Protocol for systematically assessing the evidence of food contact chemicals monitored in humans

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1 Introduction

Foods and beverages come into contact with food packaging and other food contact articles (FCAs) during their production, transport, processing, preparation, and consumption. FCAs consist of a wide variety of materials (food contact materials, FCMs) that often release chemicals (food contact chemicals, FCCs) into the food/beverage. This process is called chemical migration and leads to continuous human exposure to chemicals. The human health effects related to such chronic, low-level chemical exposures to FCCs are poorly understood (Muncke et al., 2020). The available scientific evidence mostly focuses on a few very well studied FCCs that are known chemicals of concern such as bisphenol A and ortho-phthalates (Warner & Flaws, 2018).

In order to better address these issues, the Food Contact Chemicals and Human Health (FCCH) project was initiated by the Food Packaging Forum and partners, where we systematically investigate the wide variety of FCCs and their potential impact on human health in several stages.

First, we compiled the Food Contact Chemicals Database (FCCdb), which is an inventory of 12,285 FCCs known to be intentionally added or associated with the manufacture of FCMs (Groh et al., 2021). The FCCdb is based on 67 FCC lists from publicly available sources, such as regulatory lists and industry inventories. However, the database does not capture non-intentionally added substances (NIAS) that may also be present in FCMs and FCAs. NIAS are not added on purpose during the production of FCMs, but they may nevertheless migrate into foods and beverages from the final FCA. Typical examples of NIAS are reaction side products, breakdown products, and contaminants (Geueke, 2018; Nerín et al., 2022).

Second, we published the Database on Migrating and Extractable Food Contact Chemicals (FCCmigex) (Geueke et al., 2022). This systematic evidence map collates empirical data on FCCs that have been measured in migrates and extracts of all types of FCMs and FCAs. At the time of its publication, it contained 2881 FCCs that have been detected in six different FCM groups (plastics, paper & board, metals, multi-materials, glass & ceramic, and other FCMs).

Together, these two databases contain a total of 14,153 FCCs, which we call the Universe of known FCCs (Geueke et al., 2022; Groh et al., 2021) (Figure 1). 1013 FCCs appear in both datasets, whereas 11,272 FCCs are included in the FCCdb only. In contrast, 1868 FCCs have been detected in migrates and/or extracts of FCMs, but they are not listed in the FCCdb. This observation implies that these FCCs are either NIAS or were intentionally used without being included in any of the 67 lists that were used to compile the FCCdb.

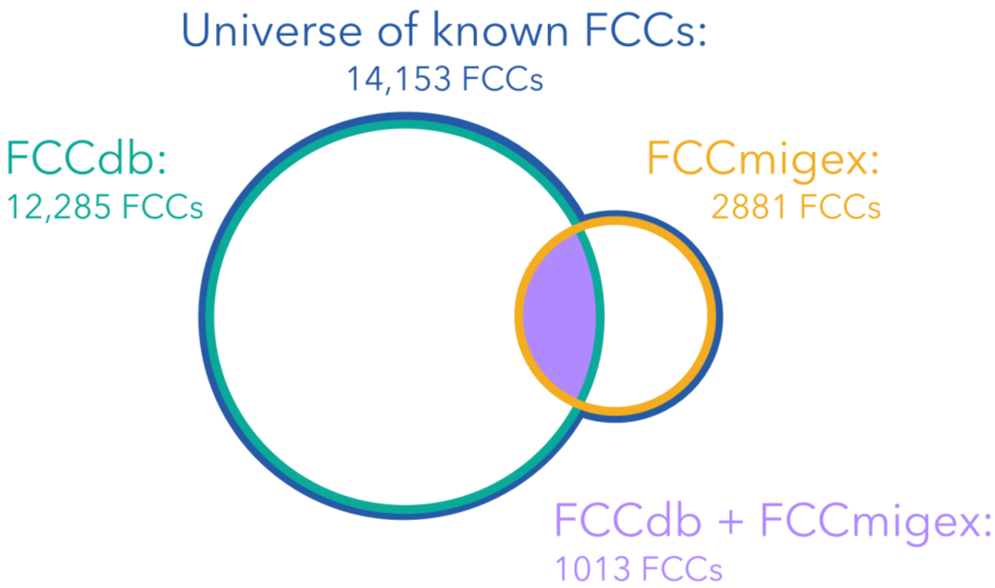

Figure 1. Universe of known FCCs (blue outline). Schematic overview of the intentionally used FCCs (green circle) and the FCCs with evidence of migration/extraction (yellow circle). The chemicals are either part of the FCCdb, FCCmigex, or both databases (indicated by the purple overlap) (Geueke et al., 2022; Groh et al., 2021).

In the next stage of this project, we will collect evidence for FCCs monitored in human samples as this has never been addressed systematically. Together with the information provided in the FCCdb and the FCCmigex, we will then be able to further categorize FCCs based on their potential uses and available hazard data, their evidence for originating from FCMs/FCAs, and their occurrence in the human body. In addition, FCCs for which no human biomonitoring data were found will be identified.

