Protocol for a systematic map of the evidence of migrating and extractable chemicals from food contact articles

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Authors:

Dr Olwenn V Martin[1], Birgit Geueke[2], Ksenia J. Groh[2], Jonathan Chevrier[3], Jean-Baptiste Fini[4], Jane Houlihan[5], Christopher Kassotis[6], Pete Myers[7], Susan C. Nagel[8], Katherine E. Pelch[9], Robert M. Sargis[10], Leonardo Trasande[11], Laura N. Vandenberg[12], Martin Wagner[13], Maricel V. Maffini[14], and Jane Muncke*[2]

*corresponding author: jane.muncke@fp-forum.org

[1] Institute for the Environment, Health and Societies, Brunel University London, Halsbury 132, Kingston Lane, Uxbridge UB8 3PH, United Kingdom

[2] Food Packaging Forum, Staffelstrasse 8, 8045 Zurich, Switzerland

[3] Department of Epidemiology, Biostatistics and Occupational Health, Faculty of Medicine, McGill University, 1020 Pine Ave West, Montréal, Québec, Canada, H3A 1A2

[4] Unité mixte de recherche 7221: CNRS (French National research center) and Museum National d'Histoire Naturelle, , Adaptation du vivant department, Paris, France

[5] Research Director, Healthy Babies Bright Futures, www.hbbf.org

[6] Nicholas School of the Environment, Duke University, Durham NC 27708, USA

[7] Environmental Health Sciences, Charlottesville, Virginia, USA & Department of Chemistry, Carnegie Mellon University, Pittsburg, Pennsylvania, USA

[8] Department of OBGYH and Women's Health, University of Missouri, Columbia, MO 65211, USA

[9] The Endocrine Disruption Exchange, P.O. Box 54, Eckert, CO 81418, USA

[10] Division of Endocrinology, Diabetes, and Metabolism, Department of Medicine, Chicago Center for Health and Environment, University of Illinois at Chicago, USA

[11] NYU School of Medicine, Departments of Pediatrics, Environmental Medicine & Population Health, New York University, USA

[12] Department of Environmental Health Sciences, School of Public Health & Health Sciences, University of Massachusetts Amherst, Amherst, MA 01003, USA

[13] Department of Biology, Norwegian University of Science and Technology (NTNU), 7491 Trondheim, Norway

[14] independent consultant, Germantown, MD USA

Authors' contributions

Authors contributed their respective different expertise to the development of the protocol: food contact materials and indirect food additives (BG, KJG, MVM and JM), systematic review (OVM, KEP), literature search and databases (OVM, KEP, KJG), endocrinology, toxicology, endocrine toxicology, mixtures (CK, MW, LNV, JBF, OVM, KEP, JC). OVM contributed her experience of developing systematic review protocols. OVM and BG conducted pilot literature searches which helped refine the literature search strategy. BG and OVM designed and piloted the data recording template. All other co-authors JBF, JH, CK, PM, SCN, KEP, RMS, LT, LNV, MW, JC reviewed the first draft of the protocol, and provided constructive input to improve the protocol.

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Role of the funder: The co-authors scientific freedom was not restricted in any way and all decisions relating to the scope and study design were made independently of the funder and FPF's donors. Donors were not involved in scoping, designing, drafting and reviewing the study protocol, and they were not informed about the project beforehand.

Competing interests

Food Packaging Forum (FPF) is a charitable foundation funded by project-specific grants and unconditional donations. All current and past FPF donors and funders are listed on http://www.foodpackagingforum.org/about-us/funding. Neither funders nor donors restrict FPF in any way and they have no influence on FPF which would impact its scientific work.

Introduction

Rationale

Approximately 10,000 substances are intentionally used in the manufacture of food contact materials (FCMs), and an estimated 40,000 to 100,000 substances are thought to be present in all different types of food contact articles (FCAs) (Grob et al. 2006). FCMs and FCAs come into direct contact with foodstuffs; their chemical constituents, food contact chemicals (FCCs), can be transferred into food by the process of chemical migration (Arvanitoyannis and Bosnea 2004). Since almost all foodstuffs come into contact with FCAs during their production, storage, processing and/or packaging, there is most likely wide exposure of the human population to FCCs (Muncke et al. 2014). However, the extent of this exposure, and the variability of exposure between individuals and populations, is essentially unknown. Further, the human health effects related to chronic, low-level chemical exposures via food are poorly understood, and the available scientific evidence mostly focuses on a few very well studied FCCs which are known chemicals of concern such as bisphenol A, ortho-phthalates, and perfluorooctanoic acid (Muncke et al. 2017; Trasande et al. 2018).

