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RESEARCH ARTICLE

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Evidence on the effects of flame retardant substances at ecologically relevant endpoints: a systematic map protocol

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ABSTRACT

Background: Flame retardant (FR) substances are known to pose a risk to environmental health. A list of potential FR substances has been developed; however, detailed information on the risk, or hazard of such substances to the environment, specifically ecologically relevant endpoints involving animals, plants, bacteria and fungi, has not yet been collated.

Methods: The main objective of this study is to identify, organise and group existing primary evidence of the ecologically relevant (eco)toxicological effects of FR substances to the environment.

Search Strategy: We will search several databases across two electronic academic indexes (Scopus and Web of Science [All Collections]).

Eligibility criteria: Eligible studies must contain primary research investigating the risk (or hazard) of one or more included FR substances and study an ecologically relevant effect in any non-human animal, plant, bacteria and/or fungi. Ecologically relevant effects include impacts on growth, development, survival, reproduction and behaviour.

Screening & extraction: Articles will be screened at title and abstract, before a full-text review. All articles will be screened by a single reviewer, with a second reviewer assessing articles for consistency. Data extraction will be performed on all articles included at full text, with articles that do not meet the eligibility criteria excluded. All articles excluded at full text will be confirmed by a second reviewer.

Study mapping & reporting: Results will be published in a narrative summary and visualised in a publicly available, user-friendly, interactive and interrogable evidence map.

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Chemical; ecology; hazard; regulation; toxicology

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 (IPBES 2019; Van Dijk et al. 2021; Wijgerde et al. 2020; Woodcock et al. 2017) with clear implication for planetary and societal wellbeing (Johnson et al. 2020; Rockstrom et al., 2009; Steffen et al. 2015). 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, Zhu, 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, Kolibaba, and Grunlan 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

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risk of fire. Widely used in articles such as furniture, textiles, plastic, electronics and building materials, FR substances are increasingly common components of most consumer products (Bajard et al., 2019; Page et al. 2023). This is especially true in the UK and Ireland where strict fire standards see significant 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 (Blum et al. 2019; Doherty et al. 2019; Hendriks and Westerink 2015; Sun et al. 2020; Xiong et al. 2019). This has resulted in greater understanding on the risk of FR substances – particularly in relation to human health (Lyche et al. 2015; Melymuk and Bajard 2022; Wikoff and Birnbaum 2011). Some FR substances are known, or considered to be hazardous to health, with pathways of 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 detected in the natural environment (aquatic and terrestrial systems) (Ekpe et al. 2020; Segev, Kushmaro, and Brenner 2009; Zuiderveen, Slootweg, and de Boer 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; Persson, Wang, and Hagberg 2018; Yao, Yang, and Li 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 (Environmental 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. 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.

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 (Sun et al. 2022; Wang, Zhu, et al. 2020). Restrictions of some FR substances have driven the market to substitute PBT compounds with compounds that are not always without risk (Bajard et al. 2019). 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 and the environment (Blum et al. 2019; Greaves and Letcher 2017; 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 including reproductive and developmental effects (EAC 2019).

1.2. Environmental Risk Assessment

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). 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 (Ford et al. 2021; Ruden et al. 2017). Such guidelines set out the regulatory accepted endpoints, experimental (study) design and information criteria. Standard (eco)toxicity 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 do not assess all aspects of environmental risk (Saaristo et al. 2018). Ecotoxicological studies (i.e., those that study the effects of a substance to a biological organism), including laboratory, mesocosm and field 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 (Agerstrand et al., 2020; Beronius et al. 2014; Rohr, Salice, and Nisbet 2016; Ruden et al., 2017). 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). However, in practice, academic (i.e. peer reviewed) ecotoxicity and toxicity studies are rarely used in regulatory decision making (Agerstrand et al., 2020). Possible reasons for the low use and inclusion of peer-reviewed literature include demands on resource to search, and maintain abreast of the academic literature, academics performing (eco)toxicity tests using non-standard endpoints, designs and/or test species, failure to align with standardised guidelines (e.g. OECD test guidelines) and/or the historical inaccessibility of data (Agerstrand et al., 2020).

