the EPIC study in 10 European countries), two were performed in the USA, and one was performed in Japan. One study was based on long-term diet and took into account changes in food consumption over time, and four studies had only baseline dietary information available. All studies presented results for red meat and processed meat separately.

The most informative four cohorts were published by Michaud et al. (2006), based on long-term diet; Larsson et al. (2009), based on 485–1001 incident cases; Ferrucci et al. (2010); and Jakszyn et al. (2011). The study by Nagano et al. (2000) included only 114 incident cases, and red meat was not specified.

The study by Michaud et al. (2006), which included data from the Health Professionals Follow-up Study (HPFS) (47 422 men) and the Nurses' Health Study (NHS) (88 471 women), was based on long-term diet (repeated validated FFQs over time). During up to 22 years of follow-up of the two American cohorts, 808 incident bladder cancer cases (504 in men, 304 in women) were confirmed, including in situ cancers. No associations were observed between risk of bladder cancer and red meat (beef, pork, lamb) as a main dish (P_{trend} = 0.35) and as a mixed dish (P_{trend} = 0.52).

There were no associations with consumption of processed meat, including sausage, salami, bologna, etc. (P_{trend} = 0.81); hot dogs (P_{trend} = 0.47); or hamburger (P_{trend} = 0.17). However, there was a statistically significant association with bacon intake of ≥ 5 servings/week versus no consumption (RR, 2.10; 95% CI, 1.24–3.55; P_{trend} = 0.006), which was confined to never-smokers only (men and women). [The Working Group noted that the analyses were based on long-term consumption and adjusted for age, energy intake, pack-years of smoking, geographical region, and total fluid intake. Stratified analyses of bacon (only) by smoking status were performed.]

Another cohort study (Ferrucci et al., 2010), based on the NIH-AARP study of 300 933 American men and women who filled in a validated, 124-item FFQ, included 854 bladder cancer cases diagnosed during 7 years of follow-up. There was no increased risk with processed meat (bacon, sausage, luncheon meats, ham, and hot dogs) (P_{trend} = 0.55). There was no evidence of effect modification for the meat exposures by smoking (data were not reported). [The Working Group noted that red meat was not analysed separately. Analyses were adjusted for age, energy intake, fruit, vegetables, beverages, and detailed smoking status. Stratified analyses by smoking status were performed.]

The two cohort studies in Europe – one was in Sweden and was based on the Swedish Mammography Cohort (SMC) and the Cohort of Swedish Men, which included 485 bladder cancer cases diagnosed during 9.4 years of follow-up of 82 002 men and women (Larsson et al., 2009), and the other was the EPIC study in 10 European countries (Jakszyn et al., 2011), which included 1001 cases diagnosed during 8.7 years of follow-up of 481 419 participants – did not support the hypothesis that red meat or processed meat consumption is associated with an increased risk of bladder cancer. [The Working Group noted that, in the Swedish cohort, red meat (beef, pork, veal; hamburger and meatballs; liver and kidney) and processed meat (ham, salami, sausage, and cold cuts) were clearly defined. In the two cohorts, risk estimates were adjusted for age, sex, education, energy intake, and detailed history of smoking status. The EPIC study additionally adjusted for the study centre. In the EPIC study, red meat included fresh and processed meat.]

Nagano et al. (2000) did not observe an association between consumption of red meat (not specified) and processed meat (ham/sausage) and bladder cancer incidence. Study subjects who filled in a 22-item FFQ were members of the Life Span Study (LSS) cohort, which included 38 540 atomic bomb survivors, among whom 114 bladder cancers were diagnosed during up to 14 years of follow-up. [The Working Group noted that the study was performed in a general population. The definition of red meat was not specified, and the study was limited by low statistical power.]

(b) Case–control studies

See Table 2.9.3 and Table 2.9.4 (web only; available at: http://publications.iarc.fr/564)

The Working Group identified 11 case–control studies that investigated the association between red and processed meat consumption and bladder cancer; eight of the studies were in men and women, and three of the studies were in men only. Men and women were studied in three population-based studies (two from the USA, one from Canada) and five hospital-based studies (two from Europe, one from the USA, one from China, one from Japan); three of the hospital-based studies (two from Spain, one from Uruguay) were in men only. Nine of the eleven studies presented results for both red meat and processed meat separately.

(i) Population-based

Hu et al. (2008) studied 1029 bladder cancer cases (56.3% response rate for ascertained and 69.7% response rate for contacted) and

5039 controls (62.1% response rate and 66.8% response rate, respectively). The controls were randomly selected within the age and sex groups of the population in eight Canadian provinces. A self-administered, 69-item FFQ was used (a modified version of the validated Block questionnaire), and diet 2 years before the study was assessed. Red meat (beef, pork, or lamb as a main dish or as a mixed dish, and hamburger) and processed meat (hot dogs, smoked meat, corned beef; bacon and sausage) were both associated with a statistically significant increased risk of bladder cancer. For Q4 versus Q1, the odds ratios were 1.3 (95% CI, 1.0–1.7; P_{trend} = 0.04) and 1.6 (95% CI, 1.2–2.1; P_{trend} < 0.0002), respectively. The mean (SD) intake of red meat was 4.7 (3.6) servings/week, and the mean (SD) intake of processed meat was 4.9 (6.5) servings/week. No difference was observed by smoking status. [The Working Group noted that specific definitions of red meat and processed meat were presented, but the response rate was relatively low. Analyses were adjusted for energy intake, BMI, smoking, alcohol, fruit and vegetables, and other variables. Analyses by smoking status were performed.]

Wu et al. (2012) presented a population-based study in three states in north-eastern USA (2001–2004). The study included 1171 cases (65% response rate) and 1418 controls (65% eligible) frequency-matched by state, sex, and age (5-year groups). Diet was assessed with a validated, self-administered, 124-item Block DHQ. Red meat (beef, veal, pork, and lamb) was not associated with an increased risk of cancer of the bladder (P_{trend} = 0.258). Processed meat (ham, bacon, sausage, hot dog, and cold cuts) was associated with a statistically significant increased risk (median for Q4 vs Q1, 13.5 vs 1.9 g/1000 kcal, OR, 1.41; 95% CI, 1.08–1.84; P_{trend} = 0.024). No difference by smoking status was observed. No association with meat-cooking methods was observed. [The Working Group noted that specific definitions of red and processed red meat were presented, but the response rate was relatively low. Analyses were adjusted for energy intake, BMI, smoking, and other variables. Stratified analyses by smoking status were performed.]

Catsburg et al. (2014) reported results from the population-based Los Angeles Bladder Cancer Study (1987–1996). The study included non-Asian individuals, and 1660 cases (80% response rate) and 1586 controls (95% response rate) matched by age (5-year), sex, and ethnicity. Assessment of usual adult dietary habits covered the consumption of 40 food groups 2 years before the in-person interview. Processed meat consumption (fried bacon, ham, salami, pastrami, corned beef, bologna, hot dogs, Polish sausage, and other lunchmeats, including red or white processed meats) was not associated with risk of bladder cancer (P_{trend} = 0.846). However, there was a statistically significant positive association observed with intake of salami/pastrami/corned beef (for weekly vs < 2 times/year OR, 1.95; 95% CI, 1.10–3.46; P_{trend} = 0.006) and liver (for 4–11 times/year vs never OR, 1.76; 95% CI, 1.09–2.85; P_{trend} = 0.016), particularly among non-smokers. Haem iron intake was also associated with an increased risk of bladder cancer among never-smokers only. For Q5 (≥ 5.2 mg/day) versus Q1 (≤ 1.0 mg/day), the odds ratio was 1.97 (95% CI, 1.16–3.33; P_{trend} = 0.010). Results from this study suggested that consumption of meat with a high amine and haem content, such as salami and liver, may be associated with an increased risk of bladder cancer. [The Working Group noted that the definition of processed meat was clearly specified. This was a large study with a high response rate. It was a strength that analyses were stratified by smoking status, and were adjusted for BMI, and other variables. Adjustment was made for total servings of food per day rather than energy intake. Red meat included corned beef (i.e. processed meat).]

(ii) Hospital-based

Riboli et al. (1991) conducted a multicentre study in Spain (1983–1986) that included 432 male cases (71.9% response rate) and 792 controls (hospital-based, 70.5% response rate; population-based, 65.7% response rate) matched by sex, age (5-year groups), and area of residence. No statistically significant association was observed with red meat (beef, pork, lamb) (Q4 vs Q1 OR, 0.67; 95% CI, 0.46–0.96; P_{trend} = 0.06) and processed meat (Q4 vs Q1 OR, 1.20; 95% CI, 0.82–1.75; P_{trend} = 0.22). [The Working Group noted that processed (cured) meat was not specified. The study used a validated, French questionnaire that was modified/adapted to Spanish food habits. The response rate was acceptable, and models were adjusted for smoking and energy intake. There was no stratification by smoking.]

The study by Tavani et al. (2000) was performed in 1983–1996 in northern Italy, and included 431 bladder cancer cases and 7990 controls (non-neoplastic patients from the same hospitals). The response rate was > 95% for both cases and controls. Red meat (beef, veal, pork) was marginally associated with bladder cancer (per 1 serving/day OR, 1.3; 95% CI, 1.0–1.6; $P_{trend} \leq 0.01$). [The Working Group noted the high response rate. The model was not adjusted for total energy intake, but was adjusted for smoking, and fat, alcohol, and fruit and vegetable intakes. It was not stratified by smoking.]

García-Closas et al. (2007) conducted a study that included 912 cases (63% eligible) and 873 hospital controls (69% response rate) from five different areas in Spain (1998–2001). A validated, 127-item FFQ was used. Neither red meat (beef, veal, lamb, pork) nor processed meat was associated with risk of bladder cancer (P_{trend} = 0.09 and 0.66, respectively). Meat-cooking method, doneness level, or HAA intake were not significantly associated with risk. [The Working Group noted that a definition of red meat was presented, but processed meat was not defined. The FFQ was validated, but dietary data collection was performed by different ways: 49% of the FFQs were administered with the help of a relative, 34% were self-administered, and 17% were administered by the interviewer. Of the FFQs, 39% were completed while in the hospital, and 61% were completed at home a few days after discharge. The response rate was not high. It was adjusted for smoking and fruit and vegetables, but not for energy. There was no stratification by smoking.]

Lin et al. (2012) recruited 884 newly diagnosed and histologically confirmed bladder cancer patients from the University of Texas MD Anderson Cancer Center and Baylor College of Medicine (92% response rate) in the USA, and 878 healthy clinic-based controls when they arrived for annual physical examinations (76.7% response rate). Controls were frequency-matched by age (5-year groups), sex, and ethnicity. The study was performed from 1999 to 2009. A validated, 135-item FFQ including questions on meat-cooking methods was administered by research interviewers to assess diet during the year before the interview. Consumption of red meat (beef, veal, lamb, pork, and game) was associated with a statistically significant increased risk (OR, 1.95; 95% CI, 1.41–2.68) for the highest versus the lowest quartile (P_{trend} < 0.001). In analyses stratified by smoking, a higher risk was observed among heavy smokers (for Q4 vs Q1 OR, 2.22; 95% CI, 1.34–3.68), but there was no statistically significant interaction. No association was observed with processed meat (hot dogs or franks, sausage, or chorizo) intake. In a subset of 177 cases and 306 controls with available data on estimates of dietary intake of HAAs, the odds ratio was 3.32 (95% CI, 1.37–8.01) for Q4 (≥ 239 ng/day) versus Q1 (≤ 52 ng/day) of total HAAs (P_{trend} = 0.003). [The Working Group noted that specific definitions of red meat and processed meat were presented. The study included around 900 cases, and the response rate was high. Analyses were adjusted for energy intake, smoking, and

ethnicity. Stratified analyses of red meat by smoking status were performed.]

Another case–control study of men was performed in Uruguay in 1996–2004 (Ronco et al., 2014). The 225 cases (97.8% response rate) and 1510 hospital controls (97.1% response rate) were interviewed face to face, and reported on their frequency of consumption of 64 food items. Red meat (beef, lamb) intake was not associated with an increased risk (P_{trend} = 0.33). Consumption of processed meat (bacon, sausage, mortadella, salami, saucisson, hot dog, ham, salted meat) was associated with an increased risk (OR, 1.55; 95% CI, 1.07–2.24) for tertile 3 versus tertile 1 (amounts were not specified) (P_{trend} = 0.018). [The Working Group noted that clear definitions of red meat and processed meat were presented. The FFQ was not validated, and there was a high response rate. The analysis was adjusted for energy intake, BMI, smoking, alcohol, fruit and vegetables, and other variables. It was not stratified by smoking.]

Small studies of men and women, one in Serbia including 130 cases and 130 hospital controls (Radosavljević et al., 2005), and one in Japan including 124 cases and 620 hospital controls (Wakai et al., 2004), were given less weight by the Working Group in the evaluation of the total evidence due to the small number of cases.

(c) Meta-analysis

The meta-analysis of red meat consumption in relation to bladder cancer risk by Li et al. (2014) included five cohorts and nine case–control studies. The summary results of the five cohort studies (4814 bladder cancer cases, 1 494 283 total population) did not show a significant association ($RR_{summary}$ for high vs low intake, 1.08; 95% CI, 0.97–1.20; $P_{heterogeneity}$ = 0.236) between red meat consumption and bladder cancer risk. The summary results of the nine case–control studies (4270 bladder cancer cases, 26 025 controls) for the highest compared with the lowest category of red meat consumption showed a $RR_{summary}$ of 1.23 (95% CI, 0.91–1.67; $P_{heterogeneity}$ < 0.0001).

The meta-analysis of processed meat consumption in relation to risk of bladder cancer was based on five cohorts and six case–control studies (Li et al., 2014). The summary results of the five cohort studies (3927 bladder cancer cases, 1 051 404 total population) did not show a significant association ($RR_{summary}$ for high vs low intake, 1.08; 95% CI, 0.96–1.20; $P_{heterogeneity}$ = 0.553). The summary results of the six case–control studies (3635 bladder cancer cases, 17 151 controls) for the highest compared with the lowest category of processed meat consumption showed a statistically significant increased risk ($RR_{summary}$, 1.46; 95% CI, 1.10–1.95; $P_{heterogeneity}$ = 0.002).

Overall, no significant association was observed in the summary risk estimates of the cohort studies for red meat or processed meat, and no heterogeneity was observed between the cohorts. In contrast, the summary risk estimates based on the case–control studies were higher (statistically significant $RR_{summary}$ for processed meat), and highly significant heterogeneity of results was observed between the case–control studies, both for red meat and processed meat.

Of note, a summary of studies from North and South America (three cohorts and four case–control studies), both on red meat and processed meat, showed a statistically significant increased risk of bladder cancer with high versus low consumption. The summary relative risks were 1.25 (95% CI, 1.02–1.54) and 1.33 (95% CI, 1.06–1.67), respectively (for both, between studies $P_{heterogeneity}$ = 0.001). No published meta-analyses stratified by smoking status were available.

2.9.7 Cancer of the ovary

(a) Cohort studies

See Table 2.9.1 and Table 2.9.2 (web only; available at: http://publications.iarc.fr/564)

Seven cohort studies addressed the incidence of cancer of the ovary in relation to red meat and/or processed meat intake. The studies were performed in the USA (four studies) and Europe (three studies), and were published between 1999 and 2011.

There were two cohorts with repeated dietary assessments: the NHS (Bertone et al., 2002) and the SMC (Larsson & Wolk, 2005). The cohorts included 15–17 years of follow-up and around 300 ovarian cases each. Three other cohorts, two from Europe (EPIC study) (Schulz et al., 2007; Gilsing et al., 2011) and one from the USA (Cross et al., 2007), including 340–581 cases with 8–16 years of follow-up, had only baseline information about diet. Results from the other two cohorts were not informative because they lacked specific information about red meat consumption (Kushi et al., 1999) or had a low number of cases (only 71 in Seventh-Day Adventist women) (Kiani et al., 2006).

The study by Bertone et al. (2002) was conducted in the USA between 1980 and 1996, with repeated dietary assessments (1980, 1984, 1986, and 1990), and included 301 incident cases of invasive epithelial ovarian cancer among 80 258 women. Consumption of red meat as a main dish (beef, pork, lamb) was not statistically significantly associated with an increased risk of ovarian cancer. The relative risk for consumption ≥ 2 times/week versus 1–3 times/month was 1.30 (95% CI, 0.93–1.82; P_{trend} = 0.16). [The Working Group noted that red meat was defined, and processed red meat was not studied. Long-term diet was assessed. Models were adjusted for age, reproductive factors, smoking status, and tubal ligation. There was adjustment for energy intake, but no adjustment for other types of meats.]

Larsson & Wolk (2005) used data from the SMC, which included follow-up from 1987 to 2004, and dietary assessments in 1987 and 1997. During an average follow-up of 14.7 years, invasive epithelial ovarian cancer was diagnosed in 288 of 61 057 women. Red meat as a main dish (beef, pork) was not associated with an increased risk of this cancer (P_{trend} = 0.27). None of the individual red meat or processed meat items were associated with ovarian cancer (all P_{trends} > 0.24). [The Working Group noted that the definition of red meat that was presented may have included processed meat. Models were adjusted for age, energy intake, BMI, education, reproductive factors, and intake of fruit, vegetables, and dairy products. They were not adjusted for other types of meats.]

Schulz et al. (2007) analysed data from the EPIC study (325 731 women from 10 European countries), which included follow-up to 2004, and baseline dietary assessment between 1992 and 2000. Primary invasive ovarian cancers were diagnosed in 581 participants. No association was observed with red meat (P_{trend} = 0.89) or with processed meat (P_{trend} = 0.23). [The Working Group noted that definitions of red meat and processed meat were not presented. Models were adjusted for age, BMI, energy intake, reproductive factors, smoking, education, and unilateral ovariectomy; there was no mutual adjustment for type of meat.]

In a study by Cross et al. (2007), an American cohort (NIH-AARP) established in 1995–1996 including 199 312 women who were followed up through 2003, 552 ovarian cancers were diagnosed. The findings were not significant for consumption of processed meat, which included bacon, cold cuts (red and white meat), ham, hamburger, hot dogs (regular and from poultry), sausages (red and white meat), luncheon meats (red and white) (P_{trend} = 0.30), as reported at baseline.

Gilsing et al. (2011) used data from the Netherlands Cohort Study (NLCS), which included 62 573 postmenopausal women at baseline in 1986, among whom 340 were diagnosed with ovarian cancer during 16.3 years of follow-up. No association was observed between consumption of red meat, including beef, pork, minced meat, and liver (P_{trend} = 0.85), or

processed meat (P_{trend} = 0.74) and risk of ovarian cancer. [The Working Group noted that red meat items were specified, but not processed meat. The model adjusted for age, energy intake, and reproductive factors.]

(b) Case–control studies

See Table 2.9.3 and Table 2.9.4 (web only; available at: http://publications.iarc.fr/564)

The Working Group identified seven case–control studies suitable for inclusion. The studies were from Australia, Canada, the USA, Italy, and China. Four of the studies were population-based. Only two of the seven studies, both population-based, presented results for red meat and processed meat separately.

(i) Population-based

Shu et al. (1989) reported results from a population-based case–control study (1984–1986) from Shanghai. The study included 172 histologically confirmed epithelial ovarian cancer cases (75.1% response rate) and 172 randomly selected population controls matched within 5-year age groups (100% response rate). Information on usual adult consumption of 63 common foods was collected through face-to-face interviews by trained interviewers. No association was observed with consumption of red meat (pork, spare ribs, pigs' feet, salted pork, pork liver, beef, and lamb), adjusted for education (P_{trend} = 0.19). [The Working Group noted that processed red meat was not studied separately, and salted pork was included in the red meat category. The model (conditional logistic regression) was adjusted only for education, and not for energy intake.]

McCann et al. (2003) conducted a population-based case–control study of diet and ovarian cancer in western New York. The study involved 124 primary, histologically confirmed ovarian cancer cases and 696 controls frequency-matched by age and county of residence. Diet in the 12-month period 2 years before the study was assessed with a detailed FFQ by in-person interview. Red meat intake (not specified if processed meat was included) was not statistically significantly associated with risk of ovarian cancer. [The Working Group noted that a specific definition of red meat was not presented. The response rate was not specified. There was a small number of cases. The model was adjusted for several variables and for energy intake.]

Pan et al. (2004) reported results from a population-based case–control study performed in seven of 10 provinces in Canada. The 442 incident, histologically confirmed cases were diagnosed between 1994 and 1997, and participated in the study (68.6% eligible). The frequency-matched control selection varied by province, depending on the availability of different provincial registries. Random samples stratified by age were selected (2135 controls represented 65% of contacted women). A self-administered, 69-item FFQ was used (a modified version based on the validated Block and NHS FFQs), and diet 2 years before the study was assessed. No association was observed with red meat (beef, pork, or lamb as a main dish or as a mixed dish; stew or casserole, pasta dish; and hamburger) (P_{trend} = 0.10) or processed meat (hot dogs, smoked meat, or corned beef; bacon and sausage) (P_{trend} = 0.82). Of note, these data (442 cases) were reanalysed by Hu et al. (2008) with the same results (P_{trend} = 0.83 and 0.72, respectively). [The Working Group noted that the definitions of red meat and processed meat were presented by Hu et al. (2008). The model was adjusted for BMI, smoking, other variables, and energy intake.]

Kolahdooz et al. (2010) analysed data from two combined population-based case–control studies in Australia. The analyses included 2049 cases and 2191 controls. Response rates in the first study (Survey of Women's Health, SWH, 1990–1993) were 90% among eligible cases and 73% among controls. Response rates in the second study (Australian Ovarian Cancer Study, AOCS, 2002–2005) were 85% and 47%, respectively. Controls in both studies were randomly

selected from the electoral roll, and matched by state of residence and 5-year age group. Dietary information was collected using validated instruments, via face-to-face interviews in SWH and self-administered in AOCS. No association was observed between consumption of red meat (beef, lamb, pork as a main dish or as a mixed dish) and risk of ovarian cancer (≥ 7 servings/week vs < 3 servings/week OR, 1.07; 0.80–1.42; P_{trend} = 0.5). Women with the highest consumption of processed meat (≥ 4 vs < 1 serving/week) had an increased risk (OR, 1.18; 95% CI, 1.15–1.21; P_{trend} = 0.03). Liver consumption was also associated with an increased risk (for ≥ 1 vs < 1 serving/month OR, 1.48; 95% CI, 1.20–1.81; P_{trend} = 0.002). [The Working Group noted that a specific definition was presented for red meat, but not for processed meat. The FFQ was validated. There was a low response rate among controls in the AOCS study. The model was adjusted for several factors (age, oral contraceptives, education, parity) and for energy intake.]

(ii) Hospital-based

Tavani et al. (2000) reported results from a multisite cancer case–control study performed in northern Italy in 1983–1996. The study included 971 cases of ovarian cancer (> 95% response rate) and 4470 hospital-based controls (> 95% response rate). The women were asked to fill in a 40-item FFQ. Consumption of red meat (beef, veal, pork) was associated with a significantly increased risk (OR, 1.3; 95% CI, 1.1–1.5 per increment of 1 portion/day; $P_{trend} \leq 0.01$). Processed meat was not studied. The model was adjusted for age, education, smoking, and alcohol, fat, fruit, and vegetable intakes. [The Working Group noted that a specific definition of red meat was presented. The 40-item FFQ was not validated. There was a high response rate among cases and controls. The model was not adjusted for energy intake.]

The study by Zhang et al. (2002), performed in China in 1999–2000, included 254 histologically confirmed ovarian cancer cases and 652 controls (mainly hospital visitors and non-neoplastic outpatients). The response rate was high (> 95%), and a 120-item FFQ was used. No linear association was observed with "fresh meat" consumption. The odds ratios were 1.78 (95% CI, 1.00–3.20) for the second quartile (7.50–13.20 vs ≤ 7.45 kg/year), 1.98 (95% CI, 1.10–3.60) for the third quartile, and 1.98 (95% CI, 1.00–3.80) for the fourth quartile (≥ 22.75 vs ≤ 7.45 kg/year). The model was adjusted for energy intake. [The Working Group noted that "fresh meat" was not specified, but was probably red meat because poultry was analysed separately. There was a high response rate.]

Di Maso et al. (2013) published a large hospital-based study performed in 1991–2009 in Italy and Switzerland (1031 ovarian cancer cases, 2411 non-neoplastic hospital controls). Response rates were similar among cases and controls (85–98%). A validated FFQ was used. A statistically significant positive association with consumption of red meat (beef, veal, pork, horse meat, and mixed red meat dishes) was observed (per increase of 50 g/day OR, 1.29; 95% CI, 1.16–1.43; $P_{trend} < 0.01$). When analysed by menopausal status, this was restricted to postmenopausal women. Cooking practices influenced the observed associations. The odds ratios were 1.33 (95% CI, 1.12–1.57) for an increase of 50 g/day of roasted/grilled red meat, 1.48 (95% CI, 1.19–1.84) for an increase of 50 g/day of boiled/stewed red meat, and 1.96 (95% CI, 1.34–2.87) for an increase of 50 g/day of fried/pan-fried meat. However, the test for heterogeneity between the observed risks for different cooking methods was not significant (P = 0.18). The model was adjusted for several factors, including age, education, BMI, smoking, alcohol, and vegetable and fruit intake. [The Working Group noted that a specific definition of red meat was presented. The FFQ was validated. There was a high response rate. The model was not adjusted for energy intake.]

(c) Meta-analyses

Results from a dose–response meta-analysis that quantitatively summarized eight prospective cohorts (Wallin et al., 2011) and included together 2349 incident ovarian cancer cases did not show a statistically significant association between red meat or processed meat and risk of ovarian cancer. For an intake increment of 4 servings/week, the summary relative risks of ovarian cancer were 1.07 (95% CI, 0.97–1.19) for red meat (100 g/serving) and 1.07 (95% CI, 0.97–1.17) for processed meat (30 g/serving). No heterogeneity between the studies was observed in red meat ($P_{heterogeneity}$ = 0.972) or processed meat ($P_{heterogeneity}$ = 0.647) analyses. Results from this dose–response meta-analysis suggested that consumption of red and processed meat was not associated with risk of ovarian cancer.

2.9.8 Cancer of the endometrium

(a) Cohort studies

See Table 2.9.1 and Table 2.9.2 (web only; available at: http://publications.iarc.fr/564)

Five prospective cohort studies on incidence of cancer of the endometrium in relation to red meat and processed meat consumption were published in 1995–2013. Two were performed in the USA, two were performed in Canada, and one was performed in Sweden. Four studies presented results for red meat and processed meat separately, and one presented results for red meat only and for haem iron. One of the studies used information on long-term diet.

Only two cohort studies were informative. The studies included 720 incident endometrial cancer cases (long-term diet) (Genkinger et al., 2012) and 1486 incident endometrial cancer cases (Arem et al., 2013). Two other studies did not specify the definition of red meat (Zheng et al., 1995; Kabat et al., 2008), and one had limited statistical power (van Lonkhuijzen et al., 2011); these studies are only described in the tables.

Genkinger et al. (2012) reported results from the Swedish prospective cohort (SMC), which included 60 895 women who filled in a validated, 67-item FFQ at baseline in 1987–1990, and 39 227 of them also filled in a 96-item FFQ in 1997. During 21 years of follow-up, 720 women developed endometrial cancer. Red meat (hamburgers, meatballs, beef, pork, and veal) and processed meat (sausage, hot dogs, bacon, ham, salami, lunchmeat, and blood pudding/sausage) were not significantly associated with an increased risk (P_{trend} = 0.11 and 0.12, respectively). Liver consumption was associated with an increased risk (HR, 1.29; 95% CI, 1.06–1.56; for intake of ≥ 100 vs < 100 g/week). Haem iron intake based on updated long-term consumption was associated with an increased risk (HR, 1.24; 95% CI, 1.01–1.53; for highest vs lowest quartile; P_{trend} = 0.03). [The Working Group noted that exposure was well defined. In addition, there was long-term dietary assessment with a validated FFQ, and a relatively large number of incident cases. Models were adjusted for age, energy intake, BMI, parity, and education.]

The largest prospective study of endometrial cancer was based on the NIH-AARP study (Arem et al., 2013). The study included 111 356 women who filled in a validated, 124-item FFQ, and 67% of them also filled in a second questionnaire (risk factor questionnaire) that included a validated meat-cooking (pan-fried, grilled or barbecued, oven-broiled, sautéed, baked, or microwaved) module at baseline in 1995–1996. During a mean follow-up of 9.3 years, 1486 cases of endometrial cancer were diagnosed. Consumption of red meat (beef, pork, hamburger, steak, and liver) and processed meat (bacon, cold cuts, ham, hot dogs, and sausage) was not associated with risk of endometrial cancer (P_{trend} = 0.45 and 0.70, respectively). No association with cooking-related mutagens was observed. [The Working Group noted that this study had the largest number of cases, with detailed questions on cooking methods and well-defined exposure.

The model adjusted for age, energy intake, BMI, and smoking status, and mutually adjusted for other meat intake.]

(b) Case–control studies

See Table 2.9.3 and Table 2.9.4 (web only; available at: http://publications.iarc.fr/564)

The Working Group identified five eligible population-based case–control studies from the USA, China, Canada, and Sweden, and two hospital-based studies from Italy.

(i) Population-based

Goodman et al. (1997) performed a case–control study in Hawaii in 1985–1993. The study included 332 histologically confirmed cases of endometrial cancer (66% response rate) and 511 population-based controls matched by age and ethnicity (73% response rate). A 250-item dietary history interview was used. Red meat consumption was associated with a significantly increased risk (for Q4 vs Q1 OR, 2.0; 95% CI, 1.1–3.7; P_{trend} = 0.03), but no association was observed with processed meat (P_{trend} = 0.38). Beef intake, analysed separately, was associated with an increased risk (for Q4 vs Q1 OR, 1.8; 95% CI not reported; P_{trend} = 0.04) but pork was not associated with an increased risk (P_{trend} = 0.53). The model was adjusted for BMI, other factors, and energy intake. [The Working Group noted that a specific definition of red meat or processed meat was not presented. The 250-item dietary history was validated. The response rate among cases was not high.]

McCann et al. (2000) performed a study of endometrial cancer in western New York that included 232 cases (51% response rate) and 639 population-based controls (51% response rate). Diet was assessed with a 172-item FFQ by trained nurse interviewers. No association was observed with consumption of red meat (P_{trend} = 0.96) or processed meat (P_{trend} = 0.64). [The Working Group noted that specific definitions of red meat and processed meat were not presented. The 172-item FFQ was not validated. There was a low response rate and a rather limited number of cases. The model was adjusted for BMI, smoking, and other factors, and mutually adjusted for other foods. It was not adjusted for energy intake.]

A study from Ontario, Canada (Jain et al., 2000), included 552 cases (70% response rate) and 563 controls (41% response rate) frequency-matched by age group and area of residence. In-person, in-home interviews inquired about detailed dietary history 1 year before the diagnosis/before the interview. The dietary history method inquired about 250 food items. No association with consumption of red meat (beef, pork, veal, lamb, game, meat stews, and meat soups) was observed (P_{trend} = 0.55). The model was adjusted for age, body weight, history of diabetes, education, smoking, reproductive factors, and energy intake. [The Working Group noted that a specific definition of red meat was presented. The 250-item dietary history was validated. There was a low response rate among controls.]

Xu et al. (2006) reported results from a case–control study in Shanghai. The study included 1204 endometrial cancer cases (82.8% response rate) diagnosed in 1997–2003 and 1212 population-based controls (74.4% response rate), who were interviewed in person with a 76-item FFQ. Consumption of red meat (pork, beef, mutton) was associated with an increased risk (for Q4 vs Q1 OR, 1.3; 1.0–1.8; P_{trend} = 0.02), but cooking methods or doneness of the meat was not associated with an increased risk. The same study was analysed by Kallianpur et al. (2010), and an increased risk associated with haem iron intake (P_{trend} < 0.01) was reported. The model was adjusted for age, menopausal status, diagnosis of diabetes, BMI, alcohol, physical activity, and energy intake, and was mutually adjusted for other kinds of meats. [The Working Group noted that a specific definition of red meat was presented. The FFQ was validated versus 24-hour dietary recall. There was a relatively high response rate.]

(ii) Hospital-based

Tavani et al. (2000) reported results from a multisite cancer case–control study performed in northern Italy in 1983–1996. The study included 750 cases of endometrial cancer and 4770 hospital controls (> 95% response rates for cases and controls). The women were asked to fill in a 40-item FFQ. Consumption of red meat (beef, veal, pork) was associated with a significantly increased risk (OR, 1.5; 95% CI, 1.2–1.9 per increment of 1 portion/day). Processed meat was not studied. The model was adjusted for BMI, smoking, fruit, and vegetables, but not for energy intake. [The Working Group noted that a specific definition of red meat was presented. The 40-item FFQ was not validated. There was a high response rate among cases and controls. The model was not adjusted for energy intake.]

Bravi et al. (2009) reported results from another case–control study performed in three Italian areas in 1992–2006. The study included 454 cases and 908 hospital controls (> 95% response rates for cases and controls). A validated 78-item FFQ (vs 2 × 7-day dietary records) was used during in-person interviews. Red meat consumption was associated with a significantly increased risk (OR, 2.07; 95% CI, 1.29–3.33; for an increment of 1 portion/day; $P_{trend} = 0.002$). No association was observed with processed meat consumption ($P_{trend} = 0.24$). Based on the same data, Di Maso et al. (2013) reported the risk for endometrial cancer related to an increment of 50 g/day of red meat consumption (OR, 1.30; 95% CI, 1.10–1.55), when the model was adjusted for age, education, BMI, smoking, alcohol, vegetable intake, and fruit intake, but not for energy intake.

[The Working Group noted that a definition of red meat was presented by Di Maso et al. (2013), but processed meat was not defined. A validated FFQ was used. The response rate was high. The model was adjusted for energy intake in the analyses by Bravi et al., but not in the analyses by Di Maso et al.]

(c) Meta-analyses

A meta-analysis of red meat (Bandera et al., 2007), based on seven case–control studies, showed an increased risk of endometrial cancer was associated with red meat consumption ($OR_{summary}$, 1.51; 95% CI, 1.19–1.93 per 100 g/day of red meat; $P_{heterogeneity} = 0.97$). Results from three cohorts – the NIH-AARP cohort (Arem et al., 2013), the SMC cohort (Genkinger et al., 2012), and a Canadian cohort (van Lonkhuijzen et al., 2011), published after the meta-analysis, did not show a statistically significant increased risk of endometrial cancer with consumption of red meat or processed meat.

2.9.9 Leukaemia

(a) Cohort studies

See Table 2.9.1 and Table 2.9.2 (web only; available at: http://publications.iarc.fr/564)

Two prospective cohort studies reported on the association between the intake of red and/or processed meat and the risk of different types of leukaemia.

The association between red and processed meat intake and risk of acute myeloid leukaemia was investigated in the NIH-AARP study (1995–2003) in a prospective cohort of 491 163 individuals (Ma et al., 2010). A total of 338 incident cases of acute myeloid leukaemia were identified during a median follow-up of 7.5 years. A 124-item, validated FFQ was used. Processed meat was defined as all types of cold cuts, bacon, ham, hot dogs, and sausages from red and white meats. Consumption of processed meat was not associated with risk of acute myeloid leukaemia. The multivariate-adjusted hazard ratio for the highest compared with the lowest quintiles of consumption was 0.84 (95% CI, 0.60–1.18; $P_{trend} = 0.64$). Different cooking methods showed no clear associations with outcome. [The Working Group noted that this was a large informative study, with comprehensive analyses

of meat variables and cooking methods. Red meat included processed meat.]

The potential associations between red meat and processed meat and leukaemia were investigated in the EPIC cohort (Saberi Hosnijeh et al., 2014). In 477 325 participants followed up for a mean of 11.34 years, 773 incident leukaemia patients (373 lymphoid leukaemia patients, 342 myeloid leukaemia patients) were identified. Neither the consumption of red meat nor processed meat was associated with risk of leukaemia. For red meat, the multivariate-adjusted, calibrated hazard ratios per 50 g/day of intake were 0.98 (95% CI, 0.79–1.22) for all leukaemia, 1.06 (95% CI, 0.76–1.49) for myeloid leukaemia, and 0.89 (95% CI, 0.65–1.22) for lymphoid leukaemia. For processed meat, the multivariate-adjusted, calibrated hazard ratio per 50 g/day of intake were 1.08 (95% CI, 0.85–1.35) for all leukaemia, 1.03 (95% CI, 0.92–1.16) for myeloid leukaemia, and 1.29 (95% CI, 0.93–1.77) for lymphoid leukaemia. Red meat and processed meat were also not associated with leukaemia subtypes (i.e. acute myeloid leukaemia, chronic myeloid leukaemia, and chronic lymphoid leukaemia). [The Working Group noted that this large study enabled the investigation of multiple leukaemia subtype outcomes. Red meat and processed meat were not defined.]

(b) Case–control studies

See Table 2.9.3 and Table 2.9.4 (web only; available at: http://publications.iarc.fr/564)

There were a few case–control studies that reported on the association between intake of red and/or processed meat and risk of different types of leukaemia, but only one was considered eligible (Liu et al., 2015). One of these studies (Yamamura et al., 2013) did not meet the criteria for inclusion [numbers for cases and controls in subgroups not provided, wide confidence intervals, and red meat definition not provided]. One case–control study (Peters et al., 1994) on processed meat intake in children and their parents and risk of childhood leukaemia was excluded because of unavailability of response rates and a limited dietary questionnaire (12 items) on usual food intake of the mother, father, and child.

A multicentre case–control study in China investigated the association between red meat consumption and risk of adult leukaemia (Liu et al., 2015). Between 2008 and 2013, 442 cases aged 15 years or older (97.8% response rate) and 442 outpatient controls were recruited. The controls were selected from a larger group that served as controls in many other case–control studies and other cancer outcomes, and were matched post hoc to cases by age group, sex, and study site; the recruitment date did not exceed that for matching to cases by more than 1 year. [The response rate of the controls was not provided.] A validated and reproducible, 103-item FFQ was administered in face-to-face interviews. Red meat consumption was derived from seven food items, including pork chops/spare ribs, pigs' feet, fresh pork (lean), fresh pork (fat and lean), pork liver, organ meats, beef, and mutton. There was no significant association between red meat consumption and risk of all leukaemias (multivariate-adjusted OR, 1.06; 95% CI, 0.91–1.22 per 50 g/day) or acute myeloid leukaemia (OR, 0.99; 95% CI, 0.77–1.28). [The Working Group noted that this study had high response rates. Although it was a hospital-based study, the setting made this study comparable to a population-based study.]

2.9.10 Cancer of the brain

(a) Cohort studies

See Table 2.9.1 and Table 2.9.2 (web only; available at: http://publications.iarc.fr/564)

There were no cohort studies reporting on the association between consumption of red and/or processed meat and risk of brain tumours in children. Michaud et al. (2009) analysed combined data from three USA prospective cohort studies with 335 adult glioma cases diagnosed during 24

years of follow-up. No associations were observed between red meat, processed meat, bacon, or hot dogs and risk of glioma. Another large USA cohort study with 585 adult glioma cases found no significant trends for glioma risk with consumption of red or processed meat (Dubrow et al., 2010).

(b) Case–control studies

See Table 2.9.3 and Table 2.9.4 (web only; available at: http://publications.iarc.fr/564)

There was an international, collaborative, pooled case–control study on maternal diet during pregnancy (including cured meat intake) and risk of childhood brain tumours in the children of the mothers (Pogoda et al., 2009). The individual case–control studies already included in this international study are, therefore, not described separately in this *Monograph* (although a follow-up publication investigating the interaction with GST variants is mentioned) (Searles Nielsen et al., 2011). There was also a joint, collaborative, pooled case–control study on adult brain tumours (Terry et al., 2009).

The international, collaborative case–control study (Pogoda et al., 2009) included nine study centres from seven countries (Sydney, Australia; Winnipeg, Canada; Paris, France; Tel Hashomer, Israel; Milan, Italy; Valencia, Spain; and Los Angeles, San Francisco, and Seattle, USA). Most of the 1218 (75% response rate based on estimates from centres for which this was available) cases were diagnosed between 1982 and 1992, and 2223 controls (71% response rate) were included. The age ranged from 0 to 19 years. Mothers were asked about their food consumption during the past year and during the index pregnancy (i.e. pregnancy with the study participant). Data collection from all nine centres was conducted via a common protocol. The dietary questionnaire focused on foods high in nitrate and/or nitrite, and on foods containing nitrosation inhibitors (i.e. vitamins C and E). Dietary consumption was estimated in average grams per day. Cured meats (a type of processed meat) included 4–10 items, depending on the centre (and thus geographical location). Cured meat consumption by the mother during pregnancy was associated with an increased risk of all brain tumours combined, but particularly astroglial tumours. The multivariable odds ratios for the top compared with the bottom quartile of consumption were 1.5 (95% CI, 1.1–2.1; P_{trend} = 0.03) for all brain tumours combined, 1.8 (95% CI, 1.2–2.6; P_{trend} = 0.01) for astroglial tumours, and 1.2 (95% CI, 0.9–1.6; P_{trend} = 0.15) for primitive neuroectodermal tumours. There was no confounding or effect modification by prenatal vitamin supplementation. [The Working Group concluded that this was an informative study because of the large size of the study, the geographical variation of the pooled studies, and the large number of food items that questioned about cured meats. However, recall bias (rumination bias) by mothers could not be excluded since diet often had to be recalled over a long period of time in the past, as the children were up to aged 19 years.]

