A plausibility database summarizing the level of evidence regarding the hazards induced by the exposome on children health

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International Journal of Hygiene and Environmental Health 256 (2024) 114311

Contents lists available at ScienceDirect

International Journal of Hygiene and Environmental Health

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

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ARTICLE INFO

Keywords:
Atmospheric pollutants
Children
Chemicals
Environment
Evidence integration
Exposome
Hazard
Review

ABSTRACT

Childhood diseases correspond to major public health issues. A large number of studies using different approaches provide evidence regarding effects of environmental exposures, encompassed in the exposome, on children's health. We aimed to summarize the overall level of evidence (LoE) from all streams of evidence regarding exposome effects on child health.

For 88 selected chemical and urban factors, we retrieved the conclusions of agency reports or literature reviews published between 2015 and 2021 regarding effects on child health, including cardiovascular, metabolic, neurodevelopmental, respiratory and other health outcomes. Adapted versions of PRISMA flowchart and AMSTAR-2 tool were used to select and assess the quality of the systematic reviews retrieved from PubMed and SCOPUS databases.

For each factor-outcome pair, conclusions in three streams of evidence (epidemiological, toxicological and mechanistic, the latter corresponding to in vitro and in silico approaches) were translated into stream-specific LoEs and then combined into an overall LoE ranging from "very unlikely" to "very likely".

The 88 environmental factors were implied in 611 factor-outcome pairs. Forty-four pairs (7%), corresponding to 16 factors, had a very likely overall LoE (≥80%); 127 pairs (21%), corresponding to 49 factors, had a likely or more overall LoE (≥60%). For 81 pairs (13%), no evidence was available in agency reports or published reviews, while for 275 pairs (45%), corresponding to 68 factors, the overall LoE was very unlikely (<20%). Exposure factors with the greatest number of associated health outcomes with a high overall LoE were HCB, PCBs, temperature (8 outcomes), PFOA (7 outcomes), PFOS, cotinine (6 outcomes), arsenic, lead (5 outcomes), bisphenols A and S, PFNA and $PM_{2.5}$ (4 outcomes), DDT, DDE and DDD, PFHxA, PFDA, green space, UV radiation (3 outcomes).

We developed an approach to extract and summarize the existing evidence about effects of environmental factors on health. The plausibility database built for children's health can be used to identify research gaps, conduct quantitative risk assessment studies. It could be expanded to consider a larger fraction of the exposome and other age groups and should be updated on a regular basis.

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https://doi.org/10.1016/j.ijheh.2023.114311
Received 3 June 2023; Received in revised form 25 November 2023; Accepted 12 December 2023
Available online 24 January 2024

1. Introduction

Humans are exposed to numerous environmental factors in their daily life through their living environment, consumer products, air, food and drinking water. It is recognized that fetal life and childhood are life stages with high vulnerability to environmental factors (Carroquino et al., 2012; Landrigan and Etzel, 2014; Slama and Cordier, 2013).

The exposome, which encompasses all exposures one experiences from conception onwards, includes a chemical, a physical, a behavioral, a biological (e.g., infectious factors) and a psychosocial domain. Focusing on the two first domains, there are over 350,000 chemicals and mixtures registered for production and use across 19 countries and regions (Wang et al., 2020), possibly 100,000 marketed substances in the EU (EEA (European Environment Agency), 2019a, p. 239), as well as dozens of physical factors such as noise, light, ionizing and non-ionizing radiations, temperature. Some components of the exposome can have higher exposure levels in urban areas (e.g., atmospheric pollutant and noise), where 73 % of the European population lives (EEA (European Environment Agency), 2023).

Examples of reported or plausible associations between exposure to environmental factors during early life and child health outcomes include lead exposure with decrease in intelligence quotient (IQ), arsenic and polychlorobiphenyls (PCBs) exposure with cognitive deficits, manganese exposure with behavioral effects, perfluoroalkyl substances (PFAS) with obesity and vaccine response, noise with sleep disturbances or particulate matter and other atmospheric pollutants with fetal growth, congenital heart malformations, blood pressure and respiratory health (Crawford et al., 2023; Frigerio et al., 2023; Grandjean and Landrigan, 2006; Lanphear et al., 2005; Liu et al., 2023; Pedersen et al., 2013; Wan et al., 2023; Ziou et al., 2022). This evidence regarding the possible effects of the exposome on children health is currently scattered, limiting the ability to provide an overview, to estimate the health burden related to the exposome and to identify possible knowledge gaps and research needs (Woodruff and Sutton, 2014). Most published reviews tend to focus on a single exposure, or a single factor-outcome pair, and often only consider a single stream of evidence (e.g., only toxicological evidence or, in the case of meta-analyses, often only the epidemiological evidence). Combining the body of evidence from toxicology, epidemiology and mechanistic studies is a way to relevantly describe the overall evidence between exposures and diseases integrating information from all relevant disciplines (Adami et al., 2011; Heindel et al., 2015; Linkov et al., 2009; National Research Council, 2014; Slama et al., 2017).

Our aim was to summarize the level of evidence (LoE) linking a large number of environmental factors to child health, considering findings from epidemiological, toxicological and mechanistic studies, in order to build a "plausibility database", which could be used in particular for future health impact assessments. To this end, we developed a pragmatic approach based on the conclusions of already-performed reviews, both from agency reports and the published scientific literature.

2. Methods

2.1. Overview

We considered 88 chemical and urban factors measured within ATHLETE project (Vrijheid et al., 2021) (see list in Table 1). We determined an overall LoE for each factor-health outcome pair by combining the LoEs from epidemiological, toxicological and mechanistic evidence (called "streams of evidence" in the present manuscript) (Rooney et al., 2014). To do so, we developed an approach based on the conclusions of already-performed reviews, primarily found in agency reports or otherwise in the scientific literature. Our approach included four major steps summarized in Fig. 1 and detailed in the following paragraphs. All domains of child health excluding transmissible diseases were considered; we a priori grouped health outcomes into *respiratory*, *cardiovascular*, *metabolism*, *neurodevelopmental* and *other* domains.

2.2. Step 1: identification of relevant sources of information

2.2.1. Agency reports

For each exposure, we first searched for recent agency reports published between 2015 and 2021. We browsed different agency databases, such as WHO, EFSA, ECHA, NTP, US EPA (Table S1). An agency report was considered a relevant source of information when a) the association between one or multiple given factors and one or multiple health outcomes was specifically investigated in the relevant population (infants, children, or animal-equivalent) and b) at least one stream of evidence (epidemiological, toxicological, mechanistic) was considered.

If no report published in 2015–2021 could be identified or if the identified reports did not altogether cover the three streams, we looked for older agency reports.

2.2.2. Published reviews

We searched for published reviews if a) one or more streams of evidence were missing from the identified agency reports, or if b) the literature included in the agency reports was still emerging or limited, in order to update the information retrieved.

PubMed and SCOPUS databases were accessed to identify reviews published in English through generic search queries including a

Table 1
List of environment factors considered.

Category/family	Specific environmental factors	Number of factors[a]
Per-and polyfluoroalkyl substances	EtFOSA, MeFSOA, PFBA, PFBS, PFDA, PFDoDA, PFDS, PFHpA, PFHpS, PFHxA, PFHxS, PFNA, PFOA, PFOS, PFOSA, PFPeA, PFTeDA, PFTrDA and PFUnDA	19
Metals and elements	Arsenic, Cadmium, Cesium, Cobalt, Copper, Lead, Methylmercury, Manganese, Molybdenum, Potassium, Sodium, and Thallium	12
Phthalates	BBzP, DCHP, DEHP, DEP, DiBP, DiDP, DiNP, DnBP, DnOP, DnPeP and DPHP	11
DINCH	DINCH	1
Phenols	Bisphenol A, Bisphenol AF, Bisphenol B, Bisphenol F, Bisphenol S, Methylparaben, Ethylparaben, Propylparaben, Butylparaben, Oxybenzone, Triclosan, Triclocarban	12
Pesticides	Organophosphate pesticides, Chlorpyrifos, Pyrethroids, 2–4 D	4[b]
Polycyclic aromatic hydrocarbons	Polycyclic aromatic hydrocarbons, Benzo (a)pyrene	2[b]
Persistent organic pollutants	BDE-47, DDT/DDE, HCB, PBDEs, PCBs	5[b]
Airborne pollutants		
Tobacco smoke	Cotinine	1
Air pollution	Coarse particles, Elemental carbon or black carbon in $PM_{2.5}$, Organic carbon in $PM_{2.5}$, $PM_{2.5}$, Secondary organic aerosols in $PM_{2.5}$, Ultrafine particles, NO_2	7
Physical factors		
Noise	Aircraft, traffic, railway noise	3
Green space	Urban green space	1
Blue space	Blue space	1
Temperature	Temperature	1
Humidity	Humidity	1
Built environment	Food environment, Accessibility, Availability, Proximity, Traffic	5
Ultraviolet radiation	UV	1
Light at night	Light at night	1
	Total number of factors	**88**

[a] In some cases (e.g., organophosphate pesticides, polycyclic aromatic hydrocarbons) a whole family of factors was counted as one.

