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

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ABSTRACT

Background: The presence of polyethylene terephthalate (PET) oligomers in food contact materials (FCMs) is well-documented. Consumers are exposed through their migration into foods and beverages; however, there is no specific guidance for their safety evaluation.

Objectives: This systematic evidence map (SEM) aims to identify and organize existing knowledge and associated gaps in hazard and exposure information on 34 PET oligomers to support regulatory decision-making.

Methods: The methodology for this SEM was recently registered. A systematic search in bibliographic and gray literature sources was conducted and studies evaluated for inclusion according to the Populations, Exposures, Comparators, Outcomes, and Study type (PECOS) framework. Inclusion criteria were designed to record hazard and exposure information for all 34 PET oligomers and coded into the following evidence streams: human, animal, organism (non-animal), *ex vivo*, *in vitro*, *in silico*, migration, hydrolysis, and absorption, distribution, metabolism, excretion/toxicokinetics/pharmacokinetics (ADME/TK/PK) studies. Relevant information was extracted from eligible studies and synthesized according to the protocol.

Results: Literature searches yielded 7445 unique records, of which 96 were included. Data comprised migration (560 entries), ADME/TK/PK-related (253 entries), health/bioactivity (98 entries) and very few hydrolysis studies (7 entries). Cyclic oligomers were studied more frequently than linear PET oligomers. *In vitro* results indicated that hydrolysis of cyclic oligomers generated a mixture of linear oligomers, but not monomers, potentially allowing their absorption in the gastrointestinal tract. Cyclic dimers, linear trimers and the respective smaller oligomers exhibit physico-chemical properties making oral absorption more likely. Information on health/bioactivity effects of oligomers was almost non-existent, except for limited data on mutagenicity.

Conclusions: This SEM revealed substantial deficiencies in the available evidence on ADME/TK/PK, hydrolysis, and health/bioactivity effects of PET oligomers, currently preventing appropriate risk assessment. It is essential

Abbreviations: ADME, Absorption, distribution, metabolism, excretion; CAS RN, Chemical abstracts service registry number; DEG, Diethylene glycol; EG, Ethylene glycol; FCC, Food contact chemical; FCM, Food contact material; IAS, Intentionally added substances; IPA, Isophthalic acid; IUPAC, International union of pure and applied chemistry; NIAS, Non-intentionally added substances; PECOS, Population, exposure, comparator, outcome, and study type; PET, Polyethylene terephthalate; PK, Pharmacokinetics; SEM, Systematic evidence map; TIAB, Title and abstract; TK, Toxicokinetics; TPA, Terephthalic acid; TTC, Threshold of toxicological concern.

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to develop more systematic and tiered approaches to address the identified research needs and assess the risks of PET oligomers.

1. Introduction

Polyethylene terephthalate oligomers are a class of substances that are ubiquitous in PET food contact materials (FCMs) and they are considered non-intentionally added substances (NIAS). The formation of such PET-specific substances is generally associated with incomplete polymerization, or thermal or hydrolytic degradation of polymer chains during the manufacture of food contact articles (Hoppe et al., 2017). PET oligomers can migrate into foods and beverages, in which different molecules have already been detected, exposing consumers to different amounts of PET oligomers (Alberto Lopes et al., 2021, Alberto Lopes and Tsochatzis, 2023; Begley et al., 1990; Castle et al., 1989; Hoppe et al., 2017; Mutsuga et al., 2005; Tsochatzis et al., 2020a). Oligomers and other NIAS consist of a very large number of substances and constitute complex mixtures.

To date, no specific guidance document for the safety assessment of oligomers exists and there are no direct recommendations for their risk assessment by food safety authorities worldwide. Oligomers with a molecular weight less than 1000 Da are usually considered for risk assessment. This threshold represents a molecular weight limit above which poor gastrointestinal absorption is assumed. ("Commission Regulation (EU) No 10/2011", 2011). Traditionally, the assessment of oligomers was covered by those of the corresponding monomers, assuming complete hydrolysis of the oligomers. The PET-related monomers ethylene glycol (EG), terephthalic acid (TPA), and isophthalic acid (IPA) have specific migration limits (SML) of 30 mg/kg, 7.5 mg/kg, and 5 mg/kg, respectively ("Commission Regulation (EU) No 10/2011," 2011). However, the validity of this approach has not been demonstrated.

The main challenge with respect to oligomers is that their chemical identity, level of migration, and toxicological properties are often unknown and consequently preventing their individual assessment (Omer et al., 2019; Hu et al., 2021; Sapozhnikova et al., 2021; Tsochatzis, 2021). Several attempts have been made to find evaluation strategies for such substances. Some focus on the assessment of genotoxicity based on structure–activity relationships (SAR) and read-across approaches. (BfR, 2022; Bolognesi et al., 2016; ILSI, 2015). An alternative strategy is to use the threshold of toxicological concern (TTC) concept to estimate safety values for PET oligomers of unknown toxicity. In the framework of the TTC concept, a previous study classified linear PET oligomers as Cramer class I substances with a corresponding exposure limit of 30 μg/kg body weight/day and cyclic oligomers as Cramer class III substances with a lower exposure limit of 1.5 μg/kg body weight/day (Alberto Lopes et al., Alberto Lopes and Tsochatzis, 2023; More et al., 2019; Tsochatzis et al., 2020b). The establishment of exposure limits is important for molecules with unknown toxicological and/or biological activity in order to characterize risks to consumers and identify those requiring mitigation measures. However, it is currently not clear whether the application of the TTC concept is appropriate for PET oligomers, and the concept has been criticized for its underlying scientific uncertainty (Bschir, 2017). Therefore, further information is needed to increase the knowledge and understanding of PET oligomer safety as a group. The objective of the present study was therefore to collect existing hazard and exposure information on 34 previously prioritized PET oligomers derived from PET in FCM to further improve access to this data and inform on their suitability for chemical risk assessment (Schreier et al., 2022b). The 34 prioritized PET oligomers can be divided into four series. The first series consists of linear oligomers with an equal number of TPA and EG units. A known modification of the oligomer is the introduction of additional ethylene glycol. The remaining three series include cyclic oligomers where one, two, and three ethylene glycol units have been replaced by diethylene glycol (DEG) units, respectively (Schreier et al., 2022b). In addition, IPA can replace a TPA moiety when used as a co-monomer (Brenz et al., 2021) and was also considered in the present study.

Systematic evidence mapping (SEM) was used as a transparent and reproducible method to identify, organize, and analyze information available for use in broad chemical risk assessment contexts to support evidence-based decision making (James et al., 2016; Keshava et al., 2020; Pelch et al., 2019; Thayer et al., 2022; Wolffe et al., 2020, 2019). All evidence obtained in the present study on hazard and exposure is provided as searchable tables in the Supplementary Material.

2. Methods

The protocol describing the methodology of this SEM was initially registered on Zenodo (Schreier et al., 2022a), then peer-reviewed and published in Environment International (Schreier et al., 2022b). An update of the protocol including any associated amendments is described in detail in the Supplementary Material. The goal of carrying out this SEM was to identify and organize the existing evidence on hazard and exposure information related to 34 oligomers derived from PET in FCM, to support future research and chemical risk assessment activities.

The 34 PET oligomers were selected in a scoping exercise and prioritized based on the identification of their chemical structure and detection in PET-based FCMs (Table 1). The first series comprises of oligomers consisting of an equal number of TPA and EG units. The remaining three series include cyclic oligomers where one, two, and three EG units have been replaced by DEG units, respectively. TPA can be replaced by IPA (CAS RN 121-91-5), which can be used as a co-monomer in the production process (Brenz et al., 2021).

Searches were performed in multiple bibliographic databases (Embase, Ovid MEDLINE, Web of Science Core Collection (WoS), Scopus), chemistry databases (SciFinder-n, and Reaxys), and 28 Gy literature sources (vetted (non-) governmental, scientific, or regulatory organizations websites). The search strategy for bibliographic databases included generic and stressor-specific search terms, and was split into two parts: a part with generic PET oligomer search terms and a stressor-specific part. The search included CAS RN, IUPAC, and common names for the PET oligomers, and was not restricted by publication date or language. Searches in the chemistry databases SciFinder-n and Reaxys, which are designed to support structure-based searches, used SMILES strings and CAS RN for the 34 PET oligomers of interest. The search strategy for the gray literature was dependent on the availability and functionality of the search engines and was decided based on a decision tree. Full details of chemical names and descriptors, search strategy, and search strings can be found in the published protocol (Schreier et al., 2022b), and amendments to the protocol are reported in the Supplementary Material.

After importing the records retrieved from bibliographic and chemical databases into EndNote 20 (Clarivate Analytics) and removing duplicates according to the Bramer method (Bramer et al., 2016), the search results were imported into the web-based interface application PICO Portal (https://picoportal.org/), an online management software for systematic reviews. To be eligible for inclusion, studies had to meet the criteria specified in the Populations, Exposures, Comparators, Outcome, and Study type (PECOS) framework (Table 2). Studies that did not meet these criteria, as well as conference abstracts, presentations, posters, book chapters, and theses/dissertations, were excluded. VNS conducted title and abstract (TIAB) screening. Studies for which a decision on inclusion or exclusion could not be made based on the title and abstract were included for further evaluation by full-text screening. Two

Table 1
List of PET oligomers included in the systematic evidence map. Oligomer category name, acronym-based abbreviation, and CAS RN. 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
First series cyclic monomer	C[TPA + EG]	7337-79-3
First series cyclic dimer	C[TPA + EG]2	24388-68-9
First series cyclic trimer	C[TPA + EG]3	7441-32-9
First series cyclic tetramer	C[TPA + EG]4	16104-96-4
First series cyclic pentamer	C[TPA + EG]5	16104-97-5
First series cyclic hexamer	C[TPA + EG]6	29644-29-9
First series cyclic heptamer	C[TPA + EG]7	29668-12-0
First series cyclic octamer	C[TPA + EG]8	42245-76-1
First series cyclic dimer + IPA	C[TPA + EG] + [IPA + EG]	Not available
First series cyclic trimer + IPA	C[TPA + EG]2 + [IPA + EG]	536746-07-3
First series cyclic tetramer + IPA	C[TPA + EG]3 + [IPA + EG]	Not available
First series cyclic pentamer + IPA	C[TPA + EG]4 + [IPA + EG]	Not available
First series linear monomer	L[TPA + EG]	1137-99-1
First series linear dimer	L[TPA + EG]2	23186-89-2
First series linear trimer	L[TPA + EG]3	16958-96-6
First series linear monomer + EG	L[TPA + EG] + EG	959-26-2
First series linear dimer + EG	L[TPA + EG]2 + EG	2144-69-6
First series linear trimer + EG	L[TPA + EG]3 + EG	16033-73-1
First series linear tetramer + EG	L[TPA + EG]4 + EG	34298-51-6
First series linear monomer + TPA	L[TPA + EG] + TPA	2225-05-0
First series linear dimer + TPA	L[TPA + EG]2 + TPA	1855-25-0
First series linear trimer + TPA	L[TPA + EG]3 + TPA	122295-57-2
Second series cyclic dimer	C[TPA + EG] + [TPA + DEG]	29278-57-7
Second series cyclic trimer	C[TPA + EG]2 + [TPA + DEG]	873422-64-1
Second series cyclic tetramer	C[TPA + EG]3 + [TPA + DEG]	2222729-29-3
Second series cyclic pentamer	C[TPA + EG]4 + [TPA + DEG]	Not available
Second series cyclic hexamer	C[TPA + EG]5 + [TPA + DEG]	Not available
Second series cyclic dimer + IPA	C[TPA + EG] + [IPA + DEG]	Not available
Second series linear monomer	L[TPA + DEG]	65087-23-2
Second series linear dimer	L[TPA + EG] + [TPA + DEG]	2222639-12-3
Second series linear monomer + EG	L[TPA + DEG] + EG	65133-69-9
Third series cyclic dimer	C[TPA + DEG]2	16104-98-6
Third series cyclic trimer	C[TPA + EG] + [TPA + DEG]2	Not available
Fourth series cyclic tetramer	C[TPA + EG] + [TPA + DEG]3	Not available

Table 2
Population, Exposure, Comparator, Outcome, and Study type (PECOS) framework.

