A vision for safer food contact materials: public health concerns as drivers for improved testing

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Abbreviations

AOP	Adverse Outcome Pathway
BPA	bisphenol A
CVD	Cardiovascular Disease
FCC	Food Contact Chemical
NCD	Non-Communicable Disease
NIAS	Non-Intentionally Added Substance
PFAS	Per- and polyfluoroalkyl Substances
PFOA	perfluorooctanoic acid
SCOD	Six Clusters of Disease

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Food contact materials (FCMs) and food contact articles are ubiquitous in today's globalized food system. Chemicals migrate from FCMs into foodstuffs, so called food contact chemicals (FCCs), but current regulatory requirements do not sufficiently protect public health from hazardous FCCs because only individual substances used to make FCMs are tested and mostly only for genotoxicity while endocrine disruption and other hazard properties are disregarded. Indeed, FCMs are a known source of a wide range of hazardous chemicals, and they likely contribute to highly prevalent non-communicable diseases. FCMs can also include non-intentionally added substances (NIAS), which often are unknown and therefore not subject to risk assessment. To address these important shortcomings, we outline how the safety of FCMs may be improved by (1) testing the overall migrate, including (unknown) NIAS, of finished food contact articles, and (2) expanding toxicological testing beyond genotoxicity to multiple endpoints associated with non-communicable diseases relevant to human health. To identify mechanistic endpoints for testing, we group chronic health outcomes associated with chemical exposure into Six Clusters of Disease (SCOD) and we propose that finished food contact articles should be tested for their impacts on these SCOD. Research should focus on developing robust, relevant, and sensitive *in-vitro* assays based on mechanistic information linked to the SCOD, e.g., through Adverse Outcome Pathways (AOPs) or Key Characteristics of Toxicants. Implementing this vision will improve prevention of chronic diseases that are associated with hazardous chemical exposures, including from FCMs.

Keywords: food packaging; hazard assessment; chronic disease; chemical safety

1. Introduction

In today's globalized food system, food contact materials (FCMs) and food contact articles (Fig. 1) such as food packaging, tableware, and food processing equipment are ubiquitous, especially those made of plastic (Chakori et al. 2021; Poças et al. 2009). This increases exposures to food contact chemicals (FCCs) migrating from FCMs (Biryol et al. 2017; Koch and Calafat 2009; Qian et al. 2018). This widespread, continuous exposure to a wide range of synthetic chemicals requires a more stringent safety assessment of FCMs than the current approaches used in low-, middle- and high-income countries (Neltner et al. 2013a; Maffini et al. 2013; Alger et al. 2013; Grob et al. 2006; Muncke et al. 2017).

[Figure 1 near here]

FCMs have been studied for over 50 years and are a known source of chemicals that migrate into foodstuffs (Castle et al. 1989; Bradley et al. 2008; Dionisi and Oldring 2002; Jickells et al. 1993; Sanchis, Yusà, and Coscollà 2017; Nerin and Asensio 2007; Geueke et al. 2022; Tsochatzis et al. 2021; Oldring et al. 2014). Numerous FCCs, either intentionally used in the manufacture of FCMs or non-intentionally added substances (NIAS) that are present in the finished food contact article and that migrate into foodstuffs (Nerin et al. 2013; Qian et al. 2018; Tisler and Christensen 2022), are known to be hazardous and implicated with adverse human health impacts (Zimmermann et al. 2022; Groh et al. 2021; Van Bossuyt et al. 2019, 2016; Souton et al. 2017; Bengtstrom et al. 2016; Symeonides et al. 2021).

However, the current approach to chemical risk assessment for FCMs is largely focused on assessing genotoxicity of single substances used to manufacture FCMs and therefore fails to account for other highly relevant mechanisms of toxicity that are of equal concern as genotoxicity (Muncke et al. 2017) and, what is more, the current

approach does not assess NIAS that also migrate from FCMs (Fig. 2) (Muncke et al. 2020; Geueke et al. 2022). Addressing both issues, the limited scope of toxicity testing as well as the lack of testing for all migrating FCCs, is necessary to protect public health, and it can be done in a cost-efficient way.

[Figure 2 near here]

Indeed, non-cancer non-communicable diseases (NCDs) of increasing prevalence in the global human population have been associated with several widely used FCCs, such as bisphenol A (BPA), bisphenol F (BPF), perchlorate, and di(2-ethyl hexyl) phthalate (DEHP), to name a few. Given that humans are in daily contact with FCMs, those materials are likely a relevant exposure source of hazardous chemicals that contribute to various NCDs.

In this article, we outline an improved assessment scheme for hazard identification of FCCs that captures all exposure-relevant chemicals (known as the *overall migrate*, i.e., all chemicals migrating as a mixture from finished food contact articles into foodstuffs) including (unknown) NIAS, and we present a vision for assessing the safety of FCMs that addresses biological effects linked to the most prevalent NCDs (Muncke 2021; Zare Jeddi et al. 2021). These include heart disease, stroke, cancer, diabetes, reproductive disorders, immunological disorders, and several neurological conditions. We provide guidance on research and policy actions that should be developed to protect the public from avoidable chronic chemical exposures originating from FCMs and finished food contact articles.

2. Problem set-up: Shortcomings of the current approach

2.1 Non-communicable diseases are increasingly prevalent and associated with chemical exposures

NCDs are a significant contributor to global mortality (WHO 2018). However, the impact of NCDs is far greater than mortality alone, especially in low- and middle-income countries where health care is often limited compared to high-income countries. Both mortality and morbidity of selected NCDs have increased substantially over the last 30 years. Premature deaths (<70 years) are primarily associated with cardiovascular disease (17.7 million deaths per year, accounting for 45% of all NCD deaths), cancer (8.8 million deaths per year, 22% of all NCD deaths), chronic respiratory disease (3.9 million deaths per year, 10% of all NCD deaths) and diabetes (1.6 million deaths per year, 4% of all NCD deaths) (WHO 2018). Expressed in Disability-Adjusted Life Years, cardiovascular diseases have increased by a factor of 1.4 from 1990 to 2017, neoplasms by a factor of 1.5, and diabetes, urogenital, blood and endocrine diseases by a factor of 1.6 (from 1990 to 2016) (Roser, Ritchie, and Spooner 2021) (Fig. S1). Furthermore, among reproductive-age women and men, infertility is now the most prevalent chronic disease (WHO 2020). Importantly, NCDs incur significant human suffering in addition to their estimated economic costs (Kassotis et al. 2020; Attina et al. 2016; Trasande et al. 2015; Trasande et al. 2016; Obsekov, Kahn, and Trasande 2022), which further stresses the need for urgent action towards prevention of morbidities associated with NCDs.

Chemical exposures are an important contributor to NCDs, especially when they occur during sensitive stages such as early life, or persist over extended periods of time. Several well-studied types of chemicals such as toxic metals, halogenated aromatics,

and some pesticides (Bergman et al. 2013; Rojas-Rueda et al. 2021), as well as some members of the endocrine disrupting compounds (Gore et al. 2015; Goralczyk 2021; Demeneix and Slama 2019; Tanner et al. 2020; Chamorro-Garcia et al. 2017) are associated with NCDs such as brain-related disorders, cancers, metabolic disorders, reproductive disorders and cardiovascular disease. Specific FCCs such as BPA and several members of the ortho-phthalates group are associated with NCDs such as heart disease, diabetes, and some forms of cancer (Martínez-Ibarra et al. 2021; Svensson et al. 2021) (Table 1). Further, the effects of chemical exposures on risk of NCDs are complex and multifaceted, with some outcomes occurring across generations through transgenerational inheritance (Walker et al. 2018; Feil and Fraga 2012; Chamorro-Garcia et al. 2017). It is also clear that these effects are not limited to laboratory animals, as mixtures of chemicals including FCCs have been associated with adverse health outcomes in prenatally exposed humans (Svensson et al. 2021; Tanner et al. 2020; Kortenkamp and Faust 2018; Bornehag et al. 2021; Bornehag et al. 2019; Caporale et al. 2022).

[Table 1 near here]

NCDs that are increasingly prevalent in the human population and that are associated with hazardous chemical exposures can be grouped into disease clusters. On this basis, we developed the novel concept of Six Clusters of Disease (SCOD) (Fig. 3). The six clusters are cancers, cardiovascular diseases, reproductive disorders, brain-related disorders, immunological disorders, and metabolic diseases. The SCOD concept provides a framework for systematically assessing the safety of chemicals in FCMs, with a focus on the prevention of chemical-associated, highly prevalent, and severe

NCDs. As such, the SCOD concept expands current efforts for chemical risk assessment of FCCs.

