Environment International 181 (2023) 108225

Contents lists available at ScienceDirect

Environment International

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

Full length article

The plastic health map: A systematic evidence map of human health studies on plastic-associated chemicals

Bhedita J Seewoo [a,b,1], Louise M Goodes [a,b,1], Louise Mofflin [a,b,2], Yannick R Mulders [a,b,2], Enoch VS Wong [a,b,2], Priyanka Toshniwal [a,f], Manuel Brunner [a,c], Jennifer Alex [a], Brady Johnston [a], Ahmed Elagali [a,b], Aleksandra Gozt [a], Greg Lyle [a,d], Omrik Choudhury [a], Terena Solomons [a,e], Christos Symeonides [a,f], Sarah A Dunlop [a,b,*]

[a] *Plastics, Minderoo Foundation, 171-173 Mounts Bay Road 6000, Perth, WA, Australia*
[b] *School of Biological Sciences, The University of Western Australia, 35 Stirling Highway, Crawley, WA 6009, Australia*
[c] *School of Molecular Sciences, The University of Western Australia, 35 Stirling Highway, Crawley, WA 6009, Australia*
[d] *School of Population Health, Curtin University, Kent St, Bentley WA 6102, Australia*
[e] *Health and Medical Sciences (Library), The University of Western Australia, 35 Stirling Highway, Crawley, WA 6009, Australia*
[f] *Murdoch Children's Research Institute, Royal Children's Hospital, 50 Flemington Rd, Parkville, VIC 3052, Australia*

ARTICLE INFO

Keywords:
Exposure
Health
Human
Plastic
Plastic chemicals
Systematic evidence map

ABSTRACT

Background: The global production and use of plastic materials has increased dramatically since the 1960s and there is increasing evidence of human health impacts related to exposure to plastic-associated chemicals. There is, however, no comprehensive, regulatory, post-market monitoring for human health effects of plastic-associated chemicals or particles and it is unclear how many of these have been investigated for effects in humans, and therefore what the knowledge gaps are.

Objective: To create a systematic evidence map of peer-reviewed human studies investigating the potential effects of exposure to plastic-associated particles/chemicals on health to identify research gaps and provide recommendations for future research and regulation policy.

Methods: Medline and Embase databases were used to identify peer-reviewed primary human studies published in English from Jan 1960 – Jan 2022 that investigated relationships between exposures to included plastic-associated particles/chemicals measured and detected in bio-samples and human health outcomes. Plastic-associated particles/chemicals included are: micro and nanoplastics, due to their widespread occurrence and potential for human exposure; polymers, the main building blocks of plastic; plasticizers and flame retardants, the two most common types of plastic additives with the highest concentration ranges in plastic materials; and bisphenols and per- or polyfluoroalkyl substances, two chemical classes of known health concern that are common in plastics. We extracted metadata on the population and study characteristics (country, intergenerational, sex, age, general/special exposure risk status, study design), exposure (plastic-associated particle/

Abbreviations: ATSDR, Agency for Toxic Substances and Disease Registry; BBP, Benzyl butyl phthalate; BPA, Bisphenol A; BPAF, bisphenol AF; BPF, Bisphenol F; BPS, Bisphenol S; DDT, Dichloro-diphenyl-trichloroethane; DEHP, Bis(2-ethylhexyl) benzene-1,2-dicarboxylate; DEHTP, Bis(2-ethylhexyl) benzene-1,4-dicarboxylate; DIDP, Di-isodecyl phthalate; DINCH, Bis(7-methyloctyl) cyclohexane-1,2-dicarboxylate; DINP, Di-isononyl phthalate; ECHA, European Chemicals Agency; HBCDD, Hexabromocyclododecane; HBM-I, Human biomonitoring value 1; ICD-11, International Classification of Disease 11th Revision; MEHP, mono(2-ethylhexyl) phthalate; NHANES, National Health and Nutrition Examination Survey; NIAS, non-intentionally added substances; OPE, Organophosphate ester; PBB, Polybrominated biphenyl; PBDE, Polybrominated diphenyl ether; PCB, Polychlorinated biphenyl; PeCB, Pentachlorobenzene; PECO, Population, Exposure, Comparator and Outcome; PFAS, Perfluoroalkyl or polyfluoroalkyl substances; PFDA, perfluorodecanoic acid; PFHxS, perfluorohexanesulfonic acid; PFNA, perfluorononanoic acid; PFOA, Perfluorooctanoic acid; PFOS, Perfluorooctane sulfonic acid; PFUnDA, perfluoroundecanoic acid; POP, Persistent organic pollutant; PRESS, Peer Review of Electronic Search Strategies; PRISMA, Preferred reporting items for systematic reviews and *meta*-analyses; SEM, Systematic evidence map; t, Tonnes or Metric ton; t/yr, Tonnes per year or Metric tons per year.

* Corresponding author.

E-mail address: plastichumanhealthreviews@minderoo.org (S.A. Dunlop).

[1] Equal first authorship

[2] Equal second authorship

https://doi.org/10.1016/j.envint.2023.108225
Received 23 November 2022; Received in revised form 15 September 2023; Accepted 19 September 2023

chemical, multiple exposures), and health outcome measures (biochemical, physiological, and/or clinical), from which we produced the interactive database 'Plastic Health Map' and a narrative summary.

Results: We identified 100,949 unique articles, of which 3,587 met our inclusion criteria and were used to create a systematic evidence map. The Plastic Health Map with extracted metadata from included studies are freely available at https://osf.io/fhw7d/ and summary tables, plots and overall observations are included in this report.

Conclusions: We present the first evidence map compiling human health research on a wide range of plastic-associated chemicals from several different chemical classes, in order to provide stakeholders, including researchers, regulators, and concerned individuals, with an efficient way to access published literature on the matter and determine knowledge gaps. We also provide examples of data clusters to facilitate systematic reviews and research gaps to help direct future research efforts. Extensive gaps are identified in the breadth of populations, exposures and outcomes addressed in studies of potential human health effects of plastic-associated chemicals. No studies of the human health effects of micro and/or nanoplastics were found, and no studies were found for 26/1,202 additives included in our search that are of known hazard concern and confirmed to be in active production. Few studies have addressed recent "substitution" chemicals for restricted additives such as organophosphate flame retardants, phthalate substitutes, and bisphenol analogues. We call for a paradigm shift in chemical regulation whereby new plastic chemicals are rigorously tested for safety before being introduced in consumer products, with ongoing post-introduction biomonitoring of their levels in humans and health effects throughout individuals' life span, including in old age and across generations.

1. Introduction

1.1. Background

Plastic is one of the most utilized materials in everyday life, with annual global use reaching 460 million metric tons in 2019 and expected to nearly triple by 2060 (OECD, 2022). It has been estimated that over three quarters of plastics produced still exists to date (Geyer et al., 2017), which has resulted in unprecedented pollution in the ocean (Cózar et al., 2014; van der Mheen et al., 2020), atmosphere (Dris et al., 2016; Liao et al., 2021); soil (Scheurer and Bigalke, 2018; Wahl et al., 2021), and water supplies (Kosuth et al., 2018; Mintenig et al., 2019; Pivokonsky et al., 2018). Although the harmful environmental impacts of plastic have been widely discussed (Davison et al., 2021), a less commonly explored perspective on plastic pollution is the relationship between plastic particles (such as micro and/or nanoplastics) and plastic-associated chemicals (such as polymers, monomers, and/or additives) and their directly measured effects on human health.

Plastic is used to manufacture a wide range of industrial and consumer goods, including construction materials, electronics, packaging materials, medical equipment, and toys. Due to plastic fragmentation during use and in the environment over time (WHO, 2022), humans can be exposed to plastic particles during the normal and intended use of plastic food contact materials (Jadhav et al., 2021; Zangmeister et al., 2022), and to plastic particles intentionally produced and added to products, such as cosmetics and personal care products (Napper et al., 2015). Plastic materials are made of various polymers (Table 1) depending on the properties required such as strength, flexibility, resistance to corrosion, heat/electrical conductivity, transparency and cost.

The functional properties of the final plastic product are improved by the addition of additives such as colorants, heat and light stabilizers, antioxidants, biocides, fillers, plasticizers, and flame retardants (Fahlman, 2018). Of all plastic additives, plasticizers, which provide flexibility (e.g., phthalates), and flame retardants, which provide fire resistance (e.g., polybrominated diphenyl ethers [PBDEs]), have the highest concentration ranges in plastic materials (ECHA, 2020). In addition to these intentionally added chemicals, plastic-based products can also contain non-intentionally added substances (NIAS) such as impurities, by-products, and breakdown products (Geueke, 2018; Wiesinger et al., 2021; Zimmermann et al., 2019). Both plastic additives and NIAS are not bound to the polymer matrix and can leach into the air, water and food products (Groh et al., 2019; Lunderberg et al., 2019; Rudel et al., 2003; Zimmermann et al., 2019), resulting in potential human exposure during use and from environmental contamination by plastic waste.

Another chemical and another chemical class associated with plastics that are important in terms of extensive published evidence demonstrating significant levels of human exposure, as well as adverse effects on human health, are bisphenol A (BPA) (Hu et al., 2018; Hwang et al., 2018; Wu et al., 2020) and perfluoroalkyl and polyfluoroalkyl substances (PFAS) (Forns et al., 2020; Luo et al., 2020; Negri et al., 2017). BPA is a monomer used to manufacture polycarbonates, epoxy resins, polysulfones, PVC, polyurethane and phenolic resins (Hahladakis et al., 2023) and may leach from items such as polycarbonate baby bottles (Simoneau et al., 2011; Siddique et al., 2021) and PVC food packaging materials (Wang et al., 2021), especially when the plastic product is exposed to heat or acidic/alkaline solutions due to polymer degradation (Luttrell and Baird, 2014). BPA has also been shown to migrate from several other plastic food contact materials into food or food simulants (Food Packaging Forum Foundation, 2022; Geueke et al., 2022). Some PFAS occur as NIAS in plastic as a by-product in the fluorination of high-density polyethylene, a commonly used treatment to reduce permeability of the plastic packaging used for a wide range of consumer and industrial products (Vitale et al., 2022). PFAS are also used as polymer processing aids and are emitted not only during the production and processing of fluoropolymers (Lohmann et al., 2020), but also during their use.

Importantly, human exposure to many of these plastic-associated chemicals can also occur through their use in other applications (Wiesinger et al., 2021), including the use of phthalates in cosmetics and personal care products (Pagoni et al., 2022), and PFAS in non-stick coatings, non-plastic food packaging materials, textile treatments and fire-fighting foam (Glüge et al., 2020). Additionally, accidental exposure to these chemicals can occur through direct contamination of food products or water supplies (Graber et al., 2019; Jamieson et al., 2011; Woolf, 1968), occupational exposure (Glüge et al., 2020); and industrial contamination (Han and Currell, 2017; Yang et al., 2015). Some plastic-associated chemicals such as polychlorinated biphenyls (PCBs) and PBDEs, which were historically added to some plastics as flame retardants, are persistent organic pollutants (POPs), and therefore, they do not easily degrade, remaining in the environment long-term, and being fat-soluble, can bioaccumulate in marine life and animal tissues and biomagnify in the food chain leading to human exposure (Ábalos et al., 2019; Corsolini et al., 2005).

Because of the ubiquitous presence of plastic products, micro and nanoplastic particles, and plastic-associated chemicals in everyday life and in the environment (Allen et al., 2022; Bergmann et al., 2019; Landrigan et al., 2020), human exposure to all of the above is inevitable, whether it is via inhalation (Brommer et al., 2012; Khalid Ageel et al., 2022; Rudel et al., 2003), ingestion (Jamieson et al., 2011; Senathirajah et al., 2021), or direct dermal contact (Lazarov and Cordoba, 2000; Lv

Table 1
Plastic types, polymers and common uses (CROW, 2021).

PLASTIC TYPE	PRINCIPAL POLYMERS (large scale production)	COMMON USES
Elastomers	Butadiene-elastomers BR	Tires, hoses
	Styrene-butadiene-elastomers SBR	Shoe soles, car tires, conveyor belts, molded rubber goods, chewing gum
	Polyurethane PUR	Flexible foam for bedding, furniture, automotive; rigid foam insulation in construction; adhesives, sealants, binders
Amorphous thermoplastics	Polycarbonate PC	Medical equipment, construction materials, food storage, electronic components
	Polymethacrylate	Optical fibers, bathroom fittings, biomedical applications, transparent glass substitutes
	Polystyrene PS	Food packaging, medical applications, housewares, toys, takeaway food containers
	Polyvinyl chloride PVC	Building and construction, water pipes, footwear, toys, automotive
	Polysulfones (e.g., polysulfone PSU, polyethersulfone PES, polyphenylsulfone PPSU)	Automotive, medical devices, printer cartridges, aerospace
Semi-crystalline thermoplastics	Polyolefins (e.g., polypropylene PP, polyethylene PE)	Food packaging, homewares, toys, automotive, clothing, carpets, disposable diapers, plastic bags, agriculture, pipes, construction materials
	Polyesters (e.g., polyethylene terephthalate PET, polybutylene terephthalate)	Medical packaging, food packaging, plastic cards, textiles, drink bottles, household appliances, automotive
	Fluoropolymers (e.g., polytetrafluoroethylene PTFE, polyvinylidene fluoride PVDF)	Aircraft, mechanical industry, chemical industry, food packaging, non-stick coatings, wire insulation and electronics
	Polyamide PA (e.g., nylon, Kevlar)	Automotive, electronic, textile, carpets, upholstery, heat shields
Thermosets	Epoxy resin ER	Electronics, structural adhesives, fiber-reinforced plastics, paints and coatings
	Phenolic resins PR	Coatings for interior of food and beverage cans, composites, adhesives, pipe linings, electrical devices
	Unsaturated polyester resins	Fiber reinforced plastics, pipes, coatings, adhesives
	Vinyl ester resins	Coatings for building and construction, fiber reinforced plastics, solvent tanks, sewer pipes
	Melamine resins	Kitchenware, laminates, glues, particleboards, floor tiles, cleaning abrasive, flame-resistant textiles
Plastic particles	Polyethylene, polypropylene, polyethylene terephthalate, nylon	Cosmetics, face washes, toothpaste, textiles (primary microplastics)
	Acrylic, melamine, polyester	Industrial scrubbers (primary microplastics)
	Various	Plastic degradation (secondary microplastics)

et al., 2017; Majasuo et al., 2012). Moreover, children can be exposed to both plastic-associated particles and chemicals through additional routes, including prenatally via the placenta (Breton et al., 2021; Braun et al., 2021), and postnatally via breast milk (Chao et al., 2007; Liu et al., 2023) or non-nutritional oral intake (Asimakopoulos et al., 2016; Aurisano et al., 2022; Catarino et al., 2018; Xue et al., 2007). Adding to the complexity of plastic-related exposure, some chemicals may induce non-monotonic responses (Vandenberg et al., 2012) or impact human health only when present in specific chemical mixtures (Tanner et al., 2020).

1.2. *Motivation for this project*

A number of systematic reviews and *meta*-analyses have been published investigating the association between plastic-associated chemicals and human health outcomes. These reviews are limited to a small number of plastic-associated chemical classes, such as PCBs (Gascon et al., 2014; Govarts et al., 2012; Leng et al., 2016), phthalates (Cai et al., 2015; Golestanzadeh et al., 2020; Lee et al., 2018), BPA (Hu et al., 2018; Hwang et al., 2018; Wu et al., 2020), PFAS (Forns et al., 2020; Luo et al., 2020; Negri et al., 2017), and PBDEs (Lam et al., 2017; Zhao et al., 2017; Zhao et al., 2015). Additionally, while these reviews report on the associations between the level of these plastic-associated chemicals measured in the human body and a range of human health impacts, including carcinogenicity (Leng et al., 2016; Zhang et al., 2015; Zani et al., 2017), diabetes (Hwang et al., 2018; Song et al., 2016; Wu et al., 2013), reproductive effects (Cai et al., 2015; Wen et al., 2019; Zhang et al., 2020), and neurodevelopmental effects (Lee et al., 2018; Lam et al., 2017; Radke et al., 2020), only specific diseases or disease-specific health outcomes are usually systematically reviewed, omitting the broader range of health outcomes that may have been studied in humans, as well as non-disease-specific health domains, such as impacts on gene expression and oxidative stress.

As well as a growing awareness of the potential implications of plastic particles for human health impacts (WHO, 2022), there is increasing scientific evidence linking exposure to plastic-associated chemicals with human health issues, and increasing levels of public concern regarding plastics and health risks, and associated support for research (Davison et al., 2021). Given the large number of hazardous chemicals and chemicals of unknown hazard associated with plastic (Wiesinger et al., 2021), the substantial number of plastic materials currently in everyday use, human exposure to plastic-associated chemicals through contact with household goods and furnishings, food packaging, electronics and construction materials and other non-plastic related sources, and the potential for human health impacts, there is an urgent need to systematically map the existing epidemiological research in this area. Although some epidemiological data are available through the Agency for Toxic Substances and Disease Registry (ATSDR), PubChem and the European Chemicals Agency (ECHA), there is currently no database that allows for the search of peer-reviewed literature both by chemical exposure and/or health outcome measure.

1.3. *Problem formulation*

1.3.1. *Scoping exercise*

We conducted preliminary searches in May 2020 in Prospero, Epistimonikos, Cochrane, OSF, Medline/PubMed and Embase databases, and as we initially aimed to conduct a scoping review, we used the term ‘scoping review’ and terms such as ‘plastic exposure’, ‘plastic particles’, ‘plastic chemicals’ (interchanged with ‘plasticizers’, ‘flame retardants’, ‘bisphenols’, ‘PFAS’) in combination with ‘human health’. We identified one published protocol for a systematic scoping review of studies on the impacts of plastics used in the entire food system, from production and processing to consumption and waste management. The purpose and scope of their study (subsequently published in 2021: Yates et al., 2021) was very different to ours – narrower in including studies exclusively on plastics used in the food system, targeting only seven plastic polymers, phthalates and BPA, and limiting their search to studies published post-2000, and broader in terms of including impacts beyond human health. The same searches conducted during preparation of our manuscript found six additional scoping reviews – organophosphate flame retardants (OPEs) and human neurodevelopmental toxicity (2002–2022) (Zhao et al., 2022); OPEs and pregnancy/birth outcomes (Gan et al., 2023); BPA structural analogues and human, animal, and mechanistic toxicity (2015–2019) (Pelch et al., 2019); as well as PFAS and glucose metabolism disorders (research published until 2020) (Margolis and Sant, 2021), non-targeted metabolomics (2000–2021) (Guo et al., 2022), and cancer (research published until Sep 2020) (Steenland and Winquist, 2021). Further searches replacing 'scoping review' with 'evidence map', 'systematic review', and 'systematic evidence map' (SEM) identified recently published SEMs that were also limited to single chemical classes – three on PFAS (including human health studies, plus *in vitro* and/or animal studies) (Carlson et al., 2022; Pelch et al., 2022; Zhang et al., 2023) and one on PCB mixtures and non-cancer health effects (Carlson et al., 2023). We also identified a SEM protocol on 34 polyethylene terephthalate oligomers (Schreier et al., 2022) and a SEM on migrating and extractable food contact chemicals without any data on human health outcomes (Food Packaging Forum Foundation, 2022; Geueke et al., 2022). Also identified was a database created by systematically mining microplastic toxicity literature, with no human epidemiological health studies included when accessed in April 2023 (Thornton Hampton et al., 2022). Throughout our study, we found no previous, or in-progress, scoping review or SEM related to the broad topic of plastic particles, multiple plastic-associated chemicals and multiple human health outcomes.

1.3.2. *Prioritized plastic particles and plastic-associated chemicals*

Our review was designed to chart the scope of peer-reviewed research published from 1960 (when plastic began to be mass-produced) to January 2022 on the potential effects of plastic particles and plastic-associated chemicals on human health with the aims of highlighting any trends or gaps in what has been investigated, to reveal opportunities and priorities for further research in specific areas, including systematic reviews, and provide recommendations on regulation policy.

In this SEM, we include plastic particles (micro and nanoplastics), being small pieces of plastic and due to their widespread occurrence and potential for human exposure (WHO, 2022); and polymers, as the main building blocks of plastics. It was not possible to review all chemicals that may be present in plastic materials, in part because many of them are unknown, especially in the case of NIAS (Groh et al., 2019; Muncke et al., 2017; Zimmermann et al., 2021). Herein, chemical classes, other than polymers, are restricted to plastic additives that act as plasticizers and/or flame retardants, considering their high concentration in plastic materials compared to other additives (ECHA, 2020), and also bisphenols and PFAS because they also occur in plastics and populations are known to be exposed to them through food contact materials (Food Packaging Forum Foundation, 2022; Geueke et al., 2022). We are cognizant that humans are also exposed to a range of other plastic-associated chemicals, but we considered the high degree of concern about human health effects associated with plasticizers, flame retardants, bisphenols and PFAS, which is reflected in their inclusion in a number of systematic reviews of health literature (see above) as well as in major human biomonitoring programs: the 'National Health and Nutrition Examination Survey (NHANES)' in the United States (Calafat, 2012), and the 'HBM4EU' biomonitoring initiative in Europe (German Environment Agency, 2022). Both these biomonitoring programs screen for specific plasticizers and flame retardants, several bisphenols and PFAS (CDC, 2022; German Environment Agency, 2022). We include all research investigating the health impacts of plastic particles and these plastic-associated chemicals regardless of the source of exposure, as all information regarding health outcomes are relevant to chemical regulation and policy.

1.4. *Objectives and specific aims*

Our primary research question was, "In primary peer-reviewed research conducted since 1960 on the effects of plastic-associated particles and chemicals on human health, which particles (micro and/or nanoplastics), polymers, plasticizers, flame retardants, bisphenols and PFAS, and which health domains have (and have not) been investigated?" We have created a SEM of included studies published between Jan 1960 – Jan 2022 consisting of the following extracted metadata:

- Population and study characteristics – the populations studied, geographically and by generation, sex, age group and general/special exposure risk status; the study designs employed.
- Exposures – plastic particles (micro and nanoplastics) and the plastic-associated chemicals that have been the focus of research during this period; the trend for plastic-associated chemicals studied in relation to human health outcomes over time; and whether multiple chemical classes were investigated within an article.
- Health outcomes – the health domains that have been the focus of research whether they are biochemical, physiological, and/or clinical outcomes/measures.

The conceptual framework for the project, including the intended scope, process, variables considered and anticipated outputs, is illustrated in Fig. 1. Given that attempts to synthesize findings across studies are complicated by the lack of consistent terminology used to name plastic chemicals and describe human health outcome measures, a secondary aim of this SEM was to provide comprehensive and searchable databases of included plastic-associated chemicals and human health outcomes indexing the multiple names, synonyms and commonly used terminology.

2. Materials and methods

2.1. *Protocol and registration*

Our protocol was determined based on consultation with a group of stakeholders including representatives from three academic institutions in Australia (polymer chemists Dr Marck Norret at the University of Western Australia, Prof Andrew Lowe at Curtin University, and environmental health scientists Prof Jochen Mueller and Prof Kevin Thomas at The University of Queensland). This consultation process was conducted in May-September 2020, and it helped narrow the scope of this SEM to plastic particles (micro and/or nanoplastics), polymers, plasticizers, flame retardants, bisphenols and PFAS (see Appendix A.1 for more details). Details about the expertise of the authors and non-author reviewers as well as their roles and responsibilities throughout this project have been provided in Appendix A.2.