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	In vivo, *ex vivo, in vitro, in silico*, mechanistic, epidemiological (human).

independent reviewers (VNS, EC) conducted the full-text screening and exclusion reasons were recorded. Exclusion of studies required agreement by two reviewers, and all disagreements were resolved through discussion. Unless otherwise stated, gray literature records were screened at full-text level for inclusion by two independent reviewers (VNS, EC), applying the same eligibility criteria as for the bibliographic sources. For gray literature sources with more than 150 identified records: EFSA, FDA, Science.gov, and NTP, records were excluded at the TIAB level. In cases where a decision could not be made at the TIAB level, these records were screened at the full-text level. Gray literature screening at the TIAB and full-text level was performed by two independent reviewers (VNS and EC). Disagreements were resolved by consensus and such cases were documented.

Eligible indexed literature was used for forward and backward citation tracking using the databases Scopus, WoS, and TheLens via citationchaser (https://estech.shinyapps.io/citationchaser/) to identify additional eligible records that may have been missed by the initial searches. Citation tracking records were imported into EndNote 20 and deduplicated before screening for eligibility as described above.

This SEM incorporated a wide range of data from multiple research areas and disciplines. Eligible evidence was coded into the following 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"*

Each identified qualitative or quantitative unit of information was recorded as an individual data entry per oligomer and evidence stream, with the exception of migration data, where reported migration values were summarized as ranges for the same conditions and same type of food contact article (Supplementary Material). If a record/reference contained information on multiple oligomers or different evidence streams for a single oligomer, all the information was retrieved and recorded as individual data entries. Unknown compositions of PET oligomer mixtures and their respective information were recorded separately as "mixture of PET oligomer" according to their evidence stream.

Although environmental risk assessment in many respects addresses different endpoints than human risk assessment, ecotoxicological studies may be useful for prioritizing future human health research and have therefore been included in this SEM. However, because the environmental fate data may be informative only in an expanded context, it was not addressed in the main text of the report, but was still recorded in a summarized form and included as supportive knowledge in the Supplementary Material.

Data coding and extraction was performed by a single reviewer (VNS), with a second reviewer (EC) confirming the accuracy and completeness of the extracted data. Free-text entries were visually reviewed for inconsistencies and normalized as needed by one reviewer (VNS), with the process confirmed by a second reviewer (EC). Any disagreements were resolved through consensus.

Because the data to be extracted, such as migration and hydrolysis, were not covered by the tools commonly used for systematic reviews or maps, a custom MS Access flat file database was used for data entry, storage, and analysis. The database contained a long form table for each evidence stream, including bibliographic information and data on stressors and the evidence stream. The tables included drop-down lists and free-text options, and the database allowed for the entry of the detailed information related to the evidence streams. Full details for data extraction and coding are described in the protocol (Schreier et al.,

2022b), with amendments reported in the Supplementary Material. The information collected in customized MS Access flat file database is provided in form of searchable MS Excel spreadsheets in the Supplementary Material.

The summarized data at different levels of granularity were visualized using MS Excel in the form of bar charts and tables (see Results and Discussion for details).

3. Results and discussion

3.1. Literature search results

Database searches for the bibliographic databases, Embase, Ovid MEDLINE, WoS, Scopus, SciFinder-n, and Reaxys were performed on June 13, 2022 and retrieved 5401 unique records that were evaluated by TIAB screening. During this process, 146 records were selected for full-text screening. 7 of these articles could not be retrieved for full-text screening and were therefore not further analyzed. Of the remaining 139 records, 37 met the eligibility criteria for this SEM. Gray literature searches were conducted between June 6 and July 1, 2022. As an amendment to the protocol (Supplementary Material), on October 14 and 15, 2022, additional searches were conducted in SciFinder-n and Reaxys repositories as gray literature sources. In total, 1047 records were identified from gray literature searches. Since gray literature records are not consistently indexed like records from bibliographic databases, this number also harbored duplicates. Of these 1047 records, 56 were included in this study. Forward and backward citation tracking was performed on July 28, 2022, using eligible indexed literature records from bibliographic databases and gray literature. After removal of duplicates, 997 unique records were screened for eligibility on TIAB and full-text, of which 3 records were included in this study (Fig. 1).

For both bibliographic and gray literature searches, most records were excluded at the full-text level because they did not pertain to the PET oligomers of interest ("other stressor(s)" n = 24); only provided information on their detection and/or chemical identification ("stressor identification only" n = 13); investigated other materials ("other material(s)" n = 42); or did not meet the criteria for hydrolysis studies ("non-eligible hydrolysis" n = 25). Only a small number of records were excluded due to lack of defined chemical structure ("Isomer(s) not defined n = 1) or duplication ("duplicate" n = 4). The exclusion reason "other reason" included all other reasons why the PECOS criteria were not met (n = 1007). This included, for example, studies that used PET oligomers for the chemical synthesis of other compounds or PET materials. Out of a total of 7445 records retrieved from all literature searches and after deduplication of indexed literature, 96 records were finally included. In addition to 55 records from SciFinder-n, Reaxys, and PubChem as sources of gray literature (supplementary material), 41 records are based on indexed scientific literature (Alberto Lopes et al., 2021; Araki et al., 2005; Bauer et al., 2019; Begley et al., 1990; Begley and Hollifield, 1989; Begley and Hollifield, 1990a, 1990b, 1990c; Brenz et al., 2021; Buiarelli et al., 1993; Castle et al., 1990, 1989; Cimecioglu et al., 1986; Diamantidou et al., 2022; Djapovic et al., 2021; Dulio et al., 1995; Eckardt et al., 2019, 2018; Freire et al., 1999; Hoppe et al., 2017; Jabarin and Balduff, 1982; Järvenpää et al., 2022; Jetten et al., 1999; Jetten and de Kruijf, 2002; Jickells et al., 1992, 1991; Kim and Lee, 2012a, 2012b; Komolprasert et al., 2001; López-Cervantes et al., 2003; Mutsuga et al., 2005; Nasser et al., 2005; Ohkado et al., 2005; Paseiro-Cerrato et al., 2016; Peebles et al., 1969; Rajbux et al., 2020; Tsochatzis et al., 2021, 2020b; Ubeda et al., 2018; Wick and Zeitler, 1983; Xu et al., 2021).

3.2. Summary of data coding and extraction results

This SEM examined 34 PET oligomers of interest to identify available

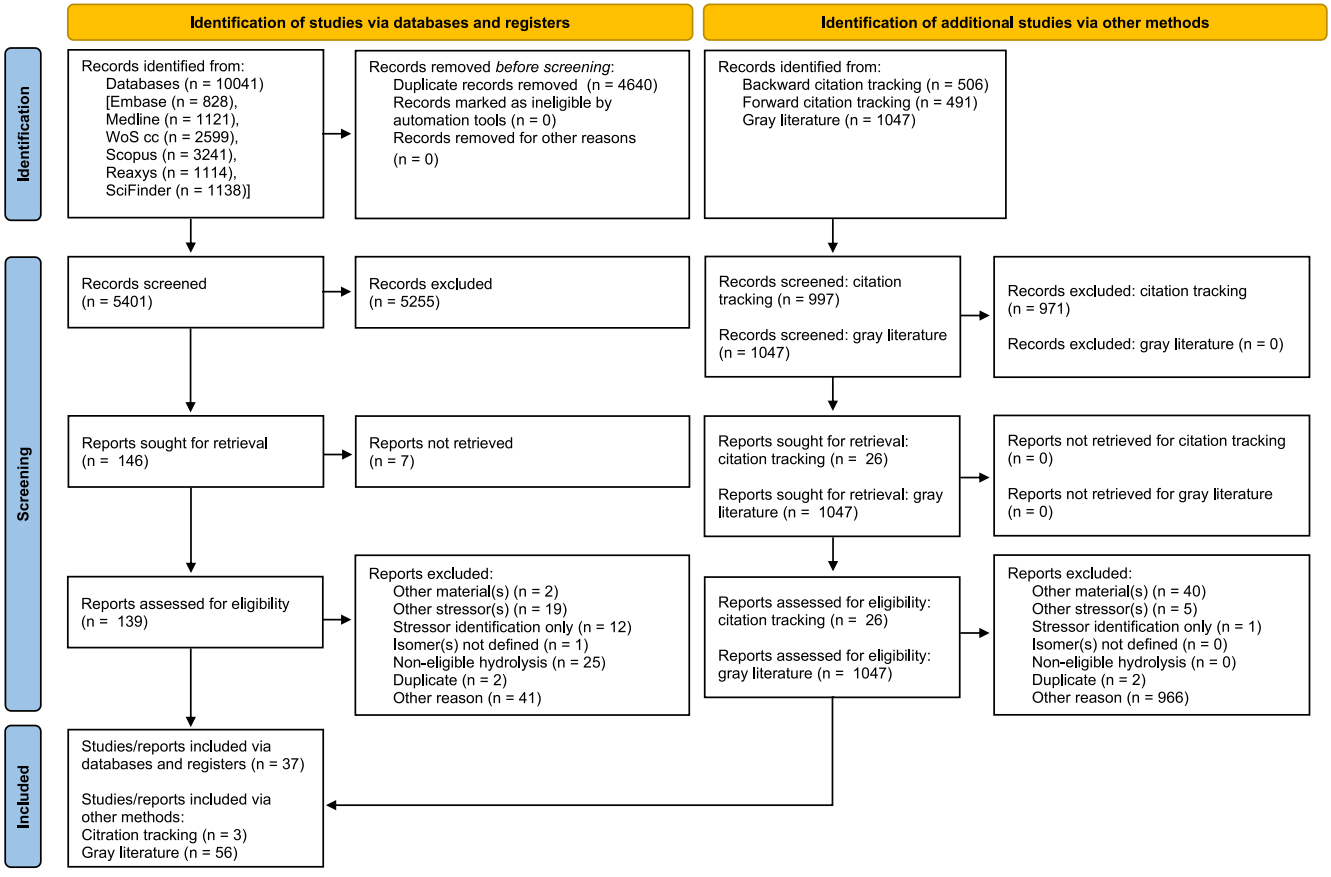

Fig. 1. PRISMA flowchart of the overall study screening and selection process.

hazard and exposure data (Table 1). Evidence on hazard and exposure was extracted and organized into the following nine evidence streams: Human, animal, organisms (non-animal), *ex vivo*, *in vitro*, *in silico*, migration, hydrolysis, and ADME/TK/PK-related studies. To provide a general overview of all available hazard and exposure data, the evidence streams were grouped into four categories: Migration, hydrolysis, ADME/TK/PK, and health/bioactivity related data. All four categories may include *in silico* data, while the three categories hydrolysis, ADME/TK/PK, and health/bioactivity may include human, animal, organism (non-animal), *ex vivo*, and *in vitro* studies. The data analysis of the summarized evidence revealed that the majority of the data pertained to migration (560 data entries) and ADME/TK/PK (253 data entries) studies, while a smaller fraction pertained to health/bioactivity data (98 data entries) and almost no data were available on hydrolysis (7 data entries) (Fig. 2a). It is worth noting that the number of data entries in the migration category does not necessarily represent the number of individual units of information and, thus, cannot be directly compared to the other categories. However, the migration data were combined for consistency in this study, meaning that the actual gap between the evidence available regarding migration and the other categories is even larger than it appears. The migration data would contain additional data entries. Despite this, it is still clear from the overview that previous research has focused primarily on migration and, therefore, exposure assessment, while health effects and hydrolysis properties have received less attention.