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

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 et al. 2016; James, Randall, and Haddaway 2016; Wikoff et al. 2020; Wolffe et al. 2019). 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 (James, Randall, and Haddaway 2016; Wikoff et al. 2020). 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 (Haddaway et al. 2016; James, Randall, and Haddaway 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 ecologically relevant effects (see table 1) of flame retardant substances in the environment. The result will be an online, interactive, interrogable, and user-friendly

database (i.e., map) (Miake-Lye et al. 2016), published alongside a narrative summary report. Previous efforts to map the evidence of the (eco)toxicological risk of harmful chemical substances have focused on the impact of pharmaceuticals (Martin et al. 2021, protocol only) and per- and polyfluoroalkyl substances (i.e, PFAS) (Carlson et al. 2022; Pelch et al. 2019, 2022). There are no systematic map and/or review protocols exploring the risk and/or hazard of FR substances registered on PROCEED (as of April 2024), with no previous and/or ongoing maps identified in the peer-reviewed literature. Previous efforts to review existing literature on the effect of FR substances have focused on the toxicity and/or ecotoxicity of known and/or legacy FR substances (i.e., PBDEs, BFRs) to both humans and the environment (Costa et al. 2008; Darnerud et al. 2001; Feiteiro, Mariana and Cairrao, 2021; Kim et al. 2014; Rahman et al. 2001). Over the last decade researchers have begun to explore and/or include the effects of novel and/or replacement FR substances (i.e., Novel BFRs, OPFRs, OPEs), however these have primarily been focused on specific groups of substances (i.e., OPEs, NBRFs; Greaves and Letcher 2017; Dong et al. 2021), effects (i.e., reproduction, neurotoxicity; Hendriks and Westerink, 2015; Zhao et al. 2022), organisms (i.e., birds, humans; Guigueno and Fernie 2017; Hales and Robaire 2020) and/or environments (i.e., marine, aquatic; Lee and Kim 2015; Hou et al. 2021). 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.

Table 1. Glossary of terms as defined by the authors for use in this protocol.

Term	Definition
Ecologically relevant effect	An effect and/or outcome involving an organism, population and/or communities ability to survive, develop, grow, behave and/or reproduce.
Endpoint	A statistical test to quantify an adverse effect and/or outcome of a hazard to an organism, population or community.
Exposure	The concentration, duration, and frequency of which a substance comes into contact with an organism, population or community.
Hazard	A substance or combination of substances (i.e., mixture) which has the potential to cause an adverse effect to living organisms or the environment.
In vivo	A research method which involves testing individual live organisms or populations of live organisms within an indoor or outdoor laboratory setting, and/or in the field.
In vitro	A research method which involves testing cells or tissues extracted from living organisms within a laboratory setting.
In silico	A research theoretical method, particularly involving computer models, to predict the likely toxicological, or other, effects of substances on an organism, population or community.
In situ	A research method which involves experiments and/or testing conducted within the actual site of the reaction mixture or system.
Response	A response at the community, population, individual and/or sub-individual level to an exposure substance, resulting in an ecologically relevant effect.
Organism	A living thing such as an animal, plant, bacteria and fungi.
Toxic	An ability to cause harm (i.e., an adverse effect) to living organisms or the environment.

1.4. Objectives

The PECO (Population, Exposure, Comparator, Outcome) framework is an approach commonly used to formulate questions which explore the association between environmental exposure and health outcomes (Morgan et al. 2018). Guided by engagement with expert stakeholders (see Section 2.1) and the development of our own PECO framework (Table 2) the primary objectives of this systematic evidence map are to:

1. Identify, organise and group existing primary evidence of the ecologically relevant 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.

Table 2. PECO framework developed for this protocol – Population, Exposure, Comparator, Outcome.

