Evidence on the effects of Flame Retardant substances at ecologically relevant endpoints: A Systematic Map Protocol

Jones, L.B[1*]. & Arnold, K.E[2]

[1] Lowenna Jones; lbjones3@sheffield.ac.uk; 0000-0002-8623-1218

Department of Politics and International Relations, University of Sheffield

[2] Kathryn Arnold; kathryn.arnold@york.ac.uk; 0000-0002-6485-6065

Department of Environment and Geography, University of York

* correspondence should be addressed to Lowenna Jones; lbjones3@sheffield.ac.uk

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Abstract

Background: Flame retardants are a diverse group of chemical substances that are widely used in products, such as furniture, textiles, electronics and building materials, to prevent or slow the development of fire. Flame retardant (FR) substances are known to pose a risk to human and environmental health, with complex and wide-ranging pathways of exposure and contamination. Once released into the environment, some FR substances are known, or predicted to have direct and indirect effects on long term survival, development, physiology and behaviour across a range of species,

including humans and wildlife. Over time, FR substances have become the focus of many environmental and (human) health risk assessments. A list of potential FR substances has been developed (i.e. Bevington et al., 2022) however, detailed information on the risk, or hazard of such substances to human, animal and environmental health has not yet been collated. Systematic Evidence Maps (SEMs) have been identified as an underutilised tool for chemical risk assessment. They provide a core and reliable approach to evidence-based toxicology, which is informed by engagement with expert stakeholders, and based on the PECO (Population, Exposure, Comparator, Outcome) approach to question formulation (Morgan et al., 2018). The goal of this systematic evidence map is to identify, organise and map the available evidence on the (eco)toxicological effects of FR substances across ecologically relevant endpoints.

Methods: We will search several electronic academic (PubMed, Web of Science, Google Scholar) databases, in addition to grey literature sites (OpenGrey) for existing evidence on the (eco)toxicological effect of FR substances to the environment. Eligible studies must contain primary research investigating the risk (or hazard) of one or more FR substances (as listed in Bevington et al., 2022) and study an ecologically relevant adverse effect, outcome and/or endpoint. Ecologically relevant effects include impacts on growth, development, survival, reproduction and behaviour. Taxonomic groups considered for inclusion are those classified as animal, plant, bacteria and/or fungi. Human data will not be included. Articles will be screened in two phases – firstly, Title and Abstract, before a full-text review. A single reviewer will screen all articles with an independent reviewer confirming articles for exclusion. Assessment of each article's quality will not be assessed for this evidence map. Results of the evidence map will be published in a narrative summary and visualised in a publicly available interactive map.

Keywords: Chemical; Ecology; Hazard; Toxicology; Regulation

Main text

1. Background

The threat of chemical pollution has been listed as one of the top three environmental crises (alongside climate change and biodiversity loss) society will face over the coming decades (UNEP, 2021). The toxic effects of chemicals and chemical mixtures present a significant threat of harm to ecosystems, biodiversity, and human health across the globe (Woodcock et al., 2017; IPBES, 2019; Wijgerde et al., 2020; Van Dijk et al., 2021) with clear implication for planetary and societal wellbeing (Rockstrom et al., 2009; Steffen et al., 2015; Johnson et al., 2020). Recent reports warn the production and release of large volumes of diverse 'novel' substances is exceeding society's ability to operate safely (Persson et al., 2022), and with new chemicals often released to market without sufficient risk assessment, there are concerns chemical substances and/or their associated effects will continue to pose significant risk to environmental and human health (Rockstrom et al., 2009; Wang et al., 2020).

1.1. Rationale

Flame retardant (FR) substances are a diverse group of chemical compounds or mixtures that are used in products to reduce flammability, and prevent, or slow the development of fire (Cressey, 2012; Keller et al., 2014; Lazar et al., 2020; Page et al., 2023). FR substances are generally considered to play an important role in safeguarding life and property, designed to improve product safety and minimise the risk of fire. Widely used in articles such as furniture, textiles, plastic, electronics and building materials, FR substances are common components of most consumer products (Bajard et al., 2018; Page et al., 2023), with their application becoming a growing chemical sector. This is especially true in the UK and Ireland where strict fire standards see an increased use of FR substances in products (Brommer and Harrad, 2015; Harrad, Brommer and Mueller, 2016; Kademoglou et al., 2017). The global market for substances with FR properties has increased considerably since their first use in the

1970s (Tian et al., 2023). In 2021 the global market value of FR substances exceeded 8 billion US dollars (Statistica, 2023), with forecasts predicting the market size of the industry will reach 13.6 billion (US dollars) worldwide by the end of the decade (2030) (Statistica, 2023).