In order to analyze the data more in depth, the four categories were divided into six oligomer-based categories to identify any differences in available knowledge and knowledge gaps for different oligomer groups. The majority of oligomers belonged to the first series cyclic and linear oligomers, with 12 and 10 oligomers respectively, and second series cyclic oligomers with 6 oligomers (Table 1). These three groups also had the most data entries per oligomer in the area of migration (with a range of 5.1 to 24.3 data entries per oligomer), hydrolysis (with a range of 0 to 0.4 data entries per oligomer), ADME/TK/PK (with a range of 2.0 to 9.3 data entries per oligomer), and health/bioactivity data (with a range of 0.6 to 3.0 data entries per oligomer) (Fig. 2b). This trend is reflected in the overall data, with a focus on migration and ADME/TK/PK-related studies, and less emphasis on health/bioactivity and hydrolysis. Additionally, six oligomers from the categories of linear oligomers of the second series, as well as cyclic oligomers of the third and fourth series, were included in this SEM. However, regardless of the category, very few data were available for these oligomers (with a range of 0 to 1.5 entries per oligomer). In general, it appears that cyclic PET oligomers were more often studied than linear PET oligomers. The preference for testing cyclic compounds might be caused by for example the generally lower abundance of linear oligomers, or due the more straightforward analytics of cyclic oligomers, combined with the greater potential risk posed by their increased hydrophobicity compared to linear PET oligomers. As a result, testing for exposure to cyclic oligomers may have been given higher priority.

In a next step, a more in-depth analysis of the data was conducted by visualizing the information available for each PET oligomer or mixture, and the four categories were again divided into the following nine evidence streams: Human, animal, organisms (non-animal), *ex vivo*, *in vitro*, *in silico*, migration, hydrolysis, and ADME/TK/PK-related studies. The collected and recorded evidence is presented in Table 3. Data were not identified for all evidence streams. Information on migration contained a combination of analytical chemical measurements (557 data entries) and *in silico* predictions (3 data entries); hydrolysis was determined through analytical chemical methods (4 data entries) and *in vitro* testing (1 data entry); the category ADME/TK/PK included analytical chemical measurements (36 data entries), human data (4 data entries), *in vitro* (1 data entry), and *in silico* data (212 data entries); and health/bioactivity-related data encompassed evidence from organisms (3 data entries), *in vitro* (2 data entries) and *in silico* sources (93 data entries). The most prominent data included the analytical chemical measurements of migration and the *in silico* predictions for ADME/TK/PK- and health/bioactivity-related information. Other evidence streams were only minimally represented, indicating larger knowledge gaps that need to be addressed. Examining the data entries for individual oligomers, the most frequently researched oligomer is C[TPA + EG]3, with a total of 134 data entries, followed by C[TPA + EG]2 and C[TPA + EG]4, with 78 and 67 data entries, respectively. Concerning linear oligomers, the most studied molecules are L[TPA + EG] + EG and L[TPA + EG], with 59 and 40 data entries, respectively. The oligomers with the least data available (0–4 data entries) belonged to the category of first and second series cyclic oligomers with isophthalic acid (IPA) modification, and C[TPA + EG] + [TPA + DEG]3.

3.3. Migration-related evidence

As defined in the SEM protocol, for simplicity, the term “migration” used in this SEM refers to both migration and extraction (Schreier et al., 2022a). Migration and extraction tests are common methods for quantitatively determining the presence of a substance in food or beverages, food simulants, and FCMs. Specifically, migration assesses the

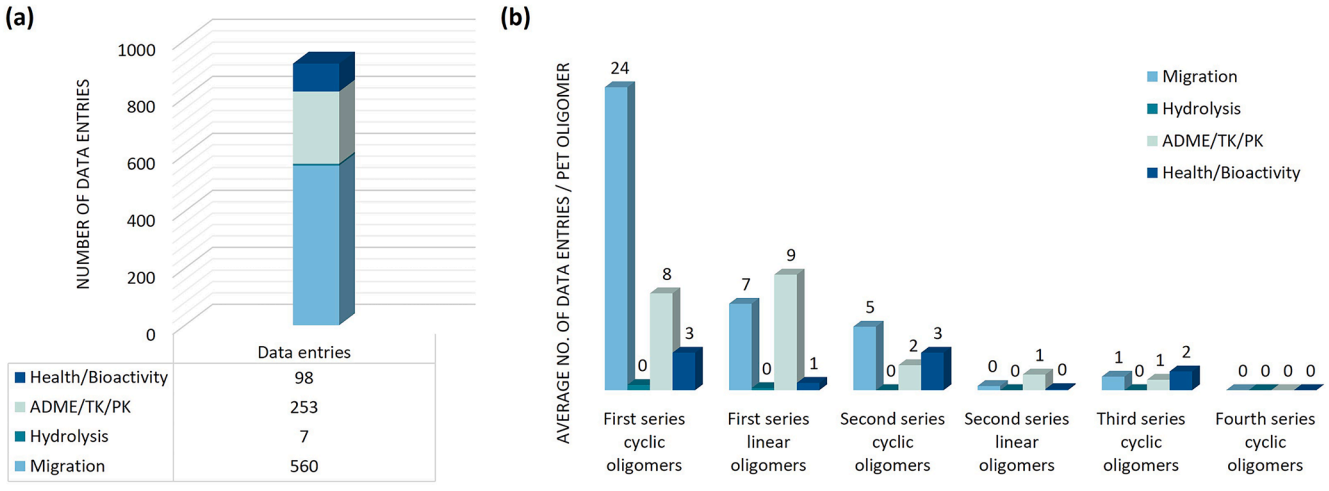

Fig. 2. Summary of all data entries from eligible records. Data entries are summarized into four categories: migration, hydrolysis, ADME/TK/PK, and health/bioactivity data. (a) Total numbers of data entries per category. (b) Average number of data entries per PET oligomer further organized into six oligomer categories: first series cyclic and linear oligomers, second series cyclic and linear oligomers, third series cyclic oligomers, and fourth series cyclic oligomers. Number of PET oligomers per group is represented in brackets behind the oligomer-based categories.

Table 3
Summary of all identified and extracted evidence for 34 PET oligomers from the categories first, second, third, fourth series, and for mixtures of PET oligomers. Analytical data (analyt.) refers to information that includes analytical chemical measurements without testing in a biological environment.

Oligomer category name			Acronym-based abbreviation	Number of database entries related to											
				Migration		Hydrolysis		ADME/TK/PK				Health/Bioactivity			Total
				Analyt.	*In silico*	*Analyt.*	*In vitro*	*Analyt.*	*Human*	*In vitro*	*In silico*	*Organism*	*In vitro*	*In silico*	
First series	cyclic	monomer	C[TPA+EG]	7	0	0	0	0	0	0	11	0	0	0	**18**
		dimer	C[TPA+EG]2	52	0	0	0	3	1	0	13	0	0	9	**78**
		trimer	C[TPA+EG]3	99	3	2	1	4	1	0	15	0	0	9	**134**
		tetramer	C[TPA+EG]4	46	0	0	0	2	1	0	9	0	0	9	**67**
		pentamer	C[TPA+EG]5	41	0	0	0	2	1	0	6	0	0	9	**59**
		hexamer	C[TPA+EG]6	24	0	0	0	1	0	0	7	0	0	0	**32**
		heptamer	C[TPA+EG]7	14	0	0	0	1	0	0	7	0	0	0	**22**
		octamer	C[TPA+EG]8	5	0	0	0	0	0	0	4	0	0	0	**9**
	cyclic	dimer + IPA	C[TPA+EG]+[IPA+EG]	0	0	0	0	0	0	0	0	0	0	0	**0**
		trimer + IPA	C[TPA+EG]2+[IPA+EG]	0	0	0	0	0	0	0	4	0	0	0	**4**
		tetramer + IPA	C[TPA+EG]3+[IPA+EG]	0	0	0	0	0	0	0	0	0	0	0	**0**
		pentamer + IPA	C[TPA+EG]4+[IPA+EG]	0	0	0	0	0	0	0	0	0	0	0	**0**
	linear	monomer	L[TPA+EG]	23	0	0	0	3	0	0	14	0	0	0	**40**
		dimer	L[TPA+EG]2	10	0	0	0	1	0	0	10	0	0	1	**22**
		trimer	L[TPA+EG]3	7	0	0	0	1	0	0	9	0	0	1	**18**
	linear	monomer + EG	L[TPA+EG]+EG	28	0	2	0	3	0	1	20	3	2	0	**59**
		dimer + EG	L[TPA+EG]2+EG	3	0	0	0	1	0	0	11	0	0	0	**15**
		trimer + EG	L[TPA+EG]3+EG	3	0	0	0	1	0	0	6	0	0	0	**10**
		tetramer + EG	L[TPA+EG]4+EG	3	0	0	0	1	0	0	6	0	0	0	**10**
	linear	monomer + TPA	L[TPA+EG]+TPA	0	0	0	0	2	0	0	6	0	0	0	**8**
		dimer + TPA	L[TPA+EG]2+TPA	3	0	0	0	2	0	0	6	0	0	0	**11**
		trimer + TPA	L[TPA+EG]3+TPA	3	0	0	0	1	0	0	6	0	0	0	**10**
Second series	cyclic	dimer	C[TPA+EG]+[TPA+DEG]	17	0	0	0	2	0	0	9	0	0	9	**37**
		trimer	C[TPA+EG]2+[TPA+DEG]	16	0	0	0	0	0	0	6	0	0	9	**31**
		tetramer	C[TPA+EG]3+[TPA+DEG]	14	0	0	0	0	0	0	5	0	0	9	**28**
		pentamer	C[TPA+EG]4+[TPA+DEG]	9	0	0	0	1	0	0	1	0	0	9	**20**
		hexamer	C[TPA+EG]5+[TPA+DEG]	5	0	0	0	0	0	0	0	0	0	0	**5**
	cyclic	dimer + IPA	C[TPA+EG]+[IPA+DEG]	0	0	0	0	0	0	0	0	0	0	0	**0**
	linear	monomer	L[TPA+DEG]	0	0	0	0	1	0	0	4	0	0	0	**5**
		dimer	L[TPA+EG]+[TPA+DEG]	4	0	0	0	0	0	0	4	0	0	0	**8**
	linear	monomer + EG	L[TPA+DEG]+EG	0	0	0	0	0	0	0	6	0	0	1	**7**
Third series	cyclic	dimer	C[TPA+DEG]2	9	0	0	0	3	0	0	7	0	0	9	**28**
		trimer	C[TPA+EG]+[TPA+DEG]2	4	0	0	0	0	0	0	0	0	0	9	**13**
Fourth series	cyclic	tetramer	C[TPA+EG]+[TPA+DEG]3	0	0	0	0	0	0	0	0	0	0	0	**0**
Mixture of PET oligomers				108	0	0	0	0	0	0	0	0	0	0	**108**

concentration of a substance in food or beverages and food simulants, while extraction uses different conditions such as total dissolution or organic solvents like dichloromethane or acetonitrile to determine the concentration of a substance in FCMs. Extraction therefore represents a measure for the maximum possible transferable level of a substance, which can be considered as a worst-case migration scenario. By using migration or extraction values, the extent of exposure to a given substance can be determined or estimated using appropriate food intake information. Both migration and extraction testing are therefore important tools for assessing exposure and ensuring food safety and quality ("Commission Regulation (EU) No 10/2011," 2011).