More research is needed to better understand the relationships between FCC exposures and human health effects. As a first step, completion of this protocol will allow us to compile the available scientific evidence about chemical migration from and/or extractable from FCAs. Follow-up studies not described in this protocol, but based on the outcome of this work, will address human exposure to FCCs, as well as the human health outcomes implicated with human exposure to FCCs, in order to characterize the state-of-the-science and identify key knowledge gaps. The focus of this work is on indirect food additives and it excludes all chemicals intentionally added to food (e.g. food additives) or unintentionally added to food through a process unrelated to FCA (e.g. pesticides, herbicides, etc).

Background, concepts and definitions

Definition of key terms

Here, we present and define the most important terms used in this protocol. This overview is intended to provide our working definitions of various terms. Importantly, these terms are not necessarily unanimously agreed upon or used in the same way in the scientific literature. We define terms to assist us with the scientific literature search. The terms are listed thematically (not alphabetically).

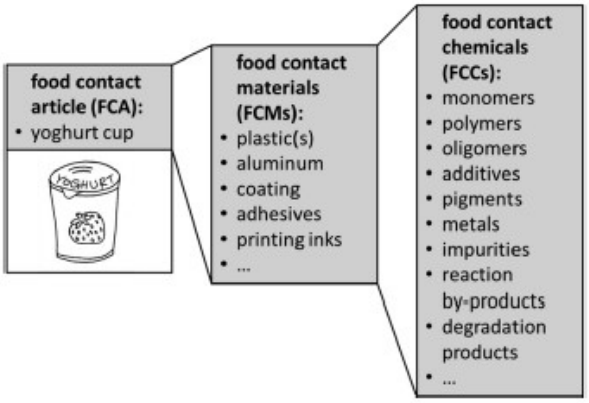

Figure 1: Key terms - Food contact articles (FCAs) are combinations of different food contact materials (FCMs), which consist of food contact chemicals (FCCs): For example, a yoghurt cup made of polystyrene with printing inks and a coated aluminium cover glued on with adhesives (from: Muncke et al. 2017).

Food: Solid or liquid non-medicinal product intended for human consumption, by any age group. This includes beverages.

Food contact articles (FCAs): Products or items which intentionally come into contact with food, such as storage containers, conveyor belts, tubes, processing equipment, packaging, tableware and cooking utensils.

Food contact materials (FCMs): Materials that are intended for use in FCAs. In the EU, 17 different types of FCMs are defined (European Union 2004): 1. Active and intelligent materials and articles; 2. Adhesives; 3. Ceramics; 4. Cork; 5. Rubbers; 6. Glass; 7. Ion-exchange resins; 8. Metals and alloys; 9. Paper and board; 10. Plastics; 11. Printing inks; 12. Regenerated cellulose; 13. Silicones; 14. Textiles; 15. Varnishes and coatings; 16. Waxes; 17. Wood.

Food contact chemicals (FCCs): Substances used and/or present in the manufacturing of FCMs and/or present in FCMs and/or FCAs. Some FCCs are intentionally used starting substances that may no longer exist in the FCM/FCA. Some FCCs are generated during manufacture of an FCM/FCA. Some FCCs are non-intentionally added substances (i.e. NIAS) but nevertheless are present in the finished FCA.

Non-intentionally added substance (NIAS): FCCs that are formed during FCM and/or FCA manufacture, present as impurities in the starting substances for FCM manufacture or break-down products of FCCs (either due to intentional or non-intentional functionality). Under European legislation, oligomers are also included in this definition.

