

1 **A research synthesis of humans, animals, and environmental**
2 **compartments exposed to PFAS: A systematic evidence map and**
3 **bibliometric analysis of secondary literature**

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32 **Type of review**

33 Systematic map of reviews

34 Highlights

- 35 • This systematic evidence map includes 175 systematic reviews addressing human, animal,
36 and environmental PFAS exposure across 35 compounds.
- 37 • Discussion focuses on literature content, reviews' methodological quality, and research
38 biases.
- 39 • A bibliometric analysis unveils reviews' network, independence, and connectedness.
- 40 • Users can access the map's database via an interactive, publicly available web page, which
41 simplifies data navigation and literature reviews.

42 Abstract

43 Background

44 Per- and polyfluoroalkyl substances (PFAS) are a class of widely used anthropogenic chemicals.
45 Concerns regarding their persistence and potential adverse effects have led to multiple secondary
46 research publications. Here, we aim to assess the resulting evidence base in the systematic
47 secondary literature by examining research gaps, evaluating the quality of reviews, and exploring
48 interdisciplinary connections.

49 Methods

50 This study employed a systematic evidence-mapping approach to assess the secondary literature on
51 the biological, environmental, and medical aspects of exposure to 35 fluorinated compounds. The
52 inclusion criteria encompassed systematic reviews published in peer-reviewed journals, pre-prints,
53 and theses. Comprehensive searches across electronic databases and grey literature identified
54 relevant reviews. Data extraction and synthesis involved mapping literature content and narrative
55 descriptions. We employed a modified version of the AMSTAR2 checklist to evaluate the
56 methodological rigour of the reviews. Furthermore, we conducted bibliometric data analysis to
57 uncover patterns and trends in the academic literature. A research protocol for this study was

58 previously pre-registered (osf.io/2tpn8) and published (Vendl et al., Environment International 158
59 (2022) 106973). The database is accessible for free on the online, interactive, and user-friendly
60 systematic evidence map at https://hi-this-is-lorenzo.shinyapps.io/PFAS_SEM_Shiny_App/.

61 Results

62 Our map includes a total of 175 systematic reviews that met the eligibility criteria. Over the years,
63 there has been a steady increase in the annual number of publications, with a notable surge in 2021.
64 The majority of reviews focused on human exposure, whereas environmental and animal-related
65 reviews were fewer and often lacked a rigorous systematic approach to literature search and
66 screening. Review outcomes were predominantly associated with human health, particularly
67 focusing on children's reproductive and developmental health. Animal reviews primarily focused on
68 studies conducted in controlled laboratory settings, and wildlife reviews were characterised by a
69 taxonomic bias. Recent reviews increasingly incorporated quantitative synthesis methodologies. The
70 methodological strengths of the reviews included detailed descriptions of study selection processes
71 and disclosure of potential conflicts of interest. However, weaknesses were observed in the critical
72 lack of detail in reporting methods. A bibliometric analysis showed a bias in research toward certain
73 geographical areas. Some regions were highly productive in terms of research, mainly with authors
74 from within the country, but they had limited and clustered international collaborations.

75 Conclusions

76 In this overview of the available systematic secondary literature, we map literature content, assess
77 reviews' methodological quality, highlight data gaps, and draw research network clusters, aiming to
78 guide future research initiatives, facilitate literature reviews, and enhance opportunities for cross-
79 country collaboration. Furthermore, we discuss how this systematic evidence map and its publicly
80 available database benefit scientists, regulatory agencies, and other stakeholders by providing
81 access to current systematic secondary literature on PFAS exposure.

82 **Keywords**

83 PFOA, PFOS, Ecotoxicology, Systematic review, ROSES, Contamination

84 1. Background

85 1.1. Rationale

86 Per- and polyfluoroalkyl substances (PFAS) are a vast group of anthropogenic organic chemicals
87 manufactured since the 1950s (OECD, 2015a). Although some are regulated or no longer
88 manufactured, many are still produced in significant quantities today (Glüge et al., 2020). They share
89 a common aliphatic carbon composition in which some (prefix: poly-) or all (prefix: per-) of the
90 hydrogen atoms have been substituted with fluorine atoms (ITRC, 2022). PFAS have amphipathic
91 properties and high thermostability, which make them highly resistant to heat, stains, grease, and
92 water. The chemical and physical properties that make PFAS useful in industrial applications also
93 make them problematic in the environment and biological systems. PFAS are highly polar, and their
94 strong carbon-fluoride bonds prevent them from breaking down entirely in the environment
95 (Cordner et al., 2019), earning them the nickname "forever chemicals". Their extensive and
96 unregulated manufacture, use, and disposal in the second half of the 20th century resulted in
97 exposure and bioaccumulation in both humans (Olsen et al., 2017) and wildlife (Routti et al., 2015;
98 Smithwick et al., 2005). Traces of PFAS have been found in even the remotest environments (Miner
99 et al., 2021; Bossi et al., 2015), suggesting their worldwide transport in the air (Shoeib et al., 2006;
100 Taniyasu et al., 2013) and water (Yamashita et al., 2005; Ahrens & Bundschuh, 2014).

101 In both humans and animals, PFAS compounds can attach to proteins (mainly albumin) in the blood
102 (Forsthuber et al., 2020) and tend to bioaccumulate in body tissues (Shi et al., 2018).

103 Biomagnification of highly fluorinated compounds has been observed across diverse wildlife taxa,
104 including birds (Haukås et al., 2007) and aquatic and terrestrial mammals (Boisvert et al., 2019).

105 Emerging research suggests PFAS could impact human development, fertility, hormone regulation,
106 cholesterol, immune function, vaccine efficacy, and cancer risk (Bach et al., 2015; Grandjean et al.,
107 2017; Vélez et al., 2015). The estimated cost of PFAS-associated diseases in the USA amounted to
108 \$5.52 billion (Obsekov et al., 2023). Consequently, the production and disposal of fluorinated

109 compounds, and persistent organic pollutants (POPs) in general, are significant environmental and
110 public health concerns (Wang et al., 2017). Driven by concerns about the potential harmful impacts
111 of certain PFAS on both the environment and human health, various initiatives have been
112 implemented to reduce exposure to long-chain perfluoroalkane sulfonic acids (PFASs) and
113 perfluoroalkyl carboxylic acids (PFCAs) (OECD, 2015b). Several international regulatory frameworks
114 have imposed restrictions on the production and use of long-chain PFCAs and PFASs, with some
115 substances, like perfluorooctane sulfonic acid (PFOS) in 2009, perfluorooctanoic acid (PFOA) in 2019,
116 and perfluorohexane sulfonic acid (PFHxS) in 2022, being added to the restricted list under the
117 Stockholm Convention on Persistent Organic Pollutants (Pinas et al., 2020) and others, including C₁₁–
118 C₁₄ PFCAs, designated as Substances of Very High Concern for Authorization under the European
119 chemicals regulation, REACH (ECHA, 2012; ECHA, 2013; ECHA, 2015).

120 In 2016, the International Agency for Research on Cancer (IARC) categorised PFOA as a Group 2B
121 substance, deeming it potentially carcinogenic to humans (IARC, 2017). At the end of 2023, the IARC
122 finalised their judgment on PFOA and PFOS, which were classified as “carcinogenic to humans”
123 (Group 1) and “possibly carcinogenic to humans” (Group 2B), respectively. The classification
124 specifically pertains to prostate, testicular, liver, and kidney cancers. It is worth noting that while
125 IARC regulation is significant, PFAS are also subject to regulation under various other regulatory
126 frameworks (e.g., legislation such as the Safe Drinking Water Act and the Clean Water Act in the
127 United States, the Stockholm Convention on Persistent Organic Pollutants (POPs), and regulations
128 set by agencies like the Environmental Protection Agency (EPA) and the European Chemicals Agency
129 (ECHA)). In response to the continued need for chemicals with similar properties to these
130 compounds, new PFAS have been developed and produced, including supposedly less-harmful
131 shorter-chain analogues (Guo et al., 2019). Nonetheless, when evaluating toxicokinetics, the toxic
132 potency seems similar between fluorinated alternatives and their predecessors (Gomis et al., 2018;
133 Chappell et al., 2020).

134 The risks posed to human and animal health and the environment emphasise the need for action
135 against persistent chemicals (Usman & Hanna, 2023), as well as increased scientific investigation.
136 Consequently, the increasing concern about the hazardous nature of PFAS has led to a growing
137 number of primary studies (i.e., empirical studies) and secondary studies (e.g., evidence syntheses
138 and reviews). Primary studies are crucial in measuring the extent of PFAS exposure and assessing
139 their toxicological effects, typically through experiments or observational studies. Such studies form
140 the building blocks of knowledge in this field and support formulating hypotheses about PFAS
141 impacts across larger scales. As the volume of primary literature addressing the impacts of PFAS
142 continued to rise, an opportunity emerged to synthesise such a body of literature.

143 Systematic evidence reviews (commonly known as 'systematic reviews') adhere to a rigorous and
144 transparent methodology aimed at addressing a particular research question. This process involves
145 identifying pertinent studies, conducting a thorough evaluation of each study's quality, extracting
146 data, analysing and synthesising the evidence, and reporting findings according to a predetermined
147 protocol. For these reasons, systematic reviews are generally considered the most trustworthy
148 evidence review (Haddaway et al., 2015). Nevertheless, the scope of systematic reviews can vary
149 significantly, meaning that the overarching patterns and emerging evidence reported differ across
150 scales and disciplines. The high heterogeneity of reviews' subjects, methods, terminology, and
151 reliability of conclusions can make it difficult to appreciate the evidence base fully. However, this
152 challenge can be effectively addressed by systematic evidence mapping, a relatively new tool used
153 to summarise the available primary or secondary research.

154 A systematic evidence map (SEM) is an overview of the distribution and abundance of evidence
155 about multifaceted elements of a broad question of policy or management relevance (Wolffe et al.,
156 2019). Consequently, SEMs are a valuable instrument for maximising the efficient utilisation of
157 present research in managing chemical risks (Wolffe et al., 2019). SEMs can enhance transparency,
158 the effectiveness of research, and regulatory efforts by becoming a starting point for further

159 evidence synthesis via targeted systematic reviews and meta-analyses. PFAS-related evidence
160 originates from various disciplines, subject areas, and methodologies, and their dependability varies
161 significantly. The large volume of available systematic secondary literature on PFAS exposure
162 presents an unprecedented opportunity to aggregate and elucidate the current evidence.