2 Objectives

The overall objective of this evidence map is to systematically document the available scientific evidence for known FCCs that have been monitored in the human body. More specifically, we will:

- Identify FCCs that have been monitored in the human body by comparing biomonitoring programs and metabolome and exposome databases to the Universe of known FCCs as well as identifying primary scientific literature containing additional evidence.
- Provide selected data and specific links to the databases and primary literature in a user-friendly way, so that end-users can directly connect to the information sources.
- Identify data gaps and research needs, discuss limitations and uncertainties, and publish these considerations and the key findings in a summary article.

3 Planning

3.1 Definition of key terms

The following list provides our working definitions for important terms used in this protocol. Alternative definitions may exist in the scientific literature. This list is sorted by topic, not alphabetically.

Food contact article (FCA): A product or item which intentionally comes into contact with food, such as storage containers, conveyor belts, tubes, processing equipment, packaging, tableware and cooking utensils.

Food contact material (FCM): Any type of material that is used in the manufacture of FCAs. Typically, FCMs are in direct contact with food, but materials that are not in direct contact may also be a source of chemical migration and can be considered FCMs (e.g., printing inks, adhesives).

Food contact chemical (FCC): Chemical substances used in the manufacture of FCMs and FCAs and/or present in the final FCMs and FCAs. FCCs are intentionally used starting substances, generated during manufacture of an FCM/FCA and/or non-intentionally added substances (NIAS).

Non-intentionally added substances (NIAS): NIAS comprise all substances that have not been added for a technical reason during manufacturing of FCMs, but that are nevertheless present in the final FCM or FCA.

Food Contact Chemicals Database (FCCdb): The database was compiled from 67 lists of FCCs from publicly available sources, including regulatory lists and industry inventories. It contains 12,285 distinct FCCs that may be used intentionally in the manufacture of FCMs (Groh et al., 2021).

Database on migrating and extractable food contact chemicals (FCCmigex): The database contains more than 3000 FCCs that have been measured in extracts and migrates of FCMs and FCAs (Geueke et al., 2022).

Database on food contact chemicals monitored in humans (FCChumon): The database will be the product of the planned evidence map as it is described in this protocol. It will provide evidence for FCCs that have been monitored in human samples.

Universe of known FCCs: The sum of all FCCs that have been listed in the FCCdb and FCCmigex (Geueke et al., 2022; Groh et al., 2021). Currently, the Universe of known FCCs comprises 14,153 FCCs that are included in at least one of the two databases (Figure 1).

Human biomonitoring: The measurement of the body burden of chemicals or their metabolites. Samples that are typically analyzed include urine, blood, plasma, and serum, but also saliva, breast milk, hair, nails, and other human tissues.

Exposome: This term comprises the totality of chemical, biological, and physical exposures that individuals encounter over their lifetimes. While the measurement of chemical exposures in biological samples can often be rather straightforward, physical exposures such as heat or noise are more difficult to quantify directly. In the context of this protocol, we only refer to chemical exposures.

Metabolome: The term describes all small molecules that are detected in a biological sample. These small molecules are either endogenously produced by the organism (e.g., amino acids, sugars, fatty acids) or taken up from exogenous sources (e.g., pesticides, drugs, FCCs).

Monitored vs. detected: Samples are often analyzed by a targeted approach to determine whether or not a specific chemical is present. In these cases, the chemical is monitored in the sample, but not necessarily detected. Only if the analytical method clearly confirms the presence of the chemical, it is considered detected.

Metabolites and parent compounds: Metabolites are the products of biochemical reactions in organisms. A metabolite is typically a small molecule derived from another molecular structure, the parent compound. Metabolites are targeted in biomonitoring studies if the parent compounds are known to be quickly converted in the organism. Specific metabolites provide evidence for exposure to the parent compounds. Depending on the source, the term biomarker may be used instead of metabolite.

3.2 Authors' contributions and scientific advisory group

All planning steps, the scoping exercise and outcomes of pilot searches were discussed regularly within the core team (BG, LVP, KJG, CDK, MVM, OVM, LZ, JM). Authors contributed their specific expertise to the development of the protocol: food contact chemicals, materials, and articles (BG, KJG, MVM, LZ, JM), research synthesis methods (OVM), literature search and databases (JD, BG, KJG, LP, OVM). BG and LVM conducted pilot literature searches, refined the literature search strategy, and designed the data recording template. BG wrote the original draft of the protocol. All co-authors reviewed the draft and provided constructive improvements of the protocol.

The scientific advisory group gave regular input during this process and its members supported the core team with their specific expertise. The scientific advisory group will continue their support during the entire ongoing project. Members of the scientific advisory group are Jonathan Chevier (McGill University, Canada), Barbara Demeneix and Jean Baptiste Fini (CNRS (French National Research Center), France), Jane Houlihan (Healthy Babies, Bright Futures, USA), Pete Myers (Environmental Health Sciences, USA), Alex Odermatt (University of Basel, Switzerland), Katie Pelch (University of North Texas, USA), Rob Sargis (University of Illinois, USA), Verena Schreier (University of Basel, Switzerland), Emma Schymanski (University of Luxembourg, Luxembourg), Leo Trasande (New York University, USA), Laura Vandenberg (University of Massachusetts Amherst, USA), and Martin Wagner (Norwegian University of Science and Technology).

3.3 Research question

Initially, we assigned the key elements of the research question following the structure of a population-outcome (PO) question. PO questions are typically used when investigating a specific descriptive parameter for a population and are important for exposure assessments (Aiassa et al., 2015; James et al., 2016).

