Environment International 167 (2022) 107387

Contents lists available at ScienceDirect

Environment International

journal homepage: www.elsevier.com/locate/envint

Full length article

Evaluating the food safety and risk assessment evidence-base of polyethylene terephthalate oligomers: Protocol for a systematic evidence map

Verena N. Schreier [a,b,*], Christian Appenzeller-Herzog [c], Beat J. Brüschweiler [d], Birgit Geueke [e], Martin F. Wilks [a,b], Thomas J. Simat [f], Benoit Schilter [g], Martin Smieško [a,b], Jane Muncke [e], Alex Odermatt [a,b], Nicolas Roth [a,b]

[a] Department of Pharmaceutical Sciences, University of Basel, Basel, Switzerland
[b] Swiss Centre for Applied Human Toxicology (SCAHT), University of Basel, Basel, Switzerland
[c] University Medical Library, University of Basel, Basel, Switzerland
[d] Federal Food Safety and Veterinary Office (FSVO), Risk Assessment Division, Bern, Switzerland
[e] Food Packaging Forum Foundation, Zurich, Switzerland
[f] Chair of Food Contact Materials, Dresden University of Technology, Dresden, Germany
[g] Nestlé Institute of Food Safety and Analytical Sciences, Lausanne, Switzerland

ARTICLE INFO

Handling Editor: Adrian Covaci

Keywords:
Oligomer
Polyethylene terephthalate
Systematic evidence map
Health risk assessment
Hazard assessment
Toxicology

ABSTRACT

Background: Polyethylene terephthalate (PET) oligomers are ubiquitous in PET used in food contact applications. Consumer exposure by migration of PET oligomers into food and beverages is documented. However, no specific risk assessment framework or guidance for the safety evaluating of PET oligomers exist to date.
Aim: The aim of this systematic evidence map (SEM) is to identify and organize existing knowledge clusters and associated gaps in hazard and exposure information of PET oligomers. Research needs will be identified as an input for chemical risk assessment, and to support future toxicity testing strategies of PET oligomers and regulatory decision-making.
Search strategy and eligibility criteria: Multiple bibliographic databases (incl. Embase, Medline, Scopus, and Web of Science Core Collection), chemistry databases (SciFinder-n, Reaxys), and gray literature sources will be searched, and the search results will be supplemented by backward and forward citation tracking on eligible records. The search will be based on a single-concept PET oligomer-focused strategy to ensure sensitive and unbiased coverage of all evidence related to hazard and exposure in a data-poor environment. A scoping exercise conducted during planning identified 34 relevant PET oligomers. Eligible work of any study type must include primary research data on at least one relevant PET oligomer with regard to exposure, health, or toxicological outcomes.
Study selection: For indexed scientific literature, title and abstract screening will be performed by one reviewer. Selected studies will be screened in full-text by two independent reviewers. Gray literature will be screened by two independent reviewers for inclusion and exclusion.
Study quality assessment: Risk of bias analysis will not be conducted as part of this SEM.
Data extraction and coding: Will be performed by one reviewer and peer-checked by a second reviewer for indexed scientific literature or by two independent reviewers for gray literature.

Abbreviations: ADME, Absorption, distribution, metabolism, excretion; CAS RN, Chemical abstracts service registry number; DEG, Diethylene glycol; EG, Ethylene glycol; FCC, Food contact chemical; FCCmigex, Database on migrating and extractable food contact chemicals; FCM, Food contact material; IAS, Intentionally added substances; IPA, Isophthalic acid; IUPAC, International union of pure and applied chemistry; NIAS, Non-intentionally added substances; PBPK, Physiologically based pharmacokinetic modeling; PECOS, Population, exposure, comparator, outcome, and study type; PET, Polyethylene terephthalate; PK, Pharmacokinetics; SEM, Systematic evidence map; SMILES, Simplified molecular-input line-entry system; TIAB, Title and abstract; TK, Toxicokinetics; ToR, Terms of reference; TPA, Terephthalic acid.

* Corresponding author at: Division of Molecular and Systems Toxicology, Department of Pharmaceutical Sciences, Klingelbergstrasse 50, 4056 Basel, Switzerland.
E-mail addresses: verena.schreier@unibas.ch (V.N. Schreier), christian.appenzeller@unibas.ch (C. Appenzeller-Herzog), beat.brueschweiler@blv.admin.ch (B.J. Brüschweiler), birgit.geueke@fp-forum.org (B. Geueke), martin.wilks@unibas.ch (M.F. Wilks), thomas.simat@tu-dresden.de (T.J. Simat), benoit.schilter@rdls.nestle.com (B. Schilter), martin.smiesko@unibas.ch (M. Smieško), jane.muncke@fp-forum.org (J. Muncke), alex.odermatt@unibas.ch (A. Odermatt), nicolas.roth@unibas.ch (N. Roth).

https://doi.org/10.1016/j.envint.2022.107387
Received 14 March 2022; Received in revised form 22 June 2022; Accepted 29 June 2022
Available online 8 July 2022

Synthesis and visualization: The extracted and coded information will be synthesized in different formats, including narrative synthesis, tables, and heat maps.
Systematic map protocol registry and registration number: Zenodo: https://doi.org/10.5281/zenodo.6224302.

1. Introduction

Today's global production and the high demand for convenience food resulted in a majority of food being processed, stored, and packaged using food contact materials (FCMs) (Muncke and Snedeker, 2014). According to the current European legislation, FCMs include all materials and their respective articles intended to come into direct or indirect contact with food, such as transport containers, production machinery, packaging, or kitchen equipment (Commission Regulation (EU) No 10/2011; Regulation (EC) No 1935/2004). In Europe, plastic materials for food packaging represent one of the largest end-use markets, with polyethylene terephthalate (PET) accounting for 7.9% of the market in 2019 (Plastics Europe-Association of Plastics Manufactures, 2020). In the manufacturing of FCMs, several thousand chemical substances are used, the so-called intentionally added substances (IAS). In addition to IAS, FCMs also contain known and unknown non-intentionally added substances (NIAS). NIAS are usually formed as by-products or degradation products during the production, recycling, use of FCMs, or can be attributed to impurities in the starting materials used (Bauer et al., 2019; Franz and Welle, 2020; Geueke et al., 2014; Horodytska et al., 2020; Tsochatzis, 2021). The manufacturer of FCMs has the obligation to ensure the safety of these NIAS in accordance with Article 3 of the Framework Regulation ((EC) No 1935/2004) and Article 19 of the Plastics Regulation ((EU) No 10/2011) (Commission Regulation (EU) No 10/2011; Regulation (EC) No 1935/2004). However, compliance work of such NIAS is often challenging as they include a very large number and complex mixtures of substances whose chemical identity and toxicological properties are often unknown (Elsa et al., 2019; Hu et al., 2021; Sapozhnikova et al., 2021; Tsochatzis, 2021). In addition, there is yet no harmonized risk assessment framework, guidance for assessing the safety or clear recommendations for risk assessment of NIAS by food safety authorities/regulatory bodies worldwide. As a result, a migration limit of 0.01 mg/kg food is often applied to NIAS, as it is the practice for non-authorized chemicals. An exception to this are substances that are classified as carcinogenic, mutagenic, or toxic to reproduction (CMR substances) (Bauer et al., 2019; Commission Regulation (EU) No 10/2011; Geueke, 2018). In the absence of clear regulatory guidance and due to the complex nature of NIAS, several industry associations have published guidance documents whose chemical risk assessment is based on the collection and generation of hazard and exposure information using a variety of tools and approaches. Among these are standard toxicological assessment of individual substances and mixtures, the use of *in silico* and read-across approaches, and the concept of threshold of toxicological concern (TTC) to assess the safety of substances of unknown toxicity but no expected genotoxicity. Exposure is usually estimated using migration levels that can be either experimentally determined or modeled (Antunovic et al., 2012; Bolognesi et al., 2016; Geueke, 2018; "ILSI / Guidance on Best Practices on the Risk Assessment of Non Intentionally Added Substances (NIAS) in Food Contact Materials and Articles").

One group generally treated as NIAS are the oligomers from (plastic/polymer) FCMs. To date, however, it has not been clarified how oligomers are to be defined and which substances are to be categorized as such. In literature, oligomers are usually described as substances that consist of two or more monomer units of their respective polymers (Begley et al., 1990; Biedermann and Grob, 2006; Brenz et al., 2018; Hoppe et al., 2018; Mutsuga et al., 2008; Pietropaolo et al., 2018; Ubeda et al., 2019). Particular attention is paid to compounds with a molecular weight below 1000 Da, since substances >1000 Da are generally considered to be poorly absorbed by the body and the potential health risk is minimal (Commission Regulation (EU) No 10/2011). The formation of oligomers is an unavoidable process in the production of plastic FCMs. As a result, all plastic FCMs contain oligomers to some extent, and these substances could even be considered as polymer-specific concomitants (Hoppe et al., 2016). The omnipresence of oligomers in plastic FCMs makes these substances of great concern because, as potential migrating chemicals, they could be harmful to consumer health. Due to their smaller size, oligomers are of higher toxicological relevance than polymers. However, to date, very few *in silico*, *in vitro*, and *in vivo* toxicity data are available for oligomers. So far, safety assessment of oligomers has not been given high priority and was often performed based on data available for monomers, assuming complete hydrolysis of the oligomers (Nelson et al., 2011). This assumption is scientifically questionable, since not all oligomers contain hydrolysable bonds or have different hydrolysis kinetics. More experimental evidence of hydrolysis and its kinetics is needed before categorically excluding any relevance of a safety evaluation of polymer-specific oligomers.

One very commonly used FCM is the polyester material PET. Its oligomers are known to transfer into food, resulting in consumer exposure (Alberto Lopes et al., 2021; Begley et al., 1990; Castle et al., 1989; Hoppe et al., 2017; Mutsuga et al., 2007; Tsochatzis et al., 2020a). In the recent years, first efforts have been made to assess the safety of PET oligomers or polyester oligomers in general. The European Food Safety Authority (EFSA) has published scientific opinions and concluded, following the guidance document for plastic FCMs, that no safety concerns are expected at a total migration of oligomers of less than 0.05 mg/kg food from the polyester materials polyethylene furanoate (PEF) and a spiroglycol (SPG)-modified PET (EFSA, 2014a, 2014b; Silano et al., 2008). The Joint Research Centre (JRC) of the European Commission (EC) and collaborators have published several studies on the analysis, quantification, and evaluation of oligomers from the polyester plastics, including PET (Alberto Lopes et al., 2021; Tsochatzis, 2021; Tsochatzis et al., 2020a, 2020b, 2019). Their study on coffee capsules showed that some capsules exceeded total migration value of 0.05 mg/kg. This raises the question of how to judge the elevated migration levels of PET oligomers and if this poses a health risk to consumers. The authors also call for the need for a more harmonized approach to risk assessment in order to evaluate oligomers in a meaningful way (Alberto Lopes et al., 2021). In addition to the lack of risk assessment guidance, regulatory actions focused mainly on migration, and thus on the exposure component, resulting in a large knowledge gap in hazard assessment.

The identification and characterization of oligomers is very challenging, due to their size, number, complexity in structure, existence in broad mixtures, and frequent lack of analytical standards. Therefore, not all PET oligomers, especially the isomeric substances, are fully characterized or yet identified. PET oligomers lack a harmonized nomenclature and most PET oligomers are not commercially available. This hampers risk assessment activities, as well as the generation of regulatory-relevant and useful hazard and exposure information. In turn, these knowledge gaps negatively impact the development of specific regulation and guidance for the safety assessment of PET oligomers. Altogether, these issues represent major challenges in the field. PET oligomers can be considered emerging contaminants and data-poor chemicals. Information on PET oligomers for use in regulatory risk assessment is scarce. Utilized information for chemical/mixture risk assessment can be: (i) data for use in hazard assessment, incl. physicochemical properties, toxicology, and mode of action information; and (ii) data for use in exposure assessment, incl. external exposure data (e.g., sources, routes) and internal exposure data (absorption, distribution, metabolism, excretion/toxicokinetics/pharmacokinetics (ADME/TK/

PK)), either measured (e.g., environmental or biomonitoring studies) or modeled (e.g., physiologically based pharmacokinetic (PBPK) modeling).

Accordingly, there is a need to identify all existing scientific information that is relevant to the safety evaluation of PET oligomers, as well as corresponding gaps in the science and regulatory evidence-base. To the best of the authors' knowledge, there has not been any attempt yet to systematically characterize the hazard and exposure evidence-base of PET oligomers for use in a food safety and risk assessment context. Among existing evidence synthesis methods, systematic evidence maps (SEMs) are effective tools for mapping broad research topic areas, exploring the nature of the evidence base, identifying and cataloging research clusters and gaps, and for knowledge consolidation. They typically take the form of a visual figure or graph (e.g., plot, heat map) or of an interactive, searchable (online) database (Miake-Lye et al., 2016). Evidence mapping is establishing itself as the method of choice to identify, organize, compare, and analyze information for use in broad chemical risk assessment and management contexts, to support evidence-based decision-making and policy (James et al., 2016; Keshava et al., 2020; Pelch et al., 2019; Wolffe et al., 2020, 2019).