Element of PECO framework	Description of the PECO element developed for this protocol
Population	Any non-human animal, plant, bacteria and/or fungi community, population and/or whole organism, exposed to a substance in any environmental compartment (aquatic – freshwater, marine, brackish, estuarine; terrestrial – soil, non soil; air).
Exposure	Exposure of any kind (i.e. route, duration, magnitude) to one or more 'likely' flame retardant substances – individually or as a mixture – listed in Bevington et al. 2022 inventory (see supplementary material).
Comparator	Any non-human animal, plant, bacteria and/or fungi community, population and/or whole organism which is the same as the study population, exposed to no (i.e. a control group) or less exposure substance.
Outcome	Ecologically relevant effect (i.e., survival, development, growth, reproduction, behaviour), response and/or endpoint that can be quantitatively measured to evaluate the ecotoxicological effect of an exposure substance on a community, population and/or individual.

3. Identify knowledge gaps and clusters across taxa (*population*), substance (*exposure*), and effect (*outcome*) to inform future research needs and/or analysis.

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; see supplemental material 2.1 for detailed reporting criteria) 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 and listed in the appendix.

2.1. Engagement with Technical Experts

An important stage in the development of a SEM protocol is to canvas feedback from technical experts on the research objectives and study design (Haddaway et al. 2017). We identified technical experts (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 expert group was diverse, including level of expertise, institution, gender and ethnicity to encompass a range of global perspectives and representation. We identified experts 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 expert (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 email addresses and organisational affiliations were freely available online and compiled into a single excel spreadsheet.

Technical experts were asked to read and comment on any aspect of the full protocol (see supplemental material 2.2) and to specifically give feedback on the research objectives (section 1.4), information sources (section 2.2) and the eligibility criteria listed in table 3. Experts 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). Ten technical experts provided written and/or verbal feedback on the full protocol by the 9th October 2023, with no further comments or input sent after this date. Sixteen experts responded to state that they would not be able to comment on the protocol, whilst the remaining experts (n = 37) did not respond to any request for input. 70% of the experts that provided feedback were based in academic institutions across Europe, the UK, Japan and Canada (n = 7) with three experts based in the UK Government. Feedback provided by the technical experts was invaluable for the development of the protocol. Feedback primarily focused on scope of the research objectives, clarity of definitions and terminology used throughout the protocol, and specificity of the eligibility criteria for inclusion and exclusion of the PECO framework to ensure the research objectives are met. All experts that provided feedback on the protocol will be made aware of its publication, following peer-review in this journal, and will be informed of major developments (i.e., publication of the database, map and/or narrative summary) as the work progresses.

2.2. 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 substances considered 'likely' to be a flame retardant through Quantitative Structure-Use Relationship models (QSUR, as performed by Bevington et al. 2022) or expert opinion (see Bevington et al. 2022 for detail) will be included. We will exclude any substance (and their related isomers,

Table 3. Eligibility criteria for inclusion and exclusion of the PECO framework.