Table 1. Key elements of the research question.

Question	Population	Outcome
Which known FCCs have been monitored in the human body?	Human samples, such as blood, urine, hair, and breast milk, from people of any age, gender, or ethnicity	Any result describing the monitoring and/or detection of a known FCC

3.4 Scoping exercise

A scoping exercise was performed to get a sense of the human biomonitoring data that are available in different databases and the primary literature. Due to the high number of known FCCs, it was particularly important to decide *a priori* how these thousands of FCCs can be compared to chemicals that have been monitored in humans, whether a prioritization strategy is needed, which data should be extracted from the different sources, and how we can link information available in the database to the respective original sources.

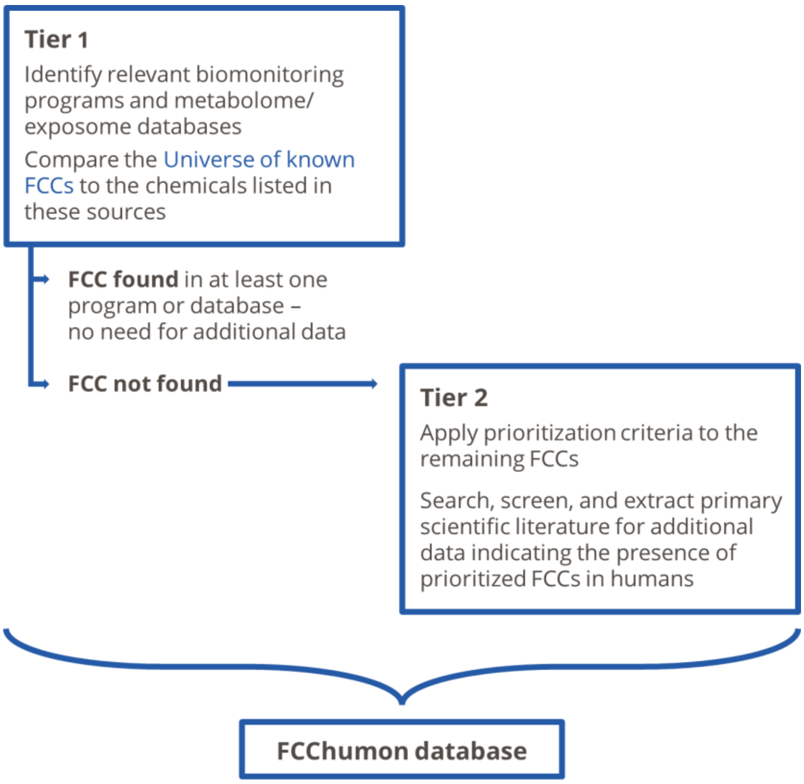

Figure 2. Tiered strategy to compare the Universe of known FCCs to biomonitoring programs and exposome/metabolome databases (tier 1) and to systematically map the evidence for the presence of FCCs in humans in the scientific literature (tier 2). Together, the results will be the basis of the Database on food contact chemicals monitored in humans (FCChumon).

During the scoping exercise, a tiered strategy was developed to obtain a comprehensive overview of FCCs monitored in humans. Specifically, different approaches will be realized as illustrated in Figure 2 and are further detailed in paragraph 4 and 5. Based on this information, the evidence for FCCs in humans will be mapped and a database of **FCC**s **mon**itored in **hu**mans (**FCChumon**) will be compiled.

3.5 Consultation process

Regular consultations within the core team and with the scientific advisory group led to the development of the tiered strategy. In particular, the following considerations were discussed and evaluated during the scoping exercise:

The high number of FCCs that form the Universe of known FCCs made it necessary to not only refer to the primary literature as information source, but also consider established databases, i.e., tertiary sources (Virginia Tech University Libraries), that provide curated scientific information about the presence of chemicals in humans as well as data from biomonitoring programs. The decision to integrate primary and tertiary sources will help to streamline the workflow and avoid duplication of effort. We are aware that this strategy does only partially follow the recommendations for scoping reviews and systematic evidence maps (Tricco et al., 2018). Therefore, we will refer to the term “evidence mapping” when describing the overall strategy and use the term “systematic evidence mapping” only for tier 2.

In order to combine the evidence from the different sources in an efficient way, we developed the tiered strategy. Tier 1 will be based on existing compilations of data that already contain comprehensive and detailed information about chemicals monitored in human samples. Linking these tertiary sources to the Universe of known FCCs will enable a quick identification of relevant FCCs. We will consider the identification of an FCC in any of these sources as sufficient level of evidence.

After we provisionally carried out the workflow as described 5.1, these pilot runs have shown that approximately 70% of the FCCs are listed in at least one of the sources applied in tier 1 (Figure 3). However, more than 4000 FCCs were not found in tier 1 (Table 2), which either means that the FCCs were monitored but never detected, or they were never monitored at all. Pilot searches of the primary literature for selected FCCs supported our hypothesis that the information sources used in tier 1 miss several FCCs for which further scientific evidence exists. Therefore, we decided to include searches of the primary literature in a second tier and systematically map the evidence for individual FCCs that were not found in tier 1 (Figure 2). For each chemical, multiple manual searches and screening of the literature will be needed, which can quickly multiply to several thousand individual literature data sets that become unmanageable. This called for a prioritization process that will allow us to focus on FCCs of special interest. The protocol for tier 2 will be applied to the prioritized group of chemicals in the first instance.