163 1.2. Objectives

164 In this study, we assess the systematic secondary evidence base on the exposure of humans,
165 animals, and the environment to 35 PFAS (according to the list of PFAS of emerging importance
166 published by Kirk et al. (2018) and Pelch et al. (2019); Supplementary Table 1). Our approach
167 involves combining systematic evidence mapping with critical appraisal and bibliometric analysis
168 (Fig. 1), commonly called 'research weaving' (Nakagawa et al., 2019). Research weaving is a powerful
169 approach that goes beyond the traditional compilation of evidence and enables the research
170 questions of greater complexity and depth to be addressed. Our main research questions are three-
171 fold:

172 1) What areas of health and environmental research related to PFAS have been systematically
173 synthesised?

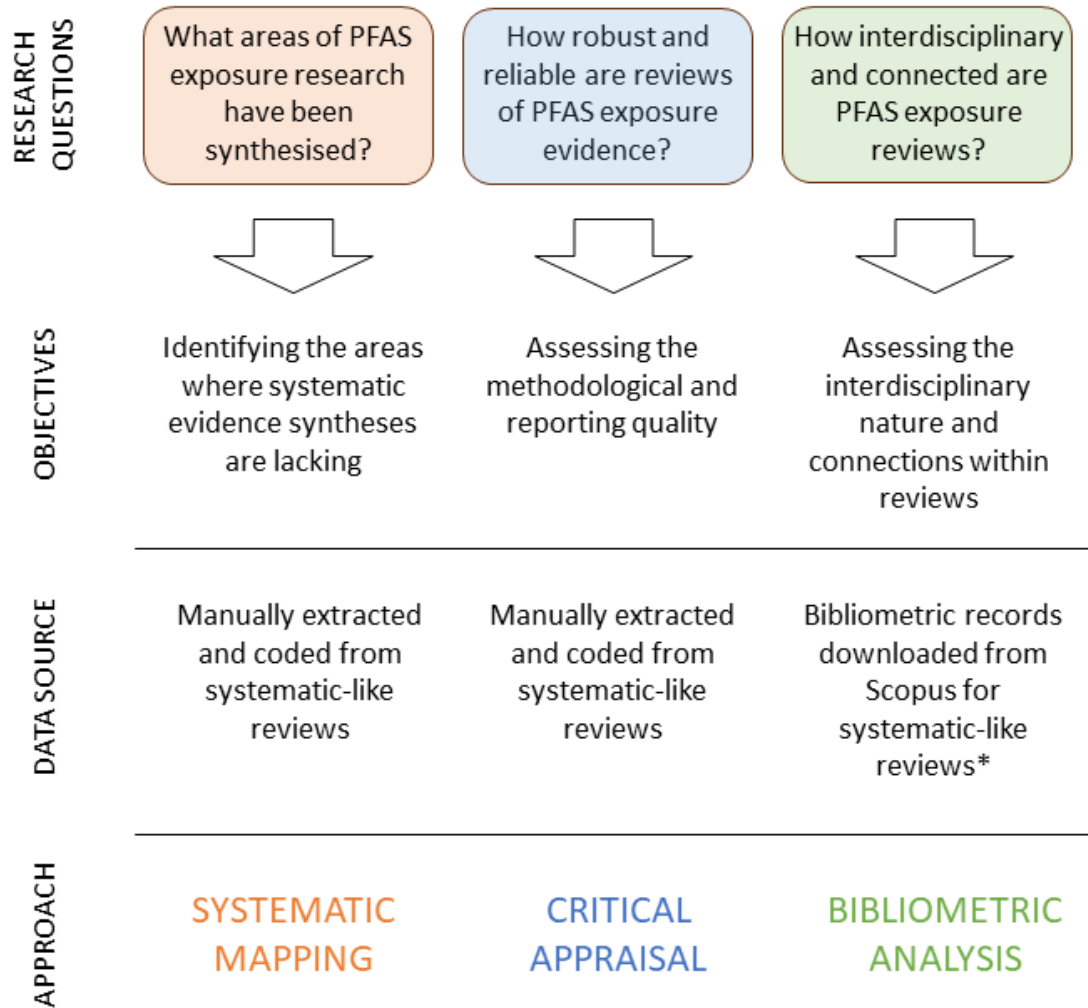
174 (2) How robust and reliable are systematic reviews of PFAS exposure evidence?

175 (3) How interdisciplinary and connected are PFAS-related reviews?

176 To address these questions, we have three primary objectives: (1) Identifying the areas where
177 systematic evidence syntheses are lacking. Specifically, we analyse whether the reviews have an
178 exclusive focus on PFAS or a broader focus on persistent organic pollutants in general, whether they
179 concentrate on one or several types of PFAS, the type of main topic, the main review subject type
180 (e.g., humans, animals, or environmental compartments) and whether the authors focus on single or
181 multiple species. (2) Critical appraisal, where we assess the reporting quality and potential bias of
182 existing reviews. We utilise various pieces of information, including the AMSTAR2 checklist scores

183 (Shea et al., 2017), the type of review funding sources, and the availability of raw data and code. (3)
184 Bibliometric analysis, where we assess the interdisciplinary nature and connections within the PFAS
185 research field by analysing bibliographic data. We look at publication time and place, co-authorships,
186 inter-jurisdictional collaboration, co-word analysis, and patterns in cited references. Lastly,
187 bibliometric coupling analysis of the references cited in the included secondary studies provides
188 information on their connectedness by primary papers. Addressing these objectives highlights
189 research patterns across different disciplines, as well as the specific questions and topics explored
190 and the overall reliability of the research.

Systematic evidence map's workflow



*We also conducted a supplementary bibliometric analysis on all types of reviews.

191

192 *Fig. 1. Workflow illustrating the main research questions, objectives, data sources, and analysis approaches.*

193 2. Methods

194 This systematic evidence map (SEM) adopts a systematic data analysis approach, comprising five
 195 fundamental procedural steps. First, we registered and published the project plan to ensure
 196 transparency and facilitate replication. Second, we conducted an extensive literature search in
 197 multiple databases to collate available systematic reviews on the research topic. The third step
 198 involved extracting and mapping pre-registered data items from the literature, followed by an
 199 analysis of the results. The fourth step entailed the development of a browsable and interactive

200 version of the database, aimed at enhancing its usability and navigational ease. Finally, we discussed
201 the implications of our findings for policy-making and scientific research, thereby advancing the
202 current state of knowledge on the research topic.

203 2.1. Protocol and reporting

204 Our SEM adhered to the highest standards of reporting guidelines for systematic evidence syntheses
205 in environmental research. Specifically, we followed the *RepOrting standards for Systematic*
206 *Evidence Syntheses* (ROSES) in environmental research, as per the adapted version for mapping
207 secondary literature (Haddaway et al., 2018) (Supplementary Table 1). We registered a pre-protocol
208 plan on the Open Science Framework and made it publicly accessible through a provided link
209 (osf.io/2tqn8). Furthermore, we published an *a priori* plan for our methods as a protocol to ensure
210 transparency and consistency in our methodology (see Vendl et al., 2022). These measures ensured
211 the study was conducted rigorously and transparently, allowing for greater scrutiny and replication
212 by the broader scientific community. Thirteen deviations and additions to the protocol were applied
213 in our SEM and are reported in Section 2.9: "Deviations and Additions to the Protocol".

214 2.2. Eligibility criteria

215 Complying with the PECO framework, the eligibility criteria were defined as:

- 216 • Population: Peer-reviewed journal articles, pre-prints, grey literature, or theses. Reviews
217 must identify themselves as one of the review types considered part of the systematic-like
218 review family by Moher et al. (2015), or they must include a systematic method of search
219 and screening of the literature reviewed and/or quantitative analysis (meta-analyses) (note:
220 to simplify, the reviews that meet the eligibility criteria are referred to as "systematic
221 reviews" within this map). Eligible review types from the systematic review family include,
222 but are not limited to: systematic reviews, scoping reviews, critical reviews, rapid reviews,
223 realist reviews, meta-analyses, and systematic maps (for review definitions, see Moher et al.
224 (2015)). Primary literature, opinions, corrections, and editorials were excluded.

- 225 • Exposure: Systematic reviews should focus on biological, environmental or medical aspects
226 of the burdens of any of the 35 PFAS of emerging importance listed in Supplementary Table
227 2. Relevant reviews on persistent organic pollutants with a significant component dedicated
228 to PFAS were also included.
- 229 • Outcome: Reviews should focus on the impact of PFAS on the health of people, animals or
230 the environment, levels of contamination, detection strategies, and analysis of toxicity (all in
231 biota/biota tissue or the environment). Methodological studies were excluded. Reviews on
232 topics such as remediation/removal technologies of PFAS from
233 wastewater/soil/environment, manufacturing technologies, policies, economic analyses or
234 risk management were also excluded.
- 235 • Other criteria: Reviews must have a full-text version available for examination. Reviews can
236 be from any year of publication and written in any language.

237 2.3. Piloting

238 We ran a pilot search in the Scopus database and a pilot data extraction during the development of
239 the research protocol. The piloting stage assessed the comprehensiveness of the search strategy and
240 the effectiveness of the data extraction process. As a first piloting step, fourteen systematic reviews
241 were manually collected as benchmark bibliographic records from Google Scholar and used to
242 validate the sensitivity of the pilot search string crafted for the Scopus database (see Table S3 from
243 Vendl et al. (2022)). As the search string did not find all fourteen studies, it was improved and tested
244 again. The final search string successfully retrieved all benchmark studies (see Table S1 from Vendl
245 et al. (2022)). Among these benchmark records, twelve could be found in the Web of Science
246 database, and our corresponding search string successfully retrieved all of them. In contrast, only
247 five benchmark records were available in PubMed, which has a stronger focus on medical content,
248 and our tailored search string, utilising MeSH Terms, captured all five pertinent reviews.

249 Subsequently, a random sample of 100 studies from the Scopus search was retrieved to test and

250 refine the screening and inclusion criteria using Rayyan QCRI (Ouzzani et al., 2016), a free web tool
251 for knowledge synthesis. Two authors (CV and ML) independently screened these studies and tested
252 data extraction tables through pilot data extraction to refine data gathering and coding procedures.

