



Review article

Overview of intentionally used food contact chemicals and their hazards

Ksenia J. Groh^{a,*}, Birgit Geueke^a, Olwenn Martin^b, Maricel Maffini^c, Jane Muncke^a^a Food Packaging Forum, Staffelstrasse 10, 8045 Zurich, Switzerland^b Institute for the Environment, Health and Societies, Brunel University London, Quad North 17a, Kingston Lane, Uxbridge UB8 3PH, United Kingdom^c Independent Consultant, Frederick, MD, USA

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ABSTRACT

Food contact materials (FCMs) are used to make food contact articles (FCAs) that come into contact with food and beverages during, e.g., processing, storing, packaging, or consumption. FCMs/FCAs can cause chemical contamination of food when migration of their chemical constituents (known as food contact chemicals, FCCs) occurs. Some FCCs are known to be hazardous. However, the total extent of exposure to FCCs, as well as their health and environmental effects, remain unknown, because information on chemical structures, use patterns, migration potential, and health effects of FCCs is often absent or scattered across multiple sources. Therefore, we initiated a research project to systematically collect, analyze, and publicly share information on FCCs. As a first step, we compiled a database of intentionally added food contact chemicals (FCCdb), presented here. The FCCdb lists 12'285 substances that could possibly be used worldwide to make FCMs/FCAs, identified based on 67 FCC lists from publicly available sources, such as regulatory lists and industry inventories. We further explored FCCdb chemicals' hazards using several authoritative sources of hazard information, including (i) classifications for health and environmental hazards under the globally harmonized system for classification and labeling of chemicals (GHS), (ii) the identification of chemicals of concern due to endocrine disruption or persistence related hazards, and (iii) the inclusion on selected EU- or US-relevant regulatory lists of hazardous chemicals. This analysis prioritized 608 hazardous FCCs for further assessment and substitution in FCMs/FCAs. Evaluation based on non-authoritative, predictive hazard data (e.g., by *in silico* modeling or literature analysis) highlighted an additional 1411 FCCdb substances that could thus present similar levels of concern, but have not been officially classified so far. Lastly, for over a quarter of all FCCdb chemicals no hazard information could be found in the sources consulted, revealing a significant data gap and research need.

Abbreviations: Carc2, Carcinogenicity Category 2 hazard classification; CAS, Chemical Abstracts Service; CFR, Code of Federal Regulation; CFSAN, Center for Food Safety and Applied Nutrition; C&L, Classification and Labeling; CMR, carcinogenic, mutagenic, toxic to reproduction; CPDat, Chemical and Products Database (a database maintained by the US EPA); CompTox, computational toxicology; CoRAP, Community Rolling Action Plan; DSSTox, Distributed Structure-Searchable Toxicity (a database maintained by the US EPA); DTXSID, Substance Identifier used in the DSSTox database; EC, European Commission; ECHA, European Chemicals Agency; EDC, endocrine disrupting chemical; EFSA, European Food Safety Authority; ENVH, environmental hazard; EPA, Environmental Protection Agency; EU, European Union; FACET, Flavours, Additives, and food Contact materials Exposure Task; FCA, food contact article; FCC, food contact chemical; FCCdb, database of intentionally added Food Contact Chemicals; FCM, food contact material; FCN, food contact substance notification; FCS, food contact substance; FDA, Food and Drug Administration; GHS, Globally Harmonized System for classification and labeling of chemicals; HH, health hazard; IAS, intentionally added substance; IER, ion-exchange resin; JRC, Joint Research Centre; Muta2, Mutagenicity Category 2 hazard classification; NIAS, non-intentionally added substance; NZIoC, New Zealand Inventory of Chemicals; OECD, Organization for Economic Cooperation and Development; PBT, persistent, bioaccumulative, toxic; PMT, persistent, mobile, toxic; PFAS, per- and polyfluoroalkyl substance; POP, persistent organic pollutant; REACH, Registration, Evaluation, Authorization and Restriction of Chemicals; Repr2, Reproductive Toxicity Category 2 hazard classification; SIN, Substitute It Now; SVHC, substance of very high concern; TEDX, The Endocrine Disruption Exchange; ToxVal, Toxicity Values (a database maintained by the US EPA); TSCA, Toxic Substances Control Act; UNEP, United Nation's Environment Programme; vPvB, very persistent, very accumulative; vPvM, very persistent, very mobile.

* Corresponding author at: Food Packaging Forum Foundation, Staffelstrasse 10, CH-8045 Zurich, Switzerland.

E-mail address: ksenia.groh@fp-forum.org (K.J. Groh).

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1. Introduction

Food contact materials (FCMs) can be defined as materials that come into contact with food and beverages during food processing, packaging, transport, storage, cooking, or serving. Different types of FCMs, for example, plastics, paper, glass, metal, adhesives, or printing inks, can be used, solely or in combination, to produce food contact articles (FCAs). A typical FCA is food packaging, such as bottles or wraps. However, food service items (e.g., cutlery) as well as food processing equipment (e.g., conveyor belts) or transport vessels also constitute a significant proportion of FCAs overall.

FCMs and, consequently, FCAs, are made of and contain diverse chemical constituents, which can be both intentionally used and non-intentionally present, here collectively referred to as food contact chemicals (FCCs) (Muncke et al., 2017). Under certain conditions, FCCs can be transferred into food, a phenomenon called migration (Arvanitoyannis and Bosnea, 2004; Grob et al., 2006). In recent years, FCMs have been subject to increasing attention and tightening regulations due to widespread exposure and association with adverse health effects in humans or in the environment (Hahladakis et al., 2018; Hermabessiere et al., 2017; Muncke et al., 2020). The bulk of regulatory and research activities currently focuses on a few substances or substance groups, such as bisphenols (Tisler et al., 2016; Vandenberg et al., 2007), phthalates (Zota et al., 2016), per- and polyfluoroalkyl substances (PFAS) (Blum et al., 2015), certain metals (Turner, 2019), or mineral oil hydrocarbons (Canavar et al., 2018; Grob, 2018). However, many more FCCs that are known or suspected to be hazardous could also be contributing to human exposure and health effects (Geueke and Muncke, 2018; Geueke et al., 2014; Grob et al., 2010; Liu and Mabury, 2019; Mertens et al., 2016; Qian et al., 2018; Simoneau et al., 2016; Zimmermann et al., 2019). For example, 175 chemicals of concern have been identified among a compiled list of approximately 6000 FCCs by comparing it with several lists of known and suspected hazardous chemicals (Geueke et al., 2014); a follow-up study reviewed migration evidence for a subset of these hazardous FCCs (Geueke and Muncke, 2018). The use of any substance in FCMs requires proper risk assessment and management (Nerin et al., 2018), but in practice this is not always ensured. For example, over half of all chemical additives allowed to be used in food in the US were found to lack appropriate toxicological data required to determine their safety (Neltner et al., 2013).

FCCs can be divided into two groups, intentionally added substances (IASs), i.e., substances that are deliberately used to manufacture FCMs or FCAs, and non-intentionally added substances (NIASs), i.e., substances that have not been added on purpose and do not perform any technical function, but are nonetheless present in the final FCMs or FCAs. NIASs can include impurities, contaminants, reaction byproducts and side products, and degradation products (Bradley and Coulier, 2007; Geueke, 2018; Nerin et al., 2013; Pieke et al., 2017). In 2016, the European Commission's Joint Research Centre (JRC) identified around 8030 IASs listed in the European member state regulations as being used in so-called 'non-harmonized FCMs,' i.e., FCMs other than plastics, glass, ceramics, or regenerated cellulose, for which a specific EU legislation exists (Simoneau et al., 2016). For NIASs, estimates of 40'000 up to 100'000 substances have been proposed (Grob et al., 2006; MacCombie, 2018). To date, no publicly available studies have established a comprehensive list of NIASs in FCMs, but there have been proposals to develop approaches to predict NIASs using modeling based on IASs information (Hoppe et al., 2016). Thus, understanding the diversity of IASs would be a required first step to a comprehensive characterization of the chemical composition of FCMs and associated chemical exposures throughout the whole life cycle of an FCA, from production to use and its disposal stages.

A concise, publicly available resource listing all known FCCs that could be intentionally used in FCMs or FCAs manufacture worldwide does not exist, and the available information is typically scattered across regulations and inventories for different FCM types, or remains

undisclosed. Therefore, the aim of this study was to compile a database of intentionally used FCCs, based on globally-sourced regulatory positive lists and industry inventories that could be openly accessed and easily interrogated. In addition, we recorded hazard information for the identified FCCs from several reputable public sources, where available. We discuss the collected information in the context of FCC use patterns in different FCMs and reported hazardous properties.

2. Materials and methods

2.1. Construction of the database of intentionally added food contact chemicals (FCCdb)

The database of intentionally added food contact chemicals (FCCdb) is a compilation of information on FCCs extracted from openly accessible and searchable regulatory lists or industry inventories, sourced from the countries considered the major economies in the world, where available. The information sources were identified based on the references given in the JRC's baseline report on non-harmonized FCMs in the EU (Simoneau et al., 2016). Notably, the JRC report referenced both European as well as non-European sources, the latter consulted there for comparative reasons. Several additional sources not referenced in the JRC report or made available only after its publication were also included. A detailed description of each information source included in the FCCdb is given in the 'Read Me' tab accompanying the FCCdb worksheets in the [Supplementary File 1](#) or on Zenodo.