Element of PECO framework	Eligibility Criteria for inclusion and exclusion
Population: Any non-human animal, plant, bacteria and/or fungi community, population and/or whole organism, exposed to a substance in any environmental compartment (aquatic – freshwater, marine, brackish, estuarine; terrestrial – soil, non soil; air).	***Included:*** Experimental and/or observational studies that occur *in vivo* (whole organism) or *in situ* (natural environment) in any non-human animal, plant, bacteria and/or fungi species, in a field, semi-field, indoor or outdoor laboratory setting. Organisms must be verifiable against standard taxonomic sources. Only organisms classified in the animal (*Animalia*), plant (*Plantae*), bacteria (*Monera*) and fungi (*Fungi*) kingdoms will be included. There will be no limitation placed on species and/or environmental compartments. ***Excluded:*** *In vitro*, *in silico*, QSAR (quantitative structure activity relationships) and read-across analysis studies will be excluded. Observations and/or studies performed on humans, cells, organs, gametes, embryos and/or yeast will also be excluded.
Exposure: Exposure of any kind (i.e. route, duration, magnitude) to one or more 'likely' flame retardant substances – individually or as a mixture – listed in Bevington et al. 2022 inventory.	***Included:*** Chemical substance – individually or as a mixture – listed by its preferred or chemical name and/or unique chemical abstract service registry number (CASRN) as listed in the Bevington et al. 2022 inventory (see supplementary material). Only substances considered 'likely' to be a flame retardant through Quantitative Structure-Use Relationship (QSUR) models and expert opinion (see Bevington et al. 2022 for detail) and substances (and their isomers) not listed under Annex A of the Stockholm Convention will be included (n = 702). Exposure of any kind, including (but not limited to that) via food (ingestion), water, injection or implant, dermal (skin), inhalation (air) and environmental and/or treatment media will be included. Inhalation studies will only be included if this is the primary route of environmental exposure. Indirect exposure studies including the pre-natal (i.e. in utero) and lactational periods will also be included. There will be no limitation on the route, duration and/or magnitude (level) of exposure. ***Excluded:*** Likely flame retardant substances included in the inventory that are not predicted to be a flame retardant substance through Quantitative Structure-Use Relationship (QSUR) models or expert opinion (see Bevington et al. 2022 for detail) will be excluded (n = 51). Verifiable Chemical Abstracts Service (CAS) number chemical substance not listed by its preferred or chemical name and/or unique chemical identification number (CAS number) as listed in Bevington et al. 2022 inventory. Inhalation studies are excluded unless this is the primary route of environmental exposure.
Comparator: Any non-human animal, plant, bacteria and/or fungi community, population and/or whole organism which is the same as the study population, exposed to no (i.e. a control group) or less exposure substance.	***Included:*** Experimental and/or observational studies that occur within a field, semi-field, indoor or outdoor laboratory setting that use a control group (i.e., no exposure or lower exposure to that which sees an effect). A control could be a baseline and/or comparator measurement with either no or less exposure (of the same substance) across spatial and/or temporal scale. All included studies should have some form of control performance criteria to demonstrate that measured effects are a direct result of exposure to a relevant substance instead of being attributed to poor husbandry and or other confounding factors. We will include any study with a control. This may include but not be limited to, studies that measure exposure and/or dosage via biomonitoring (i.e., detection in body fluid and/or tissue) or detection in the environment and those that meet the BACI (Before/After – Control/Impact) design framework (Green 1979; Stewart-Oaten and Bence 2001). No limit will be placed on the form of control and/or comparator. ***Excluded:*** Experimental and/or observational studies that occur within a field, semi-field, indoor or outdoor laboratory setting that do not use a control group (i.e., no exposure or lower exposure to that which sees an effect) will be excluded. All studies should have some form of control performance criteria to demonstrate that measured effects are a direct result of exposure to a relevant substance instead of being attributed to poor husbandry and or other confounding factors. Any study that does not have a control and/or comparator will be excluded.
Outcome: Ecologically relevant effect (i.e., survival, development, growth, reproduction, behaviour), response and/or endpoint that can be quantitatively measured to evaluate the ecotoxicological effect of an exposure substance on a community, population and/or individual.	***Included:*** Studies must investigate an ecologically relevant effect (i.e., survival, development, growth, reproduction and/or behaviour) to be included. Studies do not have to report an effect to be included (i.e., no effect responses will be included), so long as the study investigates an ecologically relevant effect. Effects must occur at the community, population and/or individual level to be included with a quantitatively measured response and/or endpoint reported. ***Excluded:*** Studies that investigate and/or report an ecologically relevant effect (i.e., survival, development, growth, reproduction and/or behaviour) through: *in silico*, modelling and/or computational analysis; genetic, pharmacokinetic (i.e., Absorption, Distribution, Metabolism, Excretion) and/or toxicokinetic analysis; and QSAR (quantitative structure activity relationships) or read across will be excluded. Studies that investigate a substance's fate and/or transport, route of exposure, persistence, mobility or capacity to bioaccumulate will be excluded. Review's and/or meta-analyses will be excluded, as well studies that report estimated and/or predicted data. Mechanistic responses (i.e., at the organ, cell, tissue, molecular level) will not be included.

n = 44) that have been listed in Annex A of the Stockholm Convention (i.e., for elimination). This is primarily due to the size and scope of the inventory, with a high number of articles expected to focus on one or more of these substances. Whilst the persistence of substances listed under the Stockholm Convention could mean hazard to the environment is still possible, we deem understanding on the risk and hazard of these substances is currently sufficient. The final inventory of all included FR substances (n = 702) can be found in supplemental material 2.3.

