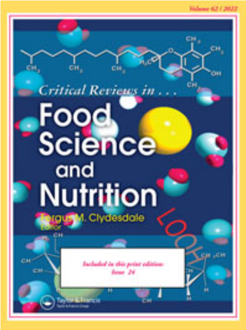

Critical Reviews in Food Science and Nutrition

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/bfsn20

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To cite this article: Birgit Geueke, Ksenia J. Groh, Maricel V. Maffini, Olwenn V. Martin, Justin M. Boucher, Yu-Ting Chiang, Frank Gwosdz, Phoenix Jieh, Christopher D. Kassotis, Paulina Łańska, John Peterson Myers, Alex Odermatt, Lindsey V. Parkinson, Verena N. Schreier, Vanessa Srebny, Lisa Zimmermann, Martin Scheringer & Jane Muncke (2022): Systematic evidence on migrating and extractable food contact chemicals: Most chemicals detected in food contact materials are not listed for use, Critical Reviews in Food Science and Nutrition, DOI: 10.1080/10408398.2022.2067828

To link to this article: https://doi.org/10.1080/10408398.2022.2067828

Published online: 18 May 2022.

CRITICAL REVIEWS IN FOOD SCIENCE AND NUTRITION
https://doi.org/10.1080/10408398.2022.2067828

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REVIEW

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Systematic evidence on migrating and extractable food contact chemicals: Most chemicals detected in food contact materials are not listed for use

Birgit Geueke[a], Ksenia J. Groh[b], Maricel V. Maffini[c], Olwenn V. Martin[d], Justin M. Boucher[a], Yu-Ting Chiang[e], Frank Gwosdz[f], Phoenix Jieh[a], Christopher D. Kassotis[e], Paulina Łańska[g], John Peterson Myers[h], Alex Odermatt[i], Lindsey V. Parkinson[a], Verena N. Schreier[i], Vanessa Srebny[j], Lisa Zimmermann[a], Martin Scheringer[k] and Jane Muncke[a]

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ABSTRACT
Food packaging is important for today's globalized food system, but food contact materials (FCMs) can also be a source of hazardous chemicals migrating into foodstuffs. Assessing the impacts of FCMs on human health requires a comprehensive identification of the chemicals they contain, the food contact chemicals (FCCs). We systematically compiled the "database on migrating and extractable food contact chemicals" (FCCmigex) using information from 1210 studies. We found that to date 2881 FCCs have been detected, in a total of six FCM groups (Plastics, Paper & Board, Metal, Multi-materials, Glass & Ceramic, and Other FCMs). 65% of these detected FCCs were previously not known to be used in FCMs. Conversely, of the more than 12'000 FCCs known to be used, only 1013 are included in the FCCmigex database. Plastic is the most studied FCM with 1975 FCCs detected. Our findings expand the universe of known FCCs to 14,153 chemicals. This knowledge contributes to developing non-hazardous FCMs that lead to safer food and support a circular economy.

KEYWORDS
Chemical migration; food contact chemicals; food contact materials; food packaging; systematic evidence map; database

Introduction

Food production is industrialized in many parts of the world and the global food supply chains are logistically demanding. The role of food packaging as an enabler of long-term food storage and distribution, and for preventing food waste, is significant (Russell 2014). The use of food packaging is steadily rising because it enables the current globalized food system (Chakori et al. 2021). However, single-use food packaging strongly contributes to household waste and plastic pollution, thus threatening the world's ecosystems (Hardesty et al. 2021; Morales-Caselles et al. 2021; Pivnenko, Damgaard, and Astrup 2019; Yates et al. 2021).

Moreover, food packaging and other food contact articles (FCAs), such as processing equipment, and kitchen utensils, can release chemicals into food and represent a considerable source of human exposure to chemicals (Hahladakis et al. 2018; Muncke et al. 2020). As some of these chemicals are toxic, detrimental effects on health can arise. The impact of chronic chemical exposure (i.e., from conception to death) on human health, even at very low levels, is serious and has been implicated with the rising prevalence of several chronic diseases (Balbus et al. 2013; Landrigan et al. 2018; Shaffer et al. 2019). Therefore, reducing the exposure to hazardous chemicals is recommended for reversing the current trends of the increasing burden of chronic diseases (Landrigan et al. 2018; Madia et al. 2019).

To better understand which chemicals humans are exposed to from food packaging and other FCAs, we previously compiled an inventory of 12,285 food contact chemicals (FCCs) known to be intentionally added or associated with the manufacture of food contact materials (FCMs), the FCC database (FCCdb) (Groh et al. 2021). The FCCdb integrates 67 FCC lists from Europe, the US, the Mercosur region, China, and Japan and covers 18 food contact materials (e.g., plastics, coatings, rubbers, paper & board, adhesives, printing inks, silicones, metals, glass).

In addition to intentionally used FCCs, FCAs also contain non-intentionally added substances (NIAS), such as impurities

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Supplemental data for this article is available online at https://doi.org/10.1080/10408398.2022.2067828

of starting substances, contaminants, reaction products and by-products, as well as degradation products (Geueke 2018). In most cases, it is very difficult, if not impossible, to detect and identify all NIAS in finished FCAs, as non-targeted analyses are not sufficiently comprehensive (Kato and Conte-Junior 2021; Peters et al. 2019; Qian et al. 2018; Zimmermann et al. 2021). The most prominent NIAS are regularly identified and quantified only for well-known chemical processes (Nerin et al. 2013; Pieke et al. 2018), while the majority remains unassessed.