One prerequisite for inclusion of a substance into the FCCdb was its identification by a Chemical Abstracts Service Registry Number (CAS number) in the interrogated source, because the subsequent merging with further sources was carried out based on the CAS identifier matching. Thus, the substances that lacked an assigned CAS number in the original source were not included in the FCCdb. An exception to this rule was made for a large group of FCCs identified by a numerical code in 977nnn-nn-n format that has been assigned by the US Food and Drug Administration's (US FDA) Center for Food Safety and Applied Nutrition (CFSAN) to those substances that do not have a CAS number.

2.2. Exploration of FCCdb chemicals' hazards and use

FCCdb chemicals' hazards to human health and the environment were explored based on hazard classifications aligned with the Globally Harmonized System for classification and labeling of chemicals (GHS), extracted from two sources: (1) classifications listed by the European Chemicals Agency (ECHA) in its Classification and Labeling (C&L) inventory (ECHA-C&L, see <https://echa.europa.eu/web/guest/information-on-chemicals/cl-inventory-database>) that includes both the harmonized classifications (i.e., officially assigned by ECHA) and the classification information received from manufacturers and importers on notified and registered substances; and (2) classification results issued by the Japanese Government (J-GHS, see https://www.nite.go.jp/chem/english/ghs/ghs_index.html). Both GHS information sources were interrogated on April 29, 2019, through the eChem portal (<http://www.echemportal.org>) maintained by the Organization for Economic Cooperation and Development (OECD). For FCCs that had respective GHS classification(s), sum hazard scores for health hazards (HH) and/or environmental hazards (ENVH) were then calculated. This was done following a previously published methodology where smaller or bigger numerical 'hazard grade scores' are assigned to each hazard classification (i.e., a combination of a class and category of hazard) depending on its severity (see [Supplementary File 2](#)). The 'sum hazard scores' for each substance are then calculated as the sum of all 'hazard grade scores' from the assigned classifications (Grob et al., 2019; Lithner et al., 2011).

The hazard classes currently included in the GHS do not cover endocrine disruption or persistency and bioaccumulation properties, but these hazards are recognized by, e.g., the Registration, Evaluation,

Authorization and Restriction of Chemicals (REACH) legislation in the EU (EU, 2006). We therefore deemed them relevant for the evaluation here as well. For endocrine disruption, we consulted (i) the Endocrine Disruptor Assessment List maintained by ECHA (<http://echa.europa.eu/ed-assessment/>, downloaded on April 30, 2020), (ii) the list of substances placed due to their endocrine disrupting properties on the Candidate List of substances of very high concern (SVHCs) for Authorization under the REACH regulation in the EU, status May 2020 (<http://echa.europa.eu/candidate-list-table>), (iii) Endocrine Disruptor Lists published by Denmark with involvement of four other European member states (<http://edlists.org>, status May 2020), and (iv) lists of recognized EDCs or potential EDCs compiled in the 2018 United Nations Environment Programme's (UNEP) report on EDCs (UNEP, 2018). For persistence and bioaccumulation-related hazards, we consulted (i) the PBT [persistent, bioaccumulative, toxic substance] Assessment List maintained by ECHA (<http://echa.europa.eu/pbt>, downloaded on April 30, 2020), (ii) the list of substances placed due to their PBT or very persistent, very bioaccumulative (vPvB) properties on the Candidate List of SVHCs for Authorization under REACH, status May 2020, (iii) lists of PBT substances identified by the US Environmental Protection Agency (US EPA), and (iv) the list of substances covered by the Stockholm Convention on Persistent Organic Pollutants (POPs) (<http://www.pops.int>). Regulatory lists of hazardous substances that we consulted included the REACH Candidate List of SVHCs for Authorization (<http://echa.europa.eu/candidate-list-table>), the REACH Authorization List (<http://echa.europa.eu/authorisation-list>), and the REACH Restriction List (<http://echa.europa.eu/substances-restricted-under-reach>), as well as the US California's Proposition 65 list (<http://oehha.ca.gov/proposition-65-list/>), all status May 2020. The hazard information obtained from all of the above-described sources is considered highly reliable as it has been agreed upon and accepted by multiple stakeholders. Therefore, we collectively refer to such hazard information and these sources themselves as "authoritative." Only the above-listed authoritative sources were considered when putting together the priority list of hazardous FCCs as described in Section 3.3.

Several other sources of hazard information can also be considered authoritative but were not used for prioritization purposes. Instead, these sources were consulted to extend the coverage of FCCdb chemicals for which highly reliable hazard information could be available. These sources included (i) the EU Community Rolling Action Plan (CoRAP) list maintained by ECHA (<http://echa.europa.eu/web/guest/information-on-chemicals/evaluation/community-rolling-action-plan/corap-table/>, downloaded May 1, 2020), (ii) the OpenFoodTox database compiled by the European Food Safety Authority (EFSA) (Ceriani et al., 2018), which provides chemical hazards data for all substances that have been evaluated by EFSA since its creation in 2002 (<https://zenodo.org/record/3693783#.Xq1dY2gzZaQ>, version published on March 27, 2020), and (iii) the US EPA's Safer Chemical Ingredients List of the chemicals that have been evaluated under the Safer Choice Program (<https://www.epa.gov/saferchoice/safer-ingredients#searchList>, status April 2020).

Since the authoritative hazard information was available for only a relatively small fraction of FCCdb chemicals, we also consulted several other sources to obtain data for more FCCdb substances, which allowed us to highlight additional substances of potential concern. We collectively refer to these sources as providing "predicted" hazard classifications. These sources included i) advisory GHS-aligned chemical classifications assigned by the Danish Environmental Protection Agency based on *in silico* modeling (<https://clp-vejlliste.mst.dk/default.aspx>, latest release searched in July 2019), ii) the Substitute It Now (SIN) list maintained by the non-governmental organization International Chemical Secretariat (ChemSec; <http://chemsec.org/business-tol/sin-list/>, November 2019 version), iii) The Endocrine Disruption Exchange (TEDX) list of potential EDCs (<https://endocrinedisruption.org/interactive-tools/tedx-list-of-potential-endocrine-disruptors/>, September 2018 version), and iv) the analysis carried out by the German Environment Ministry to identify persistent substances presenting

significant mobility-related hazards, i.e., persistent, mobile and toxic (PMT), or very persistent, very mobile (vPvM) substances (Arp and Hale, 2019). Since the hazardousness of PMT substances has been recognized only recently, this analysis represents one of the most comprehensive studies on the topic existing to date. Lastly, we searched the Toxicity Values (ToxVal) database compiled by the US EPA, which allowed us to further explore the general availability of hazard data for FCCdb substances that could be obtained from governmental agencies such as US EPA, JRC or OECD, as well as from scientific publications, since the ToxVal database compiles toxicity information from many such sources (Williams et al., 2017). For this analysis, the version 5 of the ToxVal database (release of August 2018) was downloaded from http://comptox.epa.gov/dashboard/chemical_lists/TOXVAL_V5.

Use-related data in the FCCdb include a substance's registration status in REACH (<https://echa.europa.eu/information-on-chemicals/registered-substances/>, accessed May 2019), regulatory status in the EU as provided by the "chemical universe mapping" study performed by ECHA (<https://echa.europa.eu/how-does-the-chemical-universe-mapping-work>, accessed December 2019), and inclusion in the ECHA's database of plastics additives (<https://echa.europa.eu/de/mapping-exercise-plastic-additives-initiative>, accessed May 2019), on the list of substances likely or possibly associated with plastic packaging (Groh et al., 2019), on the US Toxic Substances Control Act (TSCA) inventory (<https://www.epa.gov/tsca-inventory/>, accessed June 2019), and on the New Zealand Inventory of Chemicals (NZIoC) (http://www.cirs-reach.com/Inventory/New_Zealand_Inventory_of_Chemicals-NZIoC.html, accessed June 2019). Additional details on the consulted information sources can be found in the 'Read Me' tab accompanying the FCCdb worksheets presented in the Supplementary File 1 or on Zenodo.

Draw Venn Diagram tool at <http://bioinformatics.psb.ugent.be/webtools/Venn/> was used to examine overlaps between data subsets.

3. Results and discussion

3.1. Development of the food contact chemicals database (FCCdb)

Currently, the FCCdb integrates 67 different FCC lists extracted from over 50 government and industry sources, and lists 12'285 substances with unique CAS or CFSAN identifier. These information sources originate from five geographical areas: Europe, the US, the Mercosur region, China, and Japan. As the consulted sources generally describe these FCCs as intentionally added substances, it can be assumed that they are being used (or have been in use until recently) in FCMS/FCAs manufacture in at least some parts of the world. The FCCdb version associated with the submission of this manuscript can be found in the Supplementary File 1. The FCCdb has also been added to the Zenodo repository under <https://doi.org/10.5281/zenodo.3240108>. This link should be consulted for the most recent version, as any future updates will be published there as well.

3.1.1. Not all FCCs which could be in use are included in the FCCdb

For practical reasons and feasibility considerations, our compilation method covered only the substances that had a CAS number (11'609 FCCdb substances) or a CAS-like identifier with a 977nnn-nn-n format as assigned by the US FDA's CFSAN (676 FCCdb substances). Most of the 676 substances with a CFSAN identifier appear only on the FDA lists, with a few also included on the lists from Japan but not on any of the European lists. Several hundred more FCCs that could be intentionally used to make FCMS/FCAs are currently not included in the FCCdb because these substances or substance groups do not have a CAS or CFSAN identifier. For example, Annex I of the Regulation (EU) No. 10/2011 (EU, 2011) lists 893 substances authorized for use in food contact plastics in the EU, but 132 entries lack either of these two identifiers (status 12th amendment, EU 2019/37). Many of these entries refer to a group of substances each having a unique CAS number. These, however,

are not listed separately, but generic descriptions of chemical nature, such as “perchloric acid, salts,” are provided instead. Similarly, Annex 10 of the Swiss ordinance on food contact materials (No 817.023.21) contains over 150 entries lacking a CAS or a CFSAN identifier.