In a follow-up study of one of the population-based case–control studies (Preston-Martin et al., 1996) included in Pogoda et al. (2009), the interaction with six GST variants was investigated (Searles Nielsen et al., 2011). A total of 202 cases of childhood brain cancer diagnosed at ≤ 10 years of age and 286 controls living in California or Washington, USA, between 1978 and 1990 were included in the study. Dietary information was obtained from mothers, on average, 5.3 years or 6.4 years after the birth of the child in cases and controls, respectively. Cured meat (processed meat) was defined as ham, bacon, hot dogs, sausage, luncheon meat, or "other cured meats" combined. Risk of childhood brain tumours rose with increasing intake of cured meat by the mother during pregnancy among children without GSTT1 (OR, 1.29; 95% CI, 1.07–1.57; for each increase in the frequency of consumption per week) or with potentially reduced GSTM3 (any –63C allele, OR, 1.14; 95%

CI, 1.03–1.26), whereas no increased risk was observed among those with GSTT1 or presumably normal GSTM3 levels ($P_{interaction}$ = 0.01 for each).

Another collaborative, pooled case–control study on cured meat consumption and adult brain tumours (Terry et al., 2009) did not show an association between cured meat consumption and risk of adult brain tumours.

2.9.11 Cancer of the breast in men

A case–control study evaluated risk factors for cancer of the breast in men, and evaluated red meat intake as one of the risk factors (Hsing et al., 1998). Consumption of red meat ≥ 7 times/week was associated with a 1.8-fold risk (95% CI, 0.6–4.9), although the trend was not significant. [The Working Group noted that the high frequency might have been due to underestimation by the authors of the effects of smoking and drinking.]

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3. CANCER IN EXPERIMENTAL ANIMALS

No long-term bioassays of full carcinogenicity with red meat or processed meat were available to the Working Group; however, the Working Group considered a variety of animal bioassays.

3.1 Mouse

See Table 3.1

3.1.1 Red meat

Groups of seven to nine male C57Bl/6J-*Apc*^{Min} mice (age, 6–8 weeks), a strain primarily susceptible to spontaneous adenomas of the small intestine, were fed American Institute of Nutrition (AIN-93G)–based diets, either a semisynthetic control diet or a modified diet in which casein, the protein source, was replaced with beef (24%), for 5–6 weeks. The beef was minced and freeze-dried before being added to the diet. [The authors did not specify whether the meat had been cooked before being minced and freeze-dried.] The control diet contained calcium at a concentration of 5.1 g/kg diet, and fat was obtained from sunflower and rapeseed oil. In the modified diet, fat was provided by beef, butter, and sunflower and rapeseed oil. The energy content was similar for both diets. The extent of intestinal neoplasms was determined by light microscopy. Statistical analyses were conducted. Mean body weight (bw) was similar for mice given the control or modified diet. Tumours were observed in the small intestine and colon/caecum. Mice fed the modified diet containing beef had a greater number of tumours in the small intestine compared with mice fed the control diet, with the difference being significant in the distal small intestine (P = 0.009) (Mutanen et al., 2000). [The Working Group noted that the tumour data were confounded by the fact that the beef diet contained considerably more fat (274.8 g/kg diet) than the control diet (70.0 g/kg diet). The control diet contained calcium at a concentration of 5.1 g/kg diet, and did not contain fibre; however, there was no increase in the incidence of tumours of the small intestine in a separate non-fibre, high-fat group.]

Groups of six to eight male and six to eight female C57Bl/6J-*Apc*^{Min} mice (age, 5 weeks) were transferred from a standard rodent chow diet and fed AIN-93G–based diets, either a semisynthetic control diet or a modified diet in which casein was replaced with beef. The control diet contained 40% fat and a fatty acid profile similar to that of a "Western-type" (i.e. enriched in fat and cholesterol) diet. The carbohydrate and protein sources were provided by dextrose and casein, respectively. The beef diet contained freeze-dried, low-fat ground beef instead of casein as the protein source. The other ingredients were adjusted to keep the proportions of energy from carbohydrate, protein, and fat similar to those in the control diet. [The authors did not specify whether the low-fat ground beef had been cooked before being freeze-dried.] The number and size of intestinal adenomas, as determined by light

Table 3.1 Studies of carcinogenicity in mice fed diets containing red meat or processed meat

Species, strain (sex) Age at start Duration Reference	Dosing regimen Animals/group at start No. surviving animals	Results For each target organ: incidence (%) and/or multiplicity of tumours	Significance	Comments
Mouse, C57Bl/6J-*Apc*^{Min} (M) Age 6–8 wk 5–6 wk Mutanen et al. (2000)	Full carcinogenicity study AIN-93G–based control diet or modified AIN-93G diet in which 24% beef replaced casein as the protein source, fed ad libitum 7–9 mice/group 7, 7	*Small intestine* Total tumours, mean (SD): 35.3 (11.6), 52.8 (13.2) *Colon and caecum* Tumour incidence: 88%, 89% Total tumours, mean (SD): 1.8 (0.9), 3.2 (2.3) *Distal small intestine* Total tumours, mean (SD): 19.6 (6.8), 36.6 (9.4)*	NS NS NS *P = 0.009 (ANOVA with Tukey post hoc test)	Limitations: tumour data were confounded by the fact that the beef diet contained considerably more fat (274.8 g/kg diet) than the control diet (70.0 g/kg diet); histopathological examination not conducted
Mouse, C57Bl/6J-*Apc*^{Min} (F) Age 5 wk 15 wk Kettunen et al. (2003)	Full carcinogenicity study Mice were fed a control diet (AIN-93G diet with 40% fat) or diet containing low-fat ground beef (AIN-93G with 40% fat, 27% beef), fed ad libitum 6–8 mice/group 6, 6	*Small intestine* Adenoma multiplicity, mean (SEM): 72.3 (15.27), 30.9 (4.90)* Total adenomas, mean (SEM): 55.8 (8.46), 28.7 (3.77)* *Small intestine* Medium adenoma, incidence, mean (SEM): 30.1% (3.8), 22.6% (3.3)*	Decrease; *P < 0.01 (multiple linear regression) Decrease; *P < 0.01 (multiple linear regression) Decrease; *P < 0.05 (both sexes combined, multiple linear regression)	Diets were balanced for carbohydrates, protein, and fat
Mouse, C57Bl/6J-*Apc*^{Min} (M) Age 5 wk 15 wk Kettunen et al. (2003)	Full carcinogenicity study Control diet or diet containing beef (g/kg diet), fed ad libitum 6–8 mice/group 8, 8	*Small intestine* Medium adenoma incidence, mean (SEM): 44.3% (2.9), 36.3% (4.6)*	Decrease; *P < 0.05 (both sexes combined, multiple linear regression)	Mice were fed a modified AIN-93G containing 40% fat or low-fat ground beef instead of casein as the protein source. Diets were balanced for carbohydrates, protein, and fat

Table 3.1 (continued)

Species, strain (sex) Age at start Duration Reference	Dosing regimen Animals/group at start No. surviving animals	Results For each target organ: incidence (%) and/or multiplicity of tumours	Significance	Comments
Mouse, BALB/c (M) Age 5 wk 54 wk Nutter et al. (1983)	Initiation–promotion study Diet containing low milk protein with low fat or low beef protein with low fat, fed ad libitum 100 mice/group 38, 23	*Colon* Tumour incidence: 23/38 (60.5%), 4/23 (17.4%)*	Decrease; *$P \leq 0.05$ (test for the equality of two proportions)	Limitations: tumour incidence in the control groups was not reported; the duration of this experiment (54 wk) was probably not sufficient to determine if the diets by themselves were tumorigenic; histopathological examination not conducted Mice were allocated to six isocaloric diet groups that differed in protein source (milk or beef), protein level (11% or 33%), and fat level (5% or 30%), and injected with DMH (11 weekly injections of 20 mg/kg bw)
	Diet containing low milk protein with high fat or low beef protein with high fat, fed ad libitum 100 mice/group 24, 28	*Colon* Tumour incidence: 19/24 (79.2%), 6/28 (21.4%)*	Decrease; *$P \leq 0.05$ (test for the equality of two proportions)	
	Diet containing high milk protein with low fat or high beef protein with low fat, fed ad libitum 100 mice/group 29, 44	*Colon* Tumour incidence: 19/29 (65.5%), 5/44 (11.4%)*	Decrease; *$P \leq 0.05$ (test for the equality of two proportions)	

*, statistically significant; AIN, American Institute of Nutrition; ANOVA, analysis of variance; DMH, dimethylhydrazine; F, female; M, male; NR, not reported; NS, not significant; SD, standard deviation; SEM, standard error of the mean; wk, week

microscopy, were assessed when the mice were placed on the control and beef diets, and then assessed after they were fed the test diets for 3 weeks or 10 weeks. Statistical analyses were conducted. Male mice fed the control diet gained less weight than male mice fed the beef diet. This difference in body weight was not observed in the female mice. Female mice fed the beef diet had significantly fewer intestinal adenomas ($P < 0.01$) and a significantly lower tumour burden (measured as mm^2; $P < 0.01$) when assessed after 15 weeks of feeding. Mice fed the beef diet also had significantly fewer medium-sized (1.0–1.5 mm) adenomas than did mice fed the control diet when both sexes were combined ($P < 0.05$) (Kettunen et al., 2003).

3.1.2 Red meat with known carcinogens

Groups of 100 male BALB/c mice (age, 5 weeks) were allocated to one of six isocaloric diet groups that differed in protein source (milk or beef), protein level (11% or 33%), and fat level (5% or 30%). [The authors did not state whether the meat had been cooked and/or freeze-dried before being added to the diet. The calcium content of the diet could not be determined.] At age 11 weeks, an unspecified number of mice from each group were given 11 weekly subcutaneous injections of 1,2-dimethylhydrazine (DMH) at a dose of 20 mg/kg bw. [The specific diets may have affected metabolism of the DMH.] The remaining mice in each group were injected with saline to serve as "non–tumour-bearing" control mice. At age 37 weeks and 59 weeks, the subgroups of mice were killed and examined grossly for tumours of the colon. Selected tumours were examined by histopathology, and statistical analyses were conducted. Mice fed diets containing beef protein consumed approximately 20–25% more calories per day than mice fed the diets containing milk protein. When assessed at age 59 weeks, mice fed the diets containing 11% or 33% beef protein with 30% fat weighed significantly more than mice fed the corresponding diets containing milk protein and fat. When assessed at 59 weeks of age, DMH-injected mice fed the beef protein diets had a significantly lower incidence of colon tumours than DMH-injected mice fed the milk protein diets, irrespective of the percentage of protein or fat ($P < 0.05$) (Nutter et al., 1983). [Tumour incidence in the control groups was not reported. The duration of this experiment (54 weeks) was probably not sufficient to determine if the diets by themselves were tumorigenic.]

3.2 Rat

See Table 3.2

3.2.1 Red meat

A study was conducted to investigate the effects of a "complete human diet" prepared under normal household conditions. Male and female Wistar rats (age, 4 weeks) were placed on one of five diets (50 males and 50 females per diet): Diet A, a commercial semisynthetic rodent diet; Diet B, a semisynthetic rodent diet supplemented with fruits and vegetables; Diet C, a complete "human" diet consisting of meat (beef, pork, and chicken), bread, eggs, and margarine, along with other semisynthetic products, including lard, potato flour, sugar, bran, and pectin; Diet D, a diet similar to Diet C, except the food was cooked under "usual household conditions"; and Diet E, a diet similar to Diet D, except supplemented with fruits and vegetables. [The authors did not specify if any of the meats, fruits, or vegetables had been freeze-dried before being added to the diets.] Diets A and B contained 21.6% fat "energy," 26.0% protein "energy," 52.4% carbohydrate "energy," and 10.7% fibre. Diets C, D, and E contained 40.6% fat "energy," 13.2% protein "energy," 46.2% carbohydrate "energy," and 5% fibre. The diets contained calcium at a concentration of 7.5 g/kg diet. The rats were maintained on their respective diets for up to 995 days for males

Table 3.2 Studies of carcinogenicity in rats fed diets containing red meat or processed meat

Species, strain (sex) Age at start Duration Reference	Dosing regimen Animals/group at start No. surviving animals	Results For each target organ: incidence (%) and/or multiplicity of tumours	Significance	Comments
Rat, Wistar (M) Age 4 wk 142 wk Alink et al. (1989)	Full carcinogenicity study Rats were fed one of five diets, A–E, ad libitum: diet A, a semi-synthetic rodent diet; diet B, diet A supplemented with fruits and vegetables; diet C, a "humanized" diet consisting of meat (including beef), bread, eggs, and margarine, alone with other semi-synthetic products; diet D, cooked diet C; diet E, diet D, supplemented with fruits and vegetables 50 rats/group 48, 46, 48, 48, 48	*Pituitary gland (pars distalis)* Tumour incidence: 26/45 (58%), 28/45 (62%), 33/48 (69%)*, 35/46 (76%)*, 35/48 (73%)* *Thyroid gland* "Light cell" adenoma or carcinoma: Incidence: 3/48 (6%), 1/46 (2%), 3/48 (5%)*, 6/48 (13%)*, 5/46 (11%)*	*P = 0.0016 (human diets, diets C, D, and E, vs rodent diets, diets A and B; two-sided Fisher exact test and IARC method) *P = 0.0014 (human diets, diets C, D, and E, vs rodent diets, diets A and B; two-sided Fisher exact test and IARC method)	Limitations: tumour data were confounded by the fact that the human diets had approximately twofold more fat and 50% less fibre than the rodent diets; rats fed the human diets weighed considerably more than rats fed the rodent diets An equal number of female Wistar rats were also treated; there were no significant differences in tumour incidence
Rat, F344 (F) Age 7 wk 30–34 wk Reddy et al. (1976)	Initiation–promotion study Rats were fed one of four diets: D_1, high soybean protein with high corn oil fat; D_2, low soybean protein with low corn oil fat; D_3, high beef protein with high beef and corn oil fat; D_4, low beef protein with low beef fat; half of the rats in each group (28 rats/group) were initiated with DMH: D_1 with DMH; D_2 with DMH; D_3 with DMH; or D_4 with DMH 28 rats/group 28, 28, 28, 28, 28, 28, 28, 28	*Ear canal* Squamous cell carcinoma: Incidence: 0/28 (0%), 0/28 (0%), 0/28 (0%), 0/28 (0%), 7/28 (25%), 6/28 (21%), 8/28 (29%), 7/28 (25%) *Colon* Tumour incidence: 0/28 (0%), 0/28 (0%), 0/28 (0%), 0/28 (0%), 15/28 (54%), 10/28 (36%), 16/28 (57%), 10/28 (36%) Tumour multiplicity (SEM): 0, 0, 0, 0, 0.90 (0.12)*, 0.44 (0.11), 1.00 (0.19), 0.50 (0.14) Adenocarcinoma: Multiplicity: 0, 0, 0, 0, 0.58 (0.13), 0.23 (0.10), 0.61 (0.14)*, 0.14 (0.06)	NS NS *P < 0.05 (significantly different from D_2) *P < 0.05 (Significantly different from D_4)	DMH-initiated rats had a low incidence (≤ 18%) of kidney mesenchymal tumours and adenocarcinoma of the small intestine. DMH (10 mg/kg bw for 20 wk). [Rats treated with DMH had a significantly increased incidence of ear canal and colon tumours compared with control rats, $P \leq 0.02$, two-tailed Fisher exact test] The duration of this experiment (30–34 wk) was probably not sufficient to determine if the diets by themselves were tumorigenic

Table 3.2 (continued)

Species, strain (sex) Age at start Duration Reference	Dosing regimen Animals/group at start No. surviving animals	Results For each target organ: incidence (%) and/or multiplicity of tumours	Significance	Comments
Rat, Sprague-Dawley (M) Age, weanling 32 wk Clinton et al. (1979)	Initiation–promotion study Rats were fed one of three diets: 20% soy protein with 20% beef tallow, 20% raw beef protein with 20% beef tallow, or 20% charcoal-broiled beef protein with 20% beef tallow, fed ad libitum After 4 wk, all the rats were initiated with DMH (1.25 mg/kg bw for 18 wk) 30 rats/group 29, 30, 28	*Small intestine* Tumour incidence: 9/28 (32%), 12/30 (40%), 8/29 (28%) Tumour multiplicity: 1.1, 1.3, 1.1 *Colon* Tumour incidence: 11/28 (39%), 13/30 (43%), 12/29 (41%) Tumour multiplicity: 1.3, 1.4, 1.4	$P = 0.17$ (number of tumours per tumour-bearing rat, Pearson χ^2) $P = 0.96$ (distribution of colon tumour frequency, Neyman χ^2) Tumour multiplicity was reported as No. of tumours per tumour-bearing rat	Limitations: histopathological examination not conducted
Rat, Wistar (M) Age 4 wk 8 mo Alink et al. (1993)	Initiation–promotion study Rats were fed one of five diets, A–E: diet A, a semisynthetic rodent diet; diet B, diet A supplemented with fruits and vegetables; diet C, a "humanized" diet consisting of meat (beef, pork, and chicken), bread, eggs, and margarine, along with other semisynthetic products; diet D, diet C, that had been cooked; or diet E, diet D, supplemented with fruits and vegetables; fed ad libitum 45 rats/group	*Colon* Adenoma, incidence: 27/43 (63%), 14/36 (39%), 20/42 (48%), 20/43 (47%), 23/43 (53%) Total adenomas: 68, 19, 31, 45, 42 Adenocarcinoma, incidence: 31/43 (72%), 22/36 (61%), 28/42 (67%)*, 34/43 (79%)*, 35/43 (81%)* Total adenocarcinomas: 67, 42, 70, 72, 100	Combined groups C,D, and E significantly higher (*$P < 0.05$; Fisher's exact test) than combined groups A and B Zymbal's gland tumours were also observed, with the incidence being significantly ($P < 0.05$; Fisher's exact test) greater in the combined C, D, and E diet groups compared to the combined A and B groups; specific incidences, NR	All rats were initiated with DMH (10 weekly injections of 50 mg/kg bw)

Table 3.2 (continued)

Species, strain (sex) Age at start Duration Reference	Dosing regimen Animals/group at start No. surviving animals	Results For each target organ: incidence (%) and/or multiplicity of tumours	Significance	Comments
Rat, presumably Sprague-Dawley (NR) Age NR NR McIntosh (1993)	Initiation–promotion study Diet containing red meat protein, whey protein, casein protein, soy protein, or fish protein; fed ad libitum 10 rats/group 10, 10, 10, 10, 10	*Intestine* Tumour incidence: 60%, 20%, 40%, 50%, 40% Tumour multiplicity: 1.1, 0.2*, 0.4, 0.9, 0.8	Incidence of intestinal tumours, NS (may be a consequence of the small number of animals per group) Decrease; *$P < 0.05$ (No. of intestinal tumours per rat; whey protein diet vs red meat protein, soy protein, or fish protein diet; statistical test not specified)	Limitations: histopathological examination not conducted Rats were fed one of five diets: 20% protein derived from red meat [type not specified], 20% protein derived from whey, 20% protein derived from casein, 20% protein derived from soy, or 20% protein derived from fish All the rats were initiated with DMH (3 weekly injections of 20 mg/kg bw)
Rat, Sprague-Dawley (M) Age 5 wk 6 mo McIntosh et al. (1995)	Initiation–promotion study Diet containing casein (20.0 g/100 g diet), whey protein concentrate (21.3 g/100 g diet), kangaroo skeletal muscle (22.8 g/100 g diet), or defatted soybean meal (33.3 g/100 g diet), fed ad libitum 20 rats/group Survival: NR	*Large intestine* Total tumours: 6*, 5*, 10, 21 *Intestine* Tumour incidence: 45%, 30%, 50%, 60% Total tumours: 12*, 7*, 21, 26	Decrease; *$P < 0.02$ (tumours per group, casein and whey protein diets vs kangaroo meat and defatted soybean meal diets, regression analysis using Poisson distribution) $P = 0.15$ (No. of surviving rats, NR, all presumed to have survived; χ^2) Decrease; *$P < 0.005$ (tumours per group, casein and whey protein diets vs kangaroo meat and defatted soybean meal diets, regression analysis using Poisson distribution)	Limitations: histopathological examination not conducted All rats were initiated with DMH (3 weekly injections of 15 mg/kg bw)

Table 3.2 (continued)

Species, strain (sex) Age at start Duration Reference	Dosing regimen Animals/group at start No. surviving animals	Results For each target organ: incidence (%) and/or multiplicity of tumours	Significance	Comments
Rat, Sprague-Dawley (M) Age, weanling 27 wk Pence et al. (1995)	Initiation–promotion study Diet containing casein protein with 5% corn oil, casein protein with 20% corn oil, casein protein with 5% beef tallow, casein protein with 20% beef tallow, beef protein with 5% corn oil, beef protein with 20% corn oil, beef protein with 5% beef tallow, or beef protein with 20% beef tallow; fed ad libitum 25 rats/groups Survival: NR	*Small intestine* Adenoma incidence: 4%, 0%, 4%, 0%, 0%, 0%, 0%, 7% Adenocarcinoma, incidence: 48%, 28%, 40%, 24%, 32%, 28%, 48%, NR Adenoma or adenocarcinoma, incidence: 32%, 48%, 28%, 40%, 24%, 32%, 28%, 52% *Colon* Adenoma, incidence: 24%, 20%, 24%, 36%, 16%, 40%, 12%, 29% Adenocarcinoma, incidence: 60%*, 48%*, 32%*, 40%*, 20%, 16%, 28%, 19% Adenoma or adenocarcinoma, incidence: 64%, 52%, 52%, 64%, 28%*, 52%, 36%, 42% *Colon and small intestine* Adenoma or adenocarcinoma, incidence: 72%, 72%, 56%, 80%, 48%, 64%, 44%, 67%	*$P < 0.05$ (casein protein diets vs beef, except 5% beef tallow, diets, irrespective of fat source; $\chi 2$) Decrease; *$P < 0.05$ (beef protein with 5% corn oil diet vs 5% casein protein with 5% corn oil diet, $\chi 2$)	Rats were fed AIN-76A–based test diets using a 2 × 2 × 2 factorial design, with the factors being the protein source (casein or lean beef), fat source (corn oil or beef tallow), and fat level (5% or 20%) Rats were initiated with DMH (10 weekly injections of 20 mg/kg bw) Ten rats per diet group served as vehicle controls; tumour incidence in the controls was NR The duration of this experiment (27 wk) was probably not sufficient to determine if the diets by themselves were tumorigenic

Table 3.2 (continued)

Species, strain (sex) Age at start Duration Reference	Dosing regimen Animals/group at start No. surviving animals	Results For each target organ: incidence (%) and/or multiplicity of tumours	Significance	Comments
Rat, Sprague-Dawley (M) Age, weanling 27 wk Lai et al. (1997)	Initiation–promotion study Rats were fed an AIN-76A–based diet containing casein (protein source) with corn oil or lean ground beef (protein source) with corn oil, fed ad libitum 30 rats/group 28, 28	*Small intestine* Adenocarcinoma: Incidence: 15/28 (52%), 18/28 (62%)	NS (χ^2)	Rats were initiated with DMH (10 weekly injections of 20 mg/kg bw) Five rats per diet group served as vehicle controls; tumour incidence in the controls was NR The duration of this experiment (27 wk) was probably not sufficient to determine if the diets by themselves were tumorigenic
		Multiplicity: 0.66, 0.90	NS (No. of tumours per rat, Student *t* test)	
		Colon Adenocarcinoma: Incidence: 18/28 (62%), 15/28 (52%)	NS (appears that two rats from each group were removed early and not included in the final tumour assessment, χ^2)	
		Multiplicity: 0.86, 0.79	NS (No. of tumours per rat, Student *t* test)	
		Colon or small intestine Adenocarcinoma: Incidence: 23/28 (79%), 24/28 (83%)	NS (χ^2)	
		Multiplicity: 1.52, 1.69	NS (No. of tumours per rat, Student *t* test)	

Table 3.2 (continued)

Species, strain (sex) Age at start Duration Reference	Dosing regimen Animals/group at start No. surviving animals	Results For each target organ: incidence (%) and/or multiplicity of tumours	Significance	Comments
Rat, Sprague-Dawley (M) Age, weanling 27 wk Pence et al. (1998)	Initiation–promotion study Diet containing low fat with low HAAs, then low fat; high fat with high HAAs, then high fat with high HAAs; low fat with low HAAs, then low fat with high HAAs; high fat with low HAAs, then high fat; low fat with high HAAs, then low fat with high HAAs; low fat with high HAAs, then low fat; high fat with high HAAs, then low fat; or high fat with high HAAs, then high fat; fed ad libitum 25 rats/group Survival, NR	*Stomach* Tumour incidence: 4%, 8%, 0%, 4%, 16%, 8%, 8%, 12% Tumour multiplicity: 0.04, 0.08, 0.00, 0.04, 0.16, 0.08, 0.08, 0.12 *Small intestine* Tumour incidence: 20%, 28%, 48%, 46%, 32%, 24%, 16%, 36% Tumour multiplicity: 0.36, 0.28, 0.56, 0.58, 0.56, 0.24, 0.24, 0.40 *Colon* Adenoma or adenocarcinoma: Incidence: 76%, 56%*, 60%, 83%, 88%, 84%, 56%*, 56%* Multiplicity: 1.20, 0.68, 0.96, 1.13, 1.40, 1.04, 0.76, 0.68	NS NS Decrease; *$P < 0.05$ (high-fat with high-HAA diets, incidence, 56%, vs low-fat with high-HAA diets, incidence, 84–88%] during wk 1–12, $\chi 2$)	Rats were fed one of four AIN-76A–based diets: low-fat (5%) with low-HAA (6.6 ng) beef, high-fat (20%) with low-HAA beef, low-fat with high-HAA (85.6 ng) beef, or high-fat with high-HAA beef Rats were initiated with DMH (10 weekly injections of 20 mg/kg bw). Ten rats on the high-fat, high-HAA diet did not receive DMH; these rats did not develop tumours The duration of this experiment (27 wk) was probably not sufficient to determine if the high-fat, high-HAA diet by itself was tumorigenic

Table 3.2 (continued)

Species, strain (sex) Age at start Duration Reference	Dosing regimen Animals/group at start No. surviving animals	Results For each target organ: incidence (%) and/or multiplicity of tumours	Significance	Comments
Rat, F344 (F) Age 5 wk 15 wk Parnaud et al. (1998)	Initiation–promotion study Diet containing low casein with lard, low casein with olive oil, low beef, low chicken, low bacon, high casein with lard, high casein with olive oil, high beef, high chicken, or high bacon; fed ad libitum 10 rats/group 10, 10, 10, 10, 10, 10, 10, 9, 10, 10	*Colon* No. of crypts per ACF, mean (SD): 3.21 (0.47), 3.11 (0.28), 3.25 (0.44), 3.16 (0.34), 2.84 (0.45), 3.27 (0.38), 2.94 (0.30), 3.15 (0.59), 3.18 (0.32), 2.62 (0.60)* No. of ACF per rat, mean (SD): 65 (34), 83 (30), 69 (23), 76 (37), 86 (47), 75 (44), 61 (43), 71 (25), 98 (30), 72 (37)	The high bacon diet was lower than high casein & lard diet (*$P < 0.001$; ANOVA and Dunnett's test)	Rats were fed low-meat or high-meat diets; fat and protein were provided by beef, chicken, bacon, olive oil, or lard; there were two control diets, where fat was provided by lard or olive oil, and protein provided by casein The rats received a single injection of azoxymethane (20 mg/kg bw)
Rat, F344 (F) Age 5 wk 45 days Parnaud et al. (2000)	Initiation–promotion study AIN-76 diet containing 28% fat (corn oil) and 40% protein (casein) with azoxymethane (20 mg/kg bw); AIN-76 diet containing 28% fat (corn oil) and 40% protein (casein); AIN-76 diets with 60% bacon 5, 10, 10 rats/group 5, 10, 10	*Colon* No. of ACF per colon, mean (range): 9 (7–154), 0, 0		The duration of this experiment (45 days) was probably not sufficient to determine if the diets by themselves were tumorigenic
Rat, F344 (F) Age 5 wk 100 days Parnaud et al. (2000)	Initiation–promotion study Rats were fed one of five AIN-76–based diets containing casein, beef, chicken, pork, or bacon; fed ad libitum 10 rats/group 10, 10, 10, 10, 10	*Colon* No. of aberrant crypts per ACF, mean (SD): 2.9 (0.2), 2.9 (0.3), 2.7 (0.2), 2.7 (0.3), 2.4 (0.2)* No. of ACF per colon, mean (SD): 137 (26), 122 (60), 151 (28), 151 (25), 134 (21) No. of ACF with > 7 crypts per ACF, mean (SD): 19.7 (6.8), 15.6 (9.8), 18.6 (8.1), 18.1 (6.8), 11.1 (4.4)*	Decrease; *$P < 0.01$ (No. of aberrant crypts per ACF, bacon diet vs casein diet, ANOVA and Dunnett test) Decrease; *$P = 0.003$ (No. of ACF with > 7 crypts per ACF, bacon diet vs casein diet, ANOVA and Dunnett test)	All rats were treated with a single injection of azoxymethane (20 mg/kg bw)

Table 3.2 (continued)

Species, strain (sex) Age at start Duration Reference	Dosing regimen Animals/group at start No. surviving animals	Results For each target organ: incidence (%) and/or multiplicity of tumours	Significance	Comments
Rat, Wistar (NR) Age 13 wk 14 wk Belobrajdic et al. (2003)	Initiation–promotion study Rats were fed one of six AIN-93–modified diets consisting of 8%, 16%, or 32% red meat, 8%, 16%, or 32% whey; fed ad libitum 12 rats/group Survival: NR	*Proximal colon* No. of ACF per rat, mean: 90, 71, 84, 61, 77, 52 No. of single ACF per rat, mean: 32, 33*, 34*, 25, 26, 16	Numbers of ACF estimated from histogram *$P < 0.05$ (No. of single ACF per rat, numbers estimated from histogram; 16% and 32% red meat diets vs 32% whey protein diet; ANOVA and Tukey multiple comparison test)	Red meat was barbecued kangaroo muscle meat Each group presumably consisted of 12 rats, although this was not stated explicitly All rats were treated with two weekly injections of azoxymethane (15 mg/kg bw)
Rat, Sprague-Dawley (M) NR (weight, 50–75 g) 11 wk Khil & Gallaher (2004)	Initiation–promotion study Rats were fed one of four AIN-93G–modified diets using a 2 × 2 factorial design,: casein with soybean oil, beef with soybean oil, casein with tallow, or beef with tallow; fed ad libitum 14 rats/group 14, 14, 14, 14	*Colon* No. of ACF per cm^2, mean (SEM): 2,98 (0.50), 3.45 (0.37), 1.89 (0.39)*, 2.87 (0.44)* No. of aberrant crypts per ACF, mean (SEM): 3.08 (0.19), 2.69 (0.11), 3.56 (0.35), 2.81 (0.08) No. of aberrant crypts per cm^2, mean (SEM): 9.61 (1.98), 9.46 (1.18), 7.02 (1.54), 8.26 (1.45)	Decrease; *$P = 0.043$ (No. of ACF per cm^2, tallow diets vs soybean oil diets, ANOVA and Duncan multiple range test)	Casein and beef were the protein sources, and soybean oil and tallow were the fat sources; the diets were balanced for protein and fat energy content All rats were treated with two injections of DMH (15 mg/kg bw)

Table 3.2 (continued)

Species, strain (sex) Age at start Duration Reference	Dosing regimen Animals/group at start No. surviving animals	Results For each target organ: incidence (%) and/or multiplicity of tumours	Significance	Comments
Rat, F344 (F) Age 5 wk 15 wk Pierre et al. (2004)	Initiation–promotion study ControlAIN-76 diet or modified diet containing skinless chicken meat (600 g/kg diet), beef meat (600 g/kg diet), black pudding (blood sausage, 600 g/kg diet), or powdered bovine haemoglobin (6.3 g/kg diet); fed ad libitum 20, 10, 10, 10, 10 rats/group 20, 10, 10, 10, 10	*Colon* No. of crypts per ACF, mean (SD): 2.7 (0.4), 2.9 (0.4)*, 2.8 (0.2), 3.1 (0.5)*, 2.9 (0.2)*	*$P < 0.05$ (No. of crypts per ACF; chicken, haemoglobin, and black pudding diets vs control diet; ANOVA and Fisher LSD test)	All rats were treated with azoxymethane (20 mg/kg bw) All the diets were balanced for protein, fat, calcium, and iron
		Total ACF crypts per colon, mean (SD): 192 (55), 267 (65)*, 280 (49)*, 285 (78)*, 301 (48)*	*$P < 0.05$ (No. of ACF crypts per colon; chicken, beef, haemoglobin, and black pudding diets vs control diet; ANOVA and Fisher LSD test)	
		No. of ACF per colon, mean (SD): 72 (16), 91 (18)*, 100 (13)*, 93 (24)*, 103 (14)*	*$P < 0.05$ (No. of ACF per colon; chicken, beef, haemoglobin, and black pudding diets vs control diet; ANOVA and Fisher LSD test)	
		No. of crypts per MDF, mean (SD): 4.65 (2.40), 4.92 (1.64), 4.23 (1.15), 4.60 (1.93), 4.29 (0.59)		
		Total MDF crypts per colon, mean (SD): 2.9 (4.0), 6.0 (3.9), 8.5 (6.9)*, 11.5 (9.0)*, 13.1 (6.0)*,**	*$P < 0.05$ (No. of MDF crypts per colon; beef, haemoglobin, and black pudding diets vs control diet; ANOVA and Fisher LSD test) **$P < 0.05$ (black pudding diet vs beef and chicken diets, ANOVA and Fisher LSD test)	

Table 3.2 (continued)

Species, strain (sex) Age at start Duration Reference	Dosing regimen Animals/group at start No. surviving animals	Results For each target organ: incidence (%) and/or multiplicity of tumours	Significance	Comments
Rat, F344 (F) Age 5 wk 15 wk Pierre et al. (2004) (cont.)		No. of MDF per colon, mean (SD): 0.55 (0.68), 1.20 (0.63), 1.90 (1.37)*, 2.40 (1.50)*, 3.00 (1.24)*,**	*$P < 0.05$ (No. of MDF per colon; beef, haemoglobin, and black pudding diets vs control diet; ANOVA and Fisher LSD test) **$P < 0.05$ (black pudding diet vs beef and chicken diets, ANOVA and Fisher LSD test)	
Rat, F344 (F) Age 5 wk 15 wk Pierre et al. (2008)	Initiation–promotion study The rats were fed one of eight AIN-76–modified diets: a low-calcium control diet; a low-calcium, beef meat diet; a high-calcium control diet; a high-calcium, beef meat diet; an olive oil–fortified control diet; an olive oil–fortified, beef meat diet; an antioxidant-fortified control diet; or an antioxidant-fortified, beef meat diet; fed ad libitum 10 rats/group 10, 10, 10, 10, 10, 10, 10, 10	*Colon* No. of crypts per ACF, mean (SD): 2.3 (0.2), 2.6 (0.2)*, 2.8 (0.2)**, 2.5 (0.2), 2.5 (0.2), 2.4 (0.2), 2.3 (0.2), 2.4 (0.3)	*$P < 0.05$ (No. of crypts per ACF, beef with low-calcium diet vs respective control diet, ANOVA and Fisher LSD test) **$P < 0.05$ (control diet with high calcium vs other control diets, ANOVA and Fisher LSD test)	All rats were treated with a single injection of DMH (190 mg/kg bw) All the diets were balanced for protein, fat, and iron
		No. of ACF per colon, mean (SD): 105 (24), 137 (26)*, 130 (22)**, 106 (24), 104 (25), 125 (20)*, 107 (22), 127 (22)*	*$P < 0.05$ (No. of ACF per colon; beef, except beef with high calcium, diets vs respective control diets; ANOVA and Fisher LSD test) **$P < 0.05$ (control diet with high calcium vs other control diets, ANOVA and Fisher LSD test)	
		No. of ACF crypts per colon, mean (SD): 245 (52), 347 (55)*, 365 (71)**, 265 (74), 258 (71), 299 (60)*, 243 (48), 300 (40)*	*$P < 0.05$ (No. of ACF crypts per colon; beef, except beef with high calcium, diets vs respective control diets; ANOVA and Fisher LSD test) **$P < 0.05$ (control diet with high calcium vs other control diets, ANOVA and Fisher LSD test)	

Table 3.2 (continued)

Species, strain (sex) Age at start Duration Reference	Dosing regimen Animals/group at start No. surviving animals	Results For each target organ: incidence (%) and/or multiplicity of tumours	Significance	Comments
Rat, F344 (F) Age 5 wk 15 wk Pierre et al. (2008) (cont.)		No. of crypts per MDF, mean (SD): 4.6 (1.7), 5.3 (1.6), 7.6 (2.4)*, 7.8 (3.1), 4.0 (1.2), 4.3 (0.7), 4.4 (1.4), 3.9 (1.4)	*$P < 0.05$ (No. of crypts per MDF, control diet with high calcium vs other control diets, ANOVA and Fisher LSD test)	
		No. of mucin-depleted crypts per colon, mean (SD): 18.2 (15.3), 40.7 (18.9)*, 58.1 (27.5)**, 24.3 (12.6), 15.6 (13.0), 22.5 (5.3), 14.7 (8.8), 22.4 (9.5)	*$P < 0.05$ (No. of mucin-depleted crypts per colon, beef with low-calcium diet vs respective control diet, ANOVA and Fisher LSD test) **$P < 0.05$ (control diet with high calcium vs other control diets, ANOVA and Fisher LSD test)	
		No. of MDF per colon, mean: 3.5 (2.0), 7.4 (2.0)*, 7.6 (3.0)**, 3.4 (1.8), 3.8 (2.5), 5.3 (1.2)*, 3.2 (1.3), 5.6 (1.1)*	*$P < 0.05$ (No. of MDF per colon; beef, except beef with high calcium, diets vs respective control diets; ANOVA and Fisher LSD test) **$P < 0.05$ (control diet with high calcium vs other control diets, ANOVA and Fisher LSD test)	

Table 3.2 (continued)

Species, strain (sex) Age at start Duration Reference	Dosing regimen Animals/group at start No. surviving animals	Results For each target organ: incidence (%) and/or multiplicity of tumours	Significance	Comments
Rat, F344 (F) Age 5 wk 15 wk Pierre et al. (2010)	Initiation–promotion study AIN-76–modified control diet or diet containing ham (550 g/kg diet), balanced for protein, fat, and iron; fed ad libitum 10 rats/group 10, 10	*Colon*		All rats were treated with a single injection of DMH (190 mg/kg bw)
		No. of crypts per ACF, mean (SD): 2.3 (0.2), 2.1 (0.1)		
		No. of ACF per colon, mean (SD): 105 (24), 119 (16)*	*$P < 0.05$ (No. of ACF per colon, ham diet vs control diet, ANOVA and Tukey multiple comparison test)	
		No. of crypts per MDF, mean (SD): 4.6 (1.7), 4.3 (1.2)		
		No. of MDF per colon, mean (SD): 3.5 (2.0), 8.5 (2.2)*	*$P < 0.05$ (No. of MDF per colon, ham diet vs control diet, ANOVA and Tukey multiple comparison test)	
Rat, F344 (F) Age 5 wk 15 wk Santarelli et al. (2010)	Initiation–promotion study The rats were fed a control diet or one of four AIN-76–modified diets: dark cooked meat with nitrite, oxidized; dark cooked meat with nitrite, anaerobic; dark cooked meat, oxidized; or dark raw meat, anaerobic; fed ad libitum 10 rats/group 10, 10, 10, 10, 10	*Colon*		All rats were treated with a single injection of DMH (180 mg/kg bw) The dark meat was pork meat with high haem The diets were balanced for protein and fat
		No. of ACF per colon, mean (SD): 81 (18), 100 (16)*, 102 (25)*, 106 (21)*, 101 (17)*	*$P < 0.05$ (No. of ACF per colon, experimental dark meat diets vs control diet, ANOVA and Fisher LSD test)	
		No. of crypts per MDF, mean (SD): 3.9 (1.5), 4.2 (1.2), 2.7 (1.7)*, 3.5 (1.2), 3.9 (1.9)	Decrease; *$P < 0.05$ (No. of crypts per MDF; dark cooked meat with nitrite, anaerobic diet vs control and dark cooked meat, oxidized diets; ANOVA and Fisher LSD test)	
		No. of MDF per colon, mean (SD): 2.9 (1.9), 4.1 (2.9)*, 2.1 (2.0), 2.8 (2.8), 3.4 (2.6)	*$P < 0.05$ (No. of MDF per colon; dark cooked meat with nitrite, oxidized diet vs control diet; Fisher LSD test)	

Table 3.2 (continued)

Species, strain (sex) Age at start Duration Reference	Dosing regimen Animals/group at start No. surviving animals	Results For each target organ: incidence (%) and/or multiplicity of tumours	Significance	Comments
Rat, F344 (F) Age 5 wk 15 wk Santarelli et al. (2010) (cont.)		No. of mucin-depleted crypts per colon, mean (SD): 11 (8), 18 (13)*, 8 (8), 10 (11), 14 (10)	*$P < 0.05$ (No. of mucin-depleted crypts per colon; dark cooked meat with nitrite, oxidized diet vs control; dark cooked meat with nitrite, anaerobic; and dark cooked meat, oxidized diets; ANOVA and Fisher LSD test)	
Rat, F344 (F) 5 wk 15 wk Pierre et al. (2013)	Initiation–promotion study One of three AIN-76–modified diets containing dark cooked meat with nitrite, oxidized by air; dark cooked meat with nitrite, oxidized by air and fortified with α-tocopherol; or dark cooked meat with nitrite, oxidized by air and fortified with $CaCO_3$; fed ad libitum 16, 10, 10 rats/group 16, 10, 10	*Colon* No. of ACF per colon, mean (SD): 126 (20), 125 (15), 124 (24) No. of crypts per MDF, mean (SD): 3.7 (1.3), 2.4 (2.1), 2.5 (1.4) No. of MDF per colon, mean (SD): 2.7 (2.1)*, 1.4 (1.5), 1.3 (1.6)	*$P < 0.05$ (No. of MDF per colon; dark cooked meat treated with nitrite, oxidized by air diet vs dark cooked meat treated with nitrite, oxidized by air and fortified with α-tocopherol or dark cooked meat treated with nitrite, oxidized by air and fortified with $CaCO_3$ diet; Fisher LSD test)	All rats were treated with a single injection of DMH (180 mg/kg bw) The dark meat was pork meat with high haem

Table 3.2 (continued)

Species, strain (sex) Age at start Duration Reference	Dosing regimen Animals/group at start No. surviving animals	Results For each target organ: incidence (%) and/or multiplicity of tumours	Significance	Comments
Rat, F344 (F) Age 5 wk 15 wk Santarelli et al. (2013)	Initiation–promotion study Low-calcium AIN-76–modified diets, either 40% hot dog [pork] meat or 50% French saucisson [pork]; the diets were balanced for protein, fat, and iron; fed ad libitum 10 rats/group 10, 10, 10	*Colon* No. of ACF per colon, mean (SD): 110 (17), 108 (32), 102 (25) No. of crypts per MDF, mean (SD): 2.6 (2.4), 4.7 (2.4)*, 3.2 (2.2) No. of MDF per colon, mean (SD): 1.2 (1.4), 3.0 (1.7)*, 2.4 (2.4)	*$P < 0.05$ (No. of crypts per MDF, hot dog with low-calcium diet vs control diet, ANOVA and Fisher LSD test) *$P < 0.05$ (No. of MDF per colon, hot dog with low-calcium diet vs control diet, ANOVA and Fisher LSD test)	All rats were treated with a single injection of DMH (180 mg/kg bw)
Rat, F344 (F) Age 5 wk 15 wk Santarelli et al. (2013)	Initiation–promotion study AIN-76–modified diet containing 40% hot dog [pork] with either low or high calcium (balanced for protein, fat, and iron), fed ad libitum 10 rats/group 10, 10	*Colon* No. of crypts per MDF, mean (SD): 3.5 (0.6), 3.3 (0.4) No. of MDF per colon, mean (SD): 2.3 (1.4)*, 1.2 (1.1) No. of ACF per colon, mean (SD): 136 (25), 118 (19)	*$P < 0.05$ (No. of MDF per colon, hot dog with low-calcium diet vs hot dog with high-calcium diet, ANOVA and Fisher LSD test)	All rats were treated with a single injection of DMH (180 mg/kg bw)

* or **, statistically significant; ACF, aberrant crypt foci; AIN, American Institute of Nutrition; ANOVA, analysis of variance; $CaCO_3$, calcium carbonate; DMH, dimethylhydrazine; F, female; HAA, heterocyclic aromatic amine; LSD, least significant difference; M, male; MDF, mucin-depleted foci; mo, month; NR, not reported; NS, not significant; SD, standard deviation; SEM, standard error of the mean; vs, versus; wk, week

and 997 days for females. All rats were examined grossly, histopathology was conducted, and statistical analyses were conducted. Rats on the human diets (Diets C, D, and E) weighed substantially more than rats on the rodent diets (Diets A and B), probably as a consequence of the greater caloric intake of the rats on the human diets. The maximum difference in weight was 200 g for male rats and 100 g for female rats. At the end of the experiment, approximately 5–22% of the male rats and 7–15% of the female rats survived. Male rats fed the human Diet C had a significantly higher mortality than rats fed the rodent Diets A or B (Alink et al., 1989, 1997).