We intend to search several sources to ensure that as many relevant articles as possible are identified (Avenell, Handoll, and Grant 2001; Grindlay, Brennan, and Dean 2012). The peer-reviewed (academic) published literature will be identified by searching Scopus and Web of Science electronic indexes, using no date or language restrictions. Both indexes will be searched using title and abstract fields. These indexes have been chosen due to the interdisciplinary nature of ecotoxicology and the ability to perform general, and/or advanced search queries. Alongside its core collection,

all databases subscribed to by the University of Sheffield (as of April 2024) will be searched in Web of Science. This is to ensure a broad coverage of the literature across both general and specific databases. A full list of databases included in the University of Sheffield Web of Science subscription are listed in supplemental material 2.4. Use of the University of Sheffield Web of Science subscription allows for inclusion of more subject specific databases including those that focus on biology (i.e. BIOSIS), plant and life science (i.e., MEDLINE®) and biodiversity (i.e., Zoological Record). Grey literature, academic theses and dissertation databases will not be searched. 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. 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) alongside the final publication. Both the spreadsheet and PRISMA 2020 flow diagram will be freely available on the Open Science Framework alongside the final manuscript.

2.3. Search Strategy

In collaboration with a librarian specialist in designing search strategies for evidence synthesis, we have developed a search string (see supplemental material 2.4) to reflect our PECO framework (search string #1). Population terms detailed aspects of the study subject (environment, organism) and species group (animal, plant, bacteria, fungi). Exposure terms (e.g. FR substance) included general terms for flame (or fire) retardant substances. Terms related to outcome (e.g. effect) included terms for ecologically relevant effects (i.e., behaviour, survival, reproduction, growth, development) and broad terms such as 'ecotox' and 'tox'. Additional search strings have been designed to include the 'preferred' chemical name (search string #2 to #12), and the unique chemical abstract service registry number (CASRN) (search string #14 to #20) of each included FR substance, as listed in the inventory. Due to the variation in syntax between electronic indexes (i.e., Web of Science, Scopus), additional search strings have been designed for use in Scopus (search string #22 to #29). No search terms related to comparator (e.g., control group) were included as it is unlikely that these will appear in bibliometric records. There will be no search limitation (i.e., NOT terms) on exposure and/or outcome to prevent missing data points. Whilst human data will not be included in this evidence map, we will not put any limitations on the population search terms to prevent missing data points. All searches will be conducted without limit in publication year or language. Full search strings to be used in both Scopus and the Web of Science can be found in the supplemental material 2.4. 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. To ensure our search strategy is sufficiently robust to identify the body of evidence, we undertook an exercise of validation using a subset of articles (n = 34) deemed relevant to our research objectives (see supplementary material 2.5 for detail). These articles were identified due to their inclusion in articles reviewing the evidence of ecologically relevant toxic and ecotoxic effects of FR substances to a range of organisms, and include both well known and obscure FR substances. Comparing the list of relevant articles to the articles identified using search string #1 in Web of Science (All Collections), we achieved a 94.1% retrieval rate. This increased to 97.1% when searching Scopus for missed articles, therefore we deem our strategy to be sufficiently robust to identify the body of evidence relevant to our research objectives.

2.4. Eligibility Criteria

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 – individually or as a mixture – listed in the inventory (Bevington et al. 2022) and study an ecologically relevant effect, at the level of the whole organism, population and/or community, to be included in this systematic evidence map (see table 4 for eligibility criteria for inclusion and exclusion). We will exclude articles that do not study an ecologically relevant effect of a substance (listed in the inventory) at the title and abstract level. Alongside standard regulatory endpoints (i.e., survival, growth, development), we will include studies assessing fitness related traits such as developmental physiology, reproduction 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

Table 4. Decision tree criteria for inclusion and exclusion of articles at the screening stage.

