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Environmental health risks to children and adolescents: an umbrella review on chemicals

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Executive Summary

The environment can have both positive and negative effects on children's health. Children respond differently compared to adults in many ways. Developmental processes from conception to adulthood are particularly prone to disruption and there are many examples that show that children are more sensitive than adults to environmental pollutants. They have a different metabolism, different body surface/mass ratio, different intake ratios (e.g. higher breathing rate and higher energy/food consumption per unit body weight) and are partly exposed to different environmental exposures in size and composition compared to adults.

Previously, EEA has reviewed the general health effects of ambient and indoor air pollution (Castro et al., 2022). The overall goal of the current report is to describe the most relevant chemicals in the environment, which pose a high health risk specifically for children and adolescents (in short 'children'). This includes a chemical characterization, description of important emission sources, characterization of exposure, characterization of health risks and discussion of the relevance for children's health on a population level.

Given the high number of chemicals in the environment, and the lack of toxicity data for many of these, particularly for children, this report focusses only on a few key chemicals/chemical groups, which were selected based on a prioritization exercise. Importance was given to those which were identified as a priority by a) the Human Biomonitoring for Europe (HBM4EU) project, b) the Partnership for the Assessment of Risks from Chemicals (PARC) project or c) by the World Health Organization (WHO). Indications for special relevance for children were used as an overall criterion. Despite their relevance, bisphenols and arsenic were excluded from the selection of high-priority chemicals because comprehensive assessments for these two substances are currently being conducted already by the European Food Safety Authority (EFSA) and the United States - Environmental Protection Agency (US-EPA), respectively. This resulted in the following chemicals/chemical groups being selected as high priority and for which detailed assessments were conducted: pesticides, lead, benzophenones and per/polyfluorinated alkyl substances (PFAS). The health impact of these chemicals to children was evaluated by means of an 'umbrella review', i.e. a systematic collection and assessment of most recent multiple systematic reviews and meta-analyses supplemented with reports from expert groups with the aim to conduct evidence rating for potentially relevant health effects for children. Following the approach of HBM4EU, weight of evidence was rated in three categories: 'strong', 'suspected' or 'lacking'.

Moreover, less detailed assessments were conducted for these medium priority chemicals: bisphenols, cadmium, chromium VI, flame retardants, arsenic, mercury, polycyclic aromatic hydrocarbons (PAHs), phthalates and acrylamide. For these compounds a short overview on the most relevant aspects for children's health without any evidence rating is provided based on key expert reports.

Pesticides

For pesticides, especially pyrethroids, human biomonitoring data show that urinary concentrations tend to increase over time in the general population. Further, exposure in children is widespread and relatively higher compared to adults. In HBM4EU it was shown that the evidence for neurobehavioral effects related to pyrethroid exposure is consistent. Adverse outcome pathways (AOPs) show the mechanistic possibilities of pyrethroids to cause neurobehavioral effects. In toxicity studies, behavioural effects (resembling ADHD) were observed in animal studies at relatively high exposure levels. Epidemiological studies show links between maternal exposure and the development of attention deficit hyperactivity disorder (ADHD) in children. Thus, the evidence for a corresponding effect is considered to be strong (Table 1.1). Other effects like impaired neurodevelopment, autism

spectrum disorder (ASD), endocrine disruption and reproductive effects including alteration of puberty timing were suspected.

Lead

Lead has played a major role as an environmental risk factor, especially as a component of fuel and being emitted mostly from cars and, to a lesser extent, as part of industrial emissions. Lead was gradually banned from many uses but still can be found in the blood and bone tissues of the European population. The Umbrella review indicated that for children especially neurological effects pose a serious threat even at low concentrations. Genotoxicity and IQ-Loss were considered to have strong evidence for a causal association with lead exposure (Table 1.1). For numerous other outcomes like ADHD, impaired cognition, haematological and immunological effects a causal association is suspected.

Benzophenones

For benzophenones and its derivate (e.g. 3-BC, BP, BP-1, BP-2, BP-3, 4-MBC, 4-HBP), the evidence base for health effects is comparably uncertain. Major hints for a potential effect were identified for endocrine disrupting effects in children and corresponding evidence can be evaluated between suspected and strong. For numerous other effects, the evidence for a link is suspected (Table 1.1).

