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Health impacts of exposure to synthetic chemicals in food

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Humans are widely exposed to synthetic chemicals, especially via food. The types of chemical contaminants in food (including food contact chemicals) are diverse, and many of these are known to be hazardous, with mounting evidence that some contribute to noncommunicable diseases. The increasing consumption of ultra-processed foods, which contain synthetic chemicals, also contributes to adverse health. If the chemical contamination of foods were better characterized, then this issue would likely receive more attention as an important opportunity for disease prevention. In this Review, we discuss types and sources of synthetic food contaminants, focusing on food contact chemicals and their presence in ultra-processed foods. We outline future research needs and highlight possible responses at different food system levels. A sustainable transition of the food system must address the health impacts of synthetic chemicals in food; we discuss existing solutions that do justice to the complexity of the issue while avoiding regrettable substitutions and rebound effects.

Modern synthetic chemistry has, to a large degree, enabled society's transformation, brought convenience and affluence, democratized consumption and continues to drive prosperity[1,2]. Modern chemistry also enables the current globalized food system, with artificial fertilizers first introduced in the early 20th century, based on the Nobel Prize-winning Haber–Bosch process invented in 1909, which produces approximately 150 million tonnes of nitrogen fertilizers annually[3]. Pesticides[4], food additives[5], plastics[6] and food contact materials[7] have had key roles in the industrialization and globalization of today's food supply by enabling storage of perishable foods and ensuring microbial food safety. Today, it is estimated that around 350,000 synthetic chemicals are available for commerce[8], with over 16,000 in plastics alone[9].

However, there are also many detrimental developments associated with the presence of chemicals in the food system, including chemical pollution of soil, drinking water and food[10–16] and the associated human health impacts from the increasing levels and types of synthetic chemicals ingested by humans[17–19]. This includes pesticides, persistent organic pollutants, food additives and food-processing contaminants, microplastics and food contact chemicals (FCCs) that migrate into foodstuffs from food packaging and other food contact articles[20]. Due to advanced analytical capabilities, synthetic chemicals and materials are found with increasing frequency in foodstuffs and in human tissue[21–25], and some have been linked to the increasing incidence of noncommunicable diseases globally[18,26,27].

This chemical contamination of food and beverages may be especially relevant for highly processed, engineered foodstuffs, often hailed (by their manufacturers) as more sustainable because of lowering carbon emissions. Examples include the use of non-animal proteins[28] or the application of novel techniques (such as high-pressure processing) that have both nutritional and environmental benefits[29,30], but the increased chemical contamination associated with them is disregarded.

In this Review, we outline the most prevalent types and sources of synthetic chemical contaminants in foodstuffs, with a focus on FCCs. We summarize knowledge on the impacts of FCCs on human health, including developmental effects on unborn children. We discuss regulatory shortcomings in chemical risk assessment of FCCs

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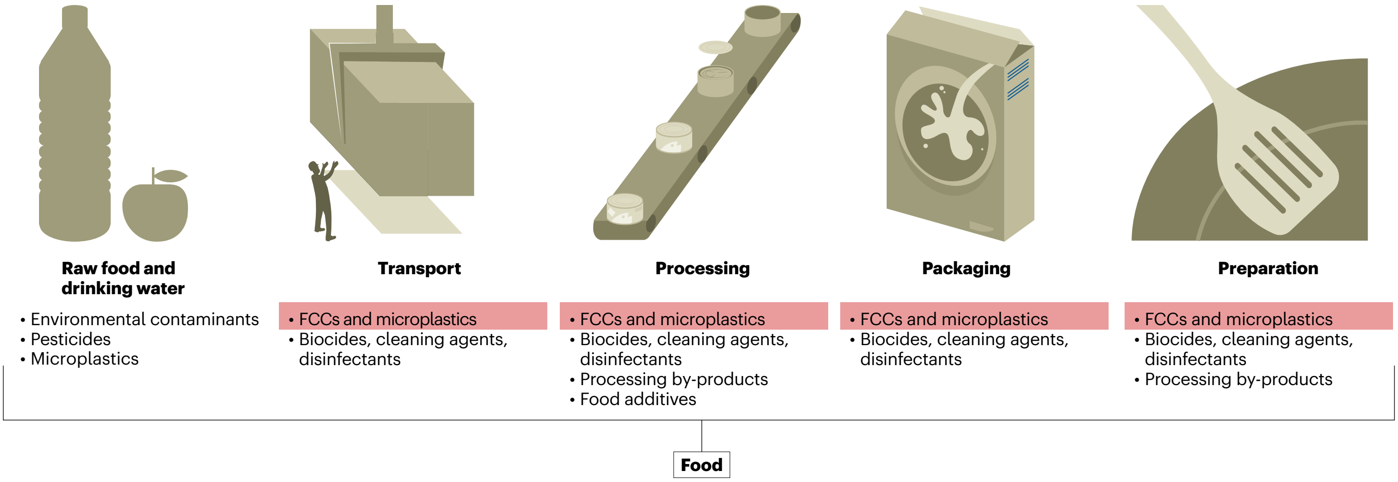

Fig. 1 | Sources and types of synthetic chemicals in foodstuffs. Food and beverages can be contaminated during different stages of the value chain and with different types of synthetic chemicals. Most attention is paid toward pesticides, while direct food additives and FCCs have received considerably less awareness, even though they are likely to contribute to the adverse health outcomes associated with the consumption of contaminated foods. The reason for this may relate to the intended use of food additives and food contact materials, such as tubing and storage containers used during food transport, conveyor belts and machinery used during food processing, packaging, tableware and kitchenware.

and highlight ultra-processed foods (UPFs) as an important source of exposure to synthetic chemicals. We hypothesize that FCCs are contributing and possibly causal factors for UPFs' observed health impacts, a link that remains underappreciated. Finally, we discuss future directions based on the current scientific understanding. Our goal is to inform medical practitioners to enable disease prevention and highlight policy-relevant research needs. As humanity grapples with many self-inflicted threats, from climate change to plastic pollution and biodiversity loss, we aim to boost evidence-based, independently informed and collaborative decision-making that contributes to humanity's healthy and sustainable food future.