Universe of FCCs: Any chemical that is either intentionally or non-intentionally used/present in FCMs and/or FCAs. Estimates for the number of chemicals belonging to the "universe of FCCs" range from 40,000 to 100,000 substances, including approximately 10,000 intentionally added FCCs (Grob et al. 2006).

Food contact chemicals database version 1.0 (FCCdb 1.0): Compilation of public sources listing known FCCs intentionally used for the manufacture of FCMs/FCAs[1].

Food contact chemicals database version 2.0 (FCCdb 2.0): Includes all FCCs from the FCCdb 1.0, as well as all substances identified to migrate from FCMs and FCAs as result of this study. The FCCdb 2.0 will be prepared after analysis of the scientific literature on chemical migration from FCMs and FCAs.

Migration: Transfer of an FCC from an FCM or FCA into food or food simulant. Migration of an FCC into food may lead to human exposure after food consumption. Migration reflects realistic, intended-use and foreseeable conditions.

Migration study: In a scientific study, evidence for migration may be obtained by adequate study design, which includes use of an appropriate control experiment (i.e. standard, lab-generated sample to which all other samples included in the study are compared, and which allows identification of chemical migration in all other samples, if migration is occurring). Migration studies investigate either the migration kinetics (i.e. measurements are made over time, in the same

[1] The FCCdb 1.0 does not yet exist as such and will be compiled specifically for this project. It will be similar to another recently published database (Groh et al. 2019) but will not contain hazard information.

samples) or the migration space (i.e. measurements are made in the same sample of food/food simulant, with known and varying distance from the FCA). Studies with identification of a substance in food, and identification of this substance in the related FCA will also be included.

Extraction: Transfer of an FCC from an FCM or FCA into a solvent when the conditions are chosen in such a way as to promote a strong interaction with an FCM, often resulting in a quicker mass transfer and equal or even exaggerated extents of migration (Franz and Stroemer 2008). Extraction is defined as worst-case migration and reflects non-foreseeable use conditions.

Food simulant: Liquid or solid substance or mixture that is well-defined and used in extraction or migration experiments. Food simulants may include those defined in EU or US regulations (European Union 2011; FDA 2007), but other types of solutions or solvents have also been used in published studies.

Data recording: We use this term synonymously with "data extraction", which is the commonly used term in systematic mapping. However, since in this study we are using the term 'extraction' as defined above, the expression 'data recording' will be adopted to avoid confusion. Recorded data will be stored in the data recording database, which is distinct from the FCCdb's different versions.

Objectives

The overall objective of this systematic evidence map (O'Leary et al. 2017) is to document the available scientific evidence (both peer-reviewed and 'grey'[2]) for chemicals (both intentionally and non-intentionally added) that migrate and/or are extractable from food contact materials (FCMs) and articles (FCAs). This will be achieved by retrieving evidence that FCCs may migrate into food and/or food simulants and/or have been extracted from FCAs/FCMs.

This objective will be realised by achieving the following **specific aims**:

- Identify literature reporting the migration and/or extraction of FCCs into foods or food simulants or extraction solvents
- Record data on FCCs migrating from FCMs or FCAs into food or food simulants, and data on FCCs extracted from FCMs or FCAs
- Synthesize the available information using a qualitative approach for mapping evidence ("known knowns") and knowledge gaps ("known unknowns")
- Compile a database of FCCs (FCCdb), containing chemicals intentionally added to and/or migrating from and/or extractable from FCMs and FCAs
- Identify knowledge gaps and define priorities for future research

Well-formulated, objective statements have a critical impact on other components of the review – including the literature search strategy, data recording, synthesis, and presentation of findings, and can take several structures, for example a Population Outcome (PO) structure (James et al. 2016). A PO structure is most appropriate for the objectives above. Table 1 gives an overview of the PO statement.

[2] "Grey" literature refers to any publications which are published outside of peer-reviewed scientific journals, such as academic theses or reports; such publications can be peer-reviewed or non-peer-reviewed.

Table 1. PO statement – migration

Question	For which FCCs is there evidence of migration/extraction from FCMs or FCAs?
Population	Universe of FCCs
Outcomes	Migration and/or extraction into food or food simulants or solvent. There are no limits on the food or food simulant or solvent composition/characteristics. There are also no limits on the FCM or FCA type, composition, or geographical origin.