[Figure 3 near here]

2.2 Current risk assessment of food contact chemicals is not sufficiently protective of human health

The universe of known FCCs comprises at least 14,153 substances, and for at least 1,822 FCCs empirical evidence for migration from food contact articles and materials is publicly available (Geueke et al. 2022). Evidence of human exposure exists for hundreds of these chemicals (Barr et al. 2003; Calafat et al. 2005; Silva et al. 2004; Caporale et al. 2022; Correia-Sá et al. 2017; Cortéjade et al. 2017; Koch and Calafat 2009; Pouech et al. 2015; Rudel et al. 2011; Susmann et al. 2019; Isaacs et al. 2022; Domínguez-Romero et al. 2022; Bil et al. 2023; Jung et al. 2022; Ruan et al. 2019). At least 388 FCCs in use today are known to be carcinogenic, mutagenic or toxic to reproduction, possess endocrine disrupting properties, or have other properties of concern such as persistence, and for at least 127 of these FCCs of concern there is evidence for migration from FCMs into food or food simulant (Zimmermann et al. 2022).

Currently, in the United States (US), Canada, the European Union (EU), China and other countries, chemical risk assessment is required for all migrating substances (Fig. 2). In practice, however, it is predominantly the intentionally used substances that are assessed for their risk to human health (Muncke et al. 2017). Humans are exposed to many more FCCs that are non-intentionally added to the finished food contact material or foodstuff. These NIAS include impurities of the starting substances, reaction by-products, or degradation products of starting substances (like additives) (Horodytska,

Cabanes, and Fullana 2020; Qian et al. 2018; Bradley and Coulier 2007; Bauer et al. 2019), and also contaminants that accumulate in reused or recycled FCMs (Geueke et al. 2023; Geueke, Groh, and Muncke 2018; Biedermann et al. 2013; Oldring et al. 2023). NIAS most often are unidentified, they are common in FCMs with high chemical complexity, and they are likely to be biologically active (Geueke 2018). Under the current chemicals risk assessment paradigm for FCMs, where a chemical's identity must be known, unidentified FCCs cannot be assessed, although, for example, the EU plastic food contact regulation requires the risk assessment of NIAS (EU 2011), and also US FDA's Food Contact Notification has information requirements on impurities and reaction by-products (FDA 2007).

A second problem is the lack of testing of substances present in the finished food contact material. Several approaches have been developed to approximate the health risks of unknown NIAS (Koster et al. 2015; Koster et al. 2013; Pieke et al. 2017; Taylor and Sapozhnikova 2022; Leeman and Krul 2015; Omer et al. 2019; Sapozhnikova, Nuñez, and Johnston 2021), but these approaches contain substantial uncertainties related to hazard estimation, chemical identification, and quantification (Bschir accepted; Van Bossuyt et al. 2017) because they are based on assumptions that cannot be entirely supported by empirical evidence. For example, generic thresholds for chronic exposures to nongenotoxic carcinogens were derived from testing chemicals at maximum tolerable doses (MTD) and at 1/2 MTD, but it depends on the exact mechanism by which a chemical exerts its toxicity whether a low-dose extrapolation from MTD dosing is appropriate or not (Bailey et al. 2009; Williams et al. 2009).

Finally, because some laws prohibit the use of chemicals that cause cancer in humans or animals, testing methods currently focus on genotoxicity as a proxy for

predicting cancer risk (Muncke et al. 2017; Neltner et al. 2013b). But other hazards that are not related to genotoxic effects are currently not systematically assessed, , including outcomes relevant to other chronic NCDs. Thus, there is a need for novel and more robust approaches to more fully evaluate all the relevant hazards to human health associated with FCCs.

3. Our vision: to make safer food contact materials

3.1 Assessing toxicological effects relevant to the Six Clusters of Disease

Chronic exposure to hazardous chemicals is a known modifiable risk factor for cancer and reducing exposure to hazardous or untested chemicals from consumer products, including FCMs, is a recommended preventive measure (Madia et al. 2019). It is reasonable to assume that the same holds true for other NCDs that are associated with chemical exposures, especially for endocrine disrupting chemicals (Table 1). Indeed, exposure reductions can lower the incidence of disease (Scholz et al. 2022), for example for neurodevelopmental disorders (Bennett et al. 2016), obesity (Mohanto et al. 2021) or male reproductive disorders (Foresta, Tescari, and Di Nisio 2018).

NCDs that are increasingly prevalent in the human population and that are associated with hazardous chemical exposures can be grouped into disease clusters. On this basis, we have developed the novel concept of SCOD (Fig. 3). The SCOD concept emerged from discussions with the Food Packaging Forum's Scientific Advisory Board (SAB) during several meetings between 2016 and 2022. The SCOD concept provides for the first time a framework for systematically assessing the safety of chemicals in FCMs, with a focus on the prevention of chemical-associated, highly prevalent and severe NCDs. As such, the SCOD concept expands current efforts for chemical risk assessment of FCCs beyond cancers induced via a genotoxic mechanism (Beneventi,

Tietz, and Merkel 2020; Muncke et al. 2017). For each disease cluster within the SCOD, many widely used FCCs have been associated with relevant diseases in both epidemiology and animal studies (Tables 1 and 2). For some, mechanistic evidence strengthens these associations (Table 2). It is also this mechanistic evidence that provides opportunities to use *in-silico* and *in-vitro* assays to better map toxicity profiles of individual FCCs in finished FCMs, before they are placed on the market, as well as mixtures, extracts and migrates from FCMs and food contact articles. The SCOD provides organizing principles for such an approach.

3.2 Assessing real-life chemical exposures: testing overall migrate from food contact materials

All FCCs that are relevant for human exposure should be tested, in other words, FCCs used in the manufacturing of FCMs should be tested as single substances, and the real-life mixture of all migrating FCCs, the *overall migrate*, should also be tested. If the overall migrate displays positive findings in the in-vitro assays, it should be subjected to non-targeted chemical analyses in order to elucidate its chemical composition, including NIAS, and to identify the substances driving the overall migrate's toxicity (Nerín et al. 2022). This combined testing and chemical identification approach could inform the development of safer FCMs by selecting less hazardous ingredients and developing manufacturing processes that generate fewer and less biologically active NIAS. Such an approach would be aligned with the proposed Safe and Sustainable by Design framework included in the EU's Chemicals Strategy for Sustainability (EU 2020a).

The already available as well as emerging *in-vitro* assays provide an opportunity to identify hazardous properties of single substances and of the overall migrate. *In-vitro* test systems are small-scale, often single-cell or small organism systems, for example

human cancer cell lines, bacteria, and fungi (e.g. yeast). Other high-throughput screening assays utilize embryos and larvae from vertebrates such as zebrafish (*Danio rerio*) or African clawed frog (*Xenopus laevis*). These assays can be performed efficiently both in terms of time and cost and are usually based on mechanistic pathways (Groh and Muncke 2017; Severin et al. 2017; Akoueson et al. 2023).

Test batteries, where several relevant assays are combined simultaneously, can also be operated as high-throughput screening methods such as those developed in Tox21 and ToxCast (Richard et al. 2016; Tice et al. 2013; Filer et al. 2022), which demonstrate the feasibility of this approach. In this way, diverse information about the interaction properties of a single chemical with different biological systems can be generated efficiently, and with lower cost, compared to whole-animal testing used in traditional toxicology. Further, overall migrate, that is, mixtures of chemicals migrating from FCMs, can be tested in such assays, too (Akoueson et al. 2023; Zimmermann et al. 2019; Bengtstrom et al. 2016).

These assessments should be guided by the SCOD concept. However, gaps exist in the current understanding of molecular pathways related to the SCOD, and these *in-vitro* assays remain insufficient to identify the full panoply of potential hazards, especially those mediated by endocrine mechanisms. *In-vitro* assays included in high-throughput test batteries need to be appropriate for predicting relevant human health outcomes; should be demonstrated to be reproducible, sufficiently specific and sensitive; and must be executed transparently (Janesick et al. 2016; Schug et al. 2013). Because of the limited *in-vitro* assays for known pathways and mechanisms of action associated with endocrine disruption and other complex biological cascades, animal testing needs to continue, but actual *in-vivo* tests will be fewer than in the past. For

example, no current *in-vitro* approaches would have revealed what is now known to be a feature of some chemical exposures, e.g., transgenerational epigenetic inheritance (Fitz-James and Cavalli 2022). Acknowledging these and other gaps, the European Commission is funding EURION, a program to develop new testing and screening methods (including many *in-vitro* approaches) for identifying endocrine disrupting chemicals (Street et al. 2021).