Types and sources of synthetic chemicals in food

In the past, it has been considered that most health concerns related to synthetic chemical contaminants in foodstuffs stem mostly from pesticides[31], including fungicides and herbicides, such as 2-phenylphenol, chlordane, prochloraz and chlorpyrifos[32–34]. Biocides, which, like pesticides, aim to control organisms but are not used in agriculture, may contaminate food during processing or storage. There is also growing awareness of environmental contaminants such as polychlorinated dibenzodioxins and dibenzofurans, polychlorinated biphenyls, dichlorodiphenyldichloroethylene and microplastics entering into raw foods from soil, air and (drinking) water. In addition, a wide range of synthetic chemicals are intentionally used by the food industry as direct food additives[35], such as aspartame, erythrosine, monoglycerides and diglycerides of fatty acids, carrageenan and carboxymethylcellulose. Additional types of synthetic chemicals in processed and packaged modern foods include processing contaminants generated during food preparation (such as acrylamide) and FCCs that migrate from processing equipment and packaging, kitchenware and tableware. These include well-known compounds such as bisphenol A (BPA), diethylhexyl phthalate (DEHP), perfluorooctanoic acid (PFOA) and styrene. In the USA, some FCCs are known and regulated as indirect food additives[36].

Notably, for synthetic FCCs, four routes of contamination are relevant, namely, during transportation, food processing, from packaging and during food preparation (Fig. 1). During each of these stages, foodstuffs encounter food contact materials and a chemical transfer known as migration can occur, in which chemicals leach (or gas out) into the foodstuffs. More than 1,000 peer-reviewed empirical studies demonstrate this phenomenon for at least 2,160 different FCCs, according to the FCCmigex database (https://foodpackagingforum.org/resources/databases/fccmigex#dashboard). Migration of FCCs depends on intrinsic properties of the FCCs (initial concentration in the food contact material, molecular weight, water solubility, etc.) and extrinsic conditions of the foodstuff (heat, contact time, fat content, salinity, pH, etc.), as well as properties of the different food contact materials (crystallinity, surface area-to-food volume ratio, inertness, etc.)[37–40] (Fig. 2).

The sources of synthetic chemicals in foods and beverages reflect the different stages of food production and consumption from field to fork (Fig. 1). The contamination of raw foods and drinking water with environmental pollutants, including residual pesticides, is relevant for a wide range of foodstuffs, from plants (fruit, vegetables) to animal products (dairy, eggs, meat, seafood) and edible mushrooms[41,42]. The indirect contamination of animal feed may also be a relevant source[43]. Synthetic contaminants measured in these foods include persistent organic chemicals, such as polychlorinated dibenzodioxins that are generated from (open) burning of plastics[44], but also legacy contaminants, such as dichlorodiphenyldichloroethylene (a metabolite of the pesticide dichlorodiphenyltrichloroethane)[45], polychlorinated biphenyls[46] and polybrominated diphenylethers[47,48] and currently used pesticides[49]. Perfluoroalkyl and polyfluoroalkyl substances (PFASs), known as 'forever chemicals', are both persistent and mobile and are therefore found in waters and soils globally, as well as in foodstuffs[50]. Importantly, microplastics and nanoplastics are also persistent and consequently have been found in drinking waters[51] and foodstuffs, for example, in bivalves (clams, mussels and others), which are active filter feeders[52], and in plants whereby plastic particles are taken up through the roots and accumulate in leafy vegetables[53].

Synthetic chemicals can also migrate into foodstuffs from storage containers, tubing and transporting equipment. For example, BPA diglycidyl ether may migrate from the coatings of coated metal food storage containers[54], and phthalates can move out of polyvinyl chloride tubing, for example, into milk[55]. Cleaning agents used in the disinfection of storage and transport containers may also be found as residuals in foods.

During food processing, different types of synthetic chemicals may be introduced into or generated directly in foodstuffs, including direct food additives and artificial flavors as intentionally included synthetic chemicals[56], FCCs (phthalates, oligomers, etc.)[57–59], processing by-products such as acrylamide[60] or industrial trans fats from vegetable

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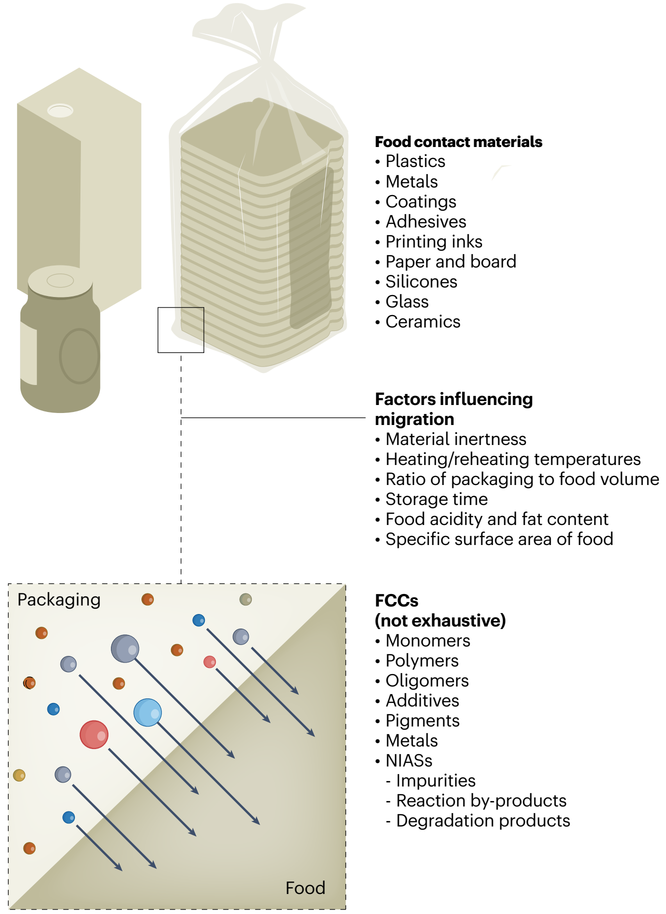