Methods

This protocol was drafted with specific regards to the PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist (Shamseer *et al.*, 2015) and giving due consideration to the Code of Practice for the Conduct of Systematic Reviews in Toxicology and Environmental Health Research (COSTER) (Whaley *et al.*, no date). We also followed the PRISMA-ScR (Extension for Scoping Reviews) 2018 checklist (Tricco et al. 2018).

Eligibility criteria

The PO statement (Table 1) formed the basis of discussions resulting in an operationalization of clear inclusion and exclusion criteria that enable transparent and reproducible screening of the literature (Table 2).

Table 2. Eligibility criteria for PO – migration

	Description	Inclusion criteria	Exclusion criteria
Populations	Universe of Food Contact Chemicals (FCCs)		
Outcomes	Migration into food or food simulants or extraction into solvent. Secondary outcomes of interest include: - Chemical identity: name, CAS (if available), level of confidence in chemical identification - Food or food simulant composition/characteristics FCM or FCA type	- FCC migrates from an FCM/FCA into food or food simulant (study with appropriate control and kinetic/spatial design) - Substance has been extracted from an FCM/FCA using a solvent - Substance is identified with at least Level 2 confidence[3] ("probable structure") - Oligomers are included with Level 3 confidence and as group	- Substance not identified with predefined levels of confidence[3] - Substance screened but not detected - Low confidence of chemical identification - No evidence of the chemical originating from the FCM/FCA - Nanomaterials without CAS - Chemicals originating from waste paper and other recycled materials with non-specified food contact use

We define the chemical space of interest as the "universe of FCCs", i.e. any chemical that is either intentionally or non-intentionally used/present in any type of FCMs and/or FCAs. The inclusion of migration/extraction studies will be based on the definitions provided in this protocol.

As the research team includes English, German, Spanish, Russian and French native speakers, publications in any of these languages will be included in the study. For relevant publications in

[3] Based on the framework for communicating confidence when identifying small molecules (Schymanski et al. 2014)

languages other than English, German, Spanish, Russian or French, a version of the full text in English will be sought by contacting authors or using automated translation and included if available.

Chemical identity

Chemicals identified using (high resolution) mass spectrometry do not always have unambiguous structures. Since the purpose of this study is to identify chemicals migrating or extractable from FCMs and FCAs, we define criteria for the confidence of a chemical's identification. For this purpose, we follow the framework proposed by Schymanski and colleagues (2014) to evaluate the confidence of a chemical's identity:

Level 1 – confirmed structure (by reference standard)

Level 2 – probable structure (by library spectrum match / by diagnostic evidence)

Level 3 – tentative candidate (structure substituent, class)

Level 4 – unequivocal molecular formula

Level 5 – exact mass of interest

All chemicals identified with Levels 1 and 2 confidence will be included. Oligomers identified with Level 3 confidence will also be included, as many oligomers are expected to fall into this category. Nanomaterials and oligomers will be included as individual entries if CAS numbers are provided. The time period of interest is not limited.

Information sources

Searches for peer-reviewed articles will be conducted in the following bibliographic databases:

- PubMed
- Web of Science Core Collection (WoS)
- Scopus
- Google Scholar[4]
- The full text database ScienceDirect[4]

Further, in order to identify ongoing research, we will examine conference papers via resources like the British Library service Zetoc (http://zetoc.jisc.ac.uk/).

To identify grey literature not listed in databases, searches will be carried out using the topic focused search engines Environar (https://environar.com/environar/desktop/en/search.html). Additional searches will be carried out in open access bibliographical databases such as OpenGrey (http://www.opengrey.eu/), which searches grey literature across Europe, or CORE (http://www.core.ac.uk), to search open access items in institutional repositories.

Finally, the grey literature search will be complemented by targeted manual searches:

- websites of European institutions such as the European Environment Agency (EEA), the European Chemical Agency (EChA), the European Food Safety Authority (EFSA), the Joint Research Centre (JRC);
- websites of US American institutions such as the Environmental Protection Agency (EPA), the National Institute of Environmental Health Sciences (NIEHS), the National Institute of Health (NIH) or the Food and Drug Administration (FDA);

[4] With less complex search syntax i.e. fewer relevant search terms. In ScienceDirect up to 8 terms can be combined per search.