253 2.4. Literature searches

254 We followed the search strategy refined in the research protocol. Accordingly, we did not restrict
255 our search based on publication date, language, or subject/discipline codes. One reviewer (LR) ran
256 literature searches for eligible reviews on the 7th and 8th of March 2022 using three main databases
257 (i.e., Scopus, Web of Science Core Collection, and PubMed) and nine secondary databases (i.e.,
258 Cochrane, Prospero, Epistemonikos, Australian Policy Observatory, PrePrints, Biorxiv, OSF, BASE, and
259 OpenGrey). LR used the final search strings developed in the research protocol to conduct the
260 literature search. The search parameters, strings, and the number of hits for each database are
261 presented in detail in Supplementary Table 3. Potential duplicates were removed using custom text-
262 processing code in R software (version 4.2.1) (R Core Team, 2022), and the remaining studies were
263 uploaded to the Rayyan QCRI online software for title and abstract screening. To ensure that the
264 systematic map remained current, LR conducted an update search on the 6th and 7th of February
265 2023 to identify relevant reviews published from the 1st of March to the 31st of December 2022. The
266 search was conducted on the same databases as the primary search using the same search strategy
267 but restricted to 2022. Reviews published between the 1st of January and the 28th of February 2022,
268 which were already included in the map, were excluded during the screening at the full-text level.
269 The results of the update search are provided in Supplementary Table 4. In addition to the primary
270 and update searches, a supplementary search was conducted on Scopus on the 5th of February 2023
271 to retrieve all types of reviews, including both systematic and non-systematic reviews. This broader
272 range of reviews was used to conduct a supplementary bibliometric analysis of the entire PFAS
273 research field. The same criteria applied to our main searches were also applied to the
274 supplementary search. A search string was customised to find all available types of reviews until the
275 end of 2022. The respective search query string, the search records, and further search details are

276 provided in Supplementary Table 5.

277 2.5. Screening of articles

278 The screening process followed well-established guidelines (Moher et al., 2009). During article
279 screening, LR and ML independently screened the title and abstract of studies based on the eligibility
280 criteria. The reviewers evaluated the inclusion criteria at the title and abstract screening level using a
281 first decision tree (see Fig. 2 from Vendl et al. (2022)). The same reviewers independently performed
282 the full-text screening following a second decision tree (see Fig. 3 from Vendl et al. (2022)). To
283 ensure an unbiased screening process, reviewers did not evaluate any articles they authored. In
284 cases where the article was written in a language other than English and known by any of the
285 reviewers, it was translated. Any decisional conflicts that arose during the title and abstract
286 screening and full-text screening were discussed and resolved by the reviewers. The percentage of
287 conflicts between the two reviewers was 6.6% (102 conflicts out of 1542 bibliographic records) and
288 5.8% (13 conflicts out of 222 bibliographic records) for the title and abstract screening and full-text
289 screening, respectively. The screening of all types of reviews for supplementary bibliometric analyses
290 followed the same steps, except that the inclusion criteria did not limit the inclusion to systematic-
291 like reviews only.

292 2.6. Data extraction, warehousing, and coding strategy

293 We used the free software Zotero (www.zotero.org, version 6.0.26) to store and reference all
294 retrieved reviews during the literature search. Data extraction was performed by LR using four inter-
295 connected Google Forms to extract the pre-determined items. A second reviewer (ML) double-
296 checked the data extracted from a random sample of 15% (i.e., 16 studies). The disagreement ratio
297 between the reviewers did not exceed 10%. Thus, only one reviewer (LR) extracted the data from
298 the remaining reviews.

299 Extracted data were stored in four different tables, organised according to the type of data collected
300 and connected through unique study IDs. The data tables include:

- 301 • "Main" - main data for the systematic map covering information on the publication and its
302 scope.
- 303 • "Species" - scientific names of all species other than humans considered in the reviews.
- 304 • "PFAS_types" - types of PFAS considered in the reviews.
- 305 • "AMSTAR2" - questions of the AMSTAR2 quality assessment scheme applied to each
306 systematic review.

307 Additionally, the table "PFAS_info" holds fixed information on the PFAS types, including their
308 abbreviations, CAS numbers, and carbon chain lengths (derived from Kirk et al. (2018) and Pelch et
309 al. (2019)). The data extraction tables were implemented as Google Forms and converted to Excel
310 sheets and .csv files. The raw extracted data, the analysis code, and additional data are stored and
311 publicly available in the GitHub repository
312 (https://github.com/ThisisLorenzo/PFAS_Systematic_Evidence_Map). The tables and their meta-
313 data are explained in detail in the code book (Supplementary Table 6). Fixed data fields (e.g.,
314 checkboxes) that required more information were accompanied by a comment field allowing free
315 text entry during data extraction. The comment fields were used to document the data extraction
316 process. As stated in the protocol, we planned to contact the review's authors if the required
317 information was not provided. However, there was no need to request any additional data. Finally,
318 data for bibliometric analyses were downloaded directly from Scopus using the included articles'
319 Digital Object Identifier (DOI) for each individual review in our SEM (Supplementary Table 13).

320 2.7. Critical appraisal

321 To assess the quality of the reviews, we conducted a critical appraisal of the included studies. We
322 employed a modified version of the AMSTAR2 checklist. This checklist focuses on the review
323 method, reporting transparency, and limitations, and consists of 16 questions, with each response
324 categorised as "yes", "partially", or "no". Subsequently, we categorised the responses into "high",
325 "medium", or "low" methodological quality (for additional information, see Supplementary Table 7).

326 Additionally, we included a comment field for each question to gather relevant information, such as
327 verbatim review text sentences or paragraphs, references to figures or tables reporting extracted
328 data, and any pertinent information on the score reason. The information from critical appraisal was
329 used in a narrative synthesis of reviews' quality for each AMSTAR2 question. Besides the AMSTAR2
330 checklist, we extracted data on conflict of interest, funding sources, and raw data and analysis code
331 availability.

332 2.8. Data mapping & synthesis criteria

333 Our approach to reviewing and mapping the evidence encompasses a narrative and concise
334 description of the results, complemented by extensive representation through tables and graphs. To
335 ensure a rigorous and standardised methodology, we organised the research outputs based on the
336 three-part division of research questions and objectives. One author (LR) turned the database into
337 an interactive web application (accessible for free at the following link: [https://hi-this-is-
338 lorenzo.shinyapps.io/PFAS_SEM_Shiny_App/](https://hi-this-is-lorenzo.shinyapps.io/PFAS_SEM_Shiny_App/)) using the "shiny" package (version 1.7.5.1) (Chang et
339 al., 2023). All analyses were conducted in the R environment (version 4.2.1) (R Core Team, 2022). For
340 data manipulation, we utilised the "tidyverse" collection of open-source packages (version 1.3.2)
341 (Wickham et al., 2019), specifically the "dplyr" package (version 1.0.10) (Wickham et al., 2022a). We
342 used the "tidyr" package (version 1.2.1) (Wickham et al., 2022b) for data cleaning and the "ggplot2"
343 package (version 3.4.0) (Wickham et al., 2016) for visualisation. For bibliometric analysis, we
344 employed the "bibliometrix" package (version 4.0.1) (Aria & Cuccurullo, 2017). The complete list of
345 packages used in this SEM is provided in Supplementary Table 8.

346 2.9. Deviations and Additions to the Protocol

347 The research protocol was subject to twelve minor changes, which are detailed, justified, and
348 qualitatively assessed in Supplementary Table 9. These modifications were necessary to ensure
349 comprehensive and precise scrutiny of the available evidence related to the subject matter and to
350 elucidate previously ambiguous aspects. Briefly, these twelve changes and additions are listed

351 below:

- 352 - Inclusion of additional PFAS types: We expanded our inclusion criteria to encompass five
353 additional types of PFAS, namely perfluorooctanesulfonamide (FOSA), N-ethyl
354 perfluorooctanesulfonamide (NEtFOSA), N-methyl fluorooctane sulfonamide (NMeFOSA),
355 bis(perfluorohexyl)phosphinic acid (6:6 PFPIA), and perfluorohexylperfluorooctylphosphinic
356 acid (6:8 PFPIA). For details on chemical compounds refer to Supplementary Table 2.
- 357 - Bibliometric analysis focus: We shifted our planned bibliometric analysis on all review types
358 to supplementary materials and performed the main bibliometric analysis exclusively on
359 systematic-like reviews.
- 360 - Literature screening assignments: Changes were made in the team of reviewers responsible
361 for the literature screening.
- 362 - Inclusion of indoor dust-related reviews: We added reviews related to indoor dust to the
363 systematic evidence map under the subject of environmental exposure.
- 364 - Inclusion of food-related reviews: We added reviews related to food and food packaging to
365 the systematic evidence map under the subject of human exposure.
- 366 - Categorization of plant reviews: Reviews focused on plants were categorised as
367 environmental exposure.
- 368 - DOI extraction: We extracted and recorded the DOIs of the included reviews (see
369 Supplementary Table 6).
- 370 - Scopus search string modification: The search string in Scopus was adjusted to retrieve
371 bibliographic records for our bibliometric analysis (see Supplementary Table 5).
- 372 - Addition of "Systematic_approach" column: A new column named "Systematic_approach"
373 was introduced in the "Main" data table to extract information regarding whether a review
374 follows a systematic approach.
- 375 - Clarification of missing species names: If the scientific or common name of the species
376 reviewed was missing, it was searched on Google and noted in the comment column in the

- 377 relative data table.
- 378 - Additional data columns: Two new columns, "Class_scientific_name" and "Broad_taxa,"
- 379 were incorporated into the "Species" data table to capture information about the class and
- 380 broad taxa of species.
- 381 - Broad PFAS group inclusion: The broad PFAS groups PFCs, PFSA, and PFCA were incorporated
- 382 into the "PFAS_types" data table.