Fig. 2 | Migration of FCCs into foodstuffs. Migration is influenced by different factors, including temperature, storage time and chemical properties of the foodstuff. The term FCCs describes all types of chemicals present in food contact materials, including NIASs, such as impurities, reaction by-products and degradation products. All migrating FCCs are relevant for human exposure as they are likely to be ingested with food and beverages. Sources are packaging but also (industrial) processing equipment, tableware and kitchenware and storage containers. Some FCCs may also have uses other than in food contact materials, leading to increased exposure from all sources.

oil hydrogenation[61] and cleaning and processing agents (biocides, etc.)[62,63]. Importantly, food-processing equipment is an underappreciated source of synthetic chemicals, including microplastics and nanoplastics, which migrate into foodstuffs.

Food packaging has received the most attention thus far as a source of synthetic FCCs[37]. Migration of FCCs increases at higher temperatures, such as when foodstuffs are pasteurized directly in their packaging for longer shelf life. Long storage times can lead to increased migration, and this is particularly relevant for small-particle foodstuffs with a large total surface area relative to their volume (such as flour, rice or polenta). Best-before dates on packaging for pantry foods (especially for those packaged in paper and cardboard) may often relate to the compliance of the packaging itself and the potential migration of FCCs over time, rather than necessarily to microbial spoilage of foodstuffs or other food safety issues[64]. Emerging research shows that it is not just the environmental degradation of plastics that leads to microplastic and nanoplastic contamination in foodstuffs; rather, the normal and intended use of plastic food contact materials also leads to the migration of these contaminants into foodstuffs[65–71].

The final stage in food preparation, when foodstuffs are prepared for consumption, often involves heating. However, higher temperatures lead to increased migration; therefore, food preparation can be another key step for the contamination of foodstuffs that has not received much attention thus far. For example, when water is boiled in an electric kettle, chemicals can migrate if the inside food contact layer of the kettle is not inert (for example, if it is made of plastic and not of stainless steel). Additional sources can be black plastic products (such as spatulas or coffee mugs) that may contain brominated flame retardants from illicitly recycled plastic waste that is not food-contact grade[72].

The underappreciated relevance of FCCs

The relevance of synthetic chemicals originating from food contact materials has been greatly underappreciated. By comparison, contamination with pesticides is much better characterized and managed and far smaller in scope (Table 1). More than 15,000 FCCs are known, with around 12,000 intentionally used in the manufacture of food contact materials and articles[73]. But finished food contact articles can also contain non-intentionally added substances (NIASs), which may migrate into foodstuffs at even higher levels; most of these substances are unknown, which hampers adequate risk assessment. Up to 100,000 FCCs are estimated to exist[74].

Indeed, the safety assessment of all (migrating) FCCs is challenged by several shortcomings[75]. First, not all chemicals that migrate are assessed. This is the case for many NIASs. Second, assessments are usually performed only for single substances, while, under normal conditions of use and for most materials, mixtures of dozens to thousands of FCCs migrate into foodstuffs simultaneously and may cause mixture effects[76] or interact with foods to form toxic substances, such as benzene formed from the reaction of benzoic acid, migrating from plastics, with ascorbic acid, present in some foods[77]. And third, assessments to determine the safety of FCCs are largely limited to genotoxicity as the only endpoint in relation to chronic disease risk. Historically, cancer was perceived as the worst possible chronic health outcome linked to synthetic chemical exposure, and since then, it has been assumed that there is no threshold for genotoxic chemicals[78–80]. However, it is clear today that cancers are only one type of several chronic diseases associated with synthetic chemical exposures[18], and other effects aside from genotoxicity (for example, endocrine disruption) can also have very low thresholds.

As a result, there are increasing concerns for human health[20]. In 2022, the US Government Accountability Office stated that some FCCs 'may pose health risks'[81], and in 2016, the European Parliament wrote in its own initiative report on the implementation of the European Union's (EU's) food contact materials ('FCMs' in the following) regulation that 'the current paradigm for evaluation of safety of FCMs is insufficient, as there is a general underestimation of the role of FCMs in food contamination and a lack of information on human exposure'[82].

One of the best-characterized FCCs is BPA. Used first as monomer in polycarbonate plastics since the 1960s, BPA was found in the 1990s to migrate from bottles and coated metal cans, showing estrogenic effects in in vitro assays[83,84]. Thirty years later, BPA has now been banned for use in food contact materials in the EU[85], due to its very low tolerable daily intake (0.2 ng BPA per kg body weight per day) that was most recently reduced by a factor of 20,000 (ref. 86), following decades of pushback by some industry stakeholders[87]. As important as this step is, it is sobering that the enforcement threshold for the presence of BPA in foodstuffs is 1,000 times higher than the newly established tolerable daily intake, because contemporary analytical chemistry methods are insufficient for measuring BPA in the ng-per-kg foodstuff range that is the assumed safe level. This means that, despite the ban, European citizens (like citizens worldwide) will continue to be exposed to BPA above the safe threshold because currently this limit cannot be enforced or because national regulations outside the EU have not adopted lower thresholds for BPA.