3.3 Shifting from the status quo to a more comprehensive approach to testing

Within the SCOD, increasingly available mechanistic information enables an understanding of how chemicals contribute to highly prevalent NCDs. Two emerging frameworks are being implemented to describe how chemicals affect complex diseases and to provide a more uniform approach to evaluating mechanistic evidence: the key characteristics concept, and adverse outcome pathways (AOPs). Both offer opportunities to shift from the status quo, modernize hazard assessments, and develop suitable *in-vitro* assays.

3.3.1 The Key Characteristics concept: modernizing chemical hazard assessments

The key characteristics concept makes use of information about the properties of hazardous chemicals that have empirical evidence linking them causally to relevant apical (disease) endpoints (Smith et al. 2016). The underlying premise is that chemicals that cause the same disease outcomes in whole organisms share molecular properties (i.e., key characteristics) that are relevant for their hazardous properties. The key characteristics for different disease outcomes are hence defined using empirical evidence for well-characterized chemicals, combined from epidemiological, *in-vivo* and mechanistic studies. These disease-specific key characteristics can then be used to develop mechanistic *in-vitro* assays to screen chemicals for their propensity to

contribute to different disease clusters and thereby reduce the need for *in-vivo* experiments while still decreasing scientific uncertainty normally associated with *in-vitro* data.

The key characteristics were first developed for carcinogens, drawing from existing mechanistic information from thoroughly assessed chemicals that are known to be carcinogenic in humans (Smith et al. 2016; Guyton et al. 2018; Krewski et al. 2019; Al-Zoughool et al. 2019; Guyton and Schubauer-Berigan 2021). Additional key characteristics of other disease-causing chemicals have also been described, such as for hepatotoxicants (Rusyn et al. 2021), endocrine disrupting chemicals (La Merrill et al. 2020), female reproductive toxicants (Luderer et al. 2019), male reproductive toxicants (Arzuaga et al. 2019), cardiovascular toxicants (Lind et al. 2021), and immunotoxicants (Germolec et al. 2022). For metabolic toxicants and neurotoxicants, work to describe key characteristics is ongoing. Taken together, the key characteristics approach provides an excellent starting point for the mechanistic understanding of how certain chemicals are associated with NCDs, such as those covered in the SCOD.

3.3.2 Using other mechanistic information to develop suitable in-vitro assays

In addition to the key characteristics, further important mechanistic understanding is becoming available and can be useful to inform development of dedicated *in-vitro* screening assays for hazard assessments of FCCs. Chemicals exert toxic effects by combinations of many different molecular-level events. These mechanistic events leading to apical endpoints of toxicity can be organized in an AOP (Ankley et al. 2010). Several AOPs relevant to NCDs in the SCOD have been proposed, such as estrogen receptor activation leading to breast cancer (Coumoul et al. 2022) and the upregulation of thyroid hormone catabolism (via activation of hepatic nuclear

receptors) leading to subsequent adverse neurodevelopmental outcomes in mammals, specifically the loss of cochlear function (Friedman, Crofton, and Gilbert 2022).Thus, AOPs are an emerging approach to organize mechanistic information so that molecular or cellular-level targets can be identified for developing *in-vitro* assays that are relevant to the SCOD.

3.3.3 The novel approach: A vision for safer food contact materials

Based on the presumption that mechanistic *in-vitro* testing of chemicals supports the prevention of NCDs within the SCOD, we propose a novel approach for testing FCCs that

(1) covers individual FCCs as well as real-life mixtures, migrating (or extractable) from finished FCMs, including all known and unknown NIAS,
(2) assesses the health impacts of FCCs and real-life mixtures with respect to the most prevalent NCDs in the human population, and
(3) evaluates effects that are upstream from the disease, relying on mechanistic information and *in-vitro* screening approaches (wherever possible) to accurately predict health effects induced by FCCs and migrates.

This shift from current practice to the proposed approach is summarized in Fig. 4, and a detailed overview is provided in Fig. 5. Our approach overcomes the most challenging shortcomings of the current testing paradigm of chemical hazard assessment of FCMs, fully recognizing that to assess all adverse effects of chemicals on biological systems, adequate *in-vivo* testing is required, where additional aspects would be addressed such as metabolic activation, unknown modes of action leading to apical endpoints, and transgenerational effects. However, we also realize that such extensive,

multigeneration *in-vivo* testing may not always be feasible for various reasons, including ethical and practical ones. Therefore, we propose this vision to improve FCC testing from the currently too limited scope towards a much more comprehensive yet feasible approach that holds promise for better protection of public health.

[Figure 4 near here]

[Figure 5 near here]

4. Implementing the vision: assessing impacts of FCCs and relevant mixtures on human health outcomes in the SCOD using mechanistic approaches

Here we review the mechanistic basis for each of the disease clusters included in the SCOD, and selectively highlight available *in-vitro* testing methods. Importantly, some available assays cover key characteristics that are relevant for several disease clusters.

This vision for expanded hazard assessment of FCMs is based on the finding that for each of the disease clusters included in the SCOD, some mechanistic understanding is available for the way that chemicals cause disease (Table 2).

[Table 2 near here]

4.1 Cancer

As defined by Willis,

> A neoplasm is an abnormal mass of tissue, the growth of which exceeds and is uncoordinated with that of the normal tissues and persists in the same excessive manner after cessation of the stimulus which evoked the change (Willis 1948).

Regarding cancer causation, the somatic mutation theory posits that cancer is a

cellular disease caused by mutations of genes that disrupt the control of cell proliferation. Yet, substantive contradictions exist between this theory and empirical evidence (Naxerova 2021), which inspired competing theories consider cancer as a problem of tissue organization akin to organogenesis (Sonnenschein and Soto 2020; Maffini et al. 2004; Rønnov-Jessen and Bissell 2009). Importantly, not all carcinogens are mutagens (Keri et al. 2007) and, thus, carcinogenicity cannot be equated with genotoxicity. Yet, because legal requirements restrict the use of cancer-causing agents in FCMs, testing of FCCs has focused on genotoxicity as a proxy to identify carcinogenic substances.

Both carcinogens and mutagens are found in FCMs including 1) formaldehyde, a known human carcinogen (IARC Group 1) (IARC 2012a), which migrates from various plastics including melamine-formaldehyde plastics used as tableware for children, and polyethylene terephthalate plastic (PET) (Kim et al. 2021; Bach et al. 2013); 2) antimony trioxide, which "is reasonably anticipated to be a human carcinogen" (NTP 2021) and "probably carcinogenic to humans" (IARC Group 2A) (IARC 2022), and it is used in the manufacture of PET, where antimony is found to migrate into soft drinks (Westerhoff et al. 2008; Bach et al. 2013); and 3) per- and polyfluoroalkyl substances (PFAS) are widely used in the manufacture of FCMs as processing aids in plastic and paper food contact material production (Trier, Granby, and Christensen 2011; Minet et al. 2022), and perfluorooctanoic acid has limited evidence for testicular and kidney cancers in humans and is "possibly carcinogenic to humans" (IARC Group 2B) (Benbrahim-Tallaa et al. 2014).

The key characteristics for carcinogens reveal that these chemicals can be mutagens, but that there are numerous other common features for these agents as well,

such as inducing oxidative stress, modulating receptor-mediated effects and inducing chronic inflammation (Smith et al. 2016; Guyton et al. 2018; Krewski et al. 2019; Al-Zoughool et al. 2019; Guyton and Schubauer-Berigan 2021). Guyton and Schubauer-Berigan (2021) recommended the use of *in-vitro* assays based on the key characteristics to identify carcinogens in high-throughput screening (Guyton and Schubauer-Berigan 2021). Further, Rider et al. (2021) proposed methods to use the key characteristics to test chemical mixtures and their propensity to affect cancer development including in mixtures of chemicals with different key characteristics of carcinogens (Rider et al. 2021). Approaches such as these will provide important information for testing mixtures such as the overall migrate from finished FCMs. Methods for evaluating genotoxicity are readily available, validated, and trusted. Chemicals are considered genotoxic if they damage the structure, information content, or segregation of DNA, with mutagenicity (i.e. changes to the nucleotide sequence) being a sub-type of genotoxicity (OECD 2015).