Migration of PET oligomers from FCMs has been widely reported in the scientific literature and was the most common type of data recorded in this SEM. The mass transfer of substances from food contact articles varies depending on the specific conditions, such as the temperature, type of food, and duration of contact (Brandsch et al., 2015). Commission Regulation (EU) 10/2011 therefore provides a framework for conducting migration tests. However, within this SEM, it was found that the reported data on this topic was heterogeneous, as different studies used different conditions, whether in compliance with the regulation or not, and also different types of food contact articles and analytical techniques were used (see Supplementary Material for experimental details). Furthermore, while utilizing ethanol–water mixtures as a food simulant may comply with regulations, these test conditions are not appropriate for accurately determining and assessing exposure to PET oligomers. Ethanol-water mixtures can cause swelling of the material, hydrolysis of existing oligomers, or the formation of new oligomers (see chapter 3.4 for more details). This can lead to an overestimation of the true exposure to PET oligomers and a skewed understanding of which specific oligomers the consumer is exposed to. The choice of experimental conditions is consequently important and its impact on migration or extraction must be taken into account. Overall, the diversity of available data and the difficulty of comparing and analyzing the data impede drawing general conclusions and making recommendations.

An attempt was made to analyze knowledge and knowledge gaps in a more general approach by categorizing and summarizing the migration data based on the type of migration or extraction experiment. These categories include migration into food (including beverages), migration into food simulants, and extraction, with further distinctions being made as to whether the information was based on analytical chemical measurements (analyt.) or *in silico* predictions (Table 4). It is important to note that two types of data were recorded: Cases where the degree of migration or concentration of oligomers in the polymer was quantified, and cases where this was tested or attempted but the respective oligomers could not be detected and/or quantified. Some cases were recorded and highlighted in bold (Table 4), where migration or extraction of an oligomer was investigated, but the oligomer could not be detected and/or quantified under any of the conditions applied. The data for all other PET oligomers included a combination of both scenarios, depending on the experimental conditions and analytical methods used.

Table 4
Summary of all identified and recorded migration related evidence for 34 oligomers from the categories first, second, third, fourth series, and for mixtures of PET oligomers. If evidence for a PET oligomer or oligomer mixture was recorded, it is labeled with "yes" and the number of data entries are given in parentheses; otherwise, "no data" is stated. Values in bold indicate cases where migration or extraction of an oligomer was investigated, but the respective oligomers could not be detected/quantified under any of the conditions applied. Analytical data (analyt.) refers to information that includes analytical chemical measurements without testing in a biological environment.

Oligomer category name			Acronym-based abbreviation	Number of database entries related to hydrolysis	
				Analyt.	*In vitro*
First series	cyclic	monomer	C[TPA+EG]	No data	No data
		dimer	C[TPA+EG]2	No data	No data
		trimer	C[TPA+EG]3	Chemical stability in 50% ethanol for 10 or 30 days at 40 °C: Hydrolysis to L[TPA+EG]3, L[TPA+EG]2, L[TPA+EG]+EG, L[TPA+EG], TPA; 0 - 30% of the parent oligomer remaining	Intestinal digestion for 1-4 hours: Hydrolysis to L[TPA+EG]3, L[TPA+EG]2+TPA, L[TPA+EG]2, L[TPA+EG]+TPA, L[TPA+EG]+EG, L[TPA+EG], after 4h < 20% of the parent oligomer remaining, no significant monomer formation
		tetramer	C[TPA+EG]4	No data	No data
		pentamer	C[TPA+EG]5	No data	No data
		hexamer	C[TPA+EG]6	No data	No data
		heptamer	C[TPA+EG]7	No data	No data
		octamer	C[TPA+EG]8	No data	No data
	cyclic	dimer + IPA	C[TPA+EG]+[IPA+EG]	No data	No data
		trimer + IPA	C[TPA+EG]2+[IPA+EG]	No data	No data
		tetramer + IPA	C[TPA+EG]3+[IPA+EG]	No data	No data
		pentamer + IPA	C[TPA+EG]4+[IPA+EG]	No data	No data
	linear	monomer	L[TPA+EG]	No data	No data
		dimer	L[TPA+EG]2	No data	No data
		trimer	L[TPA+EG]3	No data	No data
	linear	monomer + EG	L[TPA+EG]+EG	Chemical stability in 50% ethanol for 10 or 30 days at 40 °C: Hydrolysis to L[TPA+EG];TPA; 55% of the parent oligomer remaining	No data
		dimer + EG	L[TPA+EG]2+EG	No data	No data
		trimer + EG	L[TPA+EG]3+EG	No data	No data
		tetramer + EG	L[TPA+EG]4+EG	No data	No data
	linear	monomer + TPA	L[TPA+EG]+TPA	No data	No data
		dimer + TPA	L[TPA+EG]2+TPA	No data	No data
		trimer + TPA	L[TPA+EG]3+TPA	No data	No data
Second series	cyclic	dimer	C[TPA+EG]+[TPA+DEG]	No data	No data
		trimer	C[TPA+EG]2+[TPA+DEG]	No data	No data
		tetramer	C[TPA+EG]3+[TPA+DEG]	No data	No data
		pentamer	C[TPA+EG]4+[TPA+DEG]	No data	No data
		hexamer	C[TPA+EG]5+[TPA+DEG]	No data	No data
	cyclic	dimer + IPA	C[TPA+EG]+[IPA+DEG]	No data	No data
	linear	monomer	L[TPA+DEG]	No data	No data
		dimer	L[TPA+EG]+[TPA+DEG]	No data	No data
	linear	monomer + EG	L[TPA+DEG]+EG	No data	No data
Third series	cyclic	dimer	C[TPA+DEG]2	No data	No data
		trimer	C[TPA+EG]+[TPA+DEG]2	No data	No data
Fourth series	cyclic	tetramer	C[TPA+EG]+[TPA+DEG]3	No data	No data
Mixture of PET oligomers				No data	No data

Further analysis of the available data revealed that it consists primarily of experimental measurements of migration or extraction, with one exception: the oligomer C[TPA + EG]3 is the only substance to have three additional data entries based on *in silico* predictions for the category, migration into food simulants. The majority of data focused on either extraction or migration into food simulants, with less emphasis on migration into food. Only the first series cyclic oligomers from dimer to heptamer, with C[TPA + EG]3 (12 data entries) being the most studied oligomer, as well as the linear oligomer L[TPA + EG] + EG (1 data entry) were studied in food. An exception was the study of oligomers as mixtures, for which the most data were found based on migration into food (48 data entries), followed by migration into food simulants (43 data entries), and extraction (17 data entries). There was also a significant amount of knowledge available related to all three categories for the first series cyclic oligomers, most likely providing a substantial evidence base for risk assessment activities. This is also the case when focusing on migration into food simulants, where data were available for the majority of oligomers. However, no data were available for migration or extraction for all of the isophthalic-containing oligomers, as well as for L[TPA + EG] + TPA, L[TPA + DEG], L[TPA + DEG] + EG, and C[TPA + EG] + [TPA + DEG]3. There may be various reasons for the absence of data. For instance, these oligomers may be present at low concentrations within the polymer matrix, thereby falling below the detection limits in migration experiments. Additionally, the lack of analytical standards required for their quantification may also hinder the determination of these oligomers in PET samples.

Given the diversity of the data, it is yet not possible to propose more detailed recommendations. Nevertheless, this SEM serves as a valuable resource for risk assessors to address the exposure of individual oligomers on a case-by-case basis, taking into account specific applications and the availability of relevant information. In this way, regulatory and research needs can be identified on an individual basis.

3.4. Hydrolysis-related evidence

Hydrolysis is a chemical process involving the cleavage of chemical bonds through the addition of water (Muller, 1994). Ester hydrolysis can significantly alter the composition of PET oligomers and ultimately influence their exposure levels, representing a vital aspect to consider in the risk assessment of these substances. The hydrolysis of PET oligomers could occur when in contact with food or beverages or as a result of physiological processes post-ingestion. Safety assessment of oligomers

has so far been given low priority due to the assumption of complete hydrolysis of PET oligomers to its respective monomers (Nelson et al., 2011). However, in reality, the hydrolysis potential of PET oligomers is not well understood. For accurate exposure assessment, it is essential to identify the hydrolysis potential of individual oligomers to avoid overestimating or underestimating their risk.

Safety evaluation of cyclic oligomers based on Cramer Class III levels may overestimate their risk, as hydrolysis to linear oligomers reduces cyclic oligomer exposure and increases linear oligomer exposure. However, linear oligomers have much higher safety threshold (Cramer Class I). Additionally, hydrolysis to monomers may lead to underestimated risk if the safety threshold for monomers is reached. Hydrolysis is therefore an important aspect that needs to be evaluated. For that reason, the identification of hydrolysis data was included in this SEM. Analysis of the eligible data identified from the indexed scientific and gray literature showed that hydrolysis data were based on analytical chemical methods (analyt.) and *in vitro* studies (Table 5). However, overall, hydrolysis-related data were obtained for only two oligomers, C[TPA + EG]3 and L[TPA + EG] + EG. The analytical studies were based on chemical instability by using a 1:1 ethanol–water mixture. C[TPA + EG]3 hydrolyzed under these conditions to its linear counterpart and to smaller linear oligomers. Monomer formation was observed and depending on the conditions 0 – 30% of the first series cyclic oligomer remained. Similar results were observed for L[TPA + EG] + EG, but 55% of the parent compound remained (Table 5). This is a crucial information regarding migration experiments in ethanol–water mixtures as food simulants. As mentioned above, this type of food simulants is therefore not suitable for a realistic exposure assessment of oligomers, because their composition changes and due to the swelling effect, the migration is overestimated. On the other hand, the situation might be different for ethanolic beverages, where the use of ethanol–water mixtures could even be useful. Ethanolic beverages could have a different composition and amounts of PET oligomers compared to non-ethanolic beverages, potentially requiring a different exposure assessment. An investigation into this matter could be considered.

In addition to analytical chemical data, *in vitro* hydrolysis data were also recorded. The *in vitro* results revealed that C[TPA + EG]3 hydrolyzed in the presence of artificial intestinal fluid to linear oligomers of various sizes. Notably, no significant monomer formation was observed after four hours and <20% of the parent oligomer was still present. This results suggest that a fraction of the cyclic oligomers can remain stable for an extended period of time, potentially allowing them to be absorbed in the gastrointestinal tract as intact molecules. The detection of intact C[TPA + EG]3 in human post-mortem further supports this hypothesis (see section 3.5 for more details). Further evaluation of hydrolysis kinetics of PET oligomers may be crucial for a comprehensive exposure evaluation of these substances. The assumption of complete hydrolysis may not be applicable and cannot be used to justify that oligomers are not risk assessed. More experimental evidence on hydrolysis and its kinetics is needed to properly evaluate the potential relevance of

Table 5
Summary of all identified and recorded hydrolysis related evidence for 34 oligomers from the categories first, second, third, fourth series, and for mixtures of PET oligomers. Analytical data (analyt.) refers to information that includes analytical chemical measurements without testing in a biological environment.