Until now, human exposure assessment for FCCs has primarily focused on a few dozen chemicals of concern, such as bisphenols (Cao et al. 2021), phthalates (Carlos, de Jager, and Begley 2021; Han et al. 2021), mineral oil hydrocarbons (Canavar, Kappenstein, and Luch 2018; Pack et al. 2020), and heavy metals (Jakubowska et al. 2017). To date, there is no systematic overview of those FCCs that have been shown to migrate into food or food simulants, or that have been extracted from FCMs and FCAs. Here, we present a systematic evidence map of published migration and extraction studies, developed according to our previously published protocol (Martin et al. 2018). This "database on migrating and extractable food contact chemicals" (FCCmigex) is a unique, first-of-its-kind evidence base of empirical data on FCCs in all types of FCMs and FCAs. The FCCmigex is publicly available via an interactive dashboard and provides access to a wealth of data that have never before been integrated in this fashion. As such, the FCCmigex is a powerful information source for advancing the risk assessment of FCMs and their sustainable management in a circular economy, and for improving the safety of food packaging in a sustainable food system.

Methods

The systematic evidence map on FCCs that have been analyzed for migration into food or food simulants, or that have been extracted from FCMs and FCAs, was compiled according to a previously published protocol (Martin et al. 2018). As detailed below and further specified in the Supplementary Information, a systematic search of the peer-reviewed and gray literature on FCCs that have been investigated in migrates or extracts of FCMs/FCAs was carried out. We developed search algorithms applicable in scientific databases, gray literature sources, and on websites of governmental institutions and various interest groups. After removal of duplicates, this literature search returned 15,915 studies and reports (Figure 1) (to simplify reporting, in the following we only refer to "studies"). The titles and abstracts of all studies were then manually screened by trained scientists for their relevance based on selected, previously published inclusion and exclusion criteria (Martin et al. 2018). 2783 studies matched our criteria for inclusion, but 273 were not available as PDFs for further screening (Figure 1). The full texts of the remaining 2510 studies were then screened by trained scientists applying the same criteria as for the screening of titles and abstracts. Finally, 1210 studies matched our criteria for inclusion. We extracted information from these eligible studies using the data extraction process as detailed below.

Inclusion and exclusion criteria

Experimental studies were eligible for inclusion if they indicated that (i) the tested sample was intended to be used in contact with food, (ii) the experimental design clearly allowed the identification of the FCM/FCA as source of the chemical, and (iii) the chemical could be identified with appropriate confidence (Martin et al. 2018). Importantly, studies were also included if they targeted chemicals in FCMs/FCAs but did not detect them in the respective migrates or extracts.

Studies were excluded if (i) FCMs/FCAs were spiked with chemicals to test their migration behavior under defined conditions, (ii) potential FCCs were measured in foods, but experimental evidence did not demonstrate that the FCM/FCA was the source, (iii) migration of active substances (such as antimicrobial compounds) was measured, because migration of such substances is intended in the case of so-called active packaging, and (iv) the FCM/FCA was still under development and not yet be present on the market.

In the literature search, we did not set any limitations regarding publication year, geographical origin, or language of a study. Besides English, we included studies in French, German, Russian, and Spanish as these correspond to the main language skills of the research team.

Search strategy

The strategy for the systematic literature search was developed by creating lists of more than 100 specific search terms that were combined according to Figure 2 of the previously published protocol (Martin et al. 2018). More details are also provided in the "Systematic literature search" section in the Supplementary Information. For databases and websites that did not allow such complex searches, we simplified the searches by including combinations of the most important terms. In total, we applied these searches to five scientific literature databases (PubMed, Web of Science, SCOPUS, ScienceDirect, Google Scholar,), two gray literature sources (Open gray, Core), and 15 websites of governmental institutions and various interest groups (e.g., non-governmental organizations, news providers, commercial labs). Two systematic searches were carried out in Jan/Feb 2019 and May/June 2021, respectively. During the first search, SCOPUS was found to be far less relevant than the other databases and was therefore excluded from the second search. Indeed, only three unique SCOPUS references that were not part of the other databases were found to be relevant and matching our criteria for inclusion. Also, not all studies that would have met the criteria for inclusion in the FCCmigex database were found in our literature search, for example, because key words did not match the search terms (Takazawa, Suzuki, and Kannan 2020).

Literature screening

We used the online evidence synthesis software "Cadima" (Kohl et al. 2018) for the reference management and a

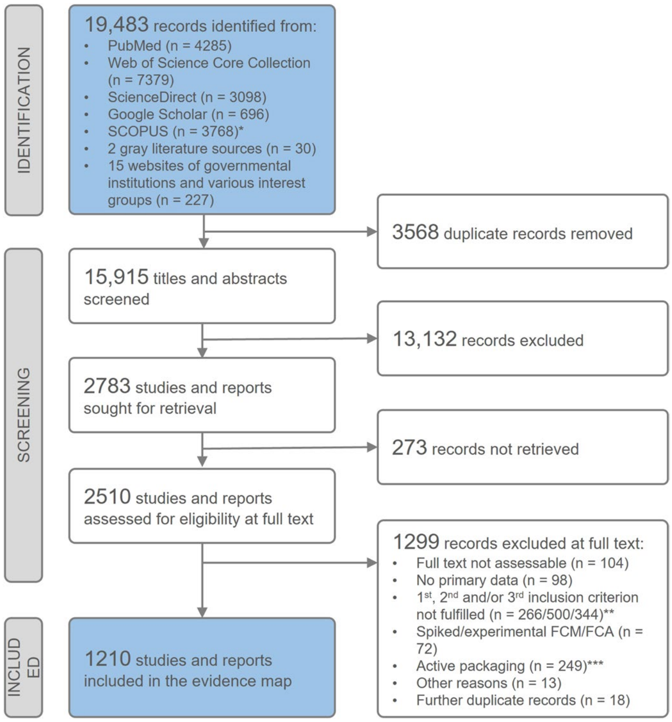

Figure 1. Flow diagram for the systematic evidence map on migrating and extractable food contact chemicals (FCCs), containing the preferred reporting items for systematic reviews and meta-analyses (PRISMA). *Based on two literature searches in Jan/Feb 2019 and May/June 2021. SCOPUS was excluded from the second search due to the inclusion of only three unique references during the first screening round. **More than one exclusion criterion could be applicable to a given record. ***Papers on active packaging were excluded because migration of active substances is generally intended and hence not in the scope of this evidence map. Abbreviations: FCA, food contact article; FCM, food contact material.

two-step screening process, in which we first focused on the titles and abstracts, followed by the full texts. As a consistency check, ten percent of the records were double-screened, and disagreements were resolved by a team of five researchers during title and abstract screening, and likewise during full-text screening. This was used to corroborate our understanding of the eligibility criteria, and to ensure their consistent application. Reasons for excluding a study at full text screening are detailed in Figure 1.