PFAS

Lastly, PFAS are persistent and bioaccumulative in the environment. Human biomonitoring has shown that human exposure is widespread. HBM4EU had previously reported that PFAS exposure was strongly associated with reduced anti-body response to vaccination, a finding confirmed by recent evidence. However, the link with increased risk of infection is not as strongly supported by epidemiological studies, but rather suspected. Based on further epidemiological studies reviewed in this report an association between birth outcomes (e.g. reduced birth weight, preterm birth, small for gestational age (SGA)), and endocrine disruption is suspected (Table 1.1).

Other chemicals

From the non-selected chemicals, the ubiquitous presence of bisphenols, flame retardants, PAHs and phthalates in the environment results in continuous exposure of the general population, including foetuses via transplacental transfer. These compounds are known to cause adverse developmental effects in children, with bisphenols, phthalates and some flame retardants having endocrine disrupting properties. Furthermore, children can be exposed to significant levels of the heavy metals' mercury and cadmium, as well as the metalloid arsenic, even before birth. These substances present an important threat to children’s health, who are particularly susceptible to the adverse health effects of these metals during sensitive developmental stages.

Table 1.1: Overview of the effects of the evaluated priority chemicals for various health outcomes in children, where evidence is suspected or strong

Chemical	Outcome	Evidence
Pesticides	attention deficit hyperactivity disorder (ADHD)	Strong
(pyrethroids)	Neurodevelopmental impairment	Suspected
	autism spectrum disorder (ASD)	Suspected
	Puberty outcomes	Suspected
	Endocrine disruption	Suspected
Lead (Pb)	Genotoxic effects	Strong
	IQ reduction	Strong
	Mood and behavioural changes	Suspected
	ADHD	Suspected
	Visual-motor integration	Suspected
	Dexterity	Suspected
	Postural sway	Suspected
	Changes in hearing and visual thresholds	Suspected
	Reduced cognitive functions	Suspected
	Hematological effects	Suspected
	Immunological effects	Suspected
	Developmental effects	Suspected
Benzophenones (3-BC, BP, BP-1, BP-2, BP-3, 4-MBC, 4-HBP)	Endocrine disruption	Suspected to strong
BP	Liver and kidneys toxicity, cancer	Suspected
BP-3	Foetal growth, damage to central nervous system, decreased gestational length (males), birth weight, puberty, anthropometric parameters, ADHD, emotions, behaviour, allergies, oxidative DNA damage	Suspected
4-MBC	Reproduction, cancer	Suspected
4-OH-BP	Psychomotor development	Suspected
PFAS	Reduced vaccine antibody response	Strong
	Preterm birth	Suspected
	SGA	Suspected
	Increased infection risk	Suspected
	Reduced birth weight	Suspected
	Endocrine disruption	Suspected

Conclusions

This report has confirmed that the monitoring of human, and in particular children, exposure to chemicals and the assessment of cumulative health effects is a challenge. Around 5,000 chemicals have been produced in large quantities and are widely distributed in the environment. Less than half of these chemicals have been tested for toxicity and epidemiological studies are scarce, in particular studies with a special focus on children, although chemical concentrations in blood or urine of children is often higher than in adults. As some synthetic chemicals have been restricted in recent years due to confirmed adverse human health effects, new related compounds have emerged for which the toxicity and health effects have to be re-evaluated. However, protection by regulation is a time-consuming process and there is a delay of several decades before effective protection of the public including children. In several instances, newly introduced related compounds have demonstrated similar health effects (also known as regrettable substitution), again requiring an extensive political process before policies are implemented to restrict their use. This situation is a challenge for assessing the health risk of the population and especially of children. In this review, little data was found about efficacy and effectiveness of interventions to minimize the health risk of chemicals to children.

In conclusion, one needs to develop solutions to mitigate the health risks from chemicals. Prenatal and early postnatal life is a high vulnerable exposure window and is a priority period for exposure reduction. Since for the future there is a growing concern for diffuse chemical pollution, human biomonitoring (HBM) is a useful tool for assessing the integrated exposure to complex mixtures of chemicals and geographical and temporal variations in exposure to chemicals. There is a need for a sustainable form of HBM covering all Member States to address exposure, time-trends and effect biomarkers in children in a harmonized way. Such data are useful for risk assessment and risk mitigation and should be complemented with high quality etiological research and intervention studies.