Health impacts of synthetic chemicals in foods

There is increasing scientific evidence demonstrating that synthetic chemicals present in foodstuffs, such as bisphenols, phthalates and PFAS, can damage human health, especially during prenatal and

Table 1 | Comparison of two types of synthetic food contaminants

	Pesticides	FCCs
Number of substances	~1,500	>15,159 known >11,550 intentionally used in food manufacture Up to 100,000 estimated to exist[a]
Level of food contamination	µg/kg (parts per billion)	mg/kg (parts per million)
Toxicological evaluation	Yes	Mostly no

Sources[36,186,194]: [a]based on the expert estimate that each intentionally added FCC is associated with five to ten non-intentionally added FCCs, originating from batch impurities, reaction by-products of polymerization, breakdown products and contaminants from reuse and recycling.

perinatal development[18,19,88,89]. For example, DEHP, phthalic acid and di-isononyl phthalate are associated with decreased gestational age and increased risk of preterm birth, which are known risk factors for a range of noncommunicable diseases later in life, including chronic kidney disease, type 2 diabetes in women and chronic hypertension and cardiovascular morbidities[90–92]. These observations of adverse health outcomes caused by exposure to synthetic chemicals during development contribute to the research area of 'developmental origins of health and disease' (known as DOHAD)[93–95], but this knowledge has yet to be implemented into regulatory testing requirements for FCCs. Effects in adults have been observed for DEHP, exposure to which is linked to adult obesity and adult diabetes, with experts estimating a probability of causation in the range of 40% to 69% (ref. 96). PFOA has been classified as carcinogenic to humans (group 1) by the International Agency for Research on Cancer[97].

One of the reasons for the occurrence of chemical exposure-related chronic diseases in the human population is shortcomings in chemical risk assessment, management and enforcement. When assessing chemical safety in animal experiments, toxicologists have traditionally tested high doses (that is, the 'maximum tolerable dose') and extrapolated findings to the low-dose exposures relevant to humans, assuming a monotonic dose–response relationship. However, non-monotonic exposure–response relationships have been widely documented for endocrine-disrupting chemicals (EDCs)[32,98–102], showing that high-to-low-dose extrapolation for setting safe exposure thresholds can be faulty. The recent reevaluation of BPA, a known EDC, in which the new safe exposure level is too low to enforce (described in the section above), highlights this. Developmental exposure to EDCs, even at very low doses, can lead to some of the observed detrimental health outcomes described in the DOHAD research area, such as obesity and diabetes[95]. This knowledge, too, has yet to be systematically implemented into regulatory chemical risk assessment[103].

An additional, concerning shortcoming of current regulatory chemical risk assessment practice is the focus on assessing the effects of single substances only, while exposures to synthetic chemicals occur in mixtures. Epidemiological data show that adverse outcomes, such as reduced IQ in boys at age 7 or abdominal obesity in adults, are linked to mixtures of EDCs[104,105]. These findings highlight that establishing safe thresholds for individual chemicals may not be sufficiently protective[106].

In sum, this knowledge questions today's reliance on 'the dose makes the poison' as a tenet of chemical safety assessment, because, in addition to the dose, the timing of exposure (that is, developmental or other sensitive life stages) and the chemical context (that is, exposure to mixtures and the wider exposome) make the 'poison', too.

Spotlight on UPFs

Recently, the link between highly processed foods and increased levels of FCCs and microplastics has been established[57,58,107]. Processed foodstuffs have become a vector for ubiquitous, global exposure to mixtures of FCCs, but UPFs still receive very little attention with respect to their synthetic chemical contaminants (especially those arising from the normal and intended use of synthetic food contact materials) and associated impacts on health.

The health impacts related to the consumption of UPFs are the subject of ongoing research. The concept and definition of UPF were developed by Carlos Monteiro and colleagues through the NOVA classification that defines UPFs as foods made by intense industrial, physical, chemical or biological processes (for example, hydrogenation, molding, extruding, preprocessing by frying) and/or formulated with food additives and other industrial ingredients not usually found in domestic kitchens (for example, glucose–fructose syrup, hydrogenated oils, flavoring agents)[108]. Globally, the proportion of daily calories ingested from UPF varies from about 15% in Romania to around 58% in the USA[109–114] (Fig. 3). In the late 2010s, the NutriNet-Santé cohort in France (2009 and ongoing), which includes 180,000 people >15 years of age, was the first epidemiological study to show associations between UPF exposure and hard endpoints such as a higher incidence of cancer[115], cardiovascular diseases[116] and type 2 diabetes[117]. Associations have been observed with many other health outcomes globally, such as obesity, premature mortality, gastrointestinal disorders, dyslipidemia, hypertension and depressive symptoms[118–125]. Developmental and reproductive health outcomes are also being studied with respect to UPF consumption, suggesting potential adverse effects on semen quality[126,127], biomarkers of reproductive diseases[128] and delayed development in children 1–35 months of age[129].

The currently available evidence linking UPF consumption with a wide range of adverse health outcomes spans over 90 prospective studies, mostly large scale (70% included >10,000 participants), covering all continents and all ages (including pregnant women)[130]. A recent umbrella review included nearly 10 million participants, comprising 13 dose–response associations and 32 associations from studies that compared only highest exposures to UPF versus lowest exposures to UPF (or exposed versus non-exposed), with no indication of dose–response association (so called non-dose–response associations)[131]. Highly consistent positive relationships have been established between UPF consumption and obesity, cardiometabolic diseases, common mental disorders and premature mortality[131]. Short-term randomized controlled trials, such as the dietary intervention studies by Hall et al.[132] and Hamano et al.[133], also provide complementary information on intermediate endpoints showing an impact of UPF on weight gain and dyslipidemia (multiple other trials are ongoing). Additional research is needed to confirm suggested associations for other outcomes, such as cancers and respiratory health.

Mechanisms of adverse effects from UPF: what role do synthetic chemicals play?

What remains unclear is how UPFs exert their adverse health impacts[57]. Research currently focuses on the identification of specific components, processes and characteristics of UPF that may cause these adverse health effects, as well as the underlying (molecular) mechanisms. Some of the effects of UPFs may be related to the on-average generally poorer nutritional profile (relatively higher energy density, higher quantity of fat, sugar and salt and lower quantity of vitamins, minerals and fibers than those of the same weight of non-UPFs), as well as the fact that they displace nutritionally healthy, minimally processed foods. However, these aspects do not explain all the observed adverse health impacts of UPFs[57].