The scientific literature on FR substances has increased in recent decades (from a few thousand publications in the 1970's to >50,000 in 2023) with hundreds of research articles reporting adverse and deleterious effects of FR substances across *in vitro, in vivo* and biomonitoring studies (Hendriks and Westerink, 2015; Blum et al., 2019; Doherty et al., 2019; Xiong et al., 2019; Sun et al., 2020). This has resulted in greater understanding on the risk of FR substances – particularly in relation to human health (Wikoff and Birnbaum, 2011; Lyche et al., 2015; Melymuk and Bajard, 2022). Some FR substances are known, or considered to be hazardous to health, with pathways to exposure wide ranging and complex. FR substances are found in air, dust, food and drinking water, and are present on indoor surfaces and textiles (Abou-Elwafa Abdallah and Harrad, 2022). Humans are exposed to FR substances at all stages of a substance lifecycle, from development and manufacture of FR containing products, throughout their direct application and (normal) use and at the end of life where products are disposed of and/or recycled (Page et al., 2023). Children are particularly vulnerable to exposure due to crawling and mouthing behaviours (Sugeng et al., 2020). Numerous FR substances, including some known or considered persistent, bioaccumulative, and/or toxic (PBT) FR substances have been reported in the natural environment (aquatic and terrestrial systems) (Segev et al., 2009; Ekpe et al., 2020; Zuiderveen et al., 2020). These substances can enter or be released into the environment through atmospheric transportation, dry and wet deposition, sludge application, waste-water discharge and surface runoff, posing a potential risk to organisms from the poles to the equator (Brommer and Harrad, 2015; Tao, Dodson et al., 2017; Persson et al., 2018; Wemken et al., 2019; Yao et al., 2021).

It is important to note that the term 'flame retardant' does not refer to a single chemical family or structure but instead refers to the function of a chemical compound within a material (ECHA, 2023).

Three primary types of organic FR substances exist globally - these are organic Brominated (BFRs), Chlorinated (CFRs) and Organophosphate (OPFRs). Brominated and Chlorinated FRs are examples of halogenated FR compounds, which together with OPFRs, make up approximately 70% of the market for organic FR substances (Environment Audit Committee, 2019). Historically, the most used FR substances were brominated due to their retardancy capabilities and efficiency - this includes the highly persistent and toxic polybrominated diphenyl ethers (PBDEs) and hexabromocyclododecane (HBCDD). FR substances can also include inorganic compounds (e.g., metals), and Nitrogen or Boron based compounds.

Over time, FR substances have become the focus of many environmental and (human) health risk assessments. Consequently, several hazardous FR substances have been restricted across the globe. For instance, penta-BDE, hexa-BDE and tetra-BDE are examples of FR substances that were previously commonly used, however concerns over their persistence, toxicity, and potential to bioaccumulate (in humans and wildlife) led to their restriction (starting in 2009) when they were included in the Stockholm Convention on Persistent Organic Pollutants (POPs) (Sun et al., 2022; Wang et al., 2020). Deca-BDE being the most recent restriction, with inclusion coming in 2017. Regulatory measures under the European Union's REACH regulation (the Registration, Evaluation, Authorisation and Restriction of Chemicals; European Commission, 2006) are also in place for CFRs and FR substances identified to exhibit persistent, bioaccumulative and/or toxic (PBT) characteristics (e.g. PBDEs, HBCDD).