The absence of a common identifier complicates systematic assessment and comparison with other lists and databases, e.g., resources that compile information on hazardous properties. To improve transparency and ease of assessment, it would be advisable that different sources addressing intentionally used FCCs align their efforts to identify more substances by a harmonized identifier type, such as the CAS number. For generic entries, CAS numbers could be provided for the main representatives of a particular group. The usefulness of the CFSAN-assigned CAS-like identifier is much more limited, as it is largely confined to US FDA sources and is rarely if ever included in databases outside this agency. Similar concerns apply to other identifiers with limited coverage that are commonly introduced internally, such as FCM reference numbers used in the EU. One promising alternative identifier is the DTXSID, which links to a specific chemical structure. This abbreviation stands for the US EPA’s Distributed Structure-Searchable Toxicity (DSSTox) database’s Substance Identifier. An ongoing US EPA initiative seeks to map all chemicals in the Computational Toxicology (CompTox) Chemistry Dashboard using DTXSID (Dionisio et al., 2018; Williams et al., 2017), with the goal of promoting its future use to connect information from different sources. However, this new identifier has yet to demonstrate its usefulness and reach universal acceptance.

3.1.2. Some FCCdb substances could be outdated and not anymore in use

The FCCdb includes 4190 substances that are listed by just one of the 67 FCC lists. While this could be due to the specificity of a substance’s use in just one FCM type, a particular application, or geographical location, the rarity of a substance’s listing could also indicate that it is outdated and not in use anymore, or has very limited use. For example, among the 4023 chemicals extracted from the “food contact” group in the Chemical and Products Database (CPDat) maintained by the US Environmental Protection Agency (Dionisio et al., 2018), 1043 substances were unique to this list, i.e., not mentioned by any other FCC sources included in the FCCdb. The developers of the largest source included in the FCCdb, the Flavours, Additives, and food contact materials Exposure Task (FACET) list for FCMs in Europe (Oldring et al., 2014), have explicitly pointed out that the presence of a substance on their list does not necessarily indicate its active FCM use at the moment. Nonetheless, only 55 of the 5640 FACET-listed FCCs were unique to this source. On the contrary, the US FDA Inventory of Indirect Additives Used in Food Contact Substances contributed 3224 FCCdb substances of which more than a quarter, 828 chemicals, were unique to this source. Five more substances from this inventory were not included in the final FCCdb list because, according to the US Code of Federal Regulation (CFR) Title 21 189 Subpart D, they are “prohibited from indirect addition to human food through food-contact sources.” These substances are lead solder (CFSAN ID 977182–76-5), tin coated lead foil (CFSAN ID 977182-75-4), poly(hydrogenated bisphenol A-co-triphenyl phosphite) (CAS 27014-73-9), and 1,2-dihydro-2,2,4-trimethylquinoline (CAS 147-47-7) and its polymer (CAS 26780–96-1). Two of these substances still appeared in the “food contact” group on CPDat, but none of them is listed by any other source outside the US, making it likely that their use in FCMs has been completely discontinued. Similarly, three fluorochemicals from the US FDA’s Inventory of Effective Food Contact Substance (FCS) Notifications (FCNs) were not included in the final FCCdb list because their FCM use has been “voluntarily ceased by the manufacturer,” and they do not appear on any FCC lists outside the US. These three substances are 2-perfluoroalkylethyl acrylate (CAS 65605-70-1), copolymers of 2-perfluoroalkylethyl acrylate, 2-N,N-diethylaminoethyl methacrylate, glycidyl methacrylate, acrylic acid, and methacrylic acid (CAS 870465-08-0), and glycine, N,N-bis(2-hydroxy-3-(2-propenyloxy)propyl-, monosodium salt, reaction products with ammonium hydroxide and pentafluoroiodoethane-tetrafluoroethylene

telomer (CAS 220459-70-1). In contrast, three more substances that are similarly prohibited or phased-out in the US were nonetheless included in the FCCdb, because they are also mentioned by some European and/or Mercosur sources, suggesting possible ongoing use: ethylene thiourea (CAS 96-45-7), 4,4'-methylenebis(2-chloroaniline) (CAS 101-14-4), and copolymer of 2-perfluoroalkylethyl acrylate, 2-(dimethylamino)ethyl methacrylate, and oxidized 2-(dimethylamino)ethyl methacrylate (CAS 479029-28-2).

The eight excluded substances are listed in the [Supplementary File 1](#) in a separate worksheet called “FCCdb_excluded_substances.” An additional worksheet called “FCCdb_orphan_substances” lists 193 substances which have been included on the final list in earlier FCCdb versions due to being listed on one of the draft positive lists for certain FCMs, but are not included there in the current version due to not being listed in the respective final lists which have come into force by now. The final FCCdb list used in all subsequent analyses presented below can be viewed in the worksheet “FCCdb_FINAL_LIST” of the [Supplementary File 1](#).

3.2. Global inventories of FCCs used in different FCM types

The information sources included in the FCCdb cover all the 17 FCM types defined in the Regulation (EC) No 1935/2004 on materials and articles intended to come into contact with food (EU, 2004), namely plastics, coatings, rubber, silicones, ion-exchange resins (IERS), paper/board, cellophane (regenerated cellulose), textiles, cork, wood, adhesives, printing inks, wax, metals, glass, ceramics, and active & intelligent materials. Colorants can be regarded as the 18th FCM type covered in the FCCdb, as this group of substances is specifically covered by several FCCdb sources, for example the French 2004 draft “Order on the coloring of plastic materials and articles, varnishes and coatings intended to come into contact with foodstuffs, food products and drinks for human and animal consumption” and the US FDA sources. The latter sources also separately listed FCCs used in certain food processing operations, e.g., as surface sanitizers, antimicrobials, rinse-aids, lubricants, or tracers.

To gain a better understanding of different FCC uses, we compiled the so-called ‘global inventories’ of FCCs used in different types of FCMs or other food contact applications. We compiled 16 global inventories in total. Fifteen of them cover the 18 FCM types listed above (the FCCs used in metal, glass, and ceramic FCMs are listed together in one global inventory for “inorganic FCMs,” and cork and wood FCCs are also included within one inventory named “cork/wood”). The 16th inventory for “other uses” includes substances used in food contact applications other than the production of FCAs, such as food processing operations. Each FCC was assigned to none, one, or several inventories based on the information provided by the source(s) where this FCC is listed. For example, all FCCs listed on the Union list for food contact plastics (Annex I of the Regulation (EU) 10/2011) were assigned to the global inventory for plastic FCMs. Many FCCs included in this global inventory also appear in other FCM inventories, since they are also mentioned by other FCCdb sources referring to other FCMs. The distribution of the 67 FCC lists from the FCCdb among the global inventories for each FCM type can be viewed in the “Read Me” tab of the database file in the [Supplementary File 1](#).

The presented inventories should be viewed as indicative only, because they often integrate information from both regulatory and non-regulatory, i.e., legally non-binding, sources, such as industry lists. We call our inventories ‘global’ because they are based on FCC lists sourced from different world regions, where available. For example, the global inventory for plastic FCMs compiles FCCs from 13 lists, originating from the US, Europe, China, Japan, and the Mercosur region. Given the ever-increasing volumes of imports and cross-border trade, this approach appears justified.

In total, 10/774 of 12/285 FCCdb substances could be assigned to at least one of the 16 global FCM inventories, while for 1511 substances information on their use could not be easily retrieved or was not

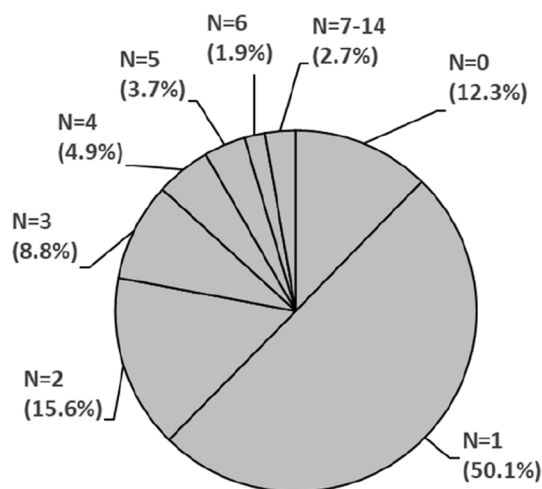


Fig. 1. Proportion of FCCdb substances with defined types of food contact use. The pie chart shows the fractions of substances (in percentage of all 12/285 FCCdb substances) which could not be assigned to any of the 16 global inventories ($N = 0$; 1511 substances) and of substances which could be assigned to at least one ($N = 1$; 6153 substances) or more ($N = 2$ up to $N = 14$; 4621 substances) inventories. The 16 global inventories cover food contact chemicals used in food contact plastics, coatings, rubber, silicones, ion-exchange resins (IERS), paper/board, cellophane (regenerated cellulose), textiles, cork/wood, adhesives, colorants, printing inks, wax, inorganics (including metals, glass, ceramics), active & intelligent materials, and other applications such as food processing operations.

available. Roughly half (6153) of all FCCdb substances are assigned to only one FCM inventory, while the remaining 4621 substances appear on two and up to 14 global FCM inventories (Fig. 1). The six most frequently mentioned substances are formaldehyde (CAS 50-00-0, assigned to 14 inventories), isopropanol (CAS 67-63-0, 13 inventories), and acrylic acid (CAS 79-10-7) along with sodium polyacrylate (CAS 9003-04-7), vinyl chloride (CAS 75-01-4), and styrene (CAS 100-42-5), each assigned to 12 inventories.