Further, this review has found that for the protection of children from chemicals policy gaps exist in the EU framework and at national level, which need to be addressed. Next to regulation, 'Environmental hygiene' is proposed as a global strategy to effectively protect pregnant women, unborn children and infants against chemical exposure. Implementable measures to reduce exposure to chemicals should be developed and their efficacy and efficiency to reduce exposure of pregnant women, unborn, infants and adolescents should be evaluated.

1. Introduction

Though most children in the European Union (EU) are generally in good health (Eurostat, 2019), there are reasons for concerns about environmental health risks to children and adolescents in Europe. Children are exposed to many environmental risks, including unsafe home environments, accidents and injuries, road traffic, polluted indoor and outdoor air, water, food, and soil; environmental radiation and noise (Valent et al., 2004). There is growing evidence that children and adolescents are particularly susceptible to many adverse environmental risk factors, since they affect children differently from adults in many ways.

For many developmental stages between conception and adolescence, there are critical periods when vulnerability to disruption by environmental hazards is particularly high (Makri et al., 2004). If these developmental stages are substantially disrupted, there is a high probability that any damage that occurs cannot be reversed later in life, resulting in permanent and irreversible dysfunction or disease in adulthood. Thus, negative health effects after childhood exposure can also occur much later (Landrigan and Garg, 2002; Röösli, 2011). For example, pre- and postnatal exposure to air pollutants impairs lung development or chemicals such as lead affect cognitive development (Veras et al., 2017; Castro et al., 2022; Heidari et al., 2022). Although this may not yet be clinically relevant in childhood, it can lead to an earlier age-related decline in lung function or cognition below a critical level decades later. For cancer, it is also important that the cell division rate is significantly higher at a young age, which additionally increases the vulnerability for undesirable developments of any mutation that may occur at early age (Kutanzi et al., 2016). Although the studies on environmental effects in the life course are still very rare, there is growing evidence for many environmental factors that chronic diseases in adulthood already have their origin in exposure in childhood (Holland et al., 2000).

Children and adolescents also differ from adults in terms of their cognition and metabolism. For example, children's ability to detoxify and excrete chemicals is significantly lower than that of adults, especially in the first months after birth (Dourson et al., 2004). The developing immune system is also more susceptible to diseases. The breathing rate of children is higher than that of adults, and thus their intake of potential pollutants per kilogram of body weight is higher than that of adults. In addition, children breathe in a greater proportion of air through the mouth than adults, which leads to greater penetration of pollutants into the lower respiratory tract (Castro et al., 2022). Because of their body size, young children breathe more air, which is closer to the ground, where some pollutants, especially from traffic, are released. Children also eat and drink more relative to their body weight compared to adults, and so the ingested dose of pollutants per kilogram of body weight is higher. The ratio of body surface area to volume is also greater, resulting in higher pollutant absorption through the skin per kilogram of body weight. In addition, children's skin is more permeable (Mancini, 2004; Sly and Flack, 2008).

Exposure conditions are also different for children than for adults. Young children also have closer contact with the ground surface and young children tend to put things in their mouths ("mouthing"). This makes them much more exposed to sedimented dust or other pollutants on the ground (Sly and Flack, 2008).

Outdoor air pollution such as particulate matter is the main environmental health risk to children in the EU, where it significantly increases the burden of childhood mortality, asthma and allergies, as well as decreased lung function and lung function development, and increased risk for respiratory infections. Other significant proven sources of environmental burden of disease in children in the EU include second-hand tobacco smoke, mould and dampness (Trasande et al., 2016; Rojas-Rueda et al., 2019). Recently, the European Environment Agency (EEA) has summarized the health risk from ambient and indoor air pollutants in a comprehensive report (Castro et al., 2022).

Beyond air pollution, children are exposed to numerous chemicals in water, soil, food or consumer products. As a result of the industrial lifestyle, more than 140,000 new chemicals and pesticides have been synthesised since 1950 (Landrigan et al., 2018) and the production volume is still increasing (OECD, 2012). Along with this, the diversity of physicochemical properties of synthesized chemicals is increasing. Around 5,000 of the 140,000 have been produced in large quantities and are widely distributed in the environment. These include endocrine disrupting chemicals, where even low doses can impair development, heavy metals such as lead and cadmium, pesticides, or persistent substances that accumulate in the body. Further, changing climate may result in unpredictable changes in exposure patterns. For instance, usage pattern of pesticides may change in a changing climate. There is also concern that children with lower socio-economic status tend to be systematically more exposed to and affected by environmental risks (Barnes et al., 2019).