These methods include (Muncke 2009):

- **Mutagenicity:** The Ames test, based on bacterial reverse mutagenicity, is the most employed test for mutagenicity (Organisation for Economic Co-operation and Development (OECD) test guideline (TG) 471). A mammalian cell (mouse lymphoma) gene mutation test (OECD TG 490) is also available (OECD 2022)
- **Chromosomal aberration:** Cultured mammalian cells are assessed for the presence of chromatid-type and chromosome-type aberrations during metaphase (OECD TG 473)
- **Micronucleus:** Micronuclei represent chromosomal damage (chromosome fragments or whole chromosomes) that have been transmitted to daughter cells.

Micronuclei can be assessed *in-vitro* by using mammalian cells (OECD TG 487) or *in-vivo* with erythrocytes collected from bone marrow or peripheral blood (OECD TG 874)

These methods are recommended or required for assessing intentionally used FCCs (EFSA 2008; FDA 2007). Several other *in-vitro* assays for assessing the genotoxic potential of FCCs are also available (Pinter et al. 2020). However, these strategies have not kept pace with discoveries in cancer biology (Chiara, Indraccolo, and Trevisan 2020). Currently, no *in-vitro* assays are available that capture features of carcinogenicity beyond genotoxicity, but research is underway to address this technical gap (Hwang et al. 2020). On the other hand, the causal role of the microenvironment in carcinogenicity, as put forward by tissue-based theories on carcinogenicity (Maffini et al. 2004), is not captured by such *in-vitro* assays, because the reciprocal interactions between stroma and parenchyma during development, regeneration, and remodeling are not being considered (Soto et al. 2013). Although *in-vivo* assays involving mammals are available, traditional 2-year rodent carcinogenicity studies (OECD TG 451), either alone or in combination with chronic toxicity studies, are rarely performed for FCCs.

4.2 Cardiovascular diseases

Cardiovascular diseases (CVDs) are a group of disorders arising due to disfunction of the heart and blood vessels. The most recognized forms of CVD, coronary heart disease and cerebrovascular disease, result in damage to tissues caused by limited or complete loss of blood supply (WHO 2021).

FCCs including several phthalates and bisphenols contribute to the causation of CVDs, independent of obesity and diabetes (Lind et al. 2021). Bisphenols can disrupt calcium signalling in myocardium and vasculature; and phthalates and bisphenols are

oxidant stressors that accelerate coronary and other arterial inflammation (Lind et al. 2021). In the US alone, 100,000 premature deaths from CVD among 55–64-year-olds each year are attributed to exposure to one phthalate, DEHP (Wen, Wang, and Zhang 2022). Other FCCs, such as antimony, may also impair cardiovascular function and accelerate CVDs (El-Kersh et al. 2022).

Lind et al. (2021) compiled the key characteristics of cardiovascular toxicants and provided a comprehensive overview of robust and sensitive *in-vitro*, *ex vivo* and *in-vivo* assays that are available for measuring dysregulation of Ca^{2+} ion homeostasis and resulting arrhythmogenic activities of chemicals. For example, the increased risk for CVDs associated with higher exposures to BPA is mechanistically associated with Ca^{2+} release and reuptake resulting in proarrhythmic delays after depolarizations in isolated cardiomyocytes. BPA promotes Ca^{2+}-mediated arrhythmias *ex vivo* in the whole heart of rats and mice (Yan et al. 2011). However, this is only one of many possible mechanisms for inducing CVDs, and further assay development is required.

Although several FCCs have been associated with CVDs, cardiovascular toxicity is generally not evaluated for FCCs, whether they are intentionally used to make FCMs or NIAS present in finished FCMs. This is in part due to a reliance on *in-vivo* guideline testing of general toxicity for chemicals migrating at very high levels and limited to assessment of neoplastic and non-neoplastic cardiac lesions in rodent models, which can be confounded by a high incidence of background pathology in many of the rodent strains used for toxicity testing (Gear, Kendziorski, and Belcher 2017). However, these are insensitive apical endpoints that only identify highly cardiotoxic chemicals that result in robust pathology but miss subtle molecular effects (Gao and Wang 2014; Jokinen et al. 2011).

We recommend that comprehensive testing for all new chemicals include *in-vitro* and *in-silico* testing harmonized with the Comprehensive *in-vitro* Proarrhythmia Assay approach (CiPA) (FDA 2022; CIPA 2019). The CiPA initiative was launched to address limitations in the current cardiac safety testing methods used to assess the risk for adverse cardiac events of new drugs. The CiPA aims to develop a new approach for evaluating the potential of drugs to cause cardiac arrhythmias, particularly a specific type known as Torsades de Pointes (TdP). It is a multi-step approach that combines *in-vitro* assays and computational modeling to assess proarrhythmic risk and predict the risk of TdP by considering the complex interactions of multiple ion channels and cellular components involved in cardiac electrophysiology. The CiPA could be used as an important approach for identifying cardiotoxic hazards of FCCs.

4.3 Brain-based disorders

Disrupted neurodevelopment can have numerous consequences including a lower intelligence quotient, delayed language acquisition, attention deficit hyperactivity disorder (ADHD), and autism (Caporale et al. 2022; Bornehag et al. 2021; Kim et al. 2022). Because the role of thyroid hormone in brain development is well established, hypothyroidism, especially during early development, is also a condition of concern upstream of neurodevelopmental disorders. Neurotoxicity can also result from impaired neuronal function due to a variety of factors, such as neuronal misplacement during development, altered synapses, hypomyelin, or degeneration. Other neurodegenerative conditions that typically arise later in life include Parkinson's disease, Alzheimer's disease, and other forms of dementia.

The role of FCCs in the causation of many brain-based disorders is well established, with substantial contribution to the burden of disease for both

neurodevelopmental and neurodegenerative disorders (Attina et al. 2016). For example, FCCs that interfere with thyroid hormone systems or sex steroids (e.g., phthalates and perchlorate) can affect brain development as well as cognitive function in adults (Bennett et al. 2016; Grandjean and Landrigan 2006). The vulnerability of the developing brain and the lack of systematic assessment of neurodevelopmental toxicity for FCCs raises serious concerns (Maffini, Trasande, and Neltner 2016; Mustieles and Fernández 2020). At present, the key characteristics of neurotoxicants remain undescribed, but relevant work is ongoing.

In addition to assays covering interference with the thyroid and sex steroid axes, *in-vitro* testing of neurotoxicants requires sophisticated and reliable models due to the complexity of the brain (Marty et al. 2021). Neuronal cell lines, primary central nervous system cells, transformed neuronal precursors and stem cell derived progenitor cells are used in neurotoxicity assays (Arshajyothirmayi and Gulia 2022) to evaluate endpoints including migration, synapsis formation, network activity and differentiation. Although single-cell cultures are informative, multi-cell type and three-dimensional models utilizing microfluidics more adequately represent the diversity and spatial properties of the brain (Caffrey, Button, and Robert 2021; Kilic et al. 2016; Maoz 2021; Park et al. 2021), but high throughput versions of these methods are not yet available, and thus their use in evaluating FCCs has been limited. Additional *in-vitro* assays for chemical screening of neurotoxicants are under development in EU-funded research programs (Cediel-Ulloa et al. 2022) and research is ongoing to develop further *in-vitro* assays targeting the thyroid system (Kortenkamp et al. 2020). Recently, the establishment of a human cell-based *in-vitro* battery has been reported; it combines 10 assays selected to cover major key events in the relevant AOPs (Sachana et al. 2021) and was shown to provide 82% sensitivity in that it was able to identify 24 out of 28 known neurotoxicants

(Blum et al. 2022).

New low- and medium-throughput screening assays have been developed. For example, the nematode is a promising model for evaluating known neurodevelopmental toxicants and could be expanded to profiling chemicals with unknown neurotoxicity (Ruszkiewicz et al. 2018; Hunt et al. 2018). Spontaneous movements (Parng et al. 2007), number and location of neurons (Rericha et al. 2022), and behavioral effects (Fitzgerald et al. 2021) are some of the neurological endpoints measured in zebrafish. Validated high-throughput screening assays using African clawed frog tadpoles are also available (OECD TG 248).