[b] Considering the amount of information on Chlorpyrifos, Benzo(a)pyrene and BDE-47, separate assessments were conducted for these chemicals.

combination of general keywords and concepts: ((common OR alternative names of the factor of interest) OR (CAS registered number of the chemical, if relevant)) AND (disease, disorder, illness, pathology, health, risk OR toxicity) AND (review OR meta-analysis) AND NOT (water, soil, sediment OR matrice) (Fig. S1). This syntax was used for each of the considered exposure factors. The syntax was then refined on a case-by-case basis with more exclusion terms according to results obtained. First, we excluded reviews that appeared out of the scope, based on title and abstract screening. Second, based on full-text screening, we selected the reviews relevant to our Population, Exposure, Comparator, Outcomes (PECO) criteria for inclusion (Table S2) (ANSES, 2017). For the epidemiological and toxicological streams, we only considered systematic reviews, since non-systematic reviews tend to report only positive results while systematic reviews relying on identification of all relevant data (including unpublished data) are less prone to evidence selection bias (Drucker et al., 2016). Regarding mechanistic data, we retained all types of reviews. We adapted the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart to describe the

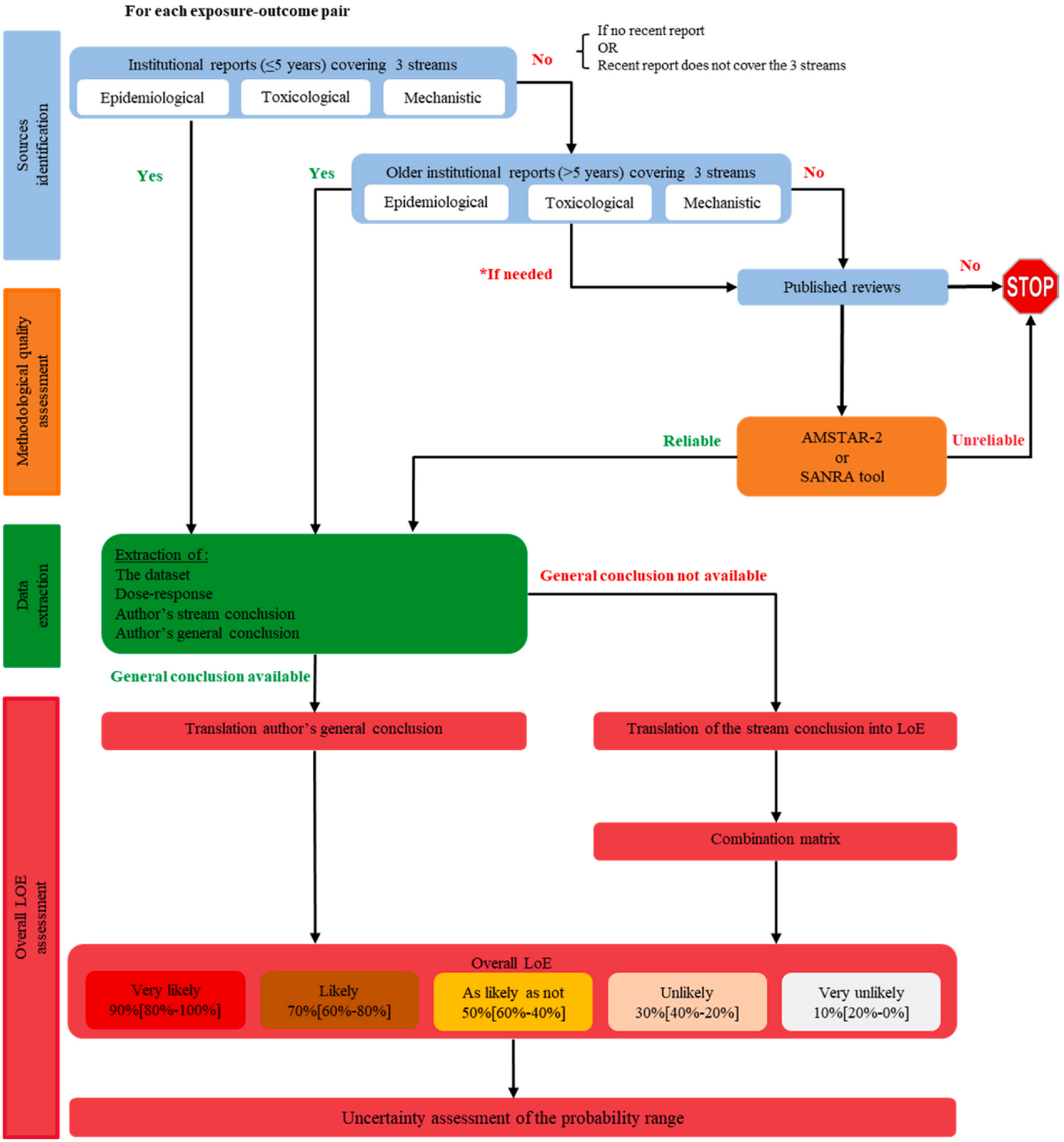

Fig. 1. Methodology flowchart summarizing the approach developed to determine the synthetic probability of causation of each factor-outcome pair.
* "If needed" represents cases in which literature included in agency reports is still emerging or limited.

identification, screening, eligibility and inclusion of reviews (Page et al., 2021).

2.3. Step 2: quality assessment of the sources of information

We a priori considered the conclusions from agency reports to be reliable, so they were all considered to establish the LoE without specific quality assessment. They sometimes follow international guidelines or recommended approaches. Moreover, they often rely on a relevant number of multi-disciplinary experts in their respective areas of expertise or on working groups of scientists with relevant expertise. To assess the quality of the systematic reviews, one assessor used a modified version of the Assessment of Multiple Systematic Reviews-2 (AMSTAR-2) tool (Table S3) (Shea et al., 2017). AMSTAR-2 tool was adapted by setting a threshold of 4 for the number of non-critical weaknesses downgrading the quality of the study (Table S3) (Shea et al., 2017). Only those scored as being of moderate or high quality according to AMSTAR-2 tool were included and considered for establishing the LoE. The non-systematic reviews dedicated to mechanistic data were assessed using SANRA (Table S4) (Baethge et al., 2019). A scoring system was implemented for SANRA tool to standardize quality assessment (Table S4) (Baethge et al., 2019). Only those evaluated as being of moderate or high quality according to the modified SANRA tool were used to establish the LoE.

2.4. Step 3: data extraction

For each factor-outcome pair, each stream of evidence and each source of information of high enough quality, we extracted the text underlying the authors' conclusions as well as the overall conclusions encompassing all streams, if available.

2.5. Step 4: evidence Integration/LoE assessment

We defined an overall LoE integrating all streams of evidence. This overall LoE was classified into 5 levels from "very unlikely" to "very likely", as modified from (Hart et al., 2019), with five probability ranges of equal size (Table 2). We considered an overall LoE with a probability of causation of 60 % or more (likely and very likely LoEs) to be high.

Two independent assessors assessed the LoEs as described below; disagreements between assessors were adjudicated by a third assessor, who used the same approach to assess the LoE.

If a general conclusion integrating all streams of evidence was available for a factor-outcome pair in the retrieved source of information, the wording used by the authors was directly translated into an overall LoE as explained in Table S5.

If only a conclusion covering one stream of evidence was available, the conclusion from this stream was translated into stream-specific LoE descriptors (Table S6). If no stream-specific conclusion was available, the two assessors independently rated the stream-specific LoE descriptors based on the data reported in the reports or reviews. The LoE was allocated based on the results of the studies and then upgraded or downgraded based on the strengths and weaknesses reported (quality of the study design, risk of bias, consistency among studies, dose response). If the report or review did not cover a given stream, the "no data" descriptor was applied. We then combined the stream-specific LoE descriptors of each of the three streams into an overall LoE. To do so, we relied on a matrix combining the evidence from all three considered streams adapted from IARC (Samet et al., 2020) and described in Table 2. This matrix in particular considers that if moderate epidemiological evidence is available, then the overall level of evidence is at least likely. This is coherent with the Navigation Guide methodology, which gives human (observational) studies an a priori rating of "moderate" (Woodruff and Sutton, 2014), which is higher than that generally given to observational studies in the field of clinical research, and which appears justified by the facts that randomization is hard to achieve in the field of environmental health, and that the development of causal inference tools allows to provide a high level of evidence on the basis of well-designed and analyzed observational studies (Hernan and Robins, 2020).

Table 2
Combination matrix to integrate levels of evidence from separate streams into an overall level of evidence.

Stream-specific level of evidence			Overall Level of Evidence and corresponding probability range.
Epidemiological stream	Toxicological stream	Mechanistic stream	
Strong	Anything from *no data* to *strong* (epidemiological evidence is considered "sufficient")	Anything from *no data* to *strong* (epidemiological evidence is considered "sufficient")	Very likely 90% [80%–100%]
Moderate	Strong	Strong	
Weak-Very weak-No data	Strong	Strong	
Moderate	Strong	Moderate	Likely 70% [60%–80%]
Moderate	Strong	Weak-Very weak-No data	
Moderate	Moderate	Strong	
Moderate	Moderate	Moderate	
Moderate	Moderate	Weak-Very weak-No data	
Moderate	Weak-Very weak-No data	Strong	
Moderate	Weak-Very weak-No data	Moderate	
Moderate	Weak-Very weak-No data	Weak-Very weak-No data	
Weak-Very weak-No data	Strong	Moderate	
Weak-Very weak-No data	Moderate	Strong	
Weak-Very weak-No data	Moderate	Moderate	
Weak-Very weak-No data	Strong	Weak-Very weak-No data	
Weak-Very weak-No data	Moderate	Weak-Very weak-No data	As likely as not 50% [40%–60%]
Weak-Very weak-No data	Weak-Very weak-No data	Strong	
Weak-Very weak-No data	Weak-Very weak-No data	Moderate	
Weak	Weak	Weak	
Weak	Weak	Very weak-No data	Unlikely 30% [20%–40%]
Weak	Very Weak-No data	Weak	
Very weak-No data	Weak	Weak	
All other combinations for which at least one level of evidence was retrieved, including "very weak" in all 3 streams			Very unlikely 10% [0%–20%]
No data retrieved in any of the 3 streams			*No overall LoE allocated*

The reliability of this matrix was tested on a limited number of exposures by checking whether the combination of the 3 streams would lead to the same overall LoE as the one obtained by direct translation of the general conclusion (Table S7). When no data could be retrieved for all three streams, no overall LoE was allocated (Table 2).