Male rats on the human diets (Diets C, D, and E) had a significantly greater tumour incidence than male rats fed the rodent diets (Diets A and B; $P < 0.014$). This difference was due to epithelial tumours ($P = 0.0008$), specifically pituitary gland (pars distalis) tumours ($P = 0.0016$) and thyroid gland (light cell adenoma or carcinoma combined) tumours ($P = 0.014$). Stepwise logistic regression analysis indicated that the increased tumour incidence in the tissues of these glands was not associated with the observed increase in body weight. [The linear regression analysis may have been compromised, as the body weights at the early time points did not differ among the groups. At the end of the study, rats fed the human diets weighed considerably more than those fed the rodent diets.] None of the other tumours reported were affected by the diets. [The tumour data were confounded by the fact that the human diets contained approximately twice the amount of fat and half the fibre of the rodent diets. In addition, the increase in tumour incidence could not necessarily be attributed to beef because the diets contained other components typically present in human diets.] There were no significant findings in female rats (Alink et al., 1989, 1997).

3.2.2 Red meat with known carcinogens

Inbred, female F344 rats were randomly divided at weaning into four groups, with 56 rats in each group. One group (designated D_1) was given a high-protein (39%), high-fat (24%) diet, with soybean as the protein source and corn oil as the fat source. Another group (designated D_2) was given a low-protein (19%), low-fat (5.4%) diet, with soybean as the protein source and corn oil as the fat source. A third group (designated D_3) was given a high-protein (40%), high-fat (23%) diet, with freeze-dried ground beef as the protein source and freeze-dried ground beef plus corn oil as the fat source. A fourth group (designated D_4) was given a low-protein (18.5%), low-fat (6.5%) diet, with freeze-dried ground beef as both the protein and fat sources. [The calcium content of the diet could not be determined.] At 7 weeks of age, half the rats in each group were initiated with weekly subcutaneous injections of DMH at a dose of 10 mg/kg bw for 20 weeks. [The specific diets may have affected metabolism of the DMH.] The tumour incidence was assessed 10 weeks after the last injection. Gross and histopathological analyses were conducted. Rats treated with DMH tended to weigh less than the control rats, especially rats fed the soybean and corn oil diets (D_1 and D_2). Rats fed the ground beef plus corn oil diet (D_3) weighed more than the other groups (Reddy et al., 1976).

Tumours were observed in the ear canal, kidney, small intestine, and colon in DMH-treated rats. There were no tumours in the control rats (i.e. those that had not been treated with DMH). [The duration of this experiment (30–34 weeks) was probably not sufficient to determine if the diets by themselves were tumorigenic.] Rats fed the high-protein, high-fat diets (D_1 and D_3) had an increased multiplicity (tumours per animal) of colon tumours ($P < 0.05$) and adenocarcinomas ($P < 0.05$), but not adenomas, compared with rats fed the low-protein, low-fat diets (D_2 and D_4). [The statistical test was not specified,

but was presumably a Student *t* test]. The source of the protein (e.g. soybean or beef) and fat (e.g. corn oil or beef) did not affect the tumour multiplicity. Rats treated with DMH had a significantly increased incidence of ear canal and colon tumours compared with control rats [$P \leq 0.02$, two-tailed Fisher exact test] (Reddy et al., 1976).

In a separate study, groups of 30 weanling, male Sprague-Dawley rats (weight, 50–60 g) were placed on one of three diets: 20% soy protein and 20% beef tallow, 20% raw beef protein (ground beef) and 20% beef tallow, or 20% charcoal-broiled beef protein and 20% beef tallow. [The calcium content of the diets could not be determined.] The charcoal-broiled ground beef was cooked to a "well-done" state, with an internal temperature of approximately 70 °C. Both the raw and cooked ground beef were freeze-dried and ground to a fine powder before being mixed into the diet. After 4 weeks, rats were initiated with intraperitoneal injections of DMH at 1.25 mg/100 g bw per week for 18 weeks. [The specific diets may have affected metabolism of the DMH.] The rats were killed 32 weeks after being placed on the diets. Eighty-seven of the initial 90 rats survived until the end of the experiment. Small intestine and colon tumours were assessed grossly; histopathology was not conducted. Statistical analyses were conducted. The distribution of colon tumour multiplicity was not significantly affected by the diets. Similarly, the number of small intestine tumours per rat did not differ significantly across the diet groups (Clinton et al., 1979).

A study was conducted to investigate the effects of a "complete human diet" prepared under normal household conditions. Male Wistar rats (age, 4 weeks) were placed on one of five diets (45 rats per diet, except Diet B, which had 36 rats): diet A, a semisynthetic rodent diet; diet B, a semisynthetic rodent diet supplemented with fruits and vegetables; diet C, a "humanized" diet consisting of meat (beef, pork, and chicken), bread, eggs, and margarine, along with other semisynthetic products, including lard, potato flour, sugar, bran, and pectin; diet D, a diet similar to diet C, except the food was cooked under "usual household conditions"; and diet E, a diet similar to diet D, except supplemented with fruits and vegetables. All the food items were freeze-dried, homogenized, and pelletized. The pellets were assessed for the presence of heterocyclic aromatic amines (HAAs). [The authors did not present the results of the HAA analyses.] Diets A and B contained 21.6% fat "energy," 26.0% protein "energy," 52.4% carbohydrate "energy," and 10.7% fibre. Diets C, D, and E contained 40.6% fat "energy," 13.2% protein "energy," 46.2% carbohydrate "energy," and 5% fibre. The diets contained calcium at a concentration of 7.5 g/kg diet. Starting at age 8 weeks, all rats were initiated with 10 weekly subcutaneous injections of DMH at a dose of 50 mg/kg bw. [The specific diets may have affected metabolism of the DMH.] The rats were maintained on their respective diets for 8 months. All animals were examined grossly, histopathology was conducted, and statistical analyses were conducted. Of the rats, 18% (range across diet groups, 8.3–28.9%) died or were removed before the scheduled termination; more than 90% of the rats from each group were evaluated for neoplasms. Food consumption was higher in rats fed diets A and B compared with those fed diets C, D, and E, presumably due to the lower caloric density of diets A and B. Body weights did not differ among the groups (Alink et al., 1993, 1997).

For all diet groups, tumours were mainly observed in the colon and small intestine, with a much lower incidence in the caecum, abdominal cavity, and liver. The overall incidence of adenocarcinomas of the colon was significantly ($P < 0.05$) higher in the combined human diet groups (diets C, D, and E) than in the combined rodent diet groups (diets A and B). The incidence of other tumours did not differ between the combined human and rodent diet groups. Zymbal gland tumours were also observed,

with the incidence being significantly ($P < 0.05$) greater in the combined human diet groups than in the combined rodent diet groups; (Alink et al., 1993, 1997). [The Working Group noted that the specific incidences were not reported in the paper. The tumour data were confounded by the fact that the human diets had approximately two-fold more fat and 50% less fibre than the rodent diets. In addition, the increase in tumours could not be necessarily attributed to beef because the diets contained other components typically present in human diets.]

In another study, groups of 10 rats [presumably Sprague-Dawley, and sex and age not specified] were initiated with DMH. Rats were fed diets containing 20% protein, derived from red meat [type not specified], whey, casein, soy, or fish. [The temporal relationship between the DMH treatment and the different diets was not specified; the preparation of the various diets and the duration of feeding were not reported. The calcium content of the diets could not be determined, and there was no indication if histopathology was conducted.] The incidence of intestinal tumours did not differ significantly among the rats fed the different protein diets. [This may have been a consequence of the small number of animals per group.] Rats fed the whey protein diet had significantly fewer intestinal tumours per rat than rats fed the red meat, soy, or fish protein diets ($P < 0.05$) (McIntosh, 1993). [The Working Group noted that the design and results of the study were very poorly reported. Whey protein has been reported to have chemopreventive activity.]

In a separate study, groups of 20 male Sprague-Dawley rats (age, 5 weeks) were fed AIN-76A–based diets formulated with one of four protein sources: casein (20.0 g per 100 g diet), whey protein concentrate (21.3 g per 100 g diet), kangaroo skeletal muscle (22.8 g per 100 g diet), or defatted soybean meal (33.3 g per 100 g diet). The kangaroo meat was dried to a constant low-moisture product at 40 °C, and then ground to a fine meal. The levels of the remaining dietary components (e.g. fat, carbohydrate, and fibre) were adjusted, so the four diets were of comparable composition. The calcium content was 5 g/kg diet. At 9–10 weeks of age, the rats were initiated with three subcutaneous weekly injections of DMH at a dose of 15 mg/kg bw. [The specific diets may have affected metabolism of the DMH.] The rats were maintained on the diets for 5–6 months. The number of rats that survived until the end of the experiment was not specified. Tumours were assessed grossly, and histopathology was conducted in selected instances. Statistical analyses were conducted (McIntosh et al., 1995).

Intestinal tumour incidence was lowest in the whey protein group (30%), followed by the casein group (45%), kangaroo skeletal muscle group (50%), and defatted soybean meal group (65%). However, differences in tumour incidence were not significant. There was a significantly lower intestinal tumour burden (tumours per group) in the two groups (combined) fed the whey protein and casein diets compared with the two groups (combined) fed the kangaroo meat and soybean meal diets ($P < 0.005$). The same was true when only large intestine tumours were considered ($P < 0.02$). The tumour mass index did not differ significantly among the groups (McIntosh et al., 1995; McIntosh & Le Leu, 2001). [Whey protein has been reported to have chemopreventive activity.]

Groups of 25 weanling, male Sprague-Dawley rats were fed AIN-76A–based test diets. The diets contained calcium at a concentration of 5.2 g/kg diet. A 2 × 2 × 2 factorial design was used, with the factors being the protein source (casein or lean ground beef), fat source (corn oil or beef tallow), and fat level (5% or 20%). Ground beef containing 20% fat was cooked in an iron skillet until the meat was no longer pink and then mixed with the remaining dietary components. After a 2-week acclimation period, the rats were initiated with 10 weekly intraperitoneal

injections of DMH at a dose of 20 mg/kg bw. [The specific diets may have affected metabolism of the DMH.] Following the DMH treatment, the rats were maintained on the experimental diets for an additional 15 weeks. An additional 10 rats per diet group served as vehicle controls. Complete necropsies were performed, and all lesions were examined microscopically. Statistical analyses were conducted. Rats fed the 20% fat diets gained more weight than those fed the 5% fat diets, irrespective of the fat source. Rats fed the casein protein diets weighed more than those fed the lean ground beef protein diets (Pence et al., 1995).

Rats fed the casein protein diets had a significantly higher incidence ($P < 0.05$) and multiplicity ($P = 0.0001$) of colon adenocarcinomas than rats fed the lean ground beef protein diets, irrespective of the fat source or fat level. The multiplicity of colon tumours was also higher in the rats fed the casein protein diets ($P = 0.0008$) (Pence et al., 1995). [The tumour incidences in the control groups were not reported. The duration of this experiment (27 weeks) was probably not sufficient to determine if the diets by themselves were tumorigenic.]

A group of 35 weanling male Sprague-Dawley rats was placed on an AIN-76A–based diet containing 17.2% casein (protein source) and 5% corn oil (fat). A second group of weanling, male Sprague-Dawley rats was placed on an AIN-76A–based diet containing 97% lean (3% fat) ground beef at 50% of the total diet (by weight) and 4% corn oil [The diets contained calcium at a concentration of 5.2 g/kg diet.] The lean ground beef was cooked in an iron skillet until the meat was no longer pink and then mixed with the remaining dietary components. Two weeks after being placed on the diets, 30 rats from each group were initiated with intraperitoneal injections of DMH at a dose of 20 mg/kg bw once per week for 10 weeks. [The specific diets may have affected metabolism of the DMH.] Five rats from each group served as vehicle controls. Fifteen weeks after the last DMH injection, the rats were killed to assess the tumour incidence. Complete necropsies were conducted, and all lesions were examined by histopathology. Rats fed the beef diet and initiated with DMH weighed more than those fed the casein diet and initiated with DMH, with the difference (~10%) being significant (as assessed by Student *t* test) towards the end of the experiment (weeks, 17–25). Mean food consumption was similar for both diet groups after correcting for the water content of the beef (Lai et al., 1997). [Although not stated, it appeared that two rats from each group were removed early and not included in the final tumour assessment.]

The only tumours reported were colon adenocarcinomas and small intestine adenocarcinomas, and the incidence and number of tumours per rat did not differ significantly (as assessed by χ^2 test and Student *t* test, respectively) between those fed the casein diet and initiated with DMH and those fed the beef diet and initiated with DMH (Lai et al., 1997). [The tumour incidence in the control groups (those not treated with DMH) was not reported. The duration of this experiment (27 weeks) was probably not sufficient to determine if the diets by themselves were tumorigenic.]

Groups of 25 weanling male Sprague-Dawley rats were fed one of four AIN-76A–based diets: low fat, low HAAs; high fat, low HAAs; low fat, high HAAs; or high fat, high HAAs. The diets contained calcium at a concentration of 5.2 g/kg diet. The fat was provided primarily by beef tallow (4% for low fat and 18.8% for high fat) and corn oil (1% for low fat and 1.2% for high fat), and the HAAs were generated by cooking the beef to give 6.6 and 85.6 ng of HAAs per gram cooked beef for low and high HAAs, respectively. The low-HAA beef was prepared by cooking crumbled beef for 11 minutes in a stainless-steel vessel [the internal temperature was not reported]; the high-HAA beef was prepared by cooking a beef patty for 11 minutes in an iron skillet to an internal temperature of 85 °C. Two weeks after being fed the diets, the rats were initiated with

10 weekly intraperitoneal injections of DMH at a dose of 20 mg/kg bw. One additional group of 10 rats, fed the high-fat, high-HAA diet, was given 10 weekly intraperitoneal injections of the vehicle. Following the last intraperitoneal injection, the rats on the low-fat, low-HAA diet were given either a low-fat AIN-76A diet or a low-fat, high-HAA diet; the rats on the low-fat, high-HAA diet were given either a low-fat AIN-76A diet or a low-fat, high-HAA diet; the rats on the high-fat, low-HAA diet were given a high-fat AIN-76A diet; and the rats on the high-fat, high-HAA diet were given either a low-fat AIN-76A diet, high-fat AIN-76A diet, or a high-fat, high-HAA diet. Twenty-seven weeks after the start of the experiment, the rats were killed to assess tumour incidence. Complete necropsies were performed, and lesions were examined by histopathology. In addition, statistical analyses were conducted (Pence et al., 1998).

Adenocarcinomas were observed in the colon, stomach, and small intestine. These only occurred in rats initiated with DMH. The most consistent observation was a decrease in the incidence of colon tumours ($P < 0.05$) in rats fed the high-fat, high-HAA diet during weeks 1–12 (colon tumour incidence, 56%) compared with those fed the low-fat, high-HAA diet during the same period (colon tumour incidence, 84–88%). (Pence et al., 1998). [The duration of this experiment (27 weeks) was probably not sufficient to determine if the high-fat, high-HAA diet by itself was tumorigenic.]

3.2.3 *Red meat and/or processed meat with known carcinogens to give aberrant crypt foci and/or mucin-depleted foci*

Groups of 10 female F344 rats (age, 5 weeks) were treated with a single intraperitoneal injection of azoxymethane at a dose of 20 mg/kg bw. One week later, the groups were placed on a low-meat (30%) or high-meat diet (60%). The protein was provided by powdered cooked meat (beef, bacon, or chicken) and casein, and the fat was provided by the meat, lard, chicken fat, olive oil, and corn oil. The high-meat diet contained approximately twice as much fat and protein as the low-meat diet. Each type of meat was cooked in the oven for 15 minutes at 180–185 °C. The estimated HAA content was 1–15 ng/g beef, 15–65 ng/g bacon, and 40 ng/g chicken. [The calcium content of the diets could not be determined.] After cooking, the meats were minced, frozen, and freeze-dried. There were also two control diet groups, where protein was provided by casein, and fat was provided by lard or olive oil. Rats fed the bacon-based diets consumed more drinking-water than rats fed the other diets. The rats were killed 105–107 days after the azoxymethane injection, and the extent of aberrant crypt foci (ACF) formation was determined by light microscopy. Statistical analyses were conducted. The number of ACF per rat did not vary significantly among the diet groups. The multiplicity of ACF was lowest in the bacon-fed rats, and compared with the high-casein, lard-fed group, the multiplicity was reduced by 20% in the high-bacon group ($P < 0.001$) (Parnaud et al., 1998).

An experiment to induce ACF was conducted in a group of five female F344 rats (age, 4 weeks). The rats were treated with a single intraperitoneal injection of azoxymethane at a dose of 5 mg/kg bw and transferred to a high-fat, semisynthetic AIN-76–based diet containing 28% fat (corn oil) and 40% protein (casein). The diet contained calcium at a concentration of 5.2 g/kg diet. A second group of 10 rats was injected with the vehicle and then given the same diet. A third group of 10 rats was injected with 0.9% sodium chloride (NaCl) and transferred to a diet containing 60% bacon, as both the protein and fat sources, and prepared as described in Parnaud et al. (1998). Both diets were identical in terms of protein and fat levels. Thirty days after being fed the bacon diet, the rats were placed on the high-fat control diet for an additional 15 days, after which all rats were assessed

for the formation of colonic ACF (i.e. 45 days after the initial intraperitoneal injection). Body weights were not affected by the diets. ACF was present only in the rats that had been initiated with azoxymethane (Parnaud et al., 2000). [The duration of this experiment (45 days) was probably not sufficient to determine if the diets by themselves were tumorigenic.]

An additional experiment was conducted that focused on the promotion of ACF by various low-fat diets. Female F344 rats (age, 4 weeks) were treated with a single intraperitoneal injection of azoxymethane at a dose of 20 mg/kg bw. One week later, groups of 10 rats were randomly transferred to either an AIN-76–based control diet consisting of 2% corn oil, 5% lard, and 25% casein [the AIN-76A diet contains calcium at a concentration of 5.2 g of calcium per /kg diet] or one of four experimental diets containing 30% low-fat beef (hamburger), pork, lean bacon, or chicken (fillet). Each meat was cooked as described in Parnaud et al. (1998). The meat diets were supplemented with casein to reach 25% protein, and with lard (for bacon and pork diets) or chicken fat (for the chicken diet) to adjust the fat content. Rats fed the low-fat meat diets weighed significantly more (7–8%) than those fed the low-fat control diet. The rats continued on their respective diets for 100 days after azoxymethane initiation and then were assessed for ACF. Statistical analyses were conducted. The number of ACF per rat did not vary significantly among the diet groups. The multiplicity of ACF was lowest in the rats fed the low-fat bacon diet compared with the low-fat control rats: multiplicity was 17% lower ($P < 0.01$), and the number of large ACF (more than seven crypts per focus) was 44% lower ($P = 0.003$). The beef, pork, and chicken diets did not have any effect on the multiplicity of ACF (Parnaud et al., 2000).

Groups of Wistar rats (age, 13 weeks) [sex not reported] were placed on one of six modified AIN-93 diets containing 8%, 16%, or 32% red meat protein or 8%, 16%, or 32% whey protein. The meat for the diets was obtained from barbecued kangaroo muscle, which was dried at 45 °C and milled to give the product 78% protein, 15.3% fat, and 1% moisture. The whey protein concentrate contained 78% protein, 8.3% fat, 4.9% lactose, and 4.2% moisture. Both protein sources were added to the diets at 10.25%, 20.5%, or 41%. The diets were low in calcium (0.1%) and fibre (2%), and fat was adjusted to 20% by the addition of sunflower seed oil. [Each group presumably consisted of 12 rats, although this was not stated explicitly.] Four weeks after being placed on their respective diets, all rats were treated with two weekly subcutaneous injections of azoxymethane at a dose of 15 mg/kg bw. [The specific diets may have affected metabolism of the DMH.] After an additional 8 weeks on the diets, the rats were killed to assess the extent of aberrant crypt formation. Statistical analyses were conducted. The final body weights of the rats fed the 32% whey protein diet were less than the body weights of those fed the 8%, 16%, or 32% red meat protein diet or 8% or 16% whey protein diet. The number of single ACF in the proximal colon was lower in rats fed the 32% whey protein diet ($P < 0.05$) than in those fed the 16% or 32% red meat protein diet (Belobrajdic et al., 2003). [Whey protein has been reported to have chemopreventive activity; as such, it may not have been the proper control for purpose of comparisons. In addition, single ACF may have limited predictive value for colon carcinogenesis (Magnuson et al., 1993).]

Male Sprague-Dawley rats (weight, 50–75 g) were treated by intragastric gavage once per week for 2 weeks with DMH at a dose of 15 mg/kg bw. One week after the second DMH treatment, the rats (14 per group) were placed on one of four modified AIN-93G diets. The diets contained calcium at a concentration of 5.1 g/kg diet. A 2 × 2 factorial design was used, with the factors being the protein source (casein or beef) and fat source (soybean oil or tallow). The beef was cooked in an oven at 93 °C, which is a temperature that minimizes HAA formation, for 2 hours.

It was then freeze-dried, minced, and mixed with the other diet components. All of the diets were balanced with respect to the protein (20%) and fat (15%) content. The extent of colonic ACF formation was assessed 9 weeks after the rats began their respective diets. Statistical analyses were conducted. Rats fed tallow as the fat source had fewer ACF per cm^2 than those fed soybean oil as the fat source ($P = 0.043$). The source of protein (casein or beef) did not affect the extent or multiplicity of ACF (Khil & Gallaher, 2004).

Female F344 rats (age, 5 weeks) were placed on a modified AIN-76 control diet. One week later, all the rats were treated with a single intraperitoneal injection of azoxymethane at a dose of 20 mg/kg bw. One week after the azoxymethane injection, 10 rats per group were transferred to one of four modified AIN-76 diets: a diet containing skinless chicken meat (600 g/kg diet), beef meat (600 g/kg diet), black pudding (blood sausage; 600 g/kg diet), or powdered bovine haemoglobin (6.3 g/kg diet). Each of the meats was freeze-dried before being added to the diets. [The authors did not indicate if the meats had been cooked.] Twenty rats continued on the control diet. All the diets were balanced for protein (50%), fat (20%), calcium (800 mg/kg diet), and iron (140 mg/kg diet, except for the black pudding diet) by the addition of casein, lard, calcium phosphate, and ferric citrate. [The protein content of the diets was approximately three times that typically used in rodent diets.] Ferric citrate was not added to the haemoglobin diet because the iron content was already 950 mg/kg diet. The rats continued on the diets for 100 days, at which time their colons were examined for ACF and mucin-depleted foci (MDF). Statistical analyses were conducted. Rats from the beef-fed group weighed significantly more (~5–10%) than those from the other groups; the body weights of the rats from the other groups did not differ (Pierre et al., 2004).

Rats fed the experimental diets had more ACF per colon ($P < 0.05$) and aberrant crypts per colon ($P < 0.05$) than rats fed the control diet. Rats fed the black pudding diet had more ACF per colon ($P < 0.05$) than rats fed the chicken diet. Rats fed the beef, haemoglobin, and black pudding diets had more MDF per colon and mucin-depleted crypts per colon than rats fed the control diet ($P < 0.05$). Rats fed the black pudding diet also had more MDF per colon and mucin-depeleted crypts per colon than rats fed the chicken or beef diet ($P < 0.05$) (Pierre et al., 2004).

Female F344 rats (age, 5 weeks) were placed on a modified AIN-76 control diet for an unspecified acclimation period before being treated with a single intraperitoneal injection of DMH at a dose of 190 mg/kg bw. One week after the DMH injection, 10 rats continued on the low-calcium control diet, while 10 rats per group were transferred to one of seven modified AIN-76 diets: a low-calcium, beef meat diet; a high-calcium control diet; a high-calcium, beef meat diet; an olive oil–fortified control diet; an olive oil–fortified, beef meat diet; an antioxidant-fortified control diet; and an antioxidant-fortified, beef meat diet. The beef meat diets contained freeze-dried meat (60%) with haem (600 nmol/kg meat). [The authors did not indicate if the meats had been cooked.] The low-calcium diets contained dibasic calcium phosphate at a concentration of 2.7 g/kg diet, and the high-calcium diets contained calcium phosphate at a concentration of 31 g/kg diet. The olive oil diet contained olive oil at a concentration of 50 g/kg diet, and replaced an equal amount of safflower oil contained in the other diets. The antioxidant diet contained rutin at a concentration of 500 mg/kg diet and butylated hydroxyanisole at a concentration of 500 mg/kg diet. All the diets were balanced for protein (50%), fat (20%), and iron (110 mg/kg diet) by the addition of casein, lard, and ferric citrate. [The protein content of the diets was approximately three times that typically used in rodent diets.] The rats continued on the diets for 99–100 days, at which

time their colons were examined for ACF and MDF. Statistical analyses were conducted. Body weights and food intake did not differ among the groups (Pierre et al., 2008).

The total number of aberrant crypt foci per colon, aberrant crypts per colon, mucin-depleted foci per colon, and mucin-depleted crypts per colon was higher in the beef diet groups (except for the beef plus high-calcium group) than in their respective control groups ($P < 0.05$). Furthermore, the number of each of these lesions was significantly higher in the high-calcium control diet group than in the other control diet groups.

Female F344 rats (age, 4 weeks) were fed a modified AIN-76 control diet. One week later, all 20 rats were treated with a single intraperitoneal injection of DMH at a dose of 190 mg/kg bw. One week after the DMH injection, 10 of the rats were transferred to a diet containing freeze-dried ham at a concentration of 550 g/kg diet (11.5% fat), while the remaining rats continued on the control diet. The diets were balanced for protein (50%), fat (21%), calcium (800 mg/kg diet), and iron (140 mg/kg diet) by the addition of casein, lard, calcium phosphate, and ferric citrate. [The protein content of the diets was approximately three times that typically used in rodent diets.] The ham diet provided haem at a concentration of 36 nmol/g diet. The rats continued on the diets for 100 days, at which time their colons were examined for ACF and MDF. Statistical analyses were conducted. Body weights did not differ among the diet groups. Rats fed the ham diet drank more water than rats fed the control diet. Rats fed the ham diet also had significantly more ACF and MDF per colon than rats fed the control diet ($P < 0.05$). There was no difference in the size (crypts per foci) of the ACF or MDF among the diet groups (Pierre et al., 2010).

Female F344 rats (age, 5 weeks) were placed on a standard AIN-76 diet. After a 5-day acclimation period, they were treated with a single intraperitoneal injection of DMH at a dose of 180 mg/kg bw. Seven days after being injected, groups of 10 rats were transferred to one of four experimental diets: dark cooked meat with nitrite, oxidized; dark cooked meat with nitrite, anaerobic; dark cooked meat, oxidized; and dark raw meat, anaerobic. Ten additional rats remained on the AIN-76 control diet. The dark meat was supraspinatus and infraspinatus pig muscle that contained 15–17 mg of haem per 100 g of tissue. The cooked meat was heated at 70 °C, and the raw meat was heated at 50 °C for 1 hour under vacuum to denature the myoglobin and free the haem. The nitrite-treated meat contained 2 g of NaCl (600 mg of sodium nitrite per 100 g of salt) per 100 g of meat. The anaerobic meat was packaged immediately in vacuum-sealed, low–oxygen permeability bags. Each of the diets contained low calcium (calcium phosphate at 2.7 g/kg diet) and contained 5 g of safflower oil per 100 g diet. The diets were balanced for protein (40%) and fat (15%). [The protein content of the diets was approximately twice that typically used in rodent diets.] The rats continued on the diets for 98–99 days, at which time their colons were examined for ACF and MDF. Statistical analyses were conducted. Body weights did not differ among the groups (Santarelli et al., 2010).

Rats fed the meat diets had a significantly increased number of ACF per colon and aberrant crypts per colon compared with rats fed the control diet. [Only the ACF per colon data were presented in the paper.] Rats fed the dark cooked meat with nitrite, oxidized diet had significantly more MDF per colon and mucin-depleted crypts per colon than rats fed the control diet ($P < 0.05$). Rats fed the dark cooked meat with nitrite, oxidized diet had more crypts per MDF and mucin-depleted crypts per colon than rats fed the dark cooked meat with nitrite, anaerobic diet ($P < 0.05$), which suggested that oxidized meat promoted the formation of MDF. Similarly, rats

fed the dark cooked meat with nitrite, oxidized diet had more mucin-depleted crypts per colon than rats fed the dark cooked meat, oxidized diet, which suggested that nitrite promoted the formation of MDF ($P < 0.05$) (Santarelli et al., 2010).

Female F344 rats (age, 5 weeks) were placed on a standard AIN-76 semipurified diet for an unspecified acclimation period before being treated with a single intraperitoneal injection of DMH at a dose of 180 mg/kg bw. One week after the DMH injection, 16 rats were transferred to a modified AIN-76 diet containing 47% (dry weight) moist, cured, dark cooked meat with nitrite, oxidized by air. The meat was prepared from dark red supraspinatus pig muscle (15–17 mg of haem per 100 g of meat) that had been cured with 2 g of salt (600 mg of sodium nitrite per 100 g of salt) per 100 g of meat and 360 mg of sodium erythorbate per 100 g of meat. The meat was heated under vacuum at 70 °C for 1 hour and then exposed in the dark to air at 4 °C for 5 days. An additional 10 rats were fed the same modified AIN-76 diet, but fortified with 0.05% α-tocopherol (added during the curing process), while 10 additional rats were fed the same modified AIN-76 diet, but fortified with 1.5 g of calcium carbonate per 100 g diet, replacing an equivalent amount of casein. The rats continued on the diets for 98–99 days, at which time their colons were examined for ACF and MDF. Statistical analyses were conducted. Body weights and food intake did not differ among the groups (Pierre et al., 2013).

Rats fed the cured, dark cooked meat with nitrite, oxidized by air diet had significantly more MDF than rats fed the same diet fortified with either α-tocopherol or calcium carbonate ($P < 0.05$). Neither the number of ACF per colon nor the size of the MDF was affected by α-tocopherol or calcium carbonate (Pierre et al., 2013). [All rats were fed a diet containing cured, dark cooked meat with oxidized nitrite; thus, the effect of meat on promoting DMH-induced lesions could not be determined.]

Female F344 rats (age, 5 weeks) were fed a standard AIN-76 diet. After a 5-day acclimation period, they were treated with a single intraperitoneal injection of DMH at a dose of 180 mg/kg bw. Seven days after being injected, groups of 10 rats were transferred to one of two experimental diets: a low-calcium (700 mg of calcium phosphate per 100 g diet) modified AIN-76 diet containing 40% hot dog meat or a low-calcium (700 mg of calcium phosphate per 100 g diet) modified AIN-76 diet containing 50% French saucisson (fermented, raw, dry sausage). [Both products were made entirely from pork.] Ten additional rats remained on the AIN-76 control diet. The diets were balanced for protein, fat, and iron by the addition of casein, lard, and ferric citrate. The rats continued on the diets for 98–99 days, at which time their colons were examined for MDF. Body weights did not differ among the groups. Rats fed the low-calcium hot dog diet had more MDF per colon and mucin-depleted crypts per colon compared with rats fed the low-calcium control diet ($P < 0.05$). The number of MDF was not increased in rats fed the saucisson diet. The number of ACF was not altered by either of the experimental diets (Santarelli et al., 2013).

In a second experiment that focused on protection rather than tumour promotion, 10 rats were fed the hot dog diet with 500 mg calcium phosphate per 100 g diet, while an additional 10 rats were fed the hot dog diet fortified with 1.5 g of calcium carbonate per 100 g diet. All other aspects were identical to the first tumour-promotion experiment. Body weights did not differ among the groups. Rats fed the hot dog diet fortified with calcium carbonate had a decrease in the number of MDF compared with rats fed the hot dog diet without calcium carbonate ($P < 0.05$) (Santarelli et al., 2013).

3.3 Haem iron

The promotion of colon carcinogenesis by haem iron was observed in two studies. In the first study, male and female *Apc*$^{Min/+}$mice (age, 4 weeks) were given a diet containing 0% (control) or 2.5% haemoglobin for 49 days. Compared with the control diet, the haemoglobin diet significantly increased the intestinal tumour [not further specified] load (114 ± 47 mm^2 vs 67 ± 39 mm^2; $P = 0.004$), the number of tumours in the jejunum ($P < 0.001$), and the number of tumours with a diameter greater than 1 mm ($P < 0.05$). However, the haemoglobin diet did not produce any tumours in wildtype C57BL/6J *Apc*$^{+/+}$ mice (Bastide et al., 2015). In the second study, F344 female rats (age, 7 weeks) were given 2 mg of *N*-methyl-*N*-nitrosourea intrarectally (six times) during the initial 2 weeks, and then fed a diet containing 0% (control) or 3% haemoglobin for 36 weeks. The number of rats with adenomas or adenocarcinomas (combined) in the colon was significantly higher in rats fed the haemoglobin diet than in those fed the control diet ($P < 0.05$) (Sawa et al., 1998).

In another study, male and female A/J$^{Min/+}$ mice (age, 3 weeks) were fed a low-calcium and low vitamin D, semisynthetic diet containing 0.5 µmol/g of hemin chloride and/or 2.8 µmol/g of sodium nitrite for 8 weeks after weaning. Mice fed the hemin chloride diet (10 males, 11 females) had a lower number of tumours ($P = 0.02$) and tumour load (mm^2 per mouse; $P = 0.019$) in the colon than mice fed the control diet (9 males, 10 females). In the small intestine, dietary hemin chloride increased the tumour size (mm^2 per group; $P < 0.001$). In addition, hemin chloride in combination with sodium nitrite had no effect on tumour development in the colon or small intestine of A/J$^{Min/+}$ mice (Sødring et al., 2015). [The Working Group noted that hemin chloride is a toxic chemical that is not present in food (see Section 4.2.6.]

In a study of male C57Bl/6 mice (age, ~8 weeks) fed a diet containing 0.2 µmol/g of hemin for 18 months, no induction of colon tumours was observed (Winter et al., 2014).

3.4 Overview of cancer bioassays for chemicals related to meat consumption

3.4.1 Heterocyclic aromatic amines

HAAs are foodborne carcinogens formed by pyrolysis of creatine, amino acids, and sugars, which are natural components of protein-rich foods, at normal cooking temperatures (Wakabayashi et al., 1992). More than 20 HAAs have been identified.

Among them, 2-amino-3-methylimidazo-[4,5-*f*]quinoline (IQ), 2-amino-3,4-dimethyl-imidazo[4,5-*f*]quinoline (MeIQ), 2-amino-3,8-dimethylimidazo[4,5-*f*]quinoxaline (MeIQx), 2-amino-1-methyl-6-phenylimidazo[4,5-*b*] pyridine (PhIP), 3-amino-1,4-dimethyl-5*H*-pyrido[4,3-*b*]indole (Trp-P-1), 3-amino-1-methyl-5*H*-pyrido[4,3-*b*]indole (Trp-P-2), 2-amino-9*H*-pyrido[2,3-*b*]indole (AαC), 2-amino-3-methyl-9*H*-pyrido[2,3-*b*]indole (MeAαC), and 2-amino-3,4,8-trimethylimidazo[4,5-*f*]quinoxaline (4,8-DiMeIQx) have been found in cooked red meat and processed meat (Wakabayashi et al., 1992; Johansson & Jägerstad, 1994). With the exception of 4,8-DiMeIQx, which was never evaluated, these HAAs have been evaluated by the *IARC Monographs* as having *sufficient evidence* of carcinogenicity in experimental animals (IARC, 1983, 1986, 1993). Studies reporting the carcinogenicity of these nine HAAs in experimental animals are summarized in this section.

(a) IQ

(i) Mouse

Male and female CDF1 mice (age, 7 weeks) fed a diet containing 0.03% IQ for 96 weeks had a higher incidence of hepatocellular adenoma or carcinoma (combined) compared with mice fed a control diet. In addition, the incidences of adenoma or adenocarcinoma (combined) of the lung, and of papilloma or squamous cell carcinoma (combined) of the forestomach were significantly higher in mice fed the IQ diet than in mice fed the control diet (Ohgaki et al., 1984a; IARC, 1993).

(ii) Rat

Male and female Fischer 344 rats (age, 8 weeks) fed a diet containing 0.03% IQ for either 55 weeks or 72 weeks had significantly increased incidences of hepatocellular carcinoma, Zymbal gland squamous cell carcinoma, colon adenocarcinoma, and small intestine adenocarcinoma. (Takayama et al., 1984; IARC, 1993).

When female Sprague-Dawley rats (age, 6 weeks) were given IQ at a dose of 0.35 mmol/kg bw by gavage three times per week during experimental weeks 1–4, twice per week during weeks 5–8, and once per week during weeks 9–31, and continued without treatment until being killed at week 52, the incidences of adenocarcinoma of the mammary gland, tumours of the liver, and squamous cell carcinoma of the Zymbal gland significantly increased (Tanaka et al., 1985; IARC, 1993).

(iii) Monkey

Male and female cynomolgus monkeys (age, 1 year) were given IQ at doses of 10 mg/kg bw (14 males, 6 females) and 20 mg/kg bw (8 males, 12 females) by gavage five times per week for up to 60 months. Hepatocellular carcinoma was observed in three (3 males) monkeys in the low-dose group and in ten (6 males, 4 females) monkeys in the high-dose group. Metastases in the lung and omentum were also observed. No such tumours occurred in more than 300 monkeys in a colony control (Adamson et al., 1990, 1991; IARC, 1993).