383 3. Results and Discussion

384 3.7. Search and screening outcomes

385 Three primary databases, namely Scopus, Web of Science Core Collection, and PubMed were

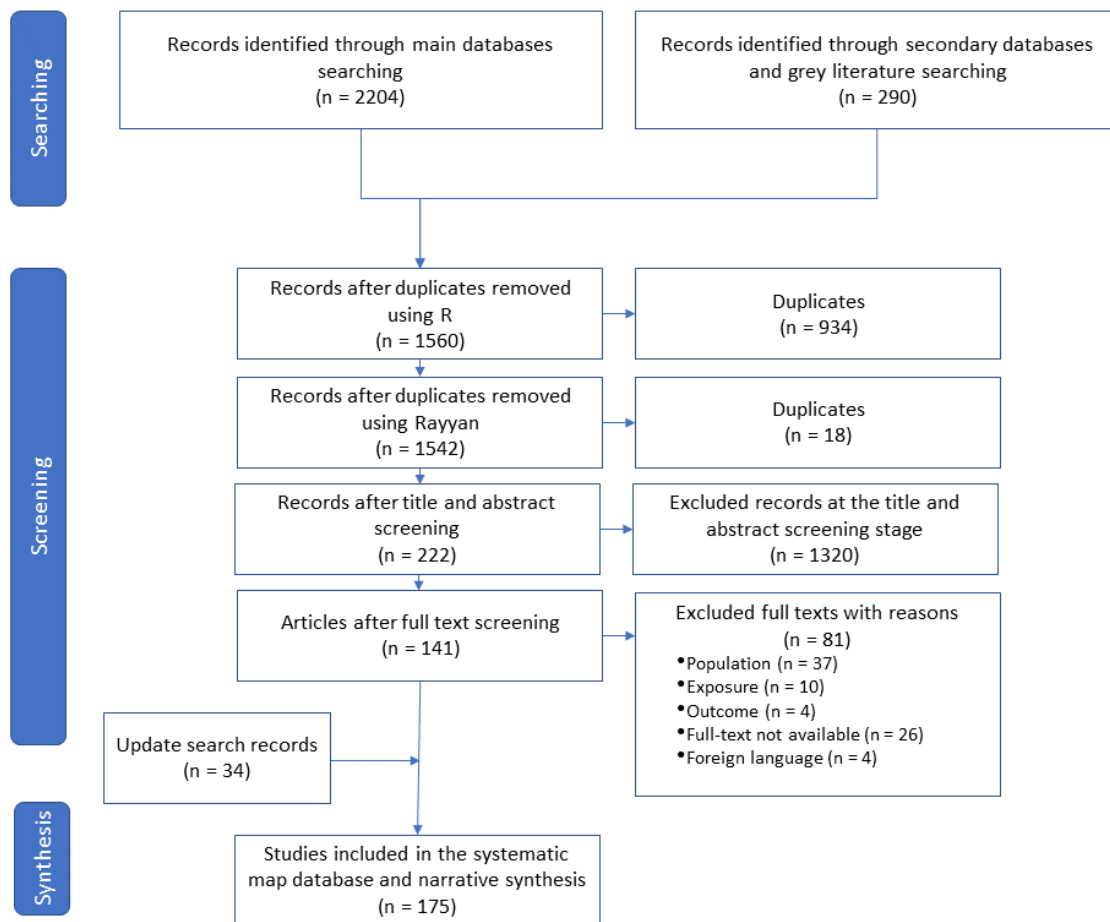
386 searched and yielded 1227, 937, and 40 bibliographic records, respectively. Including grey literature

387 and additional databases further increased the number of studies identified for screening (i.e., an

388 additional 290 bibliographic records), as presented in Supplementary Table 3. In total, 2494

389 bibliographic records were identified in our searches. The flow diagram below shows the screening

390 process (Fig. 2).



391

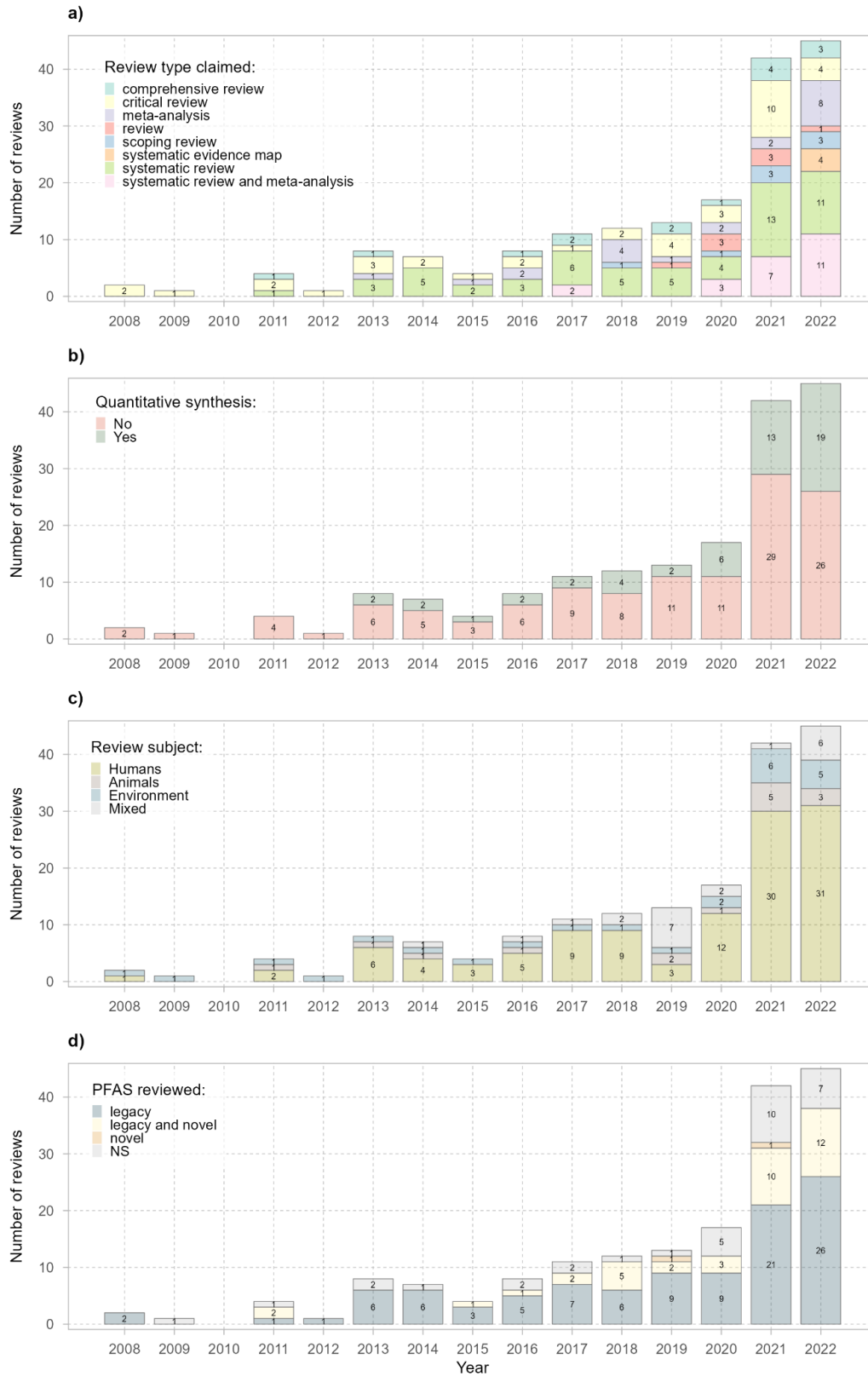
392 *Fig. 2. ROSES flow diagram illustrating the process of study selection. Note: an additional flowchart regarding the search*
 393 *update conducted in February 2023 is available in Supplementary Figure 1.*

394 At the end of the study selection process, 141 (approximately 9%) bibliographic records were
 395 retained. In addition, 34 eligible records were identified as a result of the update search (see
 396 Supplementary Figure 1), bringing the total number of systematic reviews included in our systematic
 397 evidence map to 175. The reasons for excluding individual records at the full-text stage were
 398 justified and recorded (see Supplementary Table 10). Individual records excluded at the full-text
 399 stage during the update search, together with a detailed list of included reviews in the map, can be
 400 found in supplementary materials (see Supplementary Tables 11, 12, and 13). The search for all
 401 review types (Supplementary Table 5) retrieved 2416 records, in which titles and abstracts were
 402 screened for inclusion by LR, ML, and CV. Of the 2416 records, 1886 were excluded. Of the 530

403 included records, 13 were not found in the Scopus database (Supplementary Table 14). Thus, a total
404 of 517 records were included in the supplementary bibliometric analysis.

405 3.8. Mapping

406 Our systematic evidence map (SEM) revealed a steady annual rise in published reviews on PFAS
407 exposures from 2016 (Fig. 3. See also Supplementary Figures 2 and Supplementary Figure 3).
408 Likewise, Pelch et al. (2022) and Vendl et al. (2024) both observed a similar rise in publications over
409 time in the primary literature concerning human health and wildlife exposure to PFAS in their
410 respective systematic maps of primary literature. These publication trends might reflect a
411 combination of a growing interest in the impacts of PFAS on the environment and a decreasing cost
412 of chemical analyses. Recent reviews on PFAS exposure are more likely to include quantitative
413 synthesis, as illustrated in Fig. 3a and Fig. 3b. In line with this trend, 24% of reviews published
414 between 2013 and 2019 include quantitative analysis, compared to 36% of reviews published
415 between 2020 and 2022. Meta-analyses are a powerful tool that can help establish a quantitative
416 evidence base, often reconciling seemingly conflicting research outcomes (Gurevitch et al., 2018).
417 From 2013, the systematic secondary literature increasingly included quantitative analyses to assess
418 the impact of PFAS exposure (Fig. 3b). Approximately 40% of reviews published in 2022 included a
419 quantitative data analysis. In the same year, reviews claiming themselves to be 'systematic' also
420 started to emerge. However, it is noteworthy that the first review claimed to be systematic and
421 focusing on a group of endocrine-disrupting chemicals, including PFAS, was published in 2011 (i.e.,
422 Caserta et al., 2011), as depicted in Fig. 3a.