- websites of national institutions including the German Bundesinstitut für Risikobewertung (BfR), the Swedish Chemical Agency (KEMI), the Netherlands National Institute for Public Health and the Environment (RIVM), the French Institut national de l'environnement industriel et des risques (INERIS), the French national agency for food, environmental and occupational health and safety (ANSES), the UK Food Standards Agency;
- websites of interest groups such as Non-governmental organizations (NGOs) such as Food Packaging Forum, THINK Chemicals, ILSI Europe or Food Watch;
- websites of commercial labs such as Fera Science.

Search strategy

To devise a specific search strategy that is sufficiently sensitive to avoid missing literature, several lists of terms were created and combined according to Figure 2 and Table 3. The lists include groups of terms that are always connected with an 'OR' Boolean operator.

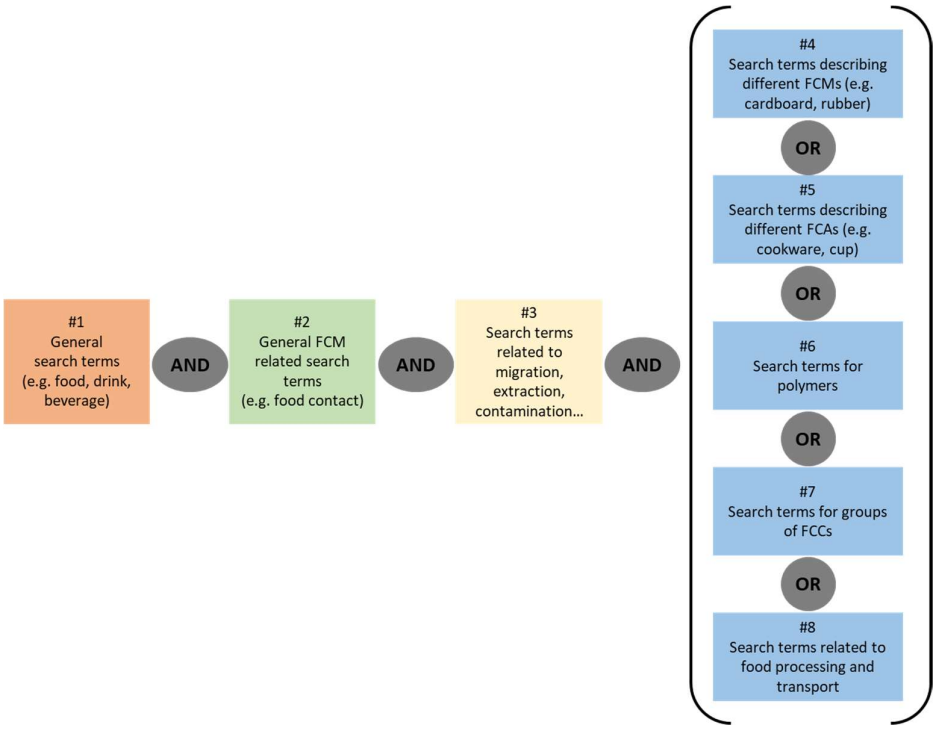

Figure 2. Overview of the search strategy for the Population Outcome. Detailed syntax for each search step is given in Table 3. Terms in each step are always connected with an 'OR' Boolean operator, while different steps are connected with 'AND'.

Searches #1-3 are based on groups of terms that are related to food/beverages, food contact and migration issues. Five lists of search terms were created describing different FCMs (#4), FCAs (#5), polymers (#6), groups of FCCs (#7) and terms that are related to food processing and transport equipment (#8). All individual search terms within one group were connected with an 'OR' Boolean operator. These 8 basic searches were subsequently combined according to the following search string: **#1 AND #2 AND #3 AND (#4 OR #5 OR #6 OR #7 OR #8)**

This search string will be applied in the databases PubMed, WoS and Scopus. Since slightly different rules apply for advanced searches in the single databases, we will modify the search terms accordingly. In WoS, lemmatization and stemming rules make individual searches for, e.g., the singular and plural

forms as well as the American and British English spellings of search terms unnecessary. Truncation of words will be used carefully and only in cases when most of the terms beginning with a given string of text are related to the search topic. Alternatively, additional frequent endings and spellings of some terms may be included separately, and a special focus will be placed on the plural forms. If supported by the database, proximity searches will be run to find some of the combined terms (e.g., chemical migration may be searched as chemical NEAR/x migration in WoS). If available, corresponding MeSH terms will be used in PubMed (e.g., for food packaging and food contamination).