(b) MeIQ

(i) Mouse

In male and female CDF1 mice (age, 6 weeks) fed a diet containing 0.01% or 0.04% MeIQ for 91 weeks, the incidence of hepatocellular adenoma or carcinoma (combined) significantly increased in female mice, and the incidence of forestomach papilloma or carcinoma (combined) significantly increased in both males and females. Many of the mice with squamous cell carcinoma of the forestomach demonstrated metastasis to the liver (Ohgaki et al., 1986; IARC, 1993).

(ii) Rat

In male and female Fischer 344 rats (age, 6 weeks) fed a diet containing 0.03% MeIQ for 40 weeks, the incidence of Zymbal gland tumours (most of these tumours were squamous cell carcinoma) significantly increased. Furthermore, the incidences of oral cavity tumours (squamous cell carcinoma or sebaceous squamous cell carcinoma), colon tumours (adenoma or adenocarcinoma), skin tumours (mainly squamous cell carcinoma), and mammary gland tumours (mostly adenocarcinoma) significantly increased (Kato et al., 1989; IARC, 1993).

In male Wistar rats (age, 6 weeks) given MeIQ at a dose of 10 mg/kg bw by gavage every day for 2 weeks, the incidence of Zymbal gland adenoma or carcinoma (combined) significantly increased after 58 weeks (Kristiansen et al., 1989; IARC, 1993).

(c) MeIQx

(i) Mouse

Male and female CDF1 mice (age, 6 weeks) were fed a diet containing 0% (control) or 0.06% MeIQx for 84 weeks. The incidences of hepatocellular adenoma or carcinoma (combined),

lung adenoma and adenocarcinoma (combined), and lymphoma or leukaemia (combined) significantly increased in mice fed the MeIQx diet compared with mice fed the control diet (Ohgaki et al., 1987; IARC, 1993).

In male *c-myc/λlacZ* mice (at weaning) fed a diet containing 0.06% MeIQx for 40 weeks, the incidence of hepatocellular carcinoma was significantly increased compared with *c-myc/λlacZ* mice fed a control diet and C57B1/*λlacZ* mice fed an MeIQx diet (Ryu et al., 1999).

(ii) Rat

In male and female Fischer 344 rats (age, 7 weeks) fed a diet containing 0.04% MeIQx for 61 weeks, the incidences of tumours of the liver (hepatocellular carcinomas or neoplastic nodules, combined) and Zymbal gland squamous cell carcinoma or papilloma (combined) significantly increased. The incidences of clitoral gland squamous cell carcinoma in females and skin tumours (squamous cell carcinoma, basal cell carcinoma, and squamous cell papilloma in males also significantly increased (Kato et al., 1988; IARC, 1993).

(d) PhIP

(i) Mouse

In male and female CDF1 mice (age, 6 weeks) fed a diet containing 0.04% PhIP for 82 weeks, the incidence of lymphoma significantly increased (Esumi et al., 1989; IARC, 1993).

Male and female Eμ-*pim*-1 transgenic mice (a strain predisposed to the development of T-cell lymphoma) and non-transgenic wildtype littermates (age, 9–12 weeks) were fed a diet containing 0.03% PhIP for 31 weeks. PhIP feeding significantly increased the incidence of lymphoma in the female Eμ-*pim*-1 transgenic mice (Sørensen et al., 1996).

Groups of male and female C57BL/6J-*Min*/+ pups were exposed for 3–6 days to breast milk from dams given eight subcutaneous injections of PhIP at a dose of 50 mg/kg, or were given a single subcutaneous injection of PhIP at a dose of 25 or 50 mg/kg. The mice were killed at age 11 weeks. Untreated pups were used as negative controls. The number of tumours of the small intestine was higher in the female pups exposed to breast milk and in the male and female pups subcutaneously injected with PhIP than in the untreated pups (Andreassen et al., 2001, 2002).

In male and female *Apc*1638N mice (age, 4 weeks) fed a diet containing 0.03% PhIP for 32 weeks, a significantly higher number of small intestine tumours (adenoma or adenocarcinoma, combined) was observed in males (Sørensen et al., 1997).

In male and female *Xpa* knockout mice [which lack a nucleotide excision repair system component] (age, 7–9 weeks) fed a diet containing 0.001% or 0.0025% PhIP for 6 months, and subsequently maintained on a normal diet for another 6 months, the incidences of lymphoma and intestinal tumours (combined) were significantly increased when both sexes were combined (Klein et al., 2001). [The Working Group noted the small number of animals.]

(ii) Rat

In male and female Fischer 344 rats (age, 6 weeks) fed a diet containing 0% (control) or 0.04% PhIP for 52 weeks, the incidence of colon adenocarcinoma was significantly higher in males fed the PhIP diet. In addition, the incidence of mammary gland adenocarcinoma was significantly higher in females, and the incidence of prostate carcinoma was significantly higher in males (Ito et al., 1991; IARC, 1993; Shirai et al., 1997).

Groups of female Sprague-Dawley rats (age, 6 weeks) were given PhIP at a dose of 0 (control) or 100 mg/kg bw by gavage twice per week for 4 weeks. All rats were killed at week 48, and there was an increased incidence of mammary gland carcinoma in the PhIP rats compared with the control rats (Kitamura et al., 2006).

(e) Trp-P-1 and Trp-P-2

(i) Mouse and rat

3-Amino-1,4-dimethyl-5H-pyrido[4,3-*b*]indole (Trp-P-1) and 3-amino-1-methyl-5H-pyrido[4,3-*b*]indole (Trp-P-2) were tested for carcinogenicity in male and female CDF1 mice, as well as in male and female F344 rats (age, 5–8 weeks). The incidence of liver tumours (mostly hepatocellular carcinoma) increased significantly in female mice and male and female rats after oral administration of 0.01–0.02% Trp-P-1, as well as in female mice and male rats after oral administration of 0.01–0.02% Trp-P-2 for 52–112 weeks. Oral administration of Trp-P-2 also significantly increased the incidence of urinary bladder transitional cell papilloma and carcinoma (combined [mainly papilloma]) in male rats (Matsukura et al., 1981; IARC, 1983; Takayama et al., 1985; Takahashi et al., 1993).

(ii) Hamster

Two groups of female Syrian golden hamsters (age, ~6 weeks) were given a single subcutaneous injection of *N*-nitrosobis(2-oxopropyl)amine (BOP) at a dose of 30 mg/kg, followed by two cycles of augmentation pressure; augmentation pressure consisted of four daily intraperitoneal injections of 500 mg/kg of DL-ethionine, a choline-deficient diet, a single intraperitoneal injection of 800 mg/kg of L-methionine, and a subcutaneous injection of BOP at a dose of 20 mg/kg. One group of hamsters was then fed a diet containing 0.02% Trp-P-1 for 50 days, while the other group was fed a basal diet. The number of invasive pancreatic ductal carcinomas was significantly higher in the Trp-P-1 group than in the control group (Mizumoto et al., 1988; Yoshimoto et al., 1999).

(f) AαC and MeAαC

(i) Mouse

In male and female CDF1 mice (age, not reported) fed a diet containing 0.08% 2-amino-9*H*-pyrido[2,3-*b*]indole (AαC) or 0.08% 2-amino-3-methyl-9*H*-pyrido[2,3-*b*]indole (MeAαC) for 73–98 weeks, the incidences of hepatocellular adenoma or carcinoma (combined) and vascular system tumours (primarily haemangioendothelial sarcoma) significantly increased with both test agents in male and female mice (Ohgaki et al., 1984b; IARC, 1986).

(ii) Rat

In groups of male F344 rats (age, 6 weeks) fed a diet containing 0.01–0.02% MeAαC for 100 weeks, the incidences of hepatocellular carcinoma, pancreatic acinar cell adenoma, and fibroma of the subcutis significantly increased (Tamano et al., 1994).

(g) 4,8-DiMeIQx

(i) Hamster

Two groups of female Syrian golden hamsters (age, not reported) were initiated with a single subcutaneous injection of BOP at a dose of 30 mg/kg followed by two cycles of augmentation pressure. The hamsters were then fed a diet containing 0% (control) or 0.06% 4,8-DiMeIQx for 50 days. The number of invasive pancreatic ductal carcinomas was significantly higher in the 4,8-DiMeIQx group than in the control group (Yoshimoto et al., 1999).

(h) Combined treatment with HAAs

Male and female F344 rats (age, 6 weeks) were given diets containing five HAAs – 0.003% Trp-P-1, 0.004% Trp-P-2, 0.006% IQ, 0.01% 2-aminodipyridol[1,2-*a*:3′,2′-*d*]imidazole (Glu-P-2), and 0.016% AαC – for 722 days. The incidences of liver tumours (primarily hepatocellular carcinoma), Zymbal gland squamous cell carcinoma, and colon adenocarcinoma in

both sexes; skin squamous cell carcinoma in males; and clitoral gland squamous cell carcinoma in females significantly increased in the HAA group compared with the control group (Takayama et al., 1987).

3.4.2 Polycyclic aromatic hydrocarbons

The Working Group has previously reviewed the evidence for the carcinogenicity of 60 non-heterocyclic polycyclic aromatic hydrocarbons (PAHs) in experimental animals (*IARC Monographs* Volume 92; IARC, 2010a). Most of the data were from studies in mice, rats, or hamsters, and the most common routes of administration were cutaneous application, intraperitoneal injection, or addition to the diet, with sites of tumorigenesis usually dependent on the route of administration. Cutaneous application often resulted in skin tumours, and intraperitoneal injection usually resulted in liver and lung tumours. Benzo[*a*]pyrene (BaP), when administered orally, produced tumours of the oral cavity, gastrointestinal tract, liver, lung, and mammary gland in mice and rats (IARC, 2010a).

The following PAHs have been identified in meat products: benz[*a*]anthracene, benzo[*b*]fluoranthene, benzo[*j*]fluoranthene, benzo[*k*]fluoranthene, benzo[*c*]fluorene, benzo[*ghi*]perylene, benzo[*a*]pyrene, chrysene, cyclopenta[*cd*]pyrene, dibenz[*a,h*]anthracene, dibenzo[*a,e*]pyrene, dibenzo[*a,h*]pyrene, dibenzo[*a,i*]pyrene, dibenzo[*a,l*]pyrene, indeno[1,2,3-*cd*]pyrene, and 5-methylchrysene (see Section 1).

The *IARC Monographs* Volume 92 Working Group (IARC, 2010a) concluded that, for the following PAHs found in meat products, there was *sufficient evidence* in experimental animals for the carcinogenicity of benz[*a*]anthracene, benzo[*b*]fluoranthene, benzo[*j*]fluoranthene, benzo[*k*]fluoranthene, benzo[*a*]pyrene, chrysene, cyclopenta[*cd*]pyrene, dibenz[*a,h*]anthracene, dibenzo[*a,h*]pyrene, dibenzo[*a,i*]pyrene, dibenzo[*a,l*]pyrene, indeno[1,2,3-*cd*]pyrene, and 5-methylchrysene. They further concluded that there was limited evidence in experimental animals for the carcinogenicity of benzo[*c*]fluorene and dibenzo[*a,e*]pyrene (IARC, 2010a). No new data released since this review would lead to changing the evaluation of the carcinogenicity in experimental animals for any of these PAHs with a prior evaluation of *limited evidence* were available to the Working Group.

PAHs that were tested by oral administration in experimental animals and identified in meat products include benz[*a*]anthracene, benzo[*c*]fluorene, benzo[*a*]pyrene, dibenz[*a,h*]anthracene, and dibenzo[*a,l*]pyrene (IARC, 2010a).

As an example, two recent oral administration studies of benzo[*a*]pyrene (BaP) are summarized below.

Groups of female B6C3F$_1$ mice (age, 5 weeks) were fed diets containing BaP at concentrations of 0, 5, 25, and 100 ppm for 2 years (Culp et al., 1998; IARC, 2012). Statistically significant increases in the incidences of tumours of the forestomach, oesophagus, tongue, and larynx were reported. Tumours at all sites were reported to be papillomas or squamous cell carcinomas.

In another study, BaP was administered to groups of male and female Wistar rats (age, 6 weeks) by gavage five times per week for 98 weeks at doses of 0, 3, 10, or 30 mg/kg bw per day (Wester et al., 2012). [Although the authors reported using statistical analyses in the Methods section, none were described for specific tumour end-points.] Significant increases in the incidences of oral tumours (papilloma and squamous cell carcinoma), forestomach tumours (papilloma and squamous cell carcinoma), hepatocellular adenoma and carcinoma, and auditory canal carcinoma in males and females were reported. The incidences of small intestine (jejunum) adenocarcinoma and kidney cortical adenoma also increased in males.

3.4.3 N-*Nitroso compounds*

Eight *N*-nitroso compounds (NOCs) have been detected in meat: *N*-nitrosodi-*n*-butylamine (NDBA), *N*-nitrosodiethylamine (NDEA), *N*-nitrosodimethylamine (NDMA), *N*-nitrosomethylethylamine (NMEA), *N*-nitrosopiperidine (NPIP), *N*-nitrosoproline (NPRO), *N*-nitrosohydroxyproline (NHPRO), and *N*-nitrosopyrrolidine (NYPR) (see Section 1). Of these, the *IARC Monographs* evaluation of carcinogenicity in experimental animals was that there is *inadequate evidence* for NPRO and NHPRO, while there is *sufficient evidence* for the others (IARC, 1978).

A brief summary of the relevant oral administration studies in experimental animals follows (IARC, 1978).

NDBA has been administered orally in lifetime studies of mice, rats, hamsters, and guinea-pigs. Tumour formation was both species- and strain-dependent, with the most common sites being the stomach, liver, oesophagus, and urinary bladder.

NDEA has been fed to mice, rats, hamsters, guinea-pigs, rabbits, dogs, pigs, and monkeys. It induced tumours in all species when fed at doses of 1–13 mg/kg bw per day for life. Tumours of many different types in various organs were reported, with the most common sites being the liver, oesophagus, forestomach, trachea, and lung.

NDMA has been administered orally to mice, rats, hamsters, guinea-pigs, rabbits, and fish. All species were susceptible to increased tumour formation at doses of 0.4–4 mg/kg bw per day. Tumours of the liver were the most prevalent followed by tumours of the lung.

NMEA has only been tested in rats and administered in drinking-water at 1–2 mg/kg bw, which resulted in 9 of 15 treated animals developing hepatocellular carcinoma over an average induction time of 500 days.

NPIP has been fed to mice at dose of 50 mg/kg diet, and rats at doses of 5 and 20 mg/kg bw per day. Mice fed NPIP developed squamous cell carcinomas of the forestomach (18/24), liver tumours (11/24), and lung tumours. Most rats fed the higher dose (20 mg/kg bw per day) died early without tumours. However, those fed the lower dose (5 mg/kg bw per day) developed oesophageal tumours (9/10) and liver tumours.

NPRO has been tested orally in mice. The mice were exposed to NPRO at a concentration of 0.05% or 0.1% in drinking-water for 26 weeks. NPRO or NHPRO has been tested in rats. The rats were exposed to NPRO or NHPRO at a concentration of 0.015% in drinking-water for 75 weeks. For both species, there was no increase in tumour incidence compared with controls.

NYPR has been given to mice at a concentration of 0.01% in drinking-water; however, most mice died early and no increase in tumour incidence was reported. NYPR has also been given at doses of 0.3–20 mg/kg bw per day in many studies in rats. The majority of the studies found that rats developed hepatocellular carcinoma at doses of 1 mg/kg bw per day or higher. A dose–response study found no increase in the incidence of hepatocellular carcinomas with NYPR at 0.3 mg/kg bw per day. However, with NYPR at 1, 3, or 10 mg/kg bw per day, there were 13/62, 30/38, and 9/24 animals with hepatocellular carcinoma, respectively.

The Working Group has previously evaluated the carcinogenic risks of ingested nitrate and nitrite (*IARC Monographs* Volume 94; IARC, 2010b). The Working Group concluded that there was inadequate evidence of carcinogenicity in mice or rats for nitrate administered in drinking-water or diet. One reviewed study showed that nitrate promoted urinary bladder carcinogenesis in rats previously initiated with *N*-butyl-*N*-(4-hydroxybutyl)-nitrosamine. In most of the reviewed studies, nitrite alone in the drinking-water or diet of rats or mice did

not increase the incidence of tumours compared with untreated controls. However, when nitrite in drinking-water or diet was given along with specific secondary or tertiary amines or amides to either mice or rats, there was an increase in tumour incidence. A similar finding was also reported in hamsters. The Working Group concluded that there was *inadequate evidence* in experimental animals for the carcinogenicity of nitrate; there was *sufficient evidence* in experimental animals for the carcinogenicity of nitrite in combination with amines or amides; and there was *limited evidence* in experimental animals for the carcinogenicity of nitrite per se. Target sites with increased tumorigenesis after exposure to nitrite in combination with various amines or amides, which are carcinogens by themselves, included the lung, forestomach, uterus, testicle, and lympho-haematopoietic system.

3.4.4 Others

(a) Advanced glycation end-products

No data were available to the Working Group.

(b) N-Glycolylneuraminic acid (Neu5Gc)

In a single study, CMP-*N*-acetylneuraminic acid (Neu5Ac) hydroxylase gene knockout male mice (*Cmah*$^{-/-}$) of a C57BL/6 background (so that they are unable to produce *N*-glycolylneuraminic acid, Neu5Gc) were immunized against Neu5Gc by injection and were fed Neu5Gc at a dose of 0.25 mg/g food. Neu5Gc derived from porcine submaxillary was fed to these mice for 80–85 weeks. Hepatocellular carcinoma was reported in 8 of the 17 mice in the *Cmah*$^{-/-}$ group immunized against Neu5Gc compared with 1 of the 14 knockout mice immunized against Neu5Ac [$P \leq 0.02$, two-tailed Fisher exact test]. Wildtype mice immunized against Neu5Gc had an incidence of hepatocellular carcinoma of 0/11, and wildtype mice immunized against Neu5Ac had an incidence of hepatocellular carcinoma of 1/11 (Samraj et al., 2015).

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4. MECHANISTIC AND OTHER RELEVANT DATA

4.1 Digestion and metabolism

The composition of red meat and processed meat, as well as their potential contaminants, is described in detail in Section 1 of this *Monograph*. Red meat and processed meat are sources of high-quality protein, fat in highly variable amounts, and a range of micronutrients. The impact of the digestion of protein and fat, and the modifications that these macronutrients may undergo in the processing of meat, is addressed in this section. The specific components of red meat and processed meat, including haem iron, lipid oxidation products, heterocyclic aromatic amines (HAAs), polycyclic aromatic hydrocarbons (PAHs), and *N*-nitroso compounds (NOCs), that are potentially involved in carcinogenesis are discussed in Section 4.5.

After the hydrolytic breakdown of dietary proteins by the activity of proteases, and the absorption of the resultant amino acids and dipeptides in the proximal gut, fermentation of excess proteins may yield toxic compounds. The amount of protein that enters the colon depends on the protein content of the ingested food and the protein digestibility (Windey et al., 2012). Digestibility of dairy and animal proteins exceeds 90%, and is generally higher than the digestibility of plant proteins (70–90%). Storage and processing of meat before consumption may alter its protein digestibility. Cooking of beef affected bovine myofibrillar protein susceptibility to proteases in vitro, with increased or decreased rates depending on the nature of the proteases, and the time and temperature parameters (Santé-Lhoutellier et al., 2008). Similarly, Bax et al. (2012) reported that ageing and mincing had little impact on the in vitro digestion of pig muscle proteins, but heat treatment had temperature-dependent effects. At 70 °C, the proteins underwent denaturation, enhancing the speed of pepsin digestion by increasing enzyme accessibility to protein cleavage sites. At above 100 °C, the proteins underwent oxidation-related aggregation, slowing the speed of pepsin digestion, but improving overall meat protein digestibility. In a study of miniature pigs fed meat from a calf, the true ileal protein digestibility averaged 95%, and was not affected by cooking temperature or by the level of meat intake (Bax et al., 2013). Chemical oxidation of pig myofibrillar proteins has been shown to reduce protein digestibility in vitro (Santé-Lhoutellier et al., 2007). Overall, the impact of thermal denaturation and oxidation of meat proteins during processing and storage on their digestibility, as well as the formation of carcinogenic compounds during digestion, is not well known.

On a normal mixed diet, the amount of protein rather than the source determines the quantity that reaches the colon (Silvester & Cummings, 1995). Hence, high-meat, low-fibre diets may stimulate protein fermentation in the colon, producing short- and branched-chain

fatty acids, ammonia, phenolic and indolic compounds, and hydrogen sulfide (O'Keefe, 2008). Bacterial proteases and peptidases are more active when pH is neutral to alkaline. In the proximal colon, pH is more acidic due to the production of short-chain fatty acids, primarily from carbohydrate fermentation, but also from reductive deamination of many amino acids. In more distal parts of the colon, pH is higher and protein fermentation becomes more prominent. In relation to meat intake, ammonia and hydrogen sulfide are the most critical compounds because of their known toxicity (Attene-Ramos et al., 2007; Windey et al., 2012). Meat is rich in sulfur-containing amino acids, possibly leading to higher hydrogen sulfide concentrations in the colon. However, hydrogen sulfide in the gut originates from both the fermentation of sulfur-containing amino acids and dietary sulfate.

A diet high in red meat or processed meat may contain high levels of fat. The digestion of food lipids consists of a series of enzyme-catalysed steps resulting in absorbable components, whereby the release of bile from the gallbladder is essential. It has been suggested that dietary fat promotes the development of cancer of the colorectum (Boyle et al., 1985; Reddy, 1992). Several mechanisms have been postulated to explain this association, including the stimulating effect of high-fat intake on the secretion of secondary bile acids in the gut; this proposed mechanism has received the most attention. These bile acids may promote tumour formation by acting as aggressive surfactants on the mucosa, thus increasing cell loss and proliferation (Bruce, 1987; Owen, 1997; Bernstein et al., 2005). Other proposed mechanisms for the promoting role of dietary fat include an increase in the amount of free fatty acids in the colonic lumen, which may damage the colonic epithelium and induce cell proliferation, and an augmented risk for obesity (Calle & Kaaks, 2004). Dietary fat intake is also associated with peroxidation of unsaturated fatty acids (see Section 4.5.2).

[The Working Group noted that the digestion of red meat and processed meat provides energy and supplies essential nutrients, such as amino acids, iron, other minerals (including zinc), long-chain fatty acids, and various vitamins. At the same time, the digestion of protein and fat yields intrinsically toxic compounds. However, protein and fat are also present in dairy, fish, poultry, and other food products (Demeyer et al., 2015).]

4.2 Mechanisms of carcinogenesis

This section summarizes the evidence for the key characteristics of carcinogens (Smith et al., 2016), concerning whether red and processed meat intake is genotoxic, induces epigenetic effects, induces oxidative stress, and alters cell proliferation, cell death, and nutrient supply. Other mechanistic effects of red and processed meat intake, including whether it induces chronic inflammation and modulates receptor-mediated effects, are also addressed. Potential indirect mediators and studies of hemin and hemin chloride are summarized. Within each topic, studies are presented according to species (human and experimental systems) and test system (in vivo and in vitro), and red meat and processed meat studies are presented separately.

4.2.1 Genetic and related effects

Red meat and processed meat have been tested in studies of DNA damage, gene mutation, chromosomal damage, and epigenetic end-points. These studies are summarized in Table 4.1 to Table 4.6.

(a) Exposed humans

(i) DNA damage and DNA adducts

See Table 4.1

Regarding studies of red meat, Lewin et al. (2006) conducted a randomized crossover study in 21 human subjects fed diets that were high in red meat (420 g/day), vegetarian, or high in

Table 4.1 Genetic and related effects of red meat or processed meat in exposed humans

Tissue or body fluid	End-point	Test	Exposure	Response, significance	Reference
Colon	DNA adducts	O^6-CMG (IHC using polyclonal antibodies)	High–red meat (420 g), vegetarian, or high–red meat, high-fibre diets for 15 days (randomized crossover study) (n = 21)	+ $P < 0.0001$	Lewin et al. (2006)
Rectum	DNA adducts	O^6-MeG adducts (IHC using monoclonal antibodies)	Red meat (300 g/day) for 4 weeks (randomized crossover study) (n = 23)	+ $P < 0.01$	Le Leu et al. (2015)
Breast	DNA adducts	PhIP-DNA adducts (IHC using polyclonal antibodies)	Well-done meat consumption (assessed via questionnaire) in women (n = 49) undergoing reduction mammoplasty;	–	Zhu et al. (2003)
Breast	DNA adducts	^{32}P-postlabelling	Meat and HAA intake (assessed via FFQ) in women undergoing reduction mammoplasty (n = 44)	+ $P < 0.05$	Rohrmann et al. (2009a)
Urine	DNA adducts	8-OHdG	Barbecued pork (15 or 30 g/kg bw) (n = 13)	+ $P < 0.05$	Chien & Yeh (2010)
Colorectal carcinoma	Mutation	K-*RAS* mutation	Red meat consumption (assessed via FFQ) in colorectal cancer patients (n = 43)	–	O'Brien et al. (2000)
Colorectal carcinoma	Mutation	K-*RAS* mutation	Red meat consumption in NLCS cancer patients (n = 608)	–	Brink et al. (2005)
Colon	Mutation	K-*RAS* mutation	High–red meat (420 g), vegetarian, or high–red meat, high-fibre diets for 15 days (randomized crossover study) (n = 21)	–	Lewin et al. (2006)
Colorectal carcinoma	Mutation	*TP53* mutation	Colorectal cancer patients (n = 185) divided according to red meat consumption assessed via FFQ	+ $P = 0.01$	Park et al. (2010)
Colorectal adenoma	Mutation	*APC* mutation	Red meat consumption (assessed via FFQ) in cases with colorectal adenoma (n = 184) vs controls (n = 259)	(+)	Diergaarde et al. (2003)
Colorectal carcinoma	Mutation	*APC* mutation	Processed meat consumption (assessed via FFQ) in colorectal cancer patients (n = 185)	+ $P = 0.04$	Gay et al. (2012)

+, positive; –, negative; 8-OHdG, 8-hydroxy-2′-deoxyguanosine; FFQ, food frequency questionnaire; HAA, heterocyclic aromatic amine; IHC, immunohistochemistry; NLCS, Netherlands Cohort Study; O^6-CMG, O^6-carboxymethyl guanine; O^6-MeG, O^6-methylguanine; PhIP, 2-amino-1-methyl-6-phenylimidazo[4,5-*b*]pyridine

red meat and fibre for 15 days. Compared with vegetarian diet, red meat intake significantly increased levels of O^6-carboxymethyl guanine (O^6-CMG), a DNA adduct putatively related to NOCs, in exfoliated colon cells. This adduct was detected by immunohistochemistry using polyclonal antiobodies. [The Working Group noted the lack of specificity of this method for this particular adduct).]

Increased levels of O^6-methylguanine (O^6-MeG), also a DNA adduct putatively related to NOCs, were shown by immunohistochemistry using monoclonal antibodies in rectal biopsies of human volunteers after an intake period of 4 weeks that was high in red meat (300 g/day) in a randomized crossover study (Le Leu et al., 2015).

No statistically significant associations were found between dietary intake of well-done meat assessed by questionnaire and DNA adducts putatively related to 2-amino-1-methyl-6-phenylimidazo[4,5-*b*]pyridine (PhIP) in normal breast tissue (Zhu et al., 2003). The study included 106 women newly diagnosed with cancer of the breast, of which 49 women underwent reduction mammoplasty. PhiP-DNA adducts were assessed by immunohistochemistry using polyclonal antibodies. [The Working Group noted the lack of specificity of this method for these adducts. The type of meat was not specified.]

Fried meat [not specified] intake, assessed by food frequency questionnaire (FFQ), was significantly correlated with the presence of bulky, non-specific DNA adducts (^{32}P-postlabelling analysis) in the breast tissue of 44 women undergoing reduction mammoplasty (Rohrmann et al., 2009a).

Chien & Yeh (2010) showed that barbecued pork meat exposure increased oxidative DNA lesions in urine. They gave one meal of barbecued pork meat (reported as 15 or 30 g/kg bw) to eight or five volunteers, respectively. Statistically significant increases in urinary 8-hydroxy-2′-deoxyguanosine (8-OHdG) were observed 2 or 3 days after barbecued pork meat consumption. A correlation was found between PAH metabolites and 8-OHdG in urine (Chien & Yeh, 2010). [The Working Group noted the very high reported intake level of pork meat and of the borderline significance of the results.]

Regarding processed meat, the study by Rohrmann et al. (2009a) previously mentioned reported a significant correlation of intake (assessed by FFQ) with the presence of bulky, non-specific DNA adducts (^{32}P-postlabelling analysis) in the breast tissue of 44 women undergoing reduction mammoplasty.

(ii) Gene mutation

See Table 4.1

Regarding red meat, no association was found between K-*RAS* mutation frequency and meat consumption, assessed by FFQ, in colorectal cancer samples from 43 patients (O' Brien et al., 2000). Similarly, there was no association between tumours with K-*RAS* mutations and meat consumption in a large cohort study of 448 patients with cancer of the colon and 160 patients with cancer of the rectum from the Netherlands Cohort Study (NLCS) (Brink et al., 2005).

In the randomized crossover study by Lewin et al. (2006) previously mentioned, no K-*RAS* mutations were present in the exfoliated colon cells of volunteers fed diets that were high in red meat (420 g/day), vegetarian, or high in red meat and fibre for 15 days.

A positive association between haem iron intake and risk of cancer of the colorectum harbouring G→A transitions in K-*RAS* and *APC* genes, and TP53 overexpression was found in a prospective study (Gilsing et al., 2013). In the European Prospective Investigation into Cancer and Nutrition (EPIC) study in Norfolk, England, *TP53* mutations in cancer of the colorectum were examined in relation to dietary and lifestyle factors (Park et al., 2010). Higher daily total meat and red meat intake (assessed by FFQ) was significantly associated with harbouring *TP53* mutations in cancer of the colorectum.

In a case–control study in the Netherlands, Diergaarde et al. (2003) evaluated the association between dietary factors and *APC* mutations in sporadic colon carcinomas (184 cases, 259 controls). Direct sequencing was used to screen the mutation cluster region of *APC* in the colon tumours. Red meat intake appeared to be associated with *APC* mutated tumours: the odds ratios (ORs) for the association between the two highest tertiles (58–87 g/day and ≥ 86 g/day) of red meat intake and *APC* mutations were 1.5 (95% confidence interval, CI, 0.7–3.0) and 1.7 (95% CI, 0.8–3.6), respectively.

Regarding processed meat, analyses of *APC* mutations and *APC* promoter 1A methylation were performed on 185 archival colorectal cancer samples from participants of the EPIC-Norfolk study, with the aim of relating these to a 7-day dietary and lifestyle data collected prospectively (Gay et al., 2012). Truncating *APC* mutations and *APC* promoter 1A methylation were identified in 43% and 23% of colorectal cancer samples analysed, respectively. Cases with *APC* mutations or *APC* promoter 1A methylation consumed significantly higher levels of processed meat and iron from red meat and red meat products. In a logistic regression model adjusted for age, sex, and cigarette smoking status, each 19 g/day (one standard deviation, SD) increment increase in processed meat consumption was associated with *APC* mutations with GC→AT transitions (OR, 1.68; 95% CI, 1.03–2.75).

(iii) Faecal water genotoxicity

See Table 4.2

Rieger et al. (1999) first reported that a diet high in fat and meat increased faecal water genotoxicity (tested with comet assay in HT-29 cell cultures) in seven healthy volunteers over a period of 12 days. Compared with a diet rich in vegetables and poor in fat and meat, a diet rich in fat (total energy intake, 50%), meat, and sugar, and poor in vegetables and free of wholemeal products [no exact composition was given], significantly increased faecal water genotoxicity. [type of meat was not specified].

Faecal water genotoxicity (tested with comet assay in HT-29 cell cultures) from two randomized controlled studies of red meat (60 or 420 g/day), a vegetarian diet, or haem iron supplements for 15 days in volunteers (n = 21) was evaluated by Cross et al. (2006). Diet had no effect on faecal water genotoxicity (i.e. red meat had no effect). This study was performed under the same conditions as those described by Rieger et al. (1999), but did not confirm those results.

Hughes et al. (2002) studied the effect of vegetables, tea, or soy on faecal water genotoxicity (tested with comet assay in Caco-2 cell cultures) in 11 volunteers fed a high–red meat (420 g/day) diet for 15 days. Low to moderate levels of genotoxicity were observed. [The Working Group noted that the study did not contain a control group consuming a low–red meat diet.]

Faecal water from volunteers (n = 12) fed a red meat (420 g/day, males; 366 g/day, females) or vegetarian diet (Joosen et al., 2009) was tested for genotoxicity by comet assay in Caco-2 cells. Surprisingly, the vegetarian diet produced more DNA strand breaks than the red meat diet. No effect of diet was found in a similar study by the same authors (Joosen et al., 2010) assessing faecal water genotoxicity in volunteers (n = 13) fed a red meat versus fish diet.

More recently, Hebels et al. (2012) showed increased faecal water genotoxicity in a heterogeneous group of inflammatory bowel disease/irritable bowel syndrome patients (n = 12) after 7 days of high–red meat intake (300 g/day), compared with the results obtained before the intervention. In 10 of the subjects, faecal water genotoxicity significantly increased with red meat intake (tested with both standard comet assay and the formamidopyrimidine procedure to measure oxidative damage in Caco-2 cells). Microarray analyses in colon biopsies indicated significant modulation of various signalling

Table 4.2 DNA damage induction by human faecal water following meat consumption

Tissue, cell line	End-point	Test	Results	Exposure[a]	Comments	Reference
HT-29	DNA strand breaks	Comet assay	+	High-fat (125.8 g) and high-meat diet (51.9 g) for 12 days ($n = 7$)	Type of meat not defined	Rieger et al. (1999)
HT-29	DNA strand breaks	Comet assay	–	Red meat (60 or 420 g/day), vegetarian, or haem iron supplemented diet for 15 days ($n = 21$)		Cross et al. (2006)
Caco-2	DNA strand breaks	Comet assay	–	High–red meat (420 g/day) diet with vegetables, tea, or soy for 15 days ($n = 11$)	No control group consuming a low–red meat diet	Hughes et al. (2002)
Caco-2	DNA strand breaks	Comet assay	–	Red meat ($n = 12$) or processed meat ($n = 16$) (males, 420 g/day; females, 366 g/day) or vegetarian diet for 10 days	Vegetarian diet increased genotoxicity of faecal water ($P < 0.05$)	Joosen et al. (2009)
Caco-2	DNA strand breaks	Comet assay	–	Red meat (males, 325 g/day; females, 260 g/day) or fish diet for 3 days ($n = 13$)		Joosen et al. (2010)
Caco-2	DNA strand breaks	Comet assay	+	High–red meat (300 g/day) diet for 7 days in IBD/IBS patients ($n = 12$)		Hebels et al. (2012)

[a] Diet consumed before faecal water collection

+, positive; –, negative; IBD, inflammatory bowel disease; IBS, irritable bowel syndrome

pathways (e.g., cytoskeleton remodelling, development, and immune response) (Hebels et al., 2012).

Regarding processed meat, the study by Joosen et al. (2009) previously described found that faecal water from subjects on the vegetarian diet compared with that from subjects on the processed meat diet produced more DNA strand breaks, as assessed by comet assay in Caco-2 cells.

(iv) Mutagenic activity in urine

See Table 4.3

The first report of mutagenic activity in the urine of subjects after ingestion of meat was published in 1982 (Baker et al. 1982). Fried pork (150 g) was given to five subjects, and bacterial mutagenicity of urine was determined. Peaks in urinary mutagenicity (in *Salmonella typhimurium* strains TA98 and TA1538 with S9) were detected 2–4 hours after ingestion.

Dolara et al. (1984) reported a modest increase in mutagenic activity in the urine of subjects fed pork fried in a pan at 200 °C. Mutagenic activity (in *S. typhimurium* strain TA1538 with S9) was present in 3 of 13 samples analysed and was much lower than that reported by Baker et al. (1982). Hayatsu et al. (1985) also documented mutagenicity (*S. typhimurium* strain TA98 with S9) in the urine of three volunteers 1.5 hours after consumption of fried ground beef.

Doolittle et al. (1989) studied the effects of different cooking methods on mutagenicity. As a small part of the study, the urinary mutagenicity of different cooking procedures was compared in 12 subjects (6 males, 6 females). Fried meat increased urinary mutagenicity (*S. typhimurium* strains TA98 and TA100 with S9) compared with boiled or baked meat.

Gabbani et al. (1998) determined urinary mutagenicity 24 hours after ingestion of two pan-fried hamburgers (2 × 100 g) in 32 volunteers. *GSTM1* and *NAT2* genotypes were also evaluated. Urinary mutagenicity was tested in *S. typhimurium* strains TA98 and YG1024, with the latter overexpressing *O*-acetyltransferase. Mutagenicity (a doubling over the spontaneous revertant number) was seen in the YG1024 strain (in 23 of 32 samples), but not in the TA98 strain. Furthermore, *NAT2* slow acetylators had higher urinary mutagenicity. Similar results (i.e. increased mutagenic activity after a pan-fried hamburger meal) were shown by Pavanello et al. (2002) in a larger group of subjects (n = 50).

Peters et al. (2004) studied urinary mutagenesis in a group of 60 volunteers who consumed red meat cooked at 100 °C for 7 days followed by red meat cooked at 250 °C for an additional 7 days. Both unhydrolysed and acid-hydrolysed urine samples, containing unmetabolized mutagens and both metabolized and unmetabolized mutagens, respectively, were tested in *S. typhimurium* strain YG1024. Unhydrolysed and hydrolysed urine samples were 22 and 131 times more mutagenic, respectively, in subjects who consumed red meat cooked at 250 °C compared with those who consumed red meat cooked at 100 °C.

Shaughnessy et al. (2011) reported increased mutagenic activity (in *S. typhimurium* strains TA98 and YG1024) in the hydrolysed urine and faeces of subjects (n = 8) who consumed red and processed meat cooked at a high temperature of 250 °C (11 minutes/side) for a period of 2 weeks.

Regarding processed meat, the previously mentioned study by Baker et al. (1982) reported increased urinary mutagenicity (in *S. typhimurium* strains TA98 and TA1538 with S9) in five subjects fed fried bacon (150 g). Similarly, Dolara et al. (1984) reported a modest increase in mutagenic activity in the urine of subjects consuming pan-fried bacon.

(v) Epigenetics

Regarding red meat, microRNA expression in the rectal mucosa of volunteers consuming a high–red meat diet, with or without supplementation with butyrylated high-amylose maize starch (HAMSB), was evaluated by Humphreys

Table 4.3 Bacterial mutagenic activity of human urine following meat consumption

Salmonella typhimurium strain	Results		Exposure	Comments	Reference
	Without metabolic activation	With metabolic activation			
TA98 and TA1538	NT	+	Fried pork or bacon (150 g), (n = 5)		Baker et al. (1982)
TA1538	NT	+	Fried pork or bacon (2 g/kg bw), (n = 7)	Modest effect	Dolara et al. (1984)
TA98	–	+	Fried ground beef (130 g), (n = 3)		Hayatsu et al. (1985)
TA98 and TA100	–	+	Meat and food cooked by different methods (n = 12)	Fried meat increased mutagenicity compared with boiled or baked meat	Doolittle et al. (1989)
TA98	NT	–	Two hamburgers (2 × 100 g) fried to taste (n = 32)		Gabbani et al. (1998)
YG1024	NT	+	Two hamburgers (2 × 100 g) fried to taste (n = 32)	23/32 urine samples were mutagenic; higher mutagenicity in *NAT2* slow acetylators	Gabbani et al. (1998)
YG1024	NT	+	Two hamburgers (2 × 100 g) fried to taste (n = 50)		Pavanello et al. (2002)
YG1024	NT	+	Meat cooked at 100 °C for 7 days followed by meat cooked at 250 °C for 7 days (n = 60)	No effect with meat cooked at 100 °C	Peters et al. (2004)
TA98 and YG1024	NT	+	Red and processed meat cooked at 100 °C or 250 °C (2 weeks at each cooking temperature in a crossover design), (n = 8)	No effect with meat cooked at 100 °C	Shaughnessy et al. (2011)

+, positive; –, negative; NT, not tested

et al. (2014). Volunteers received the high–red meat diet for 4 weeks, with washout periods and different orders of treatments. HAMSB significantly lowered a cluster of microRNAs (miR17–92, designated oncomir-1) associated with carcinogenesis. This effect was attributed more to a decrease of these microRNAs by HAMSB than an increase of these microRNAs by red meat.

Tarallo et al. (2014) showed an association between microRNA (miR-92a) levels in the plasma of healthy individuals and consumption of processed meat and other dietary factors (Tarallo et al., 2014).

(b) Human cells in vitro

See Table 4.4

The basic fraction of a beef extract did not induce chromosomal aberrations in human lymphocyte cultures (irrespective of the presence of S9) (Aeschbacher & Ruch, 1989). A small but statistically significant increase in sister-chromatid exchange was seen in the presence of S9.

No study of processed meat in human cells in vitro was available to the Working Group.