Element of PECO framework	Decision tree criteria	Screening stage
Not applicable	Is the article primary research (i.e., not literature review, thesis, conference proceedings etc) reported in an electronic bibliographic index?	*Title and Abstract*
Population	Does the article use a valid test organism (i.e., whole organism – non human animal, plant, bacteria and/or fungi) as the study subject?	*Title and Abstract & Full text*
Exposure	Does the article test a study subject to at least one flame retardant substance – individually or as a mixture – listed in the inventory (Bevington et al. 2022)?	*Title and Abstract & Full text*
Comparator	Does the article have a control group or expose the study subject to an exposure lower than that being studied?	*Full text*
Outcome	Does the article study an ecologically relevant effect (i.e., development, survival, growth, reproduction and/or behaviour) (at the level of the whole organism) on a given individual, population or community?	*Title and Abstract & Full text*

behavioural studies could act as an early warning signal for lethal and/or chronic toxicity, requiring a smaller exposure for adverse effects (Guigueno and 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 effect in this protocol.

We will only include data produced in a 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 include both experimental and observational studies so long as they meet the criteria for control (i.e., no, different and/or less exposure of the same substance, across spatial and/or temporal scale, than that which sees an effect). This includes observational studies in wildlife that study the effect of a measured concentration of a FR substance through biomonitoring (i.e., detection in body fluid and/or tissue) or detection in the environment, and those that meet the BACI (Before-After-Control-Impact) design framework; Green 1979; Stewart-Oaten and Bence 2001). We will exclude observations that occur due to the unplanned release of a chemical substance unless a comparator sample is provided. Observational studies that report environmental exposure to an FR substance without studying an ecologically relevant effect will be excluded. 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.

2.5. Study Selection

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 (Ouzzani et al. 2016), an AI and machine learning supported web tool designed to help researchers undertake systematic reviews, where they will be manually screened at the title and abstract level. Articles will be excluded at the title and abstract level if they do not meet all criteria for inclusion (Table 4). Rayyan's machine learning algorithm uses the reviewers relevance labelling and use of key words, alongside text mining to predict which of the titles are relevant for inclusion (Ouzzani et al. 2016). In a 2023 study on the usefulness of machine learning softwares to screen articles, Rayyan was identified to be the most sensitive software when compared to manual (i.e., human) review (dos Reis et al. 2023). Rayyan's machine learning (i.e., assisted screening) correctly identified 99% of the true negatives (i.e., articles for exclusion) and 78% of the true positives (i.e., articles for inclusion) (dos Reis et al. 2023). Another study found Rayyan to be a reliable tool for excluding ineligible records, whilst less reliable

for finding eligible records (Valizadeh et al. 2022). 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 exclusion at this stage (dos Reis et al. 2023).

All articles imported from Mendeley will be screened at the level of title and abstract by a single reviewer (LJ). A second reviewer (KA) will assess 10% of all articles screened at the title and abstract level for consistency. To ensure consistency, a single IRR (inter-rater reliability) test (Belur et al. 2021; McHugh 2012), will be carried out between reviewers. 10% of all articles (both included and excluded) at the level of title and abstract will be assessed for the IRR, with both the percentage agreement and Cohen's Kappa (k) statistic of agreement reported (Cohen 1960). A Cohen Kappa test statistic (k) of 0.91-1 (i.e., near perfect agreement) will be deemed acceptable for reviewer agreement. Discrepant screening results and disagreements will be resolved via discussion. If agreement cannot be reached, a third, independent opinion, (i.e., a member of the stakeholder panel) will be sought.

2.6. Data Coding and Extraction

Data extraction will be carried out on all articles included at full text by a single reviewer (LJ). Extraction of the raw data will be undertaken on all studies included at full-text using a custom designed spreadsheet in Microsoft Excel (see supplemental material 2.6 for the extraction database). The spreadsheet has been designed to ensure consistency in the data extraction process and to aid the identification, documentation and validation (by a second reviewer) of excluded articles. Detailed information will be collected from all included articles – alongside the article citation, this includes detailed information about the study population (i.e., organism classification, species name, sex, life stage etc), substance (i.e., exposure substance, CASRN, purity % etc), experimental design (i.e., exposure, control, test habitat, number of replicates etc) and outcome (i.e., ecologically relevant effect, response, endpoint) as well as information on the availability of data, and conflict of interest and/or funding statements. Extraction of the raw data is an iterative process, hence, there is no way of knowing the full array of expected data points, ahead of screening. Where possible, the extraction spreadsheet has been designed with known and/or expected data points (i.e., ecologically relevant effects, endpoints), whilst built in functions such as 'Lookup & Reference' for free text values, and/or additional validation rules will be continually developed as articles are screened. This will ensure consistency in terminology and reduce reviewer error. A detailed extraction template used to pilot this protocol can be found in the supplementary material.