Indeed, in many prospective studies, UPF–health associations were sometimes weakened but remained statistically significant even after adjustment for total energy intake and various nutritional quality indicators, suggesting that factors other than poor nutritional quality also contribute to these associations[57,134]. Therefore, it is now recognized that the nutritional and food-processing–formulation

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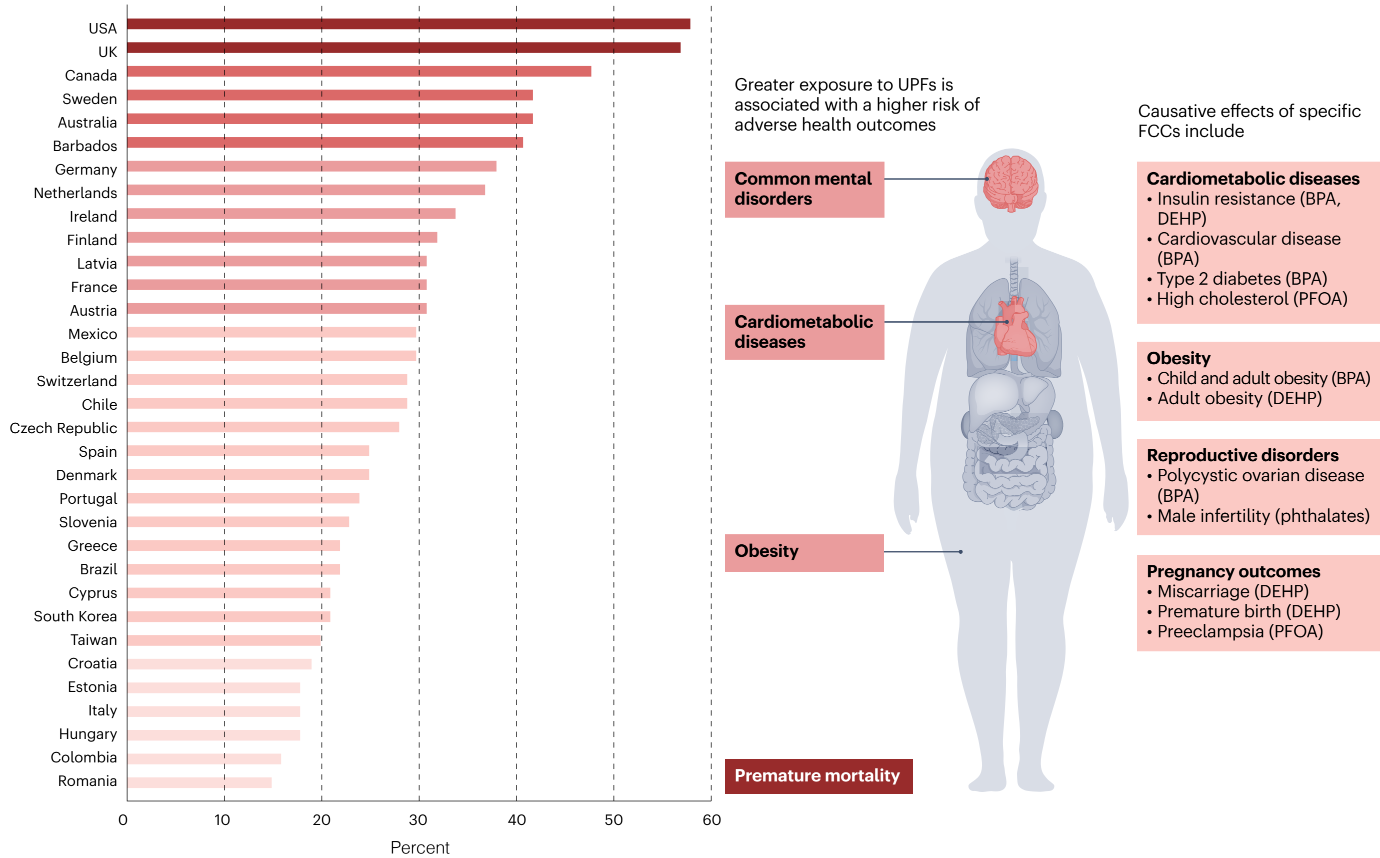

Fig. 3 | Proportion of daily energy intake from UPF across countries and health impacts of UPFs and FCCs with convincing evidence. Globally, there is a large disparity in the percentage of daily energy intake from UPFs. Several health outcomes have been studied, including respiratory health, gastrointestinal health, metabolic health and cancers, based on data from multiple population-based studies worldwide, including >9.8 million people in total. The density of evidence is the highest for cardiometabolic diseases, obesity, common mental disorders and premature death[131]. Several FCCs are not fully specific to UPFs but have been detected in larger quantities in the urine of consumers of larger amounts of UPFs[59,137]. For the FCCs BPA, DEHP, phthalates as group and PFOA, causative health outcomes are shown (data sources: refs. 88,89,96,113,114,131,195).

aspects are complementary and that both impact human health. Among other theories currently being explored[130] are deconstructed food matrices that may impact bioavailability, digestibility and eating rate, as well as contaminants created during food processing, such as acrolein, furans, acrylamide, industrial trans fatty acids or advanced glycation end products, for which evidence of harmful effects is accumulating[61,135–138].

Direct food additives, that is, intentionally added synthetic chemicals in foods, are also being investigated for their role in health outcomes. There are more than 350 food additives listed in the global Codex Alimentarius database (https://www.fao.org/gsfaonline/additives/index.html). Although food additives are subject to safety evaluation by authorities, such assessments generally focus on very specific toxic effects, with no human epidemiological data on long-term chronic disease risk available in premarket evaluations[139,140]. In the USA, synthetic food additives may also be legally used as GRAS (generally recognized as safe), but this can imply that their safety has not sufficiently been assessed[141,142]. Mounting evidence from experimental research in animal models and humans[143,144] and epidemiological studies[145–153] suggests adverse health effects of some widely used food additives, such as some artificial sweeteners and emulsifiers, linking them with higher risks of noncommunicable diseases such as hypertension, cardiovascular diseases, type 2 diabetes and cancers, as well as microbiota dysbiosis. A recently published in vitro study suggests cytotoxicity and genotoxicity of some food additive mixtures beyond the effect of individual substances[154]. Processed foods can also contain endocrine-disrupting food additives[155].