Table 4.4 Genetic and related effects of meat extract in human cells in vitro

Tissue, cell line	End-point	Test	Results		Exposure	Comments	Reference
			Without metabolic activation	With metabolic activation			
Human lymphocytes	Chromosomal damage	Chromosomal aberrations	–	–	Beef extract (200 mg/mL)		Aeschbacher & Ruch (1989)
Human lymphocytes	Chromosomal damage	Sister-chromatid exchange	–	±	Beef extract (200 mg/mL)	Small but statistically significant increase	Aeschbacher & Ruch (1989)

+, positive; –, negative; ±, small magnitude of effect

(c) Non-human mammals in vivo

See Table 4.5

(i) DNA damage

In studies of DNA adducts after red meat consumption, Winter et al. (2011) quantified O^6-MeG adducts by immunohistochemistry in CBJ57 mouse colonocytes after mice were fed different diets (containing 15% or 30% protein as casein or red meat, 30% protein with high-amylose maize starch) for 4 weeks. O^6-MeG and *para*-cresol, a protein metabolite with reported genotoxic activity, significantly increased ($P < 0.02$) with consumption of red meat compared with casein. O^6-MeG adducts were present at the apex of the crypts. Starch attenuated the increase in DNA adduct levels.

DNA damage in colonocytes (assessed by comet assay) was measured in Sprague-Dawley rats fed diets containing 25% cooked lean red meat (300 g/kg diet) or casein (15% or 25%), with or without high-amylose maize starch for 4 weeks (Toden et al., 2006). When starch was absent from the diet, red meat caused a significant increase in DNA damage (26%) compared with casein ($P < 0.05$). When starch was present in the diet, the red meat effect was not significant. The same authors later fed rats diets of 15%, 25%, or 35% cooked beef or chicken, with or without high-amylose maize starch (Toden et al., 2007). DNA single- and double-strand breaks (assessed by comet assay in colonocytes) were significantly higher in the groups fed high levels of both meats compared with those fed low levels of meat. Red meat was more active than chicken, and starch prevented the damage. Apoptotic cells were also increased by red meat (see Section 4.2.3).

The effect of red meat on colonocyte DNA damage was also studied in pigs (Belobrajdic et al., 2012). Ten male animals (Large White strain) were fed diets containing 300 g/kg of cooked red meat or the same diet supplemented with arabinoxylans (arabinoxylan-rich fraction from wheat) for 4 weeks. The comet assay was performed on colonocytes, together with additional determinations (short-chain-fatty-acids (SCFA), phenol, cresol in the feces, bacterial profile). There was a significant decrease in DNA damage in the diet supplemented with arabinoxylans.

Regarding processed meat, 7-methyldeoxyguanosine levels were measured by immuno-slot-blot assay in the colonic DNA of Swiss mice fed hot dogs containing beef or pork (18% of the diet) for 7 days. The levels of this non-mutagenic adduct were similar in control ($n = 5$) and treated mice ($n = 4$) (Mirvish et al., 2002).

Table 4.5 Genetic and related effects of red meat or processed meat in non-human mammals in vivo

Species, strain, sex	Tissue	End-point	Test	Results	Dose (LED or HID)	Route, duration, dosing regimen	Comments	Reference
Mouse, CBJ57, male	Colon	DNA adducts	O^6-MeG (IHC)	+	Diets of 15% or 30% protein as red meat or casein, or 30% protein with starch	Oral, 4 wk	Starch inhibited the increase in DNA strand breaks with red meat	Winter et al. (2011)
Mouse, Swiss albino, male and female	Colon	DNA adducts	7-MedG (immuno-slot-blot assay)	–	Hot dogs with beef and pork (18% of diet)	Oral, 7 days		Mirvish et al. (2002)
Rat, Sprague-Dawley, male	Colon	DNA strand breaks	Comet assay	+	Red meat (25%) or casein (15% or 25%) diet, with or without starch	Oral, 4 wk	Starch inhibited the increase in DNA strand breaks with red meat	Toden et al. (2006)
Rat, Sprague-Dawley, male	Colon	DNA strand breaks	Comet assay	+	Red meat or chicken (15%, 25%, 35%) diet, with or without starch	Oral, 4 wk	Red meat more active than chicken; inhibitory effect of starch	Toden et al. (2007)
Pig, Large White, male	Colon	DNA strand breaks	Comet assay	±	Cooked red meat (300 g/kg bw), with or without arabinoxylans	Oral, 2 meals/day, 4 wk	Significantly lower DNA strand breaks with arabinoxylans; no control diet (without red meat)	Belobrajdic et al. (2012)
Mouse, Swiss albino, male	Urine	Reverse mutation	*Salmonella typhimurium* TA98	–	Beef extract	Oral or intraperitoneal		Dolara et al. (1980)
Mouse, Swiss albino, male	Host-mediated assay	Reverse mutation	*Salmonella typhimurium* TA98	–	Beef extract	Oral or intraperitoneal		Dolara et al. (1980)
Mouse, NMRI, male	Host-mediated assay	Reverse mutation	*Salmonella typhimurium* TA98	±	Pan-fried sausage extract (500 mg/kg bw)	Intraperitoneal	Low mutagenicity with Aroclor pretreatment	Gocke et al. (1982)

Table 4.5 (continued)

Species, strain, sex	Tissue	End-point	Test	Results	Dose (LED or HID)	Route, duration, dosing regimen	Comments	Reference
Mouse, C57BL, female	Whole body	Mutation	Mouse spot test	–	Pan-fried sausage extract (500 mg/kg bw)	Intraperitoneal, gestation period	Only one dose tested	Gocke et al. (1982)
Mouse, NMRI, male and female	Bone marrow	Chromosomal damage	Micronuclei	–	Pan-fried sausage extract (1000 mg/kg bw)	Intraperitoneal		Gocke et al. (1982)
Rat, Sprague-Dawley	Caecal water	Chromosomal damage in cultured WIL2-NS cells	Micronuclei	+	Barbecued beef (in a high fat, low fibre, low calcium diet) or casein (in a low fat, high fibre and high calcium diet)	Oral, 15 days		Benassi et al. (2007)

+, positive; –, negative; +/–, small magnitude of effect; 7-MedG, 7-methyldeoxyguanosine; HID, highest ineffective dose; IHC, immunohistochemistry; LED, lowest effective dose; O^6-MeG, O^6-methyl-2-deoxyguanosine; wk, week

(ii) Gene mutation

Dolara et al. (1980) reported no increase in the mutagenicity of the urine after administration of a beef extract to Swiss albino mice. Similarly, the beef extract did not have a mutagenic effect as assessed by intrasanguine host-mediated assay.

Regarding processed meat, the mutagenic activity detected by intrasanguine host-mediated assay in NMRI mice given an extract of pan-fried sausage was very low (Gocke et al., 1982). An extract of pan-fried sausage (500 mg/kg bw) fed to pregnant female C57Bl mice did not increase the frequency of coat-coloured spots in the mouse spot test (Gocke et al., 1982).

(iii) Chromosomal aberrations

A basic extract of pan-fried sausage (up to 1000 mg/kg bw) did not increase the frequency of micronucleated erythrocytes in mouse bone marrow (Gocke et al., 1982).

The caecal water from Sprague-Dawley rats fed a high fat, low fibre, and low calcium diet containing barbecued beef as the protein source (equivalent to 17% of the total diet) for 2 weeks significantly increased all the parameters assessed – micronuclei, nucleoplasmic bridges, and nuclear buds –in the WIL2-NS human B-lymphoblastoid cell line. Control rats were fed 17% casein as the protein source in a diet low in fat, and high in fibre and calcium (Benassi et al., 2007).

(d) Non-mammalian experimental systems

See Table 4.6

(i) Drosophila

No study of red meat in *Drosophila* was available to the Working Group. Regarding processed meat, an extract of pan-fried sausage did not increase the frequency of sex-linked recessive lethals in *Drosophila* (Gocke et al., 1982).

(ii) Bacteria

In red meat studies in vitro, extracts of the charred surface of broiled beef meat and fish, together with smoke produced from the broiling of fish, were first demonstrated to be mutagenic by Sugimura and colleagues Nagao et al. (1977). The charred parts of medium-broiled beef were suspended in dimethyl sulfoxide and tested using the Ames test. The dimethyl sulfoxide extract of the charred meat was mutagenic in *S. typhimurium* strain TA98 with S9 prepared from the liver of rats treated with polychlorinated biphenyl (PCB). This mutagenic activity was much higher than that anticipated from the benzo[*a*]pyrene (BaP) content of the cooked food.

Commoner et al. (1978) reported that cooked red meat was highly mutagenic (in *S. typhimurium* strain TA1538). Hamburger meat cooked rare, medium, or well done was extracted with methylene chloride, dried, and dissolved in dimethyl sulfoxide. Mutagenic activity was dependent on the presence of S9. The mutagens formed did not belong to the class of BaP or protein and amino acid pyrolysis products. Mutagens were produced during common cooking procedures, including the use of electrically heated hot plates.

A sharp rise in the frequency of mutations in *S. typhimurium* strain TA1538 with S9 was detected when beef was boiled for different periods of time and reached temperatures between 140 °C and 180 °C. The mutagenic activity of the beef (hamburger) cooked under different conditions was limited to the surface layer; uncooked meat or microwave-cooked meat did not produce mutagenic activity (Dolara et al., 1979).

Similarly, Pariza et al. (1979) demonstrated that the mutagenic activity of pan-fried hamburger meat was dependent on cooking time and temperature. Mutagenic activity (in *S. typhimurium* strain TA1538) was not detected in uncooked hamburger or hamburger pan-fried at 143 °C. In contrast, hamburger pan-fried at 191 °C or 210 °C for up to 10 minutes generated

Table 4.6 Genetic and related effects of red meat or processed meat in non-mammalian experimental systems

Species, strain	End-point	Test	Results		Dose (LED or HID)	Comments	Reference
			Without metabolic activation	With metabolic activation			
Drosophila melanogaster Berlin K (wildtype) and Basc tester strain	Mutation	Sex-linked recessive lethal mutations	–	NA	Extract of pan-fried sausage (0.1 µg/fly)		Gocke et al. (1982)
Salmonella typhimurium TA98	Mutation	Reverse mutation	–	+	Extracts of the charred surface of broiled beef meat and fish (12 mg/plate)		Nagao et al. (1977)
Salmonella typhimurium TA1538	Mutation	Reverse mutation	–	+	Beef extract (0.1 g dry weight/plate) and red meat (5 g dry weight/plate) cooked under normal conditions		Commoner et al. (1978)
Salmonella typhimurium TA1538	Mutation	Reverse mutation	–	+	Extracts of boiled beef, or hamburger cooked at different times and temperatures (5 g dry weight/plate)	Negative results with uncooked or microwave-cooked meat	Dolara et al. (1979)
Salmonella typhimurium TA1538	Mutation	Reverse mutation	–	+	Extract of hamburger cooked at different times and temperatures (10 g/plate)	Negative results with uncooked meat, or meat cooked at 143 °C	Pariza et al. (1979)
Salmonella typhimurium TA98	Mutation	Reverse mutation	NT	+	Extract of meat cooked at 100 °C or 250 °C (0.06–1.25 g/eq per plate)	No effect at 100 °C	Peters et al. (2004)
Salmonella typhimurium TA1538	Mutation	Reverse mutation	–	+	Beef extract (50 mg dry weight/plate)		Dolara et al. (1980)
Salmonella typhimurium TA98, TA1538	Mutation	Reverse mutation	–	+	Fried sausage extract (100 µg/plate)		Gocke et al. (1982)

+, positive; –, negative; HID, highest ineffective dose; LED, lowest effective dose; NA, not applicable; NT, not tested

considerable mutagenic activity. Higher mutagenic activity was observed when S9 was from Aroclor 1254–treated rats.

Another study with *S. typhimurium* strain TA98 showed meat cooked only at a high temperature of 250 °C had mutagenic activity (Peters et al., 2004).

Dolara et al. (1980) reported that the mutagenic activity of a beef extract required the presence of S9 fractions from the liver of rats treated with PCB or 3-methylcholanthrene, but no induction was necessary when the liver came from Swiss albino mice. CD-1 mice had intermediate activation capabilities, which increased after the addition of 0.75% butylhydroxyanisole to their diet. S9 from the liver of human donors had low-activation capabilities.

Regarding processed meat, an extract of pan-fried sausage was mutagenic in *S. typhimurium* strains TA1538 and TA98 in the presence of S9 mix (Gocke et al., 1982).

4.2.2 Oxidative stress

(a) Humans

(i) Red meat

In a randomized crossover study, Pierre et al. (2006) measured the excretion of 1,4-dihydroxynonane mercapturic acid (DHN-MA), the major urinary metabolite of 4-hydroxynonenal (4-HNE). Eight volunteers were fed different diets providing 55, 55, 80, 205, and 110 mg/day of haem for 15 days: red meat (60 g/day) baseline diet, red meat (60 g/day) with non-haem iron diet, red meat (60 g/day) with haem iron in the form of liver pâté diet, red meat (60 g/day) with haem iron in the form of blood sausage diet, or red meat (120 g/day) diet. The blood sausage diet increased urinary DHN-MA by about two-fold ($P < 0.001$), but mean urinary 8-iso-prostaglandin $F_{2\alpha}$ was similar in all groups (Pierre et al., 2006).

In contrast, Hodgson et al. reported no elevation in oxidative stress markers with consumption of lean red meat (Hodgson et al., 2007). Sixty participants were randomized to maintain their usual diet for 8 weeks or to partially replace carbohydrate-rich foods with 200 g/day of lean red meat. In terms of the mean between-group difference in comparison to the control diet, the red meat diet increased iron intake (3.2 mg/day; 95% CI, 1.1–5.4), lowered urinary F_2-isoprostane excretion (–137 pmol/mmol of creatinine; 95% CI, –264 to –9), and did not change plasma F_2-isoprostanes (–12 pmol/L; 95% CI, –122 to 100) or serum γ-glutamyltransferase (–0.8 U/L; 95% CI, –3.2 to 1.5).

Montonen et al. (2013) reported an association between red meat intake and a blood oxidative stress marker. In 2198 participants selected from the EPIC-Potsdam study, higher consumption of red meat was significantly associated with higher levels of γ-glutamyltransferase, even after adjustment for potential confounding factors related to body mass index (BMI), waist circumference, lifestyle, and diet (Montonen et al., 2013).

Lam et al. (2014) identified several genes involved in oxidative stress that were differentially expressed in patients with lung adenocarcinoma who consumed more red meat. Genome-wide expression (HG-U133A) was measured in the tumour tissue and non-involved lung tissue of 64 patients with adenocarcinoma. Gene expression of 232 annotated genes in the tumour tissue significantly distinguished patients who consumed above or below the median intake of fresh red meat. Several genes were involved in lipid metabolism (e.g. *NCR1*, *TNF*, *UCP3*) and oxidative stress (e.g. *TPO*, *SGK2*, *MTHFR*) (Lam et al., 2014).

(ii) Processed meat

As previously noted, Pierre et al. (2006) reported that a blood sausage diet significantly increased DHN-MA by about two-fold. In a later study, Pierre et al. (2013) showed that cured meat intake increased lipid peroxidation and nitroso compounds in human stool. In a single-blind,

crossover, randomized controlled trial, 18 volunteers first followed a low-meat diet for a one week control period and were then fed the following diets for four days each, in a random order: cooked, cured pork shoulder meat (similar to air-exposed picnic ham, 180 g/day); cooked, cured pork shoulder meat with a calcium carbonate capsule (1 g/day of calcium); and cooked, cured pork shoulder meat with α-tocopherol (0.05%). Thiobarbituric acid reactive substances (TBARS) and apparent total *N*-nitroso compounds (ATNC) increased in the faecal water of volunteers given ham compared with control periods. Calcium carbonate normalized both biomarkers, whereas α-tocopherol normalized only lipid peroxidation in the faeces of volunteers (Pierre et al., 2013).

Belinova et al. (2014) showed that consumption of "cooked-pork seasoned meat" was accompanied by increased oxidative stress marker levels in diabetic patients. In a randomized crossover study, 50 type 2 diabetic patients and 50 healthy subjects underwent two 3-hour meal tolerance tests. The acute effects of a processed hamburger meat meal (150 g/meal) were compared with those of a vegan meal (235 g/meal). During the postprandial phase, consumption of the hamburger meat meal was associated with a significant increase in TBARS in the diabetic patients, but not in the healthy subjects, compared with the consumption of the vegan meal. However, superoxide dismutase activity in the healthy subjects was significantly increased after the vegan meal compared with the hamburger meat meal. In the diabetic patients, plasma concentrations of superoxide dismutase, reduced glutathione, or ascorbic acid did not change during the postprandial phase for either meal (Belinova et al., 2014).

No data concerning direct evaluation of red meat or processed meat in human cells in vitro were available to the Working Group.

(b) Rodents

(i) Red meat

Pierre et al. repeatedly showed that diets containing red meat or haemoglobin significantly increased lipid peroxides in faecal water (TBARS) and urinary DHN-MA, a metabolite of the lipid oxidation product 4-HNE, in rats. In a seminal study by Pierre et al. (2004), groups of carcinogen-initiated rats were given one of three low-calcium, meat-based diets containing 60% freeze-dried meat products: raw chicken (low haem), beef (medium haem), or blood sausage (high haem). Two additional groups of rats were given a non-haem control diet supplemented with ferric citrate or a haem control diet supplemented with haemoglobin to match the iron and haem concentrations of the beef diet, respectively. The blood sausage diet increased TBARS in faecal water by 23-fold. The haemoglobin and beef diets increased TBARS in faecal water by two- to four-fold (all $P < 0.01$), but the chicken diet did not affect TBARS in faecal water compared with the control diets (Pierre et al., 2004). A recent carcinogenesis study confirmed that only diets containing haemoglobin increased faecal and urinary oxidation biomarkers ($P < 0.001$), independent of dietary HAAs or nitrates and nitrites, and resulting faecal ATNC (Bastide et al., 2015). Other rat studies by the same researchers on beef meat, haemoglobin, or hemin chloride (see Section 4.2.6 for hemin chloride studies) confirmed that dietary haem induced faecal and urinary lipid peroxides (Pierre et al., 2003, 2006, 2008; Guéraud et al., 2015). Additionally, dietary calcium phosphate (31 g/kg) normalized faecal TBARS induced by beef consumption (Pierre et al., 2008). In contrast, dietary antioxidant agents (rutin and butylated hydroxyanisole, 0.05% each) and olive oil (5%) did not reduce faecal TBARS (Pierre et al., 2008).

(ii) Processed meat

Several studies showed that cured meat intake increased lipid peroxidation and nitroso compound (ATNC) formation in rat stool (Pierre et al., 2010, 2013; Santarelli et al., 2010, 2013). For instance, Santarelli et al. (2013) reported increased urinary DHN-MA in rats fed nine different types of purchased cured meats, including hot dogs, sausages, raw and cooked ham, and pâté. Fermented, raw, dry sausages induced 1.8 times more TBARS in faecal water than hot dogs, but only hot dogs promoted preneoplastic lesions in the colon (see Section 4.3). Thus, no association was found between the occurrence of preneoplastic lesions and the biomarkers of lipid oxidation (Santarelli et al., 2013).

No data from non-human mammalian in vitro studies of red meat or processed meat and oxidative stress were available to the Working Group.

4.2.3 Alteration of cell proliferation and cell death

(a) Humans

Regarding red meat, Le Leu et al. (2015) reported an increase in epithelial proliferation in the rectal biopsies of 23 volunteers given cooked lean red meat (300 g/day) for 4 weeks. Proliferating cell nuclear antigen (PCNA) staining revealed a 38% increase in positive cells per crypt ($P < 0.001$). Caderni et al. (1999) observed that subjects who reported consuming a diet low in red meat had decreased colorectal mucosa proliferation. The labelling index in the upper part of the crypt was increased in subjects at high risk of cancer of the colon. In a study of 69 subjects who previously underwent surgery for at least two sporadic colon adenomas, dietary habit information was collected by FFQ, and proliferation was measured by [^{3}H]thymidine incorporation into colorectal biopsies. Subjects with low–red meat consumption showed decreased proliferation in the upper part of the crypt (mean ± SD: 2.4 ± 2.1, 5.3 ± 4.6, and 5.9 ± 4.8 for low, middle, and high consumption, respectively; $P < 0.01$) (Caderni et al., 1999).

Humphreys et al. (2014) reported decreased expression of *CDKN1A*, an inhibitor of cell proliferation, and increased cell proliferation in the rectal cells of volunteers fed a high–red meat diet, with or without supplementation with HAMSB.

In contrast, O'Brien et al. (2000) observed no correlation between red meat consumption and rectal crypt cell proliferation. Crypt cell proliferation was significantly higher in the normal mucosa of patients with left-sided colorectal carcinoma than in that of healthy controls. Meat consumption was assessed by FFQ, and crypt cell proliferation was determined using rectal biopsies obtained before surgery (O'Brien et al., 2000).

Regarding processed meat, Pierre et al. detected no effect of cured meat intake (180 g/day of a model ham for 4 days) in 18 volunteers on faecal water cytotoxicity in two cell lines, nor on genotoxicity (measured by γ-H2AX induction) (Pierre et al., 2013).

No data concerning direct examination of red meat or processed meat on human cells in vitro were available to the Working Group. As described in Section 4.2.6, contrasting effects of hemin chloride on the proliferation of human colon cancer cells were shown in vitro.

(b) Rodents

Regarding red meat, apoptosis (determined by halo assay) increased in a dose-dependent manner in colonocytes isolated from rats fed diets containing 15%, 25%, or 35% cooked beef or chicken for 4 weeks (Toden et al., 2007). In contrast, lean beef meat was without effect on proliferation or apoptosis in the colon in mice fed a standard American Institute of Nutrition (AIN)-76 diet with 15% or 30% protein as casein or cooked, dried lean beef meat for 4 weeks

(Winter et al., 2011). Neither the amount nor the type of protein had an effect on cell proliferation (Ki-67), cell mass (crypt height), or rate of apoptosis (terminal deoxynucleotidyl transferase dUTP nick end labelling, TUNEL, assay)

Khil & Gallaher (2004) showed no proliferative effect of dietary beef protein or beef tallow in 1,2-dimethylhydrazine (DMH)-initiated rats given either casein or beef as the protein source and soybean oil or tallow as the fat source in a 2 × 2 factorial design for 9 weeks. However, there was a significantly greater apoptotic labelling index in the distal colonic mucosa of rats fed the beef tallow compared with the soybean oil (Khil & Gallaher, 2004).

Yang et al. (2002) showed that a beef-based diet (24% freeze-dried beef meat vs casein control) reduced caspase-3 activity and neutral ceramidase activity in the colonic mucosa, but had no effect on sphingomyelinase activity in the colonic mucosa.

Pierre et al. repeatedly showed that diets containing red meat or haemoglobin significantly increased faecal water cytotoxicity. In a seminal study, groups of carcinogen-initiated rats were given one of three low-calcium, meat-based diets containing 60% freeze-dried meat products: raw chicken (low haem), beef (medium haem), or blood sausage (high haem). Two additional groups of rats were given a non-haem control diet supplemented with ferric citrate or a haem control diet supplemented with haemoglobin to match the iron and haem concentrations of the beef diet, respectively. The haem control diet was supplemented with haemoglobin to match the haem concentration of the beef diet. The blood sausage diet enhanced erythrocyte cytolysis by more than 50-fold and CMT93 cell toxicity by eight-fold compared with the non-haem control diet. The haemoglobin and beef diets increased CMT93 cell toxicity by four-fold compared with the non-haem control diet; the chicken diet did not increase CMT93 cell toxicity. A correlation was seen between haem intake and faecal water cytotoxicity (r = 0.98), which was correlated with carcinogenesis promotion (r = 0.65; all $P < 0.01$) (Pierre et al., 2004). Other studies of dietary beef, haemoglobin, or hemin chloride have confirmed that dietary haem can induce faecal water cytotoxicity (Pierre et al., 2003, 2008; Guéraud et al., 2015).

In in vitro studies, faecal water of rats given a diet with red meat or haemoglobin was more cytotoxic to the wild type $Apc^{+/+}$ murine cells than to premalignant $Apc^{-/+}$ murine cells (Pierre et al., 2007; Bastide et al., 2015). Trapping of aldehydes from the faecal water of haem-fed rats reduced peroxides by 95% and cytotoxicity by 75%.

Regarding processed meat, several studies by a single research group showed that cured meat intake in rats can increase faecal water cytotoxicity. For instance, faecal water cytotoxicity increased three-fold in rats given a diet with 55% freeze-dried cooked ham for 100 days (Pierre et al., 2010). Santarelli et al. (2010) tested the effect on faecal water cytotoxicity of 16 types of cooked ham diets fed for 2 weeks to rats, with dark or light muscle colour (a proxy for haem level), low or high processing temperature, added nitrite or none, and plastic anaerobic packaging or none, in a 2 × 2 × 2 × 2 design. Faecal water cytotoxicity depended mostly on processing temperature, with cooked ham being more cytotoxic than raw ham, and nitrite, with nitrite being more cytotoxic than no nitrite. [The Working Group noted that both red meat and processed meat were cytotoxic.]

4.2.4 Other mechanisms of carcinogenesis

(a) Chronic inflammation

(i) Humans

Regarding red meat, four observational studies in humans (Azadbakht & Esmaillzadeh, 2009; Montonen et al., 2013; Viscogliosi et al., 2013; Ley et al., 2014) lent little or no support to the hypothesis that red meat intake is directly associated with inflammation markers. Three

intervention studies in volunteers found no effect of red meat intake on inflammation markers (Hodgson et al., 2007; Joosen et al., 2010; Maduro et al., 2013).

Regarding processed meat, two studies were identified. In a nested case–control study of 656 women with type 2 diabetes and 694 healthy women from the Nurses' Health Study (NHS), Schulze et al. (2005) observed that a dietary pattern including processed meat was strongly related to inflammatory markers. This dietary pattern was high in sugar-sweetened soft drinks, refined grains, diet soft drinks, and processed meat, but low in wine, coffee, cruciferous vegetables, and yellow vegetables. Among the inflammatory markers examined, interleukin-6, C-reactive protein, and E-selectin were correlated with processed meat intake. Scores were adjusted for age and BMI, as well as for six other possible confounders (Schulze et al., 2005).

Spehlmann et al. (2012) reported an association between processed meat intake and inflammatory bowel disease in twins. In German monozygotic and dizygotic twins, where at least one sibling had inflammatory bowel disease (n = 512), a high consumption of processed meat, including sausage, was one of the variables most significantly associated with Crohn disease or ulcerative colitis. Likewise, differences in consumption of red meat were also detected in all discordant twin and non-twin Crohn disease groups (Spehlmann et al., 2012).

The hypothesis associating *N*-glycolylneuraminic acid (Neu5Gc) and chronic inflammation is discussed in Section 4.5.7 (Samraj et al., 2015).

No data from human in vitro studies of red meat or processed meat and inflammation were available to the Working Group.

(ii) Rodents

Regarding studies of red meat, mice fed grain-finished beef for 2 weeks showed enhanced prostaglandin E2 from peritoneal macrophages after inflammatory stimulation. The release of prostaglandin E2 was lowest with diets of range-fed beef, range-fed bison, and elk, and highest in mice fed grain-finished beef ($P < 0.05$). Prostacyclin release was highest in mice fed elk, intermediate in mice fed feedlot-finished beef or bison, and significantly decreased in mice fed range-fed bison, range-fed beef, or chicken (Broughton et al., 2011). [The Working Group noted that the study design did not include a no-meat control group. Thus, the comparison was done between types of meat, but the effect of meat per se was not assessed.]

Studies that reported on the effect of dietary haem on inflammation markers are described in Section 4.2.6 and Section 4.5.1.

(b) Modulation of receptor-mediated effects (hormones)

Regarding red meat, three observational human studies were found suggesting that red meat intake may be associated with slightly unfavourable insulin-like growth factor-1, sex hormone–binding globulin, or fasting insulin profiles. The associations (expressed as mean or median change across categories of red meat intake) were usually weak, and were often not confirmed by more than one study. In addition, sometimes the trend over categories lost statistical significance when BMI was included in the model (Allen et al., 2000; Brinkman et al., 2010; Ley et al., 2014).

No data from in vitro human studies, or from experimental systems, on hormones or receptor-mediated effects were available to the Working Group.

(c) Telomere length

O'Callaghan et al. (2012) showed that telomere length in colonocytes in Sprague-Dawley rats decreased in proportion to the level of red meat (15%, 25%, and 35% for 4 weeks) in their diet. High-amylose starch attenuated the effect of red meat.

4.2.5 Other relevant data and potential indirect mediators

(a) Dysregulation of the gut microbiota

Diet is a key factor in determining the composition of the human gut microbiota (Graf et al., 2015). A role for microbiota in the development of cancer has been described (Louis et al., 2014; Garrett, 2015), acting via various mechanisms. Bacterial metabolites such as hydrogen sulfide, secondary bile acids, polyamines, and reactive oxygen species (ROS) may provoke inflammation and affect carcinogenesis, while other metabolites such as acetate, propionate, and butyrate may exert protective activities (O'Keefe, 2008). Pathogenic bacteria, in particular, exert proinflammatory effects and might thus increase carcinogenesis (Louis et al., 2014). Specifically, several studies have reported a positive association between the gram-positive *Streptococcus gallolyticus* (previously named *Streptococcus bovis*) and cancer of the colorectum (Ellmerich et al., 2000; Tjalsma et al., 2006; Abdulamir et al., 2011).

As discussed in Section 4.5.2(b), Martin et al. (2015) observed reduced faecal TBARS when haemoglobin-fed rats were treated with a cocktail of antibiotics. Some *Lactobacillus* strains reportedly exert antioxidant behaviour by preventing the Fenton reaction (Sun et al., 2010), while other bacterial species such as *Enterococcus faecalis* can stimulate extracellular superoxide (Huycke & Moore, 2002). Although the lower faecal TBARS in antibiotic-treated rats in the study by Martin et al. (2015) could be the result of a diminished or altered colonic microbiome, this reduction could be attributed to the direct antioxidant or pro-oxidant effects of the applied antibiotics. For example, metronidazole, which was among the antibiotics administered by Martin et al. (2015), has been described to scavenge ROS in a cell-free environment (Narayanan et al., 2007) and to have an antioxidant effect in colonic tissues (Pélissier et al., 2007).

[The Working Group noted that no direct data on the dysregulation of the gut microbiota by red meat or processed meat were available.]

(b) Type 2 diabetes

A link between high–processed meat intake and diabetes has been hypothesized, and epidemiological meta-analyses have observed a positive association between diabetes and a variety of cancers, including cancer of the liver (El Serag et al., 2006), pancreas (Ben et al., 2011), endometrium (Zhang et al., 2013), colorectum (Larsson et al., 2005), and bladder (Larsson et al., 2006). Various mechanisms have been proposed, such as increased oxidative stress (Ihara et al., 1999; Ceriello & Motz, 2004). Hua et al. (2001) reported lower insulin sensitivity in healthy meat eaters compared with lacto-ovo-vegetarians. Lowering the iron content of the body by phlebotomy improved insulin sensitivity in the meat eaters. The development of insulin resistance increases circulating levels of insulin, triglycerides, and non-esterified fatty acids, which may stimulate colon cell proliferation (Bruce et al., 2000). Other possible mechanisms include the formation of NOCs, advanced glycation end products (AGEPs), trimethylamine *N*-oxide, branched amino acids, endocrine disruptor chemicals, and inflammation (Azadbakht & Esmaillzadeh, 2009; Tong et al., 2009; Kim et al., 2015). [The Working Group noted that a high–red meat and/or high–processed meat consumption may have an indirect stimulating effect on carcinogenesis by contributing to an increased BMI, which has also been linked to insulin resistance and an increased risk of diabetes.]

4.2.6 Studies of hemin and hemin chloride

In many rodent studies not previously mentioned, a model haem molecule was added to the diet as a surrogate for red meat: hemin chloride. This molecule is a protoporphyrin IX containing a ferric iron ion (haem B) stabilized

with a chloride ligand (Deo et al., 2015). It is not present in human diets, is not soluble in water, and quickly induces oxidation of polyunsaturated oils.

(a) Hemin and proliferation

The Van der Meer group repeatedly showed that dietary hemin chloride increased colonic epithelial proliferation and faecal water cytotoxicity in rats (e.g. Sesink et al., 1999, 2000, 2001). For instance, colonic epithelial proliferation increased in rats fed a purified diet supplemented with 1.3 μmol/g of hemin for 14 days. The faecal water of haem-fed rats contained approximately three-fold higher levels of faecal TBARS and was highly cytotoxic compared with that of control rats (Sesink et al., 1999). Cytotoxicity and proliferation were independent of dietary fat content, but were suppressed by dietary calcium phosphate and by dietary chlorophyll both of which bind physically to hemin (Sesink et al., 2000, 2001; de Vogel et al., 2005).

Winter et al. (2014) also showed that dietary hemin chloride increased proliferation in the short term and inhibited apoptosis in the long term in mice fed a high-fat, low-calcium control diet or a high-fat, low-calcium diet with hemin chloride (0.013%). Changes from 1 to 18 months showed increased cell proliferation ($P < 0.01$) in all groups, but only hemin chloride–fed mice showed reduced apoptosis ($P < 0.01$) (Winter et al., 2014).

(b) Hemin and inflammation

Several studies investigated the effect of dietary hemin on inflammation markers, showing various effects on myeloperoxidase in the gut mucosa (decreased, increased, or no change). In mice, dietary hemin exacerbated colitis induced by trinitrobenzene sulfonic acid, but decreased myeloperoxidase activity (Schepens et al., 2011). In mice fed a "Western-type" diet with 40% fat (mainly palm oil) and low calcium (30 μmol/g) for 14 days, dietary hemin resulted in a ruffled intestinal epithelium, which was attributed to luminal necrosis. However, there was no indication of local inflammation: no infiltration of neutrophils or macrophages in the lamina propria, no change in the expression of inflammation markers for macrophages (CD14, CD68, CD11b, and F4/80) and for neutrophils (myeloperoxidase, lactoferrin, neutrophil elastase, and EMR4), and no effect on mucins or on gene expression of secreted MUC2 (IJssennagger et al., 2012b). Finally, in rats given a high-fat safflower oil diet, dietary hemin chloride significantly increased colonic myeloperoxidase activity (Guéraud et al., 2015).

(c) Hemin in vitro

Hemin chloride was a potent growth factor in iron-depleted human colon cancer HT-29 cells, but it showed dose-dependent cytotoxic effects on the same cell line (Klenow et al., 2009). It had hyperproliferative effects on Caco-2 cells mediated by haem oxidase and hydrogen peroxide, which was shown using the inhibitors zinc protoporphyrin and catalase (Ishikawa et al., 2010).

[The Working Group noted that dietary hemin chloride markedly increased faecal water cytotoxicity and proliferation of the colonic epithelium in rats and mice. However, the relevance to red meat intake was unclear since the hyperproliferative effect was not reproduced with natural haemoprotein or meat.]

4.3 Precancerous lesions

4.3.1 Precancerous colorectal lesions

(a) Humans

(i) Red meat

Several cohort and case–control studies examined the association between red meat consumption and risk of colorectal adenomas. Of the cohort studies, all showed a positive, but not

statistically significant, association between red meat and risk of adenomas (Nagata et al., 2001; Chan et al., 2005a; Wu et al., 2006; Rohrmann et al., 2009b; Tantamango et al., 2011; Ferrucci et al., 2012). However, in a meta-analysis of these studies, the overall association was statistically significant: per 100 g/day increase in intake of red meat, the relative risk (RR) increased by 20% (95% CI, 1.06–1.36) (Aune et al., 2013). The meta-analysis of 10 case–control studies also yielded a positive association (OR, 1.34; 95% CI, 1.12–1.59). Several sensitivity analyses examined potential confounders, also addressed in Section 2.1.5 of this *Monograph*. These did not appreciably change the risk estimates, such that the associations of the meta-analysis were still statistically significant (Aune et al., 2013). As they are more likely to progress to adenocarcinomas than smaller adenomas, large adenomas were specifically evaluated in some studies, including the EPIC-Heidelberg study (OR, 1.98; 95% CI, 1.09–3.58; top vs bottom quintile) (Rohrmann et al., 2009b) and the Health Professionals Follow-Up Study (HPFS) (OR, 1.95; 95% CI, 0.97–3.91; top vs bottom quintile) (Wu et al., 2006). In single studies, differences in the adenoma characteristics and/or types of red meat were sometimes noted. For example, in the EPIC-Heidelberg study, a high intake of red meat and processed meat (combined) was related to an increased risk of colon adenomas (OR, 1.53; 95% CI, 1.01–2.30) and large adenomas (as noted above), but there was no statistically significant association with adenomas at all sites or small adenomas (Rohrmann et al., 2009b). Ferrucci et al. (2012) did not observe an association between red meat consumption and all types of adenomas. However, they found a statistically significant association between grilled meat (OR, 1.56; 95% CI, 1.04–2.36; top vs bottom quartile), and also well-done or very well-done meat (OR, 1.59; 95% CI, 1.05–2.43), and risk of rectal adenomas. No association was found between these meat types and colon adenomas.

The meta-analysis by Aune et al. (2013) also examined the effects of meat intake by type, and reported statistically significant positive associations between beef and pork intake and risk of adenoma (Aune et al., 2013). A meta-analysis of case–control studies reported a statistically significant increased risk of colorectal adenoma with beef consumption (meta-RR, 1.56; 95% CI, 1.15–2.10; I^2, 49.9%) (Carr et al., 2016).

(ii) Processed meat

Fewer studies examined the association between processed meat consumption and risk of colorectal adenomas. In the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial, a non-statistically significant increased risk of colorectal adenomas was observed with high–processed meat consumption (OR, 1.23; 95% CI, 0.99–1.52; top vs bottom quartile) (Ferrucci et al., 2012). In the HPFS, an association was found between high–processed meat consumption and risk of distal colon adenomas (OR, 1.52; 95% CI, 1.12–2.08; top vs bottom quintile), which was stronger than that found for red meat (OR, 1.18; 95% CI, 0.87–1.62; top vs bottom quintile) (Wu et al., 2006). A combined analysis of these two studies revealed a 45% increase in the risk of colorectal adenoma (95% CI, 1.10–1.90) per 50 g increase in consumption of processed meat per day (Aune et al., 2013). The only study that examined adenoma recurrence did not find any statistically significant association between processed meat consumption and risk of recurrence for any adenoma types, advanced adenomas, or multiple adenomas (Mathew et al., 2004). Overall, case–control studies showed positive associations between intake of processed meat and colorectal adenomas, but only a minority of these findings were statistically significant. For example, a 30% increased risk of adenoma (95% CI, 1.1–1.5) was observed in the Tennessee Colorectal Polyp Study (TCPS) with 1881 cases (Fu et al., 2011), but no increased risk of adenoma was found in

the PLCO trial with 3696 cases (OR, 1.04; 95% CI, 0.90–1.19) (Sinha et al., 2005b). A meta-analysis of eight case–control studies found a positive association that did not reach statistical significance (OR, 1.23; 95% CI, 0.99–1.52) (Aune et al., 2013).

Several studies reported on specific types of processed meats, including bacon and sausage. Higher intake of bacon and sausage was associated with an increased risk of colorectal adenoma (OR, 1.14; 95% CI, 1.00–1.30) in the PLCO trial (Sinha et al., 2005b). Similarly, in the TCPS, several different types of processed meats (e.g. hot dogs, sausage, or bacon) were associated with an increased risk of adenoma (Fu et al., 2011).

[The Working Group noted that the epidemiological studies supported a positive association between red meat and processed meat consumption and risk of colorectal adenomas. However, results differed with respect to the type of meat, as well as the site, size, number, and histology of the adenomas.]

(b) Experimental systems

(i) Red meat

Parnaud et al. (1998) first studied the effect of meat (beef, chicken, and bacon) on aberrant crypt foci (ACF). Azoxymethane-induced F344 female rats were randomized to 10 different AIN-76–based experimental diets, all high in calcium. Five diets were adjusted to include 14% fat and 23% protein (standard levels), and five other diets were adjusted to include 28% fat and 40% protein (high levels). Fat and protein were supplied by either lard and casein, olive oil and casein, beef, chicken with skin, or bacon. The meat diets contained 30% or 60% freeze-dried, fried meat. The rats were fed ad libitum for 100 days, and ACF multiplicity (the number of crypts forming each focus) was assessed as a parameter related to tumour promotion. ACF multiplicity was similar among the rats, except for the bacon-fed rats.

The same investigators studied the effects of various meats on ACF, using diets high in calcium (Parnaud et al., 2000). Rats fed a diet containing beef, pork, or chicken meat had a lower concentration of faecal NOCs than those fed the control diet ($P < 0.01$). In the promotion experiment, unprocessed, cooked meat–based diets did not change the number or multiplicity of ACF compared with the control diet.

Hypothesizing that a high level of calcium in the diet may mask the potential carcinogenicity of red meat, subsequent studies administered meat to azoxymethane-induced F344 rats fed a low-calcium diet (0.8%; mimicking the "Western-type" diet). Accordingly, Pierre et al. (2004) formulated the meat-based diets to contain varying concentrations of haem with the addition of raw chicken (low haem), beef (medium haem), or black pudding (blood sausage, high haem). Chicken, beef, and black pudding were administered at 60% of the diet, thus providing a higher intake of protein than the standard nutritional intake of protein (20% of the diet) for rats. Only diets with haem significantly promoted mucin-depleted foci (MDF) formation ($P < 0.01$), but all meat diets promoted ACF formation. MDF promotion was greater with the high-haem black pudding diet than with the medium-haem beef diet. MDF promotion was also correlated with increased lipid peroxides in faecal water, measured by TBARS, and cytotoxicity in erythrocytes and the mouse epithelial cell line CMT93 ($r = 0.65$; $P < 0.01$).