The protocol was drafted using the PRISMA (Preferred reporting items for systematic reviews and *meta*-analyses) Protocols guidelines (Shamseer et al., 2015) and used the methodological framework recommended for scoping reviews (Peters et al., 2020; Tricco et al., 2018), with V1.0 registered prospectively with OSF, the Open Science Framework-Standard Pre-Data Collection Registration (https://osf.io/gbxps; doi: 10.17605/OSF.IO/GBXPS), on 18 August 2021, disseminated via the preprint server medRxiv (Goodes et al., 2022) and V2.0 subsequently published as open-access (Goodes et al., 2022). A protocol update, V2.1, was uploaded to OSF on 01 February 2023 (https://osf.io/8w7nr). In summary, this protocol update included the following points:

- Extension of the project by producing an interactive database and converting the study design from a scoping review to a SEM, herein referred to as the 'Plastic Health Map'. This deviation led to a change in the title and the addition of several methodological steps for producing a SEM. Herein, our reporting conforms with recommendations made by Thayer et al. (2022).
- A narrower search strategy. Protocol V2.0 stated that we would "review the reference lists associated with a related 'Umbrella Review' of systematic reviews with *meta*-analyses on this topic". The V2.1 update stated this would now not be performed due to the different timelines of the two reviews and the small overlap in

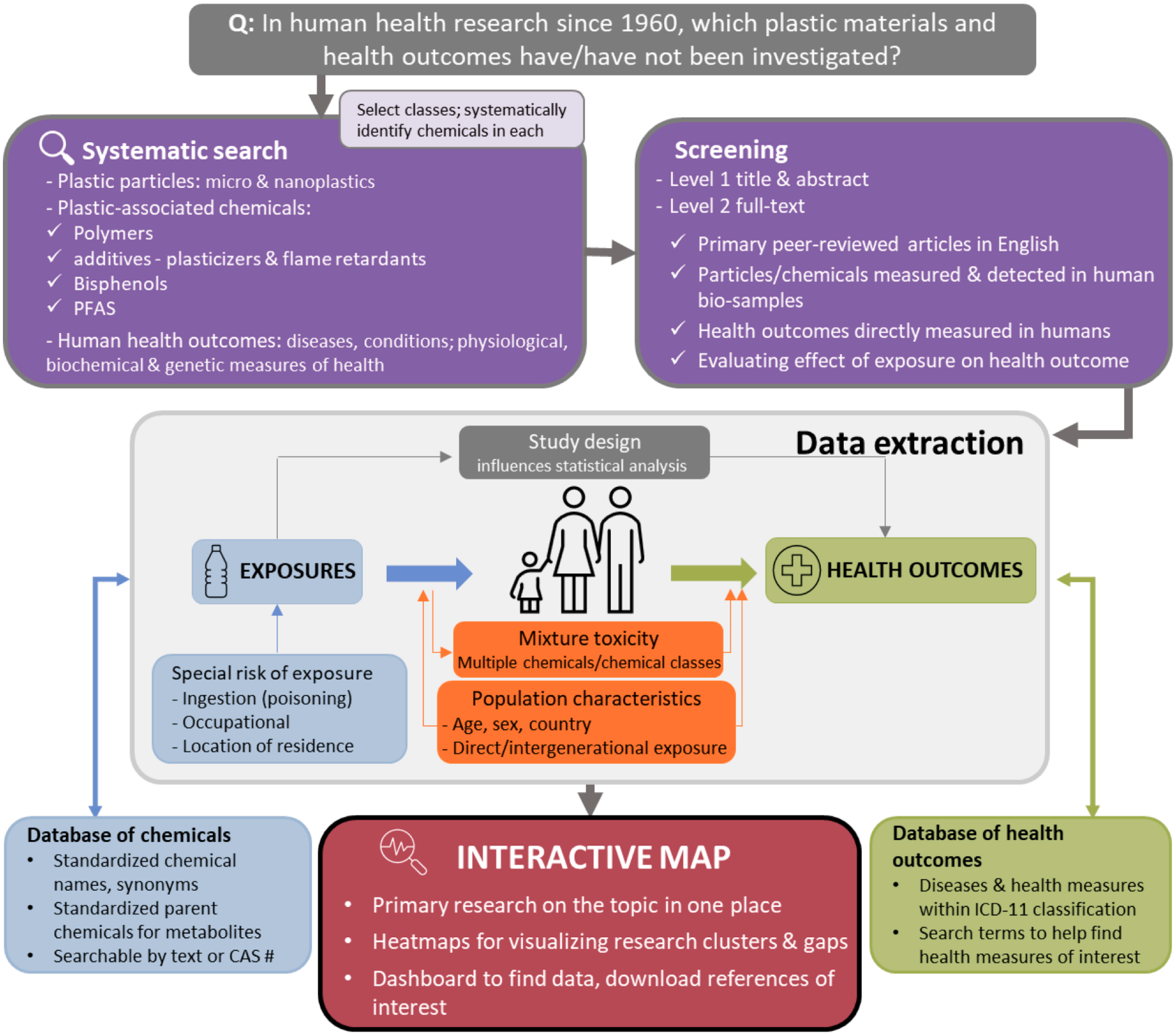


Fig. 1. Conceptual framework showing the intended scope of the project, the process, the variables considered and anticipated outputs. Orange boxes are the effect modifiers.

included chemicals. (The intention stated in protocol V2.0 not to check the reference lists of included articles was retained in V2.1.)

- More details regarding how the search strategy was developed, inclusion/exclusion criteria and the data extraction/management process.
- Additional detail on data extraction in relation to the studied population, specifically whether this population was at a special/higher risk of exposure to the plastic-associated chemicals (e.g., due to their occupation, poisoning event or residence in a high-risk environment).

All versions of the protocol, project updates, a link to an instructional video for using the interactive database and a link to the Plastic Health Map are available at https://osf.io/fhw7d/.

2.2. Pilot searches

The pilot searches were conducted, and the electronic search strategy developed in consultation with Research Librarian TS. Initially, pilot searches of Medline and Embase using the Ovid® search platform were conducted to identify a variety of articles on the topic and explore the keywords highlighted, the keyword search fields and the hierarchy of indexing terms (subject headings) in each database, as well as approaches for excluding articles describing animal-only studies. In the Medline and Embase pilot searches, for *Population*, we used the term ‘human’; combined with broad terms for *Exposure* such as ‘plastics’, ‘plastic particles’, ‘microplastics’ and ‘nanoplastics’, ‘polymers’, and functional terms for the included plastic chemical classes, i.e., ‘plasticizer/plasticiser’ and ‘flame retardant/fire retardant’, as well as class names, including ‘phthalates’, ‘bisphenols’ and ‘PFAS’; and also combined with general terms for *Outcome*, including ‘human health’, ‘health outcomes’ and ‘epidemiology’. From the found articles, we identified search terms for human health outcomes to incorporate into our search strategy, including keywords, and in each database, indexing terms to capture the broadest possible range of health outcomes, only excluding sections of the indexing hierarchy obviously unrelated to plastic-associated chemical exposure and likely to result in the retrieval of irrelevant results.

Secondly, indexing terms were identified in each database to capture plastic particles and included chemical classes to incorporate into our search. A database of chemicals in the included groups/classes were selected by chemists JA and MB for the search strategy based on preselected references identified via afore-mentioned consultation with Dr Norret – seven for plastic additives (ATSDR, 2020; ECHA, 2020a; ECHA, 2020b; ECHA, 2020c; Groh et al., 2019; Stockholm Convention, 2019; Stockholm Convention, 2019) and seven for polymers (Braun et al., 2013; CROW, 2021; Koltzenburg et al., 2017; Lithner et al., 2011; Ravve, 2012; Salamone, 1996; Wypych, 2016) (detailed in Excel Table B.1). For items sourced from the ECHA Plastic Additive Initiative list that were chemical mixtures/groups, constituent chemicals were also included in the search strategy if they were specifically itemized on the ECHA website. Plastic chemicals were excluded from the search strategy if the pilot searches revealed they have primarily been studied in biomedical applications or as food additives, with many thousands of retrieved studies designed to evaluate the effectiveness of procedures/treatments for health conditions (e.g., a prosthesis in orthopedic surgery), rather than to analyze the effects of the plastic material itself in the body.

Thirdly, further pilot searches were undertaken to identify indexing terms in each database for well-studied specific chemicals, and to test terms for the specific polymers in our chemical database. For the chemical additives, search strings were constructed to include the CAS number, IUPAC name, commonly used names and synonyms (each separated by 'OR') for each chemical. We ran pilot searches of groups of polymers and chemical additives, combined with keyword strings and indexing terms for health outcomes, again identifying the source of very large numbers of irrelevant search results, and testing useful exclusion terms (e.g., plasticity, plastic surgery, drug delivery) to minimize the number of unsuitable articles retrieved by the search. We also tested the use of syntax such as proximity operators and the truncation symbol * to streamline the search strategy.

Scopus and Web of Science databases were also investigated as sources; however, these were deemed unsuitable. Unlike when accessing Medline and Embase using the Ovid platform, it is not possible to conduct complex searches of these databases that combine groups of exposure terms with groups of health outcome and exclusion terms (each group consisting of multiple indexing terms and multiple long keyword strings), which was necessary for our SEM (See Appendix A.3 for complex search strategy). In addition, there is a lack of indexing terms and filters for human-only studies.

2.3. *Search strategy*

2.3.1. *Medline and Embase original searches*

Informed by the pilot searches, the electronic search strategy was developed in accordance with the Peer Review of Electronic Search Strategies (PRESS) checklist (see complete search strategy for each database in Appendix A.3) (McGowan et al., 2016). Advice was provided by a Senior Training Consultant from Ovid® and the search strategy was peer reviewed by an Information Retrieval Specialist (York Health Economics Consortium and Independent Consultant) who has extensive experience conducting Cochrane Collaboration literature searches. A series of electronic searches were constructed for each database (30 in Medline and 30 in Embase) using the Ovid® search platform, with a validated search filter specific to each database used to identify human (*Population*) studies and exclude animal-only studies (Bramer et al., 2020; Tessier, 2019; Venn, 2020). Each search combined clusters of indexing and keyword terms through the use of the Boolean operators 'AND', 'OR' and 'NOT' via the strategy: [a group of plastic *Exposures*] AND [all health *Outcomes*] NOT [all exclusions], limited to English language and the date range 1960–21 Jan 2021. Each search addressing a particular group of plastic exposures included the same keyword terms but was tailored for each database in terms of indexing terms. The syntax used in both databases included '/exp' to explode (broaden) exposure and health outcome indexing terms when appropriate to capture associated narrower terms, the truncation symbol * (for example, 'plasticizer*' to capture both 'plasticizer' and 'plasticizers'), quotation marks around exact phrases, and occasional use of the proximity operator 'ADJ' for keyword searching of title and abstract fields to capture terms adjacent within a tested number of words, for example, 'health adj2 (implication* or impact* or effect* or toxicity or consequence* or hazard* or outcome*)'. Syntax differed slightly between databases in terms of the selected keyword search fields (the range of options being unique to each).

2.3.2. *Benchmarking*

During September 2020, the search strategy was tested for sensitivity against a set of 16 pre-determined primary articles: 14 were selected as being relevant and suitable from the reference lists of two key literature reviews (Hengstler et al., 2011; Meeker et al., 2009) and a book chapter (Galloway, 2015), and included articles on health outcomes in relation to human exposure to phthalates and BPA; and two further articles were selected relating to human health effects of PFAS exposure (Steenland and Woskie, 2012; Vieira et al., 2013). The source publications and individual articles are listed in Appendix A.4.1. All 16 of the pre-determined articles were captured by our Medline and Embase searches. Full details and results of the benchmarking exercise are available in Appendix A.4.2.

2.3.3. *Other resources consulted*

As another source of potentially suitable articles, a set of 63 systematic reviews with *meta*-analyses investigating potential human health effects associated with exposure to plastic chemicals (listed in Excel Table C.1) was consulted. 1,337 of the articles cited in these reviews were uploaded into DistillerSR systematic review software application (DistillerSR, 2021).

2.3.4. *Search update in Medline and Embase*

In 2022, an update of the bibliographic searches was undertaken in Medline and Embase using the same search strategy as reported in Appendix A.3 to identify new research between 21 Jan 2021 to 31 Jan 2022.

2.4. *Eligibility criteria*

Articles were eligible for inclusion if they were peer-reviewed primary research articles published in English between Jan 1960 and Jan 2022. We started our search from 1960 because, while the large-scale production and use of plastics date back to the 1950s, plastic pollution only increased significantly from the 1960s onward (Geyer et al., 2017). In line with standard SEM methodology, articles were not excluded based on quality in terms of sample size adequacy or scientific rigor of the methodology or quality of statistics (Thayer et al., 2022), but were excluded if not published in peer-reviewed journals, since a peer review process indicates that some level of assessment of scientific rigor has been done.

The inclusion and exclusion criteria were formulated for the search and screening of articles prior to screening, based on the population, exposure, comparator and outcome (PECO) criteria described in Table 2 (Munn et al., 2018; Moola et al., 2015). Articles were eligible if they involved humans, measured levels of exposure to plastic particles or one or more included plastic-associated chemicals in a human bio-sample and reported a human health outcome.

In terms of Exposure specifically, articles were eligible for inclusion if they investigated plastic particles (micro or nanoplastics) and/or synthetic thermoplastics and thermosetting polymers, plastic additives that act as plasticizers and/or flame retardants, bisphenols, or PFAS. Excel Table B.1 and the "Chemical Search" tab of the Plastic Health Map display the complete list of chemicals, including those sourced from our preselected references, as well as additional plastic chemicals identified during data extraction as belonging to included chemical classes and added to the database according to expert decision by Authors JA and MB (doctoral degrees in chemistry). Excel Table B.1 also presents information about the function of the included chemicals and the reason for inclusion in this SEM. Ineligible for inclusion were articles only investigating other additives (such as colorants, stabilizers, antioxidants and fillers), monomers apart from bisphenols, or other chemicals involved in plastic manufacturing (e.g., processing agents), recycling or disposal.

While many of these included chemicals are known to be used in other (non-plastic) applications, the source of exposure to these

Table 2
Inclusion and exclusion criteria for article selection.

Criteria	Inclusion	Exclusion
Document type	Primary peer-reviewed research article, including case studies, case series and short communications.	Pre-prints, reviews, *meta*-analyses, book chapters, conference proceedings/abstracts, cohort profiles, letter to editor, editorial, podcast, grey literature and any other non-primary peer-reviewed research article.
Population	Humans of either sex or any age group, including developing fetus.	In chemico, in silico, *in vitro*, animal and mechanistic studies.
Exposure	At least one exposure measured and detected is/contains a plastic particle (micro and nanoplastics) or an included plastic-associated chemical (individual polymer or polymer class, additive – plasticizer or flame retardant, bisphenol, or PFAS). For a full list, see Excel Table B.1.	Exposure to plastic material, plastic particles (micro and nanoplastics) and/or included plastic chemicals associated with a medical intervention or procedure, e.g., implant or medical device.
	Measured directly via human bio-samples and detected OR an experimental exposure (including patch tests and skin prick tests).	Human exposure levels only estimated via measurements of chemical concentrations in environmental samples.
	All sources and pathways of exposure. Individual populations may have ‘general’ exposure risk, they may be exposed experimentally, or they may have a ‘special’ exposure risk whereby they are at an increased risk of exposure associated with their occupation, ingestion/poisoning events or residential location.	
Comparators/ controls	All studies with or without a comparator/control group.	
Outcome	Any health outcome (including physiological changes, mental health and developmental outcomes/measures) assessed by investigators, or reported in a previous study, or extracted from medical records, research database or validated surveys. For a full list of categories see Excel Table B.2.	No health outcome assessed (i.e., exposure-only, or toxicokinetics/pharmacokinetics studies); health risk only estimated/modelled; use of non-validated health questionnaires for self-reported symptoms, parent-reported child symptoms or developmental milestones.
	Aim of study is to examine the effect of exposure on the human health outcome.	No analysis of differences in exposure by health outcome, or differences in health outcome by exposure. Examination of the function/efficacy of a plastic item/material as an intervention for a health condition, or use of plastic material in a study methodology.
Study design	All study designs are relevant.	

chemicals (via plastic or otherwise) was not relevant for inclusion/exclusion. Articles were excluded if they described the use of a plastic material/chemical in a study that was not designed to examine the effects of the plastic material/chemical itself on a health outcome, such as the use of a plastic film in microscopy. We also excluded articles where plastic materials were used in medical applications, in order to be consistent with our search strategy that necessarily contained several exclusion terms for medical procedures/treatments.

In terms of Outcome specifically, articles were eligible for inclusion if a health outcome, i.e., any disease state (or death), or any quantifiable physiological change, or quantifiable measure of health/disease (including mental health) or fetal/child development, was directly assessed in the same members of the population assessed for Exposure.

2.5. Data management and screening in DistillerSR

All identified articles were uploaded into the DistillerSR and deduplicated. Eligibility screening and subsequent data extraction were then performed using DistillerSR and the forms were designed within DistillerSR. Articles were screened in two stages: “Level 1” and “Level 2” screening. Before each stage, reviewers were provided with screening guidelines (Appendix D.1-D.2) and underwent in-depth training using example articles. Training included defining and reinforcing how to interpret and apply eligibility criteria. Pilot testing of the eligibility criteria and consistency checking were performed prior to both levels of screening, with reviewers required to achieve an 85% agreement rate with resolved group decisions for a subset of n = 300 pre-selected articles at each stage and exclude no more than 2% of eligible articles.

At Level 1 Screening, articles were screened for relevance by title, abstract and index terms. Articles for which an abstract was not available, but were potentially relevant, were included at this stage. Due to the large number of articles retrieved, Level 1 screening was performed by a single reviewer and to minimize the number of potentially eligible articles being excluded, the inbuilt artificial intelligence tool within the Distiller software (DistillerAI) (DistillerSR, 2022; Hamel et al., 2020) was used to identify possible false exclusions and when found, these articles were re-screened. Out of 1,946 articles detected by DistillerAI from the original search and 47 from the updated search, upon re-screening by a second independent reviewer, 139 articles were re-included in the SEM from the original search and one from the updated search. Additionally, auditing was performed by three experienced reviewers (BJS, YM, EW) on a random 5% of screened articles to evaluate screening accuracy. No false exclusions were detected during auditing.

At Level 2 screening, full-text articles were procured and reviewed for eligibility by one reviewer. Included articles proceeded to data extraction, while excluded articles required confirmation by a second reviewer before being discarded. Any disagreements were resolved by a third reviewer with relevant experience for health outcomes (LM, CS, and BJS) and for chemicals (JA and MB). The “codebook” for full-text screening at Level 2 has been provided in Excel Table E.1. No data were extracted at this level. The list of articles excluded at Level 2 has been provided in Excel Table F.1, along with the reasons for exclusion.

2.6. Data extraction and coding

Data extraction forms were designed in DistillerSR to confirm that articles fulfilled the inclusion criteria and to extract data items described in Section 2.7. Articles could be excluded during data extraction if they were found to not meet the eligibility criteria or if it was not possible to extract relevant data items due to ambiguity. The list of articles excluded at the data extraction stage has been provided in Excel Table F.1, along with the reasons for exclusion. With the aim to make our data extraction process consistent and reproducible, coding of all data items, except for chemical names and health outcome measures, involved selecting one or more listed pre-defined options or “codes”, avoiding the need to enter free text. The data “codebook” is available in Excel Table E.2.

During the training period, the coding strategy/data extraction process/forms were pilot tested against a subset of 75 articles by two independent reviewers per article. Minor revisions were made to the forms before implementation (e.g., “ambiguous reporting of data” coding option added). Coding of chemical names and health outcome measures were standardized using an interactive web application (Shiny app) using the Shiny package (Chang et al., 2021) within RStudio (RStudio Team, 2021; R Core Team, 2021) to guide reviewers during data extraction. The Plastic Health Map contains a comprehensive and searchable database of included plastic chemicals (“Chemicals Search” tab) and health outcomes (“Health Outcomes” tab), including clinical signs and measures of body function, structure, and pathology. Both search tabs contain several synonyms and possible search terms and a “fuzziness” function to allow for spelling errors or differences in syntax of chemical names during searches. Reviewers were then required to copy the pre-defined output (“Extracted Name” in “Chemical Search” tab and “Extracted Outcome” in “Health Outcomes” tab) over to the DistillerSR form in order to minimize inconsistencies. During validation of the forms and data extraction process/codes, consistency of data extraction between pairs were evaluated for a random set of 100 articles.

Data from each full-text article were extracted by two independent reviewers. To identify potential inconsistencies within reviewer pairs, random assignment was used. By avoiding constant pairing between two individuals, the possibility of consistently paired reviewers overlooking the same mistakes was minimized. Reviewer pairs discussed and resolved any inconsistencies after independently reviewing a batch of 10–20 articles, with input from a third reviewer (LM, BJS, MB) if assistance was required to resolve decisions. In addition, all reviewers met weekly throughout the data extraction process, which spanned over a period of one year, to resolve inconsistencies and discuss any uncertainties related to data extraction. With the aim to optimize our searchable database of chemicals and health outcomes, additional synonyms for the included plastic chemicals and health outcomes were added throughout the data extraction process to help ensure consistency in the coding process. Following data extraction, auditing was performed on a random set of 530 articles by four experienced reviewers (BJS, EW, YM, AG) to check for consistency. The result of the audit was verified among the reviewers and a small number of changes were made to completed forms as appropriate.

2.7. Data items

For further details on each set of data items, see codebook provided in Excel Table E.2; and see guidelines for data extraction in Appendix D.3.

2.7.1. Population and study characteristics

The countries of the first and last authors and the investigated populations were extracted from included full-text articles, as were the years of publications. Multiple entries were possible for the country of investigated populations.

Populations investigated in each study were categorized as: 1) “individuals,” whereby the exposure and health outcomes were measured within the same individuals, 2) “mother–child pairs,” if the study investigated the influence of maternal exposure on the child’s health outcome, 3) “father-child pairs,” if the study investigated the influence of paternal exposure on the child’s health outcome, and 4) “father-mother-child family,” if the study investigated the influence of parental exposure on the child’s health outcome. The same article could potentially have two population types (e.g., exposure levels measured in mother correlated with health outcomes measured in both mother and child).

Information on biological sex of the investigated population (male-only, female-only, mixed, or unknown/unavailable), age at which exposure was measured, and age at which health outcome was measured were also extracted. Our age ranges were: prenatal (<0 days), neonate (0-<28 days), infant (28 days-<12 months), child (12 months-<10 years), adolescent (10-<18 years), and adult (18+). The age category “older adult/elderly” was used if either term was specified in an article and separate analyses were done on that population. “Unspecified” was used if the age of the studied population was not specified in the article. In instances where a study examined exposures and/or health outcome measures across a range of age groups, multiple age categories could be selected.

Due to the wide range of study designs reported in included studies (e.g., multiple populations/timepoints/sub-analyses), we implemented broad categories of study designs, which comprised “Experimental study” (either with a control/comparator group or without, e.g., skin patch test), “Longitudinal study” with multiple time points of exposure and/or health outcome measures, “Cross-sectional study” with a single time point for exposure and health outcome measure (not necessarily measured at the same time), and “Case study/series”. When an article reported findings for multiple population types, a study design was extracted for each population type. As a result, a single article could have multiple study designs.

2.7.2. Exposure

All included plastic-associated particles/chemicals that had been directly measured via bio-samples and detected in at least one study participant (>the analytical method’s limit of detection), and that were evaluated for their health impacts, were extracted, irrespective of whether an association with the health outcome was found. However, for patch test and skin prick test studies, only included plastic chemicals that caused a positive skin reaction were extracted due to the extensive numbers of chemicals used in patch test series. For studies that measured the metabolites of included plastic chemicals, the corresponding parent chemicals were extracted; and if the metabolite was non-specific, all potential parent chemicals were extracted. In addition, we recorded whether more than one chemical class was measured in each study, irrespective of whether the additional chemical was an included plastic chemical from our database. The statistical methods employed, including analyses to determine potential mixed effects in the case of multiple exposures, were not extracted.

We also documented whether the studied population had a special risk of exposure, that is, if the article indicated the population had a potentially increased risk of exposure associated with occupation (e.g., working in a plastic production factory), an ingestion/poisoning event (e.g., rice bran oil mass poisoning events in Yusho/Yucheng population (Masuda and Schecter, 1994; Woolf, 1968), or other factors such as residence in a high-risk environment (e.g., living near e-waste recycling sites). If there was a special risk population studied with respect to exposure, we then noted whether there was a comparator group for which a group analysis was performed.

2.7.3. Outcome

Health outcome measures included any assessment of change in structure or function of the human body, whether undertaken at the clinical, functional, physiological, or cellular level or related to a disease/disorder. All health outcome measures were classified within the categories for diseases and disorders, using the hierarchical structure of the *International Classification of Disease 11th Revision* (ICD-11) (WHO, 2019) with 20 levels and an additional category created to capture “Health-related measures not related to a specific system” (e.g., oxidative stress markers in urine, see Excel Table B.2). Only health outcome measures analyzed against the levels of exposure were extracted and any measures used only as covariates/confounders were excluded. For self-reported data, to ensure a degree of reliability, these outcome measures were extracted only if reporting clinical diagnoses or part of a validated questionnaire; and similarly, parent-reported childhood developmental milestones were extracted only if recorded at the time of occurrence (not retrospectively, which would rely on memory) via questionnaires. The effects of plastic particle/chemical exposure on health outcome measures (positive/negative/null associations) were not relevant for inclusion/exclusion and were not documented in this SEM. Due to the extensive clinical assessments performed in case studies/series, without analysis of the effect of exposures on assessment findings, only the final diagnoses and/or clinical test results outside normal ranges were recorded.