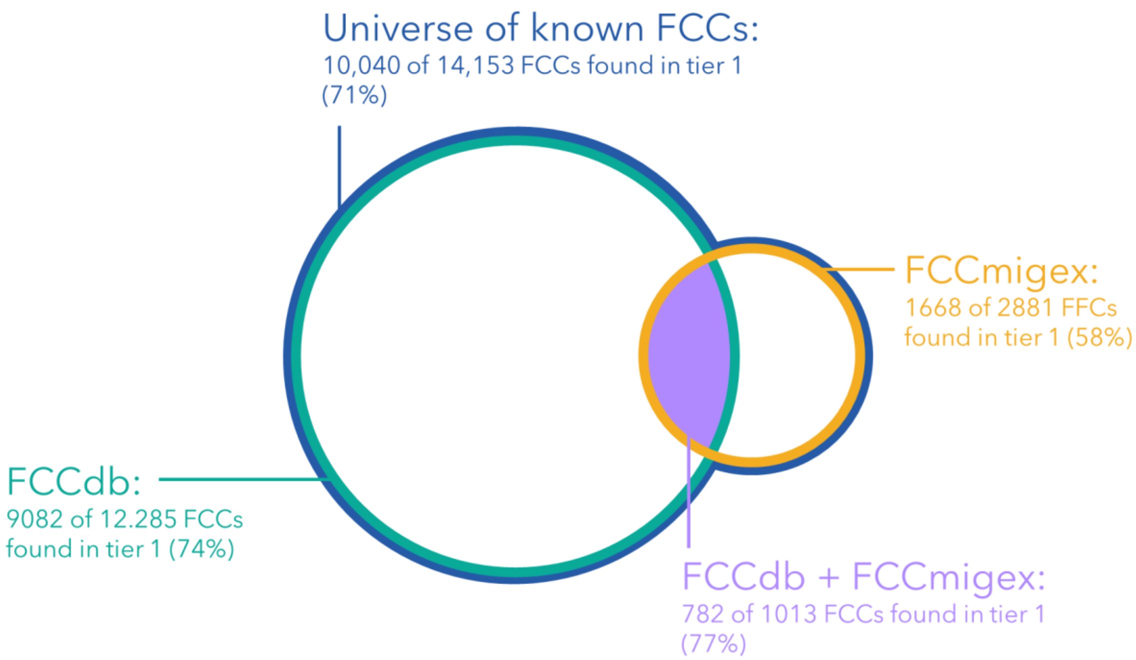

Figure 3. Schematic overview of FCCs with evidence for having been monitored in humans based on preliminary results of tier 1.

Prioritization as defined in this context is a decision tool that typically results in different outcomes and strongly depends on the criteria identified *a priori*, their application, and expert judgement. During the scoping exercise, we applied different prioritization criteria (and combinations thereof) to the >4000 FCCs that were not found in tier 1 (Table 2). This exercise helped to get an estimate of the expected numbers of FCCs and to discuss the relevance of the applied criteria based on concrete lists of FCCs.

First, we compared the percentage of tier-1 FCCs in terms of their listing in the FCCmigex and/or FCCdb (Figure 3). The FCCmigex includes FCCs that have evidence of or the potential for chemical migration into foods. These FCCs are likely to result in human exposure, but it is remarkable that over 40% of the chemicals in the FCCmigex are not listed in any biomonitoring program or metabolome/exposome database, compared to the 26% not listed in the FCCdb. This observation may be an indication for data gaps, e.g., caused by the presence of many NIAS in the FCCmigex, which could be filled or confirmed in tier 2. Therefore, we decided to prioritize the FCCs that have been detected in migrates and/or extracts of FCMs/FCAs (i.e., are included in the FCCmigex).

Then, we applied further prioritization criteria to the 1140 FCCs to make this number more manageable (**1a**, Table 2) and discussed the strengths and weaknesses of each approach:

- A high number of database entries in the FCCmigex is associated with a higher level of evidence of migration into food or a higher potential for such migration. Table 2 shows different options depending on the number of database entries (**1a-e**), which will allow the selection of a manageable list of prioritized FCCs.

- Additional filtering for FCCs that have been detected only in migrates, but not in extracts increases the focus on FCCs with higher evidence for human exposure (**2a-c**). However, by excluding FCCs detected only in extracts, we would miss potential links between FCCs that can theoretically migrate and their presence in humans.
- FCCs that are listed in the FCCmigex and FCCdb (**3a-b**) have additional evidence for intentional use in FCMs/FCAs. 77% of the chemicals from this group were found in the sources used in tier 1 (Figure 3). This indicates that data gaps are less likely. Furthermore, we would miss many NIAS that have been measured in extracts and/or migrates, if we would choose to work with this group of prioritized FCCs.

Based on these scenarios, we decided to prioritize FCCs that were detected in migrates and/or extracts of FCMs/FCAs. We will start with the 112 FCCs that have at least five database entries in the FCCmigex (**1e**), but may further extend the list of FCCs by lowering the number of required database entries per FCC (**1a-d**).