The total numbers and overlaps between the FCCs assigned to the 16 global inventories are shown in Table 1. For example, the global inventory for plastic FCMs includes 4742 substances in total, of which 1437 are unique to food contact plastics, as they do not appear on global inventories for any other FCM type. Global inventories for food contact plastics and coatings share 2008 substances, which corresponds to 42% of plastics FCCs and 70% of coatings FCCs (Table 1). Compared to the numbers of FCCs that the JRC's baseline study found to be known to or regulated by different EU member states (Simoneau et al., 2016), our global inventories contain higher substance numbers for all FCM types, underscoring the global nature of the included sources. The highest numbers of FCCs are found in the global inventories for printing inks, plastics, paper/board, and coatings, with 5625, 4742, 2950, and 2886 included substances, respectively. These FCM types also harbor particularly high numbers of unique FCCs, especially the printing inks with 2926 unique substances (52% of all FCCs assigned to this FCM type). The large number of diverse substances used in printing inks has been highlighted previously in the JRC's report on FCMs (Simoneau et al., 2016). Contrary to our study, the JRC report did not discuss colorants as a separate FCM type. In our comparison, however, only 183 out of 316 substances on the global inventory for food contact colorants (58%) were also assigned to the printing inks inventory, thus justifying the identification of the former as a separate FCM type.

The smallest numbers of FCCs are included in the global inventories for active & intelligent materials (100), inorganics (101), and wax (142), with correspondingly low numbers of unique substances (Table 1). However, the total number of substances on a given inventory may reflect not only the actual diversity of chemicals used in a given FCM type, but also the abundance or scarcity of available information sources for this material. For example, while the global inventory for plastic FCMs currently compiles information from 13 different lists, only two dedicated sources could be identified for active & intelligent materials. This FCM type is used to make FCAs with rapidly growing market share

which are intended to either actively interact with packaged food (e.g., by releasing antioxidants to prolong shelf life) or provide information about the condition of packaged food (e.g., sensors of ripeness or spoilage) (Dey and Neogi, 2019; Sohail et al., 2018; Vilela et al., 2018). The two sources on this FCM type are a non-binding "Register of substances" last updated in 2011, which lists 39 substances intended to be considered for a later inclusion on a positive list under the European Regulation (EC) No 450/2009 on active and intelligent materials, and a list of 61 substances extracted from the Recommendation XXXVI/3 for "Absorber pads based on cellulosic fibers for food packaging," issued by the German Institute for Risk Assessment in 2009. Surprisingly, these two lists overlapped by only one substance, cellulose (CAS 9004-34-6). One more substance, not listed by these two sources, was identified in the US FDA FCN inventory as being used as a component of an oxygen sensor, thus resulting in the total number of 100 substances included on the global inventory for active & intelligent FCMs. Due to a high uncertainty and the current lack of comprehensive and binding positive lists, this inventory is likely to be incomplete. However, even among such a low total number of substances listed, 8 substances are unique to this list only and have not been reported as FCCs intentionally used in any other FCM type: 3,5,4'-trihydroxystilbene (resveratrol) (CAS 501-36-0), monosodium glutamate (CAS 16177-21-2), (terephthalic acid, dimethyl ester, polymer with 1,4-butanediol, cyclized, polymers with glycidyl methacrylate, hydroxyl-terminated polybutadiene, methyl methacrylate and styrene) copolymer (CAS 1223402-34-3), calcium chloride hexahydrate (CAS 7774-34-7), chabazite (calcium aluminum silicate, CAS 12251-32-0), clinoptilolite (CAS 12173-10-3), palladium (CAS 7440-05-3), and platinum 5,10,15,20-tetrakis(pentafluorophenyl) porphyrin (CAS 109781-47-7). While some of these substances are better known and some are even directly added to food or drugs (e.g., resveratrol, sodium monoglutamate), the safe use of others may need additional assessment. For example, palladium is suspected to be a potent allergen (Faurischou et al., 2011; Wiseman and Zereini, 2009), frequent use of antimicrobials could be of concern in a context of global spread of antimicrobial resistance (Gillings, 2017; Hegstad et al., 2010), and the safety of nanomaterials used in FCMs is still debated (Groh et al., 2017; Jokar et al., 2017; Morais et al., 2019). Given the high pace of development and marketing of FCAs that employ active & intelligent FCMs, better oversight and more data on the associated FCCs and resulting exposures are needed.

Table 1

Total numbers and overlaps between substances assigned to 16 global inventories for different food contact materials and other food contact applications.

		global inventory, FCM type: plastics															
overlap with global inventories for other FCM types	plastics	4742															
	coatings	2008	2886														
	rubber	726	582	1043													
	silicones	507	471	254	784												
	IERs	415	378	203	298	555											
	P & B	2950															
	paper/board	1334	1270	488	350	281	2950										
	cellophane	301	262	156	111	79	257	365									
	textiles	77	77	37	14	16	169	25	207								
	cork/wood	124	168	79	53	43	184	32	12	219							
	adhesives	1275	981	461	254	205	1032	216	51	163	1788						
	colorants	224	129	44	31	14	88	15	4	8	40	316					
	inks	5625															
	wax	142															
	inorganics*	101															
	A & I	100															
other**	208																
unique substances	1437	331	172	144	84	745	17	20	6	154	38	2926	3	26	8	42	
prioritized hazardous substances	total	325	219	175	75	76	256	22	19	33	147	10	377	8	28	18	19
	unique	36	6	12	2	5	39	0	0	2	1	0	83	0	5	0	0

*Covers metals, glass, ceramics

**Covers other food contact uses, e.g., during food processing or preparation.

Abbreviations: FCM, food contact material; IERs, ion-exchange resins; P & B, paper and board; A & I, active and intelligent materials.

3.3. Prioritization of FCCdb chemicals recognized as hazardous by authoritative sources

Sound chemicals management should encourage continuous efforts to substitute hazardous chemicals used in processes and products with safer alternatives in order to enable the transition to a toxic-free environment (Goldenman et al., 2017) and to facilitate the emergence of clean circular economy based on non-toxic material cycles (Bodar et al., 2018; Geueke et al., 2018; Turner, 2018). To support these efforts in the area of FCMs, we sought to assemble a comprehensive list of FCCs that should be most urgently considered for substitution due to their intrinsic hazardous properties making them harmful to human health and/or the environment. A multitude of resources providing different types of hazard information can be found in the public domain, which, however, have widely variable recognition and reliability status, and also differ in their coverage of chemical space and hazard types. Therefore, we first focused on selected authoritative sources of hazard information, which we searched by CAS identifiers available for 11'609 FCCdb substances (Table 2). The 676 FCCdb substances that have no CAS number but only a CFSAN-assigned identifier had to be omitted from this analysis, because none of the sources consulted offered a CFSAN identifier-based search. Thus, the numbers and percentages given in Table 2 and discussed below should be interpreted in relation to the 11'609 FCCdb substances with a unique CAS number.

3.3.1. Prioritization based on GHS-aligned classifications for health and environmental hazards

We explored the FCCdb chemicals' hazards to health (HH) or the environment (ENVH) based on respective GHS-aligned classifications extracted from two authoritative sources: the ECHA's Classification and Labeling inventory (ECHA-C&L; classifications available for 900 (7.8%)

of CAS-identified FCCdb substances) and the list maintained by the Japanese government (J-GHS; classifications available for 1177 (10.1%) of CAS-identified FCCdb substances). Together, these two sources provided at least one HH or ENVH classification for only 1466 (12.6%) of CAS-identified FCCdb substances (Table 2). Hazard ranking was performed following previously published methodology (Groh et al., 2019; Lithner et al., 2011), where hazard classifications available for each substance are assigned pre-defined numerical scores reflecting their severity (see Supplementary File 2), and the sum hazard scores for each substance are then calculated by adding up the hazard scores for individual HH and ENVH classifications. In this framework, substances that have at least one carcinogenic, mutagenic, or toxic to reproduction (CMR) classification with the highest hazard category of 1 would receive the sum hazard score for HH that equals or exceeds 10'000. Therefore, all substances receiving the sum hazard score for HH $\geq 10'000$ were considered priority hazardous substances. For ENVH, we prioritized substances with the sum hazard score of 1000 and above, because this range covers substances that have the highest hazard category of 1 for the chronic aquatic toxicity, with or without acute toxicity classification. Based on classifications from the ECHA-C&L source, 187 and 146 substances were prioritized for HH and ENVH, respectively, while analysis based on J-GHS classifications prioritized 146 and 182 substances for HH and ENVH, respectively. Somewhat unexpectedly, the lists of HH or ENVH priority substances thus derived from ECHA-C&L and J-GHS sources showed only a moderate overlap, both in terms of the identity of classified chemicals and in terms of classifications assigned to overlapping chemicals. Specifically, only 70 substances received the HH sum hazard scores of $\geq 10'000$ from both ECHA-C&L and J-GHS sources, and only 62 substances had the ENVH sum hazard score ≥ 1000 from both sources. Given the apparent differences in the scope of substances covered by these two sources, we decided to consider hazard

Table 2

Availability of hazard information for CAS-identified FCCdb chemicals in the sources consulted.