Data extraction

In the PDF file of each study, we identified and highlighted the FCCs that were investigated in migrates and extracts of FCMs, using the software "tagtog" (Cejuela et al. 2014). To take into account the use of different synonyms and abbreviations for individual FCCs, we linked these names and, if available, the CAS number in tagtog. The identity of highlighted FCCs was then automatically exported by an algorithm into the systematic data extraction software "SciExtract", which was newly developed for this project. SciExtract is an application that interacts with tagtog and displays the synthesized data output. It enables the user to select, organize, and store information. During a piloting phase, criteria for data extraction were defined, tested and refined, and documented in a curation guideline that supports consistent data extraction (see Supplementary Information).

In SciExtract, precoded information on the FCA, FCM(s), type of experiment, and detection was manually assigned to each FCC by a trained scientist from our research team. Depending on the design and content of the study, we generated between one and more than hundred database entries per study. Each database entry is linked to the reference from which it was generated. The following questions define what information constitutes a single database entry (Figure 2):

1. Which FCC was investigated? (name and/or CAS number)
2. What type of FCA was tested? (single-use/repeat-use/unknown or unclear)
3. Which FCM was tested? 28 FCM types (structure giving material, such as plastics, paper & board, glass)
4. Optional: Which additional FCMs were specified as potential sources of FCCs? 6 FCM types (additional material, such as printing inks, adhesives, coatings)
5. Which type of experiment was performed? (migration into food/migration into food simulant/extraction)
6. Was the chemical detected? (yes/no/unknown or unclear)

More details on these questions are provided in the Supplementary information.

Eleven researchers were trained to extract data. As part of this training and to ensure consistent interpretation of the findings, pairs of researchers were formed, and the two individuals of the pair extracted data from a set of at least ten papers in parallel. Subsequently, the pair discussed any discrepancies in their data extraction, and their findings were then shared. In this iterative way, the data extraction was refined and optimized. At any later time during data extraction, a second opinion was called for whenever there were questions about the interpretation of the study results.

Post-processing and data analysis

If the CAS number of an FCC was reported in a study, it was directly linked to the chemical name and exported together. When this information was not available, CAS numbers were assigned to FCCs after data extraction. We performed semi-automated searches in a Google Colab notebook with custom written Python 3 code using an internal dictionary based on the FCCdb and PubChem. Ten percent of the assigned and all ambiguous CAS numbers were reviewed and verified manually. For missing CAS numbers, manual searches were carried out. The assignment of CAS numbers allows for the analysis of database entries by individual FCCs, for example during frequency mapping. Nevertheless, chemicals for which no CAS number was found were kept as part of the evidence map, but the corresponding database entries were not included in the data

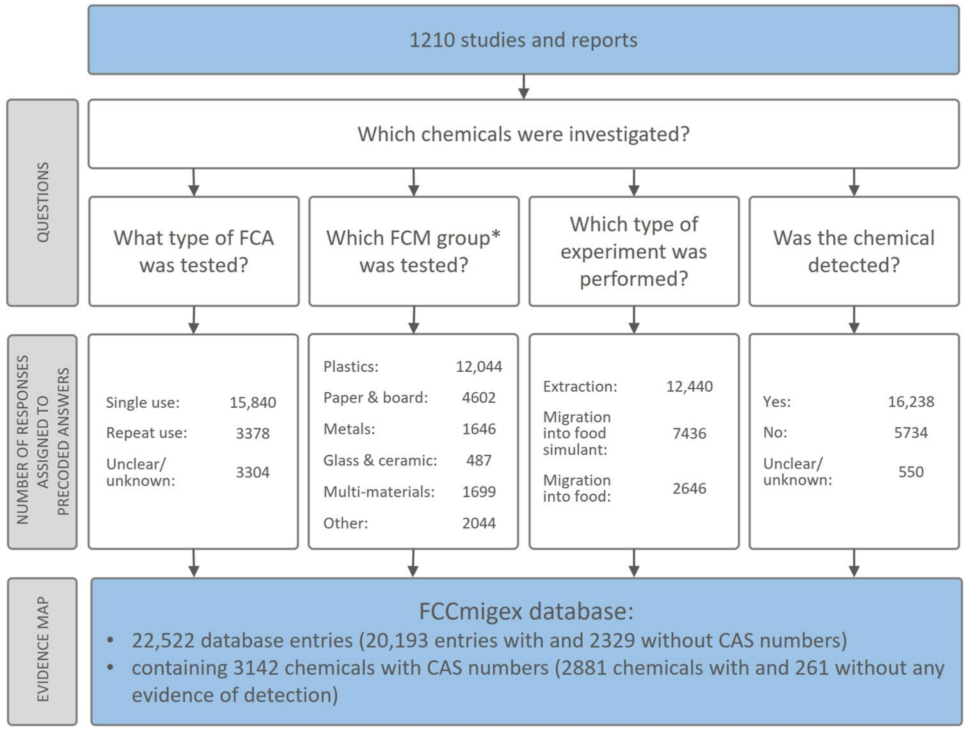

Figure 2. Data generation process. Question types and number of database entries for each included study/report related to the investigated chemicals, food contact articles (FCAs), food contact materials (FCMs), type of experiment, and evidence of detection. *For more detailed information on the FCM groups, see Figure 4 and Table S1.