Table 2. Application of different prioritization criteria to FCCs that were not identified in tier 1. The reported numbers are the results of a pilot run of tier 1 and thus preliminary.

Possible prioritization criteria		**Preliminary number of FCCs**
	FCCs not identified in tier 1	4113
	AND listed in	
1a	FCCmigex (filter: detection “yes”, ≥1 database entry per FCC)	1140
1b	FCCmigex (filter: detection “yes”, ≥2 database entries per FCC)	467
1c	FCCmigex (filter: detection “yes”, ≥3 database entries per FCC)	249
1d	FCCmigex (filter: detection “yes”, ≥4 database entries per FCC)	165
1e	FCCmigex (filter: detection “yes”, ≥5 database entries per FCC)	112
2a	FCCmigex (filters: detection “yes”, type of experiment: “migration into food” + “migration into food simulant”; ≥1 database entry per FCC)	563
2b	FCCmigex (filters: detection “yes”, type of experiment: “migration into food” + “migration into food simulant”; ≥2 database entries per FCC)	321
2c	FCCmigex (filters: detection “yes”, type of experiment: “migration into food” + “migration into food simulant”; ≥3 database entries per FCC)	204
3a	FCCdb + FCCmigex (filter: detection “yes”)	227
3b	FCCdb + FCCmigex (filters: detection “yes”, type of experiment: “migration into food” + “migration into food simulant”)	150

4 Information sources

The following biomonitoring programs, databases, and literature sources were identified during the scoping exercise and will be included.

4.1 Biomonitoring programs

We selected five biomonitoring programs that encompass a broad range of different chemicals, including known FCCs, as well as wide geographic coverage.

- National Health and Nutrition Examination Survey (NHANES) (Centers for Disease Control and Prevention, 2021)
- Canadian Health Measures Survey (CMHS) (Health Canada, 2021)
- European Human Biomonitoring Initiative (HBM4EU) (HBM4EU, 2022; IPCHEM, 2022)
- Korean National Environmental Health Survey (KoNEHS) (Jung et al., 2022)
- Biomonitoring California (Biomonitoring California, 2022)

Other major human biomonitoring programs in chemical exposure assessment were also reviewed but not included because they frequently monitored chemicals specific to non-FCM sources (e.g., pesticides) or the same chemicals that are targeted in the selected biomonitoring programs (Choi et al., 2015; World Health Organization. Regional Office for, 2015).

4.2 Metabolome/exposome databases

Additionally, three databases were chosen that contain comprehensive information about chemicals that have been monitored in humans. These databases either refer to the metabolome or exposome of humans and/or mammals. They were selected after consulting with scientific experts and information specialists, and after supplementary in-house research.

- Human Metabolome Database (Wishart et al., 2022)
  The Human Metabolome Database (HMDB) is freely available and compiles information about small molecules found in the human body. It contains chemical, clinical and molecular biology/biochemistry data for over 250,000 chemicals.
- Blood Exposome Database (Barupal & Fiehn, 2019)
  The Blood Exposome Database (BlExpDB) is a collection of chemical compounds and related information associated to chemicals in the blood of mammals. The information was automatically extracted by text mining the content of PubMed and PubChem databases.
- Exposome Explorer (Neveu et al., 2019)
  Exposome-Explorer (Exp-Exp) is the first database dedicated to biomarkers of exposure to environmental risk factors for diseases. It aims to provide comprehensive data on all known biomarkers of exposure to dietary factors, pollutants, and contaminants monitored in population studies.

4.3 Bibliographic databases

During the scoping exercise, a significant part of all known FCCs were identified in biomonitoring programs and/or metabolome/exposome databases. However, other FCCs that have been frequently detected in migrates and extracts of FCMs were not found. Therefore, we developed a strategy that allows us to search and screen the primary literature for FCCs that were not identified in the above-mentioned sources. The following databases will be used to search for specific FCCs monitored in humans:

- PubMed
- Web of Science Core Collection (WoS)
- ScienceDirect
- CAS SciFinder^{n}

5 Methods

The tiered approach illustrated in Figure 2 applies different methods to map the available evidence on FCCs monitored in humans. Table 3 provides an overview of the steps that will be applied to investigate the three different types of information sources and how these are assigned to the two tiers.

Table 3. Overview of the proposed workflow to map the evidence for FCCs monitored in humans.

<table>
<tr><th colspan="2">Tier 1</th><th>Tier 2</th></tr>
<tr><td colspan="2">Compare the Universe of known FCCs to chemicals from</td><td rowspan="2">Map additional evidence from primary literature</td></tr>
<tr><td>• biomonitoring programs</td><td>• metabolome and exposome databases</td></tr>
<tr><td>Export/copy names and CAS IDs of chemicals that have been monitored in the five biomonitoring programs

If applicable: Identify pairs of parent compounds and metabolites

If applicable: Include whether the chemical has been detected in at least one of the biomonitoring samples, has never been detected or whether this is unknown</td><td>Export chemical names, CAS IDs, and, if needed, further information and identifiers, from three metabolome/ exposome databases

Link FCCs to the respective database entries</td><td>Define eligibility criteria

Identify FCCs that were not found in tier 1 and apply prioritization criteria to these FCCs

Run literature searches

Manage and screen the literature

Extract data and apply data coding strategy</td></tr>
<tr><td colspan="3">Integration of results</td></tr>
</table>

5.1 Tier 1: Comparing the Universe of known FCCs with tertiary sources

The Universe of known FCCs will be compared with chemicals included in national biomonitoring programs and/or listed in metabolome and exposome databases. Chemical information will be exported or copied from the sources and databases mentioned in 4.1 and 4.2 and the data will be stored, edited, formatted, and handled using Microsoft Excel or Microsoft Access.