The present work reports a protocol for a SEM. The choice of the method was justified by: (i) a broad and exploratory research question; (ii) the need to get an overview on the regulatory status of PET oligomers; (iii) the need to identify the nature and the extent of the toxicological/environmental health evidence-base; (iv) the need to assess the relevance of the evidence-base for use in risk assessment; (v) the need to identify knowledge gaps and research needs to orientate future research and to support regulatory decision-making.

2. Objectives

The overall objective of this SEM is to map the existing hazard and exposure information related to oligomers derived from PET in food contact application, to support future chemical risk assessment activities. The work follows up on a series of publications that have identified a number of scientific and regulatory challenges for food contact chemicals (FCCs), in particular the need to compile existing information on NIAS (i.e., information on chemical identity, migration, hazard, and exposure), and to develop strategies and work plans to fill data gaps, to facilitate the safety assessment of NIAS (Franz and Welle, 2020; Muncke et al., 2020, 2017; Nerin et al., 2013).

Specific objectives are the following:

- Identify and map the available literature on hazard and exposure for 34 PET oligomers (see Table 3), present as single molecules or mixtures, measured in humans, animals, organisms, *ex vivo*, *in vitro*, or *in silico* models.
- Identify and map areas of uncertainty and knowledge gaps in the hazard and exposure evidence-base for 34 PET oligomers.
- Make recommendations for future research and chemical risk assessment activities, including toxicity testing and exposure assessments, to support regulatory decision-making.
- Publish results of the SEM and related recommendations.

Since we aim to explore *a priori* a data-poor environment, we do not plan at this stage to make the results available in an online database, but to visualize the outcome of the SEM based on a graphical and table-format representation. As the project develops and data become more available in the future, we will update the map accordingly, and consider displaying the results in an interactive online database. The SEM is planned to be completed and submitted for peer-review by December 2022.

3. Planning

This protocol was prepared using the Preferred Reporting Items for Systematic Reviews and Meta-analysis Protocols (PRISMA-P) guideline according to the methodology for systematic evidence maps (Moher et al., 2016). In case of updates to the search strategies or changes to the protocol, the changes will be noted as modifications to the registered protocol in the final publication. As part of planning, a rapid scoping exercise was conducted to inform the whole problem formulation stage, and the further development of the SEM protocol.

3.1. Review team, advisory group, and sponsor

In the early stages of planning, core project partners (VNS, AO, BJB) identified a pool of subject matter experts in the topic of interest willing to contribute to the work, either as members of the research team (i.e., acting as reviewers and co-authors), or as members of the advisory group (i.e., acting as advisors only). The goal was to ensure a broad scientific representation of partners from academia, industry, regulatory authorities, and non-governmental organizations, in Switzerland and possibly abroad, with multidisciplinary expertise in materials and food safety sciences, biochemistry, chemistry, toxicology, human health risk assessment, environmental health, information sciences, and research synthesis methods. A Terms of Reference (ToR) document (**Supplemental File 1**) was developed by the lead authors (NR, VNS) to establish the roles and responsibilities of the different partners (i.e., reviewers, advisors, and sponsor) involved in the project, and the modalities of their interaction over the entire project duration. The ToR is meant as a guiding aid to support planning as well as to facilitate the development and implementation of an efficient project communication and management strategy. We followed the *Cochrane Handbook Guidance for establishing and managing Review Advisory Groups* (Higgins et al., 2021), the International Committee of Medical Journal Editors (ICMJE) criteria for authorship, and referred to COSTER (Whaley et al., 2020) and Hoffmann et al. (2017) to help us establish roles and responsibilities. The ToR was shared with and agreed on by all project partners, and their respective roles and responsibilities are briefly detailed in the next sections.

3.1.1. Review team

Authors will contribute their respective different field of expertise to the development of the protocol and conduct of the SEM, as summarized in Table 1.

The core review team (CAH, NR, VNS) will be involved in all stages of the SEM. CAH will support all activities related to information sciences. NR supervises the SEM. VNS is the guarantor of the SEM, and is responsible for the overall scientific integrity of the work as well as for developing and implementing an efficient communication and project management strategy. VNS will coordinate and share the various inputs from the advisors and the sponsor with the research team. AO, BG, BJB, BS, JM, MFW, MS, and TJS will be involved in various activities related to the development, writing and publishing of the SEM protocol and SEM, including conceptualization, visualization, and writing – review & editing, in accordance with their respective areas of expertise (Table 1).

3.1.2. Advisory group

An advisory group was constituted to have a broader stakeholder representation with specific expertise bridging material and food safety science and regulatory chemical risk assessment, which is constituted by the three following members: Dr. Frank Welle, Product Safety and Analytics, Fraunhofer Institute for Process Engineering and Packaging (IVV), Freising, Germany; Dr. Koni Grob, retired from Kantonales Labor Zürich (Official Food Control Authority of the Canton of Zurich), Zurich, Switzerland; Dr. Rüdiger Helling, Saxon State Ministry of Social Affairs and Consumer Protection, Dresden, Germany. The advisory group gave input during planning and scoping to support the research team strategically in identifying relevant background information (e.g., gray literature sources, risk assessment, and regulatory activities on the topic), and contributing to shaping the research project general aims and

Table 1
Review team and the different fields of expertise.

Field of expertise	List of SEM reviewers and authors										
	VNS	***CAH***	***BJB***	***BG***	***TJS***	***BS***	***MS***	***JM***	***MFW***	***AO***	***NR***
Materials & food safety sciences			X	X	X	X		X			
Biochemistry	X	X				X				X	
Analytical chemistry	X				X					X	
Organic chemistry	X				X						
Molecular biology	X	X				X				X	
Toxicology	X		X			X			X	X	X
Computational pharmacology & toxicology						X	X				
Human health risk assessment & regulatory toxicology			X			X			X		X
Environmental health				X				X	X	X	X
Research synthesis methods		X							X		X
Information science		X									

objectives. The advisory group will support the research team at the strategical level during the entire project duration, contribute to the interpretation of the findings, as well as with the dissemination of the project outcome to the broader stakeholder community. Advisors will not take part in the technical/operational conduct of the work. The guarantor of the review (VNS) will be responsible for coordinating with the advisory group and implementing an efficient and transparent communication between the review team and the advisors.

3.1.3. Sponsor

Funding is provided by the Swiss Federal Food Safety and Veterinary Office (FSVO), a governmental organization acting as main sponsor of the work (contract number 0714001652). FSVO acted in an advisory capacity at the outset of the project, during *planning*, for orientation and prioritization purposes. The sponsor will have no involvement in the conduct of the work, in particular during *scoping* and *framing;* and in the development of the SEM protocol; in the writing of the manuscript; and in the decision to submit the manuscript for publication. The sponsor will be involved once the work is completed, i.e., after the actual SEM has been published, to ensure outcome dissemination. The SEM guarantor (VNS) will keep the sponsor updated with regard to timeframe and resources as the project develops.

The sponsor will be represented by Dr. Gérard Gremaud, Head of the Research Platform, Swiss Federal Food Safety and Veterinary Office, Bern, Switzerland.

3.2. Scoping exercise

We initially checked if there are ongoing systematic reviews or maps on the topic of PET oligomers. Databases commonly used for registration of SEM protocols were searched using the search term "oligomer", "polyethylene terephthalate", and "PET", as single words or in combination. The following databases were searched: PROSPERO (https://www.crd.york.ac.uk/prospero/), Open Science Framework Registry (https://osf.io/registries), and Zenodo (https://zenodo.org/). Also, MEDLINE and Web of Science were searched using the key words: "oligomer", "polyethylene terephthalate", "PET", and "systematic map", or "evidence map". No previously existing or ongoing systematic review or map on PET oligomers was found.

The aim of the scoping exercise was to get a sense of the topic and on the literature available, clarify the conceptual boundaries, identify the breadth and depth of analysis required, facilitate the setting up of a research team, and explore further aspects related to resources, timeframe, and feasibility. Scoping is part of problem formulation, which can be defined as "a systematic approach that identifies all factors critical to a specific risk assessment and considers the purpose of the assessment, scope and depth of the necessary analysis, analytical approach, available resources and outcomes, and overall risk management goal" (Solomon et al., 2016). Scoping is therefore pivotal in SEM and systematic reviews for prioritizing the type of information required for use in a hazard/risk assessment context, e.g., in deciding which theoretical elements to include *a priori* to answer the question(s) of interest, and how this knowledge will be used in the overall assessment (Roth et al., 2020). To this end, a targeted strategy was developed and implemented stepwise, combining two approaches: (i) stakeholder engagement; and (ii) exploration of a FCC database (Geueke et al., 2022). The scoping exercise was conducted between March and December 2021.

3.2.1. Consultation process

Input was initially collected through consultation with a multidisciplinary pool of experts from academia (University of Basel, Dresden University of Technology), industry (Nestlé, Swiss Quality Testing Services), regulatory authorities (Swiss Federal Food Safety and Veterinary Office, German Federal Institute for Risk Assessment), research organizations (Fraunhofer Institute, EC Joint Research Centre, Kantonales Labor Zürich (Official Food Control Authority of the Canton of Zurich)), and non-governmental, non-profit organizations (Food Packaging Forum, Swiss Centre for Applied Human Toxicology).

3.2.2. In particular, the consultation process allowed us to

(I) Identify relevant regulatory risk assessment activities, technical documents, and key scientific publications on PET oligomers that were used as seed references for orientation purposes (Alberto Lopes et al., 2021; Brenz et al., 2021; Tsochatzis et al., 2020b). The references identified during the expert consultation provided an initial overview of the state of knowledge regarding the chemical identity of PET oligomers, important research activities in the field of chemical analysis, and a first insight into knowledge gaps and needs regarding the toxicological evaluation of PET oligomers. In a second step, the seed references were searched manually for relevant references and sources to further inform scoping and framing, in particular identification and prioritization of the PET oligomers of interest. An important concept identified in the consultation phase is hydrolysis. The term hydrolysis is in our SEM defined as a process that causes cleavage of ester bonds by addition of water during contact of PET oligomers with food/beverages or via physiological mechanisms after ingestion of PET oligomers. The hydrolytic cleavage of these ester bonds leads to a change in the composition of the PET oligomers and therefore strongly influences the exposure. This phenomenon has already been observed with PET oligomers and is therefore considered an important information for chemical risk assessment (Eckardt et al., 2019). Migration of chemicals into food and beverages is a commonly used method to support and estimate oral exposure and is therefore a relevant study concept in this SEM. Other specific information relevant to the safety assessment of PET oligomers was also identified during the consultation process; the information collected is summarized in Table 2.

Table 2
Information characteristics and prioritization needs for use in chemical risk assessment. Summary of the category and type of information and its population, exposure, comparator, outcome, and study type (PECOS) component is represented. The PECOS statement of this SEM is summarized in Table 4.

Category	Type/nature	PECOS
Stressor	Chemical identity, physico-chemical properties, and chemical stability of PET oligomers.	E
Hazard	Toxicology, toxicodynamics, bioactivity and mode of action.	P, O
Exposure	External exposure pathways (sources, routes, migration) and internal exposure pathways (physiological processes, ADME/TK/PK).	E

(II) Identify relevant gray literature sources. In the context of chemical risk assessment and management, the gray 'regulatory toxicology' literature typically covers information relevant to hazard and exposure assessment. It contributes also to inform on research activities, technical developments, as well as science and policy gaps in relation to the specific context of the risk assessment. Therefore, the gray 'regulatory toxicology' literature constitutes a crucial entry portal to the scientific and regulatory literature when conducting chemical risk assessment. This type of information is covered in technical reports such as risk assessments, scientific opinions, research reports, white papers, unpublished government reports, etc. produced by (non-) government or research organizations whose primary activity is not publishing. These documents are in general publicly available and can be accessed in specific online databases or repositories hosted by these organizations. However, this information can be difficult to locate in gray literature sources like GreyNet or OpenGrey, because it is often largely invisible, with the indexed scientific literature overwhelmingly dominating the search results (Bramer et al., 2017; Corlett, 2010; Haddaway et al., 2015; Mahood et al., 2014). Gray literature information sources include a number of regulatory toxicology databases and websites from vetted research or regulatory organizations at international (OECD, FAO, WHO), regional (U.S. and Canada, E.U., Australasia), and national (E.U. Member States) level; as well as non-governmental, non-profit organizations (NGOs), which play a key role in chemical safety regulation, human health risk assessment, food and consumer safety, public health and environmental health. The complete list of gray literature sources being used in this SEM is given under search strategy **section 5.3**.

3.2.3. *FCCmigex database*

In addition to identifying multiple PET oligomers during the consultation phase, prioritization of all PET oligomers for inclusion in the SEM was supported by a search of the FCCmigex database (https://www.foodpackagingforum.org/fccmigex; unpublished version) (Geueke et al., 2022; Martin et al., 2018). The objective of the evidence map associated with the database was to collect information on all chemicals, both IAS and NIAS, identified in migration or extraction studies with food contact materials and articles. According to the inclusion criteria and search strategy, PET and their respective oligomers are also covered. It was therefore decided that the FCCmigex is an important source to collect data on PET oligomers, including chemical structures and migration-related data. For this reason, the FCCmigex database was searched to identify PET oligomer-relevant literature that can be used to prioritize PET oligomers for the SEM. The database searches, screening, selection, and extraction process was conducted by a single reviewer (VNS), and is documented in the supplementary material **section S1**. In general, the identification and characterization of oligomers is challenging and often must be done without reference standards to confirm the structure (Alberto Lopes et al., 2021). However, to include not only PET oligomers confirmed via reference standard, which is a fraction of oligomers, a compromise was made. Molecules

Table 3
List of PET oligomers included in the systematic evidence map. Chemical structure information and identifiers, including the categories from the chemical tree (Fig. 1), acronyms, CAS RN, and source of information. Abbreviations: TPA (terephthalic acid, CAS RN 100-21-0), IPA (isophthalic acid, CAS RN 121-91-5), EG (ethylene glycol, CAS RN 107-21-1), DEG (diethylene glycol, CAS RN 111-46-6), C (cyclic), and L (linear).