2.8. Data management and storage

Following data extraction, additional consistency checks were performed in RStudio$_{4.1.2}$ by searching for unlikely data combinations (e.g., multiple chemicals from different classes recorded, but "multiple exposures" not selected) or input of non-pre-defined chemical exposure or health outcome (full scripts available on Github) (RStudio Team, 2021). Detected inconsistencies in categorization of data items were discussed among experienced reviewers YM, BJS, LM and EW and changes to the original DistillerSR forms were made on consensus where necessary. An additional round of duplication check was performed at this stage using a weighted pair comparison of both the DOI and the title separately, using the "RecordLinkage" package in R (Sariyar and Borg, 2010). Using the weighted pair comparison approach enabled the identification of duplicates which had minor spelling variations (e.g., punctuation marks). Access to the forms and extracted data within DistillerSR is available upon request for users with DistillerSR access. The finalized data from DistillerSR were exported in a single data frame as a csv file in a wide format and wide columns collapsed based on data items listed in the codebook (except for multiple populations). Included plastic chemicals were grouped into the following classes: PCBs, phthalates, bisphenols, PFAS, PBDEs, polybrominated biphenyls (PBBs), OPEs, other plasticizers, other flame retardants, other mixed use, and polymers (see Excel Table B.1). Final data used for synthesis of results are provided in Excel Table F.2. Extracted health outcome measures were grouped into their respective ICD-11 categories. Definitions of each fundamental entity used in this SEM and in the interactive database are provided in Excel Table E.3 and their relationships presented in Excel Table E.4.

2.9. Synthesis of results

Countries were grouped according to the World Bank's 2022 classification of economic status (see Excel Table B.3) (World bank country and lending groups, 2022). Production volume and hazard classification data (by aggregated regulatory sources) published by Wiesinger and colleagues (2021) were added for individual included chemicals where available (see Excel Table B.1). In order to compare trends for the timing of research on PBDEs, phthalates and BPA, with research on their respective emerging substitute/alternative chemicals (OPEs, phthalate substitutes and bisphenol analogues respectively), dates associated with the first instances of restriction/banning of original chemicals, and dates associated with significant increases in production/usage of the corresponding substitute/alternative chemicals, were identified from published literature (He et al., 2018; Oliviero et al., 2022; Kasper-Sonnenberg et al., 2019; Simoneau et al., 2011; The commission of the European communities, 1999).

The highest level of classification within ICD-11 was used for total counts of health outcome measures reported in the heatmaps herein and within the Plastic Health Map and additional sub-categories of health outcome measures were used for more detailed heatmaps within the interactive database (see Excel Table B.2 and/or "Health Outcomes" tab of the Plastic Health Map for classification hierarchy). For each presented data item, the count of the unique articles that fitted the categorization was reported. As multiple combinations of population, exposure and/or health outcome may have been extracted from a single article for some data items (e.g., multiple age groups or both "individual" and "mother–child pairs"), the total counts of articles across categories and/or data items may be different from the total number of articles included in this SEM. For example, a single article that investigated both "individuals" and "mother-child pairs" would be counted in both population categories, resulting in an increase of two in the total count.

Users can interrogate the metadata directly (Excel Table F.2) using filtering functions on columns to identify studies across one or more specific categories within data items. Using the Shiny package (Chang et al., 2021) within RStudio (RStudio Team, 2021; R Core Team, 2021), the Plastic Health Map was developed (see GitHub for codes) and is available via OSF at https://osf.io/fhw7d/. The Plastic Health Map comprises three interactive heatmap tabs (Overview, Heatmap Health and Heatmap Chemicals), with heatmaps showing number of articles by plastic chemical classes (and their sub-categories) and category (and sub-categories) of health outcome measures; and two look-up tables (Chemicals Search and Health Outcomes tabs) containing the controlled vocabulary terms used for data extraction.

All heatmap plots can be filtered by selecting the data items on the left in "Dashboard" view; the bibliographical details of associated articles can then be viewed and downloaded as a CSV file in "References" view. If an article contains information on more than one chemical class and/or more than one health outcome category, each intersection is shown as an individual count/record. The "Overview" tab shows the overall trend of the number of articles published per year by plastic chemical class and the geographical distribution of included studies (Fig. 2). The "Heatmap Health" tab (Fig. G.1) allows a more granular view of health outcomes investigated for each chemical class (highest level of classification for chemical exposure). The "Heatmap Chemicals" tab (Fig. G.2) allows a more granular view of chemical exposures investigated for each ICD category (highest level of classification for health outcome).

The "Chemicals Search" tab (Fig. G.3) is a searchable look-up table of all chemicals included in the SEM showing the IUPAC Name, extracted name, synonyms, CAS number, metabolites, the Chemical Class name used for the plots in each tab and classifications associated with each chemical. To retrieve all articles in the database which investigate a specific chemical, the CAS number can be entered in the lower left text box, and bibliographical details of the associated articles can then be viewed and downloaded in "References" view. The "Health Outcomes" tab (Fig. G.4) is a searchable look-up table for the hierarchical structure of health outcome classification showing ICD category, ICD subcategories (Levels 1, 2, 3), associated search terms (specific disorders, anatomy, tests, etc.), the Extracted health outcome, and the associated Health Outcome Group used for the "Heatmap Health" tab.

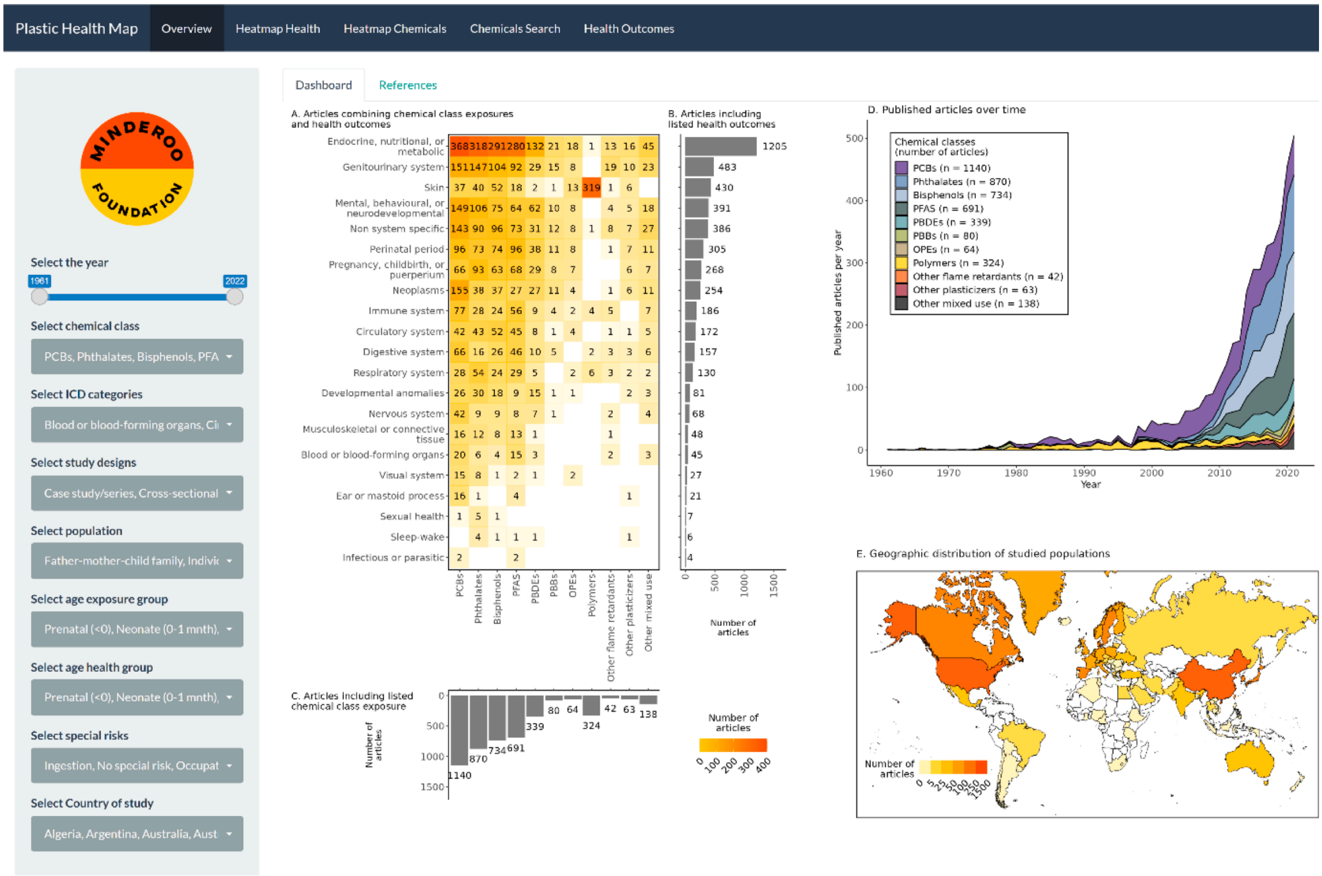
3. Results

3.1. Search and selection of eligible primary research articles

After 54,316 duplicates were removed, the literature search conducted in Medline and Embase (Ovid®) databases and systematic reviews reference lists yielded a total of 100,949 potentially relevant articles. Based on the title and the abstract, 6,161 articles met the eligibility criteria at Level 1 screening, and the corresponding full-text articles were procured for Level 2 screening. Six articles could not be procured and consequently were not included in this review. After eligibility screening of the full-text articles, 3,911 articles were taken through to the data extraction stage, out of which 3,587 articles were included in this SEM. 2,244 articles were excluded during Level 2 full-text screening and 324 articles were excluded during data extraction. Reasons for exclusion for each article assessed at these two stages are given in Excel Table F.1. The flow of articles from identification through to final inclusion is represented in Fig. 3 (PRISMA).

3.2. Population and study design

The included articles were for studies conducted across 78 countries based on investigated population (Fig. 4A, Plastic Health Map), 61 countries based on affiliation of the last author, and 67 countries based on the affiliation of the first author (Fig. G.5), with USA and China contributing to ~40% of the evidence in our SEM based on investigated population (Fig. 4B). Interestingly, while several articles investigated populations from countries such as Cambodia, Chile, Ukraine and Vietnam, these countries were not listed as a country of affiliation for



Select the year: 1961 – 2022

Select chemical class: PCBs, Phthalates, Bisphenols, PFA

Select ICD categories: Blood or blood-forming organs, Ci

Select study designs: Case study/series, Cross-sectional

Select population: Father-mother-child family, Indivi

Select age exposure group: Prenatal (<0), Neonate (0-1 mnth),

Select age health group: Prenatal (<0), Neonate (0-1 mnth),

Select special risks: Ingestion, No special risk, Occupat

Select Country of study: Algeria, Argentina, Australia, Aust

A. Articles combining chemical class exposures and health outcomes

	PCBs	Phthalates	Bisphenols	PFAS	PBDEs	PBBs	OPEs	Polymers	Other flame retardants	Other plasticizers	Other mixed use	B. Articles including listed health outcomes
Endocrine, nutritional, or metabolic	368	318	291	280	132	21	18	1	13	16	45	1205
Genitourinary system	151	147	104	92	29	15	8		19	10	23	483
Skin	37	40	52	18	2	1	13	319	1	6		430
Mental, behavioural, or neurodevelopmental	149	106	75	64	62	10	8		4	5	18	391
Non system specific	143	90	96	73	31	12	8	1	8	7	27	386
Perinatal period	96	73	74	96	38	11	8		1	7	11	305
Pregnancy, childbirth, or puerperium	66	93	63	68	29	8	7			6	7	268
Neoplasms	155	38	37	27	27	11	4		1	6	11	254
Immune system	77	28	24	56	9	4	2	4	5		7	186
Circulatory system	42	43	52	45	8	1	4		1	1	5	172
Digestive system	66	16	26	46	10	5		2	3	3	6	157
Respiratory system	28	54	24	29	5		2	6	3	2	2	130
Developmental anomalies	26	30	18	9	15	1	1			2	3	81
Nervous system	42	9	9	8	7	1			2		4	68
Musculoskeletal or connective tissue	16	12	8	13	1				1			48
Blood or blood-forming organs	20	6	4	15	3				2		3	45
Visual system	15	8	1	2	1		2					27
Ear or mastoid process	16	1		4						1		21
Sexual health	1	5	1									7
Sleep-wake		4	1	1	1					1		6
Infectious or parasitic	2			2								4
C. Articles including listed chemical class exposure	1140	870	734	691	339	80	64	324	42	63	138	

Fig. 2. Screenshot of the "Overview" tab of the Plastic Health Map. All plots can be filtered using the data items on the left and viewed in "Dashboard" view. Based on applied filters, the bibliographical details of the associated articles can be viewed and downloaded as a CSV file from the "References" view.

any of the last authors. The majority of included articles investigated populations from high-income countries (~82%, Fig. 4C). Only three articles investigated populations from low-income countries (one on Ethiopia, one on Uganda and one on Guinea-Bissau, see Excel Table B.3).

Population demographics and study designs of the included studies are summarized in Fig. 5. Regarding the population of interest for included studies, over one quarter (28.5%) investigated the effect of maternal exposure on the child, there were only 13 studies (~0.4%) on the effect of parental exposure (both mother and father) on the child and no studies on the effect of paternal exposure on the child (Fig. 5A). Over 60% of included studies involved a mixed (male and female) population (Fig. 5B); and of the single-sex studies, a greater number (n = 905) investigated females compared to males (n = 454). Data were extracted based on biological sex assigned at birth (male or female) and 101 studies did not report the sex of the studied population. Although adults were the most studied age group, both in terms of exposure levels and health outcome measures (~59%, Fig. 5C & 5D), only <4% of included studies specifically investigated an elderly adult population.

The majority of studies investigated the effects of exposure in general-risk populations (74.5%, Fig. 5E). Around 25.5% (n = 916) of included studies investigated a population with special risk of exposure. Of these, only ~21% (n = 191) conducted an analysis using a non-special risk comparator group. Of 3,257 observational epidemiological studies, cross-sectional design was the most common (n = 2,466, Fig. 5F), and there were considerably fewer longitudinal studies (n = 757). Of 347 experimental studies, most described skin patch tests, however 5 were analytical, involving experimentally controlled chemical exposure and inclusive of a control group.

3.3. *Plastic particle/chemical exposures measured*

3.3.1. *Plastic particles/chemicals studied over time*

There were no included studies investigating the health effects of microplastics or nanoplastics in humans and only 9% of included articles investigated polymers. Of the 1,202 plastic additives and 355 polymers in our database (excluding sum terms), 418 plastic additives and 22 polymers were found (measured and detected in human participants and analyzed against health outcome measures) in included articles (see full list in Excel Table B.1). PCBs were the most investigated plastic chemical class (>31% of articles), followed by phthalates (~24%), bisphenols (>20%), PFAS (~19%), and PBDEs (>9%). Around 37% of included articles investigated the effects of multiple chemical exposures.

Fig. 6A shows the growing number of published articles over time, with 45.5% (1,629/3,587) of included articles published in the last five years (Jan 2017 – Jan 2022, Plastic Health Map). Fig. 6B-D compares the trend of publications per year on three groups of restricted/banned chemicals to publications on their substitutes, e.g., Fig. 6C comparing phthalates and "phthalate substitutes" (structurally similar chemicals, inclusive of bis(7-methyloctyl) cyclohexane-1,2-dicarboxylate (DINCH), terephthalates, trimellitates and *iso*-phthalates). Significant bodies of research on the potential health effects of the substitutes did not start until several years after commencement/marked increase in their usage – 12 years for both OPEs and phthalate substitutes, and six years for bisphenol analogues.

3.3.2. *Production volumes and hazard data for included plastic additives*

On comparing our plastic additives list to Wiesinger et al., (2021) of the 661 additives included in both lists, no production volume data were available for 397 additives; 71 additives were found to not be currently

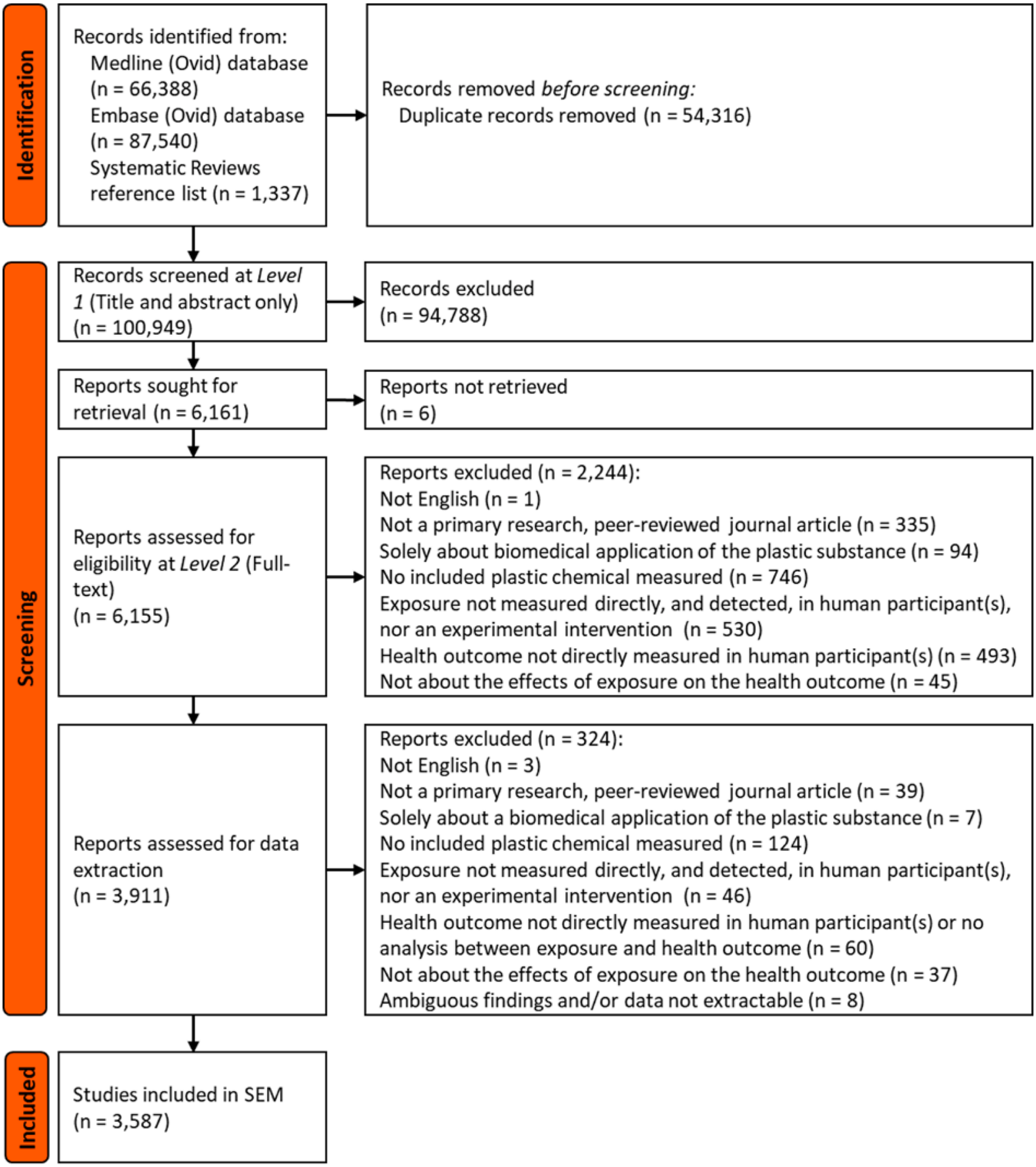


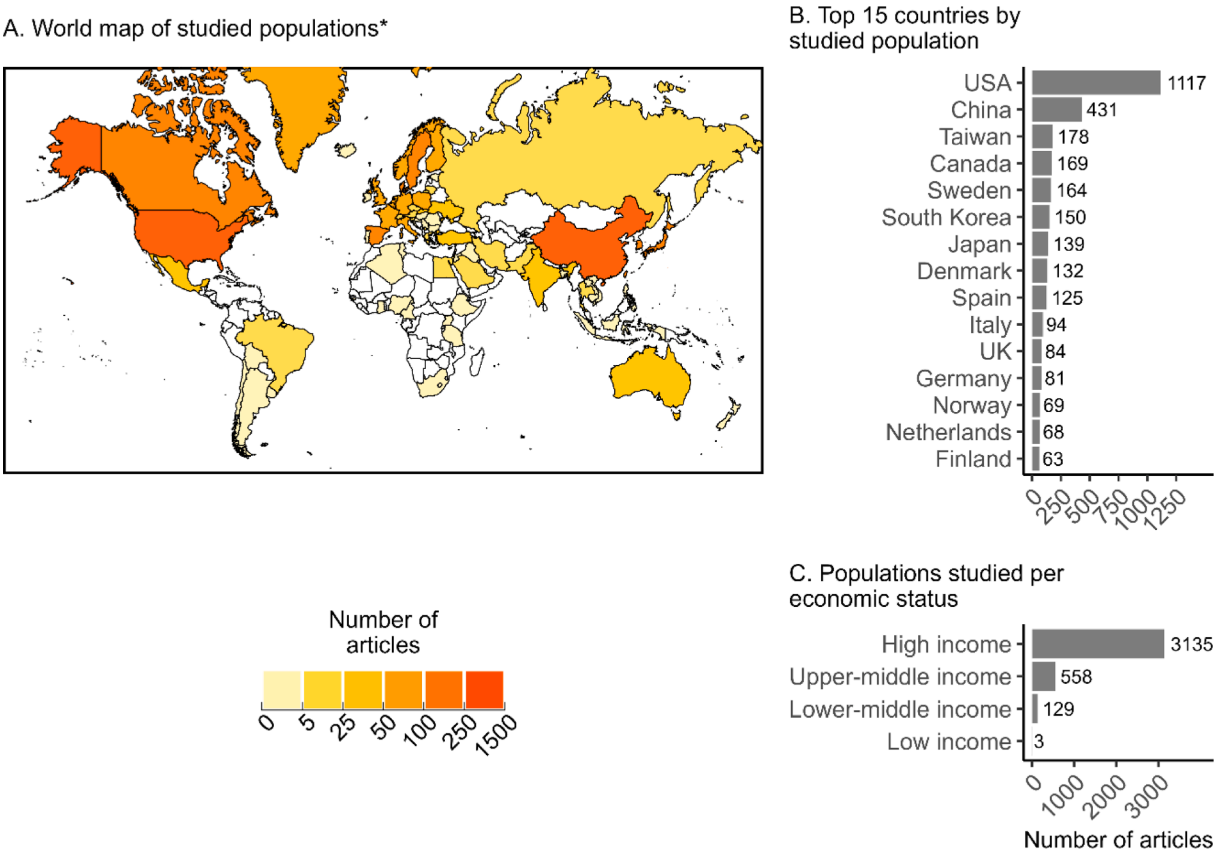
Fig. 3. PRISMA flowchart of records identification, screening, and selection process.

produced or production data were claimed as confidential (production volume ≤ 0); and while 193 of our included additives are known to be currently produced, we found only 63 of these in included articles. In relation to hazard, no data were available for 512 of the 661 included additives in both lists; and while 149 additives have been identified as having medium to high level of hazard concern, only 114 of these have been investigated in included articles.

3.4. Health outcomes evaluated in relation to plastic exposures

Across all the studies identified in this SEM, there was at least one outcome evaluated within each of the 20 ICD system-specific categories. Over 90% of health outcomes reported in included articles fell within 11 of the 21 health categories used in this SEM (see “Overview” tab of the Plastic Health Map: “Endocrine, nutritional, or metabolic” through to “Respiratory system”). The intersections that have been investigated between categories of health outcome measures and classes of plastic chemicals can be visualized in the interactive database.

For these intersections between health outcome measures and exposures, we were particularly interested in articles examining the effects of general exposure. In Fig. 7, we focus on studies evaluating health effects of plastic chemical exposure in general-risk populations and have excluded 1) experimental studies, 2) studies involving special risk of exposure due to occupation or ingestion/poisoning events and 3) case studies and case series as no analysis was performed between exposure and health outcome measures. Overall, “Endocrine, nutritional, or metabolic” disorders were the most studied (1,122/2,664), with a focus on the effects of plastic chemicals on thyroid disorders, overweight or



* Studies with unknown population (n = 19) are omitted from map

Fig. 4. Distribution of included articles by country of studied population. (A) Heatmap demonstrating the geographical locations and number of included articles investigating those populations on a world map. (B) The top 15 countries whose population were most studied. (C) The distribution of articles based on the economic status of the studied population as per the 2022 classification by the World Bank. Note that one article can include populations from more than one country.

obesity, glucose homeostasis (e.g., diabetes) and gonadal hormones (e.g., testosterone/estrogen levels). Sub-categories of health outcome measures can be viewed in the "Heatmap Health" tab of the Plastic Health Map. Excel Table F.2 can also be used to find and filter specific health outcome measures extracted from individual studies.

In the articles excluded from Fig. 7, the most frequently studied plastic types were polymers (n = 322), followed by PCBs (n = 130), bisphenols (n = 59) and phthalates (n = 40). Polymers were almost exclusively studied for their potential health impact on the skin (319/322; ICD 14 – Disorders of the skin; with these studies mostly being skin patch tests, excluded from Fig. 7 as experimental studies), while a wide distribution of health outcome measures was studied in association with PCBs exposure following ingestion/poisoning events or occupational exposure. These intersections can be explored in the interactive database.