In-vivo testing in rodents can be used to assess different functional aspects of neurotoxicity including impacts on cognition, learning and memory; and anxiety-like, depressive-like and reproductive behaviors. OECD developmental neurotoxicity (OECD TG 426) and extended one-generation reproductive toxicity assays (OECD TG 443) include optional measurements of learning and memory, motor and sensory function, motor activity, and auditory startle. Neurodegeneration is not covered because this endpoint can only be studied in animals which age, and animals used in assays are typically not kept until the end of their natural lifetime where neurodegeneration would manifest itself (Huff, Jacobson, and Davis 2008).

4.4 Obesity and Metabolic diseases

Metabolic diseases, including obesity, involve the many tissues that comprise the metabolic system (Mohajer et al. 2021). These include adipose tissue, skeletal muscle, pancreas, liver, gastrointestinal tract, bone, and brain. Type-2 diabetes, an important metabolic disease with increasing prevalence in human populations, occurs due to systemic insulin resistance, often with an increasing production of insulin by the

pancreas. Type-1 diabetes occurs due to a progressive loss of β-cell insulin secretion. Non-alcoholic fatty liver disease is another metabolic disease with increasing prevalence in human populations.

While poor diet and insufficient physical activity are considered the chief drivers of the obesity and diabetes twin pandemics, chemical exposures (for example, to phthalates, bisphenols, parabens, PFAS, etc.) can disrupt the balance between energy expenditure and energy intake (Heindel et al. 2022). A large comprehensive review of metabolic disrupting chemicals, including those that can induce obesity (obesogens), provides strong evidence that numerous FCCs are associated with type-2 diabetes, obesity, and fatty liver disease (Heindel 2019). The key characteristics of metabolic disruptors and obesogens are being compiled. Rusyn et al. (2021) have described the key characteristics of acute and chronic human hepatotoxicants and note that only one of 12 key characteristics are specific to liver tissue (KC9: causing cholestasis) (Rusyn et al. 2021), indicating that there are overlaps with the key characteristics of other toxicants, i.e. carcinogens, cardiovascular toxicants, endocrine disrupting chemicals, and male and female reproductive toxicants.

The simplest assays to identify an obesity hazard are those that measure the effect of chemical exposures on the development of adipocytes (Kassotis et al. 2022; Kassotis and Stapleton 2019; Seo, Shin, and Kim 2019). Primary preadipocyte cultures, or mesenchymal stem cell assays, use animal or human cells to assess proliferation and differentiation into adipocytes (Desai et al. 2018b; Shoucri et al. 2018; Kassotis and Stapleton 2019; Chamorro-Garcia and Blumberg 2019; Lane et al. 2014; Tang, Otto, and Lane 2004; Pillai et al. 2014). Using this *in-vitro* assay, a recent study found that around one third of tested plastic food contact articles contained metabolic disrupting

chemicals (Völker et al. 2022). Recently, spheroid adipocyte models have been developed that improve the efficiency and speed of differentiation (Turner et al. 2017) and can be used for a more comprehensive understanding of adipocyte physiology than monolayer cultures. The zebrafish obesogenic test offers an *in-vivo* approach to screening chemicals that target adiposity; it measures adipocyte lipid droplet size and normalized triacylglycerol content as an assessment of adiposity in a whole-organism assay of larvae to test for obesogenic and anti-obesogenic chemicals and mixtures (Tingaud-Sequeira, Ouadah, and Babin 2011).

Other non-adipocyte cell lines, when well characterized such as the mouse bone marrow-derived mesenchymal stem cells (mBMSCs), are also useful for mechanistic studies (Auerbach et al. 2016; Janesick et al. 2016). In addition to adipocyte differentiation, several other mechanisms are implicated with metabolic disease causations, for example the disruption of energy homeostasis at the level of the hypothalamus and brain. Therefore, *in-vitro* assays that examine effects on hypothalamic neurons are useful (Ye et al. 2016; Loganathan et al. 2018).

No assays have been developed to identify metabolic disruptors acting as diabetogens. Ongoing projects are developing assays to measure β-cell function and survival (Audouze et al. 2020; Legler et al. 2020; Küblbeck et al. 2020) using rodent β-cell lines (INS-1E and MIN-6) and a human β-cell line (ENDOC-βH1). Assays of insulin function on the human liver cell line HepaRG, the skeletal muscle cell line C2C12, and adipocytes are also under investigation (Legler et al. 2020). One well established system of assays employing both *in-vitro* and *in-vivo* methods has been used to explore the relationship between BPA and type-2 diabetes (Dos Santos et al. 2022).

The most used assays to screen chemicals for effects on the liver use the

HepaRG and HepG2 cell lines. The HepG2 cell line can be customized with different expression levels of various drug metabolizing enzymes (Tolosa et al. 2018). Other 2D and 3D *in-vitro* approaches use primary hepatocytes, immortalized liver cell lines, and hepatocytes derived from stem cells that are grown in monolayers, as spheroids or organoids, or used in emerging technologies (like organ-on-a-chip) to identify liver toxicants (Yang et al. 2023). Each of the approaches available has strengths and weaknesses; for example, the use of human primary hepatocytes in 2D culture can produce patient-specific evaluations that account for differences in metabolism and sensitivity, but these assessments come at high cost. Several of these methods are currently being used to evaluate liver toxicity in the screening of pharmaceuticals (Serras et al. 2021), making them similarly well suited to evaluate FCCs for potential effects on liver outcomes.

4.5 Immunological disorders

The immune system is an intricate network of many different, highly specialized cells interacting with each other and with the nervous and endocrine systems (Nicholson 2016). Disorders of the immune system include autoimmune disorders such as multiple sclerosis, Graves' and Hashimoto's diseases, lupus, Celiac's, Addison's, and rheumatoid arthritis, among others. Other diseases including type-1 diabetes and asthma have an important immune component. Therefore, assays for immunotoxicity need to capture a multitude of potential effects, including immunosuppression, immunostimulation, hypersensitivity reactions, mechanisms of autoimmunity, and developmental immunotoxicity, e.g., delayed immunotoxic responses to toxic influences (Germolec et al. 2017).

The human immune system is highly effective, but also sensitive to synthetic

chemical insults during development and adult life. Effects of chemicals on the immune system are less well understood in humans than other disease endpoints, but emerging evidence implicates PFAS exposure in reducing immune response to vaccines and increasing susceptibility to infections in early life (Grandjean et al. 2017). Other FCCs including bisphenols and phthalates increase the risk of atopy and asthma (Xie et al. 2016; Wang, Chen, and Bornehag 2016; Kim et al. 2017), and infections in early life (Gascon et al. 2015).

The key characteristics of immunotoxicants have been described (Germolec et al. 2022). This offers a starting point for development of suitable *in-vitro* assays for testing FCCs for immunotoxicity. Due to the complexity of the immune system components and responses, a comprehensive battery of *in-vitro* assays covering all relevant aspects of immunotoxicity has not been established. However, several *in-vitro* assays, dealing for example with direct immunosuppression, allergic hypersensitivity, or autoimmunity, are being developed to detect a range of immunotoxicants (Corsini and Roggen 2017; Luebke 2012; Deprouw et al. 2022; Naidenko et al. 2021) and these assays could be used to screen FCCs (Ogungbesan, Neal-Kluever, and Rice 2019).

4.6 Reproductive disorders

In industrialized countries, male reproductive health has declined over the past decades, including a 50-60% decrease in sperm counts since 1973 (Levine et al. 2017; Skakkebæk et al. 2022; Levine et al. 2022) and an increase in testicular cancer (Znaor et al. 2022). Female fertility is also affected, as are maternal health and pregnancy outcomes, and conditions such as polycystic ovary syndrome (PCOS), endometriosis, and premature ovarian failure (Boomsma et al. 2006).

643 The sperm count decrease is associated with chemical exposures (to, e.g.
644 phthalates), especially during fetal development (Skakkebæk, Rajpert-De Meyts, and
645 Main 2001). Strong evidence from animal experiments support this interpretation (Gore
646 et al. 2015; Skakkebaek et al. 2016; Jorgensen et al. 2021; Kortenkamp 2020). FCC
647 exposures are also associated with PCOS (Soave et al. 2020), and other aspects of
648 reproductive toxicity (Nerín et al. 2020; Garcia-Calvo et al. 2020a). These adverse
649 outcomes have even been found for FCCs promoted as safer alternatives to hazardous
650 chemicals such as the plasticizer 1,2-cyclohexane dicarboxylic acid diisononyl ester
651 (tradename Hexamoll DINCH) (Boisvert et al. 2016), which is used as a replacement
652 for DEHP and other phthalates. Several FCCs such as BPA have been studied for
653 mechanistic-level impacts on female fertility, including oogenesis, folliculogenesis, and
654 altered expression of gonadotropin and gonadotropin hormone-releasing hormone
655 receptors (Vessa et al. 2022a). The key characteristics of male (Arzuaga et al. 2019) and
656 female reproductive toxicants (Luderer et al. 2019) have been described. Development
657 and function of the reproductive system is fundamentally dependent on sex hormone
658 action. Thus, the key characteristics of endocrine disrupting chemicals (La Merrill et al.
659 2020)are also relevant to the study of chemicals that affect reproductive outcomes.
660 However, a systematic overview of available *in-vitro* assays for hazard identification of
661 endocrine disrupting chemicals that affect male and female fertility is unavailable.