If several eligible reports or publications reported different overall LoEs for a given factor-outcome pair, the final LoE provided corresponded to the average of these LoEs.

Each LoE was provided with an uncertainty interval (or "probability range") centered around the point estimate of the LoE. By default, the probability range was assumed to have a range of 20% (Table 2). In the case when several reports reported different LoEs, the probability range associated with the LoE was enlarged to encompass the range of

probabilities from all sources. For instance, if two sources reported "likely (70% [60%–80% [)" and "very likely (90% [80%–100% [)" as LoEs for a given exposure-outcome pair, our final LoE was "80% [60–100% [(from likely to very likely)".

We summarized the results of the plausibility database in several ways: 1) by listing all exposure factor-outcome pairs with an overall LoE (i.e., the center of the uncertainty range) of 60% or more; 2) by plotting the distribution of all overall LoEs across all exposure factor-outcome pairs; 3) by plotting, for each exposure factor, the number of associated health outcomes for factor-outcome pairs with an overall LoE of 60% or more; and finally 4) by showing the highest overall LoE of each exposure factor within each health outcome domain, ranking exposure factors by increasing average LoE across all four main health domains (cardiovascular, metabolism, neurodevelopment, respiratory health).

3. Results

3.1. Distribution of the overall level of evidence across exposure factors

The 88 considered exposure factors (Table 1) corresponded to 611 factor-outcome pairs. Overall, 44 pairs (7%) from 16 environmental factors (18% of the considered environmental factors) had a very likely (90%) overall LoE, and 127 pairs involving 49 factors had an overall LoE of 60% or more (considered as a high level of evidence; Table 3 and Fig. 2). These data have been compiled in the *plausibility database, v.1.2* (available in Athlete project Toolbox at https://athleteproject.eu/download/1526/?tmstv=1682836829).

From the stream-specific evidence available in the literature reviewed, an overall LoE from "very unlikely" to "very likely" could be derived for 530 pairs (87%), while no evidence could be retrieved for the remaining 81 pairs (13%, Fig. 2). The factors with the largest number of associations with a high overall LoE (60% or more) were HCB, PCBs, temperature (8 associations each), PFOA (7 associations), PFOS, cotinine/tobacco smoke (6 associations), arsenic, lead (5 associations), bisphenols A and S, PFNA and $PM_{2.5}$ (4 associations), DDT, DDE and DDD (considered altogether), PFHxA, PFDA, green space, UV radiation (3 associations, Fig. 3). Fig. 4 provides a ranking of all exposures according to their overall LoE; it shows in particular the compounds with the highest number of health domains for which no data could be retrieved.

3.2. Distribution of the level of evidence across health outcomes

The 127 factor-outcome pairs with an overall LoE of 60% or higher were mainly related to neurodevelopmental effects (30 pairs, or 23.6%), metabolism (27 pairs, or 21.2%), respiratory effects (18 factor-outcome pairs, or 13%) and reproduction (14 factor-outcome pairs, or 11%, Fig. 3, Fig. S2E and Table 3). For the cardiovascular system, one environmental factor (sodium) showed a high overall LoE for at least one outcome, which was blood pressure. Effects on neurodevelopment with a LoE of 60% or more were related to several persistent organic pollutants (PCBs, HCB, PBDEs, benzo(a)pyrene), metals (lead, arsenic, cadmium, methylmercury, manganese), pesticides (organophosphate pesticides, chlorpyrifos), phenols (bisphenols A and S), perfluoroalkyl substances (PFOA, PFOS, PFHxS) and aircraft noise. Sixteen environmental exposures, including persistent organic pollutants (PCBs), metals (arsenic, cadmium, thallium), cotinine, phenols (bisphenol A), perfluoroalkyl substances (PFOA, PFOS, PFHxA, PFNA, PFDA, PFUnDA, PFBS, PFDoDA), cotinine, food environment and green space were linked to metabolic outcomes (including birth weight and postnatal growth). Regarding the respiratory system, the 9 environmental factors with high LoE were persistent organic pollutants (HCB, PCBs), a metal (lead), cotinine, several air pollutants (NO_2, $PM_{2.5}$, coarse particles, elemental carbon in $PM_{2.5}$) and temperature.

We provide below illustrations of the implementation of our approach for three contrasted factor-outcome pairs.

Table 3
List of the 127 factor-outcome pairs (corresponding to 49 exposure factors) with a high overall level of evidence (central estimate, 60% or more).

Exposure factor	Target system	Effects
Very likely effect (80–100%)		
Lead	Neurodevelopment	Cognitive outcomes
Lead	Neurodevelopment	Behavioral outcomes
Lead	Reproductive function (male and female)	Delayed Puberty onset
Lead	Hematological	Decreased RBC survival and function + Altered Heme Synthesis
Bisphenol A	Neurodevelopment	Cognitive outcomes
Bisphenol B	Reproductive function (male)	Alteration of spermatogenesis
Organophosphate pesticides	Neurodevelopment	Cognitive outcomes
Organophosphate pesticides	Neurodevelopment	Behavioral outcomes
Methylmercury	Neurodevelopment	Cognitive outcomes
Methylmercury	Neurodevelopment	Behavioral outcomes
HCB	Neurodevelopment	Neurological effects (including weakness, paresthesia, sensory shading, myotonia locomotor skill impairment)
HCB	Neurodevelopment	Social behavior
HCB	Infant death	Infant death [ACCIDENTAL EXPOSURE]
HCB	Dermal	Skin lesion [ACCIDENTAL EXPOSURE]
Copper	Hepatic	Increased genetic susceptibility to copper toxicity (Wilson's Disease, Indian Childhood Cirrhosis, Idiopathic Copper Toxicosis)
Cotinine	Infant death	Neonatal mortality, Sudden infant death syndrome (SIDS), Neonatal mortality
Cotinine	Fetal death	Stillbirth
Cotinine	Congenital malformations (= Birth defects)	Orofacial clefts
Cotinine	Respiratory	Chronic respiratory symptoms (Cough, phlegm, wheeze, dyspnea, etc.), influenza, pneumonia, infections and acute respiratory illnesses. Middle ear disease and adenotonsillectomy, asthma
Cotinine	Respiratory	Asthma, cough
Cotinine	Metabolism	Lower birth weight
PCB	Neurodevelopment	Cognitive outcomes (Lower IQ, impaired language, mental, memory)
PCB	Neurodevelopment	Psychomotor effects
PCB	Neurodevelopment	Attention disorders, personal/social development, more behavioral disorders, higher activity levels
PCB	Metabolism	Lower birth weight, altered growth rate
PCB	Metabolism	Lower head circumference
PCB	Immune system	Weaker immune system
PCB	Respiratory	Higher prevalence of bronchitis or pneumonia and respiratory tract infections (accidental exposure)
Thallium	Metabolism	Birth weight reduction
NO_2	Respiratory	Asthma exacerbation
$PM_{2.5}$	Respiratory	Asthma development
$PM_{2.5}$	Respiratory	Lung function and development
$PM_{2.5}$	Respiratory	Asthma exacerbation
Green space	Physical activity	Physical activity
Green space	Metabolism	Birth weight
Green space	Metabolism	Obesity and overweight
Temperature	Dehydration	Dehydration
Temperature	Birth outcomes	Birth outcomes

(*continued on next page*)

Table 3 (*continued*)