4. Discussion

This SEM collates data from 3,587 articles published from Jan 1960 to Jan 2022 describing primary human research where the concentration of plastic particles (micro and nanoplastics) and plastic-associated chemicals (polymers, plasticizers, flame retardants, bisphenols and/or PFAS) was directly measured in human participants, and a human health outcome measured. We have collected and categorized these articles in an interactive database, the Plastic Health Map, that can be filtered by year of publication, plastic chemical (class or specific chemical/congener), category of health outcome measure, study design, population type, age group at exposure and health assessments, special risk of exposure status, and country of population. We have identified several important broad research gaps in the existing literature and discuss some examples in relation to future directions for research and implications for chemical regulation below.

4.1. *Population and study characteristics*

4.1.1. *Country of investigated population and lack of social equity*

The results of our SEM have highlighted a discrepancy in available health outcome data according to the socioeconomic status of different countries. Investigations into the effects of plastic-associated chemical exposure on human health outcomes have predominantly been conducted in populations from high-income countries (Fig. 4C), where waste management is generally well-regulated and of a high standard (Kaza et al., 2018). For example, the USA is the most studied population (1,117/3,587, 31%) in this SEM and similar findings were reported in a SEM on health studies on PFAS (192/505, 38%) (Pelch et al., 2022) and several scoping reviews, including neurodevelopmental toxicity of OPEs (6/9, 67%) (Zhao et al., 2022), birth and pregnancy outcomes of OPE exposure (5/8, 62.5%) (Gan et al., 2023), PFAS and cancer (~15/28, ~54%) (Steenland and Winquist, 2021), and metabolomic effects of PFAS (6/11, 55%) (Guo et al., 2022).

In contrast, relatively few studies have been conducted to date within populations originating from low- and middle-income countries, where risk of exposure to plastic-associated chemicals is thought to be higher than in developed nations due to a combination of increasing plastic production and consumption rates (Kaza et al., 2018; Lebreton and Andrady, 2019; Liang et al., 2021), mismanaged waste disposal, recycling and treatment practices, and waste import from other countries (Barnes, 2019; Kaza et al., 2018). For example, our SEM did not identify

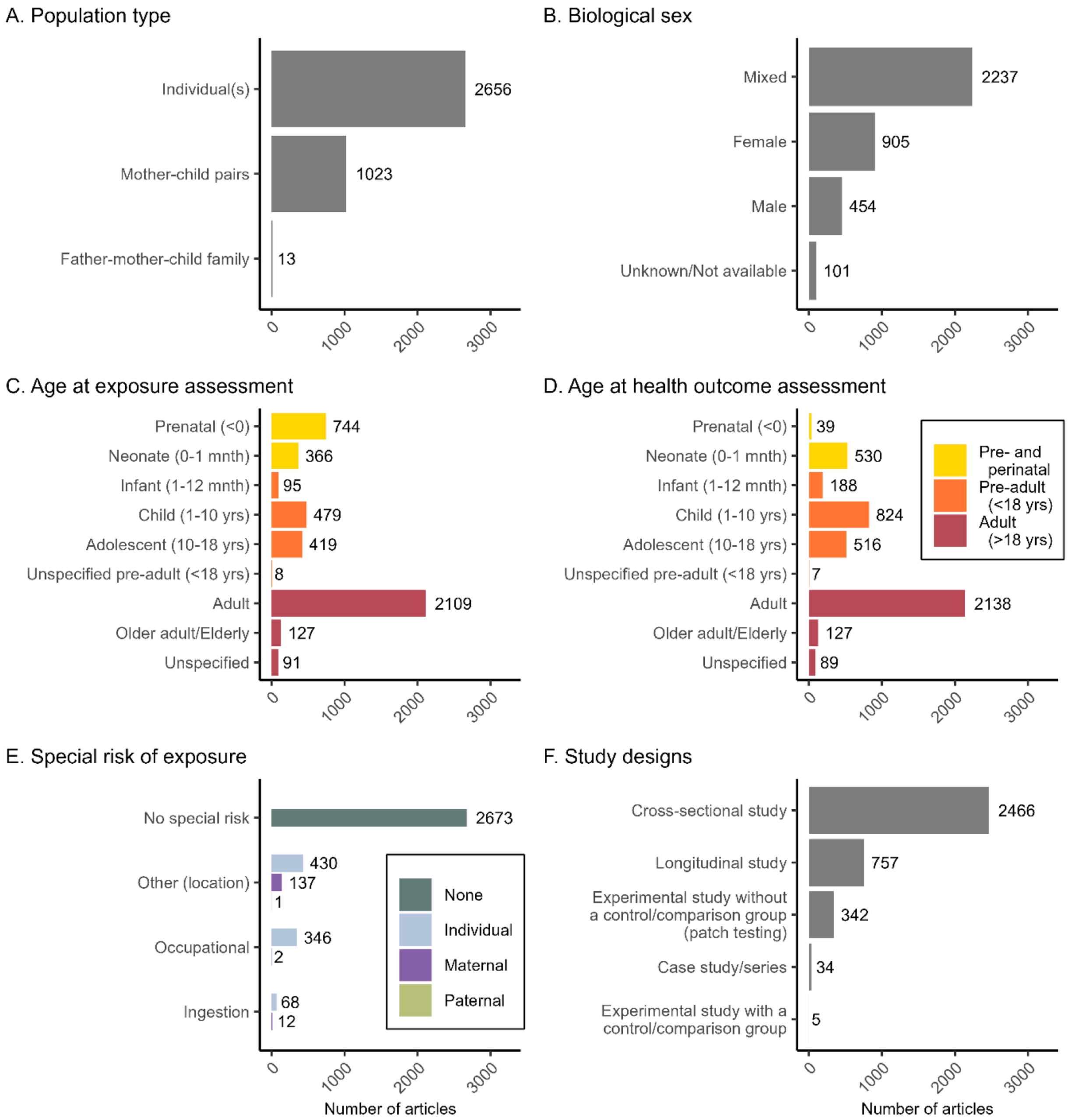


Fig. 5. Bar graph showing population demographics (A-E) and number of articles with each study design (F). E shows whether the studied population had a special risk of exposure, that is, if the article indicated the population had a potentially increased risk of exposure associated with an ingestion/poisoning event (e.g., rice bran oil mass poisoning events in Yusho/Yucheng population), occupation (e.g., working in a plastic production factory), or other factors such as residence in a high-risk environment (e.g., living near e-waste recycling sites).

any studies on populations from middle-income countries such as Sri Lanka, Vanuatu, Guyana, Maldives, Tonga, Comoros, Fiji, and Marshall Islands, all eight of which have been classified amongst the top 10 producers of mismanaged plastic waste per person per day as litter or otherwise inadequately disposed (Barnes, 2019).

With the amount of waste generated in low-income countries expected to increase more than threefold by 2050 (Kaza et al., 2018), biomonitoring of plastic-associated chemical exposure in the world's most vulnerable populations, and investigations into potential health impacts, are urgently required. Implementation and support of initiatives that help build and foster greater research capacity can help overcome barriers that have traditionally precluded and/or hindered the ability to conduct research in developing nations (Beran et al., 2017; Franzen et al., 2017; McKee et al., 2012). We suggest that the producers of plastic have a responsibility to contribute much needed funding for these initiatives, particularly in low-income countries that can least afford biomonitoring and longitudinal health studies, but are most heavily impacted by the effects of plastic pollution.

4.1.2. Parental exposure to plastic-associated chemicals and health outcomes in offspring

This SEM identified 1,023/3,587 studies that assessed the effects of maternal plastic-associated chemical exposure on the offspring. The full reference details and intersections of categories of health outcome measures and exposures for these articles can be obtained from the Plastic Health Map using "mother–child pairs" filter as the population type. These studies, along with the broader *in vitro* and animal literature, have demonstrated that many plastic-associated chemicals, such as

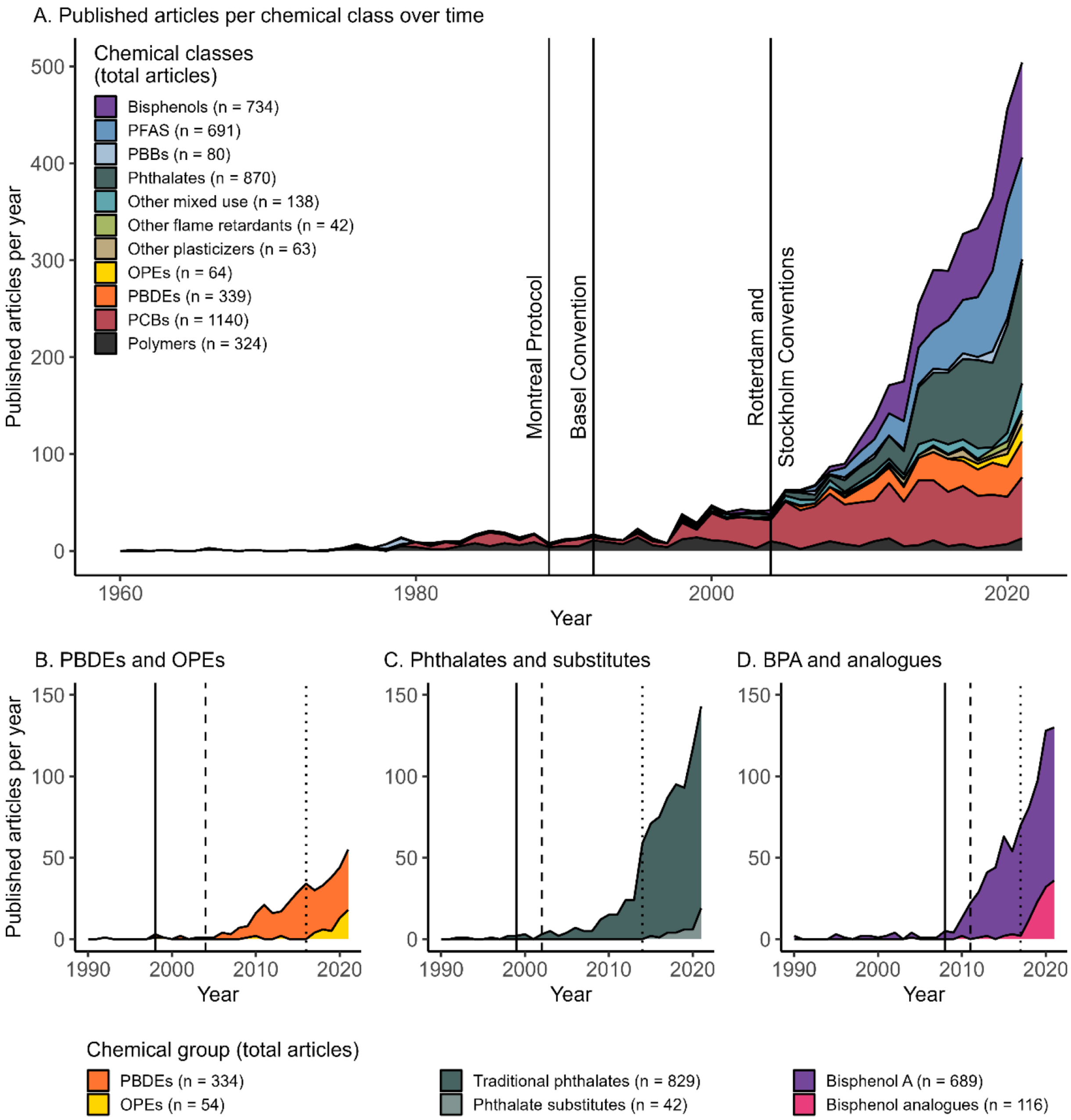
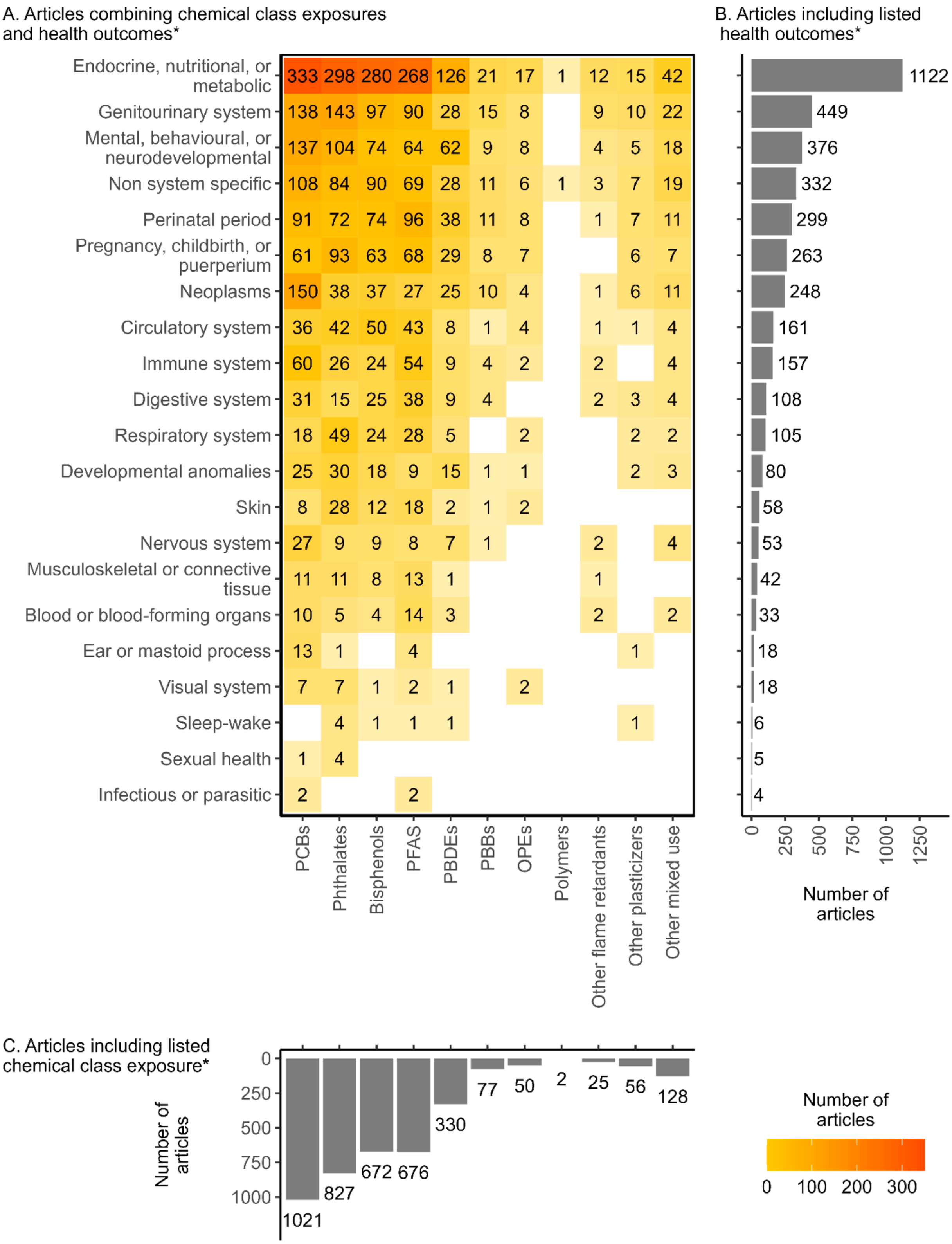


Fig. 6. Trend of the number of articles published per year for major plastic chemical classes. (A) The trend in the number of included articles published per year from Jan 1960 to Dec 2021. The cumulative total number of articles on the effects of each chemical class is shown in brackets in the legend. (B)-(D) The trend in the number of included articles published per year on chemical groups and their substitutes from Jan 1990 to Dec 2021, with the cumulative total number of articles in brackets in the legend. Full line indicates first regulation of the old chemical (1998 for PBDE, 1999 for several traditional phthalates, 2008 for BPA), dashed line indicates when substitution with the alternative(s) was reflected in commencement/marked increase in its usage (2004 for OPEs, 2002 for DINCH, 2011 for BPS), dotted line indicates the start of significant body of research on the potential health effects of the alternative(s) (2016 for OPEs, 2014 for alternative plasticizers, 2017 for bisphenol analogues). PFAS, perfluoroalkyl and polyfluoroalkyl substances; PBBs, polybrominated biphenyls; OPEs, organophosphate esters; PBDEs, polybrominated diphenyl ethers; PCBs, polychlorinated biphenyls; BPA, bisphenol A; DINCH, bis(7-methyloctyl) cyclohexane-1,2-dicarboxylate; BPS, bisphenol S.

PCBs, phthalates, BPA and PBDE, have the capacity to disrupt human endocrine systems (Kahn et al., 2020), even at low doses (Vandenberg et al., 2012).

In line with the Developmental Origins of Health and Disease theory (Barker, 2007; Barker, 2004), early life exposures to chemicals *in utero* and during infancy have the potential to cause permanent anatomical, physiological, metabolic, and genetic changes to the body that can affect health outcomes later in life (Heindel and Vandenberg, 2015). The fetus can be affected both by perturbation of insulin, glucocorticoid, estrogenic, and thyroid pathways in the mother, and more directly via transplacental transfer of plastic-associated chemicals. The potential health impacts of exposure to plastic-associated chemicals are particularly concerning at this early developmental stage of fetal hormone production, tissue development, and epigenetic programming (Heindel and Vandenberg, 2015). Moreover, certain plastic-associated chemicals, including PCBs, BPA, PFAS and PBDE, transfer to the mother’s milk (Lehmann et al., 2018; Mendonca et al., 2014), extending early life parental exposure to another critical developmental window in the neonatal and infancy period (Hoffman et al., 2021). To evaluate the long-term health effects of maternal chemical exposure on offspring, more longitudinal epidemiological studies (only 396 found out of 1,023) are needed to track the effects of early exposure over time.



	PCBs	Phthalates	Bisphenols	PFAS	PBDEs	PBBs	OPEs	Polymers	Other flame retardants	Other plasticizers	Other mixed use	B. Articles including listed health outcomes*
Endocrine, nutritional, or metabolic	333	298	280	268	126	21	17	1	12	15	42	1122
Genitourinary system	138	143	97	90	28	15	8		9	10	22	449
Mental, behavioural, or neurodevelopmental	137	104	74	64	62	9	8		4	5	18	376
Non system specific	108	84	90	69	28	11	6	1	3	7	19	332
Perinatal period	91	72	74	96	38	11	8		1	7	11	299
Pregnancy, childbirth, or puerperium	61	93	63	68	29	8	7			6	7	263
Neoplasms	150	38	37	27	25	10	4		1	6	11	248
Circulatory system	36	42	50	43	8	1	4		1	1	4	161
Immune system	60	26	24	54	9	4	2		2		4	157
Digestive system	31	15	25	38	9	4			2	3	4	108
Respiratory system	18	49	24	28	5		2			2	2	105
Developmental anomalies	25	30	18	9	15	1	1			2	3	80
Skin	8	28	12	18	2	1	2					58
Nervous system	27	9	9	8	7	1			2		4	53
Musculoskeletal or connective tissue	11	11	8	13	1				1			42
Blood or blood-forming organs	10	5	4	14	3				2		2	33
Ear or mastoid process	13	1		4						1		18
Visual system	7	7	1	2	1		2					18
Sleep-wake		4	1	1	1					1		6
Sexual health	1	4										5
Infectious or parasitic	2			2								4
C. Articles including listed chemical class exposure*	1021	827	672	676	330	77	50	2	25	56	128	

*No experimental or case studies, no special risk of exposure by occupation or poisoning/ingestion events

Fig. 7. Intersection between plastic chemical classes and categories of health outcome measures investigated in included articles studying the health effects of plastic chemical exposure in general-risk populations. (A) Heatmap showing number of articles by plastic chemical classes and categories of health outcome measures. Numbers within each cell indicate the number of included articles for a given chemical class and health outcome category intersection. Empty cells indicate no articles. Articles may appear in more than one column or row if exposure has been measured in multiple chemical classes and/or health outcomes have been investigated in multiple categories. (B) Total number of articles on each health outcome category. (C) Total number of articles on each plastic chemical class. PCBs, polychlorinated biphenyls; PFAS, perfluoroalkyl and polyfluoroalkyl substances; PBDEs, polybrominated diphenyl ethers; PBBs, polybrominated biphenyls; OPEs, organophosphate esters.

Research into the potential effects of paternal exposure on the health of offspring is significantly lacking, only 13/3,587 studies were found that investigated both mother and father exposure and health impacts on the child, and no studies looking at paternal exposure alone. Both maternal (Guerrero-Bosagna and Skinner, 2012; Manikkam et al., 2012; Manikkam et al., 2013; Robaire et al., 2022; Thorson et al., 2021; Wolstenholme et al., 2012) and paternal exposure (Pembrey et al., 2006; Singh and Li, 2012; Van Cauwenbergh et al., 2020) studies are essential to investigate effects in generation one as well as any potential *trans*-generational transmission of effects of plastic-associated chemical exposure via germ line changes.

4.1.3. Exposure impacting the health of older populations

This SEM identified only 127/3,587 articles specifically investigating older adults. The global population of older adults is growing, with a corresponding increase in burden of disease (GBD 2019 Ageing Collaborators, 2019). Elderly populations are expected to be especially vulnerable to environmental exposures due to changes in cellular function resulting in an impaired ability to maintain physiological homeostasis, which can be further complicated by underlying disease, medications, and poor nutritional status (Geller and Zenick, 2005). In addition, older adults have an entire lifetime of lifestyle factors and cumulative environmental chemical exposures that may affect disease predisposition (Misra, 2020). Given the higher expected vulnerability of older individuals, future studies investigating the effects of plastic-associated chemical exposure on health outcomes should separately examine older populations instead of adding age as a covariate in analyses.

4.2. Plastic-associated particle and chemical exposure

4.2.1. No relevant articles on potential health effects of micro and/or nanoplastics

Microplastics (1–5000 μm in size) (Rahman et al., 2021; Thompson et al., 2004) and nanoplastics (<1 μm in size) (Gigault et al., 2018; Gigault et al., 2021) are ubiquitously present in the environment, whether it is in the air (Dris et al., 2016; Liao et al., 2021; Wesch et al., 2017), soil (Scheurer and Bigalke, 2018), water supplies (Danopoulos et al., 2020; Pivokonsky et al., 2018), or food products (Danopoulos et al., 2020; Danopoulos et al., 2020; Oliveri Conti et al., 2020; Shruti et al., 2020). As a result, human exposure to these particles is unavoidable, and micro and nanoplastics have been reported as detected in human lung tissue due to exposure via inhalation (Amato-Lourenço et al., 2021; Jenner et al., 2022; Pauly et al., 1998), and in colonic mucosa (Ibrahim et al., 2021) and stool (Schwabl et al., 2019; Wibowo et al., 2021; Zhang et al., 2021) due to exposure via ingestion, as well as in human blood (Leslie et al., 2022), liver (Horvatits et al., 2022), spleen (Horvatits et al., 2022), placenta (Braun et al., 2021; Ragusa et al., 2021) and testis and semen (Zhao et al., 2023). The extent to which exposure to micro and nanoplastics affect human health is still unclear and several projects have recently emerged attempting to study human health impacts of micro and nanoplastics (CUSP cluster, 2021; Momentum, 2023; Plastics Europe, 2023; University of Queensland, 2023). One study has reported a correlation between the concentration of microplastics in the feces of patients with inflammatory bowel disease severity, although the cause-and-effect relationship between microplastics and inflammatory bowel disease is unclear (Yan et al., 2022).

In this SEM, there are no articles on micro and/or nanoplastics that fulfilled our inclusion criteria. Similarly, no human epidemiological health studies were found on microplastics in the ToMEx database (Thornton Hampton et al., 2022) or in a rapid review protocol (Cooper et al., 2022). The limited number of studies on the potential human health effects of micro and/or nanoplastics meeting our inclusion criteria may be because the methods for detecting, classifying, and quantifying micro and nanoplastics remain in early stages of development (CUSP cluster, 2021). There is a lack of a standardized method for quantifying exposure in human bio-samples/tissues, including fully managing risk of sample contamination (Skåre et al., 2019).

There are increasing numbers of animal and *in vitro* studies investigating the potential health impacts of micro and nanoplastics and the mechanisms underlying its toxicity (Blackburn and Green, 2022; Prata et al., 2020; Rahman et al., 2021; Sripada et al., 2022; WHO, 2022; Yong et al., 2020). For example, experimental exposure to micro and nanoplastics have been shown to exhibit cytotoxic effects *in vitro* by increasing reactive oxygen species generation in human gut (Huang et al., 2021) and lung cells (Dong et al., 2020; Paget et al., 2015; Ruenraroengsak and Tetley, 2015; Yang et al., 2021), and by increasing pro-inflammatory markers in human lung epithelial cells (Ruenraroengsak and Tetley, 2015; Xu et al., 2019). *In vivo* animal studies have also shown a range of health impacts associated with micro and nanoplastic exposure including evidence of pulmonary toxicity in rats (Xu et al., 2004), metabolic disorder in the offspring of exposed mice (Luo et al., 2019), and disturbed energy and lipid metabolism (Deng et al., 2017), neurotoxicity (Deng et al., 2017), and gut microbiota dysbiosis (Lu et al., 2018; Li et al., 2020) in mice. Human studies from occupational settings with high levels of exposure to microplastics, such as synthetic textile production sites, have shown an increase in respiratory symptoms (Atis et al., 2005; Kremer et al., 1994; Turcotte et al., 2013) and stomach and esophageal cancers (Gallagher et al., 2015). Given this evidence of toxicity and the inevitable exposure of humans to microplastics (WHO, 2022), there is an urgent need to prioritize the development of new measurement techniques to drive the assessment of potential human health risks associated with day-to-day/general exposure to microplastics.