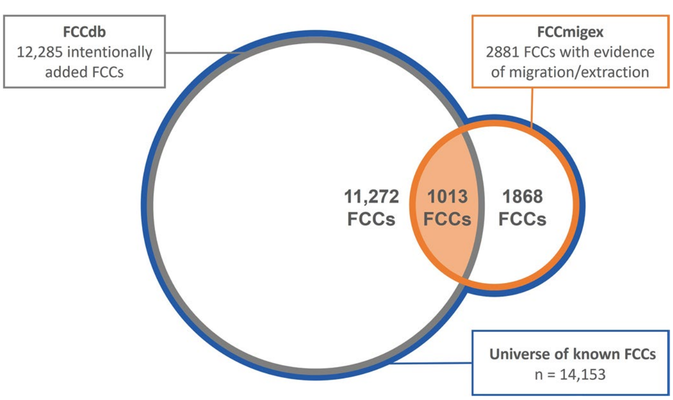

Figure 3. Universe of known FCCs. Schematic representation of the number of intentionally used FCCs (source: FCCdb; gray circle), the number of FCCs with evidence of migration/extraction (source: FCCmigex; orange circle) and their overlap (orange field). Together, these databases characterize the universe of known FCCs (blue border).

underlying the dashboard. One exception was made for mineral oil saturated hydrocarbons (MOSH) and mineral oil aromatic hydrocarbons (MOAH), which are poorly defined groups of FCCs that do not have CAS numbers. However, due to the frequent occurrence of these chemicals in FCMs and FCAs, database entries for MOSH and MOAH were merged based on available synonyms and counted accordingly.

Data post-processing, cross-tabulation, frequency calculation, and mapping was done using the Python pandas and NumPy libraries. Data was subsequently uploaded to Microsoft Power BI to create an interactive dashboard for public engagement with the FCCmigex database.

Results

Findings in the context of the FCC universe

We identified 1210 studies investigating a total of 3142 FCCs. Of these, 2881 FCCs had analytical evidence of detection in food, food simulants or extracts of FCMs. We then compared these chemicals to the intentionally used FCCs listed in the FCCdb (Groh et al. 2021). Surprisingly, the overlap is remarkably small: only 1013 of the 2881 FCCs (or 35%) appear in both datasets, while 1868 FCCs (or 65%) that were detected in migration or extraction experiments are not included in the FCCdb (Figure 3). This indicates that they either are NIAS or were used intentionally for manufacture of FCAs without being recorded in any of the 67 global regulatory or industry lists from which the FCCdb was compiled (Groh et al. 2021). For example, among the 20 FCCs with the highest number of database entries in the FCCmigex (and not listed in the FCCdb), six are perfluorinated carboxylic acids and therefore belong to the class of per- and polyfluoroalkyl substances (PFAS). These chemicals of concern were frequently studied and detected, but they are not listed in the FCCdb as intentionally used.

Further, it is also noteworthy that 11,272 of the 12,285 FCCs from the FCCdb, corresponding to 91.8% of previously known intentionally used FCCs, were not investigated in any study included in this evidence map. Overall, the universe of known FCCs comprises 14,153 FCCs that are included in the FCCmigex and FCCdb databases (Figure 3).

Of the 3142 chemicals with CAS numbers in the FCCmigex, 261 have no empirical evidence for presence in FCAs, meaning that they were targeted but never detected in a migration or extraction experiment (Figure 2).

Evidence mapping for the FCCmigex database

In total, the FCCmigex database contains 22,522 entries, each informing about the FCC, FCM, FCA, type of experiment, and evidence of detection (Figure 2). The FCCmigex database is searchable and publicly available (https://www.foodpackagingforum.org/fccmigex).

Around half (55.2%) of the FCCmigex database entries correspond to extraction experiments, indicating the presence of an FCC. Roughly the other half of database entries relates to migration of FCCs, either into foodstuffs (33.0%) or into food simulants (11.8%), i.e., solvents that resemble the properties of foods but have a clearly defined chemical composition. Evidence for migration of an FCC implies that the chemical is directly relevant for human exposure, while chemicals detected in extracts typically require further migration testing to confirm exposure potential.

In most studies (70.3%), single-use FCAs such as food and beverage packaging were tested. Repeat-use FCAs like kitchen utensils and reusable containers accounted for 15.0% of the database entries, while for 14.7% the type of FCA could not be specified.

We defined six different FCM groups: Plastics, Paper & Board, Metal, Multi-materials, Glass & Ceramic, and Other FCMs (Table S1). 759 of 1210 studies reported results on plastics and generated more than half of the database entries (53.5%), followed by paper & board (238 studies and 20.4% of database entries). For metals, we found 169 studies (corresponding to 7.3% of database entries), while 96 studies were on multi-materials and generated 7.5% of all entries. Finally, we found 49 studies on glass & ceramic (2.2% of database entries). Silicone, rubber, textile, wood, cork, and all FCMs that did not fit into any of the previous groups or were not sufficiently specified, were categorized as Other FCMs, and accounted for 9.1% of all database entries (126 studies).

The six FCM groups include 28 FCM types (Table S1), with the highest numbers of database entries collected for paper & board (virgin or non-specified, *n* = 3164), plastics (non-specified or other, *n* = 2760), polyethylene (PE, *n* = 1842), polypropylene (PP, *n* = 1763), and multi-materials (*n* = 1699) (Figure 4).

Polyethylene terephthalate (PET) and paper & board often contain recycled content when they are used in contact with food, and studies exist that differentiated between virgin and recycled content in these materials. Therefore, we defined recycled PET (rPET) and recycled paper & board as two of the 28 FCM types. Recycled content was explicitly mentioned in 20 studies on rPET, resulting in 207 database entries. These numbers are low compared to the 157 studies on virgin or non-specified PET, with 1258 database entries.