Protecting our children has been frequently cited as a key reason in the political statements (e.g. European Commission, 2021b) accompanying the major EU policies on climate and the environment, though mentions of children in the actual policy documents vary across areas. The Zero Pollution Action Plan and Chemicals Strategy for Sustainability (European Commission, 2020) both identify them as susceptible and vulnerable to pollution and specifically targets chemical safety in child products, respectively. A few regulatory protective measures exist to reduce exposure of children to hazardous chemicals. Few examples are the EU Toy Safety Directive (EU, 2022) and the opinion of the European consumer voice in standardisation (ANEC) on how to proceed with this regulation as well as the safety requirements for bath rings, bathing aids and bathtubs (Decision 2010/9/EU), safety requirements to be met by European standards for childcare products in the sleeping environment of children (Decision 2010/376/EU) and safety requirements to be met by European standards for seats for children (Decision 2013/121/EU). The EU also adopted regulation on childcare products, outside the Toy Directive, which were screened for the mention of chemicals. In addition, for children's products in general, there is a new EU proposal being developed tackling the presence of chemical substances/mixtures. Finally, documents of the Organisation for Economic Cooperation and Development (OECD) were screened on the assessment of exposure to chemicals in risk assessment and particularly for children which have different skin surface/body weight ratio, metabolism, etc. and are still in a vulnerable developing phase. Also, recent information (September 2023) on the guidance of the Scientific Committee on Consumer Safety (SCCS) on risk assessment of chemicals suspected of having an endocrine disrupting effects and applied as cosmetic ingredient was added with the focus on children's health (SCCS, 2023).

Despite these positive examples, legislation on environmental pollution does usually not differentiative between children and adults. It is thus important to note that children are not in a position to make informed decisions to protect themselves from environmental pollution and should thus be able to rely on adults engaging for safe environment.

2. Objectives

The overall goal of this report is to describe relevant chemicals in the environment, which pose the highest risk to children and adolescents. This includes chemical characterization, description of the emission sources, characterization of exposure, characterization of health risks and discussion of the relevance for children's health on a population level.

3. Methods

As a result of the industrial lifestyle, more than 140,000 new chemicals have been synthesised since 1950 (Landrigan et al., 2018). Of those, around 5,000 have been produced in large quantities and are widely distributed in the environment. Less than half of these chemicals have been tested for toxicity. Child-specific data are particularly sparse. Given the large number of chemicals, no conclusive discussion of all possible health hazards can be made in this framework.

We applied a two-stage process. In a first step we conducted a scoping and prioritization to select the chemicals, which were reviewed in depth. In a second step we conducted an Umbrella review for the selected chemicals. For some chemicals that we have not selected, a short summary of the main aspects is provided based on selected key reports.

3.1. Scoping and prioritization

For the prioritization of chemicals or chemical groups, it was decided to follow a criteria-based approach. To do so, the following chemicals were preselected based on expert guidance: bisphenols, cadmium, chromium VI, flame retardants, polycyclic aromatic hydrocarbons, per-/poly-fluorinated compounds, phthalates and Hexamoll® DINCH, acrylamide, aprotic solvents, arsenic, diisocyanates, lead, mercury, mycotoxins, pesticides and benzophenones. Despite their relevance bisphenols and arsenic were excluded from the prioritisation approach, because comprehensive assessments for these two substances have been recently or are currently conducted by the European Food Safety Agency (EFSA) and the United States Environmental Protection Agency (US-EPA), respectively. In a next step it was reviewed which of these chemicals were already on priority lists from a) the Human Biomonitoring for Europe (HBM4EU) project (HBM4EU, 2016) and b) the Partnership for the Assessment of Risks from Chemicals (PARC) project or were c) considered as priority substances by the World Health Organization (WHO). The last criterion was d) the special relevance for children. In a deliberative process the experts from the European Topic Centre on Human Health and the Environment (ETC-HE) scored the pre-selected substances. The final scores were discussed among the ETC-HE and EEA experts, and after considering the existing resource constraints the following four substances/substance groups were selected for the analyses: per-/poly-fluorinated compounds, lead, pesticides and benzophenones. For the remaining, non-selected substances only short summaries of the probable relevance for children are provided.