Oligomer category name	Acronym-based abbreviation	CAS RN	Source of information
First series cyclic dimer + IPA	C[TPA + EG] + [IPA + EG]		FCCmigex,(Brenz et al., 2021)
First series cyclic trimer + IPA	C[TPA + EG]2 + [IPA + EG]	536746-07-3	FCCmigex,(Brenz et al., 2021)
First series cyclic tetramer + IPA	C[TPA + EG]3 + [IPA + EG]		FCCmigex,(Brenz et al., 2021)
First series cyclic pentamer + IPA	C[TPA + EG]4 + [IPA + EG]		FCCmigex,(Brenz et al., 2021)
Second series cyclic dimer + IPA	C[TPA + EG] + [IPA + DEG]		FCCmigex,(Brenz et al., 2021)
First series linear monomer	L[TPA + EG]	1137-99-1	FCCmigex,(Brenz et al., 2021)
First series linear monomer + TPA	L[TPA + EG] + TPA	2225-05-0	FCCmigex,(Brenz et al., 2021)
First series linear monomer + EG	L[TPA + EG] + EG	959-26-2	FCCmigex,(Brenz et al., 2021)
First series linear dimer	L[TPA + EG]2	23186-89-2	FCCmigex,(Tsochatzis et al., 2020b)
First series linear dimer + TPA	L[TPA + EG]2 + TPA	1855-25-0	FCCmigex,(Brenz et al., 2021)
First series linear dimer + EG	L[TPA + EG]2 + EG	2144-69-6	FCCmigex,(Brenz et al., 2021)
First series linear trimer	L[TPA + EG]3	16958-96-6	FCCmigex
First series linear trimer + TPA	L[TPA + EG]3 + TPA	122295-57-2	FCCmigex,(Brenz et al., 2021)
First series linear trimer + EG	L[TPA + EG]3 + EG	16033-73-1	FCCmigex,(Brenz et al., 2021)
First series linear tetramer + EG	L[TPA + EG]4 + EG	34298-51-6	FCCmigex
First series cyclic monomer	C[TPA + EG]	7337-79-3	FCCmigex
First series cyclic dimer	C[TPA + EG]2	24388-68-9	FCCmigex,(Alberto Lopes et al., 2021; Tsochatzis et al., 2020b)
First series cyclic trimer	C[TPA + EG]3	7441-32-9	FCCmigex,(Alberto Lopes et al., 2021; Brenz et al., 2021; Tsochatzis et al., 2020b)
First series linear tetramer	C[TPA + EG]4	16104-96-4	FCCmigex,(Alberto Lopes et al., 2021; Brenz et al., 2021; Tsochatzis et al., 2020b)
First series cyclic pentamer	C[TPA + EG]5	16104–97-5	FCCmigex,(Alberto Lopes et al., 2021; Brenz et al., 2021; Tsochatzis et al., 2020b)26,35,49
	C[TPA + EG]6	29644-29-9	FCCmigex,(Alberto Lopes et al., 2021; Brenz et al.,

(*continued on next page*)

Table 3 (*continued*)

Oligomer category name	Acronym-based abbreviation	CAS RN	Source of information
First series cyclic hexamer			2021; Tsochatzis et al., 2020b)
First series cyclic heptamer	C[TPA + EG]7	29668-12-0	FCCmigex,(Alberto Lopes et al., 2021; Tsochatzis et al., 2020b)
First series cyclic octamer	C[TPA + EG]8	42245-76-1	FCCmigex
Second series linear monomer	L[TPA + DEG]	65087-23-2	FCCmigex,(Brenz et al., 2021)
Second series linear monomer + EG	L[TPA + DEG] + EG	65133-69-9	FCCmigex
Second series linear dimer	L[TPA + EG] + [TPA + DEG]	2222639-12-3	FCCmigex,(Tsochatzis et al., 2020b)
Second series cyclic dimer	C[TPA + EG] + [TPA + DEG]	29278-57-7	FCCmigex,(Brenz et al., 2021; Tsochatzis et al., 2020b)
Second series cyclic trimer	C[TPA + EG]2 + [TPA + DEG]	873422-64-1	FCCmigex,(Brenz et al., 2021; Tsochatzis et al., 2020b)
Second series cyclic tetramer	C[TPA + EG]3 + [TPA + DEG]	2222729-29-3	FCCmigex,(Brenz et al., 2021; Tsochatzis et al., 2020b)
Second series cyclic pentamer	C[TPA + EG]4 + [TPA + DEG]		FCCmigex,(Brenz et al., 2021; Tsochatzis et al., 2020b)
Second series cyclic hexamer	C[TPA + EG]5 + [TPA + DEG]		FCCmigex
Third series cyclic dimer	C[TPA + DEG]2	16104-98-6	FCCmigex,(Tsochatzis et al., 2020b)
Third series cyclic trimer	C[TPA + EG] + [TPA + DEG]2		FCCmigex,(Tsochatzis et al., 2020b)
Fourth series cyclic tetramer	C[TPA + EG] + [TPA + DEG]3		FCCmigex

were selected if they fulfilled the following inclusion/exclusion criteria:

- The source of oligomers must be PET.
- Molecules consisting of at least two monomers: one diacid and one diol.
- The oligomers must be PET-specific and therefore consist of the monomeric units terephthalic acid and ethylene glycol, but potential co-monomer additions or impurities with isophthalic acid were also considered. Oligomers containing diethylene glycol modifications were also included.
- An unambiguously defined structure must be assignable. Molecules that were classified as "tentative" or "probable" were excluded.
- For oligomers with multiple possible isomeric forms, the identified isomers must be defined.
- No limitations in molecular weight were applied.

If it was not clear whether the predefined criteria for a molecule from a publication applied, the authors were contacted for confirmation. For one study, the authors were contacted for clarification on the interpretation of the acronyms and assignment/identification of the isomers. The authors' response resolved the situation and the molecules in question did not meet the inclusion criteria for unambiguous structure or isomer identification.

3.2.4. Prioritized PET oligomers

With the help of the identified literature during the scoping exercise, the following 34 PET oligomers were eligible for inclusion and prioritized for this SEM (Table 3):

During the scoping exercise, we noticed that there are no consistent names for PET oligomers in the literature reported. Acronym-based abbreviations are often used to describe these molecules, which can vary depending on the source or are not clearly defined. It can therefore be very difficult and time-consuming to translate these into a chemical structure. In addition, only a few molecules have commonly used names and International Union of Pure and Applied Chemistry (IUPAC) names can be extremely complex and not easy to understand, making their use usually impractical (Supplemental **Table S1**). More unique chemical identifiers such as chemical structures, Chemical Abstracts Service Registry Number (CAS RN), or Simplified Molecular-Input Line-Entry System (SMILES) are rarely used in literature. In order to identify available information and have consistent and universal identifiers for all oligomers, all PET oligomers were assigned additional information about their chemical identifiers, including SMILES and CAS RN, whenever possible by performing a structure-based search in SciFinder-n. For molecules without a database entry in SciFinder-n, SMILES strings were generated with the help of ChemDraw 20.1 (Table 3 and Supplemental **Table S1**).

In general, PET-specific oligomers are chemically build up by connecting the monomer terephthalic acid (TPA, CAS RN 100-21-0) and ethylene glycol (EG, CAS RN 107-21-1) via ester bonds in a repetitive manner, leading to the so-called "first series" oligomers (Ubeda et al., 2018). TPA can be replaced by isophthalic acid (IPA, CAS RN 121-91-5), which can be used as a co-monomer in the production process (Brenz et al., 2021). One EG being replaced by one diethylene glycol (DEG, CAS RN 111-46-6), or two EG being replaced by two DEG, result in the so-called "second or third series" of oligomers, respectively (Ubeda et al., 2018). The molecule with three DEG was previously not categorized, but in accordance with the logical order for the other groups, assigned as "fourth series" in this SEM. As an easy-to-read identifier, one type of acronym-based abbreviation was extracted from literature or was applied accordingly if not available (Brenz et al., 2021). The acronym-based abbreviation starts with C for cyclic or L for linear, which corresponds to a cyclic or linear molecule. A unit consisting of a diacid terephthalic acid (TPA) or isophthalic acid (IPA) and a diol ethylene glycol (EG) or diethylene glycol (DEG) is shown in parentheses. The diacids and diols are alternately linked by ester bonds. The number of one unit type is represented by the number after the parentheses. Different units can also be connected by a "+" sign (Table 3). The hierarchical relationship of the PET oligomers is represented in Fig. 1.

4. Information sources

4.1. Bibliographic databases

Potentially relevant indexed scientific literature will be identified by searching in the following bibliographic databases:

- **Embase**

This biomedical and pharmacological database contains more than 30 million records and has a very good coverage of drug research, pharmacology, and toxicology.

- **Ovid MEDLINE**

This database has over 33 million biomedical and life sciences records, and has an excellent coverage of human toxicology studies.

- **Scopus**

This abstract and citation database is covering a broad range of publications and peer-reviewed journals across a wide variety of disciplines.

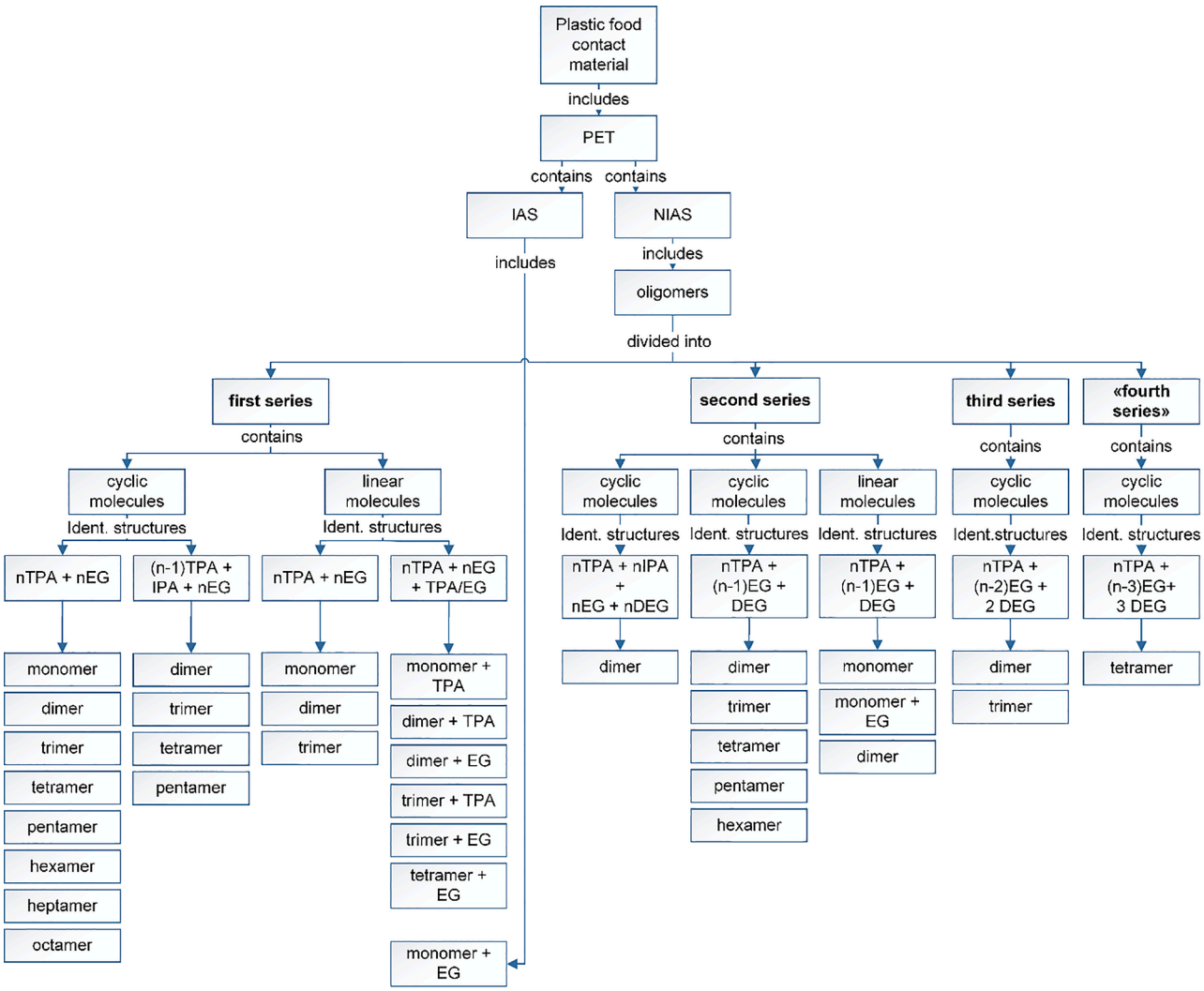

Fig. 1. Overview and chemical tree of the 34 PET oligomers prioritized for inclusion in the SEM. Abbreviations: TPA (terephthalic acid, CAS RN 100-21-0), IPA (isophthalic acid, CAS RN 121-91-5), EG (ethylene glycol, CAS RN 107-21-1), DEG (diethylene glycol, CAS RN 111-46-6). "n" represents the number of units of the individual oligomers. For the monomer n = 1, dimer n = 2, trimer n = 3, tetramer n = 4, pentamer n = 5, hexamer n = 6, heptamer n = 7, octamer n = 8. The identified isomer of the linear second series dimer is specified in Supplemental **Table S1**. By searching the FCCdb database (Groh et al., 2020), only the molecule "monomer + EG" (category nTPA + nEG + EG) could be assigned as an IAS, therefore all other oligomers were categorized as NIAS.