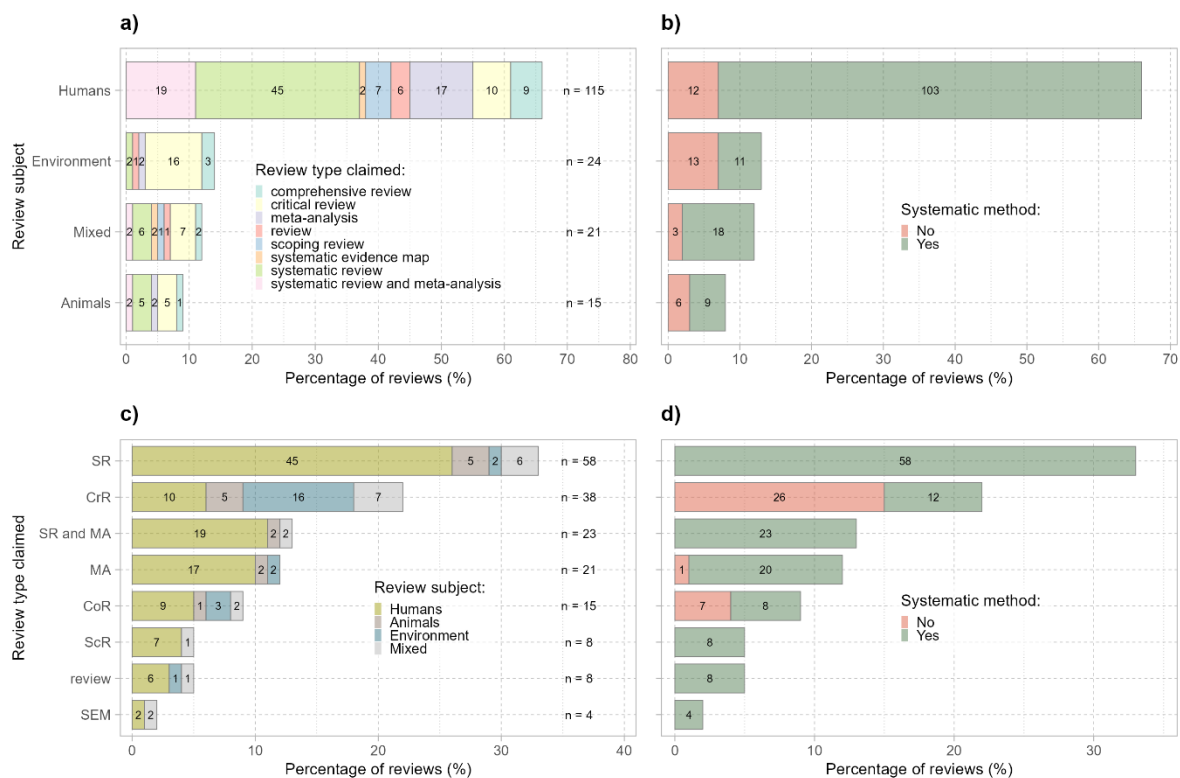
423

424 Fig. 3. Bar charts showing publication time trends. **a)** The number of self-claimed review types over time (CoR =
 425 comprehensive review, CrR = critical review, MA = meta-analysis, ScR = scoping review, SEM = systematic evidence map, SR
 426 = systematic review, SR and MA = systematic review and meta-analysis), **b)** the distribution of review subjects over time, **c)**

427 *the proportion of reviews that included a meta-analysis over time, d) the proportion of reviews that focused on legacy or*
428 *novel PFAS types over time (NS = not specified).*

429 A notable proportion (i.e., 61%) of the available systematic reviews is focused solely on human
430 exposure, while reviews on environmental, animal, or a mix of these subjects are limited (Fig. 3c, Fig.
431 4c, and Supplementary Figure 4a). The increasing concern regarding the effects of these chemicals
432 on human health has led to a substantial amount of primary literature being produced. Due to the
433 diverse range of findings within this primary literature, reviews, and particularly meta-analyses, have
434 endeavoured to gauge an overall effect by addressing this diversity. Following this pattern, we show
435 that the most frequently used Medical Subject Headings and Qualifiers (MeSH) terms were
436 "humans" and "toxicity," followed by "fluorocarbons" and "chemically induced" (Supplementary
437 Figure 7). Furthermore, we categorised the outcomes of the reviews into six primary groups. The
438 analysis revealed that the most frequently occurring outcomes were associated with general human
439 health (38% of reviews), followed by those specifically concerning reproductive and developmental
440 health (26% of reviews) (Supplementary Figure 4b).

441 The number of studies incorporated in a review is predominantly influenced by the research subject
442 and the extent of corroborative evidence accessible. In this SEM, we did not notice a significant
443 difference in the number of primary studies included in systematic reviews among different subjects
444 (Supplementary Figure 8a). Moreover, we found that while most reviews on human health employ,
445 and claim to employ, a systematic method (Fig. 4b and Fig. 4c), such approach is rare in reviews on
446 the environment or animals, which similarly claim to be critical and comprehensive, but lack a
447 systematic search and screening of the literature (Fig. 4a and Fig. 4d). By employing a systematic
448 method, systematic reviews reduce bias, resulting in more dependable findings that can be used as a
449 foundation for drawing reliable conclusions and making evidence-based decisions (Lasserson et al.,
450 2022).

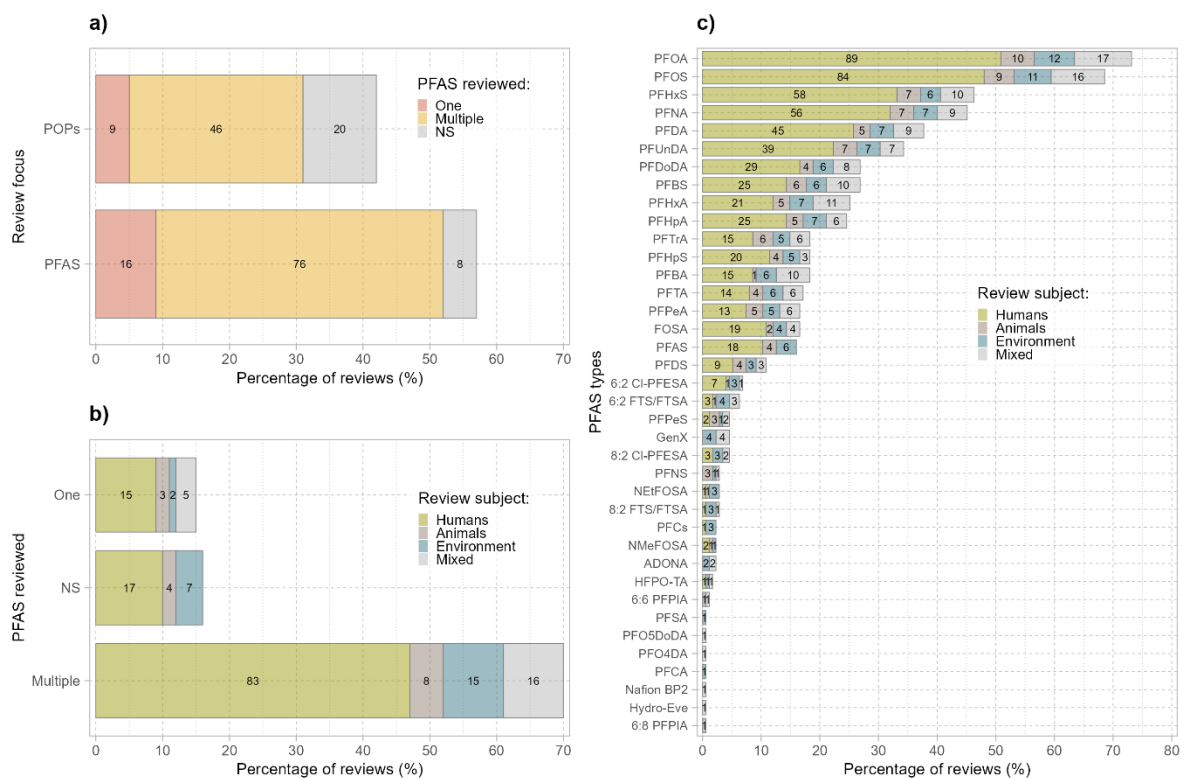


451

452 *Fig. 4. Bar charts depicting the distributions of review subjects and self-claimed review types. a) the distribution of reviews*
 453 *across various subjects and the proportion of each review type claimed for each subject, b) the percentage of reviews*
 454 *categorised by subject, further divided into those that utilised a systematic method and those that did not, c) the*
 455 *distribution of different self-claimed review types across subjects, along with the proportion of each subject reviewed by*
 456 *each type (SR = systematic review, CrR = critical review, SR and MA = systematic review and meta-analysis, MA = meta-*
 457 *analysis, CoR = comprehensive review, ScR = scoping review, SEM = systematic evidence review), d) the percentage of*
 458 *reviews categorised by type, further divided into those that utilised a systematic method and those that did not. The*
 459 *numerical values within the bars represent the review counts.*

460 An analysis of the reviewed compounds revealed that most of the reviews focused on PFAS
 461 specifically (i.e., 57%), rather than having a broader focus on POPs (Fig. 5a and Supplementary Figure
 462 9a). This zoom-in on the fluorinated compounds by the systematic secondary research may be
 463 attributed to the increasing demand for specific reviews from institutions and stakeholders.
 464 Additionally, 70% of reviews cover the exposure to multiple PFAS rather than focusing on only one
 465 (Fig. 5a and Fig. 5b). However, the mere inclusion of various PFAS types in these reviews does not
 466 automatically imply a specific emphasis on the toxicity of PFAS mixtures. Instead, these reviews tend

467 to adopt a broader perspective. Nonetheless, deepening our understanding of the toxicity associated
468 with PFAS mixtures holds great significance in evaluating their risk, since synergistic effects influence
469 the combined toxicity of PFAS mixtures (Ojo et al., 2020). In 2021, there has been an increase in the
470 number of published reviews that covered both legacy and novel compounds (i.e., 25% of the total
471 number of reviews in 2020, 35% in 2021, and 32% in 2022), as shown in Fig. 3d. However, reviews
472 focused solely on novel compounds were only 2 out of 175 reviews included in this SEM. These two
473 reviews were a systematic evidence map published in 2022 (Pelch et al., 2022), which included
474 Nafion by-product 2 and hydrofluoroether-based compounds (Hydro-Eve), and a systematic review
475 and meta-analysis on animals (Banyoi et al., 2022), which included
476 perfluorohexylperfluorooctylphosphinic acid (6:8 PFPiA). The widely detected legacy compounds
477 PFOA and PFOS were the most frequently reviewed (Supplementary Figure 6a), followed by
478 perfluorohexane sulfonate (PFHxS), perfluorononanoic acid (PFNA), and perfluorodecanoic acid
479 (PFDA) (Fig. 5c). The median and mean number of primary studies included in reviews on legacy
480 compounds (median = 27, mean = 38) did not significantly differ from those encompassing both
481 legacy and novel compounds (median = 39, mean = 62) (Supplementary Figure 6b). Despite a lower
482 quantity of reviews focusing on novel compounds compared to those centred on legacy compounds,
483 the number of primary studies forming the basis for these reviews is comparable.