3.2. Umbrella review

To review the literature, we conducted an Umbrella review. Umbrella indicates that results from systematic review papers and expert reports were evaluated. Depending on the available literature, we conducted an evidence rating for various chemical-outcome combinations. For these we used the three categories as provided within the HBM4EU substance reports: “strong evidence”, “suspected evidence” and “lacking evidence”. Ideally, the basis for the evidence rating was from a recent systematic review that has applied a grading of recommendations, assessment, development and evaluation (GRADE) rating or a similar suitable approach. In case of missing evidence rating in the reviews, an expert judgement was conducted in analogy to the HBM4EU approach. Evidence for a causal association was considered to be strong if associations are observed in epidemiological studies backed-up with experimental research (in vivo and in vitro studies). Suspected evidence was assigned if epidemiological studies indicated an association without contributing evidence from experimental research or the other way round, experimental studies indicated an association without corresponding epidemiological findings.

3.3. Literature search

Since the availability of literature differed somewhat for the variously selected chemicals, different literature search strategies were applied, which are described in the following for each chemical separately.

3.3.1. Pesticides

It was decided to focus in this report on pyrethroids since they have been gaining more attention, are increasingly used and represent an alternative to organophosphates. The starting point was the documents drawn up by the HBM4EU project. Additional information and data were then searched to supplement the information considered in those documents and to provide more recent insights from the period after the publication of the HBM4EU documents (2022). Other major institutional and project websites were first consulted such as the Agency for Toxic Substances and Disease Registry (ATSDR), the EEA, the Insecticide Resistance Action Committee (IRAC), the US-EPA, and the European Chemicals Agency (ECHA). Second, a search was performed in the scientific peer reviewed literature using PubMed (used keywords: pyrethroid*, child*/adolescent* and the health outcome) and further supplemented with already known literature. Primarily, reviews and meta-analyses were searched and, if no reviews were available, supplemented by individual studies.

3.3.2. Lead

In a first step, major institutional and project websites were consulted and latest important reports on lead were identified. We searched the websites from the WHO, the HBM4EU-Project, the International Agency for Research on Cancer (IARC), US-EPA and the ATSDR for relevant content with respect to the health effects of lead. This search resulted in eleven relevant reports especially covering major synthesizing work from the US-EPA and ATSDR (United States Environmental Protection Agency, 2013; Centers for Disease Control and Prevention, 2012). In addition, as a second step, a literature search was performed in PubMed focusing on the identification of review articles in the time frame from 2017 to 2023 using the following search string: ("lead"[Title/Abstract] AND "metal"[Title/Abstract] AND "child*"[Title/Abstract]) AND (review[Title/Abstract]). This search was intended to supplement the reports identified in the first step. Only review articles were used, because the review of a large amount of single studies was not feasible with the available resources. Overall, eleven review articles were identified from which eight were used in the underlying report.

3.3.3. Benzophenones

First, major institutional or project websites were consulted and the latest important reports on benzophenones were identified. We searched the websites from the WHO, HBM4EU, IARC, US-EPA, ATSDR, EFSA and ECHA. This search resulted in seven relevant reports or fact sheets, especially covering work from the HBM4EU project. In addition, a literature search was performed in PubMed investigating review articles in the time frame from 2017 to 2023 using the following search string: (benzophenone) AND (child* OR adolescent*) AND (review). This search was intended to supplement the reports identified from the websites. In total, 14 articles were identified. Of these, however, only seven reviews were reviews dealing with benzophenones. Finally, five of them were included in this report (Mustieles et al., 2023; Govarts et al., 2023; Wnuk et al., 2022; Bigambo et al., 2020; Fivenson et al., 2021). One other systematic review was identified through a non-systematic search (Mao et al., 2022).

3.3.4. Per-/poly-fluorinated compounds

The starting point was the documents drawn up by the HBM4EU project. Additional information and data were then searched to supplement the information considered in those documents and to

provide more recent insights from the period after the publication date of the HBM4EU documents (2022). Other major institutional and project websites were first consulted such as ATSDR, EEA, US-EPA, ECHA and EFSA. Second, a search was performed in the peer reviewed scientific literature using PubMed (used keywords: PFAS*, child*/adolescent* and the health outcome) and further supplemented with already known literature. In first instance reviews and meta-analyses were searched and supplemented by individual studies where reviews were lacking.