- **Web of Science Core Collection (WoS)**

This database is a major cross disciplinary database covering scientific publications in agricultural, biological, and environmental sciences, engineering, technology, applied science, medical and life sciences, and physical and chemical sciences.

The combination of the Embase, Medline, and WoS bibliographic databases is widely used in the toxicology/risk assessment/environmental health fields. It is considered as a combination that provides adequate coverage (Bramer et al., 2017; Gehanno et al., 1998; Masic and Milinovic, 2012). The additional search via Google Scholar can even increase coverage, but it is also debatable as to whether Google Scholar is suitable for systematic searches (Bramer et al., 2017; Gusenbauer and Haddaway, 2020). It was therefore decided to conduct a search without the inclusion of Google Scholar, but to include the large cross-disciplinary database Scopus instead.

4.2. Chemistry databases

Potentially relevant chemical literature will be identified by searching in the following chemistry databases:

- **SciFinder-n**

This database is one of the most comprehensive databases for chemical literature covering literature from chemistry, biochemistry, chemical engineering, materials science, nanotechnology, physics, environmental science, and other science and engineering disciplines. It is a core tool for identifying chemical substances and their related chemical structures, chemical names, regulatory information, properties, and CAS RN.

- **Reaxys**

This database is an expert-curated chemistry database for the identification of chemistry information and data from published literature, including journals and patents. It is a leading database for bioactivity data.

SciFinder-n and Reaxys are not typically databases used for systematic searches. However, given that PET oligomers have poorly defined names, these databases are considered important additional sources of information on chemical data and bioactivities by allowing name-independent searches by structure and CAS RN.

4.3. Gray literature

In line with our research objectives, we aim to identify documents in the gray (regulatory) literature available from vetted government agencies and scientific organizations that have covered the topic of PET oligomers in a hazard/risk assessment context. As described in **section 3.2**, these organizations play a key role in assessing and/or regulating chemicals and emerging contaminants to protect human health (general population, consumers, workers) from harmful chemical exposures. For example, in the US, food safety issues fall under the remits of the USFDA, in Europe it is EFSA. The E.U. scientific committee SCHEER covers emerging contaminants in a non-food context, whereas JECFA and the Codex Alimentarius cover food contaminants at international level. Regulatory toxicology literature includes e.g. technical reports, risk assessments, scientific opinions, position statements, white papers, and unpublished governmental research. The identification and prioritization of relevant gray literature sources was informed by: (i) the expert consultation process between the research team and the advisors; (ii) best practice recommendations in the field (Haddaway et al., 2015; Paez, 2017); and (iii) the authors own experience and best professional judgment.

Prioritized regulatory toxicology databases from vetted (non-) government scientific or regulatory organizations websites:

International level

- OECD, Organisation for Economic Co-operation and Development, http://www.oecd.org/
- Codex, Joint Food and Agriculture Organization of the United Nations (FAO) and the World Health Organization (WHO) Codex Alimentarius, http://www.fao.org/fao-who-codexalimentarius/en/
- INCHEM, Chemical Safety Information from Intergovernmental Organizations database, International Programme on Chemical Safety, http://www.inchem.org
- JECFA, Joint FAO/WHO Expert Committee on Food Additives, http://www.fao.org/food/food-safety-quality/scientific-advice/jecfa/en/

Regional level - Europe

- European Commission, https://ec.europa.eu/commission/index_en
- JRC, Joint Research Centre (JRC) of the European Commission, https://ec.europa.eu/jrc/en
- ECHA, European Chemicals Agency, http://www.echa.europa.eu
- EFSA, European Food Safety Authority, http://www.efsa.europa.eu
- SCCS, Scientific Committee on Consumer Safety, https://ec.europa.eu/health/scientific_committees/sccs_en
- SCHEER, Scientific Committee on Health, Environmental and Emerging Risks, https://ec.europa.eu/health/scientific_committees/scheer_en

Regional level - U.S.

- NIEHS, National Institute of Environmental Health Sciences, http://www.niehs.nih.gov
- FDA, U.S. Food & Drug Administration, http://www.fda.gov
- U.S. Science.gov Alliance Interagency, https://www.science.gov
- NTP, National Toxicology Program, https://ntp.niehs.nih.gov/
- PubChem, https://pubchem.ncbi.nlm.nih.gov/

Regional level - Canada

- Health Canada, https://www.canada.ca/en/health-canada.html

Regional level - Australasia

- New Zealand Food Safety, https://www.mpi.govt.nz/nzfoodsafety/
- Australia Food Safety, http://www.foodstandards.gov.au

National level - European Member States

- BfR, German Federal Institute for Risk Assessment, http://bfr.bund.de
- Anses, French Agency for Food, Environmental and Occupational Health & Safety, http://www.anses.fr
- UK Food Safety, http://www.food.gov.uk
- Danish Environment & Food Ministry, https://en.mfvm.dk/
- NVWA, Netherlands Food and Consumer Product Safety Authority https://english.nvwa.nl/
- RIVM, Dutch National Institute for Public Health and the Environment, https://www.rivm.nl/

Non-governmental organizations (NGOs)

- Food Packaging Forum, https://www.foodpackagingforum.org/
- ILSI Europe, https://ilsi.eu/

5. Searching the evidence

Search strategies were developed according to our research objectives and in an iterative process during scoping, building on the outcome of the expert consultation process and the exploration of the FCCmigex database. Search strategies cover indexed scientific literature and the gray literature, and were developed by VNS, CAH, and NR. A search update will be performed and reported, if required. The number of studies found from the individual searches will be recorded in a PRISMA flowchart (Fig. 4).

5.1. Development and implementation of the search strategy for bibliographic databases

At the scoping stage, we found that the PET oligomers of interest are inconsistently described in the literature and different concepts and names need to be included in the search strategy to identify all relevant information for this SEM. In addition, all types of exposure and hazard information are of interest in this SEM, requiring a broad search strategy without limits. For the systematic literature search, ECHA/EFSA proposes two different search strategies to find relevant data on health effects related to endocrine endpoints of all types: a broad single-concept strategy that only includes search terms related to chemicals and their synonyms, or a more targeted search strategy that additionally includes endpoint-related terms (Andersson et al., 2018). It should be noted that single-concept searches are the most sensitive way to go, as inclusion of one or more additional search concepts with Boolean ANDs always narrows the search result. According to ECHA/EFSA, the single-concept strategy should be first choice to allow an unbiased search and, therefore, the collection of all relevant information (Andersson et al., 2018). Based on the this and in agreement with published work (Pelch et al., 2019), we chose to search with chemical/stressor-related terms only. The applicability of such sensitive searching was tested and verified (CAH, VNS) in a pilot search in Embase and WoS (core collection) based on a combination of general terms on PET and oligomers, CAS RN, and chemical names.

The detailed search strategy was developed by including all identified terms and names of the 34 PET oligomers of interest and is graphically summarized in Fig. 2. It was developed by CAH and VNS, conceptually discussed with NR, and validated by CAH. Oligomer-specific search terms (Fig. 1 and Table 3) were identified by screening the PET oligomer-relevant data collected during the scoping exercise. IUPAC and common names were identified by searching the chemical databases SciFinder-n and Reaxys with no restriction to language (Supplemental **Table S1**).

For Embase and Ovid MEDLINE, the text word search strategy was

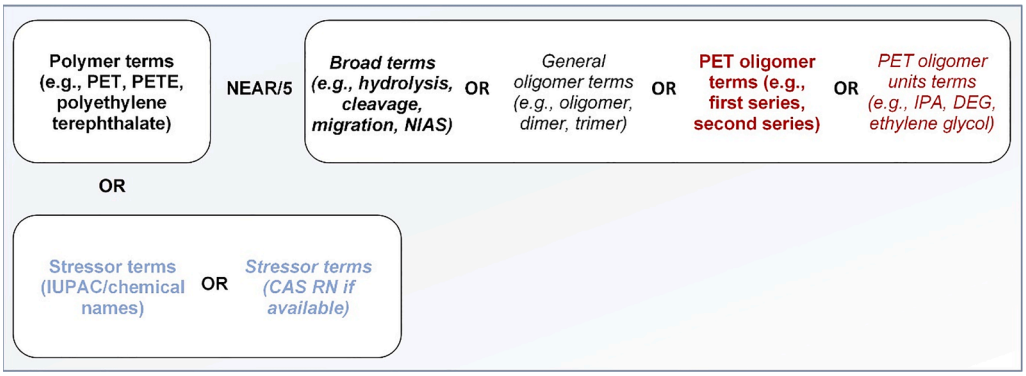

Fig. 2. Overview and graphical representation of the single-concept search strategy based on the PET oligomers as stressors. Search terms are connected via the Boolean operators 'NEAR/5' (Embase and WoS syntax, corresponds to 'ADJ5' or 'W/5' for Ovid MEDLINE or Scopus, respectively) or 'OR'. Color-coding and formatting correspond to colors and formatting used for the full search strategy in supplementary material **section S2**.

complemented by database-specific subject headings (Emtree and MeSH, respectively), whereas the PET polymer subject heading 'polyethylene terephthalate' was restricted by "toxicology/pharmacology/metabolism-subheadings" (Adverse drug reaction, Drug toxicity, Pharmacokinetics, Pharmacology for Embase/Emtree; Adverse Effects, Analogs & Derivatives, Metabolism, Pharmacokinetics, Pharmacology, Toxicity for Medline/MeSH). The restriction of the subject heading search by subheadings is not completely congruent to the proximity operator effect in the text word strategy (see below), but likely comparable.

The text word search strategy is split into two parts: a part with generic PET oligomer search terms and a stressor-specific part. For the part with generic PET oligomer search terms, PET polymer terms are restricted by proximity operator to hydrolysis/cleavage and (PET) oligomer terms. The width of the proximity operator of five intercalating non-stop words was chosen by subtracting the search results of a string with respective shorter width proximity operators and analyzing the relevance of the results. The stressor-specific search includes all available CAS RN, IUPAC, and common names (Table 3 and Supplemental **Table S1**). Compounds for which no IUPAC name was available were identified using ChemDraw 20.1 and Chemicalize (https://chemicalize.com/welcome) and their structure-to-name conversion option. In all IUPAC or common names the characters, < > () [ ] were replaced with spaces. IUPAC names for most oligomers are very long and complicated, making modifications like e.g. truncation for most names not useful and impractical. Therefore, only for a selection of short chemical names, identified in Reaxys, stemming and synonyms were added. In this selection the term "ethylene terephthalate" was not included, because it produced a high background noise due to its lack of specificity.

No publication date or language restrictions were applied. Full search strategies for Embase, Ovid MEDLINE, Scopus, and WoS can be found in supplementary material **section S2**.

5.2. Development and implementation of the search strategy for chemistry databases

SciFinder-n and Reaxys are databases designed to support structure-based searches. Both databases allow text searches, but their operation is highly restricted in their applicability of complex and long search strings. For this reason, and also because it is a comparable approach to the IUPAC/chemical name search in the other databases, the literature in SciFinder-n and Reaxys is identified by structure- and CAS RN-based searches only. This will be done for each of the 34 PET oligomers. The searches based on structure and CAS are performed independently and substructure searches will not be considered. Structure-based searches will be performed by applying SMILES strings to the implemented identifier conversion tool available for both databases. Information on structure and CAS RN can be found in Table 3 and Supplemental **Table S1**.

5.3. Development and implementation of the search strategy for the gray literature sources

A number of online platforms/databases allow the use of Boolean operators (AND, OR, NOT), truncation and synonym search/wildcards (*) or have advanced search engines (e.g., NVWA, BfR, NTP, ECHA, EC, INCHEM, JRC, Codex). On the other hand, other platforms/databases have no search engine option or only very basic query functions to offer that do not support Boolean logic, but only the use of single words or CAS RN (all other gray literature sources are mentioned in **section 4.3**). Accordingly, the use of search terms and search strings needs to be adapted on a case-by-case basis. A decision tree will be applied to decide which strategy is used for the individual gray literature source (Fig. 3).

The decision tree and strategy will be adapted if required and documented. The list of databases will be further refined (additions, deletions, revisions) at the searching stage, if necessary. The period of publication will not be restricted; language will be restricted to English.

5.4. Citation tracking

To identify possible additional eligible records that were missed by the initial electronic searches, we will screen the cited and citing records of all studies that were finally selected for SEM inclusion (see **section 5.5**). To assemble a deduplicated list of cited and citing literature, we will use the electronic citation indexes citationchaser (https://estech.shinyapps.io/citationchaser/) and Scopus.