Restrictions of some FR substances have driven the market to substitute PBT compounds with compounds that are not always without risk (Bajard et al 2018). Since the 1970s, halogenated and phosphorus-containing FRs have commonly replaced brominated FRs (Li et al., 2019; Tian et al., 2023). Organophosphorus FRs (OPFRs) are common substitutions for known PBT FR substances (such as PBDEs) due to their widespread global production and similar technical characteristics (Li et

al., 2019; Tian et al., 2023). As a result, their global production and use has exceeded 1 million tonnes a year (1.05 million tonnes in 2018; Li et al., 2019), accounting for more than 30% of global consumption (Tian et al., 2023). Chemical constituents of OPFRs (e.g., organophosphate esters OPE) are proven carcinogens meaning substitution by these hazardous compounds poses further risk to health (Greaves and Lecture, 2016; Blum et al., 2019; Xie et al., 2022). Similarly, alternative chlorinated OPFR compounds TCEP, TCPP and TDCP replaced the use of Deca-BDE following its restriction in 2017, however these chemical substances are now being considered for restriction due to similar hazardous properties (EAC, 2019).

1.2. Environmental Risk Assessment

In 2010, 200+ scientists from (30) countries across the globe signed the San Antonio statement (DiGangi et al., 2010) to publicly raise concerns around the lack of information on flame retardant substances and call attention to neglected scientific information on brominated and chlorinated FR substances in regulation (DiGangi, 2012). Finally, in 2023, the European Chemicals Agency (ECHA) released its regulatory strategy for flame retardant substances (European Chemicals Agency, 2023) suggesting more (regulatory) data are required to determine the need for restriction of many aliphatic brominated and organophosphorus flame retardant substances. As FR substances perform a function (i.e., not considered a single chemical group) the list of potential FR substances is continually evolving, with large numbers of alternatives emerging on the market.

Standard hazard testing for chemical risk assessment is typically based upon empirical toxicity tests, performed or undertaken *in vivo* (in or on whole organisms) by approved laboratories and/or researchers (ECHA, 2011; Ruden et al., 2017; Olker et al., 2022). Studies are performed according to test guidelines, such as those set out by the Organisation for Economic Cooperation and Development (OECD, 2023) (Ruden et al., 2017) and typically focus on effects that are generally considered relevant to environmental risk and regulatory decision making (Ruden et al., 2017; Ford et al., 2021).

Such guidelines set out the regulatory accepted endpoints, experimental (study) design and information criteria. Such tests predominantly relate to the hazard of a chemical substance on an individual or population's survival, growth, development and/or reproduction (Ruden et al., 2017), however, only focus on a select number of species and/or endpoints and hence may not assess all aspects of environmental risk. Ecotoxicological studies published in the peer-reviewed literature can aid regulatory decision making by contributing relevant data on non-standard test species, non-standard endpoints and non-standard design (Beronius et al., 2014; Rohr et al., 2016; Ruden et al., 2017; Agerstrand et al., 2020). In the EU, a series of regulations (i.e., European Commission, 2006; 2009; 2012) now mandate the consideration of all relevant literature (including peer-reviewed and non-standard tests) in a 'weight of evidence' approach (Ruden et al., 2017).

Growing pressure from animal rights groups and campaigners to reduce the use of animals in toxicity testing, has focused scientific efforts on the development of new and alternative approach methodologies (NAM's) (e.g., *in silico, in chemico* and *in vitro* methods, Table 1) (see Schmeisser et al., 2023 for discussion; ECHA, 2017; Herrmann et al., 2019; Olker et al., 2022). Validating the use and reliability of NAM's data has, and continues to be a major challenge for regulators, with most test methods requiring biologically relevant *in vivo* toxicology studies for verification (see Parish et al 2020; Olker et al., 2022). Furthermore, there is a perception that NAM's data are 'less safe', introducing a greater level of uncertainty if used as a standalone method (Berrgren and Worth, 2023). As a consequence, additional or higher tier animal testing is often required to meet the needs of regulatory science, making the process more costly (both financially and in the use of animals) and less efficient (Berrgren and Worth, 2023). Thus, the identification, curation and evaluation of all existing empirical data on the toxicity of chemical substances - from both novel and traditional endpoints - can provide accessible (and ecologically relevant data), to aid the development, evaluation and adoption of new approach methodologies (Olker et al., 2022; Schmeiser et al., 2023).