662 *In-vitro* assays that identify chemical interference with sex hormone production
663 and signalling have been validated (OECD TG 493, 455, 458, 456). These include
664 assays based on nuclear receptor activation and steroid hormone synthesis. The bovine
665 oocyte maturation assay (ECVAM TM 2010-05) is also a reproduction-relevant *in-vitro*
666 assay. A good correlation between *in-vitro* results and *in-vivo* observations has been
667 established for female fertility endpoints (Corton et al. 2022; Pinto et al. 2018).

Validated *in-vivo* assays exist to evaluate reproductive toxicity for impacts on both male and female fertility (OECD TG 443), but these may not be sufficiently sensitive or comprehensive, as they fail to evaluate numerous key characteristics of male and female reproductive toxicants (Luderer et al. 2019; Arzuaga et al. 2019).

5. What is needed to implement the vision for safer food contact materials?

To achieve our vision, we propose a multi-pronged approach that is grounded in the SCOD concept, which includes many of the most prevalent NCDs of high relevance to human health. We identified three components needed to realize this vision: analytical methods and testing strategies, data integration and interpretation, and science to inform decision making.

5.1 Analytical methods and testing strategies

In Section 4 we list several available and emerging assays used in the identification of hazard for each of the SCOD. However much more is needed, especially high-throughput non-animal and low-medium throughput assays with non-mammalian models that are specific, sensitive, reliable and robust, and adequate for predicting effects relevant to humans. These assays would overcome challenges with cost, time, and scientific relevance as the selection of suitable *in-vitro* assays would be based on robust mechanistic evidence from key characteristics and AOPs. Identification of the key characteristics for brain disorders and metabolic diseases will form the basis for identification and/or development of relevant *in-vitro* assays to identify hazardous chemicals related to these clusters. For *in-vitro* testing based on mechanistic pathways to succeed, additional dedicated expertise and financial support are needed to identify assays that would address relevant key characteristics. This work is ongoing and the website keycharacteristics.org collates all available information and publications in this

692 area (Key Characteristics 2022). It also remains to be shown if *in-vitro* assays based on
693 the key characteristics of hazardous chemicals will be sufficiently predictive of
694 chemical hazards when used in pre-market assessments, rather than in ex-ante
695 evaluations (where the key characteristics are currently used).

696 Another important aspect of testing is the development and validation of
697 methods that reflect real-world chemical exposures from FCMs, including the effects of
698 metabolites formed from FCCs in the human body. Migration testing protocols exist but
699 ongoing research efforts need to be expanded and validated to ensure minimal loss of
700 potentially hazardous chemicals during sample preparation (e.g. by using polar and
701 apolar food simulants and by capturing not only non-volatile compounds, but also those
702 that are semi-volatile and volatile) (Nerín et al. 2022; Oldring et al. 2023).

703 Lastly, a battery of screening assays addressing the SCOD needs to be defined
704 and validated. This step will need the contribution of experts in each field to ensure that
705 the selected endpoints are reliable and result in high confidence.
706 Implementation of this vision will depend on the successful progress in all of
707 these areas.

708 ***5.2 Data interpretation and integration***
709 Methods must be developed to interpret and corroborate *in-vitro* test results.
710 Individual assays should be integrated into an overall high-level / aggregated scheme
711 (e.g. using visualization approaches such as ToxPi (Rajkumar et al. 2022; Marvel et al.
712 2018)). Also, non-targeted chemical analyses are challenging, as confirmation of
713 identified compounds is very time- and labour intensive, and at times not possible at all.
714 Also, reliable quantification of chemicals that lack analytical standards is not possible.
715 Therefore, non-targeted approaches need to be advanced to allow for better

identification of currently unknown compounds, especially when present at low concentrations. One way to improve the latter is to create comprehensive and open mass spectrometry libraries of FCCs, including NIAS. Ideally, an open-access repository of information about food contact material manufacturing processes and the major FCCs associated with specific materials should be generated. Confidential business information poses a critical obstacle, as the full disclosure of the chemical composition of FCMs is commonly not available. Accordingly, a mechanism needs to be developed that enables such an FCC library without infringing on intellectual property rights.

5.3 Science for decision making

The results of testing single chemicals or overall migrate (or, for a worst-case assessment, the extract) from a finished FCM (i.e., an FCA) using a battery of assays for each of the SCOD would need to be interpreted and integrated with available evidence to reach a conclusion within a regulatory context. A framework, similar to that available for read-across (Lizarraga et al. 2023; European Chemicals Agency 2017), should be developed to effectively utilize results and support conclusions that are actionable for policy makers and regulatory enforcement. The experience gained from development of effect-based trigger values for water quality assessment in Europe could be highly informative (Escher et al. 2018; Neale et al. 2023). Here, effect-based trigger values have been developed as a means to interpret the results of *in-vitro* assays through linking the existing water quality guideline values to observed levels of bioactivity elicited by a reference chemical. Then, if a test chemical or mixture causes an activity above the trigger value set for a specific assay, it is highlighted for a follow-up assessment, such as calculation of concentration factors and *in-vitro* to *in-vivo* extrapolation (Escher and Neale 2021; Robitaille et al. 2022; Escher, Neale, and Leusch 2015). In theory, effect-based trigger values for FCMs could be developed following the

same principle, e.g. by matching effect concentrations in relevant bioassays with existing specific migration limits for FCCs of concern, and possibly factoring in additional exposure-related parameters. This approach appears highly promising, since it has been demonstrated that derivation of effect-based trigger values greatly facilitates regulatory and practical uptake of *in-vitro* methods into specific assessment pipelines (Neale et al. 2023), but it is evident that further dedicated efforts are required for an effective implementation of such an approach to the safety assessment of FCMs.

6. Conclusion

The novel approach we present here is in line with the goals laid out in the EU's Chemicals Strategy for Sustainability (EU 2020a), the EU Farm to Fork Strategy (EU 2020b), and the European Parliament's report on FCMs (European Parliament 2016), which emphasize the need for revising the food contact material regulation in Europe to adequately reflect recent scientific understanding and improve compliance. Further, this work adds to previous publications on policies and methods related to the risk assessment of food contact chemicals and materials (Zimmermann et al. 2022; Muncke et al. 2020; Muncke et al. 2017), and to the use of new approach methodologies for assessing the health impacts of industrial chemicals (Stucki et al. 2022).

We think that our vision to create safer FCMs by linking hazard identification more directly to human health has the potential to spur innovation in assay development and testing, and ultimately, for safer materials as such. Additionally, new findings on the key characteristics for the NCDs included in the SCOD, as well as mechanistic understanding derived from AOP research, will support the development of new assays.

Awareness of adverse health effects of synthetic chemicals is increasing globally, and the need is obvious for significant and urgent improvements in the ways that risks

765 are assessed and managed for FCCs (Fenner and Scheringer 2021).

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768 **Declarations**

769 *Competing Interests*

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Authors' contributions

This manuscript was initiated by the FPF's SAB and guests participating in SAB meetings in 2017, 2018, 2019, 2020, 2021; AMA, MVM, JM, JPM, RTZ and MS were responsible for preparing an outline and a first version; JM, LVM, MVM and MS edited the final draft, and all authors contributed to the various intermediate versions, wrote separate sections of the manuscript, and approved the final version.

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Table 1. Food contact chemicals (FCCs) associated with non-communicable diseases (NCDs) from each of the Six Clusters of Disease (SCOD) (non-exhaustive and non-systematic overview of epidemiological studies). Identification of FCCs was based on the Food Contact Chemicals database (FCCdb) (Groh et al. 2021) and the database on migrating and extractable food contact chemicals (FCCmigex) (Geueke et al. 2022). This overview is not a complete list of FCCs that are associated with adverse health outcomes. Cancer agents are classified by cancer site (IARC 2022).