Description of grouping or prioritization criteria	Included substances		Consulted information sources (for more details see Section 2.2)	
	N	% of total		
All CAS-identified substances included in the FCCdb	11'609	100	FCCdb; only chemicals with CAS identifier	
Having at least one classification for HH and/or ENVH	1466	12.6	ECHA-C&L and J-GHS inventories of substance classifications for health hazards (HH) and/or environmental hazards (ENVH) aligned with Globally Harmonized System (GHS) for chemical classification and labeling	
Prioritized for HH (i.e., sum hazard score $\geq 10'000$)	263	2.3		
Prioritized for ENVH (i.e., sum hazard score ≥ 1000)	266	2.3		
Criterion 1: Prioritized as above for HH and/or ENVH*	482	4.2		
On the ECHA's Endocrine disruptor assessment list	61	0.5	Selected authoritative sources on assessment and identification of endocrine disrupting chemicals (EDCs), persistent, bioaccumulative, toxic (PBT) and very persistent, very bioaccumulative (vPvB) chemicals, and persistent organic pollutants (POP), e.g., by European Union (EU), European Chemicals Agency (ECHA), US Environmental Protection Agency (US EPA), United Nations Environment Programme (UNEP), national authorities	
On the EDC Lists by the Danish Environmental Protection Agency	67	0.6		
EDC or potential EDC listed in the UNEP report (UNEP, 2018)	47	0.4		
On the ECHA's PBT assessment list	83	0.7		
Recognized as EDC in the EU under REACH or Biocides regulations	22	0.2		
Recognized as PBT and/or vPvB in the EU and/or US, or as POP	32	0.3		
Criterion 2: Prioritized as recognized EDC, PBT and/or vPvB, or POP	54	0.5		
Included on REACH Candidate List of SVHCs for Authorization	123	1.1		Selected regulatory lists of hazardous substances relevant for the EU (Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) lists) or the US (California Proposition 65 List); SVHC, substance of very high concern
Included on REACH Authorization List**	36	0.3		
Included on REACH Restriction List	255	2.2		
Included on US California Proposition 65 List (Prop65)	175	1.5		
Criterion 3: Prioritized as substance on REACH list(s) or Prop65 list	378	3.3		
Prioritized based on any of the three criteria highlighted in bold above	608	5.2	All authoritative sources listed above	
Included on the EU Community Rolling Action Plan (CoRAP)	248	2.1	Additional authoritative sources not used for prioritization described above but to further explore the availability of reliable hazard data for FCCdb substances	
Included in the EFSA's OpenFoodTox database (Ceriani et al., 2018)	1424	12.3		
Included on the US EPA's Safer Chemical Ingredients List	655	5.6		
Covered by at least one of the sources above	3001	25.9	All authoritative sources listed above	
Having no information in any of the sources above	8608	74.1		
Having at least one predicted classification for HH and/or ENVH	2889	24.9	Advisory GHS-aligned classifications for HH and/or ENVH predicted by the Danish EPA through <i>in silico</i> modeling; CMR, carcinogenic, mutagenic, or toxic to reproduction properties	
Predicted HH of concern (i.e., predicted CMR properties)	864	7.4		
Predicted ENVH of concern (i.e., highest category of aquatic toxicity)	436	3.8		
Prioritized due to concern about potential genotoxicity	106	0.9	(Van Bossuyt et al., 2017)	
Included on the TEDX list of potential EDCs	367	3.2	TEDX list of potential EDCs	
Assessed for PMT/vPvM properties	198	1.7	Report on persistent, mobile, toxic (PMT) and very persistent, very mobile (vPvM) substances (Arp and Hale, 2019)	
Identified as PMT/vPvM based on self-defined "high quality" assessment	45	0.4		
Included on the SIN List	308	2.7	Substitute It Now! (SIN) list	
Identified as chemical of potential concern based on predictive sources	1798	15.5	Predictive (non-authoritative) sources above	
Covered by at least one of the sources above	4986	42.9	All sources listed above, authoritative and non-authoritative (predictive)	
Having no information in any of the sources above	6623	57.1		
Found in the ToxVal database (Williams et al., 2017)	8328	71.7	Toxicity Values (ToxVal) database by US EPA	
Covered by at least one of the sources above	8711	75.0	All sources listed above, authoritative and non-authoritative (predictive)	
Having no information in any of the sources above	2898	25.0		

*Rows in bold show prioritization criteria and numbers of substances prioritized according to these criteria based on selected authoritative sources (see sections 3.3.1–3.3.4). Blue, orange and green backgrounds correspond to Venn diagram colors used in Fig. 2.

**All substances on this list are also included in the REACH SVHC List.

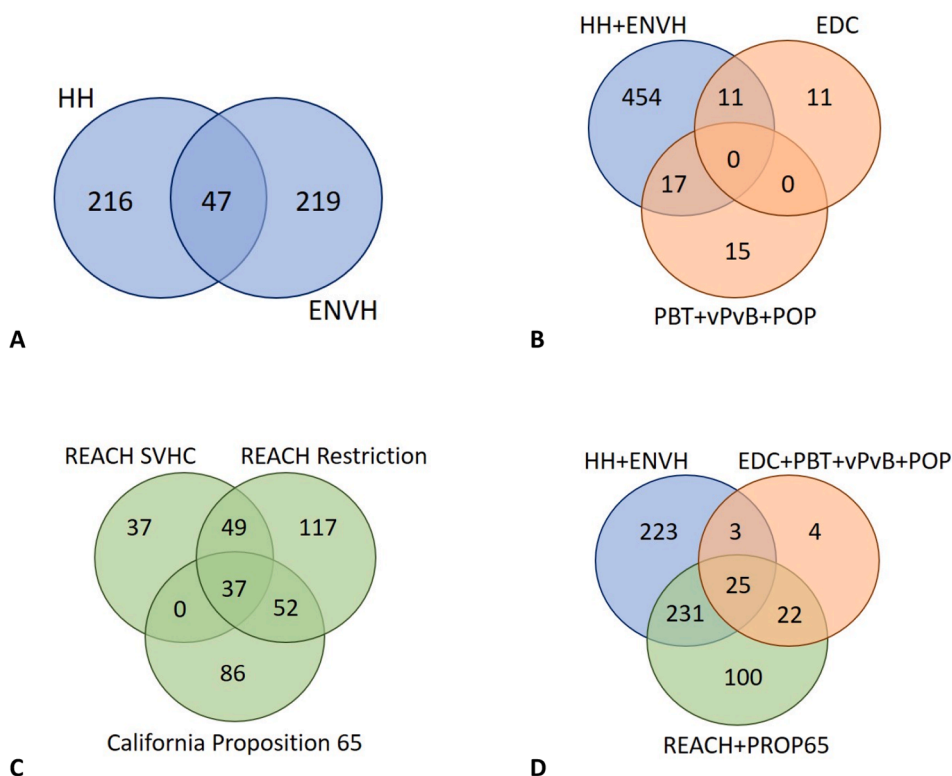


Fig. 2. Total numbers and overlaps between 608 FCCdb substances prioritized for substitution based on selected authoritative sources of hazard information. (A) Prioritization based on globally harmonized system (GHS)-aligned classifications for health hazards (HH, N = 263) and environmental hazards (ENVH, N = 266), total N = 482. (B) Prioritization based on the authoritative identification as substance of concern due to endocrine disrupting or persistence-related hazards (total N = 54, includes endocrine disrupting chemicals (EDCs) recognized in the EU under the REACH or Biocides legislation (EDC, N = 22) and substances recognized in the EU or US as persistent, bioaccumulative and toxic (PBT), or very persistent, very bioaccumulative (vPvB), or as persistent organic pollutants (POPs) under Stockholm convention (PBT + vPvB + POP, N = 32)) and overlap with substances prioritized based on GHS classifications (HH + ENVH, N = 482). (C) Prioritization due to inclusion on the EU- or US-relevant regulatory lists of hazardous substances (total N = 378): EU Registration, evaluation, authorization and restriction of chemicals (REACH) legislation's list of substances of very high concern (SVHC), also called Candidate list of SVHCs for authorization (REACH SVHC, N = 123), REACH Restriction list, also called Annex XVII (REACH Restriction; N = 255), and US California Proposition 65 list (N = 175). (D) Combined list of hazardous substances prioritized as described in A-C, including HH + ENVH (as described in (A), N = 478), EDC + PBT + vPvB + POP (as described in (B), N = 54), REACH + PROP65 (as described in (C), N = 378); with overlaps, the combined list includes the total N = 608 of hazardous FCCdb substances prioritized based on selected authoritative sources of hazard information.

classifications provided by either one of them for the final prioritization, since this allowed to increase the coverage of globally sourced FCCs. In total, 263 substances with HH sum hazard scores $\geq 10,000$ and 266 substances with ENVH sum hazard scores ≥ 1000 were prioritized. With a small overlap of 47 substances having priority sum hazard scores for both HH and ENVH classification types, this amounts to 482 priority hazardous substances for HH and/or ENVH identified based on GHS-aligned hazard classifications (Fig. 2A, Table 2). The list of all substances prioritized based on this criterion is given in the Supplementary File 3.