UPFs are generally prepackaged and kept for several weeks, months or even years in their packaging. Many are even directly heated in their packaging (for example, ready-to-eat dishes in plastic trays reheated in the microwave), enhancing the migration of FCCs into food. In addition, the many processing steps in the manufacture of UPFs create a multitude of encounters with different food contact materials. If these food contact materials are plastic or other non-inert materials, they will be a source of synthetic chemicals leaching into foodstuffs[13,57]. Therefore, an emerging hypothesis relates to the migration of FCCs and microplastics from the normal and intended use of food contact materials, such as processing equipment, storage containers, tubing and packaging[13,57]. Studies from the USA have shown that greater higher consumption of UPFs, as well as dining out, are both associated with elevated levels of FCCs measured in people and in food[58,156], although the causal link still needs to be established. Current research aims to unravel more definitively the contribution of FCCs to the observed health effects of UPF consumption to identify opportunities for disease prevention (Box 1). In sum, these findings point toward an additional, emerging hypothesis for how UPFs cause adverse effects, namely by means of not only their nutritional content but also the synthetic chemicals intentionally added and those that migrate into UPFs during processing and preparation and from packaging.

Economic costs of exposure-associated disease burden

Several systematic reviews and meta-analyses estimate the disease burden and costs attributable to exposure to synthetic (mainly plastic-associated) chemicals[96,157]. Although these studies looked at

BOX 1

Research to identify the most relevant FCCs and their health impacts

Given that commercial interests today strongly influence the regulatory agenda, it is essential to provide a reliable, independently compiled evidence base, demonstrating the adverse health outcomes linked to FCC exposure via food. Such data can support progressive regulations aimed at better protecting human health. Studies from the USA have shown that increased consumption of UPFs and dining out are associated with higher levels of FCCs[57,156]; however, it is not clear whether this decreases with lower UPF dietary fractions or is linked to processed food consumption in general. To advance knowledge in this field, we are establishing a research program based on the French NutriNet-Santé cohort's unique dataset that contains barcodes as distinctive, product-specific identifiers of consumed industrial food consumed and also provides packaging information. In addition, we will use French national FCC and food contact material surveillance data[196,197], in combination with the Food Packaging Forum's systematically compiled datasets of over 15,000 currently known FCCs[21,37,73], to screen for the potential impacts of FCCs in UPFs (and other foodstuffs) on adverse health outcomes identified in the NutriNet-Santé cohort. This approach will enable us to develop hypotheses regarding the most harmful food-packaging materials and associated migrating chemicals and allow us to test for hazardous FCCs in human blood and urine samples from the NutriNet-Santé cohort. Combined with physiological and toxicological experiments, these data and findings will be used to inform targeted regulatory action to reduce the most detrimental impacts associated with FCCs and food or UPF consumption. Importantly, these data can also be integrated into existing tools enabling consumers' informed consumption behavior, such as the Open Food Facts (https://world.openfoodfacts.org), an open-access, crowd-sourced tool that provides details on nutrition, direct food additives, etc. to its users when a product's barcode is scanned. Additional work is needed to establish the evidence base for adverse health outcomes that are associated with or causally linked to all FCCs, and this work is currently ongoing at the Food Packaging Forum. These data can then be used to determine weights of evidence, that is, the probabilities of causation for the links between certain FCCs or food contact materials and specific disease outcomes[96], as well as to estimate the health costs associated with FCC exposure.

disease burden and costs related to exposure from all sources, not only food contact plastics, a large majority of these costs is likely due to the approximately 20% of all globally produced plastics that are used in food packaging[36]. Studies estimate costs of €163 billion per year for diseases attributed to EDCs in the EU and $340 billion per year in the USA[96,158]. Also in the USA, a cost burden of $5–62 billion per year was estimated for diseases attributed specifically to PFASs (including low birth weight and childhood obesity)[159]; newer data attributing disease to phthalates suggest an additional $24 billion per year in cardiovascular mortality[160] and $4 billion in preterm birth[161]. In the USA in 2018, the estimated costs to society of diseases attributed to plastic-related chemicals totaled $249 billion (uncertainty analysis: $226 billion to $289 billion)[162]. For the same year, the health costs specifically associated with PFOA and/or perfluorooctanesulfonic acid were anticipated to be at least $5.5 billion annually, with possible projections of up to $62.6 billion per year[159]. Another recent study from Cropper and colleagues estimated that plastic chemicals were attributed to $1.5 trillion purchasing power parity dollars in health costs globally in 2015 and to associated instances of ischemic heart disease, stroke and increased premature mortality[163].

Research needs

The health impacts and economic costs discussed above provide a compelling rationale for investment in research to better understand the impacts of FCCs on health, with the goal to develop strategies for reducing exposures. Below, we outline three priority areas for future research.

Identifying hazardous chemicals

In addition to the effects of single, well-known hazardous compounds, there is reason for concern regarding a much wider range of chemicals and chemical mixtures present in foodstuffs[106,164]. Mitigation is only possible when the most hazardous chemicals in foods are identified[165] and adequately tested for all their impacts on health, using appropriate study designs and test systems[17,166]. This could potentially be achieved by analyzing epidemiological data in combination with data on chemical migration (Box 1) and by improving chemical safety assessments: leveraging innovative tools to analyze mechanisms of toxicity at the cellular or molecular levels toward elucidating biological relevance in whole organisms. In line with this, the Adverse Outcome Pathways and the Key Characteristics of Toxicants framework offer promising approaches[167,168], but high-throughput screening assays need to be developed for testing FCCs. As chemical exposure contributes to cancers, cardiovascular diseases, metabolic disorders, brain-related diseases and immune system-relevant diseases, as well as reproductive disorders, reliable and informative safety assessments need to address all these six clusters of disease[166].