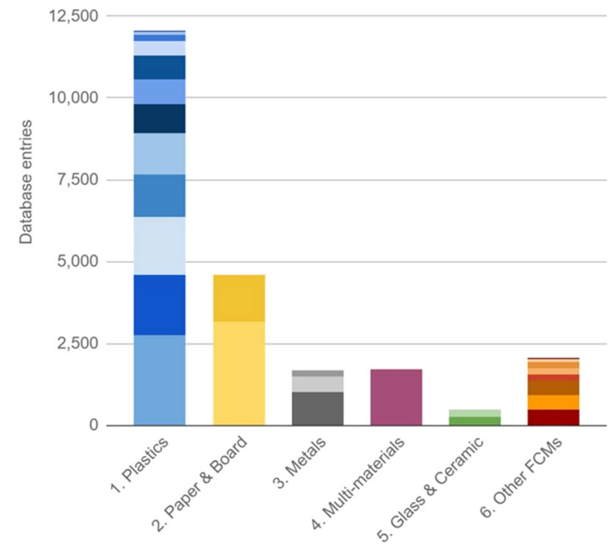

Figure 4. Number of database entries in the FCCmigex database for six FCM groups comprising 28 FCM types. The FCM group on Plastics (1.) includes 12 FCM types (from bottom to top of column, number of database entries in parentheses): plastics, non-specified or other (*n* = 2760), PE (*n* = 1842), PP (*n* = 1763), multilayer plastic (*n* = 1306), PET (*n* = 1258), polystyrene (*n* = 880), polyamide (*n* = 753), polyvinyl chloride (*n* = 736), polycarbonate (*n* = 437), rPET (*n* = 207), melamine (*n* = 84), polyurethane (*n* = 18). The other five FCM groups display data for 2. Paper & Board (paper & board, virgin or non-specified (*n* = 3164), paper and board, recycled (*n* = 1438)), 3. Metals (metal, non-specified or other (*n* = 1006), steel (*n* = 477), aluminum (*n* = 189)), 4. multi-materials (*n* = 1699), 5. Glass (*n* = 242) and Ceramic (*n* = 219), and 6. Other FCMs (silicone (*n* = 478), unclear/unknown FCM (*n* = 447), other FCM (*n* = 422), rubber (*n* = 218), wood (*n* = 192), cork (*n* = 170), combined FCMs (*n* = 91), and textiles (*n* = 26)).

72 of 283 studies on paper & board specified recycled content, with 1438 database entries for recycled, and 3164 entries for virgin or non-specified paper & board.

In addition to the 28 FCM types included in the six FCM groups in Figure 4, also printing inks, coatings, adhesives, plastic laminates, and waxes are sources of FCCs. Since these FCMs can only be used in combination with another material, such as plastic, paper & board, or metal, we allocated them into a second, "additional" FCM category. Figure 5 illustrates the number of database entries for FCCs from printing inks, coatings, adhesives, plastic laminates, and waxes in relation to the six FCM groups. For 22.9% of all database entries, FCMs of this additional FCM category were specified as a possible source of FCCs. 6.7%, 6.6%, and 5.9% of all database entries relate to FCCs from printing inks, coatings, and adhesives, respectively. Printing inks and adhesives were most commonly investigated in combination with paper & board, plastics, and multi-materials. Coatings were mentioned as possible sources of FCCs in 61.5% of the database entries for Metal FCMs. Paper & board are the FCM group for which the highest variety of FCMs from the additional category were mentioned as potential source of FCCs, whereas for glass & ceramic almost exclusively coatings were relevant.

Of the 2881 FCCs that were detected in at least one experiment (extraction or migration), more than two thirds of the FCCs (1975) were identified in Plastic FCMs, followed by paper & board (887), Other FCMs (760), and

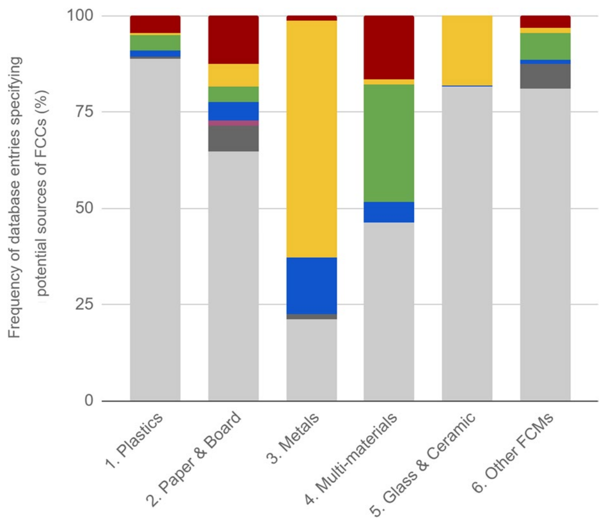

Figure 5. FCMs as sources of FCCs. Frequency of database entries in the FCCmigex database for FCM types of the "additional" FCM category, shown for the six main FCM groups. Potential sources of FCCs are: printing inks (red), coatings (yellow), adhesives (green), plastic laminates (blue), and waxes (magenta). Database entries without an FCM of the additional category are light gray, and those that are unclear/unknown are dark gray.

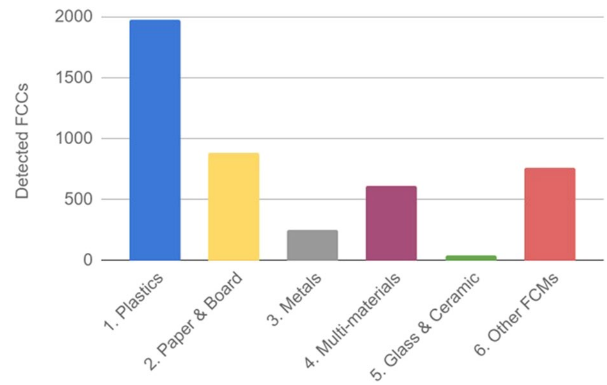

Figure 6. Absolute number of detected food contact chemicals per FCM group.

multi-materials (614). The fewest FCCs were detected in metal (251) and glass & ceramic (47) (Figure 6).