484

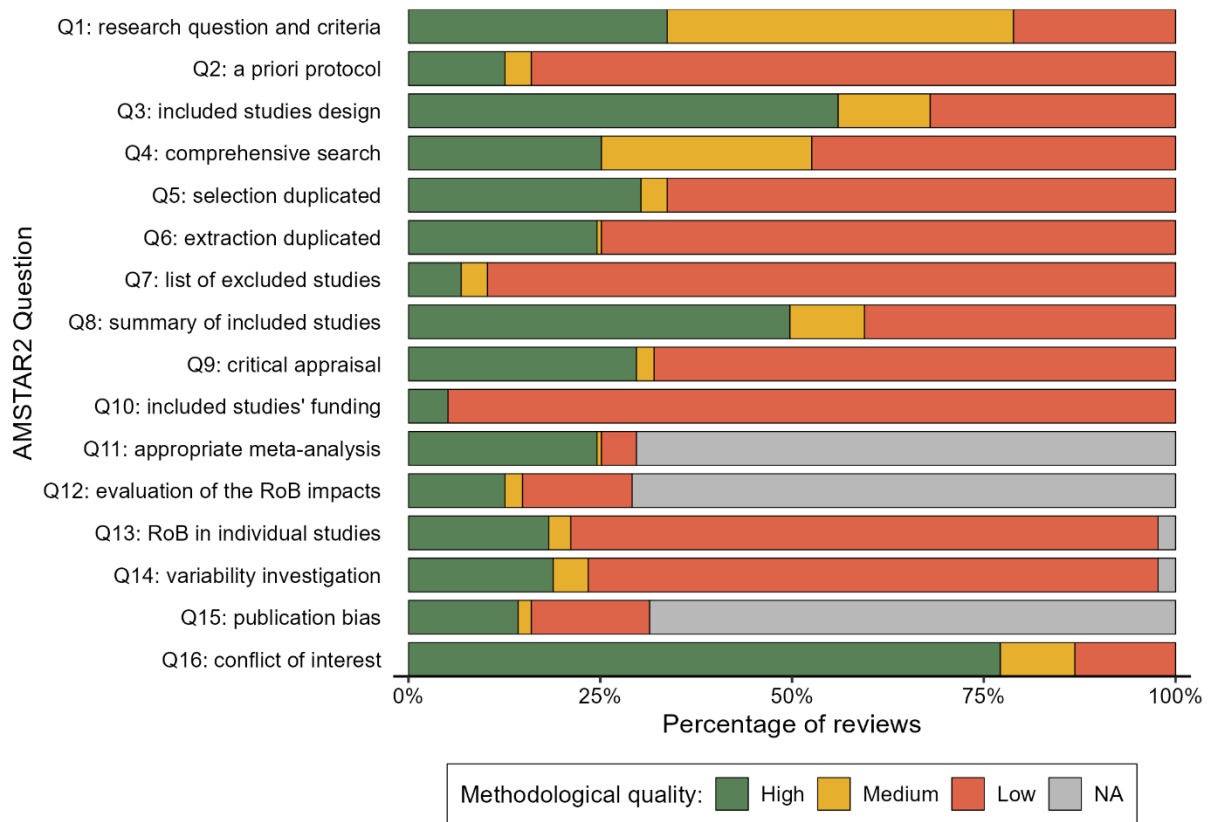
485 *Fig. 5. Bar charts summarising the PFAS-related focus of the included reviews. A) The percentage of reviews focused on*
 486 *PFAS or on POPs in general, along with the proportion of reviews that cover either one or multiple types of PFAS (NS = not*
 487 *specified), b) the distribution of reviews covering one or multiple PFAS compounds, with the proportion of each subject*
 488 *reviewed by each type, c) the different types of PFAS reviewed and the subjects that each type of PFAS was reviewed in. The*
 489 *numerical values within the bars represent the review counts.*

490 Moreover, our results did not show a particularly growing body of secondary research on the effects
 491 of PFAS exposure on animals (Fig. 3c), although five reviews were published in 2021. More than half
 492 (i.e., 56%) of reviews of animal studies were focused on laboratory animals (Supplementary Figure
 493 10), such as rats and mice, which may not accurately represent the effects of PFAS exposure on
 494 wildlife species and its indirect effects on ecosystem functionality. Only one systematic review (i.e.,
 495 Jha et al., 2021) collected evidence on human health risks associated with PFAS exposure through
 496 meat and milk consumption produced in crop-livestock systems. The lack of systematic reviews on
 497 this aspect of PFAS exposure is probably due to the limited number of primary studies addressing
 498 PFAS in livestock and game (Death et al., 2021). Around a third of reviews (i.e., 34%) covered wildlife
 499 species and 3 reviews (i.e., 9%) covered both laboratory and wildlife species (Supplementary Figure

500 10). The most reviewed classes were mammals, ray-finned fishes, and birds (Supplementary Figure
501 11a). The most commonly reviewed species were the two laboratory mammals *Rattus norvegicus*
502 and *Mus musculus*, followed by the model animal *Danio rerio* (Zebrafish, Supplementary Figure 6b).
503 Among reviews on PFAS exposure in wildlife, birds and fish species were overrepresented
504 (Supplementary Figure 12a and Supplementary Figure 12b), suggesting a taxonomic bias. Finally, the
505 limited systematic secondary literature on PFAS in the environment was not skewed towards any
506 specific environmental compartment (Supplementary Figure 13). Half of these reviews covered a
507 mixture of different compartments and around 40% of them covered freshwater or a mix of aquatic
508 compartments.

509 3.9. Critical appraisal

510 Via the AMSTAR2 checklist, we identified areas of strength and weakness in the 175 systematic
511 reviews examined. Overall, reviews scored well in terms of methodology (green colour in Fig. 6)
512 when clearly explaining their selection of study designs for inclusion (Question 3), detailing the
513 included studies (Question 8), and reporting potential sources of conflict of interest (COI) (Question
514 16). These results indicate that the systematic secondary research on PFAS exposure generally
515 satisfies the recommendations of guidelines for systematic review in environmental science and
516 management (Pullin & Stewart, 2006; Liberati et al., 2009). Of the reviews that included a COI
517 statement, a small proportion (i.e., 8%) acknowledged the presence of conflict, while the majority
518 (i.e., 92%) acknowledged the absence of conflict (Supplementary Figure 14a and Supplementary
519 Figure 14b). However, the reviews were of a medium or low methodological quality (orange and red
520 colours in Fig. 6) in the reporting of funding sources for studies included in the review (Question 10)
521 and providing a list of excluded studies with justification (Question 7). Notably, 45% of reviews did
522 not clearly delineate research questions and inclusion criteria (Question 1), and more than 80% did
523 not explicitly state that the review methods were established *a priori* (Question 2). Such weaknesses
524 are characteristic of traditional narrative syntheses (Campbell et al., 2019), which lack a planned
525 systematic and transparent reviewing approach.



526

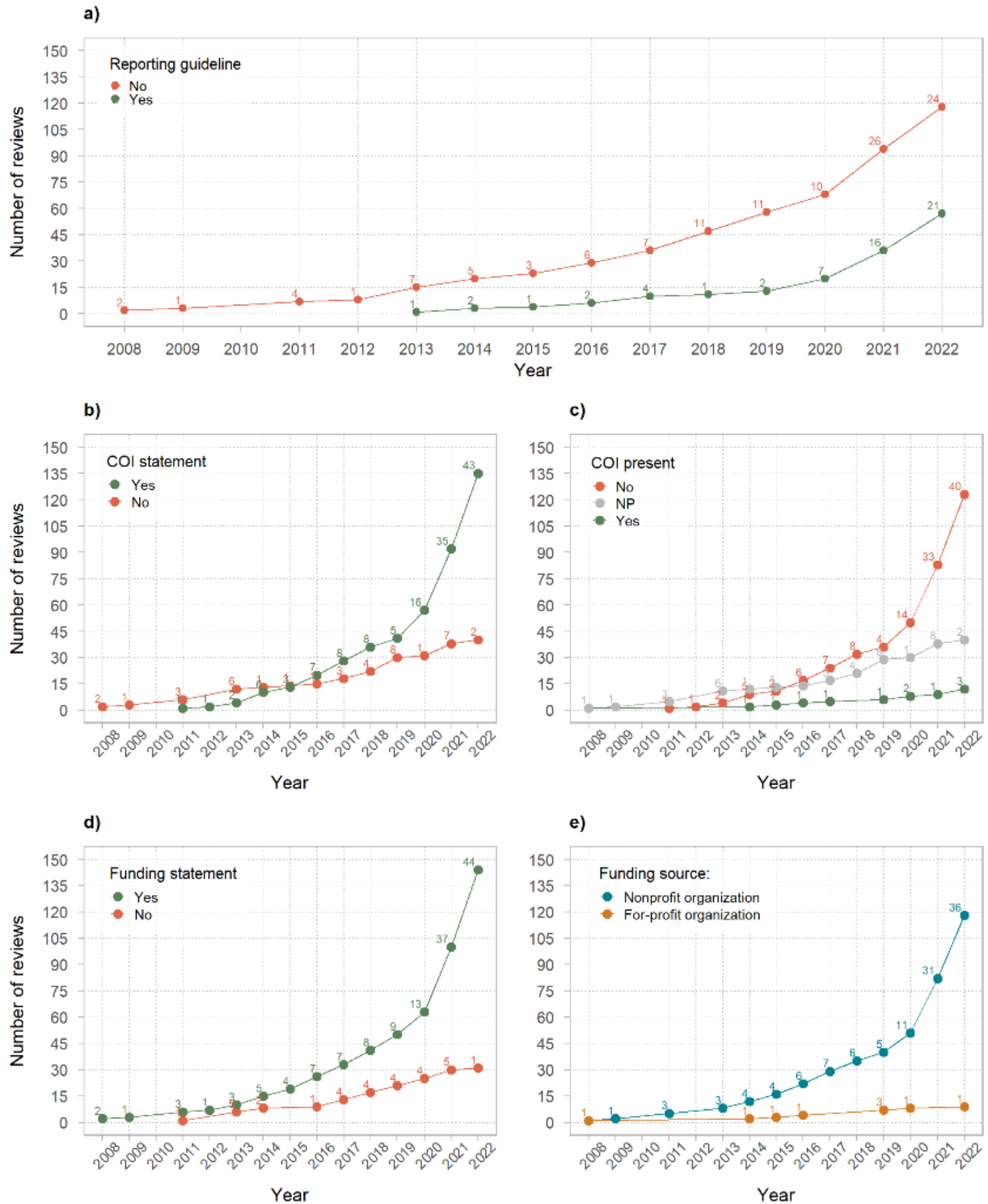
527 *Fig. 6. Distribution of methodological quality scores for each of the 16 AMSTAR2 items across 175 systematic-like reviews*
 528 *on PFAS exposures. The bars are colour-coded as follows: Green: percentage of reviews that exhibit a high methodological*
 529 *quality for the corresponding AMSTAR2 item. Red: percentage of reviews demonstrating a low methodological quality for*
 530 *the corresponding AMSTAR2 item. Orange: percentage of reviews that exhibit a medium methodological quality for the*
 531 *corresponding AMSTAR2 item. Grey: item not applicable.*