4.2.2. Few plastic-associated chemicals have been studied for potential health effects

This SEM found relevant studies investigating potential human health effects of only 440/1,557 (excluding sum terms) plastic-associated chemicals included in our database. PCBs were the most investigated plastic chemical class (1,140/3,587 of articles), with the majority of studies focused on endocrine, nutritional and metabolic health outcomes, as reported by a recent SEM of studies on non-cancer health effects of PCBs (Carlson et al., 2023). Despite our comprehensive search strategy, no relevant studies were found for more than 70% of the plastic-associated chemicals in our chemical database. We anticipated there may be gaps in the literature in terms of the chemicals studied, which may in part be attributed to low production volumes (10–200 t/year for 33 included plastic additives) or uncertainty around whether they are currently in use (no production volume data found for 949 included plastic additives, see Excel Table B.1). However, of the 784 searched plastic additives with no relevant human health research, 26 are produced at ≥1000 t/year and have been identified as being of medium to high level of hazard concern, and an additional 81 have a high production volumes and no hazard classification (Wiesinger et al., 2021). For example, we did not find any relevant study, nor hazard classification, for the phthalate substitute tris(2-ethylhexyl) benzene-1,2,4-tricarboxylate (a trimellitate plasticizer), despite its estimated global annual production volume increasing more than two-fold from 40,000–100,000 t in 2002 (OECD, 2002) to 200,000 t in 2019 (Wiesinger et al., 2021), the availability of techniques for measuring exposure through metabolites in urine (OECD, 2002), its metabolites being present at detectable levels in the urine of children and adolescents (Murawski et al., 2021), and existing toxicological evidence of hematology effects and changes in liver and spleen function and weight in animal studies (AICIS, 2022).

The PFAS chemical class undoubtedly has the largest number of chemicals unstudied in relation to health. There are many thousands of PFAS in existence globally; 14,735 are listed by the United States Environmental Protection Agency (US EPA, 2022). Of the 197 PFAS in our database, we found that only ~24% were investigated in included articles, and data pertaining to these 47 PFAS can be explored in the

Plastic Health Map. Perfluorooctanoic acid (PFOA), perfluorooctane sulfonic acid (PFOS), perfluorohexanesulfonic acid (PFHxS), perfluorononanoic acid (PFNA), perfluorodecanoic acid (PFDA), and perfluoroundecanoic acid (PFUnDA) were the most studied PFAS (>200 articles on each), with recent SEMs reporting similar findings – PFOA and PFOS most studied in Zhang et al., 2023; PFHxS, PFNA, PFDA and PFUnDA most studied in Pelch et al., 2022 (PFOA and PFOS excluded) and PFUnDA most studied in Carlson et al., 2022 (well-studied PFAS, including PFOA and PFOS, excluded). Our SEM demonstrates that a wide range of human health outcomes have been studied in relation to included PFAS, however similar to the findings from Pelch et al., 2022 and Carlson et al., 2022, most studies measured outcomes in categories equivalent to the ICD-11 category 'Endocrine, Nutritional, Metabolic.' Of the remaining 150 PFAS in our SEM that appear not to have been investigated in relation to human health, 59 are known to be produced at ≥1000 t/year, out of which 33 are used in food contact materials, but only three have hazard classifications. There is an urgent need to prioritize high-production plastic-associated chemicals in biomonitoring and human health safety assessments, along with chemicals demonstrated to be persistent, bioaccumulative and/or toxic.

4.2.3. *Multiple exposures and mixture toxicity of plastic-associated chemicals*

Chemical risk assessments are traditionally performed at an individual chemical level (Groh et al., 2019; Quiros-Alcala and Barr, 2023). While this SEM has revealed that the effects of multiple plastic-associated chemicals within the same class are increasingly being examined (2,161/3,587), we found that only 646/3,587 articles measured plastic-associated chemicals from more than one included class and 720/3,587 articles measured plastic-associated chemicals from one included class in addition to non-included chemicals such as dioxins and DDT (dichloro-diphenyl-trichloroethane). However, plastics are composed of a wide variety of chemicals, and in realistic conditions and everyday exposure scenarios, humans are exposed to multiple chemicals concurrently (Wang et al., 2021; Zimmermann et al., 2021). As there is limited knowledge on whether these chemicals (and/or their metabolites) work synergistically, antagonistically, or independently across the various biological pathways that lead to adverse human health impacts (Quiros-Alcala and Barr, 2023; Sonavane and Gassman, 2019), regulating these chemicals based on individual thresholds does not necessarily protect against combination effects and mixture toxicity of multiple plastic-associated chemicals (Andreas and Michael, 2018; Quiros-Alcala and Barr, 2023; Savitz and Hattersley, 2023). It is necessary to carry out research that will inform regulatory policy and tackle plastic chemical exposure problems based on mixture toxicity information, especially on mixtures of chemicals most likely to co-occur in and leach from commonly used plastic products (Quiros-Alcala and Barr, 2023; Savitz and Hattersley, 2023). For these reasons, we agree with recommendations to encourage studies that investigate the effects of multiple exposures (Caporale et al., 2022; Muncke, 2021; Lioy et al., 2015; Lioy and Rappaport, 2011; Savitz and Hattersley, 2023).

4.3. *Human health concerns in relation to regulation of plastic-associated chemicals and regrettable substitutions*

As the production of plastic additives has proliferated, regulation and regulators have struggled to keep pace with the quantity of new chemicals and the complexity of determining their potential health impacts (Sachs, 2011). Globally, regulation of chemicals generally assumes safety until proven otherwise (Silbergeld et al., 2015), with no systematic process of post-market human health monitoring (Maffini et al., 2021). Where evidence of harm has emerged, there have been some major regulatory successes, with global strategies restricting some toxic chemicals (Zimmermann et al., 2022) and several plastic-associated chemical classes captured in this SEM are being phased out or are under strict regulations. For example, POPs such as PCBs, PFOA, its salts and PFOA-related compounds (classified under "PFAS"), several PBDEs, hexabromobiphenyl (classified under "PBBs"), hexabromocyclododecane (HBCDD, classified under "other flame retardants"), and pentachlorobenzene (PeCB, classified under "other flame retardants") are listed under the Stockholm Convention for phasing out and eventual elimination, and the production and use of PFOS (classified under "PFAS") and its derivatives are restricted (Stockholm Convention, 2019).

The introduction of regulations and bans of these POPs have resulted in a dramatic decline in exposures in most countries (Drage et al., 2019; Henríquez-Hernández et al., 2021; Bjerregaard et al., 2013; Göckener et al., 2020). Increased regulation of some plastic-associated chemicals in response to emerging evidence and increased public awareness of health risks has led to manufacturers introducing new substitutes to the market. Only comprehensive post-market human biomonitoring will identify if and where "regrettable substitution" (Maertens et al., 2021; Qadeer et al., 2022) may be occurring. For example, regulation of POPs has led to a decrease in the use of PBDE flame retardants, and a corresponding increase in the use of OPE flame retardants as a replacement (Blum et al., 2019). While OPEs were expected to be less environmentally persistent than PBDEs because of their chemical and physical properties, OPEs, particularly chlorinated OPEs, are more water-soluble, and can persist and travel long ranges in surface waters (Zhang et al., 2016; Rodgers et al., 2018). Therefore, while OPEs are not classified and regulated as POPs under the Stockholm Convention, they are "persistent mobile organic compounds" (Rodgers et al., 2018) and their concentrations have reached much higher levels than PBDEs in remote Arctic regions and local areas (Li et al., 2017; Sühring et al., 2016; Ma et al., 2017; Cristale et al., 2013). Even though the use of OPEs (van der Veen and de Boer, 2012) and human exposure to OPEs (Yang et al., 2022) is rising, this SEM identified only 64/3,587 relevant articles on health impacts of OPEs, compared to 339 articles on PBDEs. This included all 7 articles with OPEs measured in bio-samples and neurodevelopmental toxicity in a 2022 systematic scoping review on this topic (Zhao, 2022) (plus one missed by Zhao and colleagues: Tanner et al., 2020) and all 8 articles on OPE exposure and pregnancy/birth outcomes in a 2023 systematic scoping review (Gan et al., 2023) (plus three missed by Gan and colleagues:Panagopoulos Abrahamsson et al., 2021; Varshavsky et al., 2021; Yang et al., 2022). *In vitro* and animal studies on OPEs have identified liver disease (Hu et al., 2023), atherosclerosis (Hu et al., 2023), and changes in gene expression (Hu et al., 2023; Su et al., 2014) as potential areas of concern, however we did not find any relevant human studies investigating these health outcomes.

A similar issue may be arising with plasticizer substitutes for phthalates. Human health concerns led to the first stages of phasing out traditional phthalates such as bis(2-ethylhexyl) benzene-1,2-dicarboxylate (DEHP) in Europe in 1999 (European Union, 2005), followed by further regulations on their use, including the banning of DEHP (Australian Competition & Consumer Commission, 2010), benzyl butyl phthalate (BBP), di-isononyl phthalate (DINP) and di-isodecyl phthalate (DIDP) in children's toys and childcare products (European Union, 2005; U.S. Consumer Product Safety Commission, 2017) and manufacture and import restrictions for DEHP and BBP by the European Union (European Union, 2011).

Since the introduction of regulation of phthalates, manufacturers have introduced new phthalate substitutes to the market. However, this SEM found no relevant articles investigating the potential health effects of 19 of the 21 included phthalate substitutes (DINCH, isophthalate dimethyl benzene-1,3-dicarboxylate, 15 trimellitates and four terephthalates), and only $n = 28$ and $n = 18$ included articles were found on DINCH and terephthalate bis(2-ethylhexyl) benzene-1,4-dicarboxylate (DEHTP) respectively, compared to $n = 870$ on traditional phthalates. Both DINCH and DEHTP are used in building and construction, children's toys, medical items, packaging and food contact materials (Wiesinger et al., 2021) and increasing levels of their metabolites are being detected in human bio-samples (Frederiksen et al., 2020; Kasper-

Sonnenberg et al., 2019; Lessmann et al., 2019; Silva et al., 2019; Silva et al., 2013). Recent studies have reported a 100% detection rate of DINCH and DEHTP metabolites in the urine of children and adolescents, with their levels exceeding the human biomonitoring value 1 (HBM-I) (HBM Commission, 2014) in some children (Lee et al., 2021; Lemke et al., 2021; Schwedler et al., 2020; Schwedler et al., 2020). While young children have been shown to have considerably higher body burden of DINCH and DEHTP compared to adolescents and adults (Lee et al., 2021; Schwedler et al., 2020; Schwedler et al., 2020), only three articles in this SEM investigated the effects of DINCH on the health of children, and an additional three articles were found on the potential health impacts of DEHTP in children. Additionally, *in vitro* and animal studies have shown several potential health impacts associated with DINCH and DEHTP and their metabolites, including cytotoxicity (Eljezi et al., 2017), steroidogenesis disruption (Boisvert et al., 2016; Campioli et al., 2017; Moche et al., 2021), and kidney toxicity (Ball et al., 2012; National Center for Biotechnology Information, 2022; Vasconcelos et al., 2019).

Comparably, a potential "regrettable substitution" trend is arising with increasing regulation of BPA. While the use of BPA in food contact materials is still permitted, stricter regulations have recently been introduced. BPA has been banned in baby feeding bottles and sippy cups since 2008 in Canada (Simoneau et al., 2011) and 2011 in Europe (European Union, 2011; Food and Drug Administration, 2012), and its limit in food contact materials was lowered from 0.6 to 0.05 mg/kg food in 2018 (European Union, 2018). More recently, the European Food Safety Authority re-evaluated the risks to public health from the presence of BPA in foodstuffs and in light of new scientific evidence (EFSA Panel on Food Contact Materials, 2023), significantly lowered the tolerable daily intake of BPA from 4 μg/kg body weight/day (assessed in 2015) to 0.2 ng/kg body weight/day in April 2023 (EFSA, 2023).

Epidemiological research and public awareness about the health effects of BPA have led many manufacturers to switch to alternatives such as bisphenol S (BPS) and bisphenol F (BPF) (Chen et al., 2016). Given that these bisphenol analogues have very similar chemical structures to BPA and similar affinity to cellular receptors, they may have similar health effects (Moon, 2019; Pelch et al., 2019; Rochester and Bolden, 2015). However, in this SEM the vast majority of research on the health effects of bisphenols conducted to date have included BPA (713/734) while only 104 relevant articles were found on BPS, 88 on BPF, 14 on bisphenol AF (BPAF) and 54 on other bisphenols (Heatmap Chemicals tab in the Plastic Health Map). Similarly, Pelch et al., 2019 reported that the most frequently studied BPA analogues in human epidemiological studies were BPS, BPF, and BPAF, with only 16, 15 and 6 articles published on the respective analogues until January 2019. The low number of studies on these analogues is of particular concern as increasing exposure levels are being detected in the general population (Gys et al., 2020; Liao et al., 2012).

Human health research into phthalate substitutes (Lemke et al., 2021), OPEs (Blum et al., 2019), bisphenol analogues (Rochester and Bolden, 2015; Usman and Ahmad, 2016), and other alternative plastic additives that have been, or will be, introduced should be prioritized and considered by chemical regulators to ensure that "regrettable substitution" is not occurring, particularly where substitutes are within the same chemical class as the chemical of concern or structurally similar (Qadeer et al., 2022). A paradigm shift is required whereby well-studied chemicals are used within their safety limits and new chemicals are required to undergo rigorous testing for safety before being introduced in consumer products, with ongoing biomonitoring in each case.

4.4. Challenges and limitations

The findings of this SEM should be considered in the light of some limitations. Due to limited resources as well as the large number of studies identified by our searches and at the data extraction stage, there were some practical limitations in the scope of the SEM and the depth of detail that could be extracted at this scale. With respect to limiting the literature searches, only Medline and Embase databases were used for the searches, backward and forward citation searches were not conducted, and this SEM does not include grey literature. However, exercises including 1) comparison of the studies included in this SEM with previous SEMs and scoping reviews using additional databases for their searches (Section 4.0), 2) backward and forward citation searches (Appendix A.5.1) and 3) *post hoc* grey literature searches (Appendix A.5.2 & Excel Table C.2) revealed that only a small portion of relevant literature was missed by applying these limits. Because of limited resources for translation, only articles published/available in the English language were included and, although we demonstrate a broad geographical distribution of the data, including more languages would have generated additional results.

Furthermore, health research on biomedical applications of plastic is not included in this SEM. This was a pragmatic decision made on the basis that a number of exclusion terms were incorporated into the search strategy to prevent retrieval of a vast number of studies unrelated to the effects of the plastic material itself on a health outcome, but rather, were designed to evaluate the effectiveness of procedures/treatments, such as in dentistry and for health conditions (e.g., polymers in dentistry, prostheses in orthopaedic surgery, and chemicals used for drug delivery). Because we used biomedical exclusion terms in our search strategy, it was important to then exclude all articles on biomedical applications of plastic materials, rather than presenting a very incomplete data set on biomedical exposures. Therefore, this SEM does not include articles about the possible health impacts of plastic-associated chemicals and particles in health care, such as exposure to DEHP via intravenous lines and blood transfusion bags. We recognize the value of this research and have provided a list of articles excluded at level 2 full-text screening and data extraction stages with "Solely about biomedical application of the plastic substance" as one of the reasons for exclusion (Excel Table F.1) for those interested in investigating this important topic.

With respect to the scope, firstly, this SEM does not contain several data items which may be of interest to users such as ethnicity and social status of the studied population, sample size, findings of the included articles (positive/negative/null associations), concentration of plastic-associated chemicals, and bio-sample in which exposure was measured.

Secondly, for patch test and skin prick test studies, only included plastic-associated chemicals that caused a positive reaction were extracted due to the extensive numbers of chemicals used in patch test series; and for case studies/series, only the final diagnoses or test results outside the normal range were extracted as health outcome measures due to the extensive clinical tests performed in case studies/series. A total of 342 patch test studies and 34 case studies/series were found in this SEM and these studies can be easily filtered out of the results from the interactive database to prevent influence of the positive bias.

Thirdly, plastic particle/chemical selection was challenging, and the scope of this SEM was ultimately limited to micro and nanoplastics, polymers, plasticizers, flame retardants, bisphenols and PFAS. Humans are potentially exposed to many other plastic-associated chemicals, including functional additives (e.g., colorants, stabilizers, fillers, and antioxidants) and chemicals involved in plastic manufacturing (e.g., other processing agents and NIAS), recycling and disposal. We focused on chemicals to which people are likely to be exposed to via end-product plastic materials, however a knowledge bias was introduced into the study by limiting (by function) the additives included, by including bisphenols and no other monomers, and by including PFAS. These limitations were applied due to practical considerations in terms of time and resources, and because it was important to include in the SEM chemicals/chemical classes associated with increasing concerns in relation to their widespread occurrence and potential human health impacts. There is potential for future expansion of our SEM to include other classes of plastic-associated chemicals.

4.5. Conclusion

While the term "plastic crisis" has largely been used to refer to the harmful environmental impacts of plastic pollution, there is increasing concern about the potential health impacts of human exposure to plastic particles and plastic-associated chemicals (Center for International Environmental Law, 2019; Geneva Environment Network, 2022; Symeonides et al., 2021). Epidemiological research about the human health effects of plastic-associated chemical exposure has greatly increased over time, with more than 45% of 3,587 included articles published in the last five years. Our interactive Plastic Health Map (https://osf.io/fhw7d) and our raw extracted data (Excel Table F.2) present a wealth of information in a user-friendly manner to facilitate scientific, regulatory and individual access to published peer-reviewed literature. The tabs on the Plastic Health Map allow for studies on specific health outcome categories to be easily compared across different plastic-associated chemical classes and *vice versa*. Additionally, we have provided our data extraction codebook (Excel Table E.2) and codes for the interactive database publicly (on GitHub), which will enable this SEM to be updated with newly published research and additional plastic-associated chemicals or creation of new SEMs. We have also provided our comprehensive and searchable databases of included plastic-associated chemicals and human health outcomes as additional tabs to the Plastic Health Map and in excel format.

This SEM can be utilized for identification of data clusters that can be used to drive future systematic reviews. The interactive database can be filtered based on the specific research question to identify articles on a particular plastic-associated chemical class (and individual chemical in separate tab), ICD category (and health outcome measure sub-category in separate tab), year of publication, study design, population type, age group at exposure and health assessments, special risk of exposure status and country of investigated population. The respective reference list can be viewed/downloaded based on selected filters. Details about extracted data from each article can then be acquired from Excel Table F.2.

This SEM can also be used to identify research gaps to inform future study and project design. We have discussed several broad research gaps that require urgent consideration. Of particular concern are the social inequity due to limited investigation of populations from low-income countries with high levels of mismanaged waste, the lack of epidemiological research on micro and nanoplastics, no health studies for plastic-associated chemicals in active production with known hazard concern, and limited studies of substitution chemicals introduced by manufacturers following increased regulation of the original chemical. Users may find other areas of focus using the interactive database or metadata.

Globally, regulation of chemicals generally assumes safety until proven otherwise (Silbergeld et al., 2015). As a result, scientists and regulators have not yet determined the health impacts of the thousands of plastic-associated chemicals currently in use. The current *ad hoc* risk assessment approach is not sufficient to protect human health, and there is a pressing need for a paradigm shift whereby new plastic-associated chemicals are rigorously tested for safety before being introduced in consumer products, with ongoing monitoring of human exposure levels and health impacts post-introduction.

CRediT authorship contribution statement

Bhedita J Seewoo: Conceptualization, Methodology, Software, Validation, Formal analysis, Data curation, Investigation, Writing – original draft, Writing – review & editing, Visualization, Project administration. **Louise M.Goodes:** Conceptualization, Methodology, Investigation, Writing – original draft, Writing – review & editing, Project administration. **Louise Mofflin:** Conceptualization, Methodology, Validation, Investigation, Writing – original draft, Project administration. **Yannick R Mulders:** Conceptualization, Methodology, Software, Validation, Formal analysis, Data curation, Investigation, Writing – original draft, Visualization. **Enoch V.S. Wong:** Conceptualization, Methodology, Software, Validation, Formal analysis, Data curation, Investigation, Writing – original draft, Project administration. **Priyanka Toshniwal:** Conceptualization, Methodology, Investigation. **Manuel Brunner:** Investigation. **Jennifer Alex:** Investigation. **Ahmed Elagali:** Software, Formal analysis, Data curation, Visualization. **Aleksandra Gozt:** Validation, Investigation. **Greg Lyle:** Investigation, Writing – review & editing. **Omrik Choudhury:** Software. **Christos Symeonides:** Conceptualization, Methodology, Writing – review & editing, Supervision. **Sarah A Dunlop:** Conceptualization, Methodology, Investigation, Writing – review & editing, Supervision.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Our raw extracted data has been provided in Excel Table F.2. We have also provided our comprehensive and searchable databases of included plastic-associated chemicals and human health outcomes as additional tabs to the Plastic Health Map and in excel format (Excel Table B.1-B.2). Additionally, we have provided our screening and data extraction guidelines (Appendix D.1-D.3), data extraction codebook (Excel Table E.2), as well as codes for data cleaning and the interactive database publicly (on GitHub). Access to the forms and extracted data within DistillerSR is available upon request for users with DistillerSR access.

Acknowledgements

The authors would like to gratefully acknowledge valuable contributions from Emily White (conceptualization, developing the plastic additives list); Tristan Dale and Hamish J. Newman (conceptualization, methods); Delia V. Hendrie (conceptualization, methods, protocol); Alina Naveed (contribution to search strategy, developing polymer database, screening); Andrew B. Lowe (consultation on plastic polymers); Marck Norret (consultation on plastic additives); Matthew Cantrell, Megan Banks, Anastazja Gorecki, Jane Edgeloe, Akila Yapa, and Elizabeth Thomas (screening and data extraction); and Joanne Webb (editing). The authors also acknowledge the UWA Library for providing access to journal articles; Allan Finn, Senior Training Consultant, Ovid® for advice on search techniques; and Julie Glanville, Health Economics Consortium and Independent Consultant for peer reviewing our search strategy. The authors would also like to thank Associate Editor, Dr Nicolas Roth, for his meticulous examination of this manuscript, editorial guidance and continuous support, as well as the anonymous reviewers for their invaluable feedback and contributions to the improvement of this manuscript.

Funding

This Systematic Evidence Map was funded by Minderoo Foundation (Australia), an independent not-for-profit philanthropic organization. Neither the foundation, nor its benefactors, had any influence on the conduct or the findings of this SEM.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2023.108225.

References

Ábalos, M., Barceló, D., Parera, J., et al., 2019. Levels of regulated POPs in fish samples from the Sava River Basin. Comparison to legislated quality standard values. Sci. Total Environ. 647, 20–28. https://doi.org/10.1016/j.scitotenv.2018.07.371.

Allen, S., Allen, D., Karbalaei, S., Maselli, V., Walker, T.R., 2022. Micro(nano)plastics sources, fate, and effects: What we know after ten years of research. J. Hazard. Mater. Adv. 6, 100057 https://doi.org/10.1016/j.hazadv.2022.100057.

Amato-Lourenço, L.F., Carvalho-Oliveira, R., Júnior, G.R., dos Santos, G.L., Ando, R.A., Mauad, T., 2021. Presence of airborne microplastics in human lung tissue. J. Hazard. Mater. 416, 126124 https://doi.org/10.1016/j.jhazmat.2021.126124.

Andreas, K., Michael, F., 2018. Regulate to reduce chemical mixture risk. Science 361 (6399), 224–226. https://doi.org/10.1126/science.aat9219.

Asimakopoulos, A.G., Elangovan, M., Kannan, K., 2016. Migration of parabens, bisphenols, benzophenone-type UV filters, triclosan, and triclocarban from teethers and its implications for infant exposure. Environ. Sci. Tech. 50 (24), 13539–13547. https://doi.org/10.1021/acs.est.6b04128.

Atis, S., Tutluoglu, B., Levent, E., et al., 2005. The respiratory effects of occupational polypropylene flock exposure. Eur. Respir. J. 25 (1), 110–117. https://doi.org/10.1183/09031936.04.00138403.