Exposure factor	Target system	Effects
Temperature	Mortality	Mortality
Temperature	Respiratory	Asthma symptoms (excaerbation)
Food environment	Metabolism	Malnutrition
Ultraviolet radiation	Skin	Sunburns
Ultraviolet radiation	Skin	Cancer: Cutenous malignant melanoma
Ultraviolet radiation	Vitamin D	Vitamin D
***Likely* to *very likely* effect (60–100%)**		
Chlorpyrifos	Neurodevelopment	Cognitive outcomes
Chlorpyrifos	Neurodevelopment	Behavioral outcomes
Bisphenol A	Mammary gland	Mammary gland development
Bisphenol A	Reproductive function (female)	Alteration of oestrus cycle
Bisphenol S	Reproductive function (female)	Alteration of oestrus cycle
DEHP	Reproductive function (male)	Phthalate syndrome (AGD, alterations in fetal testosterone concentration)
BBP or BBzP	Reproductive function (male)	Phthalate syndrome (AGD, alterations in fetal testosterone concentration)
DiBP	Reproductive function (male)	Phthalate syndrome (alterations in fetal testosterone concentration)
DBP or DnBP	Reproductive function (male)	Phthalate syndrome (AGD, hypospadia, alterations in fetal testosterone concentration)
Butylparaben	Reproductive function (male)	Alteration of spermatogenesis
DCHP	Reproductive function (male)	Phthalate syndrome
PFOS	Immune system	Decreased antibody response to vaccines
Coarse particles (PM10–2.5)	Respiratory	Hospital admissions
PFHxS	Immune system	Decreased antibody response to vaccines
PFOA	Immune system	Decreased antibody response to vaccines
Likely effect (60–80%)		
Lead	Respiratory	Asthma
Benzo(a)pyrene	Neurodevelopment	Behavioral outcomes
Bisphenol F	Reproductive function (male)	Alteration of spermatogenesis
Bisphenol S	Neurodevelopment	Anxiety-related behavior (Toxicological data)
Bisphenol S	Reproductive function (male)	Alteration of spermatogenesis
Bisphenol S	Mammary gland	Mammary gland development
DDT, DDE, and DDD	Fetal death	Spontaneous abortion and preterm birth
DDT, DDE, and DDD	Preterm birth	Spontaneous abortion and preterm birth
DDT, DDE, and DDD	Reproductive function (male)	Alteration of male reproductive function
PBDE	Neurodevelopment	Behavioral outcomes
PBDE	Neurodevelopment	Cognitive outcomes
Arsenic (inorganic)	Metabolism	Birth weight/fetal growth, postnatal growth
Arsenic (inorganic)	Neurodevelopment	Cognitive outcomes
Manganese	Neurodevelopment	Behavioral outcomes
HCB	Neurodevelopment	Thyroid hormones levels
HCB	Respiratory	Asthma, wheeze
HCB	Respiratory	Chest infection
Sodium (sodium chloride)	Cardiovascular	Blood pressure
DnPeP or DPP	Reproductive function (male)	Phthalate syndrome
PCB	Neurodevelopment	Thyroid hormones levels
PFDA	Metabolism	Birth Weight
PFDA	Fetal death	Miscarriage/prenatal losses
PFDoDA	Fetal death	Miscarriage/prenatal losses
PFHxA	Metabolism	Birth Weight
PFHxA	Metabolism	Growth in infancy or childhood/postnatal growth
PFHxA	Fetal death	Miscarriage/prenatal losses
PFNA	Metabolism	Birth Weight
PFNA	Metabolism	Growth in infancy or childhood/postnatal growth
PFNA	Fetal death	Miscarriage/prenatal losses
PFOA	Metabolism	Birth Weight
PFOA	Metabolism	Growth in infancy or childhood/postnatal growth
PFOA	Fetal death	Miscarriage/prenatal losses
PFOS	Metabolism	Birth Weight
PFOS	Metabolism	Growth in infancy or childhood/postnatal growth
PFOS	Fetal death	Miscarriage/prenatal losses
PFUnDA/PFUnA	Metabolism	Birth Weight
PFUnDA/PFUnA	Metabolism	Growth in infancy or childhood/postnatal growth
NO_2	Respiratory	Asthma development
Elemental carbon or black carbon in PM2.5	Respiratory	Hospital admissions
Aircraft noise	Neurodevelopment	Cognition, long term memory, reading comprehension, attetion. annoyance, cornitive performance, oral comprehension,
Arsenic (inorganic)	Respiratory	Immunological outcomes (including increased susceptibility to respiratory tract infections)
Arsenic (inorganic)	Fetal death	Fetal death
Arsenic (inorganic)	Infant death	Infant death
HCB	Cardiovascular	Cardiovascular failure [ACCIDENTAL EXPOSURE]
PFDA	Immune system	Decreased antibody response to vaccines
Elemental carbon or black carbon in PM2.5	Metabolism	Birth weight
PM2.5	Respiratory	Allergy exacerbation
Railway noise	Neurodevelopment	Emotional and conduct disorder, hyperactivity
Road traffic noise	Neurodevelopment	Attention, hyperactivity and emotional disorders
Temperature	Respiratory	General respiratory diseases (ER visits and hospital admissions)
Temperature	Neurodevelopment	Central nervous system
Temperature	Renal	Renal disease
Temperature	Gastrointestinal	Gastrointerstinal diseases
Humidity	Respiratory	Asthma
Light at night	Circadian rhythm	Eveningness and DSPD (Delayed Sleep Phase Disorder)
***As likely as not* to *very likely* (40–100%)**		
Cadmium	Metabolism	Birth weight
Bisphenol A	Metabolism	Obesity and hormonal effects
PFOS	Metabolism	Increase in cholesterol levels
***As likely as not* to *Likely* (40–80%)**		
Cadmium	Neurodevelopment	Cognitive outcomes
PFBS	Metabolism	Birth Weight
PFBS	Metabolism	Growth in infancy or childhood/postnatal growth
PFDoDA	Metabolism	Growth in infancy or childhood/postnatal growth
PFHxS	Neurodevelopment	Behavior/Motor activity
PFOA	Neurodevelopment	Behavior/Motor activity
PFOA	Mammary gland	Delay in mammary gland development
PFOS	Neurodevelopment	Behavior/Motor activity
***Unlikely* to *Very likely* (20–100%)**		
PFNA	Immune system	Decreased antibody response to vaccines
PFOA	Metabolism	Increase in cholesterol levels

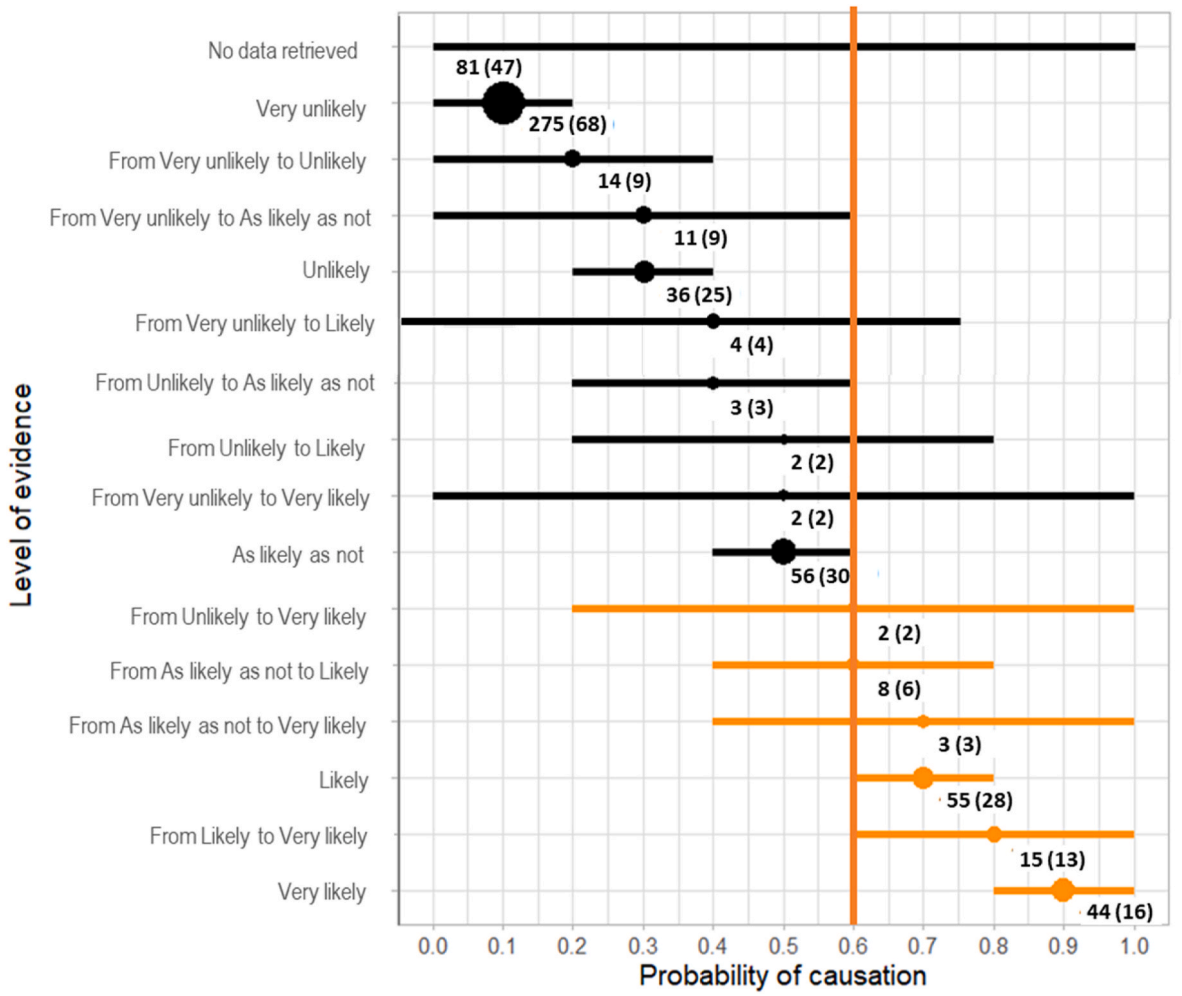

Fig. 2. Distribution of the number of factor-outcome pairs according to the overall LoE and the corresponding uncertainty (indicated by the horizontal line). Numbers indicate the number of factor-outcome pairs (the corresponding number of environmental factors is given in the parentheses). Factor-outcome pairs with a probability of causation above 60% are shown in orange. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

3.3. LoE assessment for methylmercury effects on neurodevelopment

Two agency reports regarding methylmercury (MeHg) were identified for the 2015–2021 time period (ECHA, 2017; EFSA, 2018). EFSA (2018) conducted an in-depth analysis of the three streams of evidence (Table 4), but no general conclusion was proposed. EFSA (2018) stated that it is recognized that children highly exposed to methylmercury are at increased risk to exhibit adverse neurodevelopmental outcomes. These effects were supported by toxicological findings, which provided evidence of persistent damage of the nervous system after developmental exposure. Based on the wording used, "strong" LoE descriptors were allocated to both epidemiological and toxicological streams (Table 4). Regarding the mechanistic stream, EFSA (2018) considered that several modes of action encompassing mitochondrial dysfunction, disruption of the neurotransmitter systems, neuronal cell damage could possibly underlie the neurotoxicity and neurodevelopmental toxicity of methylmercury; a "moderate" LoE descriptor was allocated. The integration of human, animal and mechanistic LoE descriptors through the combination matrix (Table 2) resulted in a "very likely" overall LoE for neurodevelopment (Table 4).