532 Furthermore, almost half of the reviews (i.e., 47%) did not provide enough information on the
 533 search strategy or did not conduct a comprehensive search of the literature (Question 4). Two-thirds
 534 of the reviews (i.e., 66%) had only one author involved in the study selection or did not provide
 535 information on how many reviewers participated in the selection process (Question 5). Similarly,
 536 75% of reviews had only one author involved in the data extraction or did not declare how many
 537 reviewers participated in the process (Question 6). In 68% of reviews, the authors did not mention a
 538 risk of bias assessment for individual studies included in the review (Question 9), and 76% did not
 539 account for the risk of bias when discussing results (Question 13). We also found a general lack of
 540 discussion of dataset heterogeneity (74% of reviews) and assessing the potential impact of risk of

541 bias on meta-analytic results (49% of reviews including quantitative analysis, Question 12) and
542 investigating publication bias (Question 15). Overall, AMSTAR2 revealed methodological concerns or
543 lack of transparency in specific aspects of review methods for more than half of the reviews (Fig. 6).
544 Subject-specific analysis revealed that the reviews with humans as the subject were generally of
545 higher quality than those focused on animals or the environment (Supplementary Figure 15). A
546 similar pattern can be observed for the quality of reviews with a systematic method of search and
547 screening of the literature, with these reviews having a relevant higher average quality rating
548 (Supplementary Figure 16). An analysis of time trends (Fig. 7) showed that even in recent reviews,
549 more than half of them do not mention following any guidelines (Fig. 7a). Historically, guidelines for
550 conducting systematic reviews in environmental and biological sciences were limited. Milestones like
551 the Navigation Guide (Woodruff & Sutton, 2014) and the Office of Health Assessment and
552 Translation (OHAT) handbook from the National Toxicology Program (NTP, 2019) have influenced
553 standards in environmental health systematic reviews. A more recent notable guideline in
554 environmental research is represented by COSTER (Whaley et al., 2020). In addition, authors can
555 ensure quality reporting of systematic reviews by using available checklists, such as PRISMA (Page et
556 al., 2021) and its ecology and evolution variant PRISMA-EcoEvo (O’Dea et al., 2021), and MOOSE
557 (Brooke et al., 2021).

558 According to our results, recent reviews are more likely to include a COI statement (95% in 2022),
559 since it became mandatory for most of the journals over the years, and a funding statement (98% in
560 2022) (Fig. 7b and Fig. 7d). These results are consistent with a systematic review by Darmon et al.
561 (2018), where the authors found that COI and funding statement rates increased in the critical care
562 literature over time. Notably, we found that 10% of reviews included in our map provided raw data
563 (Supplementary Figure 14f) and only three reviews out of 175 made their analysis code available
564 (Supplementary Figure 14g). This lack of transparency contributes to the reproducibility crisis, which
565 is currently eroding the credibility of science. For example, Miyakawa (2020), as an Editor-in-Chief of

566 *Molecular Brain*, requested the raw data for 41 manuscripts and found out that 97% of the authors
567 did not provide it. Wallach et al. (2018) surveyed a random sample of 149 biomedical articles
568 published between 2015 and 2017 and discovered that only 18% of the sample discussed publicly
569 available data and only 1% included a link to a study protocol. In this SEM, none of the included
570 reviews provided a link to a study protocol published before conducting the review. However, study
571 protocols are crucial for transparency, minimising bias, maintaining consistency, promoting
572 collaboration, and documenting changes or deviations during the review process (Al Shakarchi,
573 2022). Protocols enhance the reliability of systematic reviews and contribute to the overall quality of
574 evidence synthesis.



575

576 *Fig. 7. Cumulative time series plots. The lines show the cumulative trend in the number of reviews that: (a) adhere to*
 577 *reporting guidelines; (b) provide a conflict of interest statement, (c) acknowledge the presence of a conflict of interest (note:*
 578 *NP = statement not provided), (d) declare a funding statement; I are funded by a nonprofit or for-profit organisation. The*
 579 *numbers next to the data points represent the number of published reviews in each category in the respective year.*

580 Systematic reviews are efficient tools for synthesising evidence and informing health policy and
581 decision-making (Cook et al., 1997). However, we have found several major shortcomings in the
582 systematic secondary literature on PFAS exposure related to transparency, rigour, and quality
583 control. The lack of transparency in data and code sharing, as well as in methodology, can impact the
584 reproducibility of the results and the reliability of the research field. These findings are consistent
585 with other assessments of systematic reviews in public health (Campbell et al., 2019) and highlight
586 the need for improvement in the rigour and quality of the reviews on PFAS exposure. Taken
587 together, this appraisal highlights the need for better implementation and reporting to ensure
588 reproducibility, transparency, comprehensiveness, and reliability.

589 3.10. Bibliometric analysis

590 The leading countries producing reviews on PFAS exposure were the United States of America (USA)
591 and China (Supplementary Figure 17). Spain and Italy are subsequent prominent contributors in this
592 domain. All the top ten nations in this field are considered to have very high gross domestic product
593 by the World Bank (The World Bank (n.d.)), the United Nations (United Nations (n.d.)), and the
594 Organization for Economic Cooperation and Development (OECD) (OECD (n.d.)). There was a
595 significant underrepresentation of countries from Africa, South-East Asia, Central America, and
596 Eastern Europe (Supplementary Figure 20). This underrepresentation could stem from various
597 factors, such as limited research funding and resources (Salager-Meyer, 2008), scarce opportunities
598 for collaboration and training, language barriers, and a lack of visibility on the global research stage.
599 It is plausible that these regions are short of opportunities and expertise in producing evidence
600 syntheses (Man et al., 2004) or prioritising alternative research domains according to their specific
601 needs.

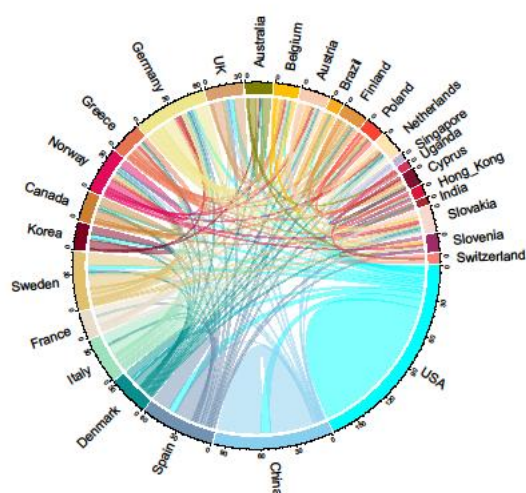
602 Moreover, except for China, the ten most productive nations exhibit a moderate or high level of
603 English proficiency, according to the world's largest ranking of countries and regions by English skills
604 (EF, 2022), with English serving as an official or commonly used language for communication and

605 education. This bias towards research originating from developed countries, particularly those with
606 English as the predominant language, is likewise observed in other research disciplines (Moriguchi,
607 2022; Neimann Rasmussen & Montgomery, 2018; Song et al., 2010).

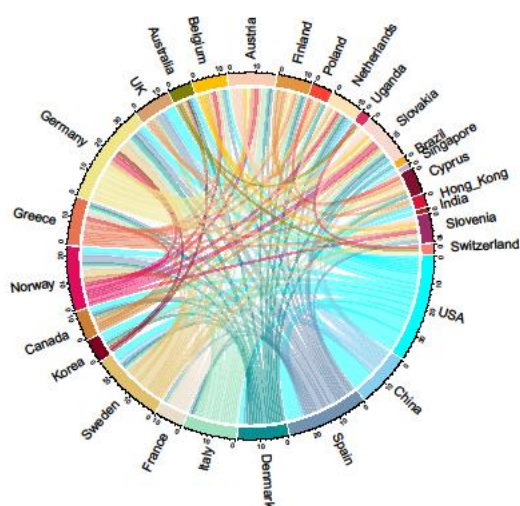
608 To address the existing research disparity, it is imperative to foster international collaborations,
609 capacity-building initiatives, and knowledge-sharing endeavours (UNESCO, 2023). International
610 cooperation holds the potential to generate reliable knowledge that is universally recognised and
611 effectively tackles the challenges associated with the lack of diversity (UNESCO, 2023). We found
612 that the two most productive countries – the USA and China – produced most of their publications
613 solely authored by researchers from their own country (i.e., 78% of publications for the USA and 76%
614 of publications for China; Supplementary Figure 17). This observation highlights the need to enhance
615 international research partnerships, enrich the exchange of knowledge, and diversify perspectives in
616 the field of PFAS exposure research.

617 An analysis of the country of affiliation of review authors uncovered the global network of
618 collaborations. Fig. 8 illustrates the network of collaborations within countries and among countries
619 in the research field. It is evident how several nations which did not have a significant network of
620 collaborations within their own borders (Fig. 8a), instead exhibited a relatively robust network of
621 inter-country collaborations (e.g., Sweden, Germany, Austria, Norway, Greece; Fig. 8b). These
622 nations, despite playing a relatively secondary role in the production of systematic reviews, still
623 contributed significantly to the global collaboration network. The possibilities of discovery on the
624 impacts of PFAS exposure can be expanded through international collaboration, allowing
625 researchers to achieve findings that surpass what a single team could accomplish independently. In
626 addition, such collaboration enables researchers to nurture their existing relationships and expand
627 their scientific network (Dusdal & Powell, 2021).