Similar to the development of evidence-based methods in health (e.g. Campbell Collaboration, 2017) and the environment (e.g., Collaboration for Environmental Evidence, 2021), 'evidence-based toxicology' (EBT) has emerged as a method to inform regulatory decision making (McKinnon et al., 2015; Haddaway et al., 2016; James et al., 2016; Wolffe et al., 2019). Through the adoption of systematic approaches, and establishment of transparent methods for the evaluation of existing toxicity data, the evidence that can be utilised by risk assessors has evolved significantly (Thayer et al., 2014; Guigeno & Fernie, 2017; Moermond et al., 2017; Rudén et al., 2017; Wikoff & Miller, 2018; Agerstrand et al., 2020; Ford et al., 2021; Pelch et al., 2022).

1.3. Systematic Evidence Maps

Systematic Evidence Maps (SEMs) are an underutilised tool for chemical risk assessment, potentially providing a core and reliable approach to EBT (Haddaway, Bernes, Jonsson, & Hedlund, 2016; James et al., 2016; Wolffe et al., 2019; Wikoff et al., 2020). SEMs have the ability to reliably collate and characterise a large body of existing evidence, on a broad research topic, relevant to regulatory decision making, whilst minimising and estimating bias (Wikoff et al., 2020; James et al., 2016). SEMs distil a potentially vast, heterogenous evidence base into a computationally accessible, comparable, and easily updated format, using transparent and reproducible methodology (Haddaway et al., 2016; Wikoff et al., 2020). SEMs often take the form of a searchable database (including references and metadata) alongside a written narrative. Removing barriers typically associated with accessing and synthesising large volumes of data (such as time, accessibility, interpretation, quality assurance; Wolffe et al., 2019), SEMs provide end users with a broad overview of the evidence base, affording fast identification and visualisation of trends, including evidence gaps and clusters (Whaley et al., 2016; Haddaway, Bernes, Jonsson, & Hedlund, 2016; James et al., 2016). As such, SEMs do not attempt to answer any one specific research question, but instead provide users with the means to explore the data and existing evidence according to their own needs. This could be to inform the basis

of future synthesis (i.e., review or meta-analysis), research (i.e., chemical hazard assessment), or regulatory action (i.e., restriction).

To this end, we will use systematic evidence mapping methodology to review existing evidence on the (eco)toxicological effects of flame retardant substances in the environment. Using the Population Exposure Comparator Outcome (PECO) approach to formulating research questions and objectives (Morgan et al., 2018), we will frame the structure of the map and its outputs to systematically explore the association between FR substance exposure and adverse effects. The result will be an online, interactive, interrogable, and user-friendly database (Miake-Lye et al., 2016), published alongside a narrative summary report. A database containing a list of potential FR substances has been curated (Bevington et al., 2022), but to our knowledge, detailed information on the risk or hazard of such substances to organisms in the environment has not yet been collated.

1.4. Stakeholder engagement

An important stage in the development of a SEM protocol is to canvas feedback from expert stakeholders on the research objectives and study design (Haddaway et al., 2017). We identified expert stakeholders (n=63) for engagement in this protocol due to their relevance and/or expertise within the fields of regulatory toxicology, flame retardant development and/or research, and systematic mapping. Effort was made to ensure the stakeholder group was diverse, including level of expertise, institution, gender and ethnicity to encompass a range of global perspectives and representation. We identified stakeholders for engagement in this protocol through one of the following methods; i. Personal Identification of current academic, regulatory or industry expertise on flame retardant substances (i.e. cherry picking); ii. Recommendation or connection through a previously identified stakeholder (i.e. snowballing); iii. Presentation of work related to the toxicology of flame retardant substances at the 33rd European Conference of the Society of Environmental Toxicology and Chemistry; iv. A listed co-author in the 2023 publication ‘A new consensus on reconciling fire safety with environmental and

health impacts of chemical flame retardants' (Page et al., 2023); and v. Backward Citation tracing for Correspondence Author addresses from all cited research in the bibliography of Page et al., 2023. All contact details (i.e., email addresses) were freely available online and compiled into a single excel spreadsheet.