3.3.2. Prioritization based on endocrine disruption- and persistence-related hazards

Because the GHS classifications do not consider endocrine disruption, we additionally covered this hazard by consulting several authoritative sources dealing with EDC assessment and identification in the EU. Currently, 20 FCCdb substances are officially recognized as EDCs under the REACH legislation (i.e., these substances are added to the Candidate list of SVHCs for authorization due to their endocrine disrupting properties harmful to human health and/or the environment). Two more FCCdb substances are recognized as EDCs under the Biocides regulation (Regulation (EU) No 528/2012). These twenty-two substances were added to the list of prioritized hazardous FCCdb substances; only half of them have already been prioritized based on the GHS classifications (Fig. 2B). Importantly, the process of EDC identification is far from being completed, with conclusive endocrine disruption assessment pending for many more substances. As follows from the ECHA's Endocrine disruptor assessment list, from the EDC lists compiled by the Danish

Environmental Protection Agency, and from the 2018 UNEP report on EDCs (UNEP, 2018), at least 95 more FCCdb substances are currently being assessed or suspected to be EDCs of concern in the EU and/or worldwide. Consideration of the TEDX inventory of putative EDCs, defined as substances with potential endocrine disrupting properties reported in the peer-reviewed publications, would have highlighted at least 294 more potential EDCs among the FCCdb chemicals. However, TEDX list cannot be considered authoritative due to its high uncertainty, therefore it shall be considered only among the non-authoritative sources as discussed later in Section 3.4.4.

The GHS classifications currently also do not cover persistence-related hazards. Therefore, we used three authoritative sources to address this gap, namely the PBT/vPvB assessments carried out in the EU, the US EPA list of PBT substances, and the Stockholm convention's list of POPs. This analysis flagged 32 FCCdb substances in total (Table 2); only 17 of these have already been prioritized based on the GHS-aligned classifications (Fig. 2B). The assessment of persistence-related chemical hazards is also an ongoing process. According to the ECHA's PBT assessment list, at least 43 additional FCCdb substances are currently being assessed in this regard.

With overlaps, consideration of authoritative sources identifying substances with endocrine disruption- or persistence-related hazards prioritized 54 FCCdb substances, roughly half of which would not have been highlighted based on GHS classifications alone (Fig. 2B, Supplementary File 3).

3.3.3. Prioritization based on inclusion on selected regulatory lists

The EU REACH list of substances of very high concern (SVHC), also

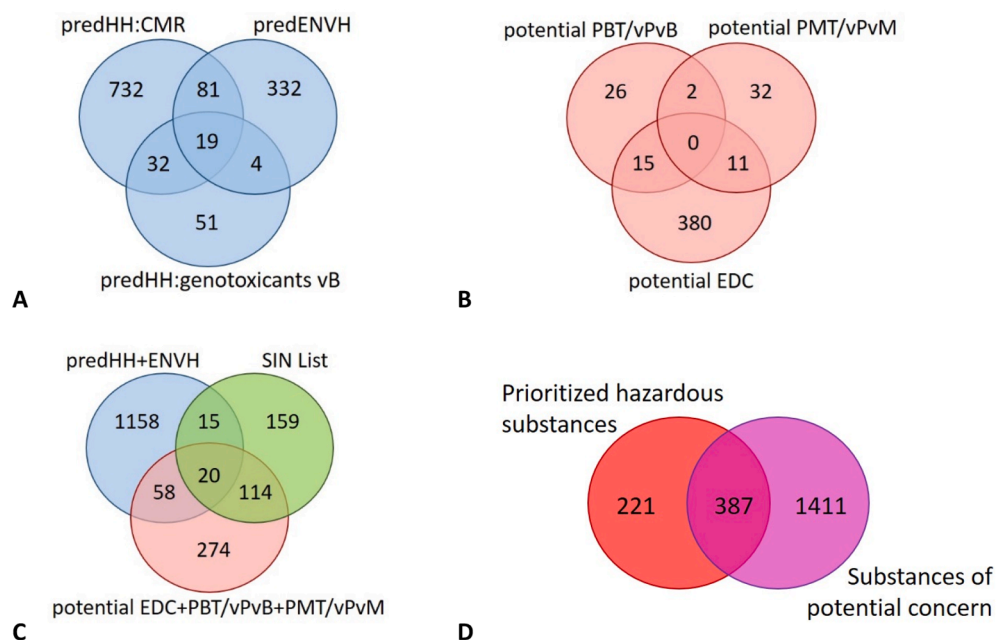


Fig. 3. Total numbers and overlaps between FCCdb chemicals identified as substances of potential concern based on selected non-authoritative (predictive) sources of hazard information. (A) Identification based on predicted health hazards (HH) and environmental hazards (ENVH) of significant concern (total N = 1251), including (i) predicted globally harmonized system (GHS)-aligned classifications, as extracted from the Danish Environmental Protection Agency (Danish EPA) database of advisory classification, labeling and packaging (CLP) classifications predicted by in silico modeling, for HH including Carcinogenicity 2 (C), Mutagenicity 2 (M) and Reproductive Toxicity 2 (R) classifications (predHH:CMR, N = 864) and for ENVH (predENVH, N = 436), and (ii) substances identified by [van Bossuyt et al. \(2017\)](#) as potential genotoxicants based on in silico modeling (predHH:genotoxicants vB, N = 106). (B) Identification due to suspected endocrine disruption- or persistence related hazards (total N = 466), including (i) 95 potential endocrine disrupting chemicals (EDCs) identified based on authoritative sources such as European Union and UN Environmental Programme and 367 putative EDCs from The Endocrine Disruption Exchange list (potential EDC, total N = 406), (ii) substances under assessment in the EU as potential persistent, bioaccumulative and toxic (PBT) or very persistent, very bioaccumulative (vPvB) substances (potential PBT/vPvB, N = 43), and (iii) substances identified as persistent, mobile and toxic (PMT) and/or very persistent, very mobile (vPvM) in a 2019 assessment by the German Environment Agency ([Arp and Hale, 2019](#)) (potential PMT/vPvM, N = 45). (C) Overlap between three groups of substances included on the list of FCCdb substances of potential concern identified based on selected non-authoritative, predictive sources (total N = 1798), including (i) substances of potential concern due to HH or ENVH, identified as in (A) (predHH + ENVH, N = 1251), (ii) substances of potential concern due to endocrine disruption- or persistence-related hazards, identified as in (B) (potential EDC + PBT/vPvB + PMT/vPvM, N = 466), and (iii) substances included on the Substitute It Now! (SIN) List maintained by the non-governmental organization International Chemical Secretariat (SIN List, N = 308). (D) Overlap between the 608 hazardous substances prioritized based on selected authoritative sources of hazard information as described in Section 3.3.4 and 1798 substances of potential concern identified as in (C).

called Candidate list of SVHCs for Authorization, includes 123 FCCdb chemicals, and 36 of these substances are also on the REACH Authorization list (Annex XIV). On the EU REACH Restriction list (Annex XVII), 255 FCCdb chemicals are found. With overlaps, 292 FCCs are listed on these three lists of hazardous substances maintained under the REACH legislation in the EU. The California Proposition 65 (Prop65) list includes 175 FCCdb chemicals, about half of which overlap with REACH-highlighted substances ([Fig. 2C](#)). Overall, the consideration of inclusion

on the selected regulatory lists of hazardous substances prioritized 378 FCCdb substances ([Supplementary File 3](#)), which are thus explicitly recognized as hazardous under the examined European and/or US-based regulatory acts, but nonetheless could possibly be used in FCMS/FCAs worldwide, potentially contributing to human exposure.

3.3.4. Combined list of hazardous FCCdb chemicals prioritized based on authoritative sources

The sources of authoritative hazard information described above in Sections 3.3.1–3.3.3 provided some hazard information for 1615 FCCdb substances (13.9%) of 11'609 chemicals with CAS numbers. Using the above-described criteria, 608 of these substances have been added to the combined list of priority hazardous FCCs (Table 2, Fig. 2D). All prioritized substances are listed in the Supplementary File 3.

The largest numbers of hazardous substances are found on global inventories for printing inks (377), plastics (325), and paper/board (256), but the inventories for other materials also include significant numbers of prioritized hazardous chemicals (Table 1). Printing inks, plastics, and paper/board inventories also had the highest numbers of unique substances included on the priority list. Fourteen prioritized substances are found on 10 or more global FCM inventories, indicating likely widespread use: formaldehyde (CAS 50-00-0, on 14 global inventories), styrene and vinyl chloride (CAS 100-42-5 and CAS 75-01-4, respectively, each on 12 global inventories), sodium tetraborate and acrylonitrile (CAS 1330-43-4 and CAS 107-13-1, each on 11 global inventories), and nine substances on 10 global inventories each: boric acid (CAS 10043-35-3), ammonia (CAS 7664-41-7), ethyl acrylate (CAS 140-88-5), 1,1-dichloroethylene (CAS 75-35-4), ethylene glycol (CAS 107-21-1), silicon dioxide (CAS 7631-86-9), zinc oxide (CAS 1314-13-2), bisphenol A (BPA, CAS 80-05-7), and epichlorohydrin (CAS 106-89-8).

3.3.5. Hazard information provided by additional authoritative sources

Three additional authoritative sources of hazard information discussed here were not used for prioritization but allowed further exploring the availability of reliable hazard data for additional FCCdb substances. The EFSA's OpenFoodTox database compiles hazard information for all chemicals that have been evaluated by EFSA since its creation in 2002 for some sort of food-related use (Ceriani et al., 2018). While this database lists only 152 of the prioritized 608 FCCdb substances, it also provides some hazard information for about a thousand additional FCCdb substances which have not been covered by the authoritative sources used for prioritization as discussed above (Table 2). Thus, together with the substances included on the EU's Community Rolling Action Plan (CoRAP) list and on the US EPA's Safer Chemical Ingredients List, and considering the sources used for prioritization, all authoritative sources examined in this work provided some hazard information for 3001 (26%) of the 11'609 CAS-identified FCCdb substances (Table 2).