Disease Cluster	**Example disease**	**Associated FCC exposure**	**References**
Cancers	Testicular cancer	PFOA	(IARC 2016; ATSDR 2021)
	Kidney cancer	PFOA	(IARC 2016; Melnick 2001)
	Breast cancer	PFOA	(Wan, Co, and El-Nezami 2022)
		Ortho-phthalates	(Wan, Co, and El-Nezami 2022)
Cardiovascular diseases	Cardiovascular diseases: including myocardial infarction, arrhythmias, dilated cardiomyopathy, atherosclerosis, and hypertension	BPA	(Moon et al. 2021; Zhang, Shan, et al. 2020; Wehbe et al. 2020; Ramadan, Cooper, and Posnack 2020)
		Ortho-phthalates	(Fu et al. 2020)
Brain-related disorders	Hypothyroid	BPA	(Rebolledo-Solleiro, Flores, and Solleiro-Villavicencio 2021)
		Ortho-phthalates	(Radke et al. 2020)

		Perchlorate	(Radke et al. 2020)
		PFAS	(Piekarski, Diaz, and McNerney 2020)
	Abnormal neurodevelopment	Ortho-phthalates: DEHP, DBP, BBP and DEP	(Eales et al. 2022)
	Attention Deficit Hyperactivity Disorder/behavior	Lead, BPA, ortho-phthalates	(Moore et al. 2022; Li et al. 2020; Park et al. 2015)
	Lower Intelligence Quotient	Endocrine disrupting chemical (EDC) mixture (Ortho-phthalates)	(Tanner et al. 2020; van den Dries et al. 2020)
	Language delay	EDC mixture	(Caporale et al. 2022)
Metabolic and endocrine diseases	Type-1 diabetes	BPA, Ortho-phthalates, PFAS	(Predieri et al. 2020)
	Type-2 diabetes	BPA	(Wang et al. 2019; Rancière et al. 2015; Akash, Sabir, and Rehman 2020)
		PFOA	(He et al. 2018)
	Pre-diabetes and diabetes	Ortho-phthalates	(Eales et al. 2022; Radke et al. 2018; Dales, Kauri, and Cakmak 2018)
	Obesity (BMI, waist circumference)	BPA	(Fu et al. 2020; Pérez-Bermejo, Mas-

			Pérez, and Murillo-Llorente 2021; Wu et al. 2020)
		PFAS	(Liu et al. 2018; Geiger et al. 2021)
	Childhood Obesity	BPA	(Ribeiro et al. 2020)
		Ortho-phthalates	(Buckley et al. 2016)
	Gestational diabetes	Antimony	(Zhang, Li, et al. 2020)
		Ortho-phthalates	(Shaffer et al. 2019)
	Non-alcoholic fatty liver disease	EDC mixture	(Midya et al. 2022)
		PFAS	(Stratakis et al. 2020)
Immunological disorders	Immunosuppression	PFAS: PFOS and PFOA	(DeWitt, Blossom, and Schaider 2019)
	Childhood asthma	Ortho-phthalates: DEHP and BBzP	(Eales et al. 2022)
	Kidney damage	Melamine	(Hsieh et al. 2012)
Reproductive disorders	Male infertility	BPA	(Sharma et al. 2020)
		Dibutyl phthalate	(Estill et al. 2019)
	Semen quality	Ortho-phthalates: DBP, BBP, DEHP, and DINP	(Radke et al. 2018; Eales et al. 2022; Thurston et al. 2016)

	Female infertility (reduced follicular count)	DEHP	(Messerlian et al. 2016)

2088

2089 Table 2. Examples of food contact chemicals (FCCs) that are associated with diseases
2090 from the Six Clusters of Disease (SCOD) by mechanisms from *in-vitro* and/or *in-vivo*
2091 studies (not including epidemiological studies). Not a complete list: Select references
2092 only.

Disease Cluster	Food Contact Chemical	Reference
Cancers	**Melamine** (CAS 108-78-1)	(IARC 2019)
	Formaldehyde (CAS 50-00-0)	(IARC 2012a)
	Benzidine (CAS 92-87-5)	(IARC 2010)
	4,4′-Diamino-3,3′ - Dichlorodiphenylmethane (MOCA) (CAS 101-14-4)	(IARC 2012a)
	Antimony trioxide (CAS 1309-64-4)	(NTP 2018)
	Perfluorooctanoic acid (PFOA) (CAS 335-67-1)	(Temkin et al. 2020; Pierozan, Jerneren, and Karlsson 2018; Charazac et al. 2022)
	Di (2-ethylhexyl) phthalate (DEHP) (CAS 117-81-7)	(Hager, Chen, and Zhao 2022; IARC 2012b)
	Bisphenol A (BPA) (CAS 80-05-7)	(Sang et al. 2021; Jun et al. 2021; Dhimolea et al. 2014; Prins et al. 2014)
Cardiovascular diseases	**Bisphenol A (BPA)** (CAS 80-05-7)	(Pant, Ranjan, and Deshpande 2011; Gao and Wang 2014;

		Kofron et al. 2021; Hyun et al. 2021; Krishna, Berridge, and Kleinstreuer 2021; Cooper and Posnack 2022)
	Triclosan (CAS 3380-34-5)	(Krishna, Berridge, and Kleinstreuer 2021)
	Tributyltin chloride (CAS 1461-22-9)	(Krishna, Berridge, and Kleinstreuer 2021)
	Diethanolamine (CAS 111-42-2)	(Jokinen et al. 2005)
	DEHP	(Mariana et al. 2016)
Brain-related disorders	**Perchlorate** (CAS 14797-73-0)	(Kirk 2006)
	Ortho-phthalates	(Hlisníková et al. 2021)
	BPA	(McDonough, Xu, and Guo 2021; Wang et al. 2020)
	Bisphenol S (BPS) (CAS 80-09-1)	(Naderi and Kwong 2020; McDonough, Xu, and Guo 2021)
Metabolic diseases	**BPA**	(Villar-Pazos et al. 2017; Martinez-Pinna et al. 2019; Wassenaar, Trasande, and Legler 2017; Desai et al. 2018a; Manikkam et al. 2013)

	Bisphenol A diglycidyl ether (BADGE) (CAS 1675-54-3)	(Wang et al. 2021)
	Organotins	(Rotenberg Iu, Mazaev, and Shlepnina 1978)
	Perchlorate	(Larsson-Nyrén et al. 2001)
	Perfluorooctanesulfonic acid (PFOS) (CAS 1763-23-1)	(Qin et al. 2020; Sant et al. 2017)
	Bisphenol F (BPF) (CAS 620-92-8)	(Marroqui et al. 2021)
	BPS	(Marroqui et al. 2021)
	2,4,7,9-tetramethyl-5-decyne-4,7-diol (TMDD; Surfynol) (CAS 126-86-3)	(Garcia-Calvo et al. 2020b; Nerin et al. 2018; Nerin et al. 2014)
	DEHP	(Li et al. 2019; Manikkam et al. 2013)
Immunological disorders	**Melamine**	(IARC 2019)
	BPA	(McDonough, Xu, and Guo 2021)
	BPF	(McDonough, Xu, and Guo 2021)
	BPS	(McDonough, Xu, and Guo 2021; Nowak, Jabłońska, and Ratajczak-Wrona 2019)

	2,4-di-tert-butylphenol (CAS 96-76-4)	(Liu et al. 2022)
	DEHP	(Nowak, Jabłońska, and Ratajczak-Wrona 2019; Hessel et al. 2015)
Reproductive disorders	**BPA**	(Liu 2021; Vessa et al. 2022b; Wang, Hafner, and Flaws 2014; Mahalingam et al. 2017)
	BADGE	(Wang et al. 2021; Nerin et al. 2014)
	BPS	(Desmarchais et al. 2020)
	DEHP	(Vessa et al. 2022b; Mariana et al. 2016)