Stakeholders were asked to read and comment on any aspect of the full protocol and to specifically feedback on the research objectives (section 1.5), information sources (section 2.2) and the eligibility criteria listed in table 3. Stakeholders were contacted in mid-August 2023 and asked to provide input. A follow up email was sent four weeks later and a final request was sent on 2nd October with a cut-off date of 9th October (approximately eight weeks after the initial request). Any comments or input sent after this date will be considered for inclusion in the final manuscript following peer review.

1.5. Objectives

Guided by the PECO framework and engagement with expert stakeholders, the primary objectives of this systematic evidence map are to:

1. Identify, organise and group existing evidence of the (eco)toxicological adverse effects (*outcome*) of flame retardant substances (*exposure*), individually or as a mixture, in and/or to the environment (*population*).
2. Present the evidence in a user-friendly, online, interactive, and interrogable database (map) that will connect end-users directly to referenced primary research and publish a narrative report of the systematic map.

This research will also address the following secondary objectives:

1. Identify knowledge gaps and clusters across taxa (*population*), substance (*exposure*), effect (*outcome*) and geographic scale to inform future research needs.

2. Identify emerging substances of concern, to inform future research and/or regulatory action, based on hazard.

The protocol described here, serves to document decisions made *a priori* regarding the conduct of the systematic evidence mapping.

2. Methods & Materials

This protocol has been prepared in accordance with the Reporting Standards for Systematic Evidence Syntheses (ROSES) (Haddaway et al., 2018) and based on guidance from the Collaboration for Environmental Evidence (Collaboration for Environmental Evidence, 2022). The protocol will be registered on PROCEED - the global registration system for titles and protocols of evidence reviews and syntheses, following publication in this journal, to ensure consistency. All tables and figures associated with this protocol, as well as any supplementary material is available on the Open Science Framework: https://osf.io/uszfh/?view_only=128383c0c7e94526ad1190a8d18c83b1 .

2.1. Information sources

Flame retardant substances were included in this evidence map due to their inclusion in a 2022 inventory of flame retardant and organohalogen flame retardant chemical substances ('the inventory') (Bevington et al., 2022). The inventory compiles information from multiple data sources – including regulatory databases, international organisations, and scientific literature – to provide a comprehensive snapshot of FR chemistries (Bevington et al., 2022). Only those considered 'likely' to be a flame retardant through Quantitative Structure-Use Relationship models (QSUR) or expert opinion (see Bevington et al., 2022 for detail) will be accepted for inclusion (n=746).

The peer-reviewed (academic) published literature will be identified by searching Web of Science (Core Collection only), PubMed, and Google Scholar electronic databases using no date or language restrictions. If a search update is needed (i.e., initial searches were completed more than two years prior to completion), the search will be repeated, but limited to studies published since the date of the last search. Several sources should be searched to ensure that as many relevant articles as possible are identified (Avenell et al., 2001; Grindlay et al. 2012).We do not expect a large grey literature outside of academic or government scientific research, therefore a single search of OpenGrey database will be undertaken. Academic theses and dissertation databases will not be searched. The number of studies retrieved from searching each database will be tracked in a spreadsheet and reported in a PRISMA 2020 flow diagram (Page et al., 2021) and its original form alongside the final publication. These will be freely available on the Open Science Framework alongside the final manuscript.

2.2. Search Strategy

From our naive search terms (see supplementary material) we used the Litsearchr package (Grames et al., 2019) to identify important terms through keyword co-occurrence and text mining. Combining the most strongly ranked terms from Litsearchr with our naive search, a detailed search string has been designed to reflect the PECO framework (search string #1). Population terms detailed aspects of the study subject (environment, wildlife, organism), exposure terms (e.g., chemical substance) included general terms for flame retardant substances, specific flame-retardant classes (e.g., brominated flame retardants) and abbreviations (e.g., BFRs, CFRs). Terms related to outcome (e.g., adverse effect) included common phrases identified using litsearchr (e.g., adverse effect) in addition to broad terms such as ‘hazard’ and ‘toxic’. No search terms included the comparator (e.g., control group) as it is unlikely that these will appear in bibliometric records. There will be no search limitation (i.e., addition of exclusion criteria in search string) on substance or outcome to prevent missing evidence/data points. Only population will have exclusion criteria (i.e., NOT human). All searches will be conducted

without limit in publication year or language. The search string for exploring the grey literature was simplified due to the structure of these search engines and the broader writing style (search string #2).