Data will be extracted and stored in a single, flat, long-form, datatable (i.e., 2-dimensional array of rows and columns; Wolffe et al. 2020). All data will be captured at the study level, with data extraction loops (i.e., expanding rows) performed when necessary (i.e., multiple populations, multiple exposures, multiple outcomes) to ensure each population-exposure-outcome triad is its own record (i.e., row entry). This is to preserve data relationships and maintain referential integrity, ensuring the underlying structures and association between the data is retained (Wolffe et al. 2020). 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 once via email. Any other missing information would be considered minor, and thus would be noted, but not chased. If, after contacting the author, the necessary information (i.e., population, exposure, comparator, outcome) cannot be identified, we will exclude the article and cease extraction, noting missing information as reason for exclusion.

To ensure consistency, a second reviewer (KA) will assess 10% of all articles at the level of full text. These will be selected at random with the second reviewer noting their agreement and/or disagreement with an article's inclusion or exclusion in the 'Review' section of the extraction spreadsheet. A second reviewer (KA) will assess 25% of all included articles to confirm the completeness, and reliability of extracted data. Any disagreement or discrepancy in the extracted data will be noted in the 'Review' section of the extraction spreadsheet and discussed in the final report. The second reviewer (KA) will also assess reasons for exclusion (i.e., eligibility criteria) on all (100%) articles excluded at full text. Discrepant screening results and disagreements will be resolved via discussion, with a third, independent opinion sought from a member of the stakeholder panel if agreement cannot be reached. An article must be excluded by all reviewers for full-text exclusion.

Prior to extraction, reviewers will trial the screening and extraction process from title and abstract to full text to ensure clarity and agreement. Any discrepancies and/or disagreements in the extraction process and/or criteria for inclusion and/or exclusion will be resolved via discussion, ahead of extraction. Following extraction, raw data will be cleaned (i.e. remove irrelevant numbers and/or symbols), coded and input to the

final FR-ecotox database (see supplemental material 2.7 for an example of the final database). Raw data will be coded by the primary reviewer (LJ) with support from an additional, employed researcher. The final codebook (see supplemental material 2.8 for an example codebook), will be amended, discussed and agreed by all reviewers ahead of use in the final database. No reviewer has authored peer-reviewed articles that would be relevant for inclusion in the systematic evidence map.

2.7. 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 first (i.e., evidence of ecologically relevant effect) and second (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 ecologically relevant effect (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, Heymann, and Jacomy 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 effect. In addition, a coded, interrogable database (i.e., evidence map) of the raw extracted data will be produced (see supplementary material for details). 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.

The outputs of our research (i.e. the narrative report and evidence map) will provide accessible, reliable, reproducible, transparent and ecologically relevant data on the ecotoxicological risk of FR substances to the environment. The data could be used to inform future research (i.e., hazard assessment), or synthesis (i.e., meta-analysis), inform regulatory action (i.e., restriction) or aid the development of evidence based methods, with the evidence map acting as a living tool for future researchers and/or interested parties to use the methods outlined in this protocol to systematically update or further the evidence map in coming years.

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Lowenna Jones: Conceptualisation, Methodology, Investigation, Writing – Original Draft, Visualisation, Project administration. **Kathryn Arnold**: Conceptualisation, Validation, Writing – Review & Editing, Supervision. **Oliver Allchin**: Conceptualisation, Methodology. All authors read and approved the final manuscript.

Disclosure Statement

The authors report there are no competing interests to declare.

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Data availability statement

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

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