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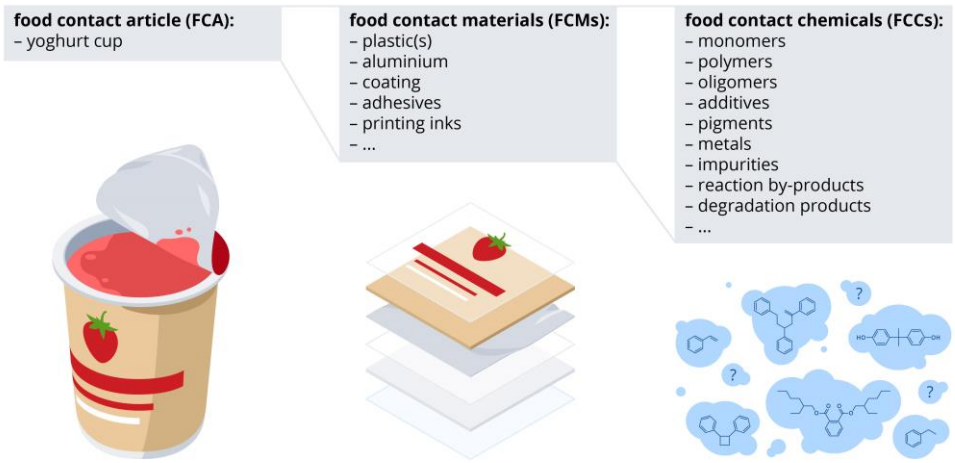

Figure 1: Illustration of the terms *food contact article* (FCA), *food contact material* (FCM), and *food contact chemical* (FCC). The terms FCA and FCM are often used interchangeably, but only FCAs can be considered "finished" while FCMs oftentimes will be used in combination with other FCMs to make a finished FCA. The term FCC describes any chemical that is present in an FCM or FCA, regardless of whether it was intentionally used, or if it is a non-intentionally added substance (NIAS), such as an impurity, a reaction by-product, a degradation product, or of other origin (e.g., a contaminant from recycling).

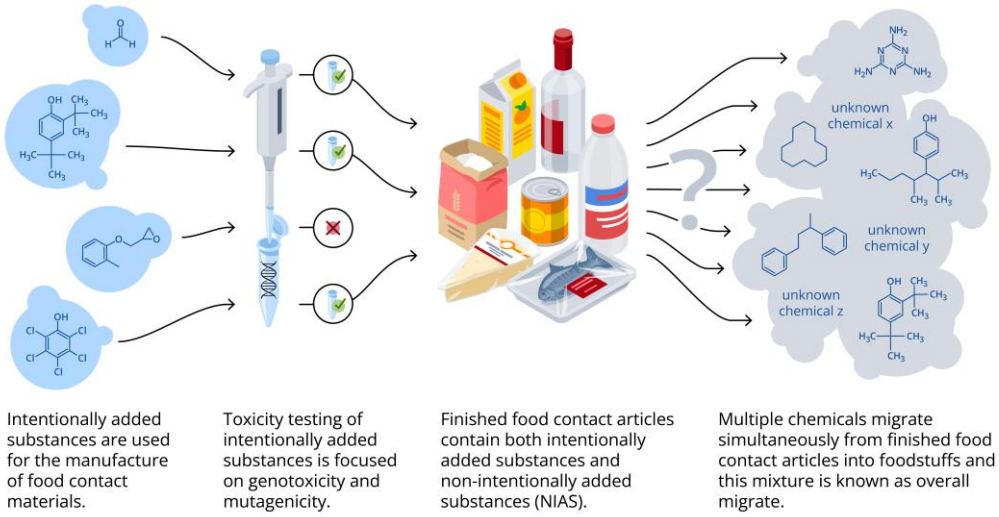

Figure 2. Chemical risk assessment for food contact chemicals (FCCs): current practice. The current approach for assessing the safety of FCCs focuses on testing single substances that are intentionally used to make FCMs. Only genotoxic carcinogenicity is currently determined as a human health relevant endpoint. However, many more chemicals can migrate simultaneously from the finished FCM, including unidentified compounds that are non-intentionally added substances (NIAS). The migrating mixture is known as the overall migrate, and it can exert adverse effects (mixture toxicity). Currently, the assessment of the overall migrate's mixture toxicity is not legally required.

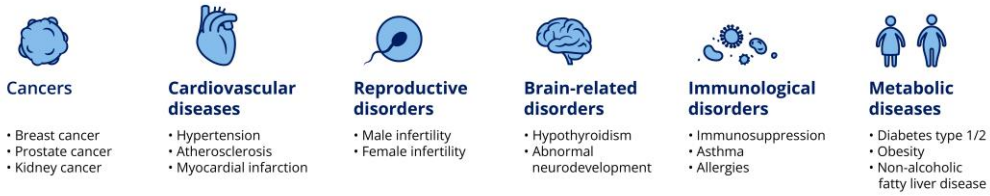

Figure 3. The Six Clusters of Disease (SCOD) concept comprises non-communicable diseases (NCDs) that are highly prevalent in the global human population, of increasing concern and associated with hazardous chemical exposures that can be clustered by disease type. The SCOD are of major concern for public health and require novel approaches for prevention, namely the identification of chemical contributors.

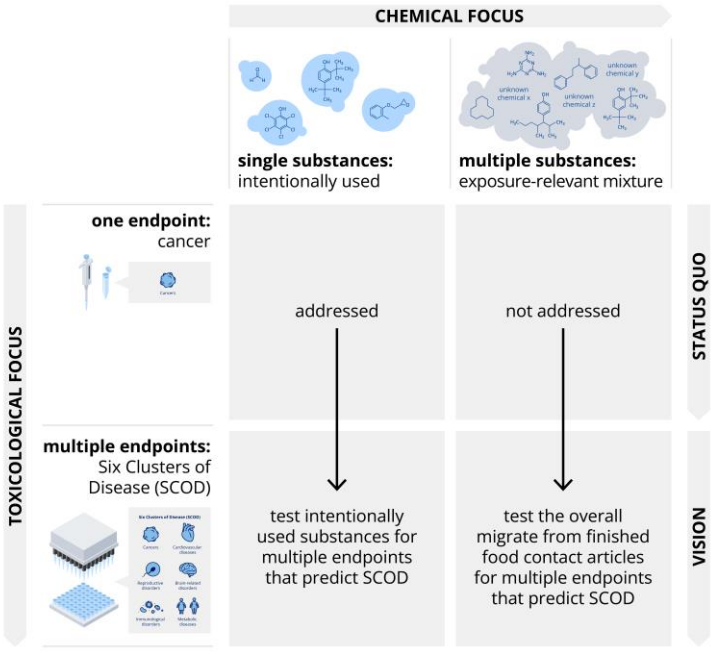

Figure 4. Overview of the current vs. proposed approach to food contact chemical (FCC) testing. The proposed new approach focuses on testing the overall migrate (i.e., the human exposure-relevant mixture of all migrating FCCs) for its potential to contribute to the Six Clusters of Disease (SCOD).

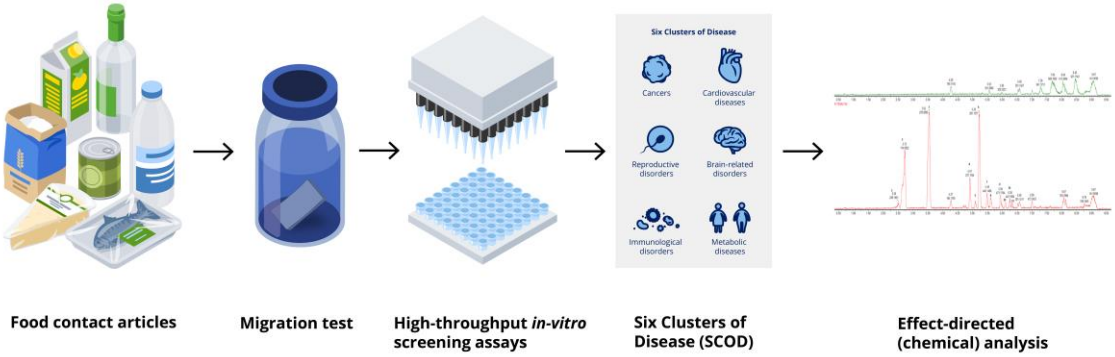

Figure 5. The vision for a novel approach to safety assessment of FCMs and food contact articles. Finished food contact articles are tested for their real-life mixture of all migrating chemicals (the *overall migrate*, i.e. the mixture of all migrating chemicals), using *in-vitro* screening assays. The screening assays are mechanism-based and identify the key characteristics, key initiating events, or other mechanisms of action of the overall migrate. Screening assays are selected around the Six Clusters of Disease (SCOD) concept. For overall migrate displaying positive findings in the in-vitro assays, non-targeted chemical analyses are carried out to identify the substances driving the overall migrate's toxicity.