Innovating for safer food contact materials

Human exposure to FCCs can be reduced by a systematic shift away from materials that are known to have the highest chemical complexity and to release the most synthetic chemicals and microplastics into foodstuffs, including paper and board, plastics and coated metal[37]. Not all applications of such non-inert materials can be easily replaced; therefore, there is a need for research to develop safer, novel and, importantly, inert materials. These materials, too, need to be adequately tested for safety with regard to migrating FCCs and microplastics, including the migrating FCC mixture, using appropriate testing methods[166]. New approaches to testing for microplastic migration from food contact materials also need to be developed[169].

Research aimed at replacing chemicals (and chemical groups) of concern in food contact materials should be approached in a holistic manner. It is conceivable that entirely new materials or even packaging-free delivery of foodstuffs can be safer and more sustainable solutions than modified versions of existing materials if they avoid unintended 'rebound' effects. Indeed, plastic pollution is such a rebound effect, as it was created by a strong push toward lightweighting food packaging to reduce carbon emissions[16,170]. The development of new, safer and more sustainable food contact materials that can be metabolized or broken down into benign constituents in the environment, in line with the principle of 'biomimicry', which involves learning from processes in nature to drive technological innovation[171], should be integrated with any efforts aimed at achieving lower migration and removing hazardous chemicals, as well as reducing the generation of microplastics (Boucher, J. M. et al., unpublished observations)[25].

Rethinking food business models for safety and sustainability

Modern food packaging has evolved from its first beginnings in the 19th century, when food preservation was the main functional requirement.

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Fig. 4 | Functions of food packaging. Food-packaging functions have evolved over time, from the basic, first functions (mid-19th century; top left), to more advanced requirements and functions emerging with a more industrialized food system (early to mid-20th century; middle), to today's modern, globalized, lean production and overconsumption-inducing food system (late 20th century to today; bottom right).

Today, highly engineered materials enable high-throughput filling lines, globalized logistics with real-time traceability, worldwide retail selling and effective marketing while also conveying information to consumers, enabling convenience and stimulating the senses (Fig. 4). Such business models certainly are highly profitable, but they fail to address many of the other issues related to food production and consumption, ranging from environmental impacts of industrial raw food production (including soil erosion, soil fertility loss, freshwater use, fertilizer consumption, pesticides, etc.) to (ultra-)processing, overconsumption and the presence of many synthetic chemicals in modern foods. Therefore, rethinking and transforming how foods are produced, marketed and consumed could lead to viable responses that not only address the issue of hazardous chemicals and unsustainable materials but also avoid rebound effects from false solutions that become tomorrow's problems[15], such as the use of single-use plastic pouches used for organic baby food.

Achieving this will require research into sustainable business models that align with human and planetary health and an understanding of how to transition from the status quo to a future-proof system. In today's globalized world, the risk of failing supply chains is a reality and a threat to food security. Mitigation of this risk implies that regional food production and consumption are invigorated, although such food sovereignty may (initially) be economically challenging when global trade is incentivized and certain unsustainable products, such as plastic packaging, are subsidized[172]. However, more local production and consumption can strengthen national sovereignty[173]. Also, regional food economies have less impact on the environment than the globalized one that relies on complex supply chains, due to fewer food miles (which account for roughly 20% of current food system CO_2 emissions)[174]. A shift away from the current extractive, destructive and short-term, finance-driven food economy to a bioregional economy focused on the creation of value and sustainability can help protect health, nature and community and is worth exploring in a world subject to rapid change and uncertainty. Such systems may rely more on reusable and inert packaging materials, such as glass or stainless steel, as opposed to single-use plastics or paper, and therefore also reduce exposure to hazardous FCCs.

Paradoxically, while certain chemicals and materials are known to have substantial health costs associated with their use[162], these costs contribute to an increase in gross domestic product, the universal measure for economic success. Clearly, poor health and premature death are not the hallmarks of a healthy society even if they might contribute to gross domestic product; therefore, there is a need for modernized metrics to quantify economic development, as well as addressing lock-ins[175].

Policy implications

Public health should be a priority for policy makers, and the importance of mitigating chemical exposures is still underappreciated. By harnessing current knowledge and by funding research and development in the key areas outlined above, publicly funded and free from conflicts of interests, regulators can support a policy agenda that emphasizes disease prevention. Below, we outline four priority areas for policy interventions.

Overhauling chemical regulations

The EU, in 2020, published its Chemicals Strategy for Sustainability, which lays out evidence-based steps that should be taken in the EU to reduce human exposure to synthetic chemicals, including from food contact materials[176]. These science-informed changes to policy entail group-based regulation (for example, for PFASs, as now implemented in the EU's Packaging and Packaging Waste Regulation) to prevent regrettable substitution, in which one known hazardous chemical of concern is replaced by a less-studied compound (that is also hazardous). Furthermore, the concept of essential use is useful for phasing out hazardous chemicals (and groups) from unnecessary uses while stimulating innovation for those uses that are necessary for health, safety and the functioning of society[177]. Additional advances could be made by simplifying and reducing the range of chemicals permitted for use in commerce[178], namely by reducing the variety of chemicals that impart the same functionality (for example, plasticizers). The EU's strategy can also inform other national regulations, as well as multinational agreements.