Oligomer category name			Acronym-based abbreviation	Number of database entries related to migration					
				Into food (analyt.)	*Into food (in silico)*	*Into food simulant (analyt.)*	*Into food simulant (in silico)*	*Extraction (analyt.)*	*Extraction (in silico)*
First series	cyclic	monomer	C[TPA+EG]	No data	No data	Yes (5)	No data	Yes (2)	No data
		dimer	C[TPA+EG]2	Yes (1)	No data	Yes (37)	No data	Yes (14)	No data
		trimer	C[TPA+EG]3	Yes (12)	No data	Yes (52)	Yes (3)	Yes (35)	No data
		tetramer	C[TPA+EG]4	Yes (9)	No data	Yes (24)	No data	Yes (13)	No data
		pentamer	C[TPA+EG]5	Yes (9)	No data	Yes (19)	No data	Yes (13)	No data
		hexamer	C[TPA+EG]6	**Yes (1)**	No data	Yes (12)	No data	Yes (11)	No data
		heptamer	C[TPA+EG]7	**Yes (1)**	No data	Yes (7)	No data	Yes (6)	No data
		octamer	C[TPA+EG]8	No data	No data	Yes (1)	No data	Yes (4)	No data
	cyclic	dimer + IPA	C[TPA+EG]+[IPA+EG]	No data	No data	No data	No data	No data	No data
		trimer + IPA	C[TPA+EG]2+[IPA+EG]	No data	No data	No data	No data	No data	No data
		tetramer + IPA	C[TPA+EG]3+[IPA+EG]	No data	No data	No data	No data	No data	No data
		pentamer + IPA	C[TPA+EG]4+[IPA+EG]	No data	No data	No data	No data	No data	No data
	linear	monomer	L[TPA+EG]	No data	No data	Yes (18)	No data	Yes (5)	No data
		dimer	L[TPA+EG]2	No data	No data	Yes (6)	No data	Yes (4)	No data
		trimer	L[TPA+EG]3	No data	No data	**Yes (3)**	No data	Yes (4)	No data
	linear	monomer + EG	L[TPA+EG]+EG	Yes (1)	No data	Yes (19)	No data	Yes (8)	No data
		dimer + EG	L[TPA+EG]2+EG	No data	No data	No data	No data	Yes (3)	No data
		trimer + EG	L[TPA+EG]3+EG	No data	No data	No data	No data	Yes (3)	No data
		tetramer + EG	L[TPA+EG]4+EG	No data	No data	No data	No data	Yes (3)	No data
	linear	monomer + TPA	L[TPA+EG]+TPA	No data	No data	No data	No data	No data	No data
		dimer + TPA	L[TPA+EG]2+TPA	No data	No data	No data	No data	Yes (3)	No data
		trimer + TPA	L[TPA+EG]3+TPA	No data	No data	No data	No data	Yes (3)	No data
Second series	cyclic	dimer	C[TPA+EG]+[TPA+DEG]	No data	No data	Yes (7)	No data	Yes (10)	No data
		trimer	C[TPA+EG]2+[TPA+DEG]	No data	No data	Yes (7)	No data	Yes (9)	No data
		tetramer	C[TPA+EG]3+[TPA+DEG]	No data	No data	Yes (6)	No data	Yes (8)	No data
		pentamer	C[TPA+EG]4+[TPA+DEG]	No data	No data	Yes (3)	No data	Yes (6)	No data
		hexamer	C[TPA+EG]5+[TPA+DEG]	No data	No data	No data	No data	Yes (5)	No data
	cyclic	dimer + IPA	C[TPA+EG]+[IPA+DEG]	No data	No data	No data	No data	No data	No data
	linear	monomer	L[TPA+DEG]	No data	No data	No data	No data	No data	No data
		dimer	L[TPA+EG]+[TPA+DEG]	No data	No data	**Yes (3)**	No data	Yes (1)	No data
	linear	monomer + EG	L[TPA+DEG]+EG	No data	No data	No data	No data	No data	No data
Third series	cyclic	dimer	C[TPA+DEG]2	No data	No data	Yes (7)	No data	Yes (2)	No data
		trimer	C[TPA+EG]+[TPA+DEG]2	No data	No data	Yes (3)	No data	Yes (1)	No data
Fourth series	cyclic	tetramer	C[TPA+EG]+[TPA+DEG]3	No data	No data	No data	No data	No data	No data
Mixture of PET oligomers				Yes (48)	No data	Yes (43)	No data	Yes (17)	No data

conducting a safety assessment of oligomers specific to the polymer. *In vitro* testing of different cyclic and linear oligomers could provide initial guidance to identify differences or similarities in hydrolysis kinetics among different types of oligomers. Additionally, major and minor hydrolysis products can be identified and prioritized in risk assessment. Ideally, an *in vivo* study would be conducted to further clarify the situation and provide additional insight into the toxico- or pharmacokinetics of these molecules.

3.5. ADME, toxico-, or pharmacokinetics-related evidence

Accurate determination of internal exposure to a substance requires consideration of various factors. This also includes physiological processes such as absorption, distribution, metabolism, excretion (ADME) and the respective kinetics, i.e., the toxicokinetics (TK) and/or pharmacokinetics (PK) of this substance (Cohen Hubal et al., 2018). To provide a comprehensive overview of the available data, physico-chemical properties as well as all ADME/TK/PK-related data were compiled and analyzed in this SEM. This study did not aim to collect all of the available physico-chemical descriptors due to their high number, but rather focused on those relevant for risk assessment. In compliance with EFSA's "Note for Guidance" document (Silano et al., 2008), we focused on the properties that are considered essential for assessing the risk of PET oligomers, including molecular weight, octanol–water partition coefficient (logP), melting point, and water solubility. All physico-chemical properties recorded can generally be determined either by analytical measurements or by *in silico* methods and they were extracted, recorded and presented according to the method of determination (Table 6 and Supplementary Material). Molecular weight was not extracted from literature as it is a unique descriptor for every molecule and its extraction would result in repeated recording of identical information. However, to ensure completeness and to have all essential physico-chemical properties united, molecular weights for all 34 PET oligomers were included in Table 6.

Our analysis of recorded data revealed that logP values and water solubility information were available for nearly all of the PET oligomers and were primarily determined through *in silico* methods. For oligomers with free carboxyl groups, the recorded water solubilities were given as ranges, representing solubilities at different pH values (indicated by an asterisk in Table 6; see Supplementary Material for further information). The identified data showed, that melting points were mostly determined through experimental analytical measurements and not *in silico* predictions. In general, the coverage of the evidence based on all physico-chemical properties was satisfactory, with the majority of oligomers having the required information. However, in the absence of experimental information on water solubility and logP, variability in actual values should be considered.

Furthermore, there were a few outliers, such as IPA-containing oligomers, for which almost no data were available. However, their physico-chemical properties can be assumed to be similar to those of the first series of cyclic oligomers. The available data for the first series of cyclic oligomers can be utilized as estimates for the missing information regarding IPA-containing oligomers, although such estimates are inevitably subject to large uncertainties. Estimations can also be made for other oligomers with missing data to complement information for all PET oligomers.

In addition to individual physico-chemical properties, data on ADME-related processes were also identified and extracted (Table 6). Lipinski's rule of five is a widely used concept in pharmacology for evaluating the potential of a substance to be an orally active drug in

Table 6
Summary of all identified and recorded ADME/TK/PK related evidence for 34 oligomers from the categories first, second, third, fourth series, and for mixtures of PET oligomers. Analytical data (analyt.) refers to information that includes analytical chemical measurements without testing in a biological environment. Molecular weight was not extracted from literature, but added to the table to have data summarized together. Values for water solubility marked with an asterisk (*) represent solubility for a range of pH values between 1 and 10.

Oligomer category name			Acronym-based abbreviation	Number of database entries related to ADME/TK/PK											
				Physico-chemical properties											
				Molecular weight [g/mol]	*logP (analyt.)*	*logP (in silico)*	*Melting point (analyt.) [°C]*	*Melting point (in silico) [°C]*	*Water solubility (analyt.) [mg/L]*	*Water solubility (in silico) [mg/L]*	Druglikeness (Lipinski's rule of five)	Absorption related data (in vitro)	Absorption related data (in silico)	Blood concentration (human)
First series	cyclic	monomer	C[TPA+EG]	192.17	No data	1.4 - 1.9	No data	50 -72	No data	386 - 1.3e3	Yes	No data	No data	No data
		dimer	C[TPA+EG]2	384.34	No data	2.9 - 4.2	175 - 229	104	No data	6.0e-3 - 2.7e4	Yes	No data	No data	Not detected
		trimer	C[TPA+EG]3	576.51	No data	3.0 - 5.7	195 - 327	132	No data	6.1e-5 - 4.0e3	Yes and No	No data	Low passive human intestinal absorption	6.50 - 23.29 µg/L (post mortem)
		tetramer	C[TPA+EG]4	768.68	No data	5.6 - 7.6	225 - 333	No data	No data	0.24	No	No data	No data	Not detected
		pentamer	C[TPA+EG]5	960.85	No data	8.4 - 9.6	247 - 362	No data	No data	0.07	No	No data	No data	Not detected
		hexamer	C[TPA+EG]6	1153.02	No data	8.2 - 11.5	304 - 306	No data	No data	0.05	No	No data	No data	No data
		heptamer	C[TPA+EG]7	1345.19	No data	9.5 - 13.4	238 - 240	No data	No data	0.1	No	No data	No data	No data
		octamer	C[TPA+EG]8	1537.36	No data	15.3	No data	No data	No data	0.43	No	No data	No data	No data
	cyclic	dimer + IPA	C[TPA+EG]+[IPA+EG]	384.34	No data	No data	No data	No data	No data	No data	No data	No data	No data	No data
		trimer + IPA	C[TPA+EG]2+[IPA+EG]	576.51	No data	5.4	No data	No data	No data	2.4	No	No data	No data	No data
		tetramer + IPA	C[TPA+EG]3+[IPA+EG]	768.68	No data	No data	No data	No data	No data	No data	No data	No data	No data	No data
		pentamer + IPA	C[TPA+EG]4+[IPA+EG]	960.85	No data	No data	No data	No data	No data	No data	No data	No data	No data	No data
	linear	monomer	L[TPA+EG]	210.19	No data	0.5 - 0.9	170 - 188	187	5.8e3 (20 °C); 2.5e4 (80 °C)	3.1 - 1.0e6*	Yes	No data	No data	No data
		dimer	L[TPA+EG]2	402.36	No data	2.1 - 3.5	215 - 220	No data	No data	7.3 - 1.4e5*	Yes	No data	No data	No data
		trimer	L[TPA+EG]3	594.52	No data	2.6 - 4.9	254 -256	No data	No data	1.4e-3 - 1.9e3*	Yes	No data	Low passive human intestinal absorption	No data
	linear	monomer + EG	L[TPA+EG]+EG	254.24	No data	(-0.02) - 1.7	102 -113	69 - 103	1.7e3 (0 °C); 7.9e5 (89.5 °C)	150 - 1.1e4	Yes	Permeation through membrane	Passive transport across membrane and high passive human intestinal absorption	No data
		dimer + EG	L[TPA+EG]2+EG	446.41	No data	1.7 - 3.1	118 -173	No data	No data	0.03 - 100	Yes	No data	Low passive human intestinal absorption	No data
		trimer + EG	L[TPA+EG]3+EG	638.58	No data	3.8 - 4.2	199 -205	No data	No data	1.7	Yes	No data	No data	No data
		tetramer + EG	L[TPA+EG]4+EG	830.75	No data	5.5 - 6.5	217 -220	No data	No data	0.06	No	No data	No data	No data
	linear	monomer + TPA	L[TPA+EG]+TPA	358.3	No data	2.9 - 3.4	280 - 304	No data	No data	35 - 5.2e5*	Yes	No data	No data	No data
		dimer + TPA	L[TPA+EG]2+TPA	550.47	No data	4.6 - 5.4	270 - 286	No data	No data	3.9 - 5.5e3*	Yes	No data	No data	No data
		trimer + TPA	L[TPA+EG]3+TPA	742.64	No data	6.3 - 7.4	268 - 276	No data	No data	8.2e-3 - 120*	No	No data	No data	No data
Second series	cyclic	dimer	C[TPA+EG]+[TPA+DEG]	428.39	No data	2.6 - 3.4	161 - 179	No data	No data	90	Yes	No data	No data	No data
		trimer	C[TPA+EG]2+[TPA+DEG]	620.56	No data	3.9 - 5.3	No data	No data	No data	6.2	No	No data	No data	No data
		tetramer	C[TPA+EG]3+[TPA+DEG]	812.73	No data	6.1 - 7.3	No data	No data	No data	1.1	No	No data	No data	No data
		pentamer	C[TPA+EG]4+[TPA+DEG]	1004.9	No data	1.4	190	No data	No data	No data	No data	No data	No data	No data
		hexamer	C[TPA+EG]5+[TPA+DEG]	1197.07	No data	No data	No data	No data	No data	No data	No data	No data	No data	No data
	cyclic	dimer + IPA	C[TPA+EG]+[IPA+DEG]	428.39	No data	No data	No data	No data	No data	No data	No data	No data	No data	No data
	linear	monomer	L[TPA+DEG]	254.24	No data	1	109 -110	No data	No data	1.2e4 - 9.9e5*	Yes	No data	No data	No data
		dimer	L[TPA+EG]+[TPA+DEG]	446.41	No data	3	No data	No data	No data	120 - 1.7e5*	Yes	No data	No data	No data
	linear	monomer + EG	L[TPA+DEG]+EG	298.29	No data	0.3 - 0.5	No data	No data	No data	1.1e4	Yes	No data	No data	No data
Third series	cyclic	dimer	C[TPA+DEG]2	472.45	No data	2.7 - 3.0	200 -223	No data	No data	250	Yes	No data	No data	No data
		trimer	C[TPA+EG]+[TPA+DEG]2	664.62	No data	No data	No data	No data	No data	No data	No data	No data	No data	No data
Fourth series	cyclic	tetramer	C[TPA+EG]+[TPA+DEG]3	812.73	No data	No data	No data	No data	No data	No data	No data	No data	No data	No data
Mixture of PET oligomers				/	/	/	/	/	/	/	/	No data	No data	No data