Findings on chemicals

The five most frequently detected FCCs across all FCM groups and for each of the six individual FCM groups are shown in Figure 7. Three phthalates (diethylhexyl phthalate (DEHP, CAS 117-81-7), dibutyl phthalate (DBP, CAS 84-74-2), and diisobutyl phthalate (DiBP, CAS 84-69-5)), bisphenol A (BPA, CAS 80-05-7), and mineral oil saturated hydrocarbons (MOSH) were the most frequently detected chemicals included in the FCCmigex database. The plasticizers DEHP and DBP were the two most commonly found FCCs in plastics and also ranked among the top five in paper & board, multi-materials, and the group of Other FCMs.

BPA was often detected in plastics (124 database entries) and metals (56 database entries), where it is mainly used as a monomer for the manufacture of polycarbonate and epoxy coatings, respectively. In Metal FCMs, aluminum, iron, nickel, and chromium were among the five most commonly detected FCCs, and lead, cadmium, aluminum, cobalt, and zinc were most frequently found in the extracts and migrates of Glass & Ceramic FCMs. Benzophenone (CAS 119-61-9) is the most abundant photoinitiator in the FCCmigex database, listed a total of 125 times and ranked with the third most detects for multi-materials.

In Paper & Board FCMs, the most frequently detected FCCs were MOSH and MOAH. MOSH and MOAH are complex mixtures of hydrocarbons that cannot be resolved into individual substances and thus do not have CAS numbers. However, we included them in the FCCmigex database because of the high number of studies providing evidence for their migration potential from FCMs and FCAs.

Other highly abundant FCCs in plastics and multi-materials were the additives diethylhexyl adipate (DEHA, CAS 103-23-1) and butylated hydroxytoluene (BHT, CAS 128-37-0). Additionally, typical NIAS also showed up among these most frequently detected FCCs, such as 2,4-di-tert-butyl phenol (CAS 96-76-4), a degradation product of several common antioxidants, and the cyclic siloxanes decamethylcyclopentasiloxane (D5, CAS 541-02-6) and dodecamethylcyclohexasiloxane (D6, CAS 540-97-6).

Discussion

Only for 1013 FCCs listed in the FCCdb there is evidence for their presence in finished FCAs, as shown by their detection in migrates or extracts (Figure 3). By contrast, around two-thirds of FCCs identified as being present in FCAs and therefore listed in the FCCmigex are not included in the FCCdb. An important example of such FCCs are six PFAS that were very frequently detected but are not publicly listed as being intentionally used in FCA manufacture. Further, many FCCs identified in the FCCmigex database likely are NIAS. Distinguishing between non-listed, but intentionally used FCCs and NIAS is not possible because the chemical composition of FCMs is usually not disclosed. A comprehensive, publicly accessible inventory of NIAS would help to fill this knowledge gap.

Conversely, 11,272 FCCs that are listed in the FCCdb have never been investigated in any migrate or extract of FCMs and FCAs and are therefore not in the FCCmigex database (Figure 3). Possible reasons for this include: first, it could simply be that FCCs are listed in the FCCdb but may have never been used, or their use has been discontinued. Second, FCCdb-listed FCCs may be commonly used, but completely converted during the manufacture of FCMs and FCAs. Third, FCCs could be present in finished FCAs but they were never analyzed in any study and analytical standards for quantification may not be available for investigation (Simoneau 2015). Fourth, compounds may be so tightly bound to the material (Müller-Simon 2010) or are of such high molecular weight (Fang and Vitrac 2017) that they do not migrate or are not extractable from finished FCAs. However, it is impossible to explain with certainty an FCC's absence in the FCCmigex. More transparent