5.1.1 Biomonitoring programs

Chemicals that have been included in the biomonitoring programs over the indicated time periods will be exported into a Microsoft Excel file. In some cases, chemicals are quickly converted into specific metabolites in the human body. These metabolites typically serve as indicators for human exposure to the parent compounds and are targeted in biomonitoring studies. In such cases, the analyzed metabolites will be paired with the parent compounds.

If provided, Chemical Abstract Service identifiers (CAS IDs) will be exported from the original sources or, alternatively, the CAS IDs will be assigned to the exported chemicals. Detection frequencies may be recorded. The CAS IDs of all FCCs that are part of the Universe of known FCCs will be compared to the chemicals listed in the five different biomonitoring programs (including parent compounds and metabolites).

5.1.2 Metabolome and exposome databases

For the HMDB, BlExpDB, and the Exp-Exp, we will download the most current version of each database and use these files for comparisons with the Universe of known FCCs. Since each database is different regarding content and structure, we will apply the following steps before running the comparisons:

- The HMDB will be filtered by “metabolite status”. We will select the filters “detected and quantified”, “detected but not quantified”, and “expected but not quantified” and record the metabolite status for each FCC found in the HMDB. The filter “predicted” will be omitted because pilot comparisons between this filtered data set and the Universe of known FCCs showed no overlaps. By choosing these three filters, the number of >251,000 metabolites listed in the HMDB was reduced to >123,000 (September 2022). Other filters will not be selected.
- The BlExpDB includes InChIKey and Canonical SMILES as chemical identifiers, but no CAS IDs. Therefore, we will extend the Universe of known FCCs by these identifiers, if available, and use them for comparison to the BlExpDB.
- All chemicals listed in the Exp-Exp will be exported and compared with the Universe of known FCCs based on the available CAS IDs.

During the scoping exercise, we ran individual searches for known pairs of FCC parent compounds and metabolites. In all cases, the parent compound was listed in the HMDB or the BlExpDB. Therefore, we did not integrate further information on (possible) FCC metabolites before comparing these sources to the Universe of known FCCs.

5.2 Tier 2: Mapping further evidence for targeted FCCs

Based on systematic searches of the primary literature, tier 2 will provide additional evidence for individual FCCs monitored in humans. This strategy is generally applicable to all FCCs, but it will only be applied to a selected set of prioritized chemicals in the first instance (see 3.5).

5.2.1 Eligibility criteria

Individual literature searches will be run for each prioritized FCC. The criteria defining whether a scientific study is eligible to be included or needs to be excluded are shown in Table 4. It is important to mention that the eligibility criteria will only be applied with respect to the FCC for which the literature search was run, i.e., other chemicals that may have been monitored in the study are not relevant in this context. Studies will only be included if the sample clearly originates from a human specimen. If an FCC was monitored but not detected the study will also be included.

No date and language restrictions will be applied. Inclusion will be limited to primary research articles showing original research data. Review articles, conference abstracts, presentations, dissertations, and book (chapters) will be excluded.

Table 4. Eligibility criteria for the literature screening.

	Inclusion criteria	**Exclusion criteria**
Population	Analyzed sample originates from a human specimen (e.g., blood, urine, breast milk). No restrictions on the sample source. No restrictions on age, sex, or life stage.	Analyzed sample originates from any other species, is an environmental sample, or undefined.
Outcome	FCC is monitored in at least one human specimen. Detection of FCC is recorded.	FCC is only mentioned in another context.

5.2.2 Prioritization of FCCs

All FCCs in the Universe of known FCCs that will not be identified in tier 1 will be selected for further prioritization (Figure 2). The following prioritization criteria will be applied:

- The FCC is not identified in tier 1 and has at least 5 database entries representing its detection in different migration and extraction experiments as reported in the FCCmigex database (Table 2, **1e**).

The criteria were chosen because FCCs that have been detected several times in migrates and extracts are likely ingested by humans. By prioritizing these FCCs, we will decrease the possibility of missing any evidence for their presence in humans.

In the future, this set of prioritized chemicals can be extended by applying other criteria, such as the hazard properties, the production volume, or the use in different FCMs. It is also possible to further combine prioritization criteria to select more specific groups of FCCs.

5.2.3 Search strategies

A single FCC can have dozens of different synonyms, including highly systematic but rarely used names as well as generic and trade names. In the FCCdb and FCCmigex, chemical names were assigned based on their common uses in the underlying source references. We will query PubMed, WoS, ScienceDirect, and SciFinder^n for these chemical names and/or the respective CAS IDs of the FCCs (Table 5). To further specify the searches, we will always combine the chemical identifier with keywords related to human biomonitoring. The search strings and settings will be slightly adapted to fit the requirements of the respective databases (Table 5).