humans. According to this rule, a substance is more likely to be absorbed or permeated, if it meets the following criteria: molecular weight of <500 g/mol, a logP value of <5, less than 10 hydrogen bond acceptors and less than 5 hydrogen bond donors. If a substance violates no more than one of these criteria, a substance is considered to be "drug-like" (Lipinski et al., 2001). This SEM found that data were available for almost all oligomers on the four Lipinski's Rule of Five criteria. According to the available data, drug-likeness is generally observed for cyclic dimers and smaller oligomers, with the exception of C[TPA + EG]3, which has been reported to be druglike as well as non-druglike. Linear trimers and smaller oligomers are reported to exhibit drug-like characteristics. Based on the available data and following the same trends, drug-likeness of the missing oligomers can be extrapolated, even if this information is currently unknown.

The initial stage in internal (oral) exposure is the absorption process, making it a crucial factor in determining the potential hazards of a substance. In this SEM, absorption data were identified for four oligomers: C[TPA + EG]3, L[TPA + EG]3, L[TPA + EG]2 + EG, and L[TPA + EG] + EG. *In silico* predictions estimated low passive intestinal absorption for C[TPA + EG]3, L[TPA + EG]3, and L[TPA + EG]2 + EG, while *in vitro* testing and *in silico* predictions estimated high passive intestinal absorption and passive transport across membranes for L[TPA + EG] + EG. A study investigating oligomer levels in human blood found that C[TPA + EG]2, C[TPA + EG]4, and C[TPA + EG]5 could not be detected under the analytical methods used. On the other hand C[TPA + EG]3 was detected and quantified (6.50 – 23.29 μg/L), despite being predicted to have low passive intestinal absorption (Table 6). This, as discussed in the previous section, suggests that C[TPA + EG]3 is not fully hydrolyzed after ingestion and that it can be absorbed in significant amounts as an intact molecule. However, this study was conducted post-mortem and may not fully reflect concentrations in living humans. Although some data is present, the current evidence is very limited and primarily based on *in silico* predictions that have not yet been validated *in vitro* or *in vivo*. Potential differences between *in silico* predictions and *in vivo* results were already highlighted by C[TPA + EG]3, which appears to behave differently *in vivo* than predicted *in silico*. As a result, the absorption potential of PET oligomers remains uncertain. There are no clear trends or conclusions that can be drawn about the absorption properties for all PET oligomers, making it a significant knowledge gap for risk assessment activities that requires further research.

In addition, PET oligomers are generally hydrophobic in nature, with increased logP values. Typically, substances with an octanol–water partition coefficient greater than three may have the potential to accumulate in the mammalian body (Silano et al., 2008). If accumulation occurs in tissues, the exposure levels change and need to be evaluated. An accumulation of C[TPA + EG]3 could, for example, be the reason why it was detected in rather high amounts in blood, even though it might indeed be only poorly absorbed. These results emphasize the need for a more comprehensive understanding of the absorption properties of PET oligomers and of the processes occurring after absorption such as the potential for accumulation, metabolism and excretion. Future research should consider *in vitro* and *in vivo* experiments to evaluate ADME/TK/PK-related processes.

3.6. Health and bioactivity-related evidence

Health and bioactivity-related outcomes for PET oligomers are vital for evaluating the safety and potential risks associated with these substances. Identification of toxicological properties can aid in determining the hazards of PET oligomers and inform future regulatory decisions. The knowledge and identified knowledge gaps will help researchers, regulators, and other stakeholders understand the potential risks, the uncertainties involved and the key research needs associated with PET oligomers.

As illustrated in Fig. 1, there was only a very limited amount of literature available on the bioactivity and potential health effects of PET oligomers. Analysis of the available data revealed that no information is available on PET oligomer and mixtures. *In silico* toxicological predictions of protein and DNA binding, mutagenicity, carcinogenicity, and genotoxicity were available for only 14 individual oligomers (Table 7). The predictions did not indicate any concerns related to all of these endpoints. However, none of the *in silico* results have yet been confirmed through *in vitro* testing, although *in silico* models for these toxicological endpoints are often reliable predictors and further *in vitro* testing may not be necessary. Nevertheless, it may be beneficial to consider *in vitro* testing on a small representative subset of PET oligomers to confirm the absence of mutagenicity and genotoxicity.

Besides the recorded *in silico* predictions, only very limited data is available on potential health effects or bioactivity of PET oligomers from other evidence streams. The only oligomer for which *in vitro* data on activity related to the androgen receptor (AR) and cytotoxicity was found, is L[TPA + EG] + EG (Table 7). However, this lack of information on bioactivity and health outcomes was anticipated, so more general data on organisms and ecotoxicological endpoints were also recorded. Although these endpoints may not be directly relevant for human risk assessment, they may still be useful for guiding and prioritizing the study of PET oligomers of interest. Unfortunately, even in this case, only one oligomer, L[TPA + EG] + EG, had any available information. None of the tests conducted for this substance - the bacterial minimum inhibitory concentration (MIC) assay, *Aliivibrio fischeri* toxicity test, and Caenorhabditis elegans survival assay - showed any activity of concern. When considering the available data so far, no adverse effects are known from PET oligomer substances. However, due to the extremely limited data available, no conclusions can be drawn and harmful effects cannot be ruled out by any means. The most significant and important knowledge gap in this SEM was therefore found to be in the area of toxicology. The investigation of potential adverse effects is crucial to determine if PET oligomers pose a risk to consumers after exposure. Currently, there is no standard way to assess their toxicological risk, and the applicability of the TTC thresholds for PET oligomers is uncertain. To perform a hazard assessment, the development of a comprehensive tiered approach is recommended, starting with *in vitro* tests and proceeding based on the results. A first evaluation could for example include toxicological endpoints such as cytotoxicity, genotoxicity, and endocrine disruption. This may also include the evaluation of PET oligomer to investigate possible synergistic, antagonistic, or additive effects. PET oligomers occur in foods and beverages as mixtures, and studying the effects of mixtures is essential for a comprehensive understanding of the potential risks associated with these substances.

4. Summary and conclusions

The purpose of this SEM was to identify and analyze the available evidence on hazard- and exposure-related data of 34 oligomers derived from PET in the context of FCMs. The overall goal was to provide valuable information for chemical risk assessment and to identify knowledge gaps to be addressed in future research activities. A total of 10′041 records were retrieved from bibliographic databases and gray literature searches, with 96 records meeting the eligibility criteria for this SEM. The analysis of the overall evidence revealed that migration and extraction of PET oligomers from FCMs has been widely studied, but the reported data were very heterogeneous, making it difficult to compare it and draw general conclusions. More systematic approaches and evaluations of migration would greatly benefit the estimation of exposure to PET oligomers and help prioritize which oligomers require further evaluation. In addition, the internal (oral) exposure pathways have not yet been elucidated. This SEM identified knowledge gaps and a lack of information regarding ADME-related aspects as well as an investigation of the potential for PET oligomers to accumulate in tissues might be considered.

This SEM revealed that the assumption of complete hydrolysis of PET oligomers to its respective monomers may not be applicable and cannot

Table 7
Summary of all identified and recorded health and bioactivity related evidence for 34 oligomers from the categories first, second, third, fourth series, and for mixtures of PET oligomers. Analytical data (analyt.) refers to information that includes analytical chemical measurements without testing in a biological environment. Molecular weight was not extracted from literature, but added to the table to have data summarized together. Abbreviations: androgen receptor (AR), chromosomal aberration (CA), micronucleus test (MNT), minimum inhibitory concentration (MIC).