Table 3: Search strategy for PO with detailed search terms and syntax for each search step.

Search number	Topic	Search terms/string
#1	General search terms	food OR drink OR beverage
#2	General FCM related search terms	"food contact" OR "food packaging" OR "food packing" OR packing OR packaging OR packaged
#3	Search terms related to migration, extraction, contamination	"chemical migration" OR "chemical analysis" OR contamination OR contaminant OR extraction OR extract OR extracted OR "food simulant" OR leaching OR leached OR migration OR migrated OR tenax OR transfer OR transferred OR detection OR detected
#4	Search terms describing different FCMs	"active material" OR "active packaging" OR adhesive OR aluminum OR board OR cardboard OR "carton board" OR cellulose OR ceramic OR coating OR cork OR elastomer OR enamel OR glass OR ink OR "intelligent material" OR "intelligent packaging" OR jute OR lacquer OR metal OR metallic OR multilayer OR nanocomposite OR paper OR paperboard OR plastic OR "printing ink" OR rubber OR silicone OR steel OR tinned OR tinplate OR varnish OR wood
#5	Search terms describing different FCAs	bottle OR cookware OR cup OR "food container" OR gasket OR jar OR "kitchen utensil" OR napkin OR plate OR film OR foil
#6	Search terms describing polymers	melamine OR PET OR PETE OR polyamide OR polycarbonate OR polyester OR polyethersulfone OR polyethylene OR polyolefin OR polypropylene OR PP OR polystyrene OR polyurethane OR polyvinyl OR PVC
#7	Search terms describing different groups of FCCs	additive OR oligomer OR pigment OR plasticizer OR stabilizer OR catalyst OR monomer OR "processing aid" OR antioxidant OR slimicide OR filler OR photoinitiator
#8	Search terms related to food processing and transport	"conveyor belt" OR pump OR hose OR grinder OR vat OR bag OR tank OR barrel OR tote OR “intermediate bulk container” OR IBC
#9	Final list of references	**#1 AND #2 AND #3 AND (#4 OR #5 OR #6 OR #7 OR #8)**

A simplified search strategy was developed for ScienceDirect, since the database only supports up to eight Boolean operators. Therefore, the following search string was developed and will be applied in Sciencedirect: (food OR beverage) AND migration AND ("food contact" OR "food packaging") AND (plastic OR glass OR metal OR paperboard). For Google Scholar a similarly simplified search strategy will be used.

Data management

Literature and all systematic review processes will be managed and coordinated with the support of the freely available online tool CADIMA established in a close collaboration between the Julius Kühn-Institut and the Collaboration for Environmental Evidence (https://www.cadima.info/index.php/area/evidenceSynthesisDatabase).

Relevance screening

The eligibility criteria will be applied to the reference list (i.e. the list of references identified in the literature searches) by two people working independently in parallel, each on one part of the reference list which will share a partial overlap with the other reference list. In the first stage, only titles and abstracts will be checked for relevance to the study questions. Clearly irrelevant studies will be excluded. In the second stage, the full text of the resulting list of included references after title/abstract screening may then be additionally examined for inclusion. The reasons for exclusion of studies after assessment of the full text will be recorded.

Multiple reports of the same research (e.g. multiple publications, conference abstracts etc.) will not be excluded but instead the methodological information from each of the reports shall be collated as part of the data recording process as one unit of evidence.

The CADIMA online tool facilitates the process of consistency checking by identifying disagreements between two evaluators. Disputes will be arbitrated and resolved by the project manager (J. Muncke). For quality control purposes, the percentage agreement between the two independent evaluators and kappa statistic will be reported.