5.5. Eligibility criteria

Eligibility criteria were developed according to the PECOS statement (Table 4 & 5). Studies will be included if they contain information on one or more PET oligomers (chemical stressors), either as single substance or mixtures. All effects of stressors including toxicological endpoints, health outcomes, kinetics, and bioactivities and all study types will be included. The inclusion of indexed scientific literature will be limited to primary research articles containing original research data. Secondary literature as well as conference abstracts, presentations, posters, book chapters, and theses/dissertations are excluded. Reviews (secondary literature) can be informative for orientation and prioritization purposes, incl. for cross-checking primary literature, and will be tagged as "*potentially useful background material, keep for later use*" and kept in a separate study repository. Patents are not considered as they are irrelevant for exposure and hazard data. The inclusion of gray literature will be limited to technical reports, human health risk assessments, narrative toxicological literature reviews, scientific opinions, position statements, white paper, and unpublished government

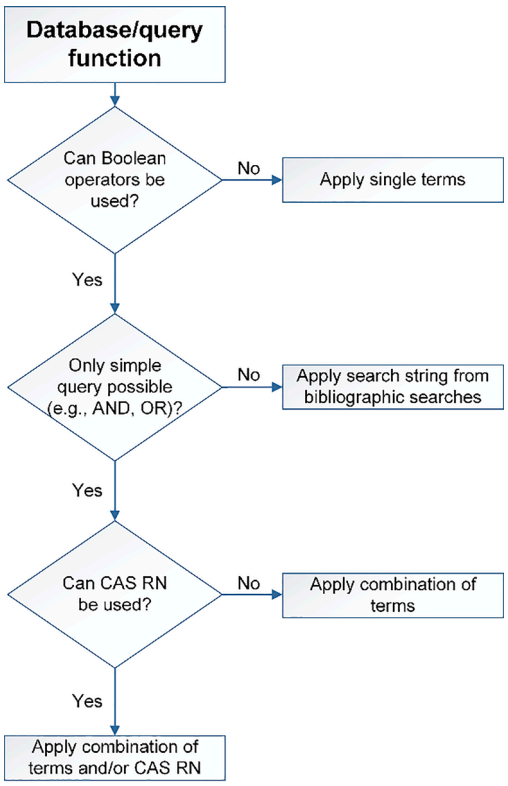

Fig. 3. Flow diagram of the search strategy applied for gray literature sources. Single terms: "polyethylene terephthalate"; oligomer(s). Combination of terms: PET AND oligomer(s); "polyethylene terephthalate" AND oligomer(s). CAS RN: if applicable/available (Table 3); bibliographic searches (supplementary material **section S2**).

research. We will identify regulatory activities and publications from regulatory agencies, non-governmental organizations, and related scientific bodies that have looked into the topic of the safety evaluation of PET oligomers in a regulatory hazard/risk assessment context.

Internal exposure is in this SEM defined as any type of exposure after ingestion and therefore via the oral route. External exposure includes processes that are non-physiological but are related to oral exposure as they affect the presence and concentrations of oligomers in consumables. Animal models that cannot be used for oral exposure e.g., due to their developmental stage (e.g. early stage zebrafish larvae) or unicellular organisms that do not allow oral exposure (e.g. *Salmonella*) are included as an exception due to their relevance in toxicity testing. The term hydrolysis is in our SEM defined as a chemical process that causes cleavage of ester bonds by addition of water during contact of PET oligomers with exposure medium (i.e., food or beverages) or via physiological processes after ingestion of PET oligomers. In this SEM, the

Table 4
Population, Exposure, Comparator, Outcome, Study type (PECOS) statement.

PECOS statement	Evidence
Population	Human, animals (whole organism), organisms, or models that use or target organs, tissues, cell lines, or cellular components.
Exposure	Any type of measured or modeled exposure to PET oligomers (stressors) via the oral route or data supporting the estimation of oral exposure (incl. migration). Single oligomers as well as mixtures will be considered.
Comparator	Humans, animals, organisms, organs, tissues, cell lines, or cellular components exposed to a lower level of PET oligomers than the more highly exposed subjects or treatment groups, vehicle-only treatment, or untreated control group.
Outcome	Any effects or health outcomes, either a toxicological response or a response with the normal biological/physiological range (incl. kinetic information), measured in the exposed human, animals (whole organism), organisms, organs, tissues, cell lines, or cellular components.
Study type	Any study type: *in vivo, ex vivo, in vitro, in silico*, mechanistic, epidemiological (human).

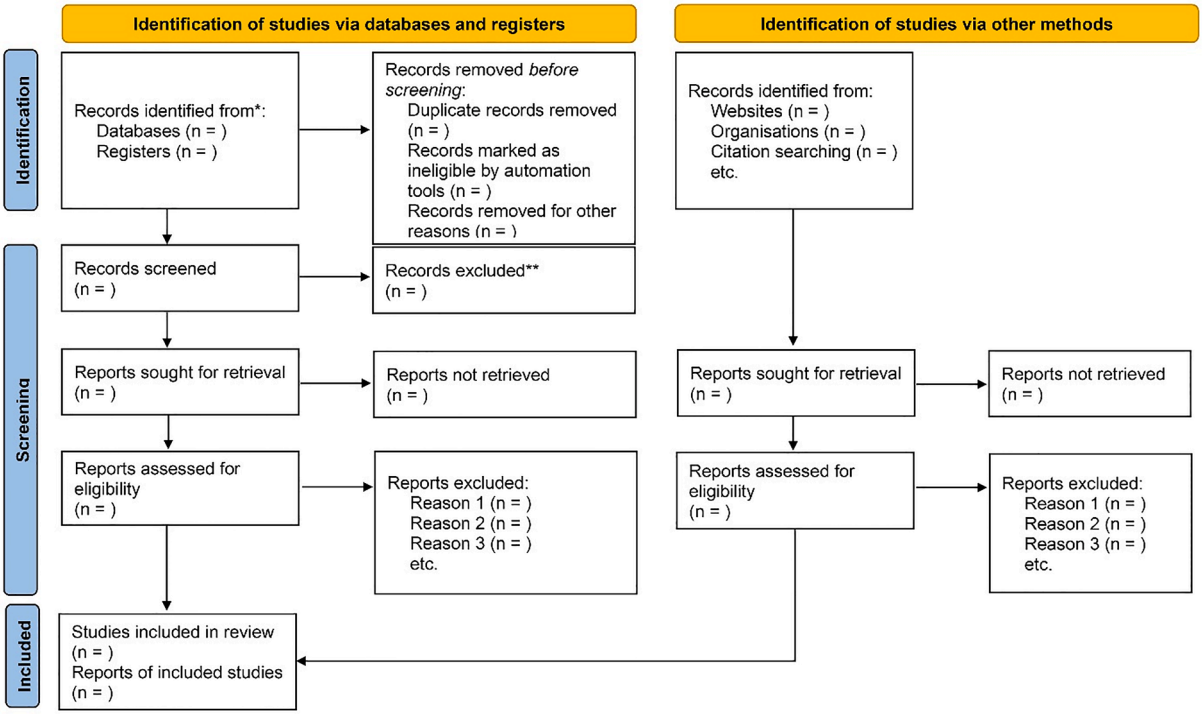

Fig. 4. Example of a PRISMA flowchart describing the study selection process (Page et al., 2021).

Table 5
Inclusion and exclusion criteria of this SEM according to the PECOS framework.

	Inclusion Criteria	Exclusion Criteria
Population		
Human	No restrictions on age, sex, or life stage at exposure or outcome assessment. Whole organisms, organs, tissues, cell lines, or cellular components are considered.	No restrictions.
Animals and organisms	No restrictions on age, sex, species, or life stage at exposure or outcome assessment. Whole organisms, organs, tissues, cell lines, or cellular components are considered.	No restrictions.
Internal exposure		
Human	Oral exposure studies. *In vitro* and *ex vivo* exposure studies. ADME/TK/PK, biomonitoring, and PBPK studies.	Any type of non-oral routes (e.g., dermal, inhalation)
Animals and organisms	Oral exposure studies. Non-oral routes if animal model cannot be used for oral administration (e.g. incubation of early stage zebrafish larvae or *Salmonella*). *In vitro* and *ex vivo* exposure studies. ADME/TK/PK, biomonitoring, and PBPK studies.	Any type of non-oral routes (e.g., dermal, inhalation).
External exposure		
Migration	Concentration measurement and/or migration of PET oligomer(s) into food, beverages or food simulants. Food simulants include oil, water, aqueous acetic acid or ethanol mixtures. Any type of extraction, including dissolution experiments or experiments with solvents such as hexane, heptane, or dichloromethane.	No restrictions.
Hydrolysis	Any type of hydrolysis in food contact context or due to physiological processes.	Studies related to biodegradability, manufacturing, engineering, or recycling processes. Environmental studies, including hydrolysis in e.g. soil or surface water.
Comparators		
Human, animals, and organisms	Human, animals, organisms, or model systems exposed to lower levels (or no exposure/exposure below detection levels) of the stressor than more highly exposed subjects and/or study must include vehicle or untreated control group. Single oligomers as well as mixtures will be considered.	No restrictions.
Outcomes		
Human, animals, and organisms	Any effects or health outcomes, either a toxicological response or a response with the normal biological/physiological range.	No restrictions.
Study type		
	Any study type, including *in vitro, in vivo, ex vivo, in silico*, mechanistic, epidemiological (human).	No restrictions.

term migration includes all types of experiments in which the transfer of a PET oligomer into e.g. food or food simulant is measured. However, it also includes all extraction experiments measuring the concentration of PET oligomers in the polymer, which is usually considered the worst-case migration because it represents the maximum amount that can potentially migrate.

Despite the fact that environmental risk assessment targets different endpoints compared to humans in many aspects, ecotoxicological endpoints such as environmental fate will be included in the SEM. It was discussed and decided that these data may still be valuable, since only a very small number of studies are expected to be available on aspects of human health. Data from ecotoxicological studies may therefore be important and useful in setting priorities and directions for future human health research.

5.6. Study selection

Retrieved references from bibliographic and chemistry databases will be imported into EndNote 20 (Clarivate Analytics) and deduplicated according to the Bramer method (Bramer et al., 2016). For screening, deduplicated references will be imported into the freely available web-based interface application PICO Portal (https://picoportal.org/). PICO Portal assists TIAB and full-text screening of literature and evidence mapping for systematic reviews. In a first step, title and abstract (TIAB) screening will be performed by one individual reviewer (VNS) and only studies that meet inclusion criteria elements will be eligible for full text-screening. Studies for which inclusion or exclusion at the stage of TIAB screening cannot be decided, will be included and further assessed in the full-text screening. In a second step, full-text screening will be performed by two independent reviewers (VNS, NR). The reasons for exclusion will be documented within PICO Portal. Disagreements will be resolved by consensus and arbitrated by a third reviewer (e.g., AO or MFW), other uncertainties will be resolved by discussion with the broader review team (AO, BG, BJB, BS, JM, MFW, MS, TJS) at any stage of the data selection process if needed; those cases will be recorded.

Gray literature records will be screened at full-text level for inclusion by two independent reviewers (VNS, NR), applying the same eligibility criteria as for the bibliographic sources.

The individual steps of the selection process including the reasons for exclusion will be reported according to the PRISMA statement and graphically illustrated in a PRISMA flowchart (Fig. 4) (Page et al., 2021).

6. Coding strategy

A fit-for-purpose approach was applied for the development of the coding strategy. We will use a combination of coding variables that cover broad/generic metadata (i.e., typical bibliographic information) with more specific qualitative (i.e., study characteristics aligned on the PE(C)OS components) and quantitative (i.e., study findings) coding variables (James et al., 2016). While this level of granularity goes beyond the meta-data typically extracted in evidence mapping, this is in line with the SEM objectives (Wolffe et al., 2019), and further planned research activities from the authors to support regulatory hazard/risk assessment; as well as future research activities, incl. systematic reviews or other evidence-based approaches on the same topic.

This SEM incorporates a wide range of data from multiple research areas and disciplines. Various data, e.g., migration and hydrolysis, and their data extraction are largely not covered by tools available for systematic reviews/maps, or the data abstraction functions need to be heavily customized. Therefore, in our SEM a MS Access flat file database will serve as a customized form for data entry, storage, and analysis. Anticipating the lack of data on PET oligomers, publication of a data-poor database is not planned, but will be considered in a future update of the SEM. All information in the database will be exported and provided as tables within a MS Excel file (.xlsx format, according to **Supplemental File 2**).

Data extraction and coding will be performed on included full-text studies. Data will be extracted into our customized MS Access database containing a long form table for each evidence stream (including bibliographic information, stressor(s), and available data on the

Table 6
List of variables for coding included records at full-text level.