Oligomer category name			Acronym-based abbreviation	Number of database entries related to health/bioactivity											
				In vitro		In silico							Organisms		
				Androgen related	*Cytotoxicity*	*DNA binding*	*DNA alerts for AMES*	*DNA alerts for CA and MNT*	*Protein binding*	*In vitro mutagenicity (AMES test)*	*In vivo mutagenicity (micronucleus)*	*Carcinogenicity*	*Bacterial MIC assay*	*Aliivibrio fischeri toxicity test*	*Caenorhabditis elegans survival assay*
First series	cyclic	monomer	C[TPA+EG]	No data	No data	No data	No data	No data	No data	No data	No data	No data	No data	No data	No data
		dimer	C[TPA+EG]2	No data	No data	No alert	No alert	No alert	Acylation	No alert	3-H-acceptor	No alert	No data	No data	No data
		trimer	C[TPA+EG]3	No data	No data	No alert	No alert	No alert	Acylation	No alert	3-H-acceptor	No alert	No data	No data	No data
		tetramer	C[TPA+EG]4	No data	No data	No alert	No alert	No alert	Acylation	No alert	3-H-acceptor	No alert	No data	No data	No data
		pentamer	C[TPA+EG]5	No data	No data	No alert	No alert	No alert	Acylation	No alert	3-H-acceptor	No alert	No data	No data	No data
		hexamer	C[TPA+EG]6	No data	No data	No data	No data	No data	No data	No data	No data	No data	No data	No data	No data
		heptamer	C[TPA+EG]7	No data	No data	No data	No data	No data	No data	No data	No data	No data	No data	No data	No data
		octamer	C[TPA+EG]8	No data	No data	No data	No data	No data	No data	No data	No data	No data	No data	No data	No data
	cyclic	dimer + IPA	C[TPA+EG]+[IPA+EG]	No data	No data	No data	No data	No data	No data	No data	No data	No data	No data	No data	No data
		trimer + IPA	C[TPA+EG]2+[IPA+EG]	No data	No data	No data	No data	No data	No data	No data	No data	No data	No data	No data	No data
		tetramer + IPA	C[TPA+EG]3+[IPA+EG]	No data	No data	No data	No data	No data	No data	No data	No data	No data	No data	No data	No data
		pentamer + IPA	C[TPA+EG]4+[IPA+EG]	No data	No data	No data	No data	No data	No data	No data	No data	No data	No data	No data	No data
	linear	monomer	L[TPA+EG]	No data	No data	No data	No data	No data	No data	No data	No data	No data	No data	No data	No data
		dimer	L[TPA+EG]2	No data	No data	No data	No data	No data	No data	No alert	No data	No data	No data	No data	No data
		trimer	L[TPA+EG]3	No data	No data	No data	No data	No data	No data	No alert	No data	No data	No data	No data	No data
	linear	monomer + EG	L[TPA+EG]+EG	Androgen related (no agonistic or antagonistic effect on AR)	Cytotoxicity related (30% decrease in MRC-5 cell proliferation at 200 µg/mL)	No data	No data	No data	No data	No data	No data	No data	Antimicrobial related (no effect)	Nonspecific toxicity related (very low inhibition of bioluminescence with maximum of ca. 30% at 125 µg/mL)	Survival related (no effect)
		dimer + EG	L[TPA+EG]2+EG	No data	No data	No data	No data	No data	No data	No data	No data	No data	No data	No data	No data
		trimer + EG	L[TPA+EG]3+EG	No data	No data	No data	No data	No data	No data	No data	No data	No data	No data	No data	No data
		tetramer + EG	L[TPA+EG]4+EG	No data	No data	No data	No data	No data	No data	No data	No data	No data	No data	No data	No data
	linear	monomer + TPA	L[TPA+EG]+TPA	No data	No data	No data	No data	No data	No data	No data	No data	No data	No data	No data	No data
		dimer + TPA	L[TPA+EG]2+TPA	No data	No data	No data	No data	No data	No data	No data	No data	No data	No data	No data	No data
		trimer + TPA	L[TPA+EG]3+TPA	No data	No data	No data	No data	No data	No data	No data	No data	No data	No data	No data	No data
Second series	cyclic	dimer	C[TPA+EG]+[TPA+DEG]	No data	No data	No alert	No alert	No alert	Acylation	No alert	3-H-acceptor	No alert	No data	No data	No data
		trimer	C[TPA+EG]2+[TPA+DEG]	No data	No data	No alert	No alert	No alert	Acylation	No alert	3-H-acceptor	No alert	No data	No data	No data
		tetramer	C[TPA+EG]3+[TPA+DEG]	No data	No data	No alert	No alert	No alert	Acylation	No alert	3-H-acceptor	No alert	No data	No data	No data
		pentamer	C[TPA+EG]4+[TPA+DEG]	No data	No data	No alert	No alert	No alert	Acylation	No alert	3-H-acceptor	No alert	No data	No data	No data
		hexamer	C[TPA+EG]5+[TPA+DEG]	No data	No data	No data	No data	No data	No data	No data	No data	No data	No data	No data	No data
	cyclic	dimer + IPA	C[TPA+EG]+[IPA+DEG]	No data	No data	No data	No data	No data	No data	No data	No data	No data	No data	No data	No data
	linear	monomer	L[TPA+DEG]	No data	No data	No data	No data	No data	No data	No data	No data	No data	No data	No data	No data
		dimer	L[TPA+EG]+[TPA+DEG]	No data	No data	No data	No data	No data	No data	No data	No data	No data	No data	No data	No data
	linear	monomer + EG	L[TPA+DEG]+EG	No data	No data	No data	No data	No data	No data	No alert	No data	No data	No data	No data	No data
Third series	cyclic	dimer	C[TPA+DEG]2	No data	No data	No alert	No alert	No alert	Acylation	No alert	3-H-acceptor	No alert	No data	No data	No data
		trimer	C[TPA+EG]+[TPA+DEG]2	No data	No data	No alert	No alert	No alert	Acylation	No alert	3-H-acceptor	No alert	No data	No data	No data
Fourth series	cyclic	tetramer	C[TPA+EG]+[TPA+DEG]3	No data	No data	No data	No data	No data	No data	No data	No data	No data	No data	No data	No data
Mixture of PET oligomers				No data	No data	No data	No data	No data	No data	No data	No data	No data	No data	No data	No data

serve as a rationale to omit the risk assessment of oligomers. The conventional assumption of complete hydrolysis of PET oligomers and thus their risk assessment via their respective monomers therefore remains questionable. Further experimental evidence on hydrolysis and underlying kinetics is needed.

Our SEM highlighted a noticeable gap in toxicological investigation as one of the key areas with a significant deficiency in knowledge. With the current state of knowledge, no hazard assessment can be performed. Therefore, the development of a tiered approach including *in vitro* toxicological testing is highly advisable. Additionally, it is recommended that further *in vitro* and/or *in vivo* testing be conducted to confirm *in silico* predictions and to gain a more comprehensive understanding of the potential health effects of PET oligomers. Importantly, to enable *in vitro* testing, the current limitation that only very few pure PET oligomers are commercially available needs to be overcome (Alberto Lopes et al., Alberto Lopes and Tsochatzis, 2023). Additionally, test strategies for the investigation of mixture effects should be developed. For such studies, mixtures of defined composition and reflecting a realistic exposure scenario should be made available.

In summary, this SEM provides a comprehensive overview of the current knowledge on hazard and exposure information for these specific PET oligomers and can serve as a valuable resource for future research and chemical risk assessment activities. However, it is clear that there are significant knowledge gaps in the areas of ADME/TK/PK, hydrolysis, and health effects, and further research is needed to fill these gaps. The study highlights the importance of a standardization of the experimental conditions and analytical techniques in order to facilitate the comparison and analysis of data. A comprehensive evaluation of PET oligomers requires a multidisciplinary and systematic approach to gain a thorough understanding of the entire group of PET oligomers. Filling the recognized knowledge gaps is crucial in accurately assessing the actual risk posed by PET oligomers, allowing for informed regulatory decisions to be made.

CRediT authorship contribution statement

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

Declaration of Competing Interest

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Data availability

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Appendix A. Supplementary data

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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.

Alberto Lopes, J., Tsochatzis, E.D., 2023. Poly(ethylene terephthalate), poly(butylene terephthalate), and polystyrene oligomers: occurrence and analysis in food contact materials and food. J. Agric. Food Chem. 71, 2244–2258. https://doi.org/10.1021/acs.jafc.2c08558.

Araki, N., Ohno, K., Nakai, M., Takeyoshi, M., Iida, M., 2005. Screening for androgen receptor activities in 253 industrial chemicals by in vitro reporter gene assays using AR-EcoScreenTM cells. Toxicol. in Vitro 19, 831–842. https://doi.org/10.1016/J.TIV.2005.04.009.

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.

Begley, T.H., Hollifield, H.C., 1989. Liquid chromatographic determination of residual reactants and reaction by-products in polyethylene terephthalate. J. AOAC Int. 72, 468–470. https://doi.org/10.1093/JAOAC/72.3.468.

Begley, T.H., Hollifield, H.C., 1990a. Evaluation of polyethylene terephthalate cyclic trimer migration from microwave food packaging using temperature-time profiles. Food Addit. Contam. 7, 339–346. https://doi.org/10.1080/02652039009373898.

Begley, T.H., Hollifield, H.C., 1990b. High-Performance liquid chromatographic determination of migrating poly(ethylene terephthalate) oligomers in corn oil. J. Agric. Food Chem. 38, 145–148. https://doi.org/10.1021/jf00091a031.

Begley, T.H., Hollifield, H.C., 1990c. Migration of dibenzoate plasticizers and polyethylene terephthalate cyclic oligomers from microwave susceptor packaging into food-simulating liquids and food. J. Food Prot. 53, 1062–1066. https://doi.org/10.4315/0362-028X-53.12.1062.

BFR, 2022. Guideline for the safety assessment of substances for the manufacture of food contact materials and articles [WWW Document]. https://www.bfr.bund.de/cm/349/guideline-for-the-safety-assessment-of-substances-for-the-manufacture-of-food-contact-materials-and-articles.pdf (accessed 2.8.23).

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. 10.2903/J.EFSA.2016.4357.

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

Brandsch, R., Dequatre, C., Mercea, P., Milana, M.R., Stoermer, A., Trier, X., Vitrac, O., Schaefer, A., Simoneau, C., 2015. Practical guidelines on the application of migration modelling for the estimation of specific migration 33. 10.2788/04517.

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. Contam. Part A Chem. Anal. Control Expo Risk Assess. 38, 160–179. https://doi.org/10.1080/19440049.2020.1828626.

Bschir, K., 2017. Risk, uncertainty and precaution in science: the threshold of the toxicological concern approach in food toxicology. Sci. Eng. Ethics 23, 489–508. https://doi.org/10.1007/S11948-016-9773-2/FIGURES/3.

Buiarelli, F., Cartoni, G., Coccioli, F., 1993. HPLC AND GC - MS detection of compounds released to mineral waters stored in plastic bottles of pet and PVC. Ann. Chim. 83, 93–104.

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.

Castle, L., Jickells, S.M., Gilbert, J., Harrison, N., 1990. Migration testing of plastics and microwave-active materials for high-temperature food-use applications. Food Addit. Contam. 7, 779–796. https://doi.org/10.1080/02652039009373940.

Cimecioglu, A.L., Zeronian, S.H., Alger, K.W., Collins, M.J., East, G.C., 1986. Properties of oligomers present in poly(ethylene terephthalate). J. Appl. Polym. Sc.i 32, 4719–4733. https://doi.org/10.1002/APP.1986.070320436.

Cohen Hubal, E.A., Wetmore, B.A., Wambaugh, J.F., El-Masri, H., Sobus, J.R., Bahadori, T., 2018. Advancing internal exposure and physiologically-based toxicokinetic modeling for 21st-century risk assessments. J. Exposure Sci. Environ. Epidemiol. 2018 29:1 29, 11–20. 10.1038/s41370-018-0046-9.

Commission Regulation (EU) No 10/2011 [WWW Document], 2011. Commission Regulation (EU) No 10/2011 on plastic materials and articles intended to come into contact with food. https://eur-lex.europa.eu/legal-content/EN/TXT/HTML/?uri=CELEX:32011R0010&from=EN (accessed 2.8.23).