Additional, separate search strings were developed to include the chemical abstract service registry number (CASRN) (search string #3) and preferred name (search string #4) of all likely FR substances listed in the inventory, in addition to a list of halogenated organic FR substances and their synonyms summarised in Bergmann et al., 2012 (search string #5). Full search strings to be used in both the scientific and grey literature can be found in the supplementary material. Any search updates or modifications to the protocol will be noted as amendments to the registered protocol.

It is important to note that no search string is exhaustive, comprehensive, or completely free of bias however, through combining our naive (PECO based) search terms, with the quasi-automatic search strategy of the Litsearchr package (Grames et al., 2019) we deem our strategy to be sufficiently robust to identify the body of evidence relevant to our research objectives.

2.3. Eligibility Criteria

To address the research objectives set out in section 1.5, we have developed a PECO (Population, Exposure, Comparator, Outcome) framework, in line with the approach commonly used to formulate good questions to explore the association between environmental exposure and health outcomes (Morgan et al., 2018). Study eligibility (i.e., inclusion and exclusion criteria) is based on the PECO framework provided in table 2. More detailed information on the individual elements of the PECO framework as well as each element's specific inclusion and exclusion criteria can be found in Table 3.

Studies must contain primary research investigating the link between one or more of the FR substances listed in the inventory (Bevington et al., 2022) and study an ecologically relevant adverse effect (see table 1 for definition), at the level of the whole organism, to be included in this systematic

evidence map. We will exclude articles that do not study an ecologically relevant adverse effect of a substance (listed in the inventory) at the title and abstract level. Mechanistic effects (as defined in table 1) will only be noted if the study reports a whole organism response (i.e., ecologically relevant adverse effect). Alongside common 'apical' endpoints (as defined in table 1), we will include studies assessing fitness related traits such as developmental physiology, and behaviour (table 3). Agerstrand et al (2020) suggest the inclusion of behavioural studies could increase the ecological relevance of environmental risk assessment (Agerstrand et al., 2020, but see, Gerhardt, 2007; Pyle and Ford, 2017; Saaristo et al., 2018) because, research suggests behavioural studies could act as an early warning signal for lethal/chronic toxicity, requiring a smaller exposure for adverse effects (Guigeno & Fernie, 2017; Agerstrand et al., 2020; Ford et al., 2021). Given its well established framework and suite of fitness related endpoints (Agerstrand et al., 2020), we have chosen to include behaviour as an ecologically relevant adverse effect in this protocol.

We will only include data produced in a (controlled) field, semi-field or laboratory (indoor and outdoor) environment, with studies having to be undertaken on a whole organism either *in vivo* or *in situ*. Studies that rely on *in vitro* or modelled *(in silico*) data will not be included in this map. We will exclude studies that investigate any other aspect of the risk of FR substances at the title and abstract level. This includes studies on a substance's release, fate, transport, and environmental monitoring, in addition to a substance's rate of absorption, distribution, metabolism, excretion, and pharmacokinetic or toxicokinetic properties (ADME/PK/TK). We will exclude observations that occur due to the unplanned release of a chemical substance unless a comparator sample (i.e., meeting the BACI (Before-After-Control-Impact) design framework; Green, 1979; Stewart-Oaten and Bence, 2001) is provided. If a systematic review or meta-analysis is identified, we will exclude it. Conference abstracts, presentations, and posters will not be included in this systematic evidence map, because they typically have not been peer reviewed. Effort will be made to include non-English language

papers that meet eligibility criteria if essential information (i.e., population, exposure, environmental/test conditions, outcome) can be identified from the text.

A PRISMA flow diagram will be maintained that describes the number of studies evaluated, included and/or excluded from all bibliographic (and other) databases searched. A list of all excluded articles at full text will be provided alongside the final manuscript, with reasons for exclusion.