3.4. FCCdb chemicals' hazards explored by selected non-authoritative sources

Since the authoritative hazard information was available for only about a quarter of FCCdb chemicals, we also consulted several non-authoritative sources of information to gain an overview of suspected or predicted hazards. This allowed us to highlight additional substances of potential concern.

3.4.1. Substances of potential concern due to predicted health and environmental hazards

The Danish Environmental Protection Agency (Danish EPA) maintains a database of over 50'000 chemicals for which GHS-aligned hazard classifications have been predicted using several *in silico* models. From this database, at least one prediction for HH or ENVH classification could be found for 2889 FCCdb chemicals (Table 2). Among them, 864 FCCdb chemicals were considered to exhibit predicted HH of serious concern, corresponding to predicted CMR classifications, i.e., Carcinogenicity Category 2 (Carc2) predicted for 178 FCCs, Mutagenicity Category 2 (Muta2) for 370 FCCs, and Reproductive Toxicity Category 2 (Repr2) for 441 FCCs, with overlaps. Note that Category 2 is the highest possible severity grade that could be assigned in this type of assessment, because Category 1 classifications for CMR properties are never assigned

based on *in silico* evidence alone. ENVH of highest concern (i.e., Chronic Aquatic Toxicity Category 1, with or without Acute Aquatic Toxicity Category 1) was predicted for 436 FCCdb chemicals; among them, 100 substances also had predicted CMR hazards (Fig. 3A).

A study using a different suite of *in silico* models has prioritized 106 potential genotoxicants among the substances used in paper and board FCMs, including printing inks (Van Bossuyt et al., 2017, 2016). We considered all 106 of these substances to also be substances of potential concern for human health due to predicted genotoxicity. Sixty-eight of these chemicals are in fact already included in the Danish database, having Muta2 classification predicted for 36 chemicals and Carc2 classification predicted for another set of 36 chemicals, with an overlap of 23 chemicals between the two groups. Additional 19 of the potential genotoxicants prioritized by Van Bossuyt et al and assessed in the Danish study did not receive any genotoxicity-related classification in the latter. This observation underscores the current lack of agreement between different *in silico* models, suggesting the need to either externally validate the reliability of the *in silico* models or routinely consider the predictions delivered by several different models in making the final assessment calls (Van Bossuyt et al., 2018). All considerations described above highlighted 1251 FCCdb substances as being of potential concern due to predicted health or environmental hazards (Fig. 3A, Supplementary File 4).

Among these 1251 substances, 515 have potential concerns for genotoxicity and/or carcinogenicity based on the assessment by the Danish EPA and Van Bossuyt et al. (2017). For 110 of these substances, experimental data on genotoxicity from the EFSA's OpenFoodTox database are also available, and among them, 8 substances have "positive" genotoxicity indication from at least one of the studies recorded in that database. These substances are 2,3-epoxypropanol (CAS 556-52-5), methyleugenol (CAS 93-15-2), ether, bis(pentabromophenyl) (CAS 1163-19-5), Ponceau 3R (CAS 3564-09-8), epoxy silane (CAS 2530-83-8), 4-prop-1-enylveratrole (CAS 93-16-3), Solvent Red 23 (CAS 85-86-9) and Solvent Red 24 (CAS 85-83-6). Only the first four of these substances are already included among the 608 substances prioritized based on authoritative sources of hazard information, and overall, only 41 of the 515 potentially genotoxic and/or carcinogenic substances are already included on the prioritized list, while 163 additional substances have hazard classifications of lower severity or other hazard information available in the consulted authoritative sources. The remaining 311 substances thus appear to have not yet been subject to an assessment by the authoritative sources we have consulted, despite being suspected to have a hazardous property of very high concern. Since most of the authoritative sources consulted in this work originate from Europe or Japan, it could be that some of these 311 FCCs appear to remain unassessed because they are not used in these geographical regions. However, this seems not to be the case, since the majority (280) of these 311 substances do have indications of use in these geographical regions, i.e., they are mentioned on the FCC lists sourced either from Europe (202), or Japan (26), or both (52). Similarly, from the 436 FCCdb substances for which the Danish *in silico* assessment predicted the Aquatic Chronic 1 classification that indicates the highest level of ENVH concern, only 25 substances are included on the list of 608 substances prioritized based on authoritative sources, and 126 additional substances have less severe classifications or other hazard information available from the consulted authoritative sources, with the remaining 285 substances likely unassessed. Again, the majority (250) of these 285 substances have indications of use in either Europe (198), or Japan (27), or both (25). Overall, these findings demonstrate a considerable gap between regulatory and scientific assessments of hazardous chemicals.

Over half of the 515 potentially genotoxic and/or carcinogenic FCCdb substances are included on the global inventory for food contact printing inks (295 substances), with further considerable contribution from plastics (160 substances), coatings (107 substances), and paper and board FCMs (101 substances). Interestingly, 49 of these 515 substances are included on the global inventory for food contact colorants, which is

a relatively high proportion for a list containing only 316 substances in total. Most of these 49 substances are also found on the global inventory for printing inks (34 substances) and some on inventories for a few other FCM types, but 9 substances are unique to the food contact colorants list, including Pigment Red 7 (CAS 6471-51-8), Pigment Red 8 (CAS 6410-30-6), Pigment Red 10 (CAS 6410-35-1), Vat Yellow 26 (CAS 3627-47-2), Solvent Yellow 130 (CAS 26846-41-3), Sudan Red G (CAS 1229-55-6), N-(9,10-dihydro-9,10-dioxo-1-anthryl)[1,1'-biphenyl]-4-carboxamide (CAS 5924-63-0), 12-oxo-12H-phthaloperinesulfanilide (CAS 75199-11-0), and 3,3'-dichloro-indanthrone (CAS 130-20-1).

3.4.2. Substances of potential concern due to predicted endocrine disruption or persistence-related hazards

As discussed in Section 3.3.2, consulted authoritative sources such as EU and UNEP identify among the FCCdb chemicals at least 95 potential EDCs and 43 potential PBT substances (see Section 3.3.2). In addition, 367 substances are identified as putative EDCs by the TEDX list. With overlaps and together with 45 potentially persistent, mobile and toxic (PMT) and/or very persistent, very mobile (PMT) substances identified as described in the next paragraph, this amounts to 466 FCCdb substances identified to be substances of potential concern due to suspected endocrine disruption- and/or persistence-related hazards (Fig. 3B).

Apart from bioaccumulation, mobility is now also considered an important hazardous property that should be closely evaluated for persistent substances. This is because chemicals which are both persistent and mobile can remain in the aquatic environment for a long time and can also be transported over long distances (Reemtsma et al., 2016). The EU is currently considering the options for inclusion of the PMT and vPvM criteria in its process for SVHC identification under REACH, but the discussions have not been finalized yet. The most comprehensive analysis on the topic available to date is the 2019 study by the German Environment Agency (Arp and Hale, 2019), therefore we used it as a source of information on predicted hazards to identify potential PMT or vPvM substances within the FCCdb. Based primarily on data availability, the agency has self-evaluated the quality of its assessments and correspondingly labeled them as high-, middle-, and low-quality assessments. In total, 198 of the FCCdb substances have been subject to one of these three types of assessment, and the high-quality assessments identify 45 FCCdb substances to be of potential concern as PMT and/or vPvM substance (Supplementary File 4). Consideration of the medium-quality and low-quality assessments would have flagged additional 91 and 13 potential PMT/vPvM substances in the FCCdb, respectively, while for the remaining substances the PM properties were not confirmed. Only one substance among the 45 PMT and/or vPvM substances identified with the highest reliability, namely the tetraethylammonium perfluorooctanesulfonate (CAS 56773-42-3), has also been recognized as a PBT/vPvB in the EU, and only 10 of these 45 substances in total are already included on the list of 608 substances prioritized based on authoritative hazard information sources.

3.4.3. Substances of potential concern highlighted through the SIN list

The Substitute It Now! (SIN) list, maintained by the NGO ChemSec, records chemicals that have been identified by ChemSec as exhibiting hazardous properties that would justify their identification as an SVHC according to the EU REACH criteria described in the REACH article 57. The scientific robustness and validity of ChemSec assessments have been recognized internationally (UNEP, 2018). For example, all but one of the 20 FCCdb substances that are recognized as EDCs under the REACH legislation in the EU (see Section 3.3.2) are already included on the SIN list. Similarly, 25 of the 32 substances prioritized due to persistent and bioaccumulative properties (see Section 3.3.2) are also found on the SIN list. Progressive companies have long recognized the value of this resource and are known to use it to identify substitution candidates ahead of future regulatory changes. In total, there are 308 SIN list-identified substances in the FCCdb, of which the majority (270 substances) are already included on the list of 608 hazardous FCCdb

chemicals prioritized for substitution based on authoritative sources (see Section 3.3.4). In contrast, only 35 out of 1251 substances of potential concern identified based on *in silico* predicted HH or ENVH (see Section 3.4.1) are currently found on the SIN List (Fig. 3C). However, SIN List includes 134 out of 466 substances identified as potential EDCs and/or PBT/vPvB and/or PMT/vPvM substances (Fig. 3C), suggesting that this resource could be particularly useful for further prioritizing the substances of potential concern with regard to endocrine disruption- or persistence-related substances.