ATSDR (Agency for Toxic Substances and Disease Registry). ATSDR's Substance Priority List. Published July 2020. Accessed July 16, 2020. https://www.atsdr.cdc.gov/spl/index.html.

Aurisano, N., Fantke, P., Huang, L., Jolliet, O., 2022. Estimating mouthing exposure to chemicals in children's products. J. Eposure Sci. Environ. Epidemiol. 32 (1), 94–102. https://doi.org/10.1038/s41370-021-00354-0.

Australian Competition & Consumer Commission. Permanent ban on children's products containing more than 1% diethylhexyl phthalate (DEHP). *Compet Consum Act 2010*. 2011;11. https://www.legislation.gov.au/Details/F2011L00192.

Australian Industrial Chemicals Introduction Scheme (AICIS). *Trimellitates (High Molecular Weight)*.; 2022. https://www.industrialchemicals.gov.au/sites/default/files/2022-05/EVA00031%20-%20Evaluation%20statement%20-%2030%20May%202022.pdf.

Ball, G.L., McLellan, C.J., Bhat, V.S., 2012. Toxicological review and oral risk assessment of terephthalic acid (TPA) and its esters: A category approach. Crit. Rev. Toxicol. 42 (1), 28–67. https://doi.org/10.3109/10408444.2011.623149.

Barker, D.J.P., 2004. Developmental origins of adult health and disease. J. Epidemiol. Community Health 58 (2), 114. https://doi.org/10.1136/jech.58.2.114.

Barker, D.J.P., 2007. The origins of the developmental origins theory. J. Intern. Med. 261 (5), 412–417. https://doi.org/10.1111/j.1365-2796.2007.01809.x.

Barnes, S.J., 2019. Understanding plastics pollution: The role of economic development and technological research. Environ. Pollut. 249, 812–821. https://doi.org/10.1016/j.envpol.2019.03.108.

Beran, D., Byass, P., Gbakima, A., et al., 2017. Research capacity building—obligations for global health partners. Lancet Glob. Health 5 (6), e567–e568. https://doi.org/10.1016/S2214-109X(17)30180-8.

Bergmann, M., Mützel, S., Primpke, S., Tekman, M.B., Trachsel, J., Gerdts, G., 2019. White and wonderful? Microplastics prevail in snow from the Alps to the Arctic. Sci. Adv. 5 (8) https://doi.org/10.1126/sciadv.aax1157.

Bjerregaard, P., Pedersen, H.S., Nielsen, N.O., Dewailly, E., 2013. Population surveys in Greenland 1993–2009: Temporal trend of PCBs and pesticides in the general Inuit population by age and urbanisation. Sci. Total Environ. 454–455, 283–288. https://doi.org/10.1016/j.scitotenv.2013.03.031.

Blackburn, K., Green, D., 2022. The potential effects of microplastics on human health: What is known and what is unknown. Ambio 51 (3), 518–530. https://doi.org/10.1007/s13280-021-01589-9.

Blum, A., Behl, M., Birnbaum, L., et al., 2019. Organophosphate ester flame retardants: Are they a regrettable substitution for polybrominated diphenyl ethers? Environ. Sci. Technol. Lett. 6 (11), 638–649. https://doi.org/10.1021/acs.estlett.9b00582.

Boisvert, A., Jones, S., Issop, L., Erythropel, H.C., Papadopoulos, V., Culty, M., 2016. In vitro functional screening as a means to identify new plasticizers devoid of reproductive toxicity. Environ. Res. 150, 496–512. https://doi.org/10.1016/j.envres.2016.06.033.

Bramer W, Fowler S, Ket J, Otten R, Riphagen I. Animal studies exclusion - bmi-online search blocks. Biomedische Informatie. Published 2020. https://blocks.bmi-online.nl/catalog/16.

Braun, T., Ehrlich, L., Henrich, W., et al., 2021. Detection of microplastic in human placenta and meconium in a clinical setting. Pharmaceutics 13 (7), 921. https://doi.org/10.3390/pharmaceutics13070921.

Braun D, Cherdron H, Rehahn M, Ritter H, Voit B. *Polymer Synthesis: Theory and Practice: Fundamentals, Methods, Experiments*. 5th ed. Springer-Verlag; 2013. https://www.springer.com/gp/book/9783642289798.

Breton, C.V., Landon, R., Kahn, L.G., et al., 2021. Exploring the evidence for epigenetic regulation of environmental influences on child health across generations. Commun. Biol. 4 (1), 1–15. https://doi.org/10.1038/s42003-021-02316-6.

Brommer, S., Harrad, S., Van den Eede, N., Covaci, A., 2012. Concentrations of organophosphate esters and brominated flame retardants in German indoor dust samples. J. Environ. Monit. JEM 14 (9), 2482–2487. https://doi.org/10.1039/c2em30303e.

Cai, H., Zheng, W., Zheng, P., et al., 2015. Human urinary/seminal phthalates or their metabolite levels and semen quality: A meta-analysis. Environ. Res. 142, 486–494. https://doi.org/10.1016/J.ENVRES.2015.07.008.

Calafat, A.M., 2012. The U.S.National Health and Nutrition Examination Survey and human exposure to environmental chemicals. Int. J. Hyg. Environ. Health 215 (2), 99–101. https://doi.org/10.1016/j.ijheh.2011.08.014.

Campioli, E., Lee, S., Lau, M., Marques, L., Papadopoulos, V., 2017. Effect of prenatal DINCH plasticizer exposure on rat offspring testicular function and metabolism. Sci. Rep. 7 (1), 11072. https://doi.org/10.1038/s41598-017-11325-7.

Caporale N, Leemans M, Birgersson L, et al. From cohorts to molecules: Adverse impacts of endocrine disrupting mixtures. *Science*. 2022;375(6582):eabe8244. doi:10.1126/science.abe8244.

Carlson, L.M., Angrish, M., Shirke, A.V., et al., 2022. Systematic evidence map for over one hundred and fifty per- and polyfluoroalkyl substances (PFAS). Environ. Health Perspect. 130 (5), 056001 https://doi.org/10.1289/EHP10343.

Carlson, L.M., Christensen, K., Sagiv, S.K., et al., 2023. A systematic evidence map for the evaluation of noncancer health effects and exposures to polychlorinated biphenyl mixtures. Environ. Res. 220, 115148 https://doi.org/10.1016/j.envres.2022.115148.

Catarino, A.I., Macchia, V., Sanderson, W.G., Thompson, R.C., Henry, T.B., 2018. Low levels of microplastics (MP) in wild mussels indicate that MP ingestion by humans is minimal compared to exposure via household fibres fallout during a meal. Environ. Pollut. 237, 675–684. https://doi.org/10.1016/j.envpol.2018.02.069.

Center for International Environmental Law. *Plastic & Health: The Hidden Costs of a Plastic Planet*.; 2019. Accessed June 20, 2022. www.ciel.org/plasticandhealth.

Centers for Disease Control and Prevention (CDC). National report on human exposure to environmental chemicals. Published December 5, 2022. Accessed December 15, 2022. https://www.cdc.gov/exposurereport/index.html.

Chang W, Cheng J, Allaire J, et al. Shiny: Web Application Framework for R. Published online 2021. https://CRAN.R-project.org/package=shiny.

Chao, H.R., Wang, S.L., Lee, W.J., Wang, Y.F., Päpke, O., 2007. Levels of polybrominated diphenyl ethers (PBDEs) in breast milk from central Taiwan and their relation to infant birth outcome and maternal menstruation effects. Environ. Int. 33 (2), 239–245. https://doi.org/10.1016/j.envint.2006.09.013.

Chen, D., Kannan, K., Tan, H., et al., 2016. Bisphenol analogues other than BPA: Environmental occurrence, human exposure, and toxicity – A review. Environ. Sci. Tech. 50 (11), 5438–5453. https://doi.org/10.1021/acs.est.5b05387.

Cooper C, Bland G, Chartres N, Woodruff T. *The Human Health Effects of Microplastics: Rapid Review Protocol*. OSF; 2022. Accessed July 20, 2023. https://osf.io/cwu87.

Corsolini, S., Ademollo, N., Romeo, T., Greco, S., Focardi, S., 2005. Persistent organic pollutants in edible fish: A human and environmental health problem. Microchem. J. 79 (1), 115–123. https://doi.org/10.1016/j.microc.2004.10.006.

Cózar, A., Echevarría, F., González-Gordillo, J.I., et al., 2014. Plastic debris in the open ocean. PNAS 111 (28), 10239–10244. https://doi.org/10.1073/pnas.1314705111.

Cristale, J., García Vázquez, A., Barata, C., Lacorte, S., 2013. Priority and emerging flame retardants in rivers: Occurrence in water and sediment, Daphnia magna toxicity and risk assessment. Environ. Int. 59, 232–243. https://doi.org/10.1016/j.envint.2013.06.011.

CROW (Chemical Retrieval on the Web). CROW Polymer Science. Published July 2021. Accessed January 25, 2023. https://www.polymerdatabase.com/.

CUSP cluster - The European research cluster to understand the health impacts of micro- and nanoplastics. Published September 2, 2021. Accessed November 24, 2022. https://cusp-research.eu/.

Danopoulos, E., Jenner, L., Twiddy, M., Rotchell, J.M., 2020. Microplastic contamination of salt intended for human consumption: A systematic review and meta-analysis. SN Appl Sci. 2 (12), 1950. https://doi.org/10.1007/s42452-020-03749-0.

Danopoulos, E., Jenner, L.C., Twiddy, M., Rotchell, J.M., 2020. Microplastic contamination of seafood intended for human consumption: A systematic review and meta-analysis. Environ. Health Perspect. 128 (12), 126002 https://doi.org/10.1289/EHP7171.

Danopoulos, E., Twiddy, M., Rotchell, J.M., 2020. Microplastic contamination of drinking water: A systematic review. PLoS One 15 (7), e0236838.

Davison SMC, White MP, Pahl S, et al. Public concern about, and desire for research into, the human health effects of marine plastic pollution: Results from a 15-country survey across Europe and Australia. *Glob Environ Change*. Published online June 17, 2021:102309. doi:10.1016/J.GLOENVCHA.2021.102309.

Deng, Y., Zhang, Y., Lemos, B., Ren, H., 2017. Tissue accumulation of microplastics in mice and biomarker responses suggest widespread health risks of exposure. Sci. Rep. 7 (1), 46687. https://doi.org/10.1038/srep46687.

DistillerSR. Published online 2021. https://www.evidencepartners.com/.

DistillerSR. The case for artificial intelligence in systematic reviews. Accessed June 14, 2022. https://www.evidencepartners.com/resources/guides-white-papers/the-case-for-artificial-intelligence-in-systematic-reviews.

Dong, C.D., Chen, C.W., Chen, Y.C., Chen, H.H., Lee, J.S., Lin, C.H., 2020. Polystyrene microplastic particles: In vitro pulmonary toxicity assessment. J. Hazard. Mater. 385, 121575 https://doi.org/10.1016/j.jhazmat.2019.121575.

Drage, D.S., Harden, F.A., Jeffery, T., Mueller, J.F., Hobson, P., Toms, L.M.L., 2019. Human biomonitoring in Australian children: Brominated flame retardants decrease from 2006 to 2015. Environ. Int. 122, 363–368. https://doi.org/10.1016/j.envint.2018.11.044.

Dris, R., Gasperi, J., Saad, M., Mirande, C., Tassin, B., 2016. Synthetic fibers in atmospheric fallout: A source of microplastics in the environment? Mar. Pollut. Bull. 104 (1–2), 290–293. https://doi.org/10.1016/j.marpolbul.2016.01.006.

ECHA (European Chemicals Agency). Mapping exercise – Plastic additives initiative. European Chemicals Agency. Accessed July 21, 2020. https://echa.europa.eu/de/mapping-exercise-plastic-additives-initiative#table.

ECHA (European Chemicals Agency). Candidate list of substances of very high concern for authorisation. European Chemicals Agency. Published July 2021. Accessed July 21, 2020. https://echa.europa.eu/candidate-list-table.

ECHA (European Chemicals Agency). Substances restricted under REACH. Accessed July 21, 2020. https://echa.europa.eu/de/substances-restricted-under-reach.

EFSA Panel on Food Contact Materials, Enzymes and Processing Aids (CEP), Lambré C, Barat Baviera JM, et al. Re-evaluation of the risks to public health related to the presence of bisphenol A (BPA) in foodstuffs. *EFSA J.* 2023;21(4):e06857. doi: 10.2903/j.efsa.2023.6857.

Eljezi, T., Pinta, P., Richard, D., et al., 2017. In vitro cytotoxic effects of DEHP-alternative plasticizers and their primary metabolites on a L929 cell line. Chemosphere 173, 452–459. https://doi.org/10.1016/j.chemosphere.2017.01.026.

European Food Safety Authority (EFSA). Bisphenol A. Published April 19, 2023. Accessed May 8, 2023. https://www.efsa.europa.eu/en/topics/topic/bisphenol.

European Union. Directive 2005/84/EC of The European Parliament and of the Council of 14 December 2005 amending for the 22nd time Council Directive 76/769/EEC on the approximation of the laws, regulations and administrative provisions of the Member States relating to restrictions on the marketing and use of certain dangerous substances and preparations (phthalates in toys and childcare articles). *Off J Eur Union.* 2005;(L344/40). https://www.legislation.gov.uk/eudr/2005/84/annex/adopted.

European Union. Commission directive 2011/8/EU of 28 January 2011 amending Directive 2002/72/EC as regards the restriction of use of Bisphenol A in plastic infant feeding bottles. *Off J Eur Union.* 2011;54(L26/II).

European Union. Commission regulation (EU) No 143/2011 of 17 February 2011 amending Annex XIV to Regulation (EC) No 1907/2006 of the European Parliament and of the Council on the Registration, Evaluation, Authorisation and Restriction of Chemicals ('REACH'). *Off J Eur Union.* 2011;(L44/2). https://eur-lex.europa.eu/legal-content/EN/ALL/?uri=celex%3A32011R0143.

European Union. Commission regulation (EU) 2018/213 of 12 February 2018 on the use of bisphenol A in varnishes and coatings intended to come into contact with food and amending Regulation (EU) No 10/2011 as regards the use of that substance in plastic food contact materials. *Off J Eur Union.* 2018;54(L26/II). https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32018R0213&from=EL.

Fahlman BD. Polymeric Materials. In: *Materials Chemistry*. Springer, Dordrecht; 2018: 373-483. https://link.springer.com/chapter/10.1007/978-94-024-1255-0_5.

Food and Drug Administration. Indirect food additives: Polymers. 2012;21 CFR 177(77 FR 41899). Accessed May 3, 2022. https://www.federalregister.gov/documents/2012/07/17/2012-17366/indirect-food-additives-polymers.

Food Packaging Forum Foundation. FCCmigex Database. Published 2022. Accessed November 21, 2022. https://www.foodpackagingforum.org/fccmigex.

Forns, J., Verner, M.A., Iszatt, N., et al., 2020. Early life exposure to perfluoroalkyl substances (PFAS) and ADHD: A meta-analysis of nine European population-based studies. Environ. Health Perspect. 128 (5), 057002 https://doi.org/10.1289/EHP5444.

Franzen, S.R.P., Chandler, C., Lang, T., 2017. Health research capacity development in low and middle income countries: reality or rhetoric? A systematic meta-narrative review of the qualitative literature. BMJ Open 7 (1), e012332.

Frederiksen, H., Nielsen, O., Koch, H.M., et al., 2020. Changes in urinary excretion of phthalates, phthalate substitutes, bisphenols and other polychlorinated and phenolic substances in young Danish men; 2009–2017. Int. J. Hyg. Environ. Health 223 (1), 93–105. https://doi.org/10.1016/j.ijheh.2019.10.002.

Gallagher, L.G., Li, W., Ray, R.M., et al., 2015. Occupational exposures and risk of stomach and esophageal cancers: Update of a cohort of female textile workers in Shanghai, China: Risk of cancer in textile workers. Am. J. Ind. Med. 58 (3), 267–275. https://doi.org/10.1002/ajim.22412.

Galloway TS. Micro- and nano-plastics and human health. In: Bergmann M, Gutow L, Klages M, eds. *Marine Anthropogenic Litter*. 1st ed. Springer Cham; 2015:343-366. doi:10.1007/978-3-319-16510-3.

Gan H, Zhang Y, Wang Y fei, Tao F biao, Gao H. Relationships of prenatal organophosphate ester exposure with pregnancy and birth outcomes: A systematic scoping review of epidemiological studies. *Ecotoxicol Environ Saf.* 2023;252:114642. doi:10.1016/j.ecoenv.2023.114642.

Gascon, M., Sunyer, J., Casas, M., et al., 2014. Prenatal exposure to DDE and PCB 153 and respiratory health in early childhood: A meta-analysis. Epidemiol. Camb. Mass. 25 (4), 544–553. https://doi.org/10.1097/EDE.0000000000000097.

GBD 2019 Ageing Collaborators. Global, regional, and national burden of diseases and injuries for adults 70 years and older: systematic analysis for the Global Burden of Disease 2019 Study. *BMJ.* 2022;376:e068208. doi:10.1136/bmj-2021-068208.

Geller, A.M., Zenick, H., 2005. Aging and the environment: a research framework. Environ. Health Perspect. 113 (9), 1257–1262. https://doi.org/10.1289/ehp.7569.

Geneva Environment Network. Plastics and the Environment. Published online June 13, 2022. Accessed June 20, 2022. https://www.genevaenvironmentnetwork.org/resources/updates/plastics-and-the-environment/.

German Environment Agency. HBM4EU. HBM4EU. Accessed December 15, 2022. https://www.hbm4eu.eu/.

German Environment Agency. HBM4EU Substances. HBM4EU. Accessed December 15, 2022. https://www.hbm4eu.eu/hbm4eu-substances/.

Geueke, B., Groh, K.J., Maffini, M.V., et al., 2022. Systematic evidence on migrating and extractable food contact chemicals: Most chemicals detected in food contact materials are not listed for use. Crit. Rev. Food Sci. Nutr. 1–11. https://doi.org/10.1080/10408398.2022.2067828.

Geueke B. Non-intentionally added substances (NIAS). Food Packaging Forum. Published June 12, 2018. Accessed October 7, 2022. https://www.foodpackagingforum.org/food-packaging-health/non-intentionally-added-substances-nias.

Geyer, R., Jambeck, J.R., Law, K.L., 2017. Production, use, and fate of all plastics ever made. Sci. Adv. 3 (7), e1700782–e. https://doi.org/10.1126/sciadv.1700782.

Gigault, J., ter Halle, A., Baudrimont, M., et al., 2018. Current opinion: What is a nanoplastic? Environ. Pollut. 235, 1030–1034. https://doi.org/10.1016/j.envpol.2018.01.024.

Gigault, J., El Hadri, H., Nguyen, B., et al., 2021. Nanoplastics are neither microplastics nor engineered nanoparticles. Nat. Nanotechnol. 16 (5), 501–507. https://doi.org/10.1038/s41565-021-00886-4.

Glüge, J., Scheringer, M., Cousins, I.T., et al., 2020. An overview of the uses of per- and polyfluoroalkyl substances (PFAS). Environ. Sci. Process Impacts 22 (12), 2345–2373. https://doi.org/10.1039/D0EM00291G.

Göckener, B., Weber, T., Rüdel, H., Bücking, M., Kolossa-Gehring, M., 2020. Human biomonitoring of per- and polyfluoroalkyl substances in German blood plasma samples from 1982 to 2019. Environ. Int. 145, 106123 https://doi.org/10.1016/j.envint.2020.106123.

Golestanzadeh, M., Riahi, R., Kelishadi, R., 2020. Association of phthalate exposure with precocious and delayed pubertal timing in girls and boys: a systematic review and meta-analysis. Environ. Sci. Process Impacts 22 (4), 873–894. https://doi.org/10.1039/C9EM00512A.

Goodes LM, Wong EVS, Alex J, et al. A scoping review protocol on in vivo human plastic exposure and health impacts. *medRxiv*. Published online April 11, 2022. doi: 10.1101/2022.02.10.22270706.

Goodes, L.M., Wong, E.V.S., Alex, J., et al., 2022. A scoping review protocol on in vivo human plastic exposure and health impacts. Syst. Rev. 11 (1), 137. https://doi.org/10.1186/s13643-022-02010-6.

Govarts, E., Nieuwenhuijsen, M., Schoeters, G., et al., 2012. Birth weight and prenatal exposure to polychlorinated biphenyls (PCBs) and dichlorodiphenyldichloroethylene (DDE): A meta-analysis within 12 European birth cohorts. Environ. Health Perspect. 120 (2), 162–170. https://doi.org/10.1289/ehp.1103767.

Graber, J.M., Alexander, C., Laumbach, R.J., et al., 2019. Per and polyfluoroalkyl substances (PFAS) blood levels after contamination of a community water supply and comparison with 2013–2014 NHANES. J. Eposure Sci. Environ. Epidemiol. 29 (2), 172–182. https://doi.org/10.1038/s41370-018-0096-z.

Groh, K.J., Backhaus, T., Carney-Almroth, B., et al., 2019. Overview of known plastic packaging-associated chemicals and their hazards. Sci. Total Environ. 651, 3253–3268. https://doi.org/10.1016/j.scitotenv.2018.10.015.

Guerrero-Bosagna, C., Skinner, M.K., 2012. Environmentally induced epigenetic transgenerational inheritance of phenotype and disease. Mol. Cell. Endocrinol. 354 (1–2), 3–8. https://doi.org/10.1016/j.mce.2011.10.004.

Guo, P., Furnary, T., Vasiliou, V., et al., 2022. Non-targeted metabolomics and associations with per- and polyfluoroalkyl substances (PFAS) exposure in humans: A scoping review. Environ. Int. 162, 107159 https://doi.org/10.1016/j.envint.2022.107159.

Gys, C., Ait Bamai, Y., Araki, A., et al., 2020. Biomonitoring and temporal trends of bisphenols exposure in Japanese school children. Environ. Res. 191, 110172 https://doi.org/10.1016/j.envres.2020.110172.

Hahladakis, J.N., Iacovidou, E., Gerassimidou, S., 2023. An overview of the occurrence, fate, and human risks of the bisphenol-A present in plastic materials, components, and products. Integr. Environ. Assess. Manag. 19 (1), 45–62. https://doi.org/10.1002/ieam.4611.

Hamel, C., Kelly, S.E., Thavorn, K., Rice, D.B., Wells, G.A., Hutton, B., 2020. An evaluation of DistillerSR's machine learning-based prioritization tool for title/abstract screening – impact on reviewer-relevant outcomes. BMC Med. Res. Method. 20 (1), 256. https://doi.org/10.1186/s12874-020-01129-1.

Han, D., Currell, M.J., 2017. Persistent organic pollutants in China's surface water systems. Sci. Total Environ. 580, 602–625. https://doi.org/10.1016/j.scitotenv.2016.12.007.

HBM Commission. [Monograph for 1,2-cyclohexane-di-isononyl (Hexamoll® DINCH®) - HBM values for the sum of metabolites of cyclohexane-1,2-dicarboxylic acid mono-hydroxyisononylester (OH MINCH) and cyclohexane-1,2-dicarboxylic acid mono-carboxy acid isooctyl ester (cx-MINCH) in the urine of adults and children: Commission Opinion "Human Biomonitoring" UBA]. *Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz*. 2014;57(12):1451-1461. doi:10.1007/s00103-014-2069-2.

He, C., Wang, X., Thai, P., et al., 2018. Organophosphate and brominated flame retardants in Australian indoor environments: Levels, sources, and preliminary assessment of human exposure. Environ. Pollut. 235, 670–679. https://doi.org/10.1016/j.envpol.2017.12.017.

Heindel, J.J., Vandenberg, L.N., 2015. Developmental origins of health and disease: a paradigm for understanding disease cause and prevention. Curr. Opin. Pediatr. 27 (2), 248–253. https://doi.org/10.1097/MOP.0000000000000191.

Hengstler, J., Foth, H., Gebel, T., et al., 2011. Critical evaluation of key evidence on the human health hazards of exposure to bisphenol A. Crit. Rev. Toxicol. 41 (4), 263–291. https://doi.org/10.3109/10408444.2011.558487.

Henríquez-Hernández, L.A., Ortiz-Andrelluchi, A., Álvarez-Pérez, J., et al., 2021. Human biomonitoring of persistent organic pollutants in elderly people from the Canary Islands (Spain): A temporal trend analysis from the PREDIMED and PREDIMED-Plus cohorts. Sci. Total Environ. 758, 143637 https://doi.org/10.1016/j.scitotenv.2020.143637.

Hoffman, D.J., Powell, T.L., Barrett, E.S., Hardy, D.B., 2021. Developmental origins of metabolic diseases. Physiol. Rev. 101 (3), 739–795. https://doi.org/10.1152/physrev.00002.2020.