Coding category	Coding variable	Type of data extracted
Bibliographic information	Full reference	• Indexed scientific literature: *author(s), title, journal, date of publication, page number(s) and DOI if available* Gray literature: *author(s), title, source, DOI/URL where available*
	Year of publication	• Date of publication in years
	Publication type (data source)	• Indexed scientific literature: *primary research* (i.e., *original study); or secondary research (review)* Gray literature: *type of technical report* (e.g., *risk assessment, scientific opinion, position statement, white paper, unpublished government research)*. In case of doubt, *"technical paper"* will be used.
	Country	• Name of country. The first author country of origin will be used. In case of records authored by researchers from more than one country, the country of the corresponding author will be used.
	Language	• Language of the record
	Study design	• Type of research *(e.g., experimental, observational, longitudinal, case study, one-generation study, two-generation study)*. If not reported, *"not reported"* will be used. If not applicable for study, *"not applicable"* will be used.
Information related to the PECO per evidence stream	Stressor(s)	• Chemical identity* name will be normalized using acronym-based abbreviation in Table 3 *(*e.g., *C [TPA + EG]2, C[TPA + EG]3)* *in case of mixtures, all identities are captured. If this information is not available, "*mixture of PET oligomers*" will be used.
	Evidence streams	• Human study[1,2] Animal study[1,2]Organism (non-animal) study[1,2] *Ex vivo* study[1,2] *In vitro* study[1,2] *In silico* study[1,2] Migration study Hydrolysis study ADME/TK/PK study [1] *each of these systems can be used to conduct mechanistic studies at the (sub)cellular level* [2] Hydrolysis *and ADME/TK/PK studies are excluded and reported under "Hydrolysis study" and "ADME/TK/PK study"*
	Human study elements	
	Population	• Study population sex: *male, female, both*
	Exposure	• Timing of exposure: *preconception, pregnancy, age* (in months or years) Timing of exposure assessment: *preconception, pregnancy, age* (in months or years) Exposure duration: *acute, subacute, chronic, subchronic, lifetime*External exposure (medium) : *dose/concentration(s) of PET oligomer(s) in reported medium* (e.g., *soft drink, baked beans, extract) with reported value and unit*External exposure (gastrointestinal phase) : *concentration(s) of PET oligomer(s) in the reported gastric and/or intestinal phase (before absorption) with reported value and unit*Internal exposure (systemic): concentration(s) of PET oligomer (s) in reported biological samples will be captured and categorized as follows: *adipose tissue, amniotic fluid, breast milk, cord blood, serum, whole blood, plasma, urine, feces; with reported value and unit.* Additions will be allowed as needed.
	Comparator	• Will be captured as free text if available/applicable, otherwise *"no comparator"* will be used
	Outcome	• Timing of outcome assessment: *preconception, pregnancy, age* (in months or years) Health outcomes: will be captured and categorized related to effects on the following organs or systems: *blood, heart, and circulation; bones, joints, and muscles; brain and nerves; cancer; digestive system; ear, nose, and throat; endocrine system; eyes and vision; female reproductive system; genetics/birth defects; immune system; injuries and wounds; kidneys and urinary system; lungs and breathing; male reproductive system; mental health and behavior; metabolic problems; mouth and teeth; mortality; pregnancy and reproduction; sexual health issues; skin, hair, and nails*. Additions will be allowed as needed.
	Animal study elements	
	Population	• Specie(s): will be captured as free textStrain(s) : will be captured as free text Study population sex: *male, female, both*
	Exposure	• Timing of exposure: *preconception (F0), pregnancy, age* (in months or years). Additions will be allowed as needed. Timing of exposure assessment: *preconception (F0), pregnancy, age* (in months or years). Additions will be allowed as needed. Exposure duration: *acute, subacute, chronic, subchronic, lifetime*External exposure (medium) : *dose/concentration(s) of PET oligomer(s) in reported medium* (e.g., *soft drink, baked beans, extract) with reported value and unit*External exposure (gastrointestinal phase) : *concentration(s) of PET oligomer(s) in the reported gastric and/or intestinal phase (before absorption) with reported value and unit*Internal exposure (systemic):

(*continued on next page*)

Table 6 (*continued*)

Coding category	Coding variable	Type of data extracted
		concentration(s) of PET oligomer (*s*)
		in reported biological samples will be captured and categorized as follows: *adipose tissue, amniotic fluid, breast milk, cord blood, serum, whole blood, plasma, urine, feces; with reported value and unit.* Additions will be allowed as needed.
	Comparator	• Will be captured as free text if available/applicable, otherwise *"no comparator"* will be used
	Outcome	• Timing of outcome assessment: *preconception (F0), pregnancy, F1 generation, F2 generation, age* (in months or years). Additions will be allowed as needed.
		Health outcomes: will be captured and categorized related to effects on the following organs or systems: *blood, heart, and circulation; bones, joints, and muscles; brain and nerves; cancer; digestive system; ear, nose, and throat; endocrine system; eyes and vision; female reproductive system; genetics/birth defects; immune system; injuries and wounds; kidneys and urinary system; lungs and breathing; male reproductive system; mental health and behavior; metabolic problems; mouth and teeth; mortality; pregnancy and reproduction; sexual health issues; skin, hair, and nails*. Additions will be allowed as needed.
	Organism (non-animal) study elements	
	Population	• Specie(s): will be captured as free textStrain(s)
		: will be captured as free text
	Exposure	• Assay type: will be captured as free text *(*e.g., *Ames test, bacterial MIC assay, L-YES)*
		Assay concentration: *reported value and unit*
		Exposure duration: *reported value* (in seconds, minutes, hours, or days)
	Comparator	• Will be captured as free text if available/applicable, otherwise *"no comparator"* will be used
	Outcome	• Outcome: will be captured as free text and categorized as follows, examples are: e*strogen related, androgen related, thyroid related, steroidogenesis related, genotoxicity related, mutagenicity related, carcinogenicity related, cytotoxicity related, survival.* Additions will be allowed as needed.
	***Ex vivo* study elements**	
	Population	• Specie(s): will be captured as free textStrain(s)
		: will be captured as free text
		Study population sex: *male, female, both*
		Organ/tissue/cell type: will be captured as free text
	Exposure	• Exposure type: will be captured as free text
		Exposure duration: *reported value* (in seconds, minutes, hours, or days)
		Exposure concentration: *reported value and unit*
	Comparator	• Will be captured as free text if available/applicable, otherwise *"no comparator"* will be reported
	Outcome	• Outcome: will be captured as free text.
	***In vitro* study elements**	
	Population	• Cell specie(s)/cell line(s): will be captured as free text
	Exposure	• Exposure target site: will be captured as free text
		Exposure duration: *reported value* (in seconds, minutes, hours, or days)
		Assay concentration: *reported value and unit*
	Comparator	• Will be captured as free text if available/applicable, otherwise *"no comparator"* will be used
	Outcome	• Outcome: description will be captured as free text and categorized as follows, examples are: e*strogen related, androgen related, thyroid related, steroidogenesis related, genotoxicity related, mutagenicity related, carcinogenicity related*
	***In silico* study elements**	
	Population	• Molecular target/mode of action: will be captured as free text *(*e.g., *DNA binding, protein binding, estrogen receptor alpha, mutagenicity, genotoxicity, chromosomal aberrations (CA), formation of micronuclei (MNT))*
	Exposure	• Method/tool: will be captured as free text *(*e.g., *molecular docking, molecular dynamics, Toxtree, Derek Nexus, Sarah Nexus, OASIS-algorithm)*
	Comparator	• Will be captured as free text if available/applicable, otherwise *"no comparator"* will be used
	Outcome	• Outcome: will be captured as free text *(e.g, reported values and units, "no alert found", "alert found")*
		In silico data experimentally confirmed: *yes, no*
	Additional information related to study findings	
	Migration	• Assay type: *experimental, modeling*
		Food contact article*: tea bag, bottle, tray, bowl, bag, pelleted material*. Additions will be allowed as needed.
		Duration: *reported value* (in seconds, minutes, hours, or days)
		Temperature/temperature range: *reported value* (in °C). In case the temperature is not reported, the application will be reported instead *(*e.g., *microwave, oven, storage at ambient temperature)*Type of medium: will be captured as free text
		(includes all type of food, food simulants, and solvents)
		Migration: *reported value/value range and unit, ND (not detected), < LOD (limit of detection), < LOQ (limit of quantification)*. Additions will be allowed as needed.
	Hydrolysis	• Hydrolysis site/type: *in vitro intestinal, in vitro gastric, human intestinal, human gastric, animal*

(*continued on next page*)

Table 6 (*continued*)

Coding category	Coding variable	Type of data extracted
		intestinal, animal gastric, human plasma, human blood, human tissue, animal plasma, animal blood, animal tissue, chemical stability in food, chemical stability in material, microbiome related. Additions will be allowed as needed. Duration: *reported value* (in seconds, minutes, hours, or days) Degradation/hydrolysis product (s) : *reported compound* (if applicable, name will be normalized using acronym-based abbreviation in Table 3 (e.g. *C [TPA + EG]2, C[TPA + EG]3)*) Related outcomes: *complete hydrolysis, partial hydrolysis, monomer formation observed, no monomer formation observed (multiselect option)*
	ADME/TK/PK	• Study type: *human (assessed population/age will be captured if available/applicable), animal (assessed population type/age will be captured as free text if available/applicable), ex vivo, in vitro, in silico* Study design/assay type: will be captured as free text (e.g., *biomonitoring, PAMPA assay, Caco-2 permeability assay, CYP3A4 metabolism)* Type of data: *physico-chemical property(ies), pKa, lipophilicity, solubility, TK/PK parameter(s), plasma concentration, blood concentration, tissue concentration, absorption related, metabolism related, excretion related, transporter related.* Additions will be allowed as needed. Outcome: will be captured as free text

evidence stream). The tables contain drop-down lists and free-text options. The database contains the possibility to enter the information listed in Table 6. The coding strategy was developed following the study of Pelch et al. (2019) and further adapted to this SEM based on James et al. (2016). The code book was tested by VNS in a pilot data extraction on three eligible studies to validate the coding strategy. A file exported from the MS Access database with exemplary extracted data on migration, *in silico*, and ADME/TK/PK data is demonstrated in **Supplemental File 2**.

One unit of research/evidence corresponds to each qualitative or quantitative entry per oligomer and evidence stream. If an information source contains information on more than one oligomer or different evidence streams for one oligomer - all the information will be retrieved and entered as individual evidence. Mixtures of oligomers and their respective information are recorded separately according to their evidence stream as individual evidence for each mixture. Data coding and extraction will be performed by a single reviewer (VNS), with a second reviewer (NR) confirming the accuracy and completeness of all extracted and coded data. Data entries recorded as free text are visually reviewed for inconsistencies and normalized as required by one reviewer (VNS) and confirmed by a second reviewer. Disagreements will be resolved by consensus and arbitrated by a third reviewer (e.g., AO or MFW), other uncertainties will be resolved by discussion with the broader review team (AO, BG, BJB, BS, JM, MFW, MS, TJS) at any stage of the data selection process if needed; those cases will be recorded. Author(s) of a study will be contacted for clarification, if necessary for inclusion of studies and coding decisions. If it remains unclear, the information will be indicated as "missing information".

7. Data management

Retrieved references from bibliographic and chemical structure databases will be imported into EndNote 20 (Clarivate Analytics) and deduplicated. For screening, deduplicated references will be imported into PICO Portal (https://picoportal.org/). TIAB screening will be performed and only studies that meet inclusion criteria elements will be eligible for full text-screening. Gray literature records will be screened at full-text level, applying the same eligibility criteria as for the bibliographic sources. Included studies and their respective information is extracted into an MS Access database. The number of studies retrieved, the source (bibliographic or gray literature), the number of studies screened, and the number of included and excluded studies at the TIAB and full-text screening stages are reported. The individual steps of the selection process including the reasons for exclusion will be reported according to the PRISMA statement and graphically illustrated in a PRISMA flowchart (Fig. 4). The collected data will be made available in the SEM report. In case of updates to the search or changes to the protocol, the changes will be noted as modifications to the registered protocol. Details of each step are described elsewhere in this protocol.

8. Appraisal

There will be no critical appraisal of included studies as part of this SEM. This in line with our research aims and objectives to identify, collect, and organize knowledge clusters and gaps associated with hazard and exposure information of PET oligomers. Assessment of internal validity (i.e., risk of bias analysis) is not a typical feature of the evidence mapping process (Wolffe et al., 2019).

9. Data visualization

Data visualization of the extracted data will be conducted using various software (e.g., Tableau Software or MS Excel). A variety of visualization techniques are considered, including bar charts to show frequencies, spider charts for comparisons, heat maps to show data densities, and tables to provide summaries. Based on the data obtained, the technique that most effectively visualizes the resulting conclusions for the reader will be selected. Each oligomer is listed individually, and the number of studies for each evidence stream and additional study findings are presented in a qualitative overview to visualize areas of sufficient knowledge and those in need of research (Fig. 5). Mixtures of oligomers and their evidence will be presented separately. The overall, qualitative, and quantitative information on all PET oligomers, collected in accordance with the coding strategy will be divided into tables that will be aligned to the evidence streams. These tables will be presented in the supporting information of the SEM report, representing the overall information collected on all evidence streams. For every element of evidence, the bibliographic information will be captured and assigned.