3.3.5. Other chemicals

In a first step, reports from major authorities and institutions, including the United Nations Environment Programme (UNEP), United Nations Children's Fund (UNICEF), WHO, IARC, HBM4EU, EFSA, ECHA and ATSDR, were searched for each chemical compound. Overarching reports previously identified for other chemicals were screened for the following compounds. To complement the evidence from the reports identified in the first step, a literature search was conducted focusing on recent review articles on children's health relevance. If review articles were not available, other epidemiological studies were included. The additional literature search was adapted to the knowledge gaps identified in the reports of the major authorities and institutions.

4. Results

4.1. Pesticides

4.1.1. Chemical characterization and emission sources

Pesticides are a large group of diverse (synthetic) substances used to treat (control, repel or kill) harmful organisms such as bacteria, fungi, plants and animals. They are mainly used in agriculture to protect crops, but they are also used for veterinary applications (treatment for mites, ticks, etc.) and domestic life (gardens, head lice treatments, etc.). Pesticides are classified according to their use:

- Bactericides target bacteria;
- Fungicides target fungi;
- Herbicides target unwanted vegetation such as weeds;
- Acaricides target ticks and mites;
- Rodenticides target rodents;
- Insecticides target insects.

Pesticides can also be classified based on their application areas. Plant protection products (e.g. insecticides) are used to protect crops for food and feed. Biocidal products are used to protect human and animal health against organisms that can cause harm. Pesticides for medical application are used in veterinary treatments and human medical products (HBM4EU, 2022m).

In 2020, 346 000 tonnes of pesticides were sold in the EU. This increased by 2.7 % to 355 175 tonnes in 2021. The highest volumes were sold in Spain (21 % of total), France (20 % of total), and Germany and Italy (both 14 % of total). Fungicides and bactericides made up the largest share (44 %), followed by herbicides, haulm destructors and moss killers (34 %) and insecticides and acaricides (14 %). The majority of EU countries (with available data, 11 of 16 countries) showed a decrease in pesticide sales between 2011 and 2021. However, some countries showed an increase in sales with Latvia and Austria showing a significant increase of 85 and 68 % respectively (Eurostat, 2023a).

Insecticides are thus pesticides that target insects. Most insecticides target the nervous system by for example inhibiting cholinesterase. There are also insecticides that act as growth regulators or endotoxins. Numerous insecticides with different modes of action exist. The IRAC, a specialist technical group of the industry association CropLife, has made a mode of action (MoA) classification with 32

MoA groups (based on the primary site of action, e.g. group 1: acetylcholinesterase (AChE) inhibitor) divided in five categories, which are based on the target protein of the insecticide in the insect, responsible for the biological effect:

- Neuromuscular toxins target the nervous system and muscles (MoA, e.g. AChE inhibitors);
- Growth regulators target growth and development (MoA e.g. juvenile hormone mimics);
- Respiratory toxins target energy metabolism (MoA e.g. inhibitors of mitochondrial Adenosine triphosphate (ATP) synthesis);
- Midgut toxins target the gut lining (MoA e.g. microbial disruptors of insect midgut membranes);
- Unknown or non-specific target (MoA e.g. miscellaneous non-specific (multi-site) inhibitors).

Seventeen major classes of insecticides have been determined and most prioritized pesticides belong the one of two major classes: organophosphates and pyrethroids (HBM4EU, 2022m).

Pyrethroids are one of the most extensively used classes of insecticides worldwide and include more than 1000 compounds. They are synthetic analogues of pyrethrins, which naturally occur in the Chrysanthemum flower and have insecticidal properties. Pyrethroids differ from pyrethrins in that pyrethroids are much more stable in the environment because they are less susceptible to photodegradation and hydrolysis. Pyrethroids are also more toxic than pyrethrins, not only to insect but also fish and mammals. Thousands of pyrethroids have been manufactured, however less than 30 are either approved or under review for professional and/or domestic use in the EU. Authorisation status differs between EU Member States. They are mainly used as plant protection products and biocidal products both professionally and domestically. Additionally, they are also used as veterinary medicinal products and human medicinal products in treatment of scabies and head lice. Pyrethroids are often paired with synergists to increase their effectiveness. In biocidal products piperonyl butoxide is often used as adjuvant/synergist, which slows down the degradation of pyrethroids. As a result, the toxicity of pyrethroids may increase because of the synergist (HBM4EU, 2020b; Agency for Toxic Substances and Disease Registry (ATSDR), 2003).