A



B



628

629 *Fig. 8. Chord diagrams illustrating country collaborations. Values on the axis show the number of systematic-like reviews on*
 630 *PFAS exposure authored by researchers from the respective country. Arcs represent the number of reviews co-authored by*
 631 *reviewers from different countries. a) the diagram shows the total number of collaborations per country (i.e., intra-country*
 632 *collaborations and collaborations between affiliated countries). b) the chord diagram shows the number of exclusive inter-*
 633 *country collaborations. Note: some of the less involved countries (i.e., countries with only one collaboration) were removed*
 634 *from the plots to enhance visual readability.*

635 Analysing the clustered network of collaborations (Supplementary Figure 21) revealed three main
 636 authorship collaboration groups led by the USA, Sweden, and Germany, respectively. Europe
 637 appears divided into two collaboration groups: Sweden's cluster is closer to the larger international
 638 cluster led by the USA and China, and Germany's cluster is closer to a smaller and isolated collective

639 led by Australia. The USA, China, and Spain collaborated exclusively with nations with limited global
640 visibility. This pattern suggests a partially fragmented scenario of international collaboration where
641 some nations engage in single or double partnerships.

642 In terms of dominating and connected study topics, examining the co-occurrence of keywords
643 (Supplementary Figure 22 and Supplementary Figure 28) identified two broad topic clusters: one
644 associated with compound nomenclature and non-human subjects of review, and a second cluster
645 comprising human-related terms. The keyword co-occurrence analysis in systematic reviews
646 (Supplementary Figure 22) demonstrated that the term "meta-analysis" is more frequently
647 associated with human-related terms than non-human subjects. This pattern aligns with our findings
648 regarding the occurrence of meta-analyses among systematic reviews across different subject areas
649 (Fig. 4b). The fact that the term "meta-analysis" is more frequently associated with human-related
650 terms suggests that there is a growing and shared interest in quantifying the human health impacts
651 of PFAS.

652 When it comes to influential publications, the most cited manuscript (Conder et al., 2008), averaging
653 51 citations per year, with a total of 821 citations, was published in 2008 and explored the
654 bioaccumulation potential of perfluorinated acids (Supplementary Figure 18). The country that has
655 received the most citations so far was the USA, with a total of 4317 citations, while Canada had the
656 highest impact per publication, with an average article citation of 278. Regarding publication
657 sources, Environmental Research emerges as the most influential journal in this research area, with
658 13 articles, followed by Science of The Total Environment and International Journal of Environmental
659 Research and Public Health, with 11 and 10 articles, respectively.

660 The findings of the bibliometric analysis suggest that fostering international collaboration could
661 advance our understanding of the impacts of PFAS exposure. The different collaboration clusters
662 identified in the study may reflect countries' research priorities and interests. The additional
663 bibliometric analysis on all types of reviews did not show substantially different results from the

664 main bibliometric analysis. The larger sample size (i.e., 517 reviews) expanded our overview but still
665 revealed the same most productive countries in producing reviews on the research topic
666 (Supplementary Figure 23 and Supplementary Figure 26). The USA and China were the major actors
667 in the global scenario, with a similar pattern of international collaborations (Supplementary Figure
668 27). Two narrative reviews, one of monitoring and toxicological findings on perfluoroalkyl acids (Lau
669 et al., 2007) and another one on sources, fate and transport of perfluorocarboxylates (Prevedouros
670 et al., 2006), lead as the most cited reviews in the PFAS exposure research topic (Supplementary
671 Figure 25).

672 4. Limitations

673 Our systematic evidence map (SEM) has inherent limitations and presents several opportunities for
674 improvement. Our literature search was conducted in English, which may potentially introduce a
675 language bias by overlooking relevant literature in other languages (Amano et al., 2016; Amano et
676 al., 2021). Furthermore, establishing research patterns and discipline categories in our evidence map
677 was based on prior knowledge of the literature. However, alternative categorisations may yield
678 slightly different results. Exploring alternative categorisations could offer valuable insights from
679 different perspectives and enhance the coverage of the evidence map. Using multiple terms to refer
680 to PFAS exposure in the literature made it challenging to comprehensively include all potentially
681 relevant search terms, including terminology specific to human, environmental, or animal health.
682 Future research can expand and refine the search strategy to encompass a broader range of terms,
683 ensuring a more comprehensive identification of relevant studies. The critical appraisal employed in
684 our work presents intrinsic limitations that are shared with its previous version (i.e., AMSTAR). These
685 limitations are extensively discussed by Faggion (2015), including the difficulties in the objective
686 interpretation of some items and the partial capture of the true methodological quality of systematic
687 reviews. Our SEM focused on 35 commonly studied PFAS compounds. There are many other PFAS
688 that have not been studied as extensively. However, as we showed in this map, the body of

689 systematic secondary literature on PFAS exposure is steeply growing, especially for novel
690 compounds. Furthermore, this SEM does not include any governmental or other agency reviews as
691 they were not included in the protocol's eligibility criteria and are beyond the scope of this map.
692 Finally, the quality of this tertiary research, intended as the completeness and correctness of the
693 information it contains, is closely dependent on the quality of the secondary research sources on
694 which it is based. By addressing these limitations and leveraging them as opportunities for
695 improvement, future evidence maps can overcome current constraints and provide a more robust
696 foundation for decision-making and further research in this field.

697 5. Gaps and Opportunities for Evidence Synthesis

698 The existing literature exhibited several notable gaps in the distribution of systematic reviews
699 concerning PFAS exposure, opening opportunities for evidence synthesis. The prevailing focus of
700 systematic reviews was on human exposure, while subjects related to animals and environmental
701 compartments were notably underrepresented. In reviews focused on human subjects, there was a
702 predominant emphasis on reproductive and developmental health outcomes, while a limited
703 number of reviews addressed other aspects of human health outcomes or the occurrence and
704 exposure of contaminants. Regarding animal-focused reviews, those examining experimental
705 laboratory studies predominated over those investigating observational studies on wildlife.
706 Furthermore, avian and actinopterygian species (ray-finned fishes) were disproportionately
707 represented in wildlife reviews, whereas taxa such as reptiles, insects, crustaceans, and mammals, to
708 a lesser extent, were underrepresented. In environmental reviews, freshwater environments
709 received the most attention, whereas terrestrial, inland ecosystems were underexamined.

710 Regarding chemical compounds, a substantial body of literature exists on perfluorooctanoic acid
711 (PFOA) and perfluorooctanesulfonic acid (PFOS); however, there remains considerable potential for
712 further research focusing on emerging PFAS. While numerous reviews explored human exposure to
713 PFOA and PFOS, most reviews addressing novel PFAS concentrate on animal and environmental

714 subjects.

715 6. Conclusions: implications and future perspectives

716 This systematic evidence map (SEM) was developed to provide an overview of the systematic
717 secondary evidence concerning the impacts of PFAS exposure on humans, animals, and the
718 environment. The SEM's publicly available database facilitates access to the body of literature
719 allowing the navigation, visualisation, and download of data. Here, we illustrate how this SEM and its
720 online database meet the needs of diverse audiences, including scientists, regulators, and
721 individuals.

722 Primarily, our SEM serves as a foundational tool for scientists across academia, government, and the
723 nonprofit sector, providing a comprehensive resource for literature reviews. Our rigorous
724 documentation eliminates the need for redundant search and screening processes, offering direct
725 access to relevant systematic reviews. Researchers can access the database through the online
726 platform and design inquiries into various aspects, including exposure of specific subjects to specific
727 compounds.

728 This SEM is also designed to streamline the identification of quality reviews on specific PFAS
729 exposure topics. With the increasing identification of PFAS-contaminated sites worldwide, residents,
730 governments, and regulatory agencies seek high-quality information on various aspects of PFAS
731 exposure. Within this SEM, we have grouped, categorised, and assessed the rigorousness of review
732 methods and provided free access to this information. Additionally, the database facilitates the
733 comparison of reviews' quality on specific aspects and steps of the review process.

734 Moreover, our SEM serves as a tool to spot data gaps. For instance, although a few systematic
735 reviews have been conducted on animal exposure in controlled environments, systematic reviews
736 on wildlife remain limited and characterised by taxonomic bias. The integration of our secondary
737 literature map with available primary literature maps, such as Vendl et al. (2024) for PFAS in wildlife,

738 provides a complete picture of the research field and its data gaps.

739 Our bibliometric results facilitate cross-disciplinary communication and collaboration between
740 researchers from diverse fields, such as environmental science, toxicology, epidemiology, and public
741 health. Different nations and research groups investigating PFAS exposure and impacts may possess
742 distinct disciplinary priorities, whether focused on human health or ecosystem function assessment.
743 By identifying research patterns, this SEM fosters interdisciplinary collaboration and recognises the
744 national diversity of research groups. Diverse collaborations would promote a more integrated
745 approach to the study of PFAS exposure and its impact on a broader scale.

746 Finally, our SEM contributes to developing best practices for reporting systematic reviews on PFAS
747 exposure by highlighting areas where transparency and reliability can be enhanced. While the
748 quantity of research expands our knowledge, the commitment to transparent methodologies, robust
749 data analysis, and reproducibility solidifies the credibility and integrity of scientific advancements. By
750 emphasising the importance of these principles, our study contributes to the ongoing improvement
751 of research practices in the field of environmental pollution.

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758 Authorship contribution statement

759 We followed the CRediT (Contributor Roles Taxonomy) (CASRAI, 2020) and MeRIT (Method
760 Reporting with Initials for Transparency) (Nakagawa et al., 2023) authorship guidelines. The
761 corresponding author ensured that all authors agreed with their contributions described in the

762 authorship statement.

763 [Authorship statement](#)

764 Conceptualisation: LR, CV, ML, SN

765 Data curation: LR

766 Formal analysis: LR, ML

767 Funding acquisition: LR, SN, GN, DH

768 Investigation: LR

769 Methodology: LR, CV, ML, SN

770 Project administration: LR

771 Software: LR, ML, SN

772 Supervision: ML, SN, MDT

773 Validation: ML

774 Visualisation: LR

775 Shiny App development: LR

776 Writing – Original Draft: LR

777 Writing – Review and Editing: all authors

778 [Competing interests](#)

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

781 [Raw data, analysis code and other materials](#)

782 Raw data, analysis code, and additional materials are stored in the following GitHub repository:
783 https://github.com/ThisIsLorenzo/PFAS_Systematic_Evidence_Map.

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