Methylmercury was classified as reprotoxicant 1 A (developmental toxicity) by ECHA (2017) due to its causal relationship with neurodevelopmental effects (Table 4). Based on the keywords used, this general conclusion was directly translated into a "very likely" overall LoE regarding effects on reproduction. Note that the use of the combination matrix to integrate the three streams led to the same synthetic probability of causation (Table S7).

The overall LoEs derived from EFSA (2018) and ECHA (2017) were similar and led to the conclusion of a "very likely [80%–100%]" LoE for the neurodevelopmental effects of methylmercury (Table 4).

3.4. LoE assessment for cadmium effects on neurodevelopment

Two reports covering cadmium were identified (ANSES, 2019a; HBM4EU, 2021). ANSES (2019a) stated that some epidemiological studies suggested the existence of discrete neurocognitive disorders, while HBM4EU (2021) concluded that the evidence for an association of cadmium exposure with neurotoxic outcomes was still limited based on epidemiological evidence alone. According to the keywords used, "weak" LoEs descriptors were allocated for the epidemiological stream (Table 4). Since these reports did not cover the three streams of evidence, we identified older reports to cover the missing streams. ATSDR (2012) stated that the most sensitive indicator of effect appears to be neuro-behavioral development in animals; a "moderate" LoE was thus allocated to the toxicological stream. Very limited mechanistic data was available according to ATSDR (2012), therefore the LoE for the mechanistic stream was considered "very weak".

Due to the limited amount of information available in ATSDR (2012)

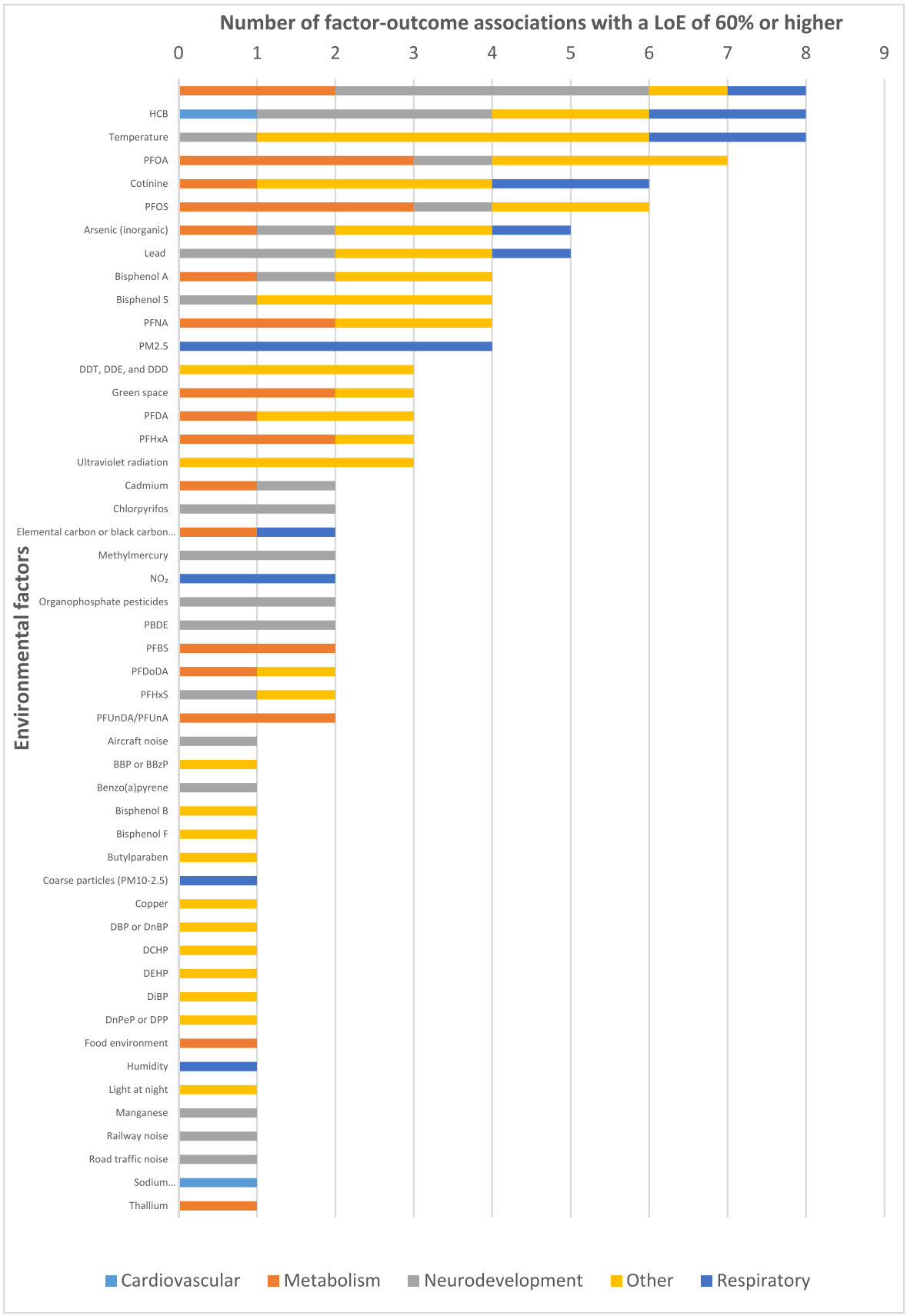

Fig. 3. Number and family of health outcomes among the 127 factor-outcome pairs (corresponding to 49 factors) with an overall LoE of 60 % or more (central estimate of the reliability interval).

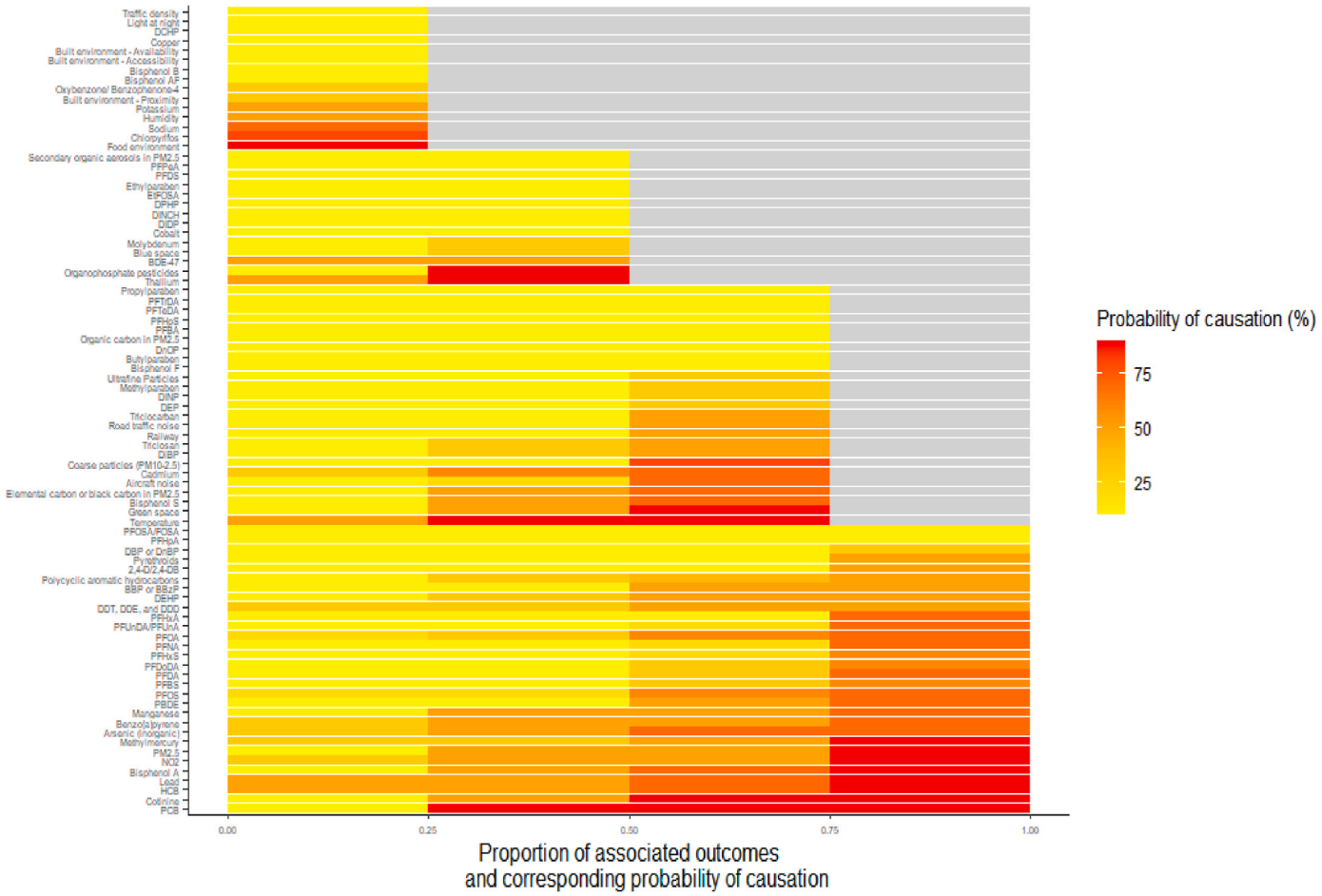

Fig. 4. Distribution of the highest level of evidence by family of health outcome across exposure factors. For simplicity, the graph was limited to effects in the four main axes of cardiovascular, metabolic, neurologic and respiratory health. Substances were sorted by increasing level of evidence. In each of the four health outcome domains, the color indicates the outcome with the highest level of evidence with the considered exposure factor. Grey indicates a lack of data. Exposure factors were ranked by increasing overall LoE across all four health outcomes domains (cardiovascular, metabolism, neurodevelopment, respiratory health). (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