10. Data synthesis

The collected evidence will be summarized and discussed narratively and prepared as a manuscript for peer-review. An objective being addressed in the SEM is the support future research activities. It was therefore decided to not only include qualitative, but also quantitative coding variables, which goes beyond the meta-data typically extracted in evidence mapping. The data will be presented in different formats, depending on the granularity and the objective pursued. Overview graphs such as heat maps or tables will provide information on available knowledge and knowledge gaps. The amount of available data is

PET Oligomer	Human study	Animal study	Organism (non-animal) study	*Ex vivo* study	*In vitro* study	*In silico* study
Oligomer 1	1	0	0	0	2	7
Oligomer 2	10	1	1	0	3	1
Oligomer 3	3	2	0	0	6	2

Fig. 5. Example data visualization. The figure is an example of an overview chart of how the data and associated data gaps can be presented in MS Excel. In the example, gray bars represent the number of studies for each evidence stream identified for the respective PET oligomer. Each row represents a PET oligomer and every column represents one evidence stream.

therefore examined and discussed in more detail. Tables will be used to address research needs and to provide detailed information on each PET oligomer. Studies addressing additional aspects of PET oligomers including environmental fate, regulatory documents, or read-across analysis will be made available and presented in one or more separate table(s). The information on exposure and hazard outcomes will be discussed for relevance in the chemical risk assessment context. Trends in knowledge and research gaps for the individual evidence streams will be discussed. Additionally, trends in the data availability for individual or a group of PET oligomers will be discussed. Respective knowledge gaps are demonstrated and research needs addressed to inform future research and to support regulatory decision-making.

Funding

The project 4.21.01 ToxOligo – *Toxikologische Charakterisierung von zyklischen Oligomeren in Kunststoffen für Lebensmittelkontaktmaterialien* (Toxicological characterization of cyclic oligomers in plastics for food contact materials) is funded by FSVO (contract number 0714001652). The APC was funded by the University of Basel.

CRediT authorship contribution statement

Verena N. Schreier: Conceptualization, Methodology, Validation, Visualization, Investigation, Writing – original draft, Project administration. **Christian Appenzeller-Herzog:** Methodology, Validation, Investigation, Data curation, Writing – review & editing. **Beat J. Brüschweiler:** Conceptualization, Writing – review & editing. **Birgit Geueke:** Conceptualization, Writing – review & editing. **Martin F. Wilks:** Conceptualization, Writing – review & editing. **Thomas J. Simat:** Conceptualization, Writing – review & editing. **Benoit Schilter:** . **Martin Smieško:** Conceptualization, Writing – review & editing. **Jane Muncke:** Conceptualization, Writing – review & editing. **Alex Odermatt:** Conceptualization, Writing – review & editing, Funding acquisition, Supervision. **Nicolas Roth:** Conceptualization, Methodology, Validation, Visualization, Writing – original draft, Supervision.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Alex Odermatt reports financial support was provided by Federal Food Safety and Veterinary Office FSVO. Alex Odermatt reports administrative support was provided by Swiss Centre for Applied Human Toxicology (SCAHT). This involves handling of reporting to the FSVO and the transfer of funds from the FSVO. Martin Wilks reports a relationship with SCAHT that includes: director. Jane Muncke and Birgit Geueke report a relationship with Food Packaging Forum that includes: employment. Jane Muncke and Birgit Geueke were not restricted in any way by the FPF in planning and conducting this work. Beat Brueschweiler reports a relationship with Swiss Federal Food Safety and Veterinary Office (FSVO) that includes: employment. Beat Brueschweiler acted in a personal expert capacity and not as a sponsor representative. Benoit Schilter reports a relationship with Nestlé R&D Centre that includes: employment. Benoit Schilter was not restricted in any way by Nestlé R&D Centre in planning and conduction this work.

Data availability

Data will be made available on request.

Acknowledgements

We would like to thank all the experts involved in the consultation process - Thomas Gude (Swiss Quality Testing Services), Gregor McCombie (Official Food Control Authority of the Canton of Zurich), Eddo Hoekstra (EC Joint Research Centre), Stefan Merkel (German Federal Institute for Risk Assessment), Thomas Tietz (German Federal Institute for Risk Assessment), and Sander Koster (Nestlé), for their valuable advice and information. We thank Simon Geiger (University of Basel) and the team of the ETH Zurich Information Center, in particular Jozica Dolenc, for their support and advice on chemistry databases. The project 4.21.01 ToxOligo – *Toxikologische Charakterisierung von zyklischen Oligomeren in Kunststoffen für Lebensmittelkontaktmaterialien* (Toxicological characterization of cyclic oligomers in plastics for food contact materials) is funded by FSVO (contract number 0714001652). The APC was funded by the University of Basel.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2022.107387.

References

Alberto Lopes, J., Tsochatzis, E.D., Karasek, L., Hoekstra, E.J., Emons, H., 2021. Analysis of PBT and PET cyclic oligomers in extracts of coffee capsules and food simulants by a HPLC-UV/FLD method. Food Chem. 345, 128739 https://doi.org/10.1016/j.foodchem.2020.128739.

Andersson, N., Arena, M., Auteri, D., Barmaz, S., Grignard, E., Kienzler, A., Lepper, P., Lostia, A.M., Munn, S., Parra Morte, J.M., Pellizzato, F., Tarazona, J., Terron, A., van der Linden, S., 2018. Guidance for the identification of endocrine disruptors in the context of Regulations (EU) No 528/2012 and (EC) No 1107/2009. EFSA J. 16, e05311 https://doi.org/10.2903/J.EFSA.2018.5311.

Antunovic, B., Barlow, S., Chesson, A., Flynn, A., Hardy, A., Jeger, M.-J., Knaap, A., Kuiper, H., Lovell, D., Nørrung, B., Pratt, I., Mortensen, A., Schlatter, J., Silano, V., Smulders, F., Boobis, A., Bridges, J., Bulder, A., Galli member until February, C., Gundert-Remy, U., Christian Larsen, J., Lhuguenot, J.-C., Mantovani, A., Piersma, A., Worth, A., Zapponi, G., Maurici, D., Steinkellner, H., 2012. Scientific Opinion on Exploring options for providing advice about possible human health risks based on the concept of Threshold of Toxicological Concern (TTC). EFSA J. 10, 2750. doi: 10.2903/J.EFSA.2012.2750.

Bauer, A., Jesús, F., Gómez Ramos, M.J., Lozano, A., Fernández-Alba, A.R., 2019. Identification of unexpected chemical contaminants in baby food coming from plastic packaging migration by high resolution accurate mass spectrometry. Food Chem. 295, 274–288. https://doi.org/10.1016/J.FOODCHEM.2019.05.105.

Begley, T.H., Dennison, J.L., Hollifield, H.C., 1990. Migration into food of polyethylene terephthalate (PET) cyclic oligomers from PET microwave susceptor packaging. Food Addit. Contam. 7, 797–803. https://doi.org/10.1080/02652039009373941.

Biedermann, M., Grob, K., 2006. GC-MS characterization of oligomers in polyadipates used as plasticizers for PVC in food contact. Packaging Technol. Sci. 19, 159–178. https://doi.org/10.1002/pts.722.

Bolognesi, C., Castle, L., Cravedi, J.-P., Engel, K.-H., Fowler, P., Franz, R., Grob, K., Gürtler, R., Husøy, T., Kärenlampi, S., Mennes, W., Rosaria Milana, M., Penninks, A., Silano, V., Smith, A., de Fátima Tavares Poças, M., Tlustos, C., Wölfle, D., Zorn, H., Zugravu, C.-A., Kolf-Clauw, M., Lampi, E., 2016. Recent developments in the risk assessment of chemicals in food and their potential impact on the safety assessment of substances used in food contact materials. EFSA J. 14, 4357. https://doi.org/10.2903/J.EFSA.2016.4357.

Bramer, W.M., Giustini, D., de Jonge, G.B., Holland, L., Bekhuis, T., 2016. De-duplication of database search results for systematic reviews in EndNote. J. Med. Libr. Assoc. 104 (3), 240–243. https://doi.org/10.3163/1536-5050.104.3.014.

Bramer, W.M., Rethlefsen, M.L., Kleijnen, J., Franco, O.H., 2017. Optimal database combinations for literature searches in systematic reviews: A prospective exploratory study. Syst. Rev. 6, 1–12. https://doi.org/10.1186/s13643-017-0644-y.

Brenz, F., Linke, S., Simat, T., 2018. Linear and cyclic oligomers in polybutylene terephthalate for food contact materials. Food Add. Contaminants: Part A 35, 583–598. https://doi.org/10.1080/19440049.2017.1414958.

Brenz, F., Linke, S., Simat, T.J., 2021. Linear and cyclic oligomers in PET, glycol-modified PET and Tritan™ used for food contact materials. Food Addit. Contaminants: Part A 38, 160–179. https://doi.org/10.1080/19440049.2020.1828626.

Castle, L., Mayo, A., Crews, C., Gilbert, J., 1989. Migration of Poly(ethylene terephthalate) (PET) Oligomers from PET Plastics into Foods during Microwave and Conventional Cooking and into Bottled Beverages. J. Food Prot. 52, 337–342. https://doi.org/10.4315/0362-028X-52.5.337.

Corlett, R.T., 2010. Trouble with the Gray Literature. Biotropica 43 (1), 3-5. URL: http://www.jstor.org/stable/41058533.

Eckardt, M., Schneider, J., Simat, T.J., 2019. In vitro intestinal digestibility of cyclic aromatic polyester oligomers from polyethylene terephthalate (PET) and polybutylene terephthalate (PBT). Food Add. Contaminants: Part A 36 (12), 1882–1894. https://doi.org/10.1080/19440049.2019.1658903.

EFSA, 2014a. Scientific Opinion on the safety assessment of the substance, furan-2, 5-dicarboxylic acid, CAS No 3238–40-2, for use in food contact materials. EFSA J. 12, 1–9. https://doi.org/10.2903/j.efsa.2014.3866.

EFSA, 2014b. Scientific Opinion on the safety assessment of the substance, 2,4,8,10-tetraoxaspiroundecane-3, 9-diethanol, β3, β3, β9, β9-tetramethyl-, CAS No 1455–42-1, for use in food contact materials. EFSA J. 12, 4–11. https://doi.org/10.2903/j.efsa.2014.3863.

Elsa, O., Emmanuelle, B., Sébastien, H., Anne-Lise, R., Fabrice, M., Hélène, G., Paul, H., Gérald, R., Gaud, D.P., Cariou, R., Bruno, L.B., 2019. Toward the characterisation of non-intentionally added substances migrating from polyester-polyurethane lacquers by comprehensive gas chromatography-mass spectrometry technologies. J. Chromatogr. A 1601, 327–334. https://doi.org/10.1016/J.CHROMA.2019.05.024.

Franz, R., Welle, F., 2020. Contamination Levels in Recollected PET Bottles from Non-Food Applications and their Impact on the Safety of Recycled PET for Food Contact. Molecules 25 (21), 4998. https://doi.org/10.3390/molecules25214998.

Gehanno, J.F., Paris, C., Thirion, B., Caillard, J.F., 1998. Assessment of bibliographic databases performance in information retrieval for occupational and environmental toxicology. Occup. Environ. Med. 55, 562–566. https://doi.org/10.1136/OEM.55.8.562.

Geueke, B., Wagner, C.C., Muncke, J., 2014. Food contact substances and chemicals of concern: A comparison of inventories. Food Additives Contaminants - Part A Chem., Analy., Control, Exposure Risk Assess 31, 1438–1450. https://doi.org/10.1080/19440049.2014.931600.

Geueke, B., Groh, K.J., Maffini, M.V., Martin, O.V., Boucher, J.M., Chiang, Y.-T., Gwosdz, F., Jieh, P., Kassotis, C.D., Łańska, P., Peterson Myers, J., Odermatt, A., Parkinson, L. V., Schreier, V.N., Srebny, V., Zimmermann, L., Scheringer, M., Muncke, J., 2022. Systematic evidence on migrating and extractable food contact chemicals: Most chemicals detected in food contact materials are not listed for use 1–11. 10.1080/10408398.2022.2067828.

Geueke, B., 2018. Dossier – Non-intentionally added substances (NIAS) 1–10. 10.5281/zenodo.1265331.

Groh, K., Geueke, B., Muncke, J., 2020. FCCdb: Food Contact Chemicals database. Version 5.0. 10.5281/ZENODO.4296944.

Gusenbauer, M., Haddaway, N.R., 2020. Which academic search systems are suitable for systematic reviews or meta-analyses? Evaluating retrieval qualities of Google Scholar, PubMed, and 26 other resources. Res. Synthesis Methods 11, 181–217. https://doi.org/10.1002/JRSM.1378.

Haddaway, N.R., Collins, A.M., Coughlin, D., Kirk, S., Wray, K.B., 2015. The role of google scholar in evidence reviews and its applicability to grey literature searching. PLoS ONE 10 (9), e0138237. https://doi.org/10.1371/journal.pone.0138237.

Higgins, J.P.T., Thomas, J., Chandler, J., Cumpston, M., Li, T., Page, M.J., Welch, V.A. (Eds.), Cochrane Handbook for Systematic Reviews of Interventions version 6.2 (updated February 2021). Cochrane, 2021. https://training.cochrane.org/handbook.

Hoffmann, S., de Vries, R.B.M., Stephens, M.L., Beck, N.B., Dirven, H.A.A.M., Fowle, J.R., Goodman, J.E., Hartung, T., Kimber, I., Lalu, M.M., Thayer, K., Whaley, P., Wikoff, D., Tsaioun, K., 2017. A primer on systematic reviews in toxicology. Arch. Toxicol. 91, 2551–2575. https://doi.org/10.1007/s00204-017-1980-3.

Hoppe, M., de Voogt, P., Franz, R., 2016. Identification and quantification of oligomers as potential migrants in plastics food contact materials with a focus in polycondensates - A review. Trends Food Sci. Technol. 50, 118–130. https://doi.org/10.1016/j.tifs.2016.01.018.