Diamantidou, D., Mastrogianni, O., Tsochatzis, E., Theodoridis, G., Raikos, N., Gika, H., Kalogiannis, S., 2022. Liquid chromatography-mass spectrometry method for the determination of polyethylene terephthalate and polybutylene terephthalate cyclic oligomers in blood samples. Anal. Bioanal. Chem. 414, 1503–1512. https://doi.org/10.1007/s00216-021-03741-6.

Djapovic, M., Milivojevic, D., Ilic-Tomic, T., Lješević, M., Nikolaivits, E., Topakas, E., Maslak, V., Nikodinovic-Runic, J., 2021. Synthesis and characterization of polyethylene terephthalate (PET) precursors and potential degradation products: toxicity study and application in discovery of novel PETases. Chemosphere 275, 130005. https://doi.org/10.1016/J.CHEMOSPHERE.2021.130005.

Dulio, V., Po, R., Borrelli, R., Guarini, A., Santini, C., 1995. Characterization of low-molecular-weight oligomers in recycled poly(ethylene terephthalate). Die Angew. Makromol. Chem. 225, 109–122. https://doi.org/10.1002/APMC.1995.052250110.

Eckardt, M., Kubicova, M., Simat, T.J., 2018. Universal response quantification approach using a Corona Charged Aerosol Detector (CAD) – application on linear and cyclic oligomers extractable from polycondensate plastics polyesters, polyamides and polyarylsulfones. J Chromatogr A 1572, 187–202. https://doi.org/10.1016/J.CHROMA.2018.08.051.

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 Addit. Contam. Part A Chem. Anal. Control Expo Risk Assess. 36, 1882–1894. https://doi.org/10.1080/19440049.2019.1658903.

Freire, T.M.D.A., Damant, A.P., Castle, L., Reyes, F.G.R., 1999. Thermal stability of polyethylene terephthalate (PET): oligomer distribution and formation of volatiles. 10.1002/(SICI)1099-1522(199901/02)12:1.

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 Addit. Contam. Part A Chem. Anal. Control Expo Risk Assess. 34, 1251–1260. https://doi.org/10.1080/19440049.2017.1322222.

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 https://doi.org/10.1016/J.FOODCHEM.2020.128625.

ILSI, 2015. Guidance on best practices on the risk assessment of non intentionally added substances (NIAS) in food contact materials and Articles [WWW Document]. 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).

Jabarin, S.A., Balduff, D.C., 1982. Gel permeation chromatography of polyethylene terephalate. J. Liq. Chromatogr. 5, 1825–1845. https://doi.org/10.1080/01483918208062857.

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

Järvenpää, J., Perkkiö, M., Laitinen, R., Lahtela-Kakkonen, M., 2022. PE and PET oligomers' interplay with membrane bilayers. Sci. Rep. 12:1 12, 1–8. 10.1038/s41598-022-06217-4.

Jetten, J., de Kruijf, N., Castle, L., 1999. Quality and safety aspects of reusable plastic food packaging materials: a European study to underpin future legislation. Food Addit. Contam. 16, 25–36. https://doi.org/10.1080/026520399284299.

Jetten, J., de Kruijf, N., 2002. Quality and safety aspects of reusable plastic food packaging materials: influence of reuse on intrinsic properties. Food Addit. Contam. 19, 76–88. https://doi.org/10.1080/02652030110071309.

Jickells, S.M., Gramshaw, J.W., Gilbert, J., Castle, L., 1991. Migration into food during microwave and conventional oven heating. Food Packag. Interact. II Chapter 2, 11–21. https://doi.org/10.1021/BK-1991-0473.CH002.

Jickells, S.M., Gramshaw, J.W., Castle, L., Gilbert, J., 1992. The effect of microwave energy on specific migration from food contact plastics. Food Addit Contam 9, 19–27. https://doi.org/10.1080/02652039209374044.

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 https://doi.org/10.1016/j.envint.2020.105956.

Kim, D.J., Lee, K.T., 2012a. Analysis of specific migration of monomers and oligomers from polyethylene terephthalate bottles and trays according to the testing methods as prescribed in the legislation of the EU and Asian countries. Polym. Test. 31, 1001–1007. https://doi.org/10.1016/J.POLYMERTESTING.2012.07.012.

Kim, D.J., Lee, K.T., 2012b. Determination of monomers and oligomers in polyethylene terephthalate trays and bottles for food use by using high performance liquid chromatography-electrospray ionization-mass spectrometry. Polym. Test. 31, 490–499. https://doi.org/10.1016/J.POLYMERTESTING.2012.02.001.

Komolprasert, V., McNeal, T.P., Agrawal, A., Adhikari, C., Thayer, D.W., 2001. Volatile and non-volatile compounds in irradiated semi-rigid crystalline poly(ethylene terephthalate) polymers. Food Addit. Contam. 18, 89–101. https://doi.org/10.1080/02652030010006096.

Lipinski, C.A., Lombardo, F., Dominy, B.W., Feeney, P.J., 2001. Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. Adv. Drug Deliv. Rev. 46, 3–26. https://doi.org/10.1016/S0169-409X(00)00129-0.

López-Cervantes, J., Sánchez-Machado, D.I., Simal-Lozano, J., Paseiro-Losada, P., 2003. Migration of ethylene terephthalate oligomers from roasting bags into olive oil. Chromatographia 58:5 58, 321–326. 10.1365/S10337-003-0034-6.

More, S.J., Bampidis, V., Benford, D., Bragard, C., Halldorsson, T.I., Hernández-Jerez, A. F., Hougaard Bennekou, S., Koutsoumanis, K.P., Machera, K., Naegeli, H., Nielsen, S. S., Schlatter, J.R., Schrenk, D., Silano, V., Turck, D., Younes, M., Gundert-Remy, U., Kass, G.E.N., Kleiner, J., Rossi, A.M., Serafimova, R., Reilly, L., Wallace, H.M., 2019. Guidance on the use of the Threshold of Toxicological Concern approach in food safety assessment. EFSA J. 17, 5708. https://doi.org/10.2903/j.efsa.2019.5708.

Muller, P., 1994. Glossary of terms used in physical organic chemistry: (IUPAC Recommendations 1994). Pure Appl. Chem. 66, 1077–1184. https://doi.org/10.1351/PAC199466051077/MACHINEREADABLECITATION/RIS.

Mutsuga, M., Tojima, T., Kawamura, Y., Tanamoto, K., 2005. Survey of formaldehyde, acetaldehyde and oligomers in polyethylene terephthalate food-packaging materials. Food Addit. Contam. 22, 783–789. https://doi.org/10.1080/02652030500157593.

Nasser, A.L.M., Lopes, L.M.X., Eberlin, M.N., Monteiro, M., 2005. Identification of oligomers in polyethyleneterephthalate bottles for mineral water and fruit juice: development and validation of a high-performance liquid chromatographic method for the determination of first series cyclic trimer. J. Chromatogr. A 1097, 130–137. https://doi.org/10.1016/J.CHROMA.2005.08.023.

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.

Ohkado, Y., Kawamura, Y., Mutsuga, M., Tamura, H.O., Tanamoto, K., 2005. Analysis of formaldehyde, acetaldehyde and oligomers in recycled polyethylene terephthalate. Shokuhin Eiseigaku Zasshi 46, 218–223. https://doi.org/10.3358/SHOKUEISHI.46.218.

Omer, E., Bichon, E., Hutinet, S., Royer, A.-L., Monteau, F., Germon, H., Hill, P., Remaud, G., Dervilly-Pinel, G., Cariou, R., Le Bizec, 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.

Paseiro-Cerrato, R., Noonan, G.O., Begley, T.H., 2016. Evaluation of long-term migration testing from can coatings into food simulants: polyester coatings. J. Agric. Food Chem. 64, 2377–2385. https://doi.org/10.1021/acs.jafc.5b05880.

Peebles, L.H., Huffman, M.W., Ablett, C.T., 1969. Isolation and identification of the linear and cyclic oligomers of poly(ethylene terephthalate) and the mechanism of cyclic oligomer formation. J. Polym. Sci. A 1 (7), 479–496. https://doi.org/10.1002/POL.1969.150070207.

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.

Rajbux, C., Pereira, J., Selbourne, M.do C., Costa-Pinto, A.R., Poças, F., 2020. Assessment of baby Bibs. GC-MS screening, migration into saliva and insight of toxicity with QSAR tools. Food Control 109, 106951. https://doi.org/10.1016/J.FOODCONT.2019.106951.

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.

Schreier, V.N., Appenzeller-Herzog, C., Brüschweiler, B.J., Geueke, B., Wilks, M.F., Simat, T.J., Schilter, B., Smieško, M., Muncke, J., Odermatt, A., Roth, N., 2022a. Evaluating the food safety and risk assessment evidence-base of polyethylene terephthalate oligomers: Protocol for a systematic evidence map. https://doi.org/10.5281/ZENODO.6224302.

Schreier, V.N., Appenzeller-Herzog, C., Brüschweiler, B.J., Geueke, B., Wilks, M.F., Simat, T.J., Schilter, B., Smieško, M., Muncke, J., Odermatt, A., Roth, N., 2022b. Evaluating the food safety and risk assessment evidence-base of polyethylene terephthalate oligomers: protocol for a systematic evidence map. Environ. Int. 167 https://doi.org/10.1016/J.ENVINT.2022.107387.

Silano, V., Bolognesi, C., 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. 10.2903/J.EFSA.2008.21R.

Thayer, K.A., Angrish, M., Arzuaga, X., Carlson, L.M., Davis, A., Dishaw, L., Druwe, I., Gibbons, C., Glenn, B., Jones, R., Phillip Kaiser, J., Keshava, C., Keshava, N., Kraft, A., Lizarraga, L., Persad, A., Radke, E.G., Rice, G., Schulz, B., Shaffer, R.M., Shannon, T., Shapiro, A., Thacker, S., Vulimiri, S. v., Williams, A.J., Woodall, G., Yost, E., Blain, R., Duke, K., Goldstone, A.E., Hartman, P., Hobbie, K., Ingle, B., Lemeris, C., Lin, C., Lindahl, A., McKinley, K., Soleymani, P., Vetter, N., 2022. Systematic evidence map (SEM) template: Report format and methods used for the US EPA Integrated Risk Information System (IRIS) program, Provisional Peer Reviewed Toxicity Value (PPRTV) program, and other "fit for purpose" literature-based human health analyses. Environ. Int. 169, 107468. 10.1016/J.ENVINT.2022.107468.

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 Packag. 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., Gika, H., Kastrup Dalsgaard, T., Theodoridis, G., 2021. Development and validation of an UHPLC-qTOF-MS method for the quantification of cyclic polyesters oligomers in pasta by applying a modified QuEChERS clean-up. Food Chem. 347, 129040 https://doi.org/10.1016/J.FOODCHEM.2021.129040.

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.

Wick, G., Zeitler, H., 1983. Cyclische oligomere in polyestern aus diolen und aromatischen dicarbonsäuren. Die Angew. Makromol. Chem. 112, 59–94. https://doi.org/10.1002/APMC.1983.051120106.

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.

Xu, T., Qiu, K., Gao, H., Wu, G., Zhang, B., Zhao, Q., Zhang, Y., 2021. Simultaneous determination of cyclic PET and PBT oligomers migrated from laminated steel cans for food. Food Control 130, 108396. https://doi.org/10.1016/J.FOODCONT.2021.108396.