2.4. Data Coding and Data Extraction

All search results from the literature will be imported into Mendeley Reference Manager (2023) where duplicate records will be identified using Mendeley's "Find / Remove Duplicates" feature . All records will be given a unique identification number upon import to Mendeley that will be maintained throughout the analysis. Records will be exported directly into Rayyan (Ouzanni et al., 2016), where they will be manually screened at the title and abstract level. Articles will be included at the title and abstract screening stage based on simple eligibility criteria (Table 4). Full text screening will be carried out on all included articles from the title and abstract screening stage on Rayyan. Articles will be excluded if they do not meet all criteria for inclusion (Table 4).

Title and abstract screening will require a single reviewer for inclusion (LJ). As Rayyan adopts a machine learning algorithm for initial title and abstract screening, we do not deem it necessary for a second reviewer to screen for inclusion at this stage (dos Reis et al., 2023). Full text review will be carried out by a single reviewer (LJ) with a secondary independent reviewer for exclusion (KA). Neither reviewer has authored peer-reviewed articles that would be relevant for inclusion in the systematic evidence map. Data extraction and coding will be conducted by a single reviewer (LJ) with a second and third reviewer confirming the completeness, and reliability of extracted and coded data. 10% of all articles screened at full text will be checked for consistency.

Data extraction will be undertaken on all studies included at full-text using Qualtrics Survey Data Software (Qualtrics, Provo, UT). A survey will be designed for use in Qualtrics to ensure consistency in the data extraction process and to aid the identification, documentation and validation (by a secondary reviewer) of excluded articles. Qualtrics Survey Data Software will be used for the sole purpose of (raw) data extraction of articles that are screened at full text. No survey will be sent to stakeholders or authors of screened articles. Only the primary and secondary reviewer (LJ & KA) will use the Qualtrics survey, as well as those checking articles for consistency. Detailed information will be collected from all articles by a single reviewer (LJ) (see supplementary material for detailed extraction criteria and coding strategy). All data will be captured at the study level, with data extraction loops performed when necessary (i.e., multiple populations, multiple exposures, multiple outcomes). Each loop within a single article will become its own data point (i.e., the same article could provide multiple data points) to aid in identifying the underlying structures and association between the data. As this is a systematic evidence map not a systematic review, study quality will not be formally assessed. In the event of missing, unclear, or ambiguous information on what organism (population), substance (exposure) and/or effect (outcome) was studied, we will attempt to contact study authors via email. Any other missing information would be considered minor, and thus would be noted, but not chased.

2.5. Study Mapping and Reporting

Results of this SEM will be summarised narratively and prepared as a manuscript for peer review. It is anticipated that this will speak to our primary (i.e., evidence of adverse effect) and secondary (i.e., presentation of the evidence) objectives. We anticipate discussing the results of the overall literature search across subject streams (population). The evidence will be discussed in terms of the number and type of chemical substances (exposure) studied to date, experimental design, the use of standard and non-standard endpoints, and adverse effects (outcome) measured. We will present the extracted and coded data by generating summary statistics, and graphs using the statistical computing and graphic

software R (R Core Team, 2021). Exploratory data analysis and visualisation of the underlying link structures and association between the data points will be carried out using Gephi (Bastian et al., 2009) - an open source network analysis and visualisation software package. This will help aid the identification of knowledge gaps and clusters across populations, substance type and effects in addition to the geographic range of FR research. Finally, an interactive, interrogable, user-friendly systematic evidence map will be produced and hosted freely online – using Tableau Public. This will allow the viewer to explore the evidence by subject stream (population), chemical substance (exposure) and effect (outcome). For example, users will easily be able to explore the evidence that exists for a specific substance by selecting a substance of interest to see only the evidence that exists on that specific chemical substance. Users will be able to identify a publication and find more information (i.e., the abstract, experimental design), link directly to its bibliographic location , as well as search and export data of interest. A link to the freely available systematic evidence map will be included in the publication.

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Availability of data and materials statement

Supplementary information and material associated with this protocol can be found: https://osf.io/uszfh/?view_only=128383c0c7e94526ad1190a8d18c83b1

Disclosure statement

The authors report there are no competing interests to declare.

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