Conscious consumption, for example, by avoiding certain types of food packaging or reducing (ultra-)processed food intake alone cannot entirely reduce human exposure to FCCs and other synthetic food contaminants. This has been demonstrated in several dietary intervention studies[179–181]. Therefore, targeted and effective regulatory interventions are needed that ban the most hazardous food additives and FCCs from use, as well as chemical groups of concern[9,182]. Furthermore, it is critical to ensure that these bans can be adequately enforced by providing mandates, funding and methods. Recent examples of such bans include the 2025 ban of BPA in food contact materials in the EU that automatically includes all bisphenols identified as hazardous and the US ban of Red Dye No. 3 in 2025.

Finally, the necessary modernization of chemical risk assessment can be achieved by testing both chemicals and finished materials for their (mixture) toxicity. While industry has an obligation to contribute to the funding effort required for actual testing of chemicals and materials for regulatory assessment, it is crucial that this assessment is carried out by independent third-party laboratories to ensure absolute independence from financial interests[17]. Better control of synthetic chemicals and materials allowed on the market is essential for preventing chronic diseases associated with exposure to synthetic chemicals[183].

Policy incentives for safe and sustainable food contact materials

A key learning from the plastic pollution crisis, amplified by an overconsumption of single-use plastic food packaging, is that it is critical to avoid unintended 'rebound' effects when alternative food packaging is incentivized by new policies. For example, the push to use more recycled content for plastics and paper means that more hazardous chemicals will migrate into foodstuffs[184,185]. Tackling plastic pollution requires moving away from siloed approaches that tackle single issues such as waste management or carbon emissions (for example, from packaging production or during long-distance transport of food products along supply chains) and adopting a holistic approach to policymaking that integrates considerations of planetary and human health, including hazardous FCCs and their impacts on health. The Understanding Packaging Scorecard (https://upscorecard.org/) is a science-based, peer-reviewed, open-access tool that allows comparisons to be made between food-packaging alternatives. The following six impact categories are included thus far: carbon emissions, freshwater use, plastic pollution, recoverability, sourcing (of feedstock), and chemicals of concern (Boucher, J. M. et al., unpublished observations)[186]. Users can compare packaging options per category (for example, hot or cold beverages, straws, etc.) and are shown both aggregate and separate results for each impact category. The tool and its underlying metrics may be useful for identifying trade-offs, and policy makers may develop policy initiatives aiming to reduce overall impacts from food packaging based on it. It also provides guidance for innovation into safe and sustainable materials.

Reducing food-packaging waste

A shift away from a linear economy in which single-use packaging becomes waste to circular business models that function profitably by employing reusable packaging, made with inert materials, supports the reduction of packaging waste while also protecting human health. Importantly, selection of the packaging type (single use or reuse) has a major impact on the business model and therefore is best integrated into business strategy development. To successfully achieve this, alliances and collaboration between different stakeholders and across supply chains are essential to build the necessary infrastructure for scaling packaging reuse as a viable, cost-effective solution. Such an undertaking cannot be implemented by single actors alone but may be feasible within regional or super-regional contexts and incentivized by appropriate policies that address the top of the waste hierarchy, namely, packaging reduction and reuse[187,188].

While some national governments (including Germany and France) are incentivizing packaging reuse, it is less developed elsewhere (such as the USA). Efforts by the Global Alliance to Advance Reuse (https://www.resolve.ngo/projects/pr3) are ongoing to support systemic change in this direction – for example, by standardization of containers and by providing other relevant standards, like for container washing. Of course, these efforts, too, must be accompanied by holistic, science-based considerations of chemical migration. For example, considerations on (migrating) chemicals were made by the state of New York in its guidance to business operators that accompanied its 2020 ban on expanded polystyrene packaging (https://dec.ny.gov/environmental-protection/recycling-composting/go-foam-free)[189].

Regulatory interventions to reduce UPF (over-)consumption

Governments worldwide are increasingly aware of the health problems associated with consuming a high proportion of daily energy intake from UPFs, and some of them have included in their official nutrition recommendations a preference for unprocessed or minimally processed foods (in Brazil, Ecuador, Peru, Uruguay, Chile, Mexico, France, Belgium, Israel, Malaysia, Zambia, Sri Lanka and Canada) or are starting to think about measures to be taken in this direction, as illustrated by a 2024 UK House of Lords report[190]. Multidisciplinary research is still needed to reliably evaluate the safety of direct and indirect food additives and industrially processed ingredients, as well as process-related contaminants. Nevertheless, existing evidence is sufficient to warrant immediate public health actions to enable citizens to identify UPFs[191,192] and to limit UPF consumption by means of fiscal, marketing and labeling regulations, not merely information requirements that aim to change consumer behavior[182]. Research understanding the behavioral, economic and systemic drivers of UPF consumption will be useful to optimize the efficiency of policies aimed to reduce exposure to these products[193].

Conclusions

Globalized business models in today's world are largely focused on economic aspects, such as short-term profit maximization through cost-efficient production, resulting in a food system that fails to prioritize human health as its core value. This has been recently exemplified by revelations of lobbying by the chemical industry to delay regulation on highly toxic PFASs (https://foreverpollution.eu/), and, as a result, PFASs (and other synthetic chemicals with strong commercial interests) are allowed to remain in the food supply. A well-known proverb is 'you are what you eat', attributed to Jean Anthelme Brillat-Savarin (1825), and today's unhealthy food supply is causing avoidable costs to society and negative health impacts for individuals, as well as threatening planetary health.

Today's packaged UPFs are convenient and hyperpalatable, but they contain a multitude of synthetic chemicals and microplastics from various sources. The more (ultra-)processed a foodstuff, the greater its burden of synthetic chemicals generally is. The health impacts of this type of food contamination are currently underappreciated and understudied, but it may explain at least some of the detrimental health effects that an increasing, relevant body of scientific evidence associates with various chronic diseases.

The evidence, research needs and policy recommendations presented here highlight opportunities for intervention, both in terms of dietary recommendations and short-term policymaking (for example, bans of certain FCCs and materials), but also in the longer term, toward safer food and food contact materials, more local food production and consumption and the urgently needed transformation of the food system toward sustainability.

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The authors declare no competing interests.

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