regarding mechanistic evidence, a literature search was further conducted and two reviews were retrieved (Branca et al., 2020; Rodríguez-Barranco et al., 2013). Rodríguez-Barranco et al. (2013) suggested that cadmium reaches the central nervous system to cause neurotoxic effects such as inhibition of sulfhydryl-containing enzymes and depression of neurotransmitters. Branca et al. (2020) stated that cadmium deleterious effects can be linked to indirect reactive oxygen species generation. Based on the keywords used, "weak" and "moderate" LoE descriptors were respectively allocated. The integration of human, animal and mechanistic LoE descriptors through the combination matrix resulted in "from *As likely as not* to *Likely*" overall LoE, with an enlarged uncertainty interval given the inconsistencies in LoE descriptors (40–80%, Table 4).

3.5. LoE assessment for green space effects on mental health

Three agency reports covering possible effects of green space exposure on mental health were identified (EEA (European Environment Agency), 2019b; Public Health England, 2020; WHO Europe, 2016). WHO Europe (2016) reported accumulating, yet sometimes inconsistent evidence for a beneficial role of green space on mental wellbeing of children. It mentioned three epidemiological studies that looked at mental health and green spaces and, based on the keywords used, we allocated a "weak" LoE for the epidemiological stream. As no toxicological or mechanistic evidence was reported, a "very unlikely" LoE was assigned according to the combination matrix of Table 2.

The EEA (EEA (European Environment Agency), 2019b) cited two epidemiological studies that reported a beneficial role of green spaces on stress reduction and social networking. Both studies were given a "weak" LoE as the report cites a very limited number of studies and refers to the associations as growing. The report of PHE (2020) cited three different epidemiological reviews, which concluded that green space has a beneficial role on mental wellbeing outcomes in children and young people. The health outcomes included: emotional wellbeing, reduced stress, improved resilience, and higher health-related quality of life. For this report a "strong" LoE for the epidemiological stream has been assigned, as three reviews reported a positive association. In this report, neither toxicological nor mechanistic evidence was reported either; overall, no report nor review could be identified that reported on toxicological or mechanistic evidence for this exposure-health outcome pair.

Given the combination matrix (Table 2), the two "Weak/Very unlikely" LoE for the epidemiological stream in the absence of toxicological and mechanistic evidence led to a "very unlikely" overall LoE, while the "strong/very likely" LoE for the epidemiological stream led to a "very likely" overall LoE. Considering these three overall LoE together led to a reliability interval ranging "from Very unlikely to Very likely" for the association between green space and mental health (Table 4).

Table 4
Example of assessment of the overall level of evidence for 3 selected factor-outcome pairs.

Exposure factor and source of information	Outcomes investigated	Stream of evidence						Overall LoE and probability range
		Epidemiological		Toxicological		Mechanistic		
		Keywords used	Corresponding LoE	Keywords used	Corresponding LoE	Keywords used	Corresponding LoE	
1. Methylmercury	**Neurodevelopment**							
EFSA (2018)	Cognitive and behavioral outcomes	Recognized	Strong	Provide evidence	Strong	Possibly	Moderate	*Very likely* - 90% [80%–100%]
ECHA (2017)	Cognitive and behavioral outcomes	Show, are responsible	Strong	Show	Strong	(None)	No data	
2. Cadmium	**Neurodevelopment**							
ANSES, 2019	Cognitive	Suggest	Weak	(None)	No data	(None)	No data	From *As likely as not* to *Likely* - 60% [40%–80%]
HBM4EU, 2021	Cognitive	Limited	Weak	(None)	No data	(None)	No data	
ATSDR (2012)	Neuro developmental effects	No update		Appears to be	Moderate	Paucity	Very weak	
Rodríguez-Barranco et al. (2013)	Neurotoxicity	No update		(None)	No data	Suggest	Weak	
Branca et al. (2020)	Neurotoxicity	No update		(None)	No data	Can	Moderate	
3. Green space	**Mental Health**							
WHO, 2016	Mental health	Accumulating, inconsistent	Weak	(None)	No data	(None)	No data	From *Very Unlikely* to *Very likely* – 50% [0%–100%]
EEA, 2019	Well-being and stress	Offer, growing	Weak	(None)	No data	(None)	No data	
Public Health England, 2020	Well-being	Systematic reviews have found positive association	Strong	(None)	No data	(None)	No data	

The keywords identified in the authors' conclusions were extracted and translated into LoE descriptors for each stream to assess the overall LoE (Table S6). For more details see the methods section. LoE: level of evidence.

4. Discussion

We developed an approach allowing the assessment of the LoE for many exposure-health outcome pairs related to children health, by compiling epidemiological, toxicological and mechanistic evidence of adverse effects. We based our conclusions on already-performed reviews, identified from agency reports and literature reviews. In addition to the qualitative assessment of level of evidence of an association, we provided quantitative uncertainty intervals on the probability of causation from a predefined probability allocation method. Using this approach, we were able to classify the LoE of 530 factor-outcome pairs. We prioritized 127 factor-outcome pairs based on their high overall LoE. This "plausibility" database is made available to allow future use (see https://athleteproject.eu/download/1526/?tmstv=1682836829).

4.1. Identification of the relevant sources of evidence

In order to gather the available evidence regarding the potential health effects of a given exposure, the gold-standard approach is to perform a systematic review (ANSES, 2019b; Trasande et al., 2015). However, conducting *de novo* systematic reviews for a large range of environmental factors (611 exposure-outcome pairs considered in our case) is very time-consuming and requires very large expert human resources. This becomes an issue when health agencies or policy makers need a rapid answer to guide their recommendations or decisions on a specific matter (Mallett et al., 2012; Tsertsvadze et al., 2015). For this reason, we developed a significantly less time-consuming approach building on the existing research synthesis from environmental health agencies reports and published reviews. We considered agency reports and reviews published from 2015 to 2021 and did not include individual studies (in the sense of studies relying on primary data and not syntheses of the existing literature). Exposure-outcome pairs for which we indicate a lack of data may therefore correspond to potential effects not studied at all, or to effects studied but for which no literature synthesis exists. Agency reports more and more tend to simultaneously consider the various streams of evidence, including from in-vitro, animal and human studies, regarding a factor and multiple health outcomes. Together with published review articles, they constitute a great synthetic source of information and an efficient way to find evidence for a large number of exposure-outcome pairs. However, these reports, as well as reviews, are in essence lagging with respect to the publication of the individual studies on which they rely. Therefore, emerging concerns regarding a chemical and its toxicity may be captured with some delay in our plausibility database. Relying on such synthetic evidence (as opposed to individual original studies) may be seen as constituting a trade-off between robustness (provided by reviews and agency reports) and up-to-datedness. Indeed, such synthetic results are likely to be more robust than a single study on the topic but may miss very recent results or concerns, and our results should therefore be seen as provisory – as any review on complex and recent topics. For instance, recent epidemiological systematic reviews published after ANSES (2019a) and HBM4EU (2021) report are in favor of a causal relationship between cadmium and cognitive outcomes (Chatterjee and Kortenkamp, 2022), while the LoE reported in our assessment focused on the 2015–2021 literature only corresponds to a *likely* effect. Another example is triclosan, which is currently undergoing an assessment as endocrine disruptor under REACH regulation. Depending on this updated assessment of toxicological and mechanistic evidence including new data requested under REACH evaluation, the overall LoE regarding neurodevelopmental toxicity of the substance may change. The draft scientific opinion from EFSA on bisphenol A re-evaluation was submitted for public consultation but was not published in December 2021, the end of our study period, and was therefore not taken into account in the LoE. There is therefore a critical need to maintain an update of this database on a regular basis. It should be mentioned that it is not certain that considering individual studies would have made our results more in line with the most recent literature, because considering individual studies implies to devote more time for literature review and synthesis, and thus would delay the publication time of a study like ours, compared to our approach that allows reviewing directly a more limited number of documents.

4.2. Evaluation of evidence

Several approaches can be used to evaluate the quality of systematic reviews. We did rely on AMSTAR-2 tool to assess the quality of

Table 5
List of the 62 factor-outcome pairs (corresponding to 29 exposure factors) for which conflicting evidence has been found across the reports/reviews.