Pyrethroids are divided in type I and type II pyrethroids based on structural differences of the compound and acute toxicity in rodents. Type I pyrethroids do not have a cyano moiety at the alpha position and causes the tremor intoxication syndrome (tremor, convulsive twitching, hypersensitivity and aggression). Type II pyrethroids do contain the α-cyano-3-phenoxybenzyl moiety and cause the choreoathetosis and salivation (CS) intoxication syndrome (HBM4EU, 2020b; Agency for Toxic Substances and Disease Registry (ATSDR), 2003).

Pyrethroids are classified by IRAC as neuromuscular toxins targeting the nervous system of insects. The specific MoA of pyrethroids is through inhibition of voltage-gated sodium channels (VGSCs) and other ion channels. Pyrethroids have neurotoxic properties in humans and other non-target organisms because there are similarities in neural function (Table 4.1).

Table 4.1: Pyrethroid overview with information on toxicology and regulation in EU

Systematic name	Type	CAS No.	Classification (EC1272/2008) and thresholds	Regulation
Permethrin (proposed lead substance)	I	52645-53-1	Acute Tox. 4 - H302; Acute Tox. 4 - H332; STOT SE 3 - H335; Skin Sens. 1 B H317; AELlong-term: 0.05 mg/kg bw/d ADI: 0.05 mg/kg bw/d (WHO/FAO JMPR) Potential ED cat.2 (JRC) (EC 2016)	Not approved as plant protection product (PPP) in EU 2000/817/EC Approved as biocidal product (BiPr) T8 and T18 Reg. (EU) No 1090/2014 → Expiry date: 30/04/2026
Acrinathrin		101007-06-1	No classification ADI: 0.01 mg/kg bw/d; ARfD: 0.01 mg/kg, AOEL: 0.007 mg/kg bw/dg (Reg (EU) 2017/358); Identified as Potential ED cat.2 (JRC) (EC 2016)	Was approved as PPP Reg. (EU) no 2021/1450, no 2019/291, no 2017/358, No 540/2011, No 974/2011 (2008/934) → Expiry date: 31 December 2021
Allethrin	I	584-79-2		Not approved as PPP Reg. (EC) 2002/2076 or BiPr in EU
Alpha-cypermethrin (alphamethrin)	II	67375-30-8	Acute Tox 3 – H301, STOT SE 3 – H335, STOT RE 2 – H373 (nervous system) ADI: 0.015 mg/kg bw/d, ARfD: =.04 mg/kg bw, AOEL: 0.01 mg/kg bw/d (Dir 4/58)	Was approved as PPP Reg. (EU) 2021/795, Reg. (EU) No 540/201 → Expiry date: 06/07/2021 Approved as BiPr T18 Reg. (EU) 2015/405 → Expiry date: 30/06/2026
Bifenthrin	I	82657-04-3	Acute Tox 2 – H300, Acute tox 3 – H331, STOT RE 1 – H372 (nervous system), Skin Sens 1B – H317, Carc 2 – H351, ADI: 0.015 mg/kg bw/dg, ARfd: 0.03 m/kg b, AOEL: 0.0075 mg/kg bw/d (Reg (EU) 2018/291 Potential ED cat.2 (JRC) (EC 2016)	Approved as PPP Reg. (EU) 2019/324, Reg. (EU) 2017/195, Reg. (EU) 2018/291, Reg. (EU) No 582/2012 → Expiry date: 31/07/2021 Was approved as BiPr T8: directive 2011/10/EU → Expiry date: 31/01/2023
Cyfluthrin	II	68359-37-5	Acute tox 2 – H300 ADI: 0.003 mg/kg bw/d, ARfD: 0.02 mg/kg bw, AOEL: 0.02 mg/kg bw/d (Dir 03/31) Potential ED cat.3 (JRC) (EC 2016)	Not approved Reg. (EU) 2022/801 Was approved as beta-cyfluthrin as PPP Reg. (EU) 2020/892 → Expiry date: 20/07/2020 Approved as BiPr T18 reg (EU) 2016/1937 → Expiry date: 28/02/2028
Cypermethrin	II	52315-07-8	Acute tox 4 – H302, Acute tox 4 – H332, STOT SE 3 – H335 ADI: 0.05 mg/kg bw/d, ARfD: 0.2 mg/kg bw, AOEL: 0.06 mg/kg bw/d (Dir 05/53), ADI: 0.02 mg/kg bw/d, ARfD: 0.04 mg/kg bw (JMPR 2006) Potential ED cat.1 (JRC) (EC 2016)	Approved as PPP Reg. (EU) 2021/2049, Reg. (EU) No 540/2011 → Expiry date: 31/01/2029 Approved as BiPr T8 Reg (EU) 945/2013 → Expiry date: 31/05/2025 and T18 Reg (EU) 2018/1130 → Expiry date: 31/05/2030
Zeta-cypermethrin		52315-07-8 (same as cypermethrin)	No classification ADI: 0.04 mg (kg bw/d, ARfD: 0.125 mg/kg bw, AOEL: 0.02 mg/kg bw/d (EFSA 08)	Was approved as PPP Reg. (EU) 2020/1643, 2009/37 Reg. (EU) No 540/2011 → Expiry date: 01/12/2020
Zyphenothrin (or cyphenothrin)		39515-40-7		Approved as BiPr PT18 Reg (EU) 2018/1292 → Expiry date: 31/01/2030