Hoppe, M., Fornari, R., de Voogt, P., Franz, R., 2017. Migration of oligomers from PET: determination of diffusion coefficients and comparison of experimental versus modelled migration. Food Add. Contaminants: Part A 34, 1251–1260. https://doi.org/10.1080/19440049.2017.1322222.

Hoppe, M., de Voogt, P., Franz, R., 2018. Oligomers in polyethylene naphthalate and polybutylene terephthalate – Identification and exploring migration. Food Packaging Shelf Life 17, 171–178. https://doi.org/10.1016/j.fpsl.2018.07.001.

Horodytska, O., Cabanes, A., Fullana, A., 2020. Non-intentionally added substances (NIAS) in recycled plastics. Chemosphere 251, 126373. https://doi.org/10.1016/j.chemosphere.2020.126373.

Hu, Y., Du, Z., Sun, X., Ma, X., Song, J., Sui, H., Debrah, A.A., 2021. Non-targeted analysis and risk assessment of non-volatile compounds in polyamide food contact materials. Food Chem. 345, 128625. https://doi.org/10.1016/j.foodchem.2020.128625.

James, K.L., Randall, N.P., Haddaway, N.R., 2016. A methodology for systematic mapping in environmental sciences. Environ. Evidence 5, 1–13. https://doi.org/10.1186/s13750-016-0059-6.

Keshava, C., Davis, J.A., Stanek, J., Thayer, K.A., Galizia, A., Keshava, N., Gift, J., Vulimiri, S.V., Woodall, G., Gigot, C., Garcia, K., Greenhalgh, A., Schulz, B., Volkoff, S., Camargo, K., Persad, A.S., 2020. Application of systematic evidence mapping to assess the impact of new research when updating health reference values: A case example using acrolein. Environ. Int. 143, 105956. https://doi.org/10.1016/j.envint.2020.105956. Epub 2020 Jul 20.

Mahood, Q., van Eerd, D., Irvin, E., 2014. Searching for grey literature for systematic reviews: Challenges and benefits. Res. Synthesis Methods 5, 221–234. https://doi.org/10.1002/jrsm.1106.

ILSI / Guidance on Best Practices on the Risk Assessment of Non Intentionally Added Substances (NIAS) in Food Contact Materials and Articles, 2015, URL https://ilsi.eu/publication/guidance-on-best-practices-on-the-risk-assessment-of-non-intentionally-added-substances-nias-in-food-contact-materials-and-articles/ (accessed 12.3.21).

Martin, O.V., Geueke, B., Groh, K.J., Chevrier, J., Fini, J.-B., Houlihan, J., Kassotis, C., Myers, P., Nagel, S.C., Pelch, K.E., Sargis, R.M., Trasande, L., Vandenberg, L.N., Wagner, M., Maffini, M. V., Muncke, J., 2018. Protocol for a systematic map of the evidence of migrating and extractable chemicals from food contact articles. doi: 10.5281/ZENODO.2525277.

Masic, I., Milinovic, K., 2012. On-line biomedical databases–the best source for quick search of the scientific information in the biomedicine. Acta Inform. Med. 20, 72. https://doi.org/10.5455/AIM.2012.20.72-84.

Miake-Lye, I.M., Hempel, S., Shanman, R., Shekelle, P.G., 2016. What is an evidence map? A systematic review of published evidence maps and their definitions, methods, and products. Syst. Rev. 5 https://doi.org/10.1186/s13643-016-0204-x.

Moher, D., Shamseer, L., Clarke, M., Ghersi, D., Liberati, A., Petticrew, M., Shekelle, P., Stewart, L.A., Estarli, M., Barrera, E.S.A., Martínez-Rodríguez, R., Baladia, E., Agüero, S.D., Camacho, S., Buhring, K., Herrero-López, A., Gil-González, D.M., Altman, D.G., Booth, A., Chan, A.W., Chang, S., Clifford, T., Dickersin, K., Egger, M., Gøtzsche, P.C., Grimshaw, J.M., Groves, T., Helfand, M., Higgins, J., Lasserson, T., Lau, J., Lohr, K., McGowan, J., Mulrow, C., Norton, M., Page, M., Sampson, M., Schünemann, H., Simera, I., Summerskill, W., Tetzlaff, J., Trikalinos, T.A., Tovey, D., Turner, L., Whitlock, E., 2016. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Revista Espanola de Nutricion Humana y Dietetica 20, 148–160. https://doi.org/10.1186/2046-4053-4-1/TABLES/4.

Muncke, J., Backhaus, T., Geueke, B., Maffini, M.V., Martin, O.V., Myers, J.P., Soto, A.M., Trasande, L., Trier, X., Scheringer, M., 2017. Scientific challenges in the risk assessment of food contact materials. Environ. Health Perspect. 125 (9), 095001. https://doi.org/10.1289/EHP644.

Muncke, J., Andersson, A.-M., Backhaus, T., Boucher, J.M., Carney Almroth, B., Castillo Castillo, A., Chevrier, J., Demeneix, B.A., Emmanuel, J.A., Fini, J.-B., Gee, D., Geueke, B., Groh, K., Heindel, J.J., Houlihan, J., Kassotis, C.D., Kwiatkowski, C.F., Lefferts, L.Y., Maffini, M.V., Martin, O.V., Myers, J.P., Nadal, A., Nerin, C., Pelch, K. E., Fernández, S.R., Sargis, R.M., Soto, A.M., Trasande, L., Vandenberg, L.N., Wagner, M., Wu, C., Zoeller, R.T., Scheringer, M., 2020. Impacts of food contact chemicals on human health: A consensus statement. Environ. Health: Global Access Sci. Source 19 (1). https://doi.org/10.1186/s12940-020-0572-5.

Muncke, J., Snedeker, S.M., 2014. Food Contact Materials: Practices, Agencies and Challenges. Mol. Integrative Toxicol. 265–297 https://doi.org/10.1007/978-1-4471-6500-2_11.

Mutsuga, M., Tojima, T., Kawamura, Y., Tanamoto, K., 2007. Survey of formaldehyde, acetaldehyde and oligomers in polyethylene terephthalate food-packaging materials. Food Addit. Contam. 22, 783–789. https://doi.org/10.1080/02652030500157593.

Mutsuga, M., Kawamura, Y., Tanamoto, K., 2008. Migration of lactic acid, lactide and oligomers from polylactide food-contact materials. Food Add. Contaminants: Part A 25, 1283–1290. https://doi.org/10.1080/02652030802017529.

Nelson, C.P., Patton, G.W., Arvidson, K., Lee, H., Twaroski, M.L., 2011. Assessing the toxicity of polymeric food-contact substances. Food Chem. Toxicol. 49, 1877–1897. https://doi.org/10.1016/J.FCT.2011.06.054.

Nerin, C., Alfaro, P., Aznar, M., Domeño, C., 2013. The challenge of identifying non-intentionally added substances from food packaging materials: a review. Anal. Chim. Acta 775, 14–24. https://doi.org/10.1016/J.ACA.2013.02.028.

Paez, A., 2017. Gray literature: An important resource in systematic reviews. J. Evidence-Based Med. 10, 233–240. https://doi.org/10.1111/jebm.12266.

Page, M.J., McKenzie, J.E., Bossuyt, P.M., Boutron, I., Hoffmann, T.C., Mulrow, C.D., Shamseer, L., Tetzlaff, J.M., Akl, E.A., Brennan, S.E., Chou, R., Glanville, J., Grimshaw, J.M., Hróbjartsson, A., Lalu, M.M., Li, T., Loder, E.W., Mayo-Wilson, E., McDonald, S., McGuinness, L.A., Stewart, L.A., Thomas, J., Tricco, A.C., Welch, V.A., Whiting, P., Moher, D., 2021. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. Syst. Rev. 10, 1–11. https://doi.org/10.1136/bmj.n71.

Pelch, K.E., Reade, A., Wolffe, T.A.M., Kwiatkowski, C.F., 2019. PFAS health effects database: Protocol for a systematic evidence map. Environ. Int. 130, 104851 https://doi.org/10.1016/J.ENVINT.2019.05.045.

Pietropaolo, E., Albenga, R., Gosetti, F., Toson, V., Koster, S., Marin-Kuan, M., Veyrand, J., Patin, A., Schilter, B., Pistone, A., Tei, L., 2018. Synthesis, identification and quantification of oligomers from polyester coatings for metal packaging. J. Chromatogr. A 1578, 15–27. https://doi.org/10.1016/J.CHROMA.2018.10.002.

Plastics Europe-Association of Plastics Manufactures, 2020. Plastics – the Facts 2020. Plastics Europe 1–64.

Regulation (EC) No 1935/2004 of the European Parliament and of the Council on materials and articles intended to come into contact with food and repealing Directives 80/590/EEC and 89/109/EEC, 2004.

Commission Regulation (EU) No 10/2011 on plastic materials and articles intended to come into contact with food, 2011.

Roth, N., Sandström, J., Wilks, M.F., 2020. A case study applying pathway-oriented thinking to problem formulation for planning a systematic review. Environ. Int. 140, 105768 https://doi.org/10.1016/j.envint.2020.105768.

Sapozhnikova, Y., Nuñez, A., Johnston, J., 2021. Screening of chemicals migrating from plastic food contact materials for oven and microwave applications by liquid and gas chromatography - Orbitrap mass spectrometry. J. Chromatogr. A 1651, 462261. https://doi.org/10.1016/J.CHROMA.2021.462261.

Silano, V., Bolognesi, Cl., Castle, L., Cravedi, J.-P., Engel, K.-H., Fowler, P., Franz, R., Grob, K., Gürtler, R., Husøy, T., Kärenlampi, S., Mennes, W., Milana, M.R., Penninks, A., de Fátima Tavares Poças, M., Smith, A., Tlustos, C., Wölfle, D., Zorn, H., Zugravu, C.-A., 2008. Note for Guidance For the Preparation of an Application for the Safety Assessment of a Substance to be used in Plastic Food Contact Materials. EFSA J. 6 (7) https://doi.org/10.2903/J.EFSA.2008.21R.

Solomon, K.R., Wilks, M.F., Bachman, A., Boobis, A., Moretto, A., Pastoor, T.P., Phillips, R., Embry, M.R., 2016. Problem formulation for risk assessment of combined exposures to chemicals and other stressors in humans. Crit. Rev. Toxicol. 46, 835–844. https://doi.org/10.1080/10408444.2016.1211617.

Tsochatzis, E.D., Alberto Lopes, J., Dehouck, P., Robouch, P., Hoekstra, E., 2020a. Proficiency test on the determination of polyethylene and polybutylene terephthalate cyclic oligomers in a food simulant. Food Packaging Shelf Life 23, 100441. https://doi.org/10.1016/j.fpsl.2019.100441.

Tsochatzis, E.D., Alberto Lopes, J., Kappenstein, O., Tietz, T., Hoekstra, E.J., 2020b. Quantification of PET cyclic and linear oligomers in teabags by a validated LC-MS method – In silico toxicity assessment and consumer's exposure. Food Chem. 317, 126427 https://doi.org/10.1016/j.foodchem.2020.126427.

Tsochatzis, E.D., Alberto Lopes, J., Holland, M.V., Reniero, F., Emons, H., Guillou, C., 2019. Isolation, characterization and structural elucidation of polybutylene terephthalate cyclic oligomers and purity assessment using a 1H qNMR method. Polymers (Basel) 11 (3), 464. https://doi.org/10.3390/polym11030464.

Tsochatzis, E.D., 2021. Food Contact Materials: Migration and Analysis. Challenges and Limitations on Identification and Quantification. Molecules 26. 10.3390/MOLECULES26113232.

Ubeda, S., Aznar, M., Nerín, C., 2018. Determination of oligomers in virgin and recycled polyethylene terephthalate (PET) samples by UPLC-MS-QTOF. Anal. Bioanal. Chem. 410, 2377–2384. https://doi.org/10.1007/s00216-018-0902-4.

Ubeda, S., Aznar, M., Alfaro, P., Nerín, C., 2019. Migration of oligomers from a food contact biopolymer based on polylactic acid (PLA) and polyester. Anal. Bioanal. Chem. 411 (16), 3521–3532. https://doi.org/10.1007/s00216-019-01831-0.

Whaley, P., Aiassa, E., Beausoleil, C., Beronius, A., Bilotta, G., Boobis, A., de Vries, R., Hanberg, A., Hoffmann, S., Hunt, N., Kwiatkowski, C.F., Lam, J., Lipworth, S., Martin, O., Randall, N., Rhomberg, L., Rooney, A.A., Schünemann, H.J., Wikoff, D., Wolffe, T., Halsall, C., 2020. Recommendations for the conduct of systematic reviews in toxicology and environmental health research (COSTER). Environ. Int. 143, 105926 https://doi.org/10.1016/j.envint.2020.105926.

Wolffe, T.A.M., Whaley, P., Halsall, C., Rooney, A.A., Walker, V.R., 2019. Systematic evidence maps as a novel tool to support evidence-based decision-making in chemicals policy and risk management. Environ. Int. 130, 104871 https://doi.org/10.1016/j.envint.2019.05.065.

Wolffe, T.A.M., Vidler, J., Halsall, C., Hunt, N., Whaley, P., 2020. A Survey of Systematic Evidence Mapping Practice and the Case for Knowledge Graphs in Environmental Health and Toxicology. Toxicol. Sci. 175, 35–49. https://doi.org/10.1093/toxsci/kfaa025.