Exposure Factor	Target system	Sources	Effect
From *Likely* to *Very likely* 80% [60%-100%]			
Chlorpyrifos	Neurodevelopment	EFSA 2019 + US EPA 2016	Cognitive outcomes
Chlorpyrifos	Neurodevelopment	EFSA 2019 + US EPA 2016	Behavioral outcomes
Bisphenol A	Mammary gland	EFSA 2015	Mammary gland development
Bisphenol A	Reproductive function (female)	ECHA 2017 ED potential under REACH regulation-SVHC, CLH Regulation	Alteration of oestrus cycle
Bisphenol S	Reproductive function (female)	HBM4EU, 2021 + ECHA 2019 CLH under CLP regulation (RAC)	Alteration of oestrus cycle
DEHP	Reproductive function (male)	NAS 2017 + HBM4EU 2017 + ECHA 2016 annex XV restriction dossier including ED potential under REACH regulation-SVHCi and CLH under CLP regulation	Phthalate syndrome (AGD, alterations in fetal testosterone concentration)
BBP or BBzP	Reproductive function (male)	NAS 2017 + HBM4EU 2017 + ECHA 2016 annex XV restriction dossier including ED potential under REACH regulation-SVHCi and CLH under CLP regulation	Phthalate syndrome (AGD, alterations in fetal testosterone concentration)
DiBP	Reproductive function (male)	NAS 2017 + HBM4EU 2017 + ECHA 2016 annex XV restriction dossier including ED potential under REACH regulation-SVHCi and CLH under CLP regulation, Health Canada 2015	Phthalate syndrome (alterations in fetal testosterone concentration)
DBP or DnBP	Reproductive function (male)	NAS 2017 + HBM4EU 2017 + ECHA 2016 annex XV restriction dossier including ED potential under REACH regulation-SVHCi and CLH under CLP regulation	Phthalate syndrome (AGD, hypospadia, alterations in fetal testosterone concentration)
Butylparaben	Reproductive function (male)	ECHA 2020 ED potential under REACH regulation-SVHC, Health Canada 2020, RIVM 2018 ED assessment	Alteration of spermatogenesis
DCHP	Reproductive function (male)	Health Canada 2015, ECHA 2016 SVHC report including ED potential under REACH regulation-SVHCand CLH under CLP regulation	Phthalate syndrome
PFOS	Immune system	ATSDR 2021 + EFSA 2108/2020 + Health Canada 2018 + USEPA 2016	Decreased antibody response to vaccines
Coarse particles ($PM_{10-2.5}$)	Respiratory	Health Canada 2016	Hospital admissions
PFHxS	Immune system	ATSDR 2021 + EFSA 2020	Decreased antibody response to vaccines
PFOA	Immune system	ATSDR 2021 + EFSA 2108/2020 + Health Canada 2018 + USEPA 2016	Decreased antibody response to vaccines
From *As likely as not* to *Very likely* 70% [40%-100%[			
Cadmium	Metabolism	ATSDR 2012 + Huang et al., 2017 + Geng et al., 2019	Birth weight
Bisphenol A	Metabolism	EFSA 2015 + ECHA 2017 ED potential under REACH regulation-SVHC	Obesity and hormonal effects
PFOS	Metabolism	ATSDR 2021 + EFSA 2108/2020 + Health Canada 2018 + USEPA 2016	Increase in cholesterol levels
From *As likely as not* to *Likely* 60% [40%-80%[			
Cadmium	Neurodevelopment	HBM4EU, 2021 + ANSES 2019 + ATSDR 2012 + Rodríguez-Barranco et al., (2013) + Branca et al., (2020)	Cognitive outcomes
PFBS	Metabolism	ATSDR 2021 + EFSA 2020	Birth Weight
PFBS	Metabolism	ATSDR 2021 + EFSA 2020	Growth in infancy or childhood/postnatal growth
PFDoDA	Metabolism	ATSDR 2021 + EFSA 2020	Growth in infancy or childhood/postnatal growth
PFHxS	Neurodevelopment	ATSDR 2021 + EFSA 2020	Behavior/Motor activity
PFOA	Neurodevelopment	ATSDR 2021 + EFSA 2108/2020 + Health Canada 2018 + USEPA 2016	Behavior/Motor activity
PFOA	Mammary gland	ATSDR 2021 + EFSA 2108/2020 + Health Canada 2018 + USEPA 2016	Delay in mammary gland development
PFOS	Neurodevelopment	ATSDR 2021 + EFSA 2108/2020 + Health Canada 2018 + USEPA 2016	Behavior/Motor activity
From *Unlikely* to *Very likely* 60% [20%-100%[			
PFNA	Immune system	ATSDR 2021 + EFSA 2020	Decreased antibody response to vaccines
PFOA	Metabolism	ATSDR 2021 + EFSA 2108/2020 + Health Canada 2018 + USEPA 2016	Increase in cholesterol levels
From *Unlikely* to *Likely* 50% [20%-80%[			
PFNA	Metabolism	ATSDR 2021 + EFSA 2020	Increase in cholesterol levels
Polycyclic aromatic hydrocarbons	Metabolism	Kim et al., 2013 + Yang et al., 2020 + WHO 2010	Birth weight/fetal growth
From *Very unlikely* to *Very likely* 50% [0%-100%[			
Cotinine	Cardiovascular	CDC US 2014 + Zhao et al., 2020 (meta-analysis)	Congenital heart defects
Green space	Mental health	WHO 2016 + EEA 2019 + PHE 2020	Mental well being
From *Very unlikely* to *Likely* 40% [0%-80%[			
Arsenic (inorganic)	Cardiovascular	FDA 2016 +ATSDR 2016	Cardiac birth defect
Polycyclic aromatic hydrocarbons	Neurodevelopment	Zhang et al., 2020 + Rezaei Kalantary et al., 2020 + WHO 2010	Behavioral outcomes
NO_2	Cardiovascular	US EPA 2016 + Health Canada 2016	Cardiac birth defect
Green space	Neurodevelopment	WHO 2016 + EEA 2019 + PHE 2020	Cognitive development, behavioral development and ADHD
From *Very unlikely* to *As likely as not* 30% [0%-60%[			
Cadmium	Cardiovascular	ATSDR 2012 + Da Cunha Martins et al., 2018 + Kukongviriyapan et al., 2016	Blood pressure
PFOA	Respiratory	ATSDR 2021 + EFSA 2108/2020 + USEPA 2016	Asthma
PFOS	Neurodevelopment	ATSDR 2021 + EFSA 2108/2020 + USEPA 2016	Cognitive outcomes
PFOS	Neurodevelopment	ATSDR 2021 + EFSA 2108/2020 + Health Canada 2018 + USEPA 2016	Thyroid hormones
PFBS	Neurodevelopment	ATSDR 2021 + EFSA 2020	Thyroid hormones
PFHxA	Immune system	ATSDR 2021 + EFSA 2020	Decreased antibody response to vaccines
PFDA	Neurodevelopment	ATSDR 2021 + EFSA 2020	Behavior/Motor activity
PFDoDA	Neurodevelopment	ATSDR 2021 + EFSA 2020	Behavior/Motor activity
Coarse particles ($PM_{10-2.5}$)	Respiratory	US EPA 2019 + Anses 2019 + Health Canada 2016	Asthma exacerbation

(*continued on next page*)

Table 5 (*continued*)

Exposure Factor	Target system	Sources	Effect
Coarse particles ($PM_{10-2.5}$)	Respiratory	US EPA 2019 + Anses 2019	Lung function and development
Proximity	Metabolism	Daniels et al., 2021 + Jin et al., 2021 + Costa Perez et al., 2020	Obesity
From *Very unlikely* to *Unlikely* 20% [0%-40%[			
DINP	Reproductive function (male)	NAS 2017 + ECHA 2018 _CLH under CLP regulation (RAC), Health Canada 2015	Phthalate syndrome (AGD, hypospadia)
PFOA	Neurodevelopment	ATSDR 2021 + EFSA 2108/2020 + USEPA 2016	Cognitive outcomes
PFOA	Neurodevelopment	ATSDR 2021 + EFSA 2108/2020 + Health Canada 2018 + USEPA 2016	Thyroid hormones
PFOA	Cardiovascular	ATSDR 2021 + EFSA 2108/2020 + USEPA 2016	Pregnancy hypertension
PFOS	Respiratory	ATSDR 2021 + EFSA 2108/2020 + USEPA 2016	Asthma
PFOS	Cardiovascular	ATSDR 2021 + EFSA 2108/2020 + USEPA 2016	Pregnancy hypertension
PFHxS	Metabolism	ATSDR 2021 + EFSA 2020	Growth in infancy or childhood/postnatal growth
PFHxS	Fetal death	ATSDR 2021 + EFSA 2020	Miscarriage/prenatal losses
PFNA	Neurodevelopment	ATSDR 2021 + EFSA 2020	Thyroid hormones
PFDA	Metabolism	ATSDR 2021 + EFSA 2020	Increase in cholesterol levels
PFDA	Neurodevelopment	ATSDR 2021 + EFSA 2020	Thyroid hormones
PFUnDA/PFUnA	Neurodevelopment	ATSDR 2021 + EFSA 2020	Thyroid hormones
PFDoDA	Immune system	ATSDR 2021 + EFSA 2020	Decreased antibody response to vaccines
Aircraft noise	Cardiovascular	Anses 2020 + WHO 2018	Blood pressure

systematic reviews. Regarding non-systematic reviews, which have been only considered to review the mechanistic evidence, we used SANRA tool (Baethge et al., 2019). We acknowledge that the same tool could have been used to evaluate the quality of systematic reviews and of reviews on the mechanistic evidence. Specifically, in the future, the implementation of the Literature Review Appraisal Toolkit (LRAT) developed at the University of Lancaster relying on several other toolkits including AMSTAR, PRISMA, Cochrane Handbook for Systematic Reviews of Interventions, could be considered for the appraisal of all literature or evidence reviews (Sutton et al., 2021).