3.4.4. Combined list of FCCdb substances of potential concern identified based on predictive sources

Based on the selection process outlined in Sections 3.4.1–3.4.3, 1798 FCCdb substances in total have been included on the combined list of FCCdb substances of potential concern identified based mainly on non-authoritative sources (Fig. 3C, Supplementary File 4). Among these substances, 387 have already been included on the list of 608 hazardous FCCdb substances prioritized based on authoritative sources of hazard information (Fig. 3D). The reasons for why a particular substance has both authoritative and predictive hazard data justifying its inclusion on both lists could be manifold. For example, it could be that this substance's hazard was first predicted and then confirmed by an authoritative source, as is the case for many substances included on the SIN list. A predictive source could also be identifying a different additional hazard which has not yet been assessed and/or classified by the authoritative source. These details should be clarified for each substance upon closer evaluation with regard to substitution options. For some of the remaining 1411 substances currently included only on the list of predicted substances of potential concern, authoritative hazard data may become available relatively soon, e.g., in the case of EDCs and PBT substances currently under assessment in the EU. At the same time, if judged based on the current regulatory procedures, many other substances of potential concern identified here might gain regulatory attention only once the now-lacking authoritative hazard data become available. Thus, the identification of potential substances of concern which lack authoritative data necessary to reach a definitive conclusion on their hazards and substitution urgency indicates a significant research and assessment need.

3.5. Over a quarter of FCCdb chemicals lack easily accessible public hazard data

Only 4986 of 11'609 CAS-identified FCCdb chemicals (43%) have some information in at least one of the above-listed hazard information sources used for prioritization of 608 hazardous substances and/or identification of 1798 substances of potential concern (Table 2). In order to also consider the availability of hazard data reported in literature, we additionally consulted the Toxicity Values (ToxVal) database compiled by the US EPA and hosted at the CompTox chemistry dashboard (Williams et al., 2017). Currently, this database includes 55'878 chemicals for which "772'721 toxicity values from 29 sources of data, 21'507 sub-sources, 4585 journals cited and 69'833 literature citations" are recorded, thus providing a broad coverage of both governmental and academic sources of chemical toxicity data. Indeed, this database lists the highest proportion of FCCdb chemicals (8328 substances in total, or 71.7%, Table 2). The extent of hazard information available for each chemical is, however, very variable. For example, 1263 substances (10.9%) have less than 10 data sub-sources recorded in the ToxVal database, while 256 substances (2.2%) have 100 or more (up to 146) recorded data sub-sources. Consideration of the data provided by the ToxVal database increased the number of FCCdb chemicals with some hazard data to 8711 (75%). For the remaining quarter (2898 substances) of the 11'609 CAS-identified FCCs, no hazard data could be obtained from any of the sources consulted in our analysis (Table 2). Together with the 676 CFSAN-identified FCCs which lack a CAS identifier and therefore could not be searched for in any of the public hazard

information sources that we have consulted, this amounts to 3574 substances that make up 29.1% of all 12'285 FCCs currently included in the FCCdb. These 3574 FCCs appear to have none or only very limited hazard data available in the public domain that are readily accessible.

Most of the 676 CFSAN-identified FCCs appear on the US FDA's Inventory of Indirect Additives used in Food Contact Substances or other FDA sources on FCCs, allowing to assume their active use in FCMs despite the absence of easily accessible hazard data. Among the 2898 CAS-identified FCCdb substances without hazard data, 218 substances have been registered under EU REACH, 401 appear on the TSCA inventory (though 254 currently labeled as "inactive"), and 648 substances are included on the NZIOEC list. With overlaps, these sources suggest the likelihood of a current commercial use in the European, North American, or New Zealand/Australian markets for up to 1017 of the 2898 substances lacking public hazard data. However, these sources are not specific to food contact uses and indeed, many more substances (1004) are included on the European FACET FCM list, 866 substances on at least one of the US FDA's four sources of information on substances used in food contact, and 722 substances on the Japanese lists for organic polymers. Together, this amounts to at least 2541 of the 2898 CAS-identified substances lacking hazard data but having high probability of actual use, particularly in FCMs. Printing inks, plastics, paper/board, coatings, and adhesives FCMs appear to have the highest numbers of chemicals with limited or absent public hazard data, with 29%, 33%, 22%, 21% and 17% of the 3574 hazard data lacking substances being assigned to the respective global inventories (with overlaps, including both CAS- and CFSAN-identified subsets). Significant knowledge gaps with regard to toxicity of direct and indirect food additives used in the US have already been highlighted previously (Neltner et al., 2013; Neltner and Maffini, 2014). With over a third of the data-lacking CAS-identified chemicals being listed on the FACET FCM list, the situation in Europe appears to be similar.

4. Conclusions

The FCCdb resource presented here currently lists 12'285 substances that could possibly be intentionally used to make FCMs/FCAs worldwide, thus demonstrating the large diversity of FCCs. Using several authoritative sources of hazard information, we prioritized 608 hazardous FCCdb substances as the most urgent candidates to be further evaluated and targeted by substitution efforts. In the next steps, it should first be confirmed that these FCCs are still in use, and if yes, then further data on their regulatory status, use patterns, and exposure potential should be collected and evaluated. This evaluation should consider, among others, regulatory provisions for food contact use which are already in place or are planned under different jurisdictions; region-specific production and import volumes; use in and migration from specific FCAs; types of food contact applications, e.g., disposable versus reuse applications, or inclusion in recycling loops; other manufacturing or life cycle characteristics which could be of relevance for substitution; similarity of chemical structures or hazard classes; data on co-occurrence in the same articles and potential for mixture effects. Using these and other criteria, the prioritized 608 substances can be split into smaller, better actionable groups.

It can be argued that some of the hazardous FCCs will likely not be present or will not migrate from the final FCA, and thus should be 'exempt' from substitution considerations. However, the hazards of these chemicals should not be disregarded on the basis of the use phase only, as the application of toxic chemicals in the production of FCMs/FCAs also contributes to occupational exposure. Moreover, as the economies worldwide strive towards more circularity and continued reuse of the scarce material resources, the need to keep toxic chemicals out of the loop becomes increasingly apparent (Geueke et al., 2018).

It has been also suggested that the continuous use of hazardous substances can be justified as long as the risks are properly assessed and carefully managed. However, reliable risk assessment would require

detailed hazard and exposure data, which are often unavailable. As we have demonstrated here, authoritative hazard data are missing for the majority of FCCdb substances, and for over a quarter no hazard data could be found in any of the globally sourced major databases that we have consulted. Furthermore, having to deal with this many substances, the risk assessment task becomes rather unfeasible, and even more so if NIASs (which are not included in the FCCdb) are also considered (Muncke et al., 2017). The use of *in vitro* bioassays to assess the toxicity of overall migrates or extracts from FCMs/FCAs is currently being explored as an integrative approach allowing to address unknown substances and mixture toxicity (Bengtstroem et al., 2016; Rosenmai et al., 2017; Severin et al., 2017; Zimmermann et al., 2019). However, this approach still needs further improvements with regard to reproducibility, sample preparation and sensitivity, as well as human health-relevance of bioassays to be included in the test panel, and interpretation of the results obtained (Groh and Muncke, 2017).

Meanwhile, regulation continues to rely on single-substance assessment and management approaches that do not incorporate the most current scientific understanding, which emphasizes the importance of mixture toxicity, low-dose effects, and non-standard testing approaches (Muncke et al., 2020, 2017; Vandenberg et al., 2019). We and others have repeatedly highlighted that both the official recognition and the management of hazardous substances are severely lagging behind academic science that has delivered both experimental and computational toxicology data for many additional substances that are used but not yet regulated in FCMs (Groh et al., 2019; Nerin et al., 2018; Van Bossuyt et al., 2016). Indeed, consideration of selected non-authoritative sources of hazard information led us to highlight further 1411 FCCdb substances of potential concern in addition to the 608 hazardous substances already prioritized based on authoritative information sources. In the long term, these 1411 substances of potential concern should be researched further to first confirm or disprove the suspected hazard properties and then to carry out a substitution-focused assessment following similar considerations as suggested above for the 608 prioritized substances.

Among the different FCM types, not only plastics and coatings but also paper and board FCMs appear to be a significant source of hazardous substances, even when printing inks are not considered (Rosenmai et al., 2017). The printing inks FCM type in fact includes the highest number of identified hazardous substances so far, many of them remaining unassessed (Van Bossuyt et al., 2016). In addition to printing inks, paper-based FCAs can also contain coatings and adhesives, both FCM types characterized by a high diversity of potentially hazardous FCCs and rather little oversight to ensure their safe use. This lack of transparency with regard to hazardous chemicals used in paper-based FCAs is of concern, especially considering the current trend towards increasing the use of paper-based products as alternative to single-use plastics, and the common use of recycled paper materials in direct contact with food in countries where this practice is not banned. Active and intelligent materials represent another FCM group with surprisingly little information publicly available on the identity and safety of their chemical constituents, despite the continuously increasing production volumes for the variety of applications reported for diverse 'smart' packaging products. Overall, more transparency on the side of producers as well as concerted efforts on the side of regulators are urgently needed in order to ensure systematic assessment and enforcement of FCM safety.

Declaration of Competing Interest

The authors declare no conflict of interest. KG, BG, and JM are employees of Food Packaging Forum Foundation (FPF), a charitable foundation dedicated to science communication and research on chemicals in all types of food contact materials and articles. MVM and OVM have project-based contracts for working with FPF and receive remuneration for this role from FPF. They are also members of the FPF scientific advisory board and they are not remunerated for this role but have received travel reimbursement from FPF for attending its meetings. FPF

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Appendix A. Supplementary material

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