The same group of researchers tested whether calcium and various antioxidants would reduce the promotion of preneoplastic lesions in DMH-induced F344 rats fed red meat (Pierre et al., 2008). Three diets with 60% beef meat were supplemented with calcium phosphate (31 g/kg diet), antioxidant agents (rutin and butylated hydroxyanisole, 0.05% each), and olive oil (5%). The beef meat diet significantly increased the number of ACF (+30%) and MDF (+100%). These results were associated with increased faecal

water TBARS (4-fold) and cytotoxicity in CMT93 cells (2-fold), and urinary DHN-MA excretion (15-fold). Calcium fully inhibited beef meat–induced ACF and MDF promotion, and normalized faecal TBARS and cytotoxicity; however, it did not reduce urinary DHN-MA. The antioxidant mix and olive oil did not normalize beef meat promotion or lipid peroxides.

The effects of red meat and whey protein on azoxymethane-induced ACF were studied by Belobrajdic et al. (2003). Wistar rats were fed red meat (barbecued kangaroo muscle meat) or whey protein concentrate to provide 8%, 16%, and 32% protein by body weight in a modified AIN-93 diet with low fibre, low calcium (0.1%), and high polyunsaturated fat. The 32% whey protein group had significantly fewer ACF in the proximal colon than the 16% and 32% red meat groups ($P < 0.05$). No effect of the diets was observed in the distal colon.

Khil & Gallaher (2004) examined the effects of individual red meat components (beef protein and tallow) on DMH-induced ACF and colon apoptosis and proliferation. DMH-induced Sprague-Dawley rats were fed either casein or beef protein as the protein source, and either soybean oil or tallow as the fat source, for 9 weeks in an AIN-93 standard diet. Rats fed tallow had fewer ACF (only determined in a portion of the distal colon) and significantly higher apoptosis compared with those fed soybean oil. In addition, faecal bile acid concentrations were significantly lower in rats fed tallow than in those fed soybean oil. There were no significant differences in mucosal cell proliferation.

[The Working Group noted that red meat given to carcinogen-initiated animals promoted the growth of preneoplastic lesions in the colon, and that this effect could be modified by factors such as calcium and antioxidants.]

(ii) Processed meat

In the study by Parnaud et al. (1998) previously mentioned, a significant reduction in ACF multiplicity was observed in bacon-fed, carcinogen (azoxymethane)-initiated rats compared with control rats when calcium levels in the diet were high.

Parnaud et al. (2000) also assessed the effect of a high-fat, high-calcium, bacon-based diet on ACF number and multiplicity in the colon of F344 rats (Parnaud et al., 2000). As previously mentioned, other meats tested were pork, chicken, and beef. The faeces of the rats fed the bacon-based diets contained 10–20 times more NOCs than the faeces of the rats fed the casein-based control diet ($P < 0.0001$). No ACF were detected in the colon of uninitiated, bacon-fed rats. The number of large ACF per rat and ACF multiplicity were consistently reduced by 12% and 20% in rats fed a 30% or 60% high-fat, bacon-based diet and by 17% in rats fed a 30% low-fat, bacon-based diet (all $P < 0.01$). [The Working Group noted the lack of effect of dietary bacon on rat colon carcinogenesis in the context of a high-calcium diet.]

Using diets containing low levels of calcium (0.8 g/kg diet), Pierre et al. (2010) showed that a freeze-dried, cooked, cured ham diet fed for 100 days to DMH-induced F344 rats significantly increased the number of MDF in the colon. Promotion was associated with cytotoxicity and lipid peroxidation. In a short-term study (14 days) by the same authors, the cytotoxicity (tested in CMT93 cell lines) and lipid peroxidation (TBARS) of faecal water, and the urinary marker of lipid peroxidation (DHN-MA), increased dramatically in ham- and hemin-fed rats; however, this effect was not observed in rats fed the haemoglobin diet or the sodium chloride (NaCl), nitrite, phosphate diet.

This group also demonstrated that experimental cured meat diets (dark cooked pork meat with nitrite, oxidized; dark cooked meat with

nitrite, anaerobic; dark cooked meat, oxidized; dark raw meat, anaerobic; with dark meat obtained from supraspinatus and infraspinatus pig muscle, which contained 15–17 mg of haem per 100 g) fed to DMH-induced rats for 100 days significantly increased the number of ACF per colon compared with the no-meat control diet (Santarelli et al., 2010).

In another study, DMH-induced rats were fed a diet containing hot dogs or saucisson (fermented, raw, dry sausage) (40% and 50% on a dry basis) for 100 days (Santarelli et al., 2013). The hot dog diet significantly increased the number of MDF per colon. The saucisson diet increased the number of MDF per colon, but the increase lacked statistical significance compared with the no-meat control diet. The addition of calcium carbonate (150 µmol/g) to the hot dog diet decreased the number of MDF per colon and faecal ATNC compared with the hot dog diet without calcium carbonate.

In DMH-induced F344 rats, the addition of calcium or α-tocopherol to a diet containing cured pork meat (47% meat diet for 100 days) also significantly reduced the number of MDF per colon, but the number of ACF was not affected (Pierre et al., 2013).

[The Working Group noted that results from a single laboratory showed three different kinds of processed meat given to carcinogen-induced animals promoted the growth of preneoplastic lesions in the colon.]

(iii) Haem and other components of red and processed meat

Pierre et al. (2003) showed that haemoglobin or hemin, the ferric porphyrin component of haemoproteins, promoted ACF in azoxymethane-induced rats when dietary calcium was low. This result suggested that myoglobin, the haemoprotein present in red meat, could also promote cancer of the colon when dietary calcium is low.

Santarelli et al. (2010) further evaluated 4 of 16 diets containing cured meat that modified biomarkers of haem-induced carcinogenesis promotion (faecal and urinary fat oxidation and cytotoxicity) in a short-term (14-day) study. The diets differed in muscle colour (a proxy for haem level), processing temperature, nitrite, and packaging. In DMH-induced rats fed for 100 days, only the cooked, nitrite-treated and oxidized, high-haem meat diets significantly increased faecal levels of apparent total *N*-nitroso compounds (ATNC) and the number of MDF per colon compared with the no-meat control diet. Specifically, the cooked, nitrite-treated and oxidized, high-haem meat diets increased the number of MDF compared with the cooked, non–nitrite-treated meat diet and with the non-oxidized, high-haem meat diet; faecal ATNC levels were 5–15 times higher in the cooked nitrite-treated and oxidized high-haem meat diets than in the other diet groups, but lipid oxidation products (TBARS) in faecal water and urinary DHN-MA were lower in these groups than in the other selected meat diet groups.

In DMH-induced F344 rats, various biomarkers (TBARS in faecal water and cytotoxicity of faecal water in CMT93 cell lines, ATNC in faeces and urinary DHN-MA) were all significantly reduced by the addition of calcium to a diet containing cured pork meat (47% meat diet for 100 days), while α-tocopherol decreased only the concentration of haem in faecal water and DHN-MA in urine (Pierre et al., 2013). Within the same report, Pierre et al. (2013) also showed that the consumption of cured meat increased ATNC and lipid peroxidation (TBARS) in the faeces of human volunteers (both $P < 0.05$). Calcium normalized both biomarkers in the human faeces, whereas α-tocopherol only decreased lipid peroxidation in the human faeces (all $P < 0.05$).

Bastide et al. (2015) investigated the role of various components present in red meat, including haem iron, HAAs, and endogenous NOCs, in causing promotion of cancer of the colon. The relative contribution of haem iron (1% of the diet), HAAs (PhIP and MeIQx, 50 + 25 µg/kg

diet), and NOCs (induced by sodium nitrite and sodium nitrate, 0.17 + 0.23 g/L drinking-water) was determined in chemically (azoxymethane) induced rats and in *Min* mice (fed a 2.5% haemoglobin diet). Haem iron increased the number of preneoplastic lesions (MDF) in rats, but dietary HAAs and NOCs had no effect. Dietary haemoglobin increased tumour load in the small intestine of the *Min* mice ($Apc^{Min/+}$) (control diet, 67 ± 39 mm^2; 2.5% haemoglobin diet, 114 ± 47 mm^2; $P = 0.004$). In vitro, faecal water from rats given dietary haemoglobin was rich in aldehydes and was cytotoxic to normal cells ($Apc^{+/+}$), but not to *Apc*-deficient cell lines ($Apc^{-/+}$). The aldehydes 4-HNE and 4-hydroxyhexenal were more toxic to normal cells than mutated cells, and were only genotoxic to normal cells. Genotoxicity (measured by γ-H2AX for DNA double-strand breaks) was also observed in the small intestine of *Min* mice given haemoglobin.

[The Working Group noted that these studies, coming from a single laboratory, highlighted the contribution of haem iron in the promotion of preneoplastic lesions by red meat. One study also suggested that in cured meat–fed rats, the driving mechanism of promotion was due to NOCs, and not to lipid peroxidation products.]

4.3.2 Other precancerous lesions in exposed humans

(a) Barrett oesophagus

Barrett oesophagus is defined as the replacement of oesophageal squamous epithelium with metaplastic columnar epithelium. Four epidemiological studies, three case–control studies and one cohort study, examined whether the consumption of meat is related to risk of Barrett oesophagus (Kubo et al., 2009; O'Doherty et al., 2011; Jiao et al., 2013; Keszei et al., 2013). Only the USA case–control study observed a statistically significant association between total meat consumption and risk of Barrett oesophagus (multivariate-adjusted OR, 1.91; 95% CI, 1.07–3.38; top vs bottom tertile) (Jiao et al., 2013), but none of the other three studies observed this same risk (Kubo et al., 2009; O'Doherty et al., 2011; Keszei et al., 2013). However, the USA case–control study by Jiao et al. (2013) did not differentiate between the consumption of red, white, and processed meat. In another USA case–control study, there was no association between total meat, well-done meat, or barbecued meat consumption and risk of Barrett oesophagus (Kubo et al., 2009), but an analysis of the same case–control study reported a positive association between a "Western-type" dietary pattern, which is characterized by a high intake of red and processed meat, and risk of Barrett oesophagus (Kubo et al., 2008).

(b) Gastric intestinal metaplasia

Gastric intestinal metaplasia is considered a precursor lesion of cancer of the stomach (Correa et al., 1975). Based on four studies (Nomura et al., 1982; Stemmermann et al., 1990; Fay et al., 1994; Chen et al., 2004), a meta-analysis reported a combined odds ratio of 1.68 (95% CI, 0.98–2.90) for the association between salted/salty meat and intestinal metaplasia, but the heterogeneity between studies was large (I^2, 55.4%), which may have been due to their use of different definitions of foods (e.g. all processed meat, cured meat, or bacon only), types of dietary assessment methods, or subgroups of the population (some studies were conducted only among men) (Dias-Neto et al., 2010).

4.4 Cancer susceptibility

4.4.1 Genetic polymorphisms

(a) Humans

(i) Red meat and certain meat components

Several studies have suggested an increased risk of cancer of the colorectum in individuals with *NAT2* rapid acetylator status (individuals

with two "rapid" alleles), assessed by phenotyping or genotyping. However, meta-analyses of the literature on *NAT2* acetylator status (rapid/intermediate vs slow genotype or phenotype) have typically not confirmed such a main effect association (Brockton et al., 2000; Liu et al., 2012; Zhang et al., 2012). This is also true of other cancers, such as those of the lung (Cui et al., 2011), stomach (Zhong et al., 2010), and breast (Ochs-Balcom et al., 2007; Ambrosone et al., 2008), as well as non-Hodgkin lymphoma (Gibson et al., 2013). Unfortunately, adding to the difficulty of interpreting these data, only a few studies, and no meta-analysis or pooled analysis, have reported risk estimates specifically for rapid acetylators– the subset expected to be at the greatest risk. Instead, grouping intermediate with rapid acetylators has been the norm, especially for populations in which the latter phenotype is relatively rare (e.g. Europeans). The inconsistent results for *NAT2* in cancer of the colorectum are in sharp contrast to those for *NAT2* in cancer of the bladder; the slow *NAT2* acetylator status has consistently been associated with an increased risk of cancer of the bladder (except for benzidine (Rothman et al., 1996)), due to the ability of NAT2 to detoxify arylamines, as shown in a meta-analysis and found in a genome-wide association study (Marcus et al., 2000; Figueroa et al., 2014).

A smaller number of studies have explored associations between polymorphisms in other genes involved in the metabolism of HAAs and PAHs (e.g. *CYP1B1*, *GSTM1*, *GSTT1*, *SULT1A1*, *UGT2B17*) and cancer risk. The results of these studies have also been inconsistent or have not been replicated (Andersen & Vogel, 2015). Genome-wide association studies have recently shown that common (i.e. allele frequency > 5%) genetic variants have only a small effect on cancer risk. Importantly, few of the risk variants identified in cancer genome-wide association studies have been in metabolic genes, suggesting that stratification of exposure and very large samples sizes are needed to identify such associations. Indeed, it can be expected that polymorphisms in xenobiotic-metabolizing enzymes (XMEs) involved in carcinogen activation or detoxification would only affect cancer risk when there is a high, biologically sufficient level of exposure to a carcinogen. Thus, it is likely important to consider both the exposure and the genetic variants to detect an association with cancer risk.

Studies that have examined the combined effects of exposure (e.g. red meat, well-done meat, or HAA intake) and metabolic genotypes or phenotypes have mainly focused on cancer of the colorectum and its precursor, adenomatous polyps. Interactions were suggested between intake of red meat, well-done meat, or HAAs and *NAT2* acetylator status (Welfare et al., 1997; Kampman et al., 1999; Chan et al., 2005b; Lilla et al., 2006; Nöthlings et al., 2009; Voutsinas et al., 2013), *NAT1* (Ishibe et al., 2002; Gilsing et al., 2012), *AHR* (Wang et al., 2011), *CYP1B1* (Cotterchio et al., 2008; Wang et al., 2011), *CYP1A1* (Turner et al., 2004, Little et al., 2006; Goode et al., 2007), *CYP2E1* (Morita et al., 2009), *EPHX1* (Cortessis et al., 2001; Ulrich et al., 2001; Goode et al., 2007), *NQO1* (Turner et al., 2004), *SULT1A1* (Cotterchio et al., 2008; Barbir et al., 2012), and *UGTs* (Butler et al., 2005; Girard et al., 2008), as well as with a combination of metabolic genes (*CYP1A2*, *CYP2E1*, *CYP1B1*, and *CYP2C9)* (Küry et al., 2007) and with a polygenic risk score based on variants in *AHR*, *CYP1A2*, *CYP1B1*, *NAT2*, *SULT1A1*, *UGT1A7*, *GSTM1*, and *GSTT1* (Fu et al., 2012) on the risk of colorectal neoplasia. A meta-analysis of three cohort studies (1404 cases, 2186 controls) (Chen et al., 1998, Chan et al., 2005b, Nöthlings et al., 2009) on the modifying effect of *NAT2* on the association between red meat and cancer of the colorectum suggested an interaction between *NAT2* status and meat intake. High–red meat intake or preference for browned meat was not associated with an increased risk of cancer of the colorectum in carriers of the slow *NAT2* phenotype. In

contrast, *NAT2* fast acetylators with high-meat intake were at increased risk (OR, 1.25; 95% CI, 0.92–2.01) compared with *NAT2* slow acetylators with low-meat intake ($P_{interaction}$ = 0.07) (Andersen et al., 2013). However, other studies, some with large sample sizes, failed to replicate this interaction between red meat intake and *NAT2* acetylator status on risk of cancer of the colorectum or adenoma (Barrett et al., 2003; Murtaugh et al., 2004; Sørensen et al., 2008; Ananthakrishnan et al., 2015; Budhathoki et al., 2015). Of note, the recent pooled analysis conducted by the Genetics and Epidemiology of Colorectal Cancer Consortium (GECCO) (8290 cases, 9115 controls) found no interaction between red meat or processed meat intake and *NAT2* acetylator status in case–control and cohort studies (separately and overall) (Ananthakrishnan et al., 2015). High–red meat intake was similarly associated with cancer of the colorectum in subjects with the rapid/intermediate *NAT2* genotype (OR, 1.38; 95% CI, 1.20–1.59) and in subjects with the slow *NAT2* genotype (OR, 1.43; 95% CI, 1.28–1.61; $P_{interaction}$ = 0.9).

Only four studies of adenoma and/or cancer of the colorectum have considered NAT2 jointly with CYP1A2 activity, which, as previously mentioned, shows high inter-individual variability and may account for individual differences in susceptibility to HAAs. Two of the four studies were case–control studies, and both found that rapid NAT2 activity combined with rapid CYP1A2 activity was a risk factor for colorectal neoplasia or cancer of the colorectum in individuals who ate well-done meat (Lang et al., 1994; Le Marchand et al., 2001). However, in one of the case–control studies, this association was limited to smokers (Le Marchand et al., 2001), which is consistent with the inducing effect of smoking on CYP1A2. In the third study, only NAT2 activity, and not CYP1A2 activity, showed an interaction with HAA intake on the risk of adenoma (Voutsinas et al., 2013). The fourth study failed to observe any modifying effect of NAT2 or CYP1A2 activity, also measured by caffeine phenotyping, on the relationship between HAAs and adenoma (Ishibe et al., 2002).

Fewer studies have examined the interaction between meat intake and genetic polymorphisms on the risk of other cancer sites. However, multiple reports have focused on cancer of the breast and *NAT2* (Ambrosone et al., 1998; Gertig et al., 1999; Deitz et al., 2000; Delfino et al., 2000; Mignone et al., 2009; Lee et al., 2013), *CYP1A2* (Lee et al., 2013), *GSTM1* (Zheng et al., 2002), and *SULT1A1* (Lee et al., 2012). Similar to the literature on cancer of the colorectum, publications on cancer of the breast have been inconsistent.

Other cancer-related mechanisms, such as DNA repair, have been explored in studies of cancer, genetic variation, and meat intake. For example, a variant in *MGMT*, a gene involved in the repair of DNA damage caused by alkylating agents, including NOCs from the diet, was found to interact with both red and processed meat intake on the risk of cancer of the colorectum (Loh et al., 2010). Variants in the nucleotide excision repair enzyme gene, xeroderma pigmentosum group D (*XPD*), have also been found to increase the risk of cancer of the colorectum when combined with a high intake of heavily browned red meat (Joshi et al., 2009).

Thus, a large number of studies have evaluated the role of genetic polymorphisms in an attempt to clarify the association between cancer susceptibility and red meat consumption. Historically, these studies have focused on suspected mechanisms, and mainly on genes involved in the metabolism of carcinogens present in cooked red meat. The results of these candidate gene studies have mostly been inconsistent. Many were underpowered and had multiple testing, publication, and reporting biases. Inconsistencies in the gene–meat interaction studies may also have resulted from differences in the comprehensiveness of the dietary assessments or the lack of consideration for cytochrome P450 (CYP) enzyme inducers (e.g. smoking). The strongest

evidence provided by these studies supported an interaction between *NAT2*, red meat intake, and risk of cancer of the colorectum. However, as previously noted, meta-analyses and pooled analyses (Brockton et al., 2000; Liu et al., 2012; Zhang et al., 2012; Ananthakrishnan et al., 2015) have failed to confirm a main effect or modifying effect of *NAT2* or other genes on cancer of the colorectum or other cancers. Insufficient focus has been given to the group expected to be at the highest risk – those with two rapid alleles. Data are lacking for populations in which this genotype is common, and that consume significant amounts of well-done meat and have high rates of cancer of the colorectum (e.g. Japan and Republic of Korea).

In recent years, genome-wide association studies have identified several cancer susceptibility loci, each with a relatively small effect on risk. Statistical methods have been developed to analyse interactions between diet and variants across the entire genome. These analyses, with the currently available sample sizes, have rarely replicated results from candidate gene studies and have not identified interactions with red meat intake (Jiao et al., 2012; Kantor et al., 2014). However, larger sample sizes are needed to detect modest or weak interactions.

(ii) Processed meat

Processed meat has not always been examined separately from red meat in studies of genetic polymorphisms. A population-based case–control study in Hawaii, USA (Le Marchand et al., 2002a) found an increased risk of cancer of the colorectum in individuals who consumed a high amount of red meat or processed meat and who carried a variant in *CYP2E1* that had been shown to alter enzyme activity (Lucas et al., 1995; McCarver et al., 1998; Le Marchand et al., 1999). This association was more pronounced for cancer of the rectum and was observed in individuals who consumed salted/dried fish and oriental pickled vegetables, both food sources of NOCs. An association with the same *CYP2E1* variant and cancer of the stomach was also observed (Nishimoto et al., 2000; Chen et al., 2004).

Finally, a genome-wide search for diet–gene interactions identified an interaction between processed meat intake and a variant (rs4143094) on 10p14 (near *GATA3*) on the risk of cancer of the colorectum (Figueiredo et al., 2014). Although the mechanism was unclear, *GATA3* was involved in cell maturation, proliferation arrest, and survival. Loss, or silencing, of expression of *GATA* genes has been described in colorectal tumours.

[The Working Group noted that few studies have explored the role of genetic susceptibility as a potential modifier of the association between processed meat and cancer. These studies have typically been small, and have not allowed for any conclusions to be drawn.]

(b) Experimental systems

Two studies by the same research group showed that mice humanized for CYP1A2 are more susceptible to HAAs (e.g. PhIP) than wild-type mice (Cheung et al., 2011; Li et al., 2012). [The Working Group noted that the doses used in these studies were greater than human exposure levels, and the relative levels of h*CYP1A2* expression may have exceeded the range in humans.]

4.4.2 Microflora

Evidence is also available concerning individual differences in intestinal microflora profiles that may affect the carcinogenic effect of red meat. In rodents, the gut microbiota has been shown to facilitate haem-induced hyperproliferation by opening the mucous barrier (Ijssennagger et al., 2015). Similarly, it has been suggested that intestinal microflora play an important role in the bioactivation of HAAs. Kassie et al. (2004) inoculated intestinal flora collected from either vegetarians or meat eaters into germ-free rats. The rats were fed a diet mimicking the donors' diets, in terms of the origin of the protein and

fat (animal or plant). After oral administration of 2-amino-3-methylimidazo[4,5-*f*]quinoline (IQ), DNA damage in both colon and liver cells, as determined by comet assay, was significantly lower in animals harbouring the flora from vegetarians than in those harbouring the flora of the meat eaters.

The human intestinal microbiota has been shown to selectively convert PhIP to a major metabolite, 7-hydroxy-5-methyl-3-phenyl-6,7,-8,9,-tetrahydropyridol[3′,2′:4,5]imidazo[1,2-*a*]pyrimidin-5-ium chloride (PhIP-M1) (Vanhaecke et al., 2008a). PhIP-M1 was found to cause cell division arrest and induce DNA strand breaks in the human epithelial intestinal colon carcinoma Caco-2 cell line (Vanhaecke et al., 2008b), suggesting that the ability of the colon microbiota to bioactivate PhIP may affect the risk of cancer of the colorectum. [The Working Group could not make any conclusions regarding effect modification due to the microbiota.]

4.5 Meat components potentially involved in carcinogenesis

4.5.1 Haem iron

(a) Iron intake and digestion

One of the defining characteristics of red meat is its haem iron content. Two types of iron occur in foods: haem iron (organic) and non-haem iron (inorganic) (Fonseca-Nunes et al., 2014). Haem, which is made up of an iron atom surrounded by a porphyrin ring, is included in haemoglobin and myoglobin, and is involved in supplying oxygen to the body's tissues (Bastide et al., 2011). The redness of meat is mainly determined by its concentration of myoglobin, with the oxidation state and sixth ligand of iron determining the specific colour of meat. Haem iron in nitrite-cured meat is mostly nitrosylated (Demeyer et al., 2015).

Iron overload has many adverse health effects, irrespective of the iron source. While the human body maintains homeostatic control of this trace element, the absorption of haem iron in the small intestine is less regulated and more efficient (15–40%) than the absorption of non-haem iron (Layrisse et al., 1969; Carpenter & Mahoney, 1992; Hooda et al., 2014). Red meat is the largest dietary source of haem iron. Non-haem iron, which is present in both animal and vegetable sources, accounts for the majority of total dietary iron intake and has a wide range of absorption (1–40%). The absorption of non-haem iron is influenced by the body's iron stores, hypoxia, and erythropoietic activity, as well as by the intake of vitamin C, calcium, and haem iron (Layrisse et al., 1969; Carpenter & Mahoney, 1992; Fonseca-Nunes et al., 2014).

Haem in meat may undergo modifications during processing and digestion. Depending on the time and temperature, myoglobin is denatured after cooking, and the haem moiety is liberated. Haem iron can also be converted, to varying degrees, into non-haem iron by heat treatment (Kristensen & Purslow, 2001; Purchas et al., 2006). Purchas et al. (2006) showed an overall loss of iron from cooking of beef, together with a marked shift from soluble haem and non-haem iron to their insoluble forms. However, after simulated stomach and duodenal digestion, solubility was regained to a significant extent. Kristensen & Purslow (2001) reported that NaCl, widely used in meat processing, increased the haem:non-haem ratio in cooked meat by preventing the haem molecule from liberating iron, whereas calcium ions had a negative effect on the haem:non-haem ratio during cooking of meat. Thus, the type of processing and the cooking conditions affected the content and solubility of haem and free iron in meat, determining the absorption of iron in the proximal gut, and thus the amount that entered the distal gut.

(b) Mechanisms of carcinogenesis

Possible mechanisms by which haem iron may promote colon carcinogenesis include its catalytic effect on the formation of NOCs and on the oxidation of polyunsaturated fats. A third potential mechanism involves its direct effect on colon cells (Bastide et al., 2011; Corpet, 2011; Fonseca-Nunes et al., 2014).

A first possible mechanism of tumour promotion by haem iron is related to NOC formation by *N*-nitrosation of amines and amides by bacterial decarboxylation of amino acids from meat in the presence of a nitrosating agent. A controlled feeding study showed that high–red meat consumption is associated with greater excretion of ATNC (Cross et al., 2003). ATNC is a collective term that encompasses nitrosyl iron, *S*-nitrosothiols, nitrosamines, and nitrosamides. In another controlled feeding study, the endogenous production of NOCs was further enhanced when the diet contained haem iron from blood sausage compared with red or white meat (Cross et al., 2003; Hammerling et al., 2015). The main ATNC in the faeces of study participants fed a red meat diet was nitrosyl haem, but in those fed cured meat, NOCs predominated (Joosen et al., 2009; Corpet, 2011). Similarly, in animal studies, diets containing red and processed meat increased faecal NOCs (Mirvish et al., 2003; Demeyer et al., 2015). Some NOCs are carcinogenic compounds, inducing multisite tumours in animals (Lijinsky, 1992).

Several mechanisms have been suggested to explain the effect of haem on faecal ATNC content. One hypothesis concerns the combined action of haem and free thiols on NOC formation. Nitrosothiols are readily formed under the acidic conditions of the stomach, a process that is promoted by haem, and may release nitric oxide (NO) once they are exposed to the alkaline and reductive conditions of the small and large intestine, thereby stimulating the nitrosylation of haem iron. Nitrosyl haem is an NO donor and can act as a nitrosating agent in the lower gut (Kuhnle et al., 2007). Although an increase in ATNC after consumption of red and processed meat has been demonstrated, the potential carcinogenicity of the NOCs formed in the gut is unclear (Demeyer et al., 2015); this is addressed further in Section 4.5.5. A second hypothesis that has been proposed is that changes in the microbiota may be related to NOC production (Ijssennagger et al., 2012, 2013, 2015). Ijssennagger et al. (2012) showed a distinctive shift in the colonic microbial composition of mice fed a Westernized diet (40% fat) supplemented with 0.5 µmol/g of haem iron compared with mice fed the same diet without haem iron. After 2 weeks, the colonic contents of the mice given haem iron contained higher amounts of Bacteroidetes (gram-negative) and lower amounts of Firmicutes (gram-positive) than those not given haem iron supplementation. After the haem iron supplementation, Ijssennagger et al. (2012) also observed an increase in the nitrate-reducing capacity of the colonic microflora, while the sulfate-reducing capacity was unchanged. This increase by haem iron in the nitrate-reducing capacity might be important, as considerable inter-individual variation was observed in the ability of different individual porcine and human microbiota to form NOCs and NOC-specific DNA adducts (Engemann et al., 2013; Vanden Bussche et al., 2014). Similarly, Van Hecke et al. (2014b) showed that haem iron had a stimulating effect on O^6-CMG production during in vitro fermentation of meat.

A second possible mechanism of tumour promotion by haem iron involves its ability to catalyse the oxidation of polyunsaturated fats (Corpet, 2011). The formation of lipid oxidation products is discussed in Section 4.5.2. Tumour promotion was found to be associated with increased urinary excretion of DHN-MA, a fat peroxidation biomarker, in rats after intake of haem (Pierre et al., 2006). An increase in this biomarker was also observed in humans

consuming blood sausage, which is high in haem (Pierre et al., 2006).

A third possible mechanism of tumour promotion by haem iron involves a direct effect of haem or one of its metabolites on colon cells. In vitro studies by Glei et al. (2002) showed that, when haemoglobin was added to a culture medium, it was taken up by human colon cells and participated in the induction of oxidative DNA damage such as DNA breaks and oxidised bases. As reported in Section 4.2.6, the Van der Meer group (e.g. Sesink et al., 1999) showed that supplementing a diet with hemin chloride, which is not present in food, increased epithelial proliferation and enhanced apoptosis in the colonic mucosa, and induced cytotoxicity in faecal water. Cytotoxicity-induced stress, rather than oxidative stress of surface cells, was the determinant of hemin-induced hyperproliferation.

(c) Epidemiological studies

Methods for estimating haem intake in epidemiological studies are varied. The information on haem iron concentrations in meats was sparse, partially due to the lack of appropriate analytical methods, and the variable concentrations across the range of meat types (e.g. beef, chicken, or pork), cuts of meats from the same animal, and methods of preparation (Kongkachuichai et al., 2002; Lombardi-Boccia et al., 2002; Cross et al., 2012). Two methods for estimating haem iron were to use 40% of total iron from meat (Lee et al., 2005) or to use meat-specific proportions (65% for beef; 39% for pork, ham, bacon, pork-based luncheon meats, and veal; and 26% for chicken and fish) (Balder et al., 2006). Recently, a haem iron database and complementary FFQs were developed to estimate haem iron intake from meats prepared by different cooking methods to a range of doneness levels (Cross et al., 2012) for use in etiological studies.

The inconclusive data for an association between haem iron intake and a variety of cancers may be partially explained by inconsistencies in the methods used to measure haem iron intake. Haem iron was positively associated with colorectal adenomas in two cohort studies: the PLCO trial (Ferrucci et al., 2012) and the National Institutes of Health – American Association of Retired Persons (NIH-AARP) Diet and Health Study (Cross et al., 2010). In a meta-analysis of five prospective studies, the summary relative risk for cancer of the colon was 1.18 (95% CI, 1.06–1.32) for those in the highest versus lowest category of haem iron intake (Bastide et al., 2011). In two other meta-analyses of eight studies each, the summary relative risks for cancer of the colorectum were 1.14 (95% CI, 1.04–1.24) for the highest versus the lowest category of haem iron intake (Qiao & Feng, 2013) and 1.08 (95% CI, 1.00–1.17) for an increase of 1 mg/day in the intake of haem iron (Fonseca-Nunes et al., 2014). Although these analyses were suggestive of a significant but modest increased risk, the measurement of haem iron intake differed in each of the studies included.

In the NIH-AARP study, individuals in the highest category of haem iron intake were at increased risk of cancer of the lung (Tasevska et al., 2009) and prostate (Sinha et al., 2009), as well as chronic liver disease mortality (Freedman et al., 2010), but not hepatocellular carcinoma (hazard ratio, HR, 0.95; 95% CI, 0.68 –1.32; top vs bottom quintile) (Freedman et al., 2010), non-Hodgkin lymphoma (Daniel et al., 2012b), or cancer of the breast (Kabat et al., 2010); haem iron intake was also not associated with cancer of the breast in the PLCO trial (Ferrucci et al., 2009). In a meta-analysis of four studies, the summary relative risk for cancer of the breast was 1.03 (95% CI, 0.97–1.09) (Fonseca-Nunes et al., 2014), and the summary relative risk for cancer of the lung was 1.12 (95% CI, 0.98–1.29) for an increase of 1 mg/day in the intake of haem iron (Fonseca-Nunes et al., 2014). Results were heterogeneous for cancer of the stomach (Fonseca-Nunes et al.,

2014) and oesophagus (Cross et al., 2011a; Steffen et al., 2012).

Regarding specific gene mutations in colorectal tumours, haem iron intake was positively associated with an increased risk of colorectal tumours with P53 overexpression, but not colorectal tumours without P53 overexpression in the NLCS (Gilsing et al., 2013). Haem iron intake was associated with an increased risk of colorectal tumours harbouring G→A transitions in *K-RAS* and *APC*, and overexpression of TP53 (Gilsing et al., 2013).

4.5.2 Lipid oxidation products

(a) Lipid oxidation in meat

The oxidation of unsaturated fatty acids in meat results in the formation of lipid oxidation products, which are in part cytotoxic and genotoxic (Kanner, 2007; Guéraud et al., 2010). Polyunsaturated fatty acids are especially sensitive to oxidation, which proceeds via a free radical chain reaction involving initiation, propagation, and termination steps. Transition metals, especially iron, catalyse this reaction, in the presence of oxygen, producing unstable ROS, including superoxide, hydrogen peroxide, and hydroxyl radicals. The ROS initiates a chain of oxidative reactions, generating lipoperoxyl radicals and lipid hydroperoxides. Lipid hydroperoxides may decompose to several low-molecular-mass break-down products, such as aldehydes and hydroxyalkenals, or condense to polymers. The main lipid peroxidation by-products are malondialdehyde (MDA) and 4-HNE (Marnett, 2000; Fig. 4.1); both of these lipid oxidation end products are risk factors to human health (Kanner, 2007; Bastide et al., 2011). MDA is most abundant and can reach 300 μM or more in meat products (Kanner, 2007). It is also toxic and binds to DNA and proteins, or undergoes further oxidation to more reactive epoxy derivatives that can be mutagenic in bacterial, mammalian, and human cells (Basu & Marnett, 1983; Esterbauer, 1993; Guéraud et al., 2010; Bastide et al., 2011). In foods, MDA is bound mainly to the lysine residues of proteins, from which it is released in the course of digestion, as N-α-acetyl-ϵ-(2-propenal) lysine (Piche et al., 1988).

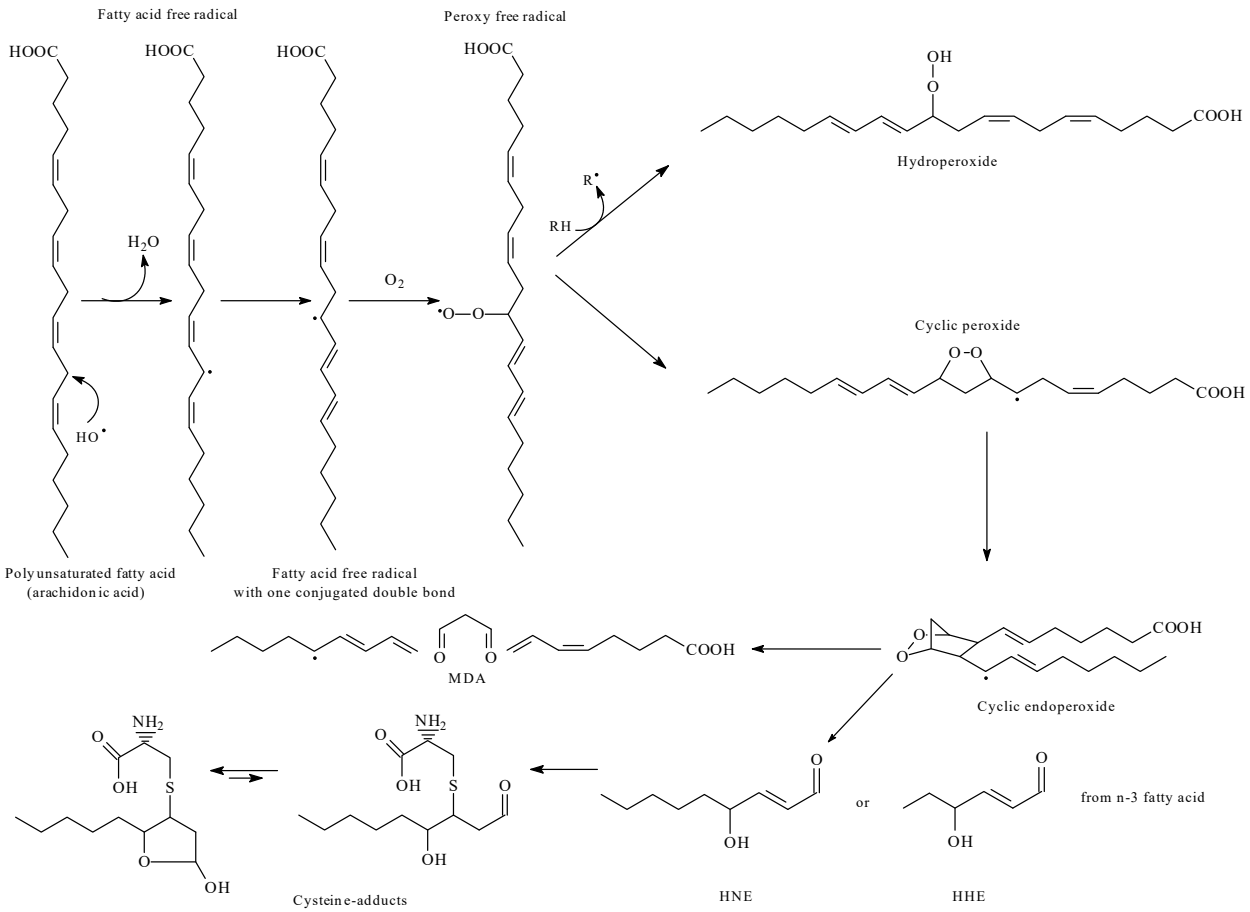
The fat fraction of meat also contains cholesterol, and it is known that dietary fatty acids and dietary cholesterol are co-oxidized (Kanner, 2007). Cholesterol oxidation via lipid free radicals results in the formation of many oxidation by-products, such as oxycholesterol, which has cytotoxic, pro-oxidant, and proinflammatory activities (Lemaire-Ewing et al., 2005). The amount of oxycholesterol in cholesterol-rich food products, including precooked meat and poultry, can reach 10–100 μM (Kanner, 2007).

The degree of lipid oxidation during the manufacturing of processed meat and storage of fresh and processed meat before consumption depends on many factors, such as the iron and polyunsaturated fatty acid content; the presence of endogenous or added antioxidants, and other additives; and the processing and storage conditions (Morrissey et al., 1998). When good storage and processing practices are followed, the levels of lipid oxidation products in meat at the time of consumption are low. Oxidation of myoglobin and other proteins also occurs, which can interfere with lipid oxidation (Faustman et al., 2010).

(b) Lipid oxidation during digestion of meat

The composition of meat and the conditions prevailing in the different compartments of the digestive tract, including interactions with other foods, determine the extent of formation of lipid oxidation products during the digestion of meat. Saliva in the mouth, acidic gastric juice in the stomach, emulsifying pancreatic and bile juice in the small intestine, and anaerobic fermentation by the microbiota in the large intestine all influence lipid oxidation in the gut. Kanner & Lapidot (2001) showed that lipid oxidation in heated muscle tissue was enhanced in the stomach due to the low pH and dissolved oxygen.

Fig. 4.1 Generic scheme of polyunsaturated fatty acid peroxidation



HHE, 4-hydroxy-2E-nonenal; HNE, 4-hydroxy-2E-hexenal; MDA, malondialdehyde

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Extensive evidence is available indicating that haem iron in red and processed meat is a key factor in promoting lipid oxidation (Carlsen et al., 2005). Feeding rats heated red turkey cutlets, which are high in haem, increased lipid hydroperoxides and MDA in the stomach (Gorelik et al., 2008). As previously noted, urinary excretion of DHN-MA was increased in rats fed haem and in humans fed blood sausage (Pierre et al., 2006). Plasma MDA concentrations were higher in rats fed beef versus chicken (Toden et al., 2010). Higher MDA, 4-HNE, and hexanal concentrations resulted from in vitro duodenal and colonic digests of beef compared with pork, followed by chicken (Van Hecke et al., 2014a).

A large proportion of ingested haem iron reaches the colon (Pierre et al., 2008), and could thus stimulate oxidation reactions in the colonic contents. However, lower MDA, 4-HNE, and hexanal concentrations resulted from in vitro colonic compared with duodenal digests (Van Hecke et al., 2014a, b; Vanden Bussche et al., 2014). This could be due to the anaerobic conditions in the colon, degradation or metabolism into other compounds. The colonic microbial composition likely also has an influence on

oxidation processes (Huycke & Moore, 2002; Sun et al., 2010; Martin et al., 2015).