4.3. Combination of evidence from various scientific streams

Our work can be seen as being primarily an exercise in hazard identification, consisting in assessing whether exposure X may cause disease Y, and what the corresponding level of evidence is. Causality is a complex concept in science in general and environmental health sciences in particular; in this area, an important line of epistemological work considers that a variety of evidence (in the sense of approaches/disciplines used to generate the evidence) is helpful to identify causal effects (Wilde and Parkkinen, 2019). In this tradition, the overall level of evidence regarding the possible effect of an environmental factor on health should ideally consider all available evidence, and in particular human, animal and mechanistic studies, which each have their relative strengths and weaknesses (National Research Council, 2014, p. 88).

Different evidence integration methods may be implemented across sources (e.g., by different agencies or authors of reviews). This heterogeneity can have consequences on the conclusion regarding the *overall* level of evidence (i.e., the final level of evidence integrating all streams of evidence). For instance, according to the CLP Regulation, the highest LoE category (category 1 A) is allocated when there is robust evidence from human data, while according to our proposed combination matrix, the highest LoE (very likely) can also be reached when both toxicological and mechanistic evidence are strong whatever the LoE for the epidemiological data is. This discordance was observed for DEHP, BBP, BPA (Table S7). Another example relates to the assessment of the endocrine disruptive potential. Indeed, when there is sufficient evidence for an adverse outcome and relevant evidence of an underlying endocrine disrupting mode of action, the substance is eligible for identification as a substance of very high concern (SVHC) according to Article 57 (f) of REACH regulation (ECHA, 2021). The criteria are different from reproductive hazard assessment under CLP Regulation since it weights the identified endocrine disruptive mode of action. This is the reason why BPA is “Very likely” to have endocrine disruptive properties in relation to the oestrus cyclicity but only “Likely” to cause this effect under CLP criteria (Table S7). These diverging weights of evidence were taken into account by widening the uncertainty interval of the LoE so that it encompasses the Likely and Very likely overall LoEs. Table 5 summarize the substances for which diverging conclusions were retrieved across reports and reviews. There is a critical need to update the information retrieved, investigate the possible divergences and draw a definitive conclusion for these exposure factors.

When agency reports did not consider all streams of evidence to provide an overall assessment of the level of evidence, we had to integrate the evidence identified for each of the streams. In the scientific literature and guidelines from health agencies, several qualitative approaches have been proposed to integrate the evidence from these different streams and possibly derive an assessment of the overall level of evidence (Hill, 1965; Hope and Clarkson, 2014; Rooney et al., 2014; Samet et al., 2020; SCENIHR, 2012; SCHEER, 2018; Woodruff and Sutton, 2014), reviewed e.g., in (National Research Council, 2014). These include in particular IARC approach (Samet et al., 2020), the Navigation Guide (Woodruff and Sutton, 2014), GRADE (Grading of Recommendations Assessment, Development and Evaluation system), which is used by the Office of Health Assessment and Translation of the US national toxicology program (NTP) (NTP (National Toxicology Program), 2019).

To integrate the three streams of evidence (epidemiological, toxicological and mechanistic), we proposed a combination matrix considering the three stream-specific levels of evidence (Table 2).

Our combination matrix allows the level of evidence to be high even when only epidemiological evidence is available (if the epidemiological LoE is high), as illustrated in the example of the possible effects of green space exposure on mental health (Table 4). If the LoE from the epidemiological stream is moderate, then a lack of toxicological and mechanistic data, or the existence of “weak” or “very weak” LoEs for these two streams will still lead to an overall LoE considered “likely”. In environmental health research, epidemiological studies usually correspond to observational studies which, in reviews on clinical questions, will typically, by default, be assigned a low quality. Our approach is coherent with the Navigation Guide methodology, which gives human (observational) studies an a priori rating of “moderate” (Woodruff and Sutton, 2014), and is justified by the facts that well-designed and analyzed observational studies can, as shown by the development of causal inference theory (Hernan and Robins, 2020), provide a high level of evidence.

The example of the assessment of the evidence between green space exposure and mental health nicely illustrated how science has progressed in the last years, and how these changes influence our results. In the WHO report of 2016, the evidence for green space and mental

wellbeing was just developing, showing potential benefits with rather limited evidence. By 2020, the evidence has accumulated and the report of Public Health England (2020) was able to gather evidence from multiple reviews. This points towards a possible limitation of our methodology, as we do not change the level of evidence based on recency. If we had only considered the newest report, we would have had an overall LoE of "Very likely". Yet as we combine multiple reports, we end up with an overall LoE of "From Very unlikely to Very likely". The time period considered is the result of a trade-off: increasing this duration above 5 years would increase the likelihood to identify data in all three streams, yet at the cost of a possible increase in heterogeneity of results (as the LoE tends to vary over time) and hence of the width of the probability range.

A somewhat symmetrical situation may occur for other environmental factors of emerging concern for which the evidence emerges this time from toxicology, for which the epidemiological evidence may require several years to develop, depending on the availability of tools to assess exposure in humans. This also applies to factors difficult to study in humans. An example may be bisphenol A, for which there are many toxicological studies on various endpoints, and for which the epidemiological studies are limited by the very short toxicological half-life of the compound in the body, entailing bias and a decreased power in human studies relying on a spot biospecimen to asses exposure (Perrier et al., 2016). If the epidemiological stream is weak or below weak (e.g., no data), then our combination matrix requires both the toxicological and the mechanistic streams to be strong for the overall LoE to be very likely. If only the toxicological stream is strong and if the other streams are not higher than moderate, then the overall LoE cannot be more than *likely*; if only the mechanistic stream is strong and the other ones not higher than moderate, then the overall LoE cannot be more than *as likely as not* - while a strong LoE in the epidemiological stream is enough to reach a *very likely* overall LoE. This reflects the somewhat larger weight given in our LoE assessment to epidemiological evidence over the toxicological and mechanistic ones.

We built a probability range around the overall LoE, that takes into account the consistency of the conclusions of the reports and reviews in the 5-year study period; a lack of consistency may be the sign of a quickly evolving literature, as may typically be the case e.g., for factors whose study started rather recently. As an illustration, among the factors with high levels of evidence (which cannot be considered as representative of all factors), those with broad reliability intervals (bottom of Table 3) correspond to factors rather recently considered in the literature (such as perfluorinated compounds) while those with narrow reliability intervals (top of Table 3) correspond to factors studied for decades, such as lead or PCBs.

4.4. Potential uses of the exposome plausibility database

The original motivation of the building of the plausibility database generated here is to serve as a basis for future health impact assessment studies (Rigaud et al.). Indeed, to estimate the health impact of one or of a set of environmental exposures, the impact being defined in terms of number of disease cases or disability adjusted life years attributable to the exposure factor(s) in a given population, one needs to identify the plausible or certain health effects of each exposure factor of interest, in addition to the corresponding exposure-response function and the distribution of exposures. Some health impact assessment studies even make more explicit use of the level of evidence regarding each factor-outcome pair (Trasande et al., 2016). The knowledge synthesis from our plausibility database can also be used to identify and highlight research gaps, as illustrated in Fig. 4. Similarly, the plausibility database can be used to point to understudied children health outcomes. The comparison of Figs. S2A–E thus show that there are fewer research syntheses covering cardiovascular outcomes than metabolic outcomes, neurodevelopment or respiratory health.

5. Conclusion

We developed a pragmatic approach to assess the overall level of evidence of cardiometabolic, neurodevelopmental, respiratory and other birth and child health outcomes. This approach results from a trade-off between the time needed to perform the level of evidence assessment, and the completeness of the assessment. We applied this method to a large number of exposure factors in order to create a "plausibility database" summarizing the current evidence regarding the effect of the part of exposome on children health. This assessment of the level of evidence can be used to provide a synthesis of the evidence across a large number of exposure factors and outcomes, to identify understudied domains of the exposome or of children health, topics of emerging concern, or to perform health impact assessment study. It represents the state of the current knowledge and is worth being updated regularly and expanded to other stages of life such as adulthood. The short-term funding of this research project does not allow such a regular update and extension to the other stages of life, which could be the role of national, regional (e.g., at the EU level) or international agencies that could expand the work done by IARC regarding carcinogenic effects.

Credit author statement

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Acknowledgments

The ATHLETE project was funded by The European Commission, through its Horizon 2020 Framework Program for Research and Innovation (grant agreement 874583). This work was also supported by HERA (Integrating Environment and Health Research: a Vision for the EU) Horizon 2020 project (grant agreement 825417). We acknowledge support from the grant CEX 2018-000806-S funded by MCIN/AEI/10.13039/501100011033, and support from the Generalitat de Catalunya through the CERCA Program. Special thanks to Claire Beausoleil, Sandrine Charles, Aurélie Mathieu-Huard, Elodie Pasquier, François Pouzaud and Fatoumata Sissoko for the review of the "plausibility database" and Matthieu MESLIN for his contribution. All authors declare that they have no actual or potential competing financial interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijheh.2023.114311.

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