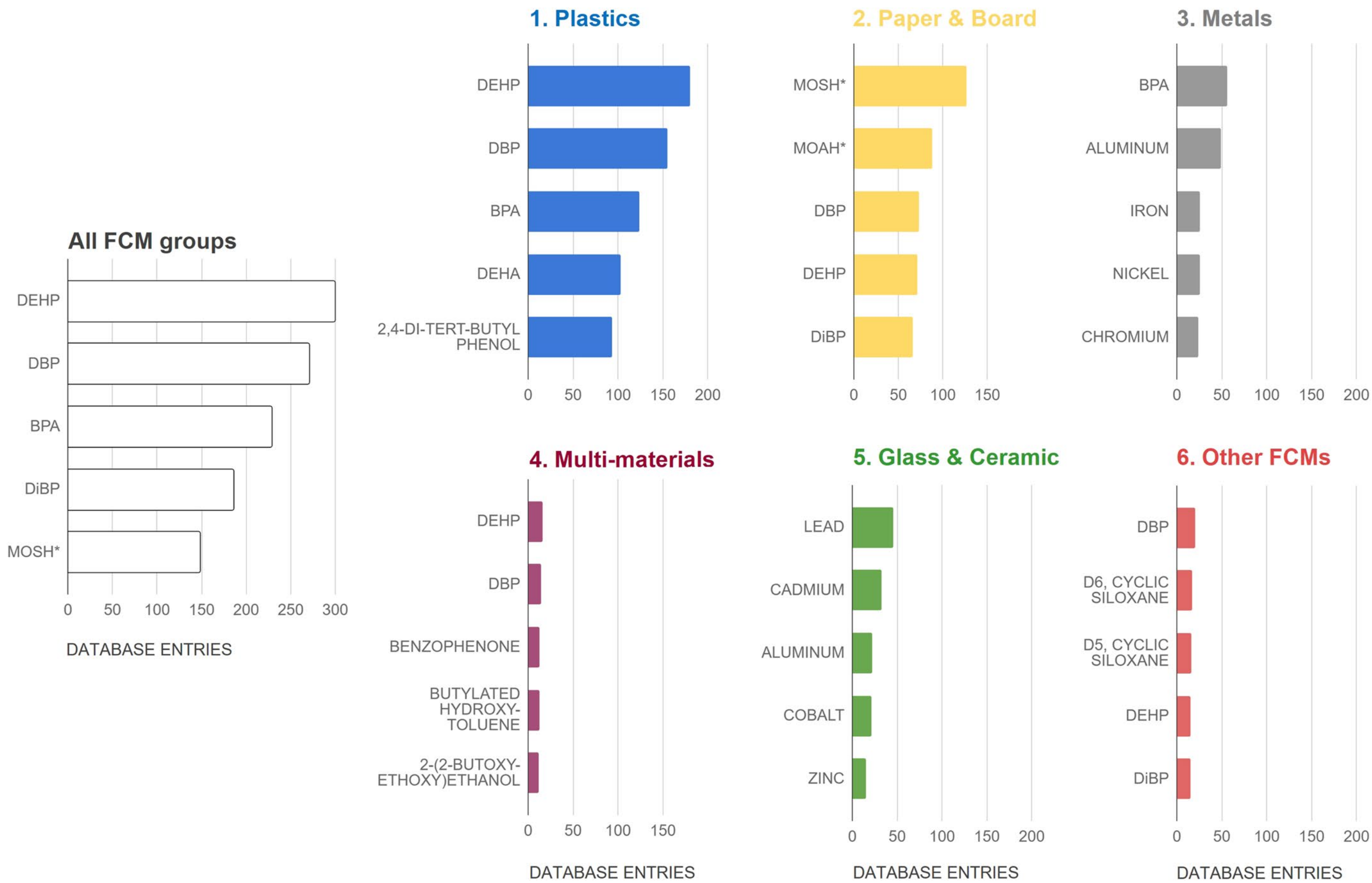

Figure 7. Top five most frequently detected FCCs (database entries) across all FCM groups and for each of the six individual FCM groups. Abbreviations: BPA, bisphenol A; DBP, dibutyl phthalate; DEHA, diethylhexyl adipate; DEHP, diethylhexyl phthalate; DiBP, diisobutyl phthalate; MOAH, mineral oil aromatic hydrocarbons; MOSH, mineral oil saturated hydrocarbons; D5, decamethylcyclopentasiloxane; D6, dodecamethylcyclohexasiloxane. *MOSH and MOAH were included due to their high relevance despite being chemical mixtures and not individual FCCs.

communication of FCC use during production would help to close this data gap in the future.

Together, the FCCdb and FCCmigex represent the universe of known FCCs, but the actual universe of FCCs is likely greater than these 14,153 chemicals. Indeed, it has been estimated that FCMs may contain up to 100,000 different chemicals, including the unknown NIAS (McCombie 2018). For some FCMs, e.g., phenolic can coatings, the number of NIAS of potential concern by far outnumbers the number of identified FCCs (Biedermann and Grob 2006; Biedermann et al. 2013). Here, we only show those FCCs that have been published as intentionally used (FCCdb) or investigated in publicly available studies (FCCmigex). Our databases provide a comprehensive overview, but it has to be acknowledged that there are many FCCs that remain unidentified.

Systematic evidence maps such as the one developed in this study contribute to compiling the available knowledge on a broad scientific research question to obtain an overview of the number and types of studies that are available on this topic. In contrast to a more focused systematic review, the quality of studies included in a systematic evidence map is not necessarily critically appraised (Wolffe et al. 2019). For this systematic evidence map, such critical appraisal steps can be applied in the future, when the FCCmigex database will be used to address specific research questions that are of interest to stakeholders.

Chemical migration from FCMs and FCAs depends on many factors such as temperature, contact time, the surface-volume ratio, and the type of food or food simulant (Arvanitoyannis and Bosnea 2004; Barnes, Sinclair, and Watson 2007), and importantly, the concentration of an FCC in an FCA (Biryol et al. 2017). For some FCMs, official guidance documents exist detailing the experimental conditions for migration studies (European Commission 2014; U.S. Food & Drug Administration 2007), but the majority of studies included in the evidence map did not follow such guidelines, and the measured FCC levels are thus difficult to compare. Other studies did not quantify concentrations, but rather reported whether or not an FCC was measured above the limit of detection (Brenz, Linke, and Simat 2017; García Ibarra et al. 2018). To capture as much information as possible while keeping the data consistent and the large number of relevant studies manageable, we chose not to record the concentrations of chemicals that migrated or were extracted from FCMs/FCAs. However, quantitative information can be obtained from the original studies as reference lists are available in the dashboard for each filtered data set.

Originally, we intended to include only chemicals for which the structure was identified with a high level of confidence (Martin et al. 2018; Schymanski et al. 2014). Since we did not validate each analytical method during data extraction, or the relevant information was simply missing in many cases, we decided to include rather than exclude a chemical in cases of doubt or lacking information. In particular, mineral oil hydrocarbons and oligomers are typically not identified with a high level of confidence. Nevertheless, we included them in the data extraction, because we did not want to miss any available evidence for these common migrants.

We identified FCCs of particular concern in the FCCmigex database, for example, genotoxicants, such as 4,4′-methylenedianiline (CAS 101-77-9) (Van Bossuyt et al. 2019), or endocrine disrupting chemicals (EDCs) that often follow a non-monotonic dose response curve, such as BPA, phthalates, and nonylphenols (Hill, Myers, and Vandenberg 2018; Montévil et al. 2020; Vandenberg et al. 2012). The presence of such chemicals in FCAs is concerning because they can cause harm even at very low levels, and no safe thresholds are thought to exist (Crump 2011; Demeneix et al. 2020). The EU's Chemicals Strategy for Sustainability defines hazard properties of concern, such as carcinogenicity, mutagenicity, reprotoxicity, and endocrine disruption, and chemicals with these properties shall be phased out, including from FCAs (European Commission 2020). We have not yet systematically addressed which of the chemicals listed in the FCCmigex database are of concern, as has been done for those listed in the FCCdb (Groh et al. 2021). In the future, however, the FCCmigex can serve as an evidence base for identifying the most hazardous FCCs.