In pilot searches, we applied these search strings to twelve of the 112 preliminary prioritized FCCs (see 5.2.2). Overall, the resulting hits matched our expectations regarding content and quantity in all four databases. Only the searches for CAS IDs in PubMed resulted in fewer and less relevant results when compared to the searches for chemical names. Therefore, we will not include searches for CAS IDs in PubMed.

For four of the twelve selected chemicals, we were aware of scientific papers reporting their measurements in humans before starting the literature search. With the exception of one, we found these papers in at least one of the databases by applying the search strategies shown in Table 5. The paper that was missed used another synonym for the chemical “PET cyclic trimer” and the CAS ID of this chemical was neither found in CAS SciFinder^n although the paper is listed (Diamantidou et al., 2022). Such limitations may be overcome by including more synonyms and proximity searches, and by omitting the quotation marks used around the chemical name. Since some FCCs may be quickly metabolized in humans, searching for typical metabolites may be another option to identify relevant papers. We will not include these options systematically, but may consider them if our search strategy proves to be incomplete.

Comparisons of searches for the chemical identifiers alone with those including all key words related to human biomonitoring showed that we did not miss relevant papers by using the full search string.

Table 5. Search strategies for PubMed, WoS, ScienceDirect, and CAS SciFinder^{n}

Database	**Chemical identifier**	**Operator**	**Search string: Key words related to human biomonitoring**	**Further settings/filters**
PubMed	"chemical name"	AND	(human OR blood OR urine OR serum OR hair OR nail OR plasma OR biomon* OR "breast milk")	• Search *all fields* • No filters applied
PubMed*	CAS ID	AND	(human OR blood OR urine OR serum OR hair OR nail OR plasma OR biomon* OR "breast milk")	• Advanced search • Search field: *EC/RN Number*
WoS	"chemical name"	AND	(human OR blood OR urine OR serum OR hair OR nail OR plasma OR biomon* OR "breast milk")	• Advanced search • Search *all fields* • Document type: Article
ScienceDirect	"chemical name"	AND	(human OR blood OR urine OR serum OR hair OR nail OR plasma OR biomonitoring OR "breast milk")	• Advanced search • Search "chemical name" in *full text* • Search all other keywords in *title, abstract or author-specific keywords* • Article type: Research article
CAS SciFinder^{n}	CAS ID	AND	(human OR blood OR urine OR serum OR hair OR nail OR plasma OR biomon* OR "breast milk")	• Searching for References • Search keywords in the main search field • Search CAS ID in *CAS Registry Number* • Filter for document type: Journal

*Pilot searches resulted in fewer and less relevant results when compared to searches using the chemical names instead. Therefore, these searches will not be applied.

5.2.4 Management and screening of the literature

For each FCC, the search results from four scientific databases will be transferred into a separate Endnote library and duplicates will be removed (Figure 4). These results will be screened first at title and abstract level, then at full text level in the freely available online tool Cadima (Kohl et al., 2018). Screening may be facilitated by automatic annotations of keywords in Cadima. Ten percent of entries will be screened by two reviewers in parallel, and discrepancies will be resolved bilaterally or by consulting the core team. Clearly irrelevant studies will be excluded. All other studies will undergo full text screening applying the same eligibility criteria, if full texts are available. Consistency checking will again be performed by two researchers working independently in parallel on the same set of references, followed by comparing the results of the literature screening and resolving the discrepancies in the core team. The reasons for exclusion after full-text screening will be recorded.

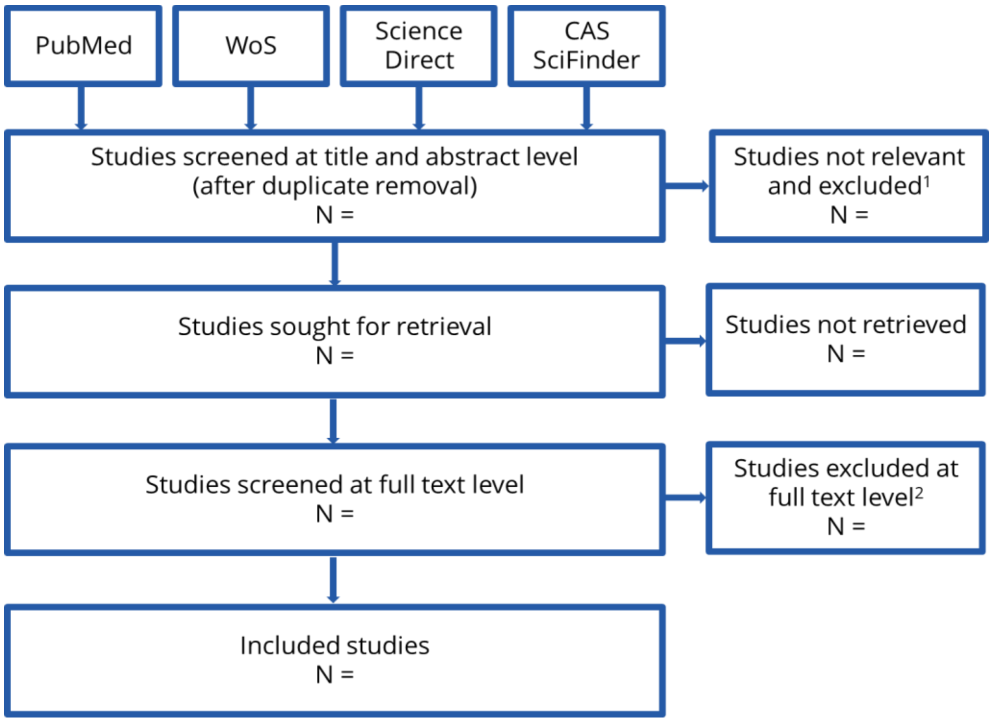

Figure 4. Example workflow, separately applicable to each prioritized FCC during tier 2. [1]Clearly irrelevant studies will be excluded during title and abstract screening. [2]Reasons for exclusion may be: full text not accessible, no primary data presented, eligibility criteria not fulfilled.