Data recording

The data recording Excel template can be found in Supplementary Information. Briefly, the data recording database generated during this step will contain the following information:

- meta-data (authors, year, journal name or report number, title, abstract, funding…)
- study type: migration or extraction
- type of food, food simulant or solvent
- type of FCM and/or FCA
- chemical substance and level of confidence for its chemical identity

Oligomers without individual CAS numbers (up to Level 3 confidence for chemical identification, i.e. with tentative structures) will be reported as a group (Schymanski et al. 2015). All other chemicals that will be recorded will have at least Level 2 confidence of chemical identification.

The data recording workload will be distributed between at least two team members with some overlap to allow the evaluation of inter-rate reliability as a quality control measure. For the purpose of quality control, we aim for a 95% concordance in response between both data recording team members. Concordance will be monitored by a third team member. The data recording process will be managed using CADIMA which allows all team members to access the same data recoding file (e.g. the database) simultaneously from different locations.

Data analysis

The data recording database will contain the results of the literature search.

The first step for developing an overview of FCCs is to compile a database of globally known intentionally added FCCs (FCCdb 1.0), based on publicly available references like authorized substances lists. The FCCdb 1.0 is being developed as part of this project as a prerequisite, but not described in this protocol. Next, the systematic mapping described in this protocol will enable us to record substances that have evidence of migration or extraction from FCMs/FCAs; these substances will be included in the FCCdb 1.0, rendering a new version, FCCdb 2.0, of this database. This updated database (FCCdb 2.0) will hence contain intentionally added substances and/or substances that are known to migrate/be extractable from FCMs/FCAs.

Data treatment

The purpose of data analysis is to illustrate the available evidence. Using the databases (FCCdb 2.0 and data recording database), we will generate graphs, tables and interrogatable/interactive outputs with all relevant information and present relevant data using various software (like Tableau Software (https://www.tableau.com/, Excel etc.)

Assessment of the evidence:

1. How many chemicals have been found to migrate from FCAs?
2. How many chemicals have been found to be extractable from FCAs?
3. How many of the known intentionally used FCCs have been studied for migration or extractability?
   → FCCs known to be intentionally used (FCCdb 1.0) vs. FCCs ever studied for migration and/or extractability
4. How many non-intentionally added substances (NIAS) have been identified in migration/extraction studies?
   → FCCs with evidence for migration (detected "YES") not found among FCCs known to be intentionally used (FCCdb 1.0)
5. For which FCM type have most migration and extraction studies been performed and what were the differences among different FCM types in terms of frequency or numbers of chemicals detected?
   → FCC migration or extraction studies by type of FCM (e.g. plastics, glass, coated/uncoated metal, printed/unprinted paperboard, multilayer-multimaterial, wood, cork, silicone, ceramics)
6. For which type of FCA (e.g. packaging, processing equipment) have most migration or extraction studies been performed?
   → FCC migration or extraction studies by type of FCA (e.g. primary packaging, secondary packaging, kitchen ware, table ware, food processing equipment, storage containers, conveyor belts, filling lines)
7. What are the most frequently analyzed FCCs? Can they be grouped?
8. In what types of food (aqueous, acidic, alcoholic, fatty; wet, dry) have migration studies been done?
9. In what types of food simulant have migration studies been done?
10. In what types of solvents have extraction studies been done?
11. In which geographical areas has migration/extraction of FCCs been studied, and where did FCA samples originate from geographically?
12. Are there any trends?
13. Do substitution efforts become visible in the database?

Reporting

A full written report (in the form of a peer-reviewed scientific article) will be prepared to accompany the systematic map database to document the methods used in the mapping process in a transparent, objective and repeatable manner, and to make the study results available. The systematic map report will include all stages of the systematic mapping including the background and rationale for the systematic map, detail of the methodology, a description of the volume and characteristics of the

evidence base, recommendations for primary research based on knowledge gaps that have been identified, priorities and scope for future systematic reviews. Particular attention will be given to following existing reporting guidelines for systematic maps, such as the RepOrting standards for Systematic Evidence Syntheses (ROSES) guidelines (Haddaway et al. 2018).

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