Three FCCs (DEHP, DBP, and BPA) represent 4.5% of all FCCmigex entries, while 1433 FCCs were detected only once. One explanation for this focus on a very small number of FCCs could be their long history of use (Warner and Flaws 2018) in combination with broad awareness of their hazardous properties (Eales et al. 2022; vom Saal and Vandenberg 2021). Although some attempts have been made to replace or ban these chemicals (ECHA 2022), they are still frequently detected in migrates and extracts of FCMs and FCAs to this day (Cao et al. 2021; Carlos, de Jager, and Begley 2021; Han et al. 2021). On the one hand, this observation shows that it is very important to continue monitoring substances that need to be phased out. On the other hand, equally hazardous chemical replacements may already be used in FCMs and FCAs but could be overlooked if the spotlight remains on a limited number of well-known chemicals (Albert et al. 2018; Eladak et al. 2015). Therefore, analyses of trends detailing the use of known chemicals of concern and their potential substitutes over time are necessary to address this potential bias. Another way to broaden the view on all chemicals potentially present in migrates or extracts is to carry out more non-targeted analyses which can lead to the detection of more than a hundred FCCs in a single sample (Nerin et al. 2013; McCombie et al. 2016; Zimmermann et al. 2021).

Plastic is reportedly the largest FCM group for food and beverage packaging (Costa et al. 2020), which explains the 759 studies on Plastic FCMs (63% of 1210 studies) included in the FCCmigex database. The public attention toward plastic packaging and the related environmental pollution is likely another explanation for this finding. Scientific interest in studying plastics may also be driven by the high chemical complexity of this FCM, as illustrated by the 1975 FCCs detected in plastics in targeted and untargeted studies (Figure 6). Multi-materials, paper & board, and the group of Other FCMs also exhibit a high number of FCCs per FCM group, suggesting that these FCMs are chemically complex materials, too. Further, coatings on Metal FCMs are also known to have high chemical complexity as has been shown by the high number of detected unknown FCCs in can coatings (Biedermann et al. 2013; Grob et al. 2006), but much fewer FCCs have been identified in this FCM group. By contrast, glass & ceramic are the FCMs with the lowest number of detected FCCs, which is in agreement with the low chemical complexity of these materials. Importantly, the chemical complexity of FCMs is related to chemical safety (Fenner and Scheringer 2021), as a higher number of chemicals in an FCM implies that not all will be thoroughly risk assessed. Reducing the chemical complexity of FCMs facilitates proper assessment of all chemical constituents, and therefore is a step toward safer FCMs (Muncke et al. 2020).

Improved knowledge of and increased awareness for hazardous and untested chemicals in all types of FCAs will contribute to improving the safety of foodstuffs, and to supporting a circular economy where chemicals are managed based on their hazard properties. This is in line with the EU's Chemicals Strategy for Sustainability which is a key element of the European Green Deal that addresses broader climate and environmental-related challenges (European Commission 2019).

A focus on safer food packaging, food processing equipment and other FCAs further contributes to a more sustainable food system. The FCCmigex database is a unique, publicly available evidence base for FCCs known to be present in FCMs and FCAs. The interactive dashboard is a tool providing a comprehensive overview of these FCCs, but also supporting detailed queries on individual FCCs or FCMs, such as rPET and virgin/unspecified PET (Gerassimidou et al. 2022). It facilitates further research into exposure to FCCs and enables the identification of known untested and hazardous FCCs. Using this evidence, the significant knowledge gaps related to chemicals in food packaging can be addressed. Therefore, this systematic evidence base supports the development of safer food packaging - which in turn leads to safer food.

Author contributions

The systematic evidence map was conceptualized by BG, KJG, MVM, OVM, and JM. Literature screening was performed by JB, BG, KJG, JM, MVM, OVM, PL, and LZ. The software SciExtract was developed by FG, PJ, BG, and JM. Data extraction was carried out by JB, YTC, BG, KJG, CK, PL, MVM, OVM, VNS, VS, LZ, and JM. The methodology and curation guideline were designed by BG, KJG, MVM, OVM, and JM. Data were post-processed by PJ, LVP, and BG. The dashboard was developed by BG and LP. The original draft manuscript was written by BG, JM, and MS. All other authors provided review and constructive input and approved the final version.

Acknowledgements

We thank Jonathan Chevrièr, Barbara Demeneix, Jean-Baptiste Fini, Jane Houlihan, Katie Pelch, Rob Sargis, Leo Trasande, Laura Vandenberg, and Martin Wagner for their contributions as members of the project's Scientific Advisory Group. We thank Joanne McPhie for her advice for developing the literature search strategy and Jozica Dolenc for help during the post-processing of the raw data.

Data availability

The data are publicly available as an interactive dashboard using Microsoft PowerBI under the following open access link (https://www.foodpackagingforum.org/fccmigex). The list of references included in this evidence map is also available under this link.

Disclosure statement

No potential conflict of interest was reported by the authors.

Supplementary information

Supplementary Information (Systematic literature search/Data extraction, excerpts from the curation guideline/Table S1. Data extraction/Table S2. Process steps).

Funding

The work presented here is part of the Food Contact Chemicals and Human health (FCCH) project. The FCCH project is funded by project-related grants from Sympany Foundation, MAVA Foundation, and Fondation Valery, as well as by the Food Packaging Forum's (FPF) own resources from unrestricted donations. All FPF funding sources are listed https://www.foodpackagingforum.org/about-us/funding. AO and VNS received funding from the Federal Food Safety and Veterinary Office, grant 4.21.01.

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