5.2.5 Data coding

Data will be extracted from the eligible full-text studies in Microsoft Excel and/or SciExtract tool that we developed previously (Geueke et al., 2022). More specifically, the collected data will provide information about the reference, the FCC, the human specimen, and whether the FCC was detected in the sample or not (Table 6).

Table 6. Data coding and extraction, tier 2.

Data category	Data captured
Bibliographic information	• Author(s) • Year of publication • Journal • Title • URL • Volume • Issue • Pages • DOI • Abstract
FCC	• Chemical name that was used in the literature search (derived from the FCCmigex/FCCdb) • CAS ID • Chemical name as it appears in the reference
Optional: Human specimen (controlled additions of terms allowed as needed)	• Blood • Urine • Plasma • Serum • Hair • Nail • Breast milk • Adipose tissue • Amniotic fluid • Cord blood • Other • Unknown/unclear
Detected in humans	• Yes • No

5.2.6 Study quality assessment

The study quality will not be assessed.

5.3 Integration of results and reporting

The outcome of this project will be described in a manuscript that will undergo peer review. The key results will be described in a narrative form and visually supported by illustrations. Limitations that we may encounter in the course of tier 1 and tier 2 will be further detailed in the planned publication. Table 7 shows a view on how the data can be collected and stored. In addition, the data will be made available in an interactive dashboard so that users can search and filter for FCCs and related information. In a next step, the results will be linked to the FCCdb and FCCmigex databases.

The FCCs monitored in humans, and those that were not found in any source, will be discussed in the context of the Universe of known FCCs. Example questions that may be answered based on the expected results are:

- Which and how many FCCs have been monitored in humans? Which and how many FCCs have been detected in humans?
- Which FCCs or groups of FCCs have been most frequently monitored in the different sources?
- Is there a correlation between the number of database entries for an FCC in the FCCmigex and the evidence from human biomonitoring studies?
- Which and how many of the tier-2 prioritized FCCs have been monitored in humans?
- Which FCCs detected in humans are listed in the FCCdb?
- How many and which FCCs monitored in humans are used in a specific FCM? How many and which FCCs detected in humans have been detected in migrates of a specific FCM?
- For which FCM types can we identify the biggest data gaps regarding biomonitoring data on chemicals used in/migrating from that FCM types?

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7 Declaration of Competing Financial Interests

The authors declare that no competing financial interests exist.

Table 7. Overview of the possible evidence that will be collected for an FCC. The bullet points indicate the answer options for each of the cells.

<table>
<tr><th rowspan="3"></th><th colspan="8">Tier 1</th><th colspan="5">Tier 2</th></tr>
<tr><th colspan="5">Biomonitoring programs[1]</th><th colspan="3">Metabolome/exposome databases[2]</th><th rowspan="2">Evidence from tier 1?[3]</th><th rowspan="2">Prioritized?[4]</th><th rowspan="2">Monitored in humans?[5]</th><th rowspan="2">Detected in humans?[6]</th><th rowspan="2">Reference(s)[6]</th></tr>
<tr><th>NHANES</th><th>CHMS</th><th>HBM4EU</th><th>KoNEHS</th><th>Biomon Cal</th><th>HMDB</th><th>BIExpDB</th><th>Exp-Exp</th></tr>
<tr><td>FCC</td><td colspan="5">• FCC: Monitored and detected
• FCC: Monitored but never detected
• FCC: Monitored but only rarely detected or detection unclear
• Metabolite: Monitored and detected
• Metabolite: Monitored but never detected
• Metabolite: Monitored but detection unclear
• Not listed</td><td>• Detected and quantified
• Detected but not quantified
• Expected but not quantified
• Not listed</td><td>• Listed
• Not listed</td><td>• Listed
• Not listed</td><td>• Yes
• No</td><td>• Yes
• No</td><td>• Yes
• No
• Unclear/ unknown</td><td>• Yes
• No
• Not applicable</td><td>• Link to Reference(s)
• Not applicable</td></tr>
</table>

[1] For each of the five biomonitoring programs, one of the seven possible outcomes needs to be selected.

[2] Ideally, links will be set into the cells that direct to the FCC-specific entry in the respective database.

[3] "Evidence from tier 1?" = "Yes", if at least one column from tier 1 has an entry other than "Not listed". In that case the other columns of tier 2 remain empty.

[4] Only applicable if "Evidence from tier 1?" = "Yes"

[5] "Monitored in humans?" = "Yes" for all studies that were included after full-text screening.

[6] Only applicable if "Monitored in humans?" = "Yes". Optional: include information on human specimen.

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