Horvatits T, Tamminga M, Liu B, et al. Microplastics detected in cirrhotic liver tissue. *eBioMedicine*. 2022;82:104147. doi:10.1016/j.ebiom.2022.104147.

Hu, W., Gao, P., Wang, L., Hu, J., 2023. Endocrine disrupting toxicity of aryl organophosphate esters and mode of action. Crit. Rev. Environ. Sci. Technol. 53 (1), 1–18. https://doi.org/10.1080/10643389.2022.2050147.

Hu, Y., Wen, S., Yuan, D., et al., 2018. The association between the environmental endocrine disruptor bisphenol A and polycystic ovary syndrome: A systematic review and meta-analysis. Gynecol. Endocrinol. 34 (5), 370–377. https://doi.org/10.1080/09513590.2017.1405931.

Huang, W., Yin, H., Yang, Y., Jin, L., Lu, G., Dang, Z., 2021. Influence of the co-exposure of microplastics and tetrabromobisphenol A on human gut: Simulation in vitro with human cell Caco-2 and gut microbiota. Sci. Total Environ. 778, 146264 https://doi.org/10.1016/j.scitotenv.2021.146264.

Hwang S, Lim J eun, Choi Y, Jee SH. Bisphenol A exposure and type 2 diabetes mellitus risk: A meta-analysis. *BMC Endocr Disord 2018 181*. 2018;18(1):1-10. doi:10.1186/S12902-018-0310-Y.

Ibrahim, Y.S., Tuan Anuar, S., Azmi, A.A., et al., 2021. Detection of microplastics in human colectomy specimens. JGH Open. 5 (1), 116–121. https://doi.org/10.1002/jgh3.12457.

Jadhav, E.B., Sankhla, M.S., Bhat, R.A., Bhagat, D.S., 2021. Microplastics from food packaging: An overview of human consumption, health threats, and alternative solutions. Environ. Nanotechnol. Monit. Manag. 16, 100608 https://doi.org/10.1016/j.enmm.2021.100608.

Jamieson, D.J., Terrell, M.L., Aguocha, N.N., Small, C.M., Cameron, L.L., Marcus, M., 2011. Dietary exposure to brominated flame retardants and abnormal pap test results. J. Womens Health 20 (9), 1269–1278. https://doi.org/10.1089/jwh.2010.2275.

Jenner, L.C., Rotchell, J.M., Bennett, R.T., Cowen, M., Tentzeris, V., Sadofsky, L.R., 2022. Detection of microplastics in human lung tissue using μFTIR spectroscopy. Sci. Total Environ. 831, 154907 https://doi.org/10.1016/j.scitotenv.2022.154907.

Kahn, L.G., Philippat, C., Nakayama, S.F., Slama, R., Trasande, L., 2020. Endocrine-disrupting chemicals: Implications for human health. Lancet Diabetes Endocrinol. 8 (8), 703–718. https://doi.org/10.1016/S2213-8587(20)30129-7.

Kasper-Sonnenberg, M., Koch, H.M., Apel, P., et al., 2019. Time trend of exposure to the phthalate plasticizer substitute DINCH in Germany from 1999 to 2017: Biomonitoring data on young adults from the Environmental Specimen Bank (ESB). Int. J. Hygiene Environ. Health 222 (8), 1084–1092. https://doi.org/10.1016/j.ijheh.2019.07.011.

Kaza, S., Yao, L., Bhada-Tata, P., Van Woerden, F., 2018. What a waste 2.0: A global snapshot of solid waste management to 2050. World Bank. https://doi.org/10.1596/978-1-4648-1329-0.

Khalid Ageel, H., Harrad, S., Abou-Elwafa, A.M., 2022. Occurrence, human exposure, and risk of microplastics in the indoor environment. Environ. Sci. Process Impacts 24 (1), 17–31. https://doi.org/10.1039/D1EM00301A.

Koltzenburg S, Maskos M, Nuyken O. *Polymer Chemistry*. Springer-Verlag; 2017. https://www.springer.com/gp/book/9783662492772.

Kosuth M, Mason SA, Wattenberg EV. Anthropogenic contamination of tap water, beer, and sea salt. Zhou Z, ed. *PLOS ONE*. 2018;13(4):e0194970. doi:10.1371/journal.pone.0194970.

Kremer, A.M., Pal, T.M., Boleij, J.S.M., Schouten, J.P., Rijcken, B., 1994. Airway hyper-responsiveness and the prevalence of work-related symptoms in workers exposed to irritants. Am. J. Ind. Med. 26 (5), 655–669. https://doi.org/10.1002/ajim.4700260508.

Lam, J., Lanphear, B.P., Bellinger, D., et al., 2017. Developmental PBDE exposure and IQ/ADHD in childhood: A systematic review and meta-analysis. Environ. Health Perspect. 125 (8) https://doi.org/10.1289/EHP1632.

Landrigan, P.J., Stegeman, J.J., Fleming, L.E., et al., 2020. Human health and ocean pollution. Ann. Glob. Health 86 (1), 1–64. https://doi.org/10.5334/aogh.2831.

Lazarov, A., Cordoba, M., 2000. Purpuric contact dermatitis in patients with allergic reaction to textile dyes and resins. J. Eur. Acad. Dermatol. Venereol. 14 (2), 101–105. https://doi.org/10.1046/j.1468-3083.2000.00025.x.

Lebreton, L., Andrady, A., 2019. Future scenarios of global plastic waste generation and disposal. Palgrave Commun. 5 (1), 11. https://doi.org/10.1057/s41599-018-0212-7.

Lee, D.W., Kim, M.S., Lim, Y.H., Lee, N., Hong, Y.C., 2018. Prenatal and postnatal exposure to di-(2-ethylhexyl) phthalate and neurodevelopmental outcomes: A systematic review and meta-analysis. Environ. Res. 167, 558–566. https://doi.org/10.1016/j.envres.2018.08.023.

Lee, I., Pälmke, C., Ringbeck, B., et al., 2021. Urinary concentrations of major phthalate and alternative plasticizer metabolites in children of Thailand, Indonesia, and Saudi Arabia, and associated risks. Environ. Sci. Tech. 55 (24), 16526–16537. https://doi.org/10.1021/acs.est.1c04716.

Lehmann, G.M., LaKind, J.S., Davis, M.H., et al., 2018. Environmental chemicals in breast milk and formula: Exposure and risk assessment implications. Environ. Health Perspect. 126 (9), 096001 https://doi.org/10.1289/EHP1953.

Lemke, N., Murawski, A., Lange, R., et al., 2021. Substitutes mimic the exposure behaviour of REACH regulated phthalates – A review of the German HBM system on the example of plasticizers. Int. J. Hyg. Environ. Health 236, 113780. https://doi.org/10.1016/j.ijheh.2021.113780.

Leng L, Li J, Luo X mei, et al. Polychlorinated biphenyls and breast cancer: A congener-specific meta-analysis. *Environ Int*. 2016;88:133-141. doi:10.1016/j.envint.2015.12.022.

Leslie, H.A., van Velzen, M.J.M., Brandsma, S.H., Vethaak, A.D., Garcia-Vallejo, J.J., Lamoree, M.H., 2022. Discovery and quantification of plastic particle pollution in human blood. Environ. Int. 163, 107199 https://doi.org/10.1016/j.envint.2022.107199.

Lessmann, F., Kolossa-Gehring, M., Apel, P., et al., 2019. German Environmental Specimen Bank: 24-hour urine samples from 1999 to 2017 reveal rapid increase in exposure to the para-phthalate plasticizer di(2-ethylhexyl) terephthalate (DEHTP). Environ. Int. 132, 105102 https://doi.org/10.1016/j.envint.2019.105102.

Li, B., Ding, Y., Cheng, X., et al., 2020. Polyethylene microplastics affect the distribution of gut microbiota and inflammation development in mice. Chemosphere 244, 125492. https://doi.org/10.1016/j.chemosphere.2019.125492.

Li, J., Xie, Z., Mi, W., et al., 2017. Organophosphate esters in air, snow, and seawater in the North Atlantic and the Arctic. Environ. Sci. Tech. 51 (12), 6887–6896. https://doi.org/10.1021/acs.est.7b01289.

Liang, Y., Tan, Q., Song, Q., Li, J., 2021. An analysis of the plastic waste trade and management in Asia. Waste Manag. 119, 242–253. https://doi.org/10.1016/j.wasman.2020.09.049.

Liao, Z., Ji, X., Ma, Y., et al., 2021. Airborne microplastics in indoor and outdoor environments of a coastal city in Eastern China. J. Hazard. Mater. 417, 126007 https://doi.org/10.1016/j.jhazmat.2021.126007.

Liao, C., Liu, F., Alomirah, H., et al., 2012. Bisphenol S in urine from the United States and seven Asian countries: Occurrence and human exposures. Environ. Sci. Tech. 46 (12), 6860–6866. https://doi.org/10.1021/es301334j.

Lioy, P.J., Hauser, R., Gennings, C., et al., 2015. Assessment of phthalates/phthalate alternatives in children's toys and childcare articles: Review of the report including conclusions and recommendation of the Chronic Hazard Advisory Panel of the Consumer Product Safety Commission. J. Eposure Sci. Environ. Epidemiol. 25 (4), 343–353. https://doi.org/10.1038/jes.2015.33.

Lioy, P.J., Rappaport, S.M., 2011. Exposure science and the exposome: An opportunity for coherence in the environmental health sciences. Environ. Health Perspect. 119 (11), a466–a467. https://doi.org/10.1289/ehp.1104387.

Lithner, D., Larsson, Å., Dave, G., 2011. Environmental and health hazard ranking and assessment of plastic polymers based on chemical composition. Sci. Total Environ. 409 (18), 3309–3324. https://doi.org/10.1016/j.scitotenv.2011.04.038.

Liu, S., Guo, J., Liu, X., et al., 2023. Detection of various microplastics in placentas, meconium, infant feces, breastmilk and infant formula: A pilot prospective study. Sci. Total Environ. 854, 158699 https://doi.org/10.1016/j.scitotenv.2022.158699.

Lohmann, R., Cousins, I.T., DeWitt, J.C., et al., 2020. Are fluoropolymers really of low concern for human and environmental health and separate from other PFAS? Environ. Sci. Tech. 54 (20), 12820–12828. https://doi.org/10.1021/acs.est.0c03244.

Lu, L., Wan, Z., Luo, T., Fu, Z., Jin, Y., 2018. Polystyrene microplastics induce gut microbiota dysbiosis and hepatic lipid metabolism disorder in mice. Sci. Total Environ. 631–632, 449–458. https://doi.org/10.1016/j.scitotenv.2018.03.051.

Lunderberg, D.M., Kristensen, K., Liu, Y., et al., 2019. Characterizing airborne phthalate concentrations and dynamics in a normally occupied residence. Environ. Sci. Tech. 53 (13), 7337–7346. https://doi.org/10.1021/acs.est.9b02123.

Luo, Y., Deji, Z., Huang, Z., 2020. Exposure to perfluoroalkyl substances and allergic outcomes in children: A systematic review and meta-analysis. Environ. Res. 191, 110145 https://doi.org/10.1016/j.envres.2020.110145.

Luo, T., Zhang, Y., Wang, C., et al., 2019. Maternal exposure to different sizes of polystyrene microplastics during gestation causes metabolic disorders in their offspring. Environ. Pollut. 255, 113122 https://doi.org/10.1016/j.envpol.2019.113122.

Luttrell, W.E., Baird, B.A., 2014. Bisphenol A. J. Chem. Health Saf. 21 (5), 22–24. https://doi.org/10.1016/j.jchas.2014.07.011.

Lv, Y., Lu, S., Dai, Y., et al., 2017. Higher dermal exposure of cashiers to BPA and its association with DNA oxidative damage. Environ. Int. 98, 69–74. https://doi.org/10.1016/j.envint.2016.10.001.

Ma, Y., Xie, Z., Lohmann, R., Mi, W., Gao, G., 2017. Organophosphate ester flame retardants and plasticizers in ocean sediments from the North Pacific to the Arctic Ocean. Environ. Sci. Tech. 51 (7), 3809–3815. https://doi.org/10.1021/acs.est.7b00755.

Maertens, A., Golden, E., Hartung, T., 2021. Avoiding regrettable substitutions: Green toxicology for sustainable chemistry. ACS Sustain. Chem. Eng. 9 (23), 7749–7758. https://doi.org/10.1021/acssuschemeng.0c09435.

Maffini, M.V., Geueke, B., Groh, K., Carney Almroth, B., Muncke, J., 2021. Role of epidemiology in risk assessment: a case study of five ortho-phthalates. Environ. Health 20 (1), 114. https://doi.org/10.1186/s12940-021-00799-8.

Majasuo, S., Liippo, J., Lammintausta, K., 2012. Non-occupational contact sensitization to epoxy resin of bisphenol A among general dermatology patients. Contact Dermatitis 66 (3), 148–153. https://doi.org/10.1111/j.1600-0536.2011.01993.x.

Manikkam M, Guerrero-Bosagna C, Tracey R, Haque MdM, Skinner MK. Transgenerational actions of environmental compounds on reproductive disease and identification of epigenetic biomarkers of ancestral exposures. *PLoS ONE*. 2012;7(2):e31901. doi:10.1371/journal.pone.0031901.

Manikkam, M., Tracey, R., Guerrero-Bosagna, C., Skinner, M.K., 2013. Plastics derived endocrine disruptors (BPA, DEHP and DBP) induce epigenetic transgenerational inheritance of obesity, reproductive disease and sperm epimutations. PLoS One 8 (1), e55387.

Margolis, R., Sant, K.E., 2021. Associations between exposures to perfluoroalkyl substances and diabetes, hyperglycemia, or insulin resistance: A scoping review. J. Xenobiotics 11 (3), 115–129. https://doi.org/10.3390/jox11030008.

Masuda Y. The Yusho rice oil poisoning incident. In: Schecter A, ed. *Dioxins and Health*. Springer US; 1994:633-659. doi:10.1007/978-1-4899-1462-0_19.

McGowan, J., Sampson, M., Salzwedel, D.M., Cogo, E., Foerster, V., Lefebvre, C., 2016. PRESS peer review of electronic search strategies: 2015 guideline statement. J. Clin. Epidemiol. 75, 40–46. https://doi.org/10.1016/j.jclinepi.2016.01.021.

McKee, M., Stuckler, D., Basu, S., 2012. Where there is no health research: What can be done to fill the global gaps in health research? PLoS Med. 9 (4), e1001209.

Meeker, J.D., Sathyanarayana, S., Swan, S.H., 2009. Phthalates and other additives in plastics: human exposure and associated health outcomes. Philos. Trans. R. Soc. B. Biol. Sci. 364 (1526), 2097–2113. https://doi.org/10.1098/rstb.2008.0268.

Mendonca, K., Hauser, R., Calafat, A.M., Arbuckle, T.E., Duty, S.M., 2014. Bisphenol A concentrations in maternal breast milk and infant urine. Int. Arch. Occup. Environ. Health 87 (1), 13–20. https://doi.org/10.1007/s00420-012-0834-9.

Mintenig, S.M., Löder, M.G.J., Primpke, S., Gerdts, G., 2019. Low numbers of microplastics detected in drinking water from ground water sources. Sci. Total Environ. 648, 631–635. https://doi.org/10.1016/j.scitotenv.2018.08.178.

Misra BB. The Chemical Exposome of Human Aging. *Front Genet.* 2020;11. Accessed November 18, 2022. https://www.frontiersin.org/articles/10.3389/fgene.2020.574936.

Moche, H., Chentouf, A., Neves, S., Corpart, J.M., Nesslany, F., 2021. Comparison of in vitro endocrine activity of phthalates and alternative plasticizers. J. Toxicol. 2021, 8815202. https://doi.org/10.1155/2021/8815202.

Momentum. Microplastics and Human Health Consortium. Published April 30, 2023. Accessed May 9, 2023. https://momentummicroplastics.nl.

Moola, S., Munn, Z., Sears, K., et al., 2015. Conducting systematic reviews of association (etiology): The Joanna Briggs Institute's approach. Int. J. Evid. Based Healthc. 13 (3), 163–169. https://doi.org/10.1097/XEB.0000000000000064.

Moon, M.K., 2019. Concern about the safety of bisphenol A substitutes. Diabetes Metab. J. 43 (1), 46–48. https://doi.org/10.4093/dmj.2019.0027.

Muncke, J., 2021. Tackling the toxics in plastics packaging. PLoS Biol. 19 (3), e3000961.

Muncke, J., Backhaus, T., Geueke, B., et al., 2017. Scientific challenges in the risk assessment of food contact materials. Environ. Health Perspect. 125 (9), 095001 https://doi.org/10.1289/EHP644.

Munn, Z., Stern, C., Aromataris, E., Lockwood, C., Jordan, Z., 2018. What kind of systematic review should I conduct? A proposed typology and guidance for systematic reviewers in the medical and health sciences. BMC Med. Res. Method. 18 (1), 5. https://doi.org/10.1186/s12874-017-0468-4.

Murawski, A., Schmied-Tobies, M.I.H., Rucic, E., et al., 2021. Metabolites of 4-methylbenzylidene camphor (4-MBC), butylated hydroxytoluene (BHT), and tris(2-ethylhexyl) trimellitate (TOTM) in urine of children and adolescents in Germany – human biomonitoring results of the German Environmental Survey GerES V (2014–2017). Environ. Res. 192, 110345 https://doi.org/10.1016/j.envres.2020.110345.

Napper, I.E., Bakir, A., Rowland, S.J., Thompson, R.C., 2015. Characterisation, quantity and sorptive properties of microplastics extracted from cosmetics. Mar. Pollut. Bull. 99 (1), 178–185. https://doi.org/10.1016/j.marpolbul.2015.07.029.

National Center for Biotechnology Information. PubChem compound summary for CID 22932, Bis(2-ethylhexyl) terephthalate. Published online 2022. Accessed July 21, 2022. https://pubchem.ncbi.nlm.nih.gov/compound/22932.

Negri, E., Metruccio, F., Guercio, V., et al., 2017. Exposure to PFOA and PFOS and fetal growth: A critical merging of toxicological and epidemiological data. Crit. Rev. Toxicol. 47 (6), 489–515. https://doi.org/10.1080/10408444.2016.1271972.

OECD. *Global Plastics Outlook: Policy Scenarios to 2060*.; 2022. doi:10.1787/aa1edf33-en.

Oliveri Conti G, Ferrante M, Banni M, et al. Micro- and nano-plastics in edible fruit and vegetables. The first diet risks assessment for the general population. *Environ Res.* 2020;187:109677. doi:10.1016/j.envres.2020.109677.

Oliviero, F., Marmugi, A., Viguié, C., Gayrard, V., Picard-Hagen, N., Mselli-Lakhal, L., 2022. Are BPA substitutes as obesogenic as BPA? Int. J. Mol. Sci. 23 (8), 4238. https://doi.org/10.3390/ijms23084238.

Organisation for Economic Co-operation and Development (OECD). *Screening Information Dataset (SIDS) Initial Assessment Report for SIAM 14 – Tris(2-Ethylhexyl) Benzene-1,2,4-Tricarboxylate.*; 2002. Accessed June 2, 2022. https://hpvchemicals.oecd.org/ui/handler.axd?id=a0422254-4c16-49af-a880-964a686199e9.

Paget, V., Dekali, S., Kortulewski, T., et al., 2015. Specific uptake and genotoxicity induced by polystyrene nanobeads with distinct surface chemistry on human lung epithelial cells and macrophages. PLoS One 10 (4), e0123297.

Pagoni, A., Arvaniti, O.S., Kalantzi, O.I., 2022. Exposure to phthalates from personal care products: Urinary levels and predictors of exposure. Environ. Res. 212, 113194 https://doi.org/10.1016/j.envres.2022.113194.

Panagopoulos Abrahamsson, D., Wang, A., Jiang, T., et al., 2021. A comprehensive non-targeted analysis study of the prenatal exposome. Environ. Sci. Tech. 55 (15), 10542–10557. https://doi.org/10.1021/acs.est.1c01010.

Pauly, J.L., Stegmeier, S.J., Allaart, H.A., et al., 1998. Inhaled cellulosic and plastic fibers found in human lung tissue. Cancer Epidemiol. Biomark. Prev. Publ. Am. Assoc. Cancer Res. Cosponsored Am. Soc. Prev. Oncol. 7 (5), 419–428.

Pelch, K.E., Reade, A., Kwiatkowski, C.F., et al., 2022. The PFAS-Tox Database: A systematic evidence map of health studies on 29 per- and polyfluoroalkyl substances. Environ. Int. 167, 107408 https://doi.org/10.1016/j.envint.2022.107408.

Pelch, K., Wignall, J.A., Goldstone, A.E., et al., 2019. A scoping review of the health and toxicological activity of bisphenol A (BPA) structural analogues and functional alternatives. Toxicology 424, 152235. https://doi.org/10.1016/j.tox.2019.06.006.

Pembrey, M.E., Bygren, L.O., Kaati, G., et al., 2006. Sex-specific, male-line transgenerational responses in humans. Eur. J. Hum. Genet. EJHG 14 (2), 159–166. https://doi.org/10.1038/sj.ejhg.5201538.

Peters, M.D.J., Marnie, C., Tricco, A.C., et al., 2020. Updated methodological guidance for the conduct of scoping reviews. JBI Evid. Synth. 18 (10), 2119–2126. https://doi.org/10.11124/JBIES-20-00167.

Pivokonsky, M., Cermakova, L., Novotna, K., Peer, P., Cajthaml, T., Janda, V., 2018. Occurrence of microplastics in raw and treated drinking water. Sci. Total Environ. 643, 1644–1651. https://doi.org/10.1016/j.scitotenv.2018.08.102.

Plastics Europe. Brigid. Published 2023. Accessed May 9, 2023. https://plasticseurope.org/sustainability/plastics-health/microplastics/brigid/.

Prata, J.C., da Costa, J.P., Lopes, I., Duarte, A.C., Rocha-Santos, T., 2020. Environmental exposure to microplastics: An overview on possible human health effects. Sci. Total Environ. 702, 134455 https://doi.org/10.1016/j.scitotenv.2019.134455.

Qadeer, A., Kirsten, K.L., Ajmal, Z., Jiang, X., Zhao, X., 2022. Alternative plasticizers as emerging global environmental and health threat: Another regrettable substitution? Environ. Sci. Tech. 56 (3), 1482–1488. https://doi.org/10.1021/acs.est.1c08365.

R Core Team. R: A language and environment for statistical computing. Published online 2021. https://www.R-project.org/.

Quiros-Alcala, Lesliam, Barr, D.B., 2023. Invited perspective: Mixtures—Are they worth the risk (assessment)? Environ Health Perspect 131 (4), 041301. https://doi.org/10.1289/EHP12596.

Radke, E.G., Braun, J.M., Nachman, R.M., Cooper, G.S., 2020. Phthalate exposure and neurodevelopment: A systematic review and meta-analysis of human epidemiological evidence. Environ. Int. 137, 105408 https://doi.org/10.1016/j.envint.2019.105408.

Ragusa, A., Svelato, A., Santacroce, C., et al., 2021. Plasticenta: First evidence of microplastics in human placenta. Environ. Int. 146, 106274 https://doi.org/10.1016/j.envint.2020.106274.

Rahman, A., Sarkar, A., Yadav, O.P., Achari, G., Slobodnik, J., 2021. Potential human health risks due to environmental exposure to nano- and microplastics and knowledge gaps: A scoping review. Sci. Total Environ. 757, 143872 https://doi.org/10.1016/j.scitotenv.2020.143872.

Ravve, A., 2012. Principles of polymer chemistry, 3rd ed. Springer-Verlag.

Robaire, B., Delbes, G., Head, J.A., et al., 2022. A cross-species comparative approach to assessing multi- and transgenerational effects of endocrine disrupting chemicals. Environ. Res. 204, 112063 https://doi.org/10.1016/j.envres.2021.112063.

Rochester, J.R., Bolden, A.L., 2015. Bisphenol S and F: A systematic review and comparison of the hormonal activity of bisphenol A substitutes. Environ. Health Perspect. 123 (7), 643–650. https://doi.org/10.1289/ehp.1408989.

Rodgers, T.F.M., Truong, J.W., Jantunen, L.M., Helm, P.A., Diamond, M.L., 2018. Organophosphate ester transport, fate, and emissions in Toronto, Canada, estimated using an updated multimedia urban model. Environ. Sci. Tech. 52 (21), 12465–12474. https://doi.org/10.1021/acs.est.8b02576.

RStudio Team. RStudio: Integrated Development Environment for R. Published online 2021. http://www.rstudio.com/.

Rudel, R.A., Camann, D.E., Spengler, J.D., Korn, L.R., Brody, J.G., 2003. Phthalates, alkylphenols, pesticides, polybrominated diphenyl ethers, and other endocrine-disrupting compounds in indoor air and dust. Environ. Sci. Tech. 37 (20), 4543–4553. https://doi.org/10.1021/es0264596.