The high-fat content of many processed meats is likely to result in an increased production of lipid oxidation products. In vitro digestion of a heated pork product containing 5% or 20% pork lard resulted in a higher production of 4-HNE and hexanal compared with heated lean pork containing 1% fat (Van Hecke et al., 2014b). The fatty acid profile is also important. Urinary MDA and DHN-MA in rats increased when haem iron was combined with fish oil (high in n-3 fatty acids) and safflower oil (high in n-6 fatty acids), but not with hydrogenated coconut oil (98% saturated fatty acids) (Guéraud et al., 2015). Similarly, levels of hepatic 4-HNE-histidine protein adducts were higher when haem iron was combined with safflower oil compared with hydrogenated coconut oil.

During the heating of meat, the content of free Fe^{2+} increases through destruction of the haem-porphyrin moiety, oxymyoglobin releases oxygen with production of hydrogen peroxide, and antioxidant enzymes (e.g. glutathione peroxidase) are inactivated (Kanner, 1994). This stimulates the Fenton reaction, and thus the formation of lipid oxidation products. Rats consuming cooked meat products had increased faecal TBARS and urinary DHN-MA compared with rats consuming raw meats (Santarelli et al., 2010). Similarly, heating compared with not heating a pork product increased the formation of MDA, 4-HNE, and hexanal before and during digestion (Van Hecke et al., 2015).

Nitrite salt is widely used as a curing agent in meat processing. Nitrite has antioxidant properties in processed meat. The formed nitric oxide myoglobin, nitric oxide ferrous complexes, and *S*-nitrosocysteine have antioxidant properties, and nitric oxide inhibits the Fenton reaction (Kanner, 1994). In acidic conditions, such as in the stomach, nitrous acid generates dinitrogen trioxide and water, which is in equilibrium with nitric oxide (NO) and nitrogen dioxide (NO_2) (Honikel, 2008). The balance between NO and ROS has been described as a determinant of the effect of nitrite on oxidant reactions whereby a 1:1 ratio of NO to ROS enhances lipid peroxidation, whereas an excess of NO inhibits oxidation (Darley-Usmar et al., 1995). A study using rats showed that addition of nitrite to meat products reduced TBARS in faecal water (Santarelli et al., 2010). Chenni et al. (2013) found that intake of nitrite through drinking-water (1 g/L) reduced haem-induced lipid peroxidation in the colon of rats by 25%. During in vitro digestion of different nitrite-cured meat products, the formation of lipid oxidation products was markedly inhibited (Van Hecke et al., 2014a, b, 2015). However, this inhibition was less efficient when the fat content of the diet was high (20% fat), and absent when the meat products were subjected to intense heating. The intensely heated meat products, in which nitrite was less efficient at preventing oxidant reactions, contained less residual nitrite.

(c) Absorption, distribution, metabolism, and excretion

A vast amount of literature is available concerning the biotransformation of lipid oxidation products. With respect to toxic aldehydes, the Working Group refers to extensive reviews of Esterbauer et al. (1991) and of Guéraud et al. (2010), and of Poli et al. (2008) for 4-HNE specifically. Most lipid peroxidation–derived aldehydes such as 4-HNE can travel across membranes by passive diffusion. Metabolism occurs in most cells and tissues, and is rapid and complete. As a first and major step is conjugation with glutathione by Michael addition, which may be considered a detoxification reaction, facilitating urinary excretion. Other modifications of the aldehyde function may also occur (e.g. reduction into an alcohol or oxidation into an acid). The liver and the kidneys are the organs primarily involved in the elimination of 4-HNE. DHN-MA appears to be the major urinary metabolite of 4-HNE. MDA is metabolized to carbon dioxide and water via

transformation into acetaldehyde, but it is also found unmodified in urine and plasma (Guéraud et al., 2010).

(d) Mechanisms of carcinogenesis

Due to their chemical reactivity, aldehyde breakdown products of lipid oxidation can covalently modify nucleic acids, proteins, and lipids (Guéraud et al., 2010). They also serve as biomarkers of oxidative stress, and are important in cell signalling in both pathological and physiological conditions, mainly in cell cycle regulation. 4-HNE is able to exert cytotoxic, mutagenic, and genotoxic effects. Similarly, MDA has mutagenic and genotoxic properties (Esterbauer, 1993; Guéraud et al., 2010).

After meat consumption, the levels of lipid peroxidation products and their adducts or metabolites increase. For instance, lipid hydroperoxides and MDA accumulation increased more than twofold in the stomach contents of rats fed red turkey cutlets and after pyloric ligation. Postprandial plasma MDA levels increased significantly by 50%. The addition of red wine polyphenols altered these outcomes (Gorelik et al., 2008). In a human study by Brown et al. (1995), urinary MDA increased from 2.1 to 23.1 μmol/day with the consumption of high quantities of cooked meat over a 7-day period. After consumption of red meat by rats and humans, excretion of both MDA and DHN-MA increased in the urine (Pierre et al., 2006, 2008).

4.5.3 Heterocyclic aromatic amines

The following discussion is restricted to studies involving exposure to HAAs as a result of the consumption of red meat or processed meat, together with studies that reported findings directly relevant to the issue of whether such exposure may account for any risk of cancer. The weight accorded to such data depended, among many other considerations, on current knowledge of the carcinogenicity of individual HAAs and of HAAs as a class. See *IARC Monographs* Volume 56 (IARC, 1993).

Meats cooked at a high temperature contain HAAs (see Section 1.2.3 and Fig. 1.2). HAAs are pyrolysis by-products formed from the reaction between creatine or creatinine found in muscle meats, amino acids, and sugars (Wakabayashi et al., 1992; Sugimura et al., 2004). HAA formation increases with the temperature and duration of cooking, and depends on the type of meat and cooking method (Cross & Sinha, 2004). More than 20 individual HAAs have been identified. After meat consumption of a fried beef meal by human subjects, 24-hour hydrolysed urine contained 2–8.5% PhIP and 13–32% MeIQx of the ingested dose (Reistad et al., 1997).

Most HAAs are potent bacterial mutagens, based on the Ames *S. typhimurium* test (Ames et al., 1973; Felton et al., 2007). In 1993, the Working Group concluded that HAAs are *possibly or probably carcinogenic to humans*, including IQ (*Group 2A*), MeIQ (*Group 2B*), MeIQx (*Group 2B*), and PhIP (*Group 2B*) (IARC, 1993).

(a) Mechanisms of carcinogenesis

Most HAAs are not mutagenic or carcinogenic in their parent form. HAAs acquire the capacity to form DNA adducts and potentially cause DNA damage only after metabolic activation. HAAs undergo rapid and extensive metabolism by phase I and II XMEs (Alexander et al., 1995; Turesky & Le Marchand, 2011), which can lead to either bioactivation or detoxification of the HAAs, as discussed in Section 4.4.

HAA–DNA adduct formation is considered a biomarker for the mutagenic and carcinogenic potential of these xenobiotic compounds (Cheng et al., 2006). Many HAAs have been shown to form DNA adducts in both in vitro and in vivo experiments (Cheng et al., 2006; Turesky & Le Marchand, 2011). The major reaction of the *N*-hydroxy-HAA derivatives with DNA occurs at deoxyguanosine (dG) to produce dG-C8-HAA adducts, where bond formation occurs between

the C8 atom of dG and the activated exocyclic amine group of the HAA (Schut & Snyderwine, 1999; Turesky & Vouros, 2004). For IQ and MeIQx, DNA adducts also form at the N^2 group of dG and the C5 atom of the heterocyclic ring structures (Turesky & Vouros, 2004; Turesky & Le Marchand, 2011). While the amount of dG-N^2 adducts formed is small relative to the dG-C8 isomers, the dG-N^2 adducts can persist in vivo (Turesky & Vouros, 2004; Turesky & Le Marchand, 2011).

In addition to DNA adduct formation, HAAs may exhibit other carcinogenic mechanisms. For example, PhIP may also possess estrogenic activity at very low doses (10^{-9} to 10^{-11} M), which can invoke a mitogenic response (Lauber et al., 2004). PhIP at doses as low as 10^{-11} M had direct effects on a rat pituitary lactotroph model, and induced cell proliferation and the secretion of prolactin. These PhIP-induced effects were suppressed by an estrogen receptor inhibitor. Such hormone-like activities of PhIP provide mechanistic plausibility for carcinogenicity in the breast (Lauber & Gooderham, 2007).

Considerable interspecies differences have been found in the carcinogenicity, mutagenicity and metabolism of HAAs (Hengstler et al., 1999). Carcinogenicity studies have been performed in rats, mice, and monkeys (Ohgaki et al., 1985; Adamson et al., 1990; Hengstler et al., 1999). In rodents, long-term feeding of HAAs induced tumours of the oral cavity, liver, stomach, colon, pancreas, and prostate gland in males and mammary gland in females (Turesky & Le Marchand, 2011). IQ was shown to be a potent hepatocarcinogen in cynomolgus monkeys, but MeIQx failed to induce hepatocellular carcinoma after a 5-year dosing period (Hengstler et al., 1999). Species differences in mutagenicity were most pronounced for MeIQx in *S. typhimurium* strain TA98 (Ames test) using liver microsomes from cynomolgus monkeys, rats, and humans. Higher mutation rates occurred with human and rat, than with cynomolgus monkey microsomes. DNA adduct levels were highest in male rats, followed by female rats, and were much lower in cynomolgus monkeys after an oral MeIQx dose. Species differences in the bioactivation of PhIP were also observed among in human, rat, and mouse hepatic microsomes, with those of human origin having the highest capacity to catalyse the initial activation step to *N*-hydroxy-PhIP (Hengstler et al., 1999).

The total dose required to induce tumours formation varied for each HAA, was species-dependent, and could range from 0.1 to 64.6 mg/kg per day in rodents (Turesky & Le Marchand, 2011). Doses of HAAs used in the animal feeding studies exceeded by several orders of magnitude the levels of HAAs found in the human diet (Stavric, 1994). However, several HAA–DNA adducts have been detected in human tissue (Turesky & Le Marchand, 2011). The results reported by Garner et al. (1999) suggest that humans metabolize HAAs differently compared with rats. After low-dose oral administration of MeIQx and PhIP, humans developed higher DNA adduct formation in colonic tissue compared with rats. Similarly, Mauthe et al. (1999) showed that low-dose MeIQx formed DNA adducts in the human colon. This implied that the human colon may be more sensitive to this compound than the mouse or rat colon. Using accelerator mass spectrometry, a tool for measuring isotopes with attomolar sensitivity, Turteltaub et al. (1999) showed that protein and DNA adduct levels in rodents were dose-dependent. The adduct levels in human tissue and blood were generally greater than those in rodents administered equivalent doses. Furthermore, the metabolite profiles for both MeIQx and PhIP differed substantially between humans and rodents, with more *N*-hydroxylation (bioactivation) and less ring oxidation (detoxification) in humans. There are also important differences between humans and rats in CYP activity and regioselectivity of HAA oxidation, which can affect the toxicological

properties of these compounds (Turesky, 2007; Turesky & Le Marchand, 2011).

(b) Epidemiological studies

Estimating HAA exposure in epidemiological studies has been difficult due to the variability of these compounds across the range of meat types, cooking methods and doneness levels. Moreover, there is a lack of gold-standard biomarkers to validate the questionnaires. Surrogate measures of HAA intake, such as cooking methods, meat doneness, and surface browning, have been used to investigate the etiological association between these mutagens and cancer risk. In addition, questionnaires with detailed cooking and doneness information have been linked to an HAA database to estimate individual HAA intake in the USA (Sinha, 2002; Sinha et al., 2005c), Sweden (Augustsson et al., 1997), and Germany (Rohrmann et al., 2009b). The HAA database was created by measuring levels of HAAs in a variety of meats cooked by different high-temperature methods to a range of doneness levels (rare, medium, well done, and very well done) (Sinha et al., 1995, 1998a, b). For example, while grilled, well-done chicken contains high levels of HAAs, roasted chicken contains very low levels of HAAs.

Urinary HAA biomarkers are good indicators of short-term intake, but such one-time measures cannot be used to estimate an individual's usual exposure level (Cross & Sinha, 2004; Turesky & Le Marchand, 2011; Busquets et al., 2013). Adducts in DNA, haemoglobin, and serum albumin have also been evaluated, but their utility in epidemiological studies at the present time is unclear (Turesky & Le Marchand, 2011). There is enthusiasm for using HAA levels in hair as a long-term measure of exposure, but the use of this measure in epidemiological studies is still being evaluated (Kobayashi et al., 2007; Turesky & Le Marchand, 2011; Kataoka et al., 2013; Iwasaki et al., 2014) (see also Section 1.4.2).

Putative DNA adducts of several HAAs have been detected in human tissues by non-specific ^{32}P-postlabelling (Totsuka et al., 1996) or immuno-histochemistry methods (Zhu et al., 2003; Tang et al., 2007), and studies have reported on the analysis of presumed PhIP–DNA adducts after acid hydrolysis of DNA in human lymphocytes or colon DNA samples (Friesen et al., 1994; Magagnotti et al., 2003). However, few studies have unambiguously identified and quantified intact HAA–DNA adducts in human biospecimens by specific tandem mass spectrometry–based methods (Gu et al., 2012).

Using detailed meat cooking questions and linkage to the HAA database, case–control and prospective studies have evaluated the association between HAA intake and cancer risk (Alaejos et al., 2008; Zheng & Lee, 2009; Abid et al., 2014). The results have been mixed, depending on the cancer site and the study population. Results considered here are from large prospective cohort studies. Both MeIQx and DiMeIQx were positively associated with cancer of the colorectum in the NIH-AARP study (Cross et al., 2010), but not with colorectal adenoma incidence in the PLCO trial (Ferrucci et al., 2012). In contrast, MeIQx was associated with colon adenomas in a cohort of men from the USA (Wu et al., 2006). PhIP intake has been linked to colorectal adenomas in the PLCO trial (Ferrucci et al., 2012) and in the EPIC-Heidelberg cohort study (Rohrmann et al., 2009b), but not to cancer of the colorectum in the NIH-AARP study (Cross et al., 2010). PhIP, MeIQx, and DiMeIQx were not associated with cancer of the colorectum in the Multiethnic Cohort Study (Ollberding et al., 2012).

Cancer of the prostate was not associated with PhIP, MeIQx, or DiMeIQx in the EPIC-Heidelberg study, the NIH-AARP study, or the Agricultural Health Study (AHS) (Koutros et al., 2008; Sinha et al., 2009; Sander et al., 2011). In contrast, in the HPFS, intake of PhIP from red meat was associated with advanced cancer of the prostate (Rohrmann et al., 2015). In the PLCO trial, PhIP, but not MeIQx or DiMeIQx,

was associated with risk of cancer of the prostate (Cross et al., 2005).

In various prospective studies, none of the HAAs considered were associated with cancer of the breast (Ferrucci et al., 2009; Kabat et al., 2009; Wu et al., 2010). Although DiMeIQx was linked to cancers of the gastric cardia (Cross et al., 2011) and pancreas (Stolzenberg-Solomon et al., 2007; Anderson et al., 2012), no association was found with cancers of the lung (Tasevska et al., 2009, 2011) or liver (Freedman et al., 2010). Similarly, no association between MeIQx intake and cancer of the liver was seen (Freedman et al., 2010). However, MeIQx intake was linked to cancers of the lung (Tasevska et al., 2009) and pancreas (Anderson et al., 2012) in the NIH-AARP study and PLCO trial, respectively. In the NIH-AARP study, both MeIQx and DiMeIQx were associated with a decreased risk of chronic lymphocytic leukaemia and small lymphocytic lymphoma (Daniel et al., 2012b). PhIP was linked to an increased risk of renal cell carcinoma (Daniel et al., 2012a), but not to cancers of the lung (Tasevska et al., 2009, 2011), bladder (Ferrucci et al., 2010b), pancreas (Stolzenberg-Solomon et al., 2007), or liver (Freedman et al., 2010).

(c) HAAs and inter-individual genetic susceptibility

As HAAs can be activated or detoxified by phase I and phase II metabolic reactions, various studies have evaluated single-nucleotide polymorphisms in the genes encoding XMEs. Results were mixed for interactions between XME polymorphisms and HAA consumption for colorectal adenomas or carcinomas (Ishibe et al., 2002; Le Marchand et al., 2002b; Chan et al., 2005b; Lilla et al., 2006; Girard et al., 2008; Shin et al., 2008; Yeh et al., 2009; Ferrucci et al., 2010a; Wang et al., 2011; Fu et al., 2012; Gilsing et al., 2012; Voutsinas et al., 2013). Some studies evaluated XMEs and HAAs for cancer of the breast (Lee et al., 2013), prostate (Nowell et al., 2004), and bladder (Lin et al., 2012). Many of these studies had a small number of cases with inadequate power or examined only a small set of single-nucleotide polymorphisms from a limited number of candidate genes. As the balance of activating and detoxifying enzymes is thought to influence carcinogen metabolism, comprehensive studies including numerous markers across multiple genes involved in xenobiotic metabolism are essential for studying this complex association. Furthermore, the inconsistencies in the data may have resulted partly from the inability of most studies to estimate specific HAAs, due to a lack of information regarding cooking technique and doneness level, or appropriate availability of biomarkers.

4.5.4 Polycyclic aromatic hydrocarbons

The following discussion is restricted to studies involving exposure to PAHs as a result of the consumption of red meat or processed meat, together with studies that reported findings directly relevant to the issue of whether such exposure may account for any risk of cancer. The weight accorded to such data depended, among many other considerations, on current knowledge of the carcinogenicity of individual PAHs and of PAHs as a class. See *IARC Monographs* Volume 92 (on PAHs) (IARC, 2010) and Volume 100F (on BaP) (IARC, 2012a).

The carcinogenicity of PAHs, specifically BaP (e.g. from active smoking, inhaling second-hand tobacco smoke, or working in coal- and tar-based industries) has prompted scrutiny of other circumstances of PAH exposure (e.g. from air pollution and dietary intake). In non-smoking, non–occupationally exposed populations, diet is frequently the major source of exposure to PAHs (IARC, 2010). Dietary intake of PAHs is often assessed by reference to levels of BaP, which is recognized as a good marker of PAH exposure. When fed to mice, BaP caused multiple tumour types, particularly in the upper gastrointestinal tract (IARC, 2010). PAHs can be formed during

the curing and processing of meat, and can be generated during cooking through pyrolysis of fat, particularly if the meat is charred or burned (Phillips, 1999). See Section 1 for further discussion on PAH levels and PAH occurrence in different meat preparations.

(a) Mechanisms of carcinogenesis

The carcinogenic mechanisms of PAHs are extensively reviewed in *IARC Monographs* Volume 92 and Volume 100F, and include activation and detoxification by phase I and II XMEs.

In a study of 114 subjects (48 women, 66 men), Cocco et al. (2007) reported that frequent intake of grilled meat was a predictor of urinary 1-hydroxypyrene levels of 0.50 μg/g creatine or greater. In the study previously described in Section 4.2 by Chien & Yeh (2010), consumption of barbecued meat (with higher PAH content) resulted in a significant correlation between urinary 8-OHdG concentrations, and 1-hydroxypyrene and 3-hydroxy-BaP concentrations.

A case–control study reported higher PAH–DNA adduct levels in colorectal adenoma cases (median, 1.4 adducts per 10^8 nucleotides) than in polyp-free controls (median, 1.2 adducts per 10^8 nucleotides; $P = 0.02$) (Gunter et al., 2007). The DNA adduct levels were measured by chemiluminescence immunoassay (using an antiserum elicited against DNA modified with (±)-7β,8α-dihydroxy-9α,10α-epoxy-7,8,9,10-tetrahydrobenzo[*a*]pyrene, which recognizes several PAHs bound to human DNA). Rothman et al. (1990, 1993) found PAHs in urine and DNA adducts in white blood cells. These data support that PAHs are absorbed from the consumption of grilled meat and have a genotoxic effect.

(b) Epidemiological studies

Dietary intake of PAHs, irrespective of the dietary source, has been examined in relation to a range of tumour types, including colorectal adenoma (Sinha et al., 2005a), cancer of the breast (Rundle et al., 2000; Jeffy et al., 2002; Mordukhovich et al., 2010), cancer of the stomach (Liao et al., 2014), and renal cell carcinoma (Daniel et al., 2011). Some positive associations were reported, specifically in relation to colorectal adenoma.

Based on the BaP intake of participants, determined using the Computerized Heterocyclic Amines Resource for Research in Epidemiology of Disease (CHARRED) developed by the National Cancer Institute (NCI), various studies have evaluated PAHs. While studying the association between meat intake and cancer of the colon, a case–control study in North Carolina, USA (Butler et al., 2003), determined levels of BaP intake. Associations with BaP intake, stratified by race, were imprecise, but stronger effects were seen among African Americans than among white Americans. In a large prospective study of meat consumption and risk of cancer of the colorectum, BaP intake was not associated with cancer of the colorectum (Cross et al., 2010). In a study of screening-detected colorectal adenoma (Sinha et al., 2005b) evaluating dietary intake of PAHs, an increased risk of adenoma of the descending colon and sigmoid colon was observed with BaP intake. exposure to BaP from meat consumption was not associated with a risk of cancer of the colorectum in an investigation of the postulated association between high consumption of meat and colorectal carcinoma in a case–control study in Western Australia (Tabatabaei et al., 2010).

No association between PAHs and cancer of the breast was found in a large population-based case–control study that evaluated dietary intake of PAHs from cooked meat, determined by self-administered Block FFQs (Steck et al., 2007). However, this same study did find an association with intake of BaP from meat in postmenopausal women whose tumours were positive for both the estrogen receptor and progesterone receptor.

Daniel et al. (2011) undertook a case–control study that examined exposure to PAHs from meat intake in 1192 newly diagnosed renal cell

carcinoma patients and 1175 controls. Risk of malignancy increased with intake of BaP. Risk of renal cell carcinoma was more than two-fold higher in African Americans and current smokers.

In a population-based case–control study, Girard et al. (2008) investigated whether cancer of the colon was associated with genetic variations in *UGT1A1* and *UGT1A9*. The *UGT1A1*–53 and –3156 genotypes significantly modified the association between dietary BaP and cancer of the colon. The strongest association between dietary BaP exposure was observed in those with less than 7.7 ng/day of BaP exposure and low-activity genotypes. These data support the hypothesis that UDP-glucuronosyltransferases (UGTs) modify the association between meat-derived PAH exposure and cancer of the colon.

4.5.5 N-*Nitroso compounds*

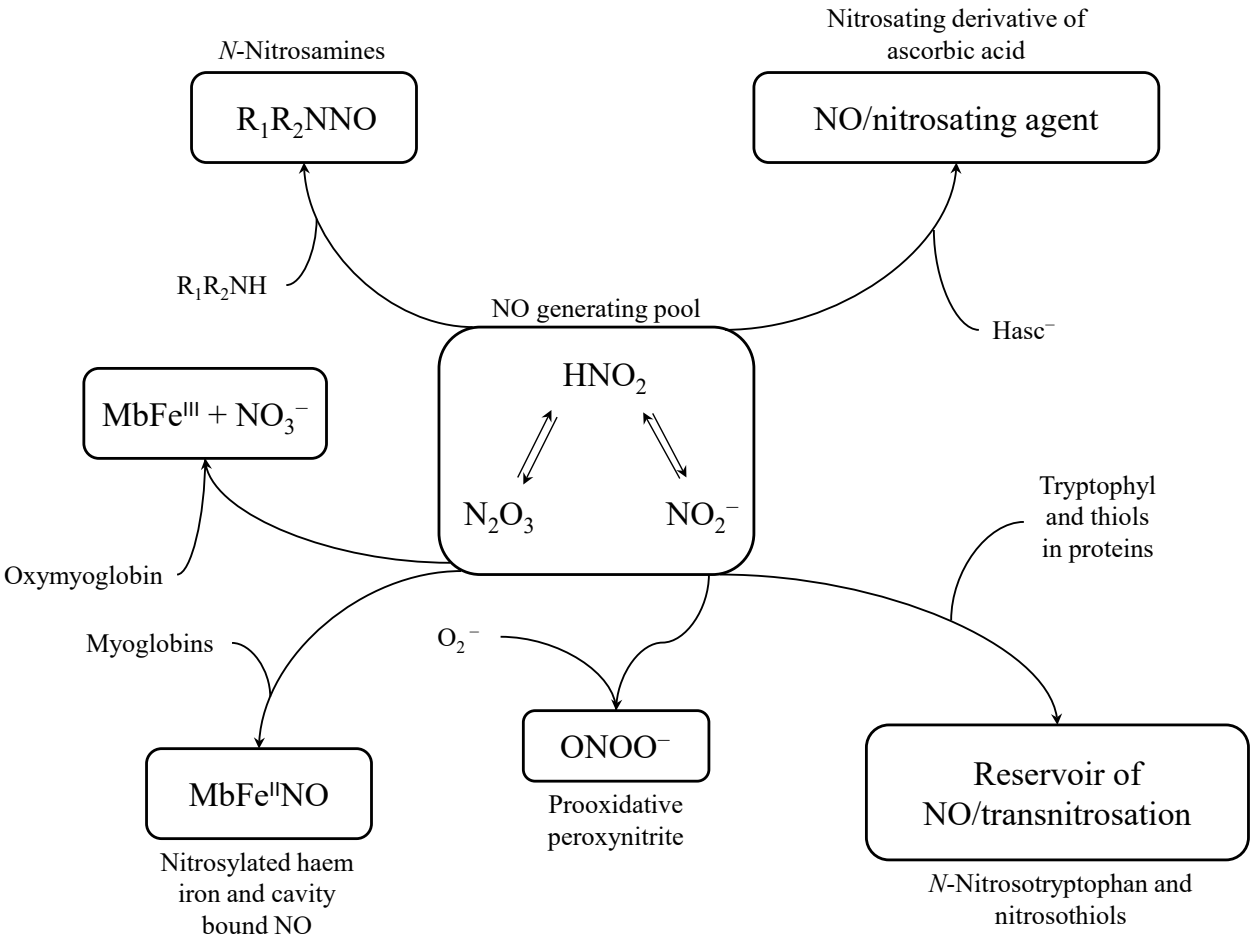
The following discussion is restricted to studies involving exposure to NOCs as a result of the consumption of red meat or processed meat, together with studies that reported findings directly relevant to the issue of whether such exposure may contribute to any risk of cancer. The weight accorded to such data depended, among many other considerations, on current knowledge of the carcinogenicity of individual NOCs and of NOCs as a class. See *IARC Monographs* Volume 89 (IARC, 2007) and Volume 100E (IARC, 2012b) for NOCs, and Volume 94 (IARC, 2010) for ingested nitrate and nitrite.

NOCs can be produced during processing, storage, and preparation of foods. They are formed by the reaction of secondary amines (R_1NHR_2) and *N*-alkylamides ($R_1NH{\cdot}CO{\cdot}R_2$) with nitrite in food or in the acidic environment of the stomach (Honikel, 2008). Metabolism of nitrosamines or spontaneous breakdown of nitrosamides can give rise to reactive alkylating intermediates, which can be identified by their reaction with DNA and other macromolecules. Nitrosation of primary amino acids, including glycine and methionine, may also give rise to alkylating intermediates (Issenberg 1976; Mirvish, 1995). NOCs are genotoxic carcinogens associated with particular mutational signatures (Rao, 2013).

The general term NOC covers all substances with *N*-nitroso groups, including *N*-nitrosamines and *N*-nitrosamides. However, the analytical method generally used to analyse NOCs in digestion does not differentiate between *N*-nitrosamines and other compounds such as *S*-nitrosothiols, *O*-nitroso compounds, and iron nitrosyls (Kuhnle & Bingham, 2007). Given this lack of specificity, the term ATNC has been used to describe the substances measured by this technique. Nitrosyl haem and nitrosothiols have been identified as major constituents of both faecal and ileal ATNC, and the formation of these compounds increases significantly after consumption of a diet rich in red meat. Nitrosothiols are readily formed under the acidic conditions of the stomach, a process that is promoted by haem. Haem becomes easily nitrosylated under the anaerobic and reductive conditions of the lower gut to form nitrosyl haem, which is an NO donor and can act as a nitrosating agent. In turn, nitrosothiols can act as NO donors and nitrosating species. Thus, the combined actions of haem and free thiol groups can promote the endogenous formation of NOCs (Kuhnle et al., 2007).

Nitrite used in meat processing is involved in many reactions with myoglobin, proteins, and lipids (Honikel, 2008; Skibsted, 2011; Demeyer et al., 2015; Fig. 4.2). When combined with myoglobin, these reactions result in nitrosomyoglobin in cured meat and nitrosyl haemochromogen after cooking, which are responsible for the characteristic colour of cured meats. Residual nitrite in cured meat proteins may be important as a "hidden NO-generating pool", a source of nitric oxide for numerous reactions during the storage and cooking of cured meats (Skibsted, 2011).

Fig. 4.2 Nitric oxide formed from nitrite during meat curing can participate in numerous reactions modifying proteins and pigments



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The occurrence of nitrate, nitrite, and NOCs in meat is discussed in Section 1. Mirvish et al. (2002) reported that NOC and NOC precursor levels in hot dogs were about 10 and 4 times higher, respectively, than those in fresh meat. The NOC precursors were considered of greater relevance to carcinogenicity, as they are more stable and approximately 1000 times more abundant than NOCs. The main NOC precursors identified were *N*-glycosyl amino acids and peptides. Dich et al. (1996) described dietary intake of nitrate, nitrite, and *N*-nitrosodimethylamine (NDMA) in 5304 men and 4750 women who participated in the Finnish Mobile Clinic Health Examination Survey in 1967–1972. Dietary nitrite was mainly provided by meat products (specified as cured meats, cooked sausage, and salami), contributing about 95% of the total intake. The mean daily intake of NDMA was calculated to be 0.052 μg, approximately half of which was derived from meat products.

(a) Absorption, distribution, metabolism, and excretion

Few studies have reported on the absorption, distribution, metabolism, and excretion of NOCs after meat consumption. Human saliva contains nitrate and nitrite due to enterosalivary circulation (Mirvish et al., 2000). Since rats convert a low amount of salivary nitrate into nitrite, it has been argued that the rat may not be a good model for humans (Cockburn et al., 2013). Therefore, Chenni et al. (2013) tested the relevance of this enterosalivary cycle by giving haem iron–fed rats drinking-water containing sodium nitrite, mimicking human salivary nitrite levels. They observed increased faecal ATNC. Phillips et al. (1975) showed that NDMA is absorbed in the rat stomach and the small intestine. Zhou et al. (2014) also reported increased urinary ATNC in rats fed sodium nitrite and/or hot dogs. In a rat model, Santarelli et al. (2010) showed that a combination of nitrite curing, cooking, and oxidation of red meat increased faecal ATNC. In addition, rats fed a diet containing commercially purchased hot dogs or fermented, raw, dry sausages had increased faecal ATNC compared with those fed a control diet without meat (Santarelli et al., 2013). Intake of sodium nitrite (0.17 g/L) and sodium nitrate (0.23 g/L) through drinking-water increased faecal ATNC in rats on a 1% haemoglobin diet (Chenni et al., 2013).

Several mechanisms have been proposed to explain the effect of red meat on the formation of NOCs. Lunn et al. (2007) observed no difference in ATNC levels in the ileal output of ileostomists and in the faecal output of healthy subjects consuming large amounts of red meat. In contrast to the stomach contents, which consisted only of nitrosothiols, nitrosyl iron was present in higher concentrations than nitrosothiols in ileal and faecal samples, with no difference in ATNC composition between both sample types (Kuhnle et al., 2007). Thus nitrosothiols formed in the acidic stomach may release NO once they are exposed to the alkaline and reductive conditions of the small and large intestine, thereby stimulating the nitrosylation of haem iron. However, the consequences of the formation of these products are unclear (Hogg, 2007). On the one hand, nitrosyl haem and nitrosothiols could act as nitrosating agents and promote the formation of NOCs in the intestinal epithelium (Kuhnle et al., 2007). On the other hand, nitrosothiols and nitrosyl iron may act as a protective mechanism by capturing NO and facilitating its excretion, thereby limiting the formation of DNA alkylating agents.

In a series of human intervention studies, Bingham and colleagues demonstrated a dose–response increase in faecal excretion of ATNC with red meat intake. This was not observed with vegetable proteins, white meat, or an Fe^{2+} supplement, but mimicked by a haem iron supplement (provided by blood sausage) (Bingham et al., 1996; Hughes et al., 2001; Bingham et al., 2002; Cross et al., 2003). Holtrop et al. (2012) conducted three dietary trials in obese men consuming body weight maintenance or weight loss diets, and measured NOCs in faecal samples. The meat-based weight loss diets increased levels of faecal NOCs ($P < 0.001$). Red meat intake was positively correlated with the faecal log NOC concentrations ($r = 0.60$; $P < 0.001$).

The genotoxic effects of faecal ATNC were investigated using different comet assay protocols in individuals consuming high levels of red meat (Cross et al., 2006a). The inter-individual effects were variable, and diet, mean transit time, and weight had no effect on faecal water genotoxicity; see also Lewin et al. (2006), as discussed in Section 4.2. Rats treated with the *N*-nitrosopeptide *N*-acetyl-*N*′-prolyl-*N*′-nitrosoglycine showed the presence of O^6-CMG in the intact small intestine. This was also observed in HT-29 cells treated with diazoacetate (Lewin et al., 2006). Since the analysis of ATNC includes both toxic and non-toxic compounds, the quantification of O^6-CMG might offer a more specific insight into the formation of genotoxic NOCs.

Although Lunn et al. (2007) and Kuhnle et al. (2007) observed no difference between ileal and faecal ATNC and its individual components, suggesting no influence of the colonic microbiota on NOC formation, other research has suggested a major facilitating role of the gut microbiota. Using a pig caecum model containing nitrate and amines/amides, Engemann et al. (2013) showed large inter-individual variation in porcine microbiota to form *N*-nitrosamines *N*-nitrosomorpholine (NMOR) and *N*-nitrosopyrrolidine (NPYR), and *N*-nitrosamides *N*-methyl-*N*-nitrosourea and *N*-ethyl-*N*-nitrosourea. Moreover, a clear increase in NOCs was observed in time, with the microbiota responsible for the reduction of nitrate to nitrite. In accordance, Vanden Bussche et al. (2014) found considerable inter-individual variation in human microbiota for the in vitro formation of the NOC-specific DNA adduct O^6-CMG during fermentation of white and red meat. This large inter-individual variation was also acknowledged by Van Hecke et al. (2014a, b, 2015). However, in vitro formation of O^6-CMG was stimulated by a higher haem iron content, a higher fat content, and more intense heating conditions, while nitrite curing was not perceived to be of influence, despite the large impact of the applied microbiota (Van Hecke et al., 2014a, b, 2015).

A broad body of evidence indicates that the formation of NOCs may be inhibited by agents including ascorbic acid and α-tocopherol (Mirvish, 1986). The inhibitory effects of nitrite, L-ascorbic acid, and α-tocopherol on the formation of NOCs in processed meat products were evaluated by comparing samples of sausage with different concentrations of these reductants (Pourazrang et al., 2002). Revertants in the *S. typhimurium* (TA100) microsome assay were significantly reduced ($P < 0.05$) by 60% when the reductants were added to the samples. In the study of Hughes et al. (2002) described in Section 4.2 evaluated the effect of soy and other dietary components on faecal NOC excretion with consumption of a high–red meat (420 g/day) diet in 11 male volunteers randomized to 15-day dietary periods. Soy significantly suppressed faecal ATNC concentrations ($P = 0.02$), but vegetables and tea extract did not affect mean faecal ATNC concentrations or faecal water genotoxicity. However, faecal weight increased and was associated with reduced transit time, decreasing contact between ATNC concentrations, nitrite, and ammonia and the large bowel mucosa.

(b) Mechanisms of carcinogenesis

For decades, experimental animal data have afforded insight into the increased risk of cancer in humans that is attributable to the consumption of different categories of meat, and specifically the possible role of NOCs (Olsen et al., 1984); see also Santarelli et al. (2010), as discussed in Section 4.3.

G→A transitions in *K-RAS* occur in cancer of the colorectum and are characteristic of the effects of alkylating agents such as NOCs (Bingham et al., 1996). The methylating agent *N*-methyl-*N*-nitrosourea produced predominantly (> 80%) transitions (GC→AT), whereas potassium diazoacetate, a stable form of nitrosated glycine, produced transitions (GC→AT) and transversions (GC→TA and AT→TA) in equivalent amounts (Gottschalg et al., 2007). The similarity in the patterns of mutations induced by potassium diazoacetate with those observed in mutated *P53* in human gastrointestinal tract tumours suggests that nitrosation of glycine (or glycine derivatives) may contribute to characteristic human *P53* mutation profiles.

(c) Epidemiological studies

Studies addressing the association between risk of cancer and dietary intake of nitrate, nitrite, or nitrosamines refer to meat as well as other relevant foods (Loh et al., 2011). [The Working Group noted that dietary intake of nitrate and nitrite does not necessarily reflect NOC intake.]

In the EPIC-Norfolk study (Loh et al., 2011), dietary NDMA intake was significantly associated with an increased risk of cancer of the rectum in women. There was no significant association between cancer risk across quartiles and dietary nitrite and endogenous NOCs. In a case–control study in Canada, NDMA intake was associated with a higher risk of cancer of the colorectum, specifically rectal carcinoma. Risk of cancer of the colorectum also increased with the consumption of NDMA-containing meats (Zhu et al., 2014). Individuals with high-NDMA and low–vitamin E intake had a significantly higher risk than those with both low-NDMA and low–vitamin E intake.

Intake of dietary nitrites and nitrosamines was positively associated with risk of cancer of the lower urinary tract in American men of Japanese ancestry (Wilkens et al., 1996). Consumption of processed meats, in particular bacon, sausage, and ham, was also significantly associated with an increased risk in American men of Japanese ancestry. Three food items accounted for all of the NOC intake: sausage (46%), bacon (33%), and luncheon meats (21%).

The association between nitrate, nitrite, and nitrosamine intake and glioma was examined by Michaud et al. (2009). Risk of glioma was not elevated among individuals in the highest intake category of nitrate, nitrite, or NDMA compared with those in the lowest intake category. In a population-based case–control study of glioma in adults, increased odds ratios were observed in males who consumed high levels of bacon, corned meats, apples, melons, and oil (Giles et al., 1994). Elevated odds ratio in men, but not women, were associated with the intake of NDMA.

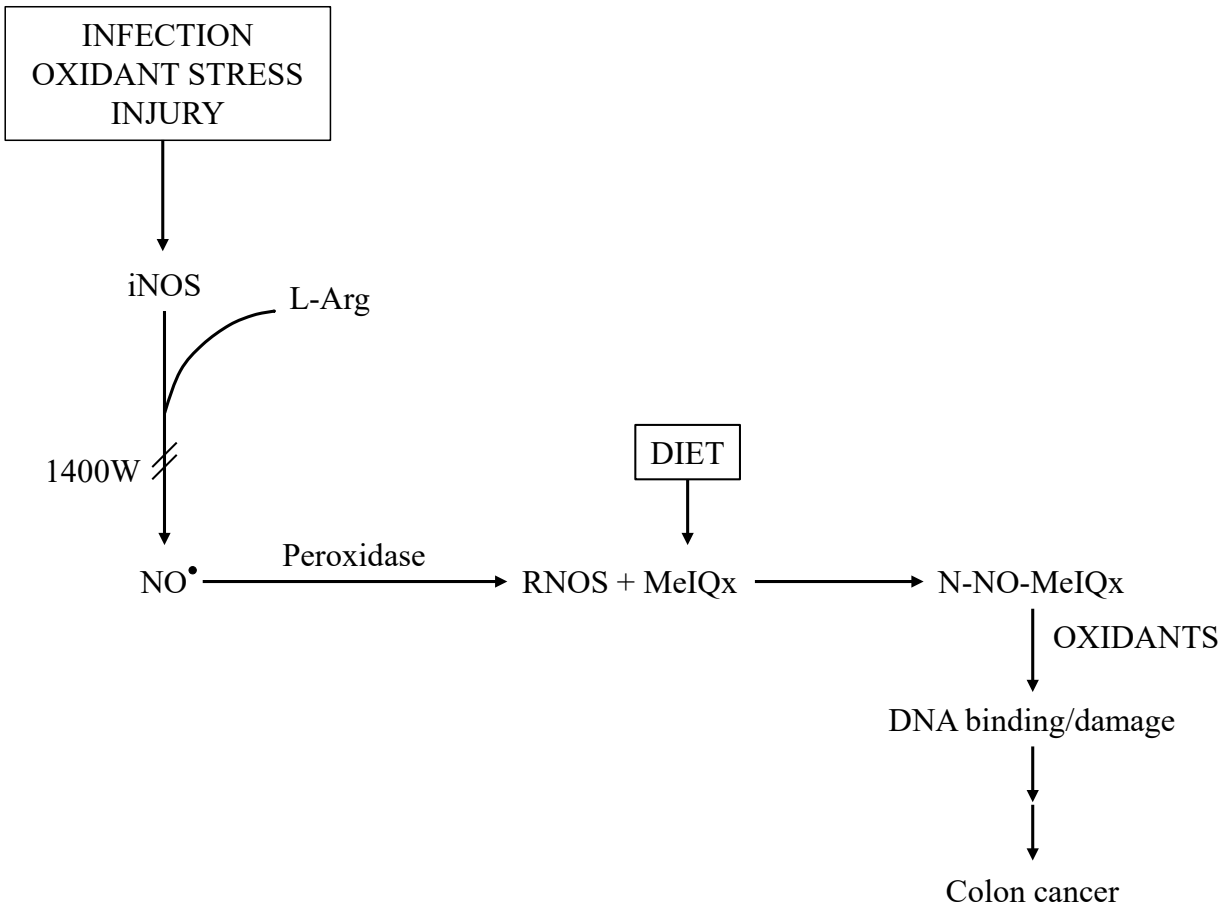
4.5.6 Interactions between NOCs, haem iron, and HAAs

Haem in red meat stimulates the endogenous production of NOCs. The effect of red meat and processed meat on endogenous nitrosation, as well as DNA damage (see Section 4.2), was investigated by Joosen et al. (2009). Faecal NOC concentrations in 5 males and 11 females on vegetarian diets were low (2.6 and 3.5 mmol/g, respectively), but significantly increased in those fed meat diets (preserved red meat, 175 ± 19 nmol/g; red meat, 185 ± 22 nmol/g; $P = 0.75$). The meat diets contained 420 g/day (males) or 366 g/day (females) of meat. The nitrite-cured meat diet had the same effect as the fresh red meat diet on endogenous nitrosation, but increased faecal water–induced oxidative DNA damage.