Ruenraroengsak, P., Tetley, T.D., 2015. Differential bioreactivity of neutral, cationic and anionic polystyrene nanoparticles with cells from the human alveolar compartment: robust response of alveolar type 1 epithelial cells. Part. Fibre Toxicol. 12 (1), 19. https://doi.org/10.1186/s12989-015-0091-7.

Sachs, N., 2011. Rescuing the strong precautionary principle from its critics. Univ. Ill. Law Rev. 2011, 1285.

Salamone JC. *Polymeric Materials Encyclopedia.* Vol 9. CRC Press; 1996:554. https://books.google.com.au/books?id=oYHJ-imh7rgC.

Sariyar M, Borg A. The RecordLinkage Package: Detecting Errors in Data. *R J.* 2010;2(2):61. doi:10.32614/RJ-2010-017.

Savitz, D.A., Hattersley, A.M., 2023. Evaluating chemical mixtures in epidemiological studies to inform regulatory decisions. Environ. Health Perspect. 131 (4), 045001 https://doi.org/10.1289/EHP11899.

Scheurer, M., Bigalke, M., 2018. Microplastics in swiss floodplain soils. Environ. Sci. Tech. 52 (6), 3591–3598. https://doi.org/10.1021/acs.est.7b06003.

Schreier, V.N., Appenzeller-Herzog, C., Brüschweiler, B.J., et al., 2022. Evaluating the food safety and risk assessment evidence-base of polyethylene terephthalate oligomers: Protocol for a systematic evidence map. Environ. Int. 167, 107387 https://doi.org/10.1016/j.envint.2022.107387.

Schwabl, P., Köppel, S., Königshofer, P., et al., 2019. Detection of various microplastics in human stool: A prospective case series. Ann. Intern. Med. 171 (7), 453–457. https://doi.org/10.7326/M19-0618.

Schwedler G, Conrad A, Rucic E, et al. Hexamoll® DINCH and DPHP metabolites in urine of children and adolescents in Germany. Human biomonitoring results of the German Environmental Survey GerES V, 2014–2017. *Int J Hyg Environ Health.* 2020;229:113397. doi:10.1016/j.ijheh.2019.09.004.

Schwedler, G., Rucic, E., Koch, H.M., et al., 2020. Metabolites of the substitute plasticiser Di-(2-ethylhexyl) terephthalate (DEHTP) in urine of children and adolescents investigated in the German Environmental Survey GerES V, 2014–2017. Int. J. Hyg. Environ. Health 230, 113589. https://doi.org/10.1016/j.ijheh.2020.113589.

Senathirajah, K., Attwood, S., Bhagwat, G., Carbery, M., Wilson, S., Palanisami, T., 2021. Estimation of the mass of microplastics ingested – A pivotal first step towards human health risk assessment. J. Hazard. Mater. 404 (Part B), 124004 https://doi.org/10.1016/j.jhazmat.2020.124004.

Shamseer, L., Moher, D., Clarke, M., et al., 2015. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: Elaboration and explanation. BMJ 350, g7647. https://doi.org/10.1136/bmj.g7647.

Shruti, V.C., Pérez-Guevara, F., Elizalde-Martínez, I., Kutralam-Muniasamy, G., 2020. First study of its kind on the microplastic contamination of soft drinks, cold tea and energy drinks – Future research and environmental considerations. Sci. Total Environ. 726, 138580 https://doi.org/10.1016/j.scitotenv.2020.138580.

Siddique, S., Zhang, G., Coleman, K., Kubwabo, C., 2021. Investigation of the migration of bisphenols from baby bottles and sippy cups. Curr. Res. Food Sci. 4, 619–626. https://doi.org/10.1016/j.crfs.2021.08.006.

Silbergeld, E.K., Mandrioli, D., Cranor, C.F., 2015. Regulating chemicals: Law, science, and the unbearable burdens of regulation. Annu. Rev. Public Health 36 (1), 175–191. https://doi.org/10.1146/annurev-publhealth-031914-122654.

Silva, M.J., Jia, T., Samandar, E., Preau, J.L., Calafat, A.M., 2013. Environmental exposure to the plasticizer 1,2-cyclohexane dicarboxylic acid, diisononyl ester (DINCH) in US adults (2000–2012). Environ. Res. 126, 159–163. https://doi.org/10.1016/j.envres.2013.05.007.

Silva, M.J., Wong, L.Y., Samandar, E., Preau, J.L., Jia, L.T., Calafat, A.M., 2019. Exposure to di-2-ethylhexyl terephthalate in the U.S. general population from the 2015–2016 National Health and Nutrition Examination Survey. Environ. Int. 123, 141–147. https://doi.org/10.1016/j.envint.2018.11.041.

Simoneau, C., Valzacchi, S., Morkunas, V., Van den Eede, L., 2011. Comparison of migration from polyethersulphone and polycarbonate baby bottles. Food Addit. Contam. Part A Chem. Anal. Control Expo. Risk Assess. 28 (12), 1763–1768. https://doi.org/10.1080/19440049.2011.604644.

Singh, S., Li, S.S.L., 2012. Epigenetic effects of environmental chemicals bisphenol A and phthalates. Int. J. Mol. Sci. 13 (8), 10143–10153. https://doi.org/10.3390/ijms130810143.

Skåre JU, Alexander J, Haave M, et al. *Microplastics; Occurrence, Levels and Implications for Environment and Human Health Related to Food. Opinion of the Steering Committee of the Norwegian Scientific Committee for Food and Environment.* Norwegian Scientific Commitee for Food and Environment (VKM); 2019. Accessed May 6, 2022. https://munin.uit.no/handle/10037/16566.

Sonavane, M., Gassman, N.R., 2019. Bisphenol A co-exposure effects: A key factor in understanding BPA's complex mechanism and health outcomes. Crit. Rev. Toxicol. 49 (5), 371–386. https://doi.org/10.1080/10408444.2019.1621263.

Song, Y., Chou, E.L., Baecker, A., et al., 2016. Endocrine-disrupting chemicals, risk of type 2 diabetes, and diabetes-related metabolic traits: A systematic review and meta-analysis. J. Diabetes 8 (4), 516–532. https://doi.org/10.1111/1753-0407.12325.

Sripada, K., Wierzbicka, A., Abass, K., et al., 2022. A children's health perspective on nano- and microplastics. Environ. Health Perspect. 130 (1), 015001 https://doi.org/10.1289/EHP9086.

Steenland, K., Winquist, A., 2021. PFAS and cancer, a scoping review of the epidemiologic evidence. Environ. Res. 194, 110690 https://doi.org/10.1016/j.envres.2020.110690.

Steenland, K., Woskie, S., 2012. Cohort mortality study of workers exposed to perfluorooctanoic acid. Am. J. Epidemiol. 176 (10), 909–917. https://doi.org/10.1093/aje/kws171.

Stockholm Convention. POPRC recommendations for listing chemicals. Published 2019. Accessed July 21, 2020. http://chm.pops.int/Convention/POPsReviewCommittee/Chemicals/tabid/243/Default.aspx.

Stockholm Convention. Listing of POPs in the Stockholm Convention. Published 2019. Accessed July 21, 2020. http://chm.pops.int/TheConvention/ThePOPs/ListingofPOPs/tabid/2509/Default.aspx.

Stockholm Convention. Stockholm Convention on persistent organic pollutants (POPS). Published July 2019. Accessed July 21, 2020. http://chm.pops.int/TheConvention/Overview/TextoftheConvention/tabid/2232/Default.aspx.

Su, G., Crump, D., Letcher, R.J., Kennedy, S.W., 2014. Rapid in vitro metabolism of the flame retardant triphenyl phosphate and effects on cytotoxicity and mRNA expression in chicken embryonic hepatocytes. Environ. Sci. Tech. 48 (22), 13511–13519. https://doi.org/10.1021/es5039547.

Sühring, R., Diamond, M.L., Scheringer, M., et al., 2016. Organophosphate esters in Canadian Arctic air: Occurrence, levels and trends. Environ. Sci. Tech. 50 (14), 7409–7415. https://doi.org/10.1021/acs.est.6b00365.

Symeonides, C., Brunner, M., Mulders, Y., et al., 2021. Buy-now-pay-later: Hazards to human and planetary health from plastics production, use and waste. J. Paediatr. Child Health 57 (11), 1795–1804. https://doi.org/10.1111/jpc.15777.

Tanner, E.M., Hallerbäck, M.U., Wikström, S., et al., 2020. Early prenatal exposure to suspected endocrine disruptor mixtures is associated with lower IQ at age seven. Environ. Int. 134, 105185 https://doi.org/10.1016/j.envint.2019.105185.

Tessier V. Human studies. CHLA Canadian Health Libraries Association. Published 2019. https://extranet.santecom.qc.ca/wiki/!biblio3s/doku.php?id=concepts:etudes-sur-les-humains.

Thayer, K.A., Angrish, M., Arzuaga, X., et al., 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 https://doi.org/10.1016/j.envint.2022.107468.

The commission of the European communities. 1999/815/EC: Commission decision of 7 December 1999 adopting measures prohibiting the placing on the market of toys and childcare articles intended to be placed in the mouth by children under three years of age made of soft PVC containing one or more of the substances di-iso-nonyl phthalate (DINP), di(2-ethylhexyl) phthalate (DEHP), dibutyl phthalate (DBP), di-iso-decyl phthalate (DIDP), di-n-octyl phthalate (DNOP), and butylbenzyl phthalate (BBP) (notified under document number C(1999) 4436). *Off J Eur Communities*. 1999;(L315/46). http://data.europa.eu/eli/dec/1999/815/oj.

Thompson, R.C., Olsen, Y., Mitchell, R.P., et al., 2004. Lost at sea: Where is all the plastic? Science 304 (5672), 838. https://doi.org/10.1126/science.1094559.

Thornton Hampton, L.M., Lowman, H., Coffin, S., et al., 2022. A living tool for the continued exploration of microplastic toxicity. Microplast. Nanoplast. 2 (1), 13. https://doi.org/10.1186/s43591-022-00032-4.

Thorson JLM, Beck D, Ben Maamar M, Nilsson EE, Skinner MK. Ancestral plastics exposure induces transgenerational disease-specific sperm epigenome-wide association biomarkers. *Environ Epigenetics*. 2021;7(1):dvaa023. doi:10.1093/eep/dvaa023.

Tricco AC, Lillie E, Zarin W, et al. PRISMA Extension for Scoping Reviews (PRISMA-ScR): Checklist and Explanation. *Httpsdoiorg107326M18-0850*. 2018;169(7):467-473. doi:10.7326/M18-0850.

Turcotte, S.E., Chee, A., Walsh, R., et al., 2013. Flock worker's lung disease. Chest 143 (6), 1642–1648. https://doi.org/10.1378/chest.12-0920.

U.S. Consumer Product Safety Commission. Prohibition of children's toys and child care articles containing specified phthalates: Determinations regarding certain plastics. 2017;16 CFR 1308(82 FR 41163):41163-41172.

United States Environmental Protection Agency. PFAS|EPA: PFAS structures in DSSTox. CompTox Chemicals Dashboard v2.2. Published August 2022. Accessed April 13, 2023. https://comptox.epa.gov/dashboard/chemical-lists/PFASSTRUCTV5.

University of Queensland. Minderoo Centre- Plastics and Human Health. Queensland Alliance for Environmental Health Sciences. Published 2023. Accessed May 9, 2023. https://qaehs.centre.uq.edu.au/minderoo.

Usman, A., Ahmad, M., 2016. From BPA to its analogues: Is it a safe journey? Chemosphere 158, 131–142. https://doi.org/10.1016/j.chemosphere.2016.05.070.

Van Cauwenbergh, O., Di Serafino, A., Tytgat, J., Soubry, A., 2020. Transgenerational epigenetic effects from male exposure to endocrine-disrupting compounds: a systematic review on research in mammals. Clin. Epigenetics 12 (1), 65. https://doi.org/10.1186/s13148-020-00845-1.

van der Mheen, M., van Sebille, E., Pattiaratchi, C., 2020. Beaching patterns of plastic debris along the Indian Ocean rim. Ocean Sci. 16 (5), 1317–1336. https://doi.org/10.5194/os-16-1317-2020.

van der Veen, I., de Boer, J., 2012. Phosphorus flame retardants: Properties, production, environmental occurrence, toxicity and analysis. Chemosphere 88 (10), 1119–1153. https://doi.org/10.1016/j.chemosphere.2012.03.067.

Vandenberg, L.N., Colborn, T., Hayes, T.B., et al., 2012. Hormones and endocrine-disrupting chemicals: Low-dose effects and nonmonotonic dose responses. Endocr. Rev. 33 (3), 378–455. https://doi.org/10.1210/er.2011-1050.

Varshavsky, J.R., Robinson, J.F., Zhou, Y., et al., 2021. Organophosphate flame retardants, highly fluorinated chemicals, and biomarkers of placental development and disease during mid-gestation. Toxicol. Sci. 181 (2), 215–228. https://doi.org/10.1093/toxsci/kfab028.

Vasconcelos, A.L., Silva, M.J., Louro, H., 2019. In vitro exposure to the next-generation plasticizer diisononyl cyclohexane-1,2-dicarboxylate (DINCH): cytotoxicity and genotoxicity assessment in human cells. J. Toxic. Environ. Health A 82 (9), 526–536. https://doi.org/10.1080/15287394.2019.1634376.

Venn M. Subject Guides: Systematic Reviews for Health: 8. Search Limits. Published 2020. https://utas.libguides.com/SystematicReviews/SearchLimits.

Vieira, V.M., Hoffman, K., Shin, H.M., Weinberg, J.M., Webster, T.F., Fletcher, T., 2013. Perfluorooctanoic acid exposure and cancer outcomes in a contaminated community: A geographic analysis. Environ. Health Perspect. 121 (3), 318–323. https://doi.org/10.1289/ehp.1205829.

Vitale, R.J., Acker, J.K., Somerville, S.E., 2022. An assessment of the potential for leaching of per- and polyfluoroalkyl substances from fluorinated and non-fluorinated high-density polyethylene containers. Environ. Adv. 9, 100309 https://doi.org/10.1016/j.envadv.2022.100309.

Wahl, A., Le Juge, C., Davranche, M., et al., 2021. Nanoplastic occurrence in a soil amended with plastic debris. Chemosphere 262, 127784. https://doi.org/10.1016/j.chemosphere.2020.127784.

Wang, A., Abrahamsson, D.P., Jiang, T., et al., 2021. Suspect screening, prioritization, and confirmation of environmental chemicals in maternal-newborn pairs from San Francisco. Environ. Sci. Tech. 55 (8), 5037–5049. https://doi.org/10.1021/acs.est.0c05984.

Wang, H., Jiang, L., Gu, S., Wang, X., 2021. Migration of bisphenol A from polyvinyl chloride plastics to solvents of different polarities and packaged food in China. Packag. Technol. Sci. 34 (2), 127–137. https://doi.org/10.1002/pts.2545.

Wen, X., Xiong, Y., Qu, X., et al., 2019. The risk of endometriosis after exposure to endocrine-disrupting chemicals: A meta-analysis of 30 epidemiology studies. Gynecol. Endocrinol. 35 (8), 645–650. https://doi.org/10.1080/09513590.2019.1590546.

Wesch, C., Elert, A.M., Wörner, M., Braun, U., Klein, R., Paulus, M., 2017. Assuring quality in microplastic monitoring: About the value of clean-air devices as essentials for verified data. Sci. Rep. 7 (1), 5424. https://doi.org/10.1038/s41598-017-05838-4.

Wibowo, A.T., Nugrahapraja, H., Wahyuono, R.A., et al., 2021. Microplastic contamination in the human gastrointestinal tract and daily consumables associated with an Indonesian farming community. Sustainability 13 (22), 12840. https://doi.org/10.3390/su132212840.

Wiesinger, H., Wang, Z., Hellweg, S., 2021. Deep dive into plastic monomers, additives, and processing aids. Environ. Sci. Tech. 55 (13), 9339–9351. https://doi.org/10.1021/acs.est.1c00976.

Wolstenholme, J.T., Edwards, M., Shetty, S.R.J., et al., 2012. Gestational exposure to bisphenol A produces transgenerational changes in behaviors and gene expression. Endocrinology 153 (8), 3828–3838. https://doi.org/10.1210/en.2012-1195.

Woolf AD. Chapter 1.10 - Japan "Yusho" poisoning, 1968 and Taiwan "Yucheng" poisoning, 1979. In: Woolf AD, ed. *History of Modern Clinical Toxicology*. History of Toxicology and Environmental Health. Academic Press; 2022:121-135. doi:10.1016/B978-0-12-822218-8.00041-7.

World bank country and lending groups – World bank data help desk. Accessed July 11, 2022. https://datahelpdesk.worldbank.org/knowledgebase/articles/906519-world-bank-country-and-lending-groups.

World Health Organization (WHO). International Classification of Diseases, Eleventh Revision (ICD-11). Published online 2019. https://icd.who.int/browse11. Licensed under Creative Commons Attribution-NoDerivatives 3.0 IGO licence (CC BY-ND 3.0 IGO).

World Health Organization (WHO). *Dietary and Inhalation Exposure to Nano- and Microplastic Particles and Potential Implications for Human Health.* World Health

Organization; 2022. Accessed October 7, 2022. https://www.who.int/publications-detail-redirect/9789240054608.

Wu, H., Bertrand, K.A., Choi, A.L., et al., 2013. Persistent organic pollutants and type 2 diabetes: A prospective analysis in the Nurses' Health Study and meta-analysis. Environ. Health Perspect. 121 (2), 153–161. https://doi.org/10.1289/ehp.1205248.

Wu W, Li M, Liu A, et al. Bisphenol A and the risk of obesity: A systematic review with meta-analysis of the epidemiological evidence. *Dose-Response*. 2020;18(2): 1559325820916949. doi:10.1177/1559325820916949.

Wypych G. *Handbook of Polymers*. Second edition. ChemTec Publishing; 2016:706. https://www.sciencedirect.com/science/article/pii/B9781895198928500021.

Xu, M., Halimu, G., Zhang, Q., et al., 2019. Internalization and toxicity: A preliminary study of effects of nanoplastic particles on human lung epithelial cell. Sci. Total Environ. 694, 133794 https://doi.org/10.1016/j.scitotenv.2019.133794.

Xu, H., Verbeken, E., Vanhooren, H.M., Nemery, B., Hoet, P.H.M., 2004. Pulmonary toxicity of polyvinyl chloride particles after a single intratracheal instillation in rats. Time course and comparison with silica. Toxicol. Appl. Pharmacol. 194 (2), 111–121. https://doi.org/10.1016/j.taap.2003.09.018.

Xue, J., Zartarian, V., Moya, J., et al., 2007. A meta-analysis of children's hand-to-mouth frequency data for estimating nondietary ingestion exposure. Risk Anal. 27 (2), 411–420. https://doi.org/10.1111/j.1539-6924.2007.00893.x.

Yan, Z., Liu, Y., Zhang, T., Zhang, F., Ren, H., Zhang, Y., 2022. Analysis of microplastics in human feces reveals a correlation between fecal microplastics and inflammatory bowel disease status. Environ. Sci. Tech. 56 (1), 414–421. https://doi.org/10.1021/acs.est.1c03924.

Yang, W., Braun, J.M., Vuong, A.M., et al., 2022. Maternal urinary OPE metabolite concentrations and blood pressure during pregnancy: The HOME Study. Environ. Res. 207, 112220 https://doi.org/10.1016/j.envres.2021.112220.

Yang, Y., Chen, P., Ma, S., Lu, S., Yu, Y., An, T., 2022. A critical review of human internal exposure and the health risks of organophosphate ester flame retardants and their metabolites. Crit. Rev. Environ. Sci. Technol. 52 (9), 1528–1560. https://doi.org/10.1080/10643389.2020.1859307.

Yang, S., Cheng, Y., Chen, Z., et al., 2021. In vitro evaluation of nanoplastics using human lung epithelial cells, microarray analysis and co-culture model. Ecotoxicol. Environ. Saf. 226, 112837 https://doi.org/10.1016/j.ecoenv.2021.112837.

Yang, Y., Xie, Q., Liu, X., Wang, J., 2015. Occurrence, distribution and risk assessment of polychlorinated biphenyls and polybrominated diphenyl ethers in nine water sources. Ecotoxicol. Environ. Saf. 115, 55–61. https://doi.org/10.1016/j.ecoenv.2015.02.006.

Yates, J., Deeney, M., Rolker, H.B., White, H., Kalamatianou, S., Kadiyala, S., 2021. A systematic scoping review of environmental, food security and health impacts of food system plastics. Nat Food. 2 (2), 80–87. https://doi.org/10.1038/s43016-021-00221-z.

Yong, C., Valiyaveettil, S., Tang, B., 2020. Toxicity of microplastics and nanoplastics in mammalian systems. Int. J. Environ. Res. Public Health 17 (5), 1509. https://doi.org/10.3390/ijerph17051509.

Zangmeister, C.D., Radney, J.G., Benkstein, K.D., Kalanyan, B., 2022. Common single-use consumer plastic products release trillions of sub-100 nm nanoparticles per liter into water during normal use. Environ. Sci. Tech. 56 (9), 5448–5455. https://doi.org/10.1021/acs.est.1c06768.

Zani, C., Ceretti, E., Covolo, L., Donato, F., 2017. Do polychlorinated biphenyls cause cancer? A systematic review and meta-analysis of epidemiological studies on risk of cutaneous melanoma and non-Hodgkin lymphoma. Chemosphere 183, 97–106. https://doi.org/10.1016/j.chemosphere.2017.05.053.

Zhang, H., Gao, F., Ben, Y., Su, Y., 2020. Association between phthalate exposure and risk of spontaneous pregnancy loss: A systematic review and meta-analysis. Environ. Pollut. 267, 115446 https://doi.org/10.1016/j.envpol.2020.115446.

Zhang, J., Huang, Y., Wang, X., Lin, K., Wu, K., 2015. Environmental polychlorinated biphenyl exposure and breast cancer risk: A meta-analysis of observational studies. PLoS One 10 (11), e0142513.

Zhang, L., Louie, A., Rigutto, G., et al., 2023. A systematic evidence map of chronic inflammation and immunosuppression related to per- and polyfluoroalkyl substance (PFAS) exposure. Environ. Res. 220, 115188 https://doi.org/10.1016/j.envres.2022.115188.

Zhang, X., Sühring, R., Serodio, D., Bonnell, M., Sundin, N., Diamond, M.L., 2016. Novel flame retardants: Estimating the physical–chemical properties and environmental fate of 94 halogenated and organophosphate PBDE replacements. Chemosphere 144, 2401–2407. https://doi.org/10.1016/j.chemosphere.2015.11.017.

Zhang, J., Wang, L., Trasande, L., Kannan, K., 2021. Occurrence of polyethylene terephthalate and polycarbonate microplastics in infant and adult feces. Environ. Sci. Technol. Lett. 8 (11), 989–994. https://doi.org/10.1021/acs.estlett.1c00559.

Zhao J yi, Zhan Z xiang, Lu M juan, Tao F biao, Wu D, Gao H. A systematic scoping review of epidemiological studies on the association between organophosphate flame retardants and neurotoxicity. *Ecotoxicol Environ Saf*. 2022;243:113973. doi:10.1016/j.ecoenv.2022.113973.

Zhao, X., Wang, H., Li, J., Shan, Z., Teng, W., Teng, X., 2015. The correlation between polybrominated diphenyl ethers (PBDEs) and thyroid hormones in the general population: A meta-analysis. PLoS One 10 (5), e0126989.

Zhao, X., Peng, S., Xiang, Y., et al., 2017. Correlation between prenatal exposure to polybrominated diphenyl ethers (PBDEs) and infant birth outcomes: A meta-analysis and an experimental study. Int. J. Environ. Res. Public Health 14 (3), 268. https://doi.org/10.3390/ijerph14030268.

Zhao, Q., Zhu, L., Weng, J., et al., 2023. Detection and characterization of microplastics in the human testis and semen. Sci. Total Environ. 877, 162713 https://doi.org/10.1016/j.scitotenv.2023.162713.

Zimmermann, L., Dierkes, G., Ternes, T.A., Völker, C., Wagner, M., 2019. Benchmarking the in vitro toxicity and chemical composition of plastic consumer products. Environ. Sci. Tech. 53 (19), 11467–11477. https://doi.org/10.1021/acs.est.9b02293.

Zimmermann, L., Bartosova, Z., Braun, K., Oehlmann, J., Völker, C., Wagner, M., 2021. Plastic products leach chemicals that induce in vitro toxicity under realistic use conditions. Environ. Sci. Tech. 55 (17), 11814–11823. https://doi.org/10.1021/acs.est.1c01103.

Zimmermann, L., Scheringer, M., Geueke, B., et al., 2022. Implementing the EU Chemicals Strategy for Sustainability: The case of food contact chemicals of concern. J. Hazard. Mater. 437, 129167 https://doi.org/10.1016/j.jhazmat.2022.129167.