A high–red meat diet (420 g/day) significantly increased nitrosyl iron and nitrosothiols in ileal and faecal samples compared with a vegetarian diet (Kuhnle et al., 2007). Faecal nitrosyl iron and haem were strongly correlated ($r = 0.776$; $P < 0.0001$), suggesting that nitrosyl haem is the main source of nitrosyl iron. Nitrosation of HAAs is depicted in Fig. 4.3 (Lakshmi et al., 2005b). Lakshmi et al. (2005a) demonstrated hemin potentiation of NO-mediated nitrosation using the HAA IQ as a target and by monitoring the formation of ^{14}C-2-nitrosoamino-3-methylimidazo[4,5-*f*]quinoline (N-NO-IQ) by high-performance liquid chromatography. Faecal NOCs (Mirvish et al., 2003) and urinary nitrite and nitrate were increased in mice with dextran sulfate sodium–induced colitis, which was consistent with increased expression of inducible NO synthase and NO synthesis.

IQ and MeIQx can be converted to their corresponding *N*-nitrosamines, N-NO-IQ and 2-nitrosoamino-3,8-dimethylimidazo[4,5-*f*]quinoxaline (N-NO-MeIQx) (Zenser et al., 2009). N-NO-IQ and N-NO-MeIQx have been shown to form several putative adducts in common with those formed by 2-hydroxyamino-3-methylimidazo[4,5-*f*]quinoline (N-OH-IQ) and 2-hydroxyamino-3,8-dimethylimidazo[4,5-*f*]quinoxaline (N-OH-MeIQx). These *N*-nitrosamines might be alternatives to their hydroxylamine analogues, as

Fig. 4.3 Nitrosation of heterocyclic aromatic amines



The relationship between chronic inflammation/infection and injury, well-done red meat in the diet, and colon cancer is depicted. The inflammatory process provides NO, MPO, H_2O_2, and HOCl. Well-done red meat provides haem and HAAs (MeIQx). Together, these pathways yield *N*-nitroso compounds (N-NO-MeIQx).
Reprinted with permission from Lakshmi et al. (2005a). Hemin potentiates nitric oxide-mediated nitrosation of 2-amino-3-methylimidazo[4,5-*f*] quinoline (IQ) to 2-nitrosoamino-3-methylimidazo[4,5-*f*]quinoline. *Chem Res Toxicol*, 18(3):528–35. doi:10.1021/tx049792r PMID:15777093. Copyright (2005) American Chemical Society

activated intermediates leading to the initiation of cancer of the colon in individuals with colitis.

4.5.7 Other components

The following subsections address components or contaminants of red meat or processed meat not considered elsewhere in Section 4.5.

(a) Advanced glycation end products

AGEPs form by Maillard reaction after the initial binding of aldehydes with amines or amides in, among other places, heated foods. Within proteins, high molecular-mass AGEPs are formed whereas reactions among small molecules yield low-molecular-mass AGEPs. Some of these compounds interact with specific pro- or anti-inflammatory receptors. In observational studies, dietary AGEPs were strongly associated with late complications in diabetes (e.g., Poulsen et al., 2013).

Levels of representative AGEPs are similar in certain cheeses, fried eggs, cereal products, and broiled steak (Uribarri et al., 2010). Monitoring of representative AGEPs in 19 healthy, overweight

individuals who were fed meals of identical ingredients, prepared by either roasting or steaming, indicated that AGEPs may affect postprandial ghrelin, oxidative stress, and glucose responses (Poulsen et al., 2014). In a prospective case–control study of cancer of the colorectum, higher prediagnostic levels of the serum-soluble receptor for AGEPs were associated with a lower risk of cancer of the colorectum in male smokers; no specific relationship with any dietary constituent was reported (Jiao et al., 2011).

(b) N-Glycolylneuraminic acid

Neu5Gc is a predominant sialic acid on most mammalian cells. Humans are genetically deficient in Neu5Gc production, and the compound is metabolically incorporated into human tissue from dietary sources, particularly red meat. Neu5Gc is thus detectable on the surface of human epithelia and endothelia, and in higher amounts in malignant tissues. This xeno-autoantigen can react with circulating anti-Neu5Gc antibodies in humans. The compound has been proposed as a cancer biomarker (Samraj et al., 2014). Among the evidence for its role in tumour progression, Hedlund et al. (2008) reported that murine tumours expressing human-like levels of Neu5Gc showed accelerated growth in syngeneic mice with a human-like Neu5Gc deficiency, which coincided with the induction of anti-Neu5Gc antibodies and increased infiltration of inflammatory cells.

Samraj et al. (2015) employed what was described as an improved method to survey foods for Neu5Gc. They showed that Neu5Gc was highly and selectively enriched in red meat. In the study, Neu5Gc-deficient mice, immunized against Neu5Gc and fed bioavailable Neu5Gc from porcine saliva, developed a much higher incidence of hepatocellular carcinoma than three groups of variously identified control mice.

(c) Proposed oncogenic bovine virus

Noting the cancer incidence in Asian communities known to consume undercooked beef, zur Hausen (2012) hypothesized that the presence of one or more thermoresistant, potentially oncogenic bovine viruses contaminates beef preparations and contributes to development of cancer of the colorectum. The same, or comparable, factors were proposed to be transmitted by the consumption of milk products (zur Hausen & de Villiers, 2015). [The Working Group took note of the lack of supporting evidence for this hypothesis.]

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5. SUMMARY OF DATA REPORTED

5.1 Exposure data

This *Monograph* focuses on the consumption of red meat and processed meat. Red meat refers to fresh unprocessed mammalian muscle meat (e.g. beef, veal, pork, lamb, mutton, horse, or goat meat), which may be minced or frozen, and is usually consumed cooked. Offal (e.g. liver, kidney, heart, thymus, or brain) when consumed as such is considered to be a specific food category in food consumption surveys; however, in some epidemiological studies, offal has been reported together with red meat. Processed meat refers to any meat that has been transformed through one or several of the following processes: salting, curing, fermentation, smoking, or other processes to enhance flavour or improve preservation. Most processed meats are made from pork or beef, but may also include other meats such as poultry and/or offal, or meat by-products such as blood.

Red meat contains proteins of high biological value and important micronutrients, including B vitamins, iron (both free iron and haem), and zinc. The fat content of red meat can vary across species and breeds. For example, the fat content of the longissimus dorsi muscle of cattle ranges from 0.6% to 16% weight per weight. The fat content can also vary depending on the animal's age, sex, breed, and diet, as well as the cut of the meat. Meat may contain residues of veterinary drugs or contaminating environmental pollutants. Meat processing, such as curing and smoking can result in the formation of carcinogenic chemicals, including *N*-nitroso compounds (NOCs) and polycyclic aromatic hydrocarbons (PAHs). The cooking of meat improves the digestibility, palatability, and organoleptic quality of meat; however, it can also produce carcinogens, including heterocyclic aromatic amines (HAAs) and PAHs. The amounts of these chemicals formed in cooked red meat can vary by more than a hundredfold, depending on the kind of meat and the method of cooking (temperature, time, and heating source). High-temperature cooking by frying, grilling, or barbecuing generally produces the highest amounts of these chemicals.

In most countries for which data are available, the consumption of red meat for consumers only is around 50–100 g/day, and high consumption is more than 200 g/day. For processed meat, the mean consumption in most countries for which data are available is also about 50–100 g/day, and high consumption is more than 200 g/day. The main source of variability between countries is the percentage of consumers, which ranges from less than 5% to 100% for red meat and from 2% to 65% for processed meat. The consumption of red meat and processed meat is lower in some countries (e.g. Japan and Thailand), despite a percentage of consumers of around 90%, due to frequent substitution of meat with fish and other seafood. In developing countries for which consumption data are available (e.g. Bangladesh, Burkina Faso, and Uganda), the percentage of

consumers of red meat is less than 10%, but mean consumption is up to 90 g/day.

The tools used to assess usual dietary intake in epidemiological studies include food frequency questionnaires (FFQs), which can be calibrated and/or validated using more robust assessment methods, such as a diet history or multiple 24-hour recalls. FFQs are designed to assess dietary habits and consumption of foods, including meat and specific products containing meat; in some cases, additional information on meat cooking practices is included to provide inferences about exposure to HAAs, PAHs, or NOCs.

Biomarkers for some of these chemicals have been established, but are not exclusively attributed to the consumption of cooked meat, since PAHs, HAAs, and NOCs are also pollutants present in tobacco or tobacco smoke, and in the environment. Urinary metabolites, protein or DNA adducts, or residues of some chemicals in hair are biomarkers of exposure to HAAs, PAHs, or NOCs. Recent metabolomics approaches using plasma and urine have been implemented to assess meat consumption. The use of long-term stable biomarkers in epidemiological studies would strengthen data on exposure and health risks derived from inferences about dietary exposures obtained from FFQs.

5.2 Human carcinogenicity data

5.2.1 Cancer of the colorectum

The association between cancer of the colorectum and consumption of red and processed meat has been examined in numerous cohort and case–control studies conducted in countries in Europe, North America, South America, Asia, and Australia. There was heterogeneity across studies regarding the study design and instruments used to assess red and processed meat intake. In particular, different definitions of red meat and processed meat were used across studies, with an important source of variability being the inclusion or not of processed meat together with (unprocessed) red meat in the total red meat variables. A subset of studies (about 20) also presented data on cooking methods or preferences.

In evaluating the evidence from the epidemiological studies, the Working Group placed the most weight on the cohort studies in the general population with quantitative data on the consumption of red and processed meat derived through validated dietary questionnaires. In addition, information from the most informative case–control studies complemented the evaluation.

For both types of epidemiological studies, the Working Group judged that the most informative studies were those with a wider range of variation of meat intake, clear definition of meat variables, sufficient number of cases to investigate cancer by location within the colorectum, and adequate control for potential confounders in the statistical analysis, specifically by adjusting for age, sex, total caloric intake, and other potential confounders, such as body mass index (BMI), alcohol drinking, tobacco smoking, and several lifestyle and dietary variables. For cohort studies, those considered to be highly informative had virtually complete case ascertainment and a low number of participants lost to follow-up. For case–control studies, more weight was given to the studies that used population-based approaches for case identification and control selection.

Close to 20 large, high-quality cohort studies were considered in the evaluation, with the results of some studies reported in several publications. The follow-ups of these studies extended from as early as the 1990s until the 2010s. A large number of case–control studies (approximately 150), conducted across the world were reviewed for this evaluation. These studies captured regions of the world with a wide range of intake of red meat and processed meat.

The Working Group considered separately the data on red meat, processed meat, as well as red and processed meat combined into a single group. Fourteen cohort studies investigated the association between consumption of red meat and risk of cancer of the colorectum. Positive associations between high consumption of red meat and cancer of the colorectum were observed in seven studies, including most of the larger studies: the European Prospective Investigation into Cancer and Nutrition (EPIC) study in 10 European countries, the Swedish Mammography Cohort (SMC), and the Melbourne Collaborative Cohort Study (MCCS).

The Working Group judged that only about 10% of all reviewed case–control studies were informative for the evaluation of the consumption of red meat. Seven studies (about half of those judged informative) showed positive associations between cancer of the colorectum and consumption of one of the red meat items investigated. In several other case–control studies, although no association with consumption of red meat was observed, significant associations emerged with cooking practices (e.g. pan-fried red meat) or doneness preferences (e.g. well-done red meat). For example, in two large case–control studies including more than 4000 cases, positive associations were found with pan-fried red meat.

Eighteen cohort studies investigated the association between processed meat and incidence of cancer of the colorectum. Positive associations between consumption of processed meat and incidence of cancer of the colorectum were observed in 12 studies, including some of the larger studies: a Japanese cohort, the Nurses' Health Study (NHS), the Health Professionals Follow-Up Study (HPFS), the EPIC study, the Cancer Prevention Study II (CPS-II), and the National Institutes of Health – American Association of Retired Persons (NIH-AARP) Diet and Health Study.

The Working Group considered that approximately 10% of all case–control studies reviewed were informative for the assessment of the consumption of processed meat in relation to incidence of cancer of the colorectum. Six of the nine studies considered showed positive associations with cancer of the colorectum.

Several cohort and case–control studies investigated the association between consumption of red meat and processed meat combined and incidence of cancer of the colorectum. Positive associations between incidence of cancer of the colorectum and consumption of red and processed meat were observed in the majority of these studies.

A meta-analysis including data from 10 cohort studies reported a statistically significant dose–response association between consumption of red meat and/or processed meat and cancer of the colorectum. The relative risks of cancer of the colorectum were 1.17 (95% CI, 1.05–1.31) for an increase in consumption of red meat of 100 g/day and 1.18 (95% CI, 1.10–1.28) for an increase in consumption of processed meat of 50 g/day.

Based on the balance of evidence, and taking into account study design, size, quality, control of potential confounding, exposure assessment, and magnitude of risk, an increased risk of cancer of the colorectum was seen in relation to consumption of red meat and of processed meat. The large amount of data, strength of association, and consistency across cohort studies in different populations, including most of the larger cohort studies, makes chance, bias, and confounding unlikely as explanations for the association of consumption of processed meat with cancer of the colorectum . However, chance, bias, or confounding could not be ruled out for consumption of red meat, as no association was observed in several of the larger studies. The available evidence from a subset of studies suggested that some cooking methods used in the preparation of red meat may contribute to the observed associations.

5.2.2 Cancer of the stomach

The association between consumption of red meat and cancer of the stomach was evaluated in several cohort studies from Europe, the USA, and China. A positive association was observed in two studies (EPIC Cohort and nested case–control study from the Shanghai Cohort). Evidence was also available from two well-designed, population-based case–control studies from the USA and Canada, but the findings were somewhat inconsistent.

Among seven cohort studies, four studies showed positive associations between processed meat consumption and stomach cancer incidence. Two of these studies (the EPIC cohort study and the Swedish Cohort) reported statistically significant results. Another large study and two smaller ones did not find an association.

The majority of well-designed, population-based case–control studies, from Canada, the USA, and Mexico that reported on the association with consumption of processed meat, showed increased risks for gastric cancer, which were also statistically significant in three of the studies. A published meta-analysis reported positive associations for case–control studies, and for cohort studies. Positive associations between processed meat consumption and stomach cancer were observed in several case–control and cohort studies in diverse populations. However, the modest number of studies and lack of association in the other cohort studies suggested that chance, bias, and confounding could not be ruled out.

5.2.3 Cancer of the pancreas

Among 9 cohort studies with relevant data, 3 studies showed positive associations between consumption of red meat and cancer of the pancreas: the Multiethnic Cohort Study, a Swedish cohort of women, and the Japan Collaborative Cohort Study (JACC Study) (about 200 to > 2000 cases each). Two of these studies reported statistically significant results. The other cohort studies, including two large ones, showed no association. Data were also available from case–control studies in the USA, Canada, Italy and China. One of the two large population-based case–control studies reported a positive, statistically significant association between consumption of red meat and cancer of the pancreas, while the other reported a null result. Positive associations between consumption of red meat and cancer of the pancreas were observed in several cohort and case–control studies in diverse populations, but the modest number of studies and lack of association found in two large cohort studies suggested that chance, bias, and confounding could not be ruled out.

Among eight cohort studies, three studies showed positive associations between consumption of processed meat and cancer of the pancreas (Multiethnic Cohort Study, the Nurses' Health Study and JACC Study), which were statistically significant only in the Multiethnic Cohort Study. The other five studies showed null results. Positive associations or trends were observed in two well-designed case–control studies from North America.

5.2.4 Cancer of the prostate

More than twenty cohort studies were evaluated for consumption of red or processed meat and cancer of the prostate. The most informative studies were those with large sample sizes and accurate exposure assessments based on many food items, FFQs, information on cooking methods, and estimates of doneness.

A pooled analysis of a consortium of 15 cohort studies was based on more than 50 000 incident cases of cancer of the prostate, and reported positive associations between consumption of red meat and cancer of the prostate (mainly at advanced stages and in studies in North America), with an increased risk of 19% in the

highest intake category (P_{trend} = 0.07). Weaker associations were found for consumption of processed meat in the same pooled analysis.

Approximately a third of the cohort studies, included or not in the pooled analysis, found statistically significant associations, usually between degree of doneness (well-done meat) and advanced cancer of the prostate (The Netherland Cohort Study, The Prostate, Lung, Colorectal, and Ovarian Study, the CLUE II Study, the Agricultural Health Study and the NIH-AARP Diet and Health Study). The association between consumption of red meat as such or processed meat as such, irrespective of cooking method, and cancer of the prostate was null or weak, and not statistically significant except for cured meat in one study.

Three population-based case–control studies from the USA and New Zealand were considered informative. These studies found associations mainly or exclusively with the degree of doneness of red meat and with cancers at advanced clinical stages. One study examined a population of subjects with high levels of prostate-specific antigen who underwent biopsy, and found an association between consumption of red meat (that included ham and sausages) and increased risk of cancer of the prostate. Inconsistent results for processed meat were reported from case–control studies.

Overall, associations were described almost exclusively between the degree of doneness and advanced stages of cancer. Subgroup analysis (multiple comparisons) and reporting bias could not be ruled out. Specific methodological problems with cancer of the prostate included the heterogeneity of the definition of clinical aggressiveness and the potential confounding introduced by prostate-specific antigen levels, which could be associated with dietary habits.

5.2.5 Cancer of the breast

The most informative data on the association between consumption of red meat or processed meat and cancer of the breast were available from cohort studies with large sample sizes, accurate exposure assessments, and adequate adjustment for confounding. About 10 cohort studies (with a total of about 20 000 cases of cancer of the breast), and a consortium of eight prospective cohort studies (> 7000 cases of cancer of the breast), assessed risk of cancer of the breast in relation to consumption of red meat (which may or may not have included processed meat) in North America and Europe. Four of these cohort studies found a statistically significant positive association between risk of cancer of the breast and consumption of red meat or red and processed meat combined. Multiple case–control studies conducted in the USA, South America, Europe, and Asia provided inconsistent evidence.

About 10 cohort studies (with a total of more than 16 000 cases of cancer of the breast) assessed risk of cancer of the breast in relation to consumption of processed meat in North America and Europe. Two of these cohort studies found a statistically significant association between intake of processed meat and risk of cancer of the breast. A cohort consortium evaluated individual processed meat items and found no association with any processed meat items. As for consumption of red meat, case–control studies provided inconsistent evidence.

The available evidence did not permit the Working Group to determine whether the association between consumption of red meat or processed meat and cancer of the breast differs by menopausal status, as large amounts of data were from postmenopausal women. Similarly, insufficient data existed to determine whether this association differs by hormone receptor status. The Working Group was not able to determine the effect on risk of cancer of the breast of cooking method and doneness of red meat, and on effect modification by genetic polymorphisms.

5.2.6 Cancer of the lung

Six cohort studies contributed to the assessment of the association between consumption of red meat or processed meat and cancer of the lung. Two of the studies had large sample sizes and highly informative designs (adjusting for tobacco smoking and energy intake, and with inclusion of incident cases): the EPIC study (Europe) and the NIH-AARP study (USA).

A positive association between increasing intake of red meat and cancer of the lung was found in most prospective studies, which was statistically significant in the NIH-AARP study. Residual confounding from tobacco smoking cannot be ruled out given the strong association between smoking and cancer of the lung. Similarly positive association between consumption of processed meat and cancer of the lung detected in some cohort studies was only significant in the NIH-AARP study in men.

Several case–control studies provided relevant data for the evaluation, particularly those that stratified by smoking habits. Associations between red meat or processed meat consumption and cancer of the lung were occasionally detected. Few case–control studies and one cohort study described an association between meat intake and cancer of the lung in never-smokers alone, finding generally positive but statistically non-significant associations.

A meta-analysis reported an overall increased risk of cancer of the lung with increasing levels of intake of red meat, but not with processed meat (adjustment for relevant confounders, particularly tobacco smoking, was heterogeneous in the contributing studies). The interpretation of the findings for cancer of the lung must also consider exposure to cooking fumes among individuals who consume high levels of meat as a potential confounding variable.

5.2.7 Cancer of the oesophagus

Only three cohort studies, two with a limited number of cases, investigated the association between consumption of red meat or processed meat and different subtypes of oesophageal cancer. The results of these studies were inconsistent. Data on the consumption of red meat or processed meat were also available from multiple case–control studies; for population-based, well-designed case–control studies, the results were inconsistent.

5.2.8 Other cancers

Associations between consumption of red meat or processed meat and cancers at several other sites, including non-Hodgkin lymphoma and leukaemia, as well as cancer of the liver, gallbladder and biliary tract, thyroid, testis, kidney, bladder, ovary, endometrium, and brain (in children and in adults), were investigated in a few studies, cohorts and mostly case–control studies. However, the number and/or quality of the available studies did not permit conclusions to be drawn.

5.3 Animal carcinogenicity data

The carcinogenicity of red meat was assessed in two feeding studies in *Apc*$^{Min/+}$ mice, a strain that spontaneously develops tumours of the small intestine. In the first study in male mice, a diet containing red meat did not affect the total number of tumours in the small intestine; however, there was a significant increase in the number of tumours in the distal small intestine. In the second study in male and female mice, a diet containing red meat did not affect the number of tumours of the small intestine in either sex.

In another study, male rats fed diets containing red meat and other substances found in typical human diets had higher incidences of

tumours of the pituitary gland (pars distalis), and light-cell adenoma and carcinoma (combined) of the thyroid gland than rats fed the control diets.

In an initiation–promotion study, in which tumours of the colon in male mice were initiated with dimethylhydrazine and promoted with red meat, there was no increase in the incidence of tumours of the colon in mice fed a diet containing red meat.

Eight studies in male rats were conducted in which tumours of the colon were initiated with dimethylhydrazine and promoted with diets containing red meat. In one of the eight studies, rats fed diets containing red meat and other substances found in typical human diets had a higher incidence of adenocarcinoma of the colon than rats fed the control diets. In the other seven studies, the incidence of tumours of the colon was not increased by diets containing red meat.

In one study without a chemical initiator, a diet containing processed meat did not induce the formation of aberrant crypt foci (ACF).

Seven studies were conducted in which male or female rats were treated with dimethylhydrazine or azoxymethane, and promoted with diets containing red meat. In three of the seven studies, red meat had no effect on the occurrence of ACF or mucin-depleted foci (MDF) in the colon. In four of the seven studies, there was an increase in the occurrence of ACF and/or MDF in rats fed diets containing red meat and with a low calcium content. In one of these four studies, the comparison was made to whey protein, which may have chemopreventive activity.

Six studies were conducted in which female rats were treated with dimethylhydrazine or azoxymethane, and promoted with diets containing processed meat. In two of the six studies, processed meat had no effect on the occurrence of ACF or MDF in the colon. In four of the six studies, there was an increase in the occurrence of ACF and/or MCF in rats fed diets containing processed meat and with a low calcium content.

Haem iron, HAAs, PAHs, and *N*-nitrosamines have been identified in red meat and processed meat.

The carcinogenicity of haem iron was assessed in two feeding studies. In one study, *Apc*$^{Min/+}$mice fed haemoglobin had an increased number of tumours in the jejunum. In an initiation–promotion study in which tumours of the colon in female rats were initiated with *N*-methyl-*N*-nitrosourea and promoted with haemoglobin, there was an increased incidence of adenoma and adenocarcinoma (combined) of the colon in rats fed diets containing haemoglobin.

The carcinogenicity in experimental animals of HAAs, PAHs, and *N*-nitrosamines found in red meat and processed meat has been evaluated by the Working Groups of previous *IARC Monographs*.

5.4 Mechanistic and other relevant data

Meat is mostly composed of highly digestible protein and fat, and provides many essential nutrients. Digestion of protein and fat, which are also provided by other food types, yields toxic compounds (secondary bile acids, ammonia, phenols, and hydrogen sulfide) in the gut. These compounds are not considered further, as they are not specific to red or processed meat.

There is *moderate* evidence that the consumption of red or processed meat is genotoxic. In humans, two intervention studies found increased levels of DNA adducts putatively related to *N*-nitroso-compound (NOCs) in colonic crypts or exfoliated colonocytes of volunteers consuming high levels of red meat (300 g/day or 420 g/day). These studies and other available data provided evidence to suggest that there may be an association between consumption of red meat, and possibly processed meat, and the formation of DNA adducts in human tissue (colon and breast). Observational data in humans

showed associations between consumption of red or processed meat and gene mutations relevant to carcinogenesis in tumours of the colon. Multiple studies indicated that consuming cooked meat increased the mutagenicity of human urine in assays in bacteria. In several studies in rodents in vivo, cooked red meat induced DNA damage (DNA adducts and DNA strand breaks) in colonocytes. No genotoxic effect was reported for processed meat in one small study of four mice. Extracts from cooked red or processed meat were mutagenic in bacteria after metabolic activation.

There is *moderate* evidence that consumption of processed meat induces oxidative stress, few data are available for red meat. In three intervention studies (with blood sausage or cured pork) in humans, consumption of processed meat increased levels of an oxidative stress marker in the urine, faeces, or plasma. One observational study in humans found an association between consumption of red meat and levels of oxidative stress markers in blood. In three studies in rats, consumption of red meat increased levels of faecal and urinary lipid oxidation products, an effect reduced by calcium but not by antioxidants. In humans and experimental animals, effects on oxidative stress markers were attributed to haem iron since they could be suppressed by blocking haem iron with calcium.

There is *weak* evidence that red meat consumption alters cell proliferation, while few data are available for processed meat. In two intervention studies and one observational study in humans, consumption of red meat increased cell proliferation in the colon. No correlation was reported in a third study of red meat. In several studies in rats, consumption of red meat increased toxicity or apoptosis in colonocytes.

There is *strong* evidence from numerous studies in humans and eight studies in rodents that red meat and processed meat consumption increase the formation of preneoplastic lesions. A recent meta-analysis of consumption of red meat and processed meat in relation to adenoma of the colorectum reported a modest but statistically significant association that was consistent across studies. Red meat promoted the growth of preneoplastic lesions of the colon in carcinogen-initiated rats in three studies from two research groups. Ham, hot dog, cured pork, or blood sausage promoted the growth of preneoplastic lesions in the colon of carcinogen-initiated rats in four studies from a single laboratory. These effects in rats could be modified by calcium and antioxidants.

A large number of studies have evaluated the associations between genetic polymorphisms and cancer susceptibility associated with consumption of red meat. These studies have focused mainly on genes involved in the metabolism of carcinogens present in cooked red meat. The results of these candidate gene studies have mostly been *inconsistent*. Many were underpowered and had multiple testing and publication biases.

There is *strong* evidence that haem iron contributes to the carcinogenic mechanisms associated with red and processed meat. Haem iron mediates the formation of NOCs and lipid oxidation products in the gut of humans and rodents. Haem iron may cause cytotoxicity in the gut, based on the results of studies in humans and rodents. As previously noted, the effects of haem can be suppressed by blocking haem iron with calcium.

Consumption of red or processed meat increases the formation of lipid oxidation products in the gut in humans and in experimental animals. In rats, lipid oxidation products from consumption of red meat, but not processed meat, promote the growth of chemically initiated preneoplastic lesions of the colon, providing *moderate* mechanistic evidence for carcinogenic mechanisms associated with the consumption of red meat.

Meat heated at a high temperature contains HAAs. There is *strong* evidence that HAAs, by causing DNA damage, contribute to carcinogenic

mechanisms associated with the consumption of red meat. After exposure to HAAs, HAA–DNA adducts have been reported in the colon in studies in humans and in rodents. The extent of activation of HAAs to genotoxic metabolites is greater in humans than in rodents, and levels of specific HAA adducts are higher in human tissue than in rodent tissue after similar exposure. However, no studies of HAA genotoxicity after consumption of red meat in humans were available.

Meat smoked or cooked over a heated surface or naked flame contains PAHs. The mechanistic evidence is *moderate* that PAHs contribute to the carcinogenic mechanisms associated with the consumption of red meat and of processed meat. PAHs cause DNA damage, but little direct evidence is available following the consumption of meat. A few epidemiological studies provided some mechanistic evidence for certain cancers.

Consumption of red meat and of processed meat in humans induces the formation of NOCs in the gut based on multiple intervention studies. Direct evidence that consumption of red meat by humans leads to NOC-derived mutagenic DNA adducts in the human colon is provided by two intervention studies. There is *strong* evidence that the formation of NOCs contributes to the carcinogenic mechanisms associated with the consumption of red meat. Evidence for processed meat is less clear due to the lack of direct studies (i.e. after consumption of processed meat).

The Working Group noted that the carcinogenic mechanisms associated with the consumption of red meat and processed meat cannot be attributed to a particular meat component, and also that meat consumption is not the only context of exposure to some of these components. However, other important considerations adding considerably to the weight of the overall evidence in support of a carcinogenic mechanism for red meat and processed meat include the following: (i) strong mechanistic evidence exists for multiple interacting meat components (haem iron, NOCs, HAAs, lipid peroxidation); (ii) at least one of the effects of these components can be experimentally suppressed (i.e. haem iron by calcium); and (iii) the extent of conversion of HAAs to genotoxic metabolites is greater in humans than in rodents.

Overall, the mechanistic evidence for carcinogenicity is *strong* for red meat, based primarily on studies of colonic preneoplastic lesions in humans and rodents, and the considerable evidence concerning haem iron, HAAs, and NOCs in humans and rodents. Fewer data in humans, especially from intervention studies, are available for processed meat than for red meat. The mechanistic evidence for carcinogenicity is *moderate* for processed meat, based primarily on studies of colonic preneoplastic lesions in humans and rodents, human and other experimental evidence for NOCs, and studies of haem iron in rodents.

The carcinogenic mechanisms discussed in this section primarily apply to the digestive tract; there is little mechanistic evidence regarding other anatomical sites. The carcinogenic mechanisms discussed are likely to operate in humans.

6. EVALUATION

6.1 Cancer in humans

There is *limited evidence* in humans for the carcinogenicity of consumption of red meat. Positive associations have been observed between consumption of red meat and cancers of the colorectum, pancreas, and prostate.

There is *sufficient evidence* in humans for the carcinogenicity of consumption of processed meat. Consumption of processed meat causes cancer of the colorectum. Positive associations have been observed between consumption of processed meat and cancer of the stomach.

6.2 Cancer in experimental animals

There is *inadequate evidence* in experimental animals for the carcinogenicity of consumption of red meat.

There is *inadequate evidence* in experimental animals for the carcinogenicity of consumption of processed meat.

There is *inadequate evidence* in experimental animals for the carcinogenicity of haem iron.

6.3 Overall evaluation

Consumption of red meat is *probably carcinogenic to humans (Group 2A).*

Consumption of processed meat is *carcinogenic to humans (Group 1).*

6.4 Rationale

In making the overall evaluation, the Working Group took into consideration all the relevant data, including the substantial epidemiological data showing a positive association between consumption of red meat and cancer of the colorectum, and the strong mechanistic evidence. Taken as a whole, this evidence led the Working Group to classify red meat as *probably carcinogenic to humans (Group 2A).*

LIST OF ABBREVIATIONS

4-HNE	4-hydroxynonenal
8-OHdG	8-hydroxy-2′-deoxyguanosine
AARP	American Association of Retired Persons
ACF	aberrant crypt foci
ADI	acceptable daily intake
AGEP	advanced glycation end product
AHS	Agricultural Health Study
AIN	American Institute of Nutrition
AOCS	Australian Ovarian Cancer Study
ATBC	Alpha-Tocopherol, Beta-Carotene Cancer Prevention
ATNC	apparent total *N*-nitroso compounds
AαC	2-amino-9*H*-pyrido[2,3-*b*]indole
BaP	benzo[*a*]pyrene
BCDDP	Breast Cancer Detection Demonstration Project
BCLL	B-cell chronic lymphocytic leukaemia
BFR	brominated flame retardant
BMI	body mass index
BOP	*N*-nitrosobis(2-oxopropyl)amine
bw	body weight
BWHS	Black Women's Health Study
CBCS	Collaborative Breast Cancer Study
CCFR	Colon Cancer Family Registry
CHARRED	Computerized Heterocyclic Amines Resource for Research in Epidemiology of Disease
CI	confidence interval
CLL	chronic lymphocytic leukaemia
CNBSS	Canadian National Breast Screening Study
CPS-II	Cancer Prevention Study II
CSFII	Continuing Survey of Food Intakes by Individuals
CYP	cytochrome P450
DBCG	Danish Breast Cancer Cooperative Group
DCPP	Pooling Project of Prospective Studies of Diet and Cancer
dG	deoxyguanosine
DHN-MA	1,4-dihydroxynonane mercapturic acid

DHQ	Diet History Questionnaire
DiMeIQx	2-amino-3,4,8-trimethylimidazo[4,5-*f*]quinoxaline
DLBCL	diffuse large B-cell lymphoma
DMH	1,2-dimethylhydrazine
DNA	deoxyribonucleic acid
EAC	oesophageal adenocarcinoma
EFSA	European Food Safety Authority
EGFR	epidermal growth factor receptor
EPIC	European Prospective Investigation into Cancer and Nutrition
ER	estrogen receptor
ESCC	oesophageal squamous cell carcinoma
EU	European Union
FABP2	fatty acid binding protein 2
FAO	Food and Agriculture Organization of the United Nations
FAOSTAT	Food and Agriculture Organization of the United Nations Statistical Databases
FDA	Food and Drug Administration
FFQ	food frequency questionnaire
GCA	gastric cardia cancer
GC-MS	gas chromatography-mass spectrometry
GECCO	Genetics and Epidemiology of Colorectal Cancer Consortium
GEMS	Global Environment Monitoring System
Glu-P-2	2-aminodipyrido[1,2-*a*:3′,2′-*d*]imidazole
GNCA	gastric non-cardia cancer
HAA	heterocyclic aromatic amine
HACCP	hazard analysis and critical control point
HAMSB	butyrylated high-amylose maize starch
HBCD	hexabromocyclododecane
HHHQ	Health Habits and History Questionnaire
HIV	human immunodeficiency virus
HPFS	Health Professionals Follow-Up Study
HR	hazard ratio
IARC	International Agency for Research on Cancer
ICD	International Classification of Diseases
ICD-O	International Classification of Diseases for Oncology
IgQx	2-amino-1-methylimidazo[4,5-*g*]quinoxaline
IQ	2-amino-3-methylimidazo[4,5-*f*]quinoline
IWHS	Iowa Women's Health Study
JACC Study	Japan Collaborative Cohort Study for Evaluation of Cancer
JPHC Study	Japan Public Health Center-based Prospective Study
KCl	potassium chloride
LC-MS	liquid chromatography-mass spectrometry
LC-MS/MS	liquid chromatography-tandem mass spectrometry
LSS	Life Span Study
MCCS	Melbourne Collaborative Cohort Study
MDA	malondialdehyde
MDF	mucin-depleted foci
MeAαC	2-amino-3-methyl-9*H*-pyrido[2,3-*b*]indole
MeIQ	2-amino-3,4-dimethylimidazo[4,5-*f*]quinoline
MeIQx	2-amino-3,8-dimethylimidazo[4,5-*f*]quinoxaline
MMR	mismatch repair

MRL	maximum residue limit
MSI	microsatellite instability
MUFA	monounsaturated fatty acid
NaCl	sodium chloride
NAT	*N*-acetyltransferase
NCI	National Cancer Institute
NDBA	*N*-nitrosodi-*n*-butylamine
NDEA	*N*-nitrosodiethylamine
NDMA	*N*-nitrosodimethylamine
Neu5Ac	*N*-acetylneuraminic acid
Neu5Gc	*N*-glycolylneuraminic acid
NHPRO	*N*-nitrosohydroxyproline
NHS	Nurses' Health Study
NIH	National Institutes of Health
NLCS	Netherlands Cohort Study
NLCS-MIC	Netherlands Cohort Study – Meat Investigation Cohort
NMEA	*N*-nitrosomethylethylamine
NMOR	*N*-nitrosomorpholine
N-NO-IQ	2-nitrosoamino-3-methylimidazo[4,5-*f*]quinoline
N-NO-MeIQx	2-nitrosoamino-3,8-dimethylimidazo[4,5-*f*]quinoxaline
NO	nitric oxide
NOC	*N*-nitroso compound
N-OH-IQ	2-hydroxyamino-3-methylimidazo[4,5-*f*]quinoline
N-OH-MeIQx	2-hydroxyamino-3,8-dimethylimidazo[4,5-*f*]quinoxaline
NPIP	*N*-nitrosopiperidine
NPRO	*N*-nitrosoproline
NPYR	*N*-nitrosopyrrolidine
NutriCoDE	Global Burden of Diseases Nutrition and Chronic Diseases Expert Group
NYPR	*N*-nitrosopyrrolidine
NYUWHS	New York University Women's Health Study
O^6-CMG	O^6-carboxymethyl guanine
O^6-MeG	O^6-methylguanine
OR	odds ratio
PAH	polycyclic aromatic hydrocarbon
PARP	poly(ADP-ribose) polymerase
PBB	polybrominated biphenyl
PBDE	polybrominated diphenyl ether
PCB	polychlorinated biphenyl
PCDD	polychlorinated dibenzodioxin
PCDF	polychlorinated dibenzofuran
PCNA	proliferating cell nuclear antigen
PhIP	2-amino-1-methyl-6-phenylimidazo[4,5-*b*]pyridine
PhIP-M1	7-hydroxy-5-methyl-3-phenyl-6,7,8,9,-tetrahydropyridol[3′,2′:4,5]imidazo[1,2-*a*]pyrimidin-5-ium chloride
PHS	Physicians' Health Study
PLCO	Prostate, Lung, Colorectal and Ovarian
PUFA	polyunsaturated fatty acid
PR	progesterone receptor
PSA	prostate-specific antigen
PUFA	polyunsaturated fatty acid

RCC	renal cell carcinoma
RNA	ribonucleic acid
ROS	reactive oxygen species
RR	relative risk
SCHS	Singapore Chinese Health Study
SD	standard deviation
SEER	Surveillance, Epidemiology, and End Results
SFA	saturated fatty acid
SLL	small lymphocytic lymphoma
SMC	Swedish Mammography Cohort
SMHS	Shanghai Men's Health Study
SQFFQ	semiquantitative food frequency questionnaire
SWH	Survey of Women's Health
SWHS	Shanghai Women's Health Study
TBARS	thiobarbituric acid reactive substances
TBBPA	tetrabromobisphenol A
TCPS	Tennessee Colorectal Polyp Study
TQ-MS	triple quadrupole-mass spectrometry
Trp-P-1	3-amino-1,4-dimethyl-5*H*-pyrido[4,3-*b*]indole
Trp-P-2	3-amino-1-methyl-5*H*-pyrido[4,3-*b*]indole
TUNEL	dUTP nick end labelling
UCP2	uncoupling protein 2
UGT	UDP-glucuronosyltransferase
UKWCS	United Kingdom Women's Cohort Study
WCRF/AICR	World Cancer Research Fund/American Institute of Cancer Research
WHO	World Health Organization
WHS	Women's Health Study
XME	xenobiotic-metabolizing enzyme
XPD	xeroderma pigmentosum group D

IARC MONOGRAPHS

This volume of the *IARC Monographs* provides evaluations of the consumption of red meat and the consumption of processed meat.

Red meat refers to unprocessed mammalian muscle meat (e.g. beef, veal, pork, lamb) including that which may be minced or frozen. Processed meat refers to meat that has been transformed through salting, curing, fermentation, smoking or other processes to enhance flavour or improve preservation. Most processed meats contain pork or beef, but may also contain other meats including poultry and offal (e.g. liver) or meat by-products such as blood.

Red meat contains proteins of high biological value, and important micronutrients such as B vitamins, iron (both free iron and haem iron), and zinc.

Carcinogens, including heterocyclic aromatic amines and polycyclic aromatic hydrocarbons, can be produced by cooking of meat, with greatest amounts generated at high temperatures by pan-frying, grilling, or barbecuing. Meat processing such as curing and smoking can result in formation of carcinogenic chemicals including N-nitroso compounds and polycyclic aromatic hydrocarbons.

An *IARC Monographs* Working Group reviewed epidemiological evidence, animal bioassays, and mechanistic and other relevant data to reach conclusions as to the carcinogenic hazard to humans of the consumption of red meat and processed meat. The Working Group assessed more than 800 epidemiological studies that investigated the association of cancer (more than 15 types) with consumption of red meat or processed meat, including large cohorts in many countries, from several continents, with diverse ethnicities and diets.

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