Systematic name	Type	CAS No.	Classification (EC1272/2008) and thresholds	Regulation
d-Allethrin		231937-89-6; 584-79-2	Acute tox 4	Not approved as BiPr T18 COMMISSION IMPLEMENTING DECISION (EU) 2023/470
Deltamethrin	II	52918-63-5	Acute tox 3 – H301, Acute tox 3 – H331 ADI: 0.01 mg/kg bw/d, ARfD: 0.01 mg/kg bw, AOEL: 0.0075 mg/kg bw/d (Dir 03/5) Potential ED cat.2 (JRC) (EC 2016)	Approved as PPP Reg. (EU) No 540/2011, Reg. (EU) No 823/2012, Reg. (EU) 2020/1511, Reg. (EU) 2021/1449, Reg. (EU) 2022/1480 → Expiry date: 31/10/2023 Approved as BiPr T18 Implementing Decision (EU) 2023/1088 (expiry date postponed until 31/03/2026)
d-Tetramethrin		1166-46-7	Acute tox 4, Carc 2, STOT SE 2 (nervous system, inhalation)	Under review as BiPr T18
Empenthrin		54406-48-3		Under review as BiPr T18
Epsilon-momfluorothrin		1065124-65-3	Acute tox 4, STOT SE 2 (nervous system)	Approved as BiPr T18 Reg (EU) 2016/2289 → Expiry date: 30/06/2027
Esbiothrin		260359-57-7		Not approved as BiPr T18 Decision (EU) 2021/98
Esfenvalerate	II	66230-04-4	Acute tox 3 – H301, Acute tox 3 – H331, Skin Sens1 – H317 ADI: 0.0175 mg/kg bw/d, ARfD: 0.0175 mg/kg bw, AOEL: 0.011 mg/kg bw/d (Reg (EU) 2015/2047) Potential ED cat.2 (JRC) (EC 2016)	Approved as PPP 00/67/EC, Reg. (EU) 2015/2047, Reg. (EU) No 540/2011, Reg. (EU) 2018/155, Reg. (EU) 2022/1480 → Expiry data : 31/12/2023 Not approved as BiPr T18 Decision (EU) 2018/1622
Etofenprox		80844-07-1	Lact.- H362 ADI: 0.03 mg/kg bw/d, ARfD: 1 mg/kg bw, AOEL: 0.06 mg/kg bw/d (EFSA 08) Potential ED cat.3 (JRC) (EC 2016)	Approved as PPP 2009/77/ECReg. (EU) No 540/2011, Reg. (EU) 2021/1449, Reg. (EU) 2022/1480 → Expiry date: 31/12/2023 Approved as BiPr T8 (Dir 2008/16/EC) → Renewal in progress expiry date postponed 31/10/2026 Decision (EU) 2022/1487 and T18 Reg (EU) 1036/2013 → Expiry date: 30/06/2025
Fenpropathrin	II	39515-41-8	Acute tox – H301, Acute tox 4 – H312, Acute tox 2 – H330, ADI: 0.03 mg/kg bw/d, ARfD 0.03 mg/kg bw (JMPR 2012)	Not approved as PPP Reg (EC) No 2076/2002
Fenvalerate	II	51630-58-1	No classification ADI: 0.0125 mg/kg bw/d (EMEA)	Not Approved as PPP 98/270/EC
Imiprothrin		72963-72-5	Acute tox 4	Approved as BiPr T18 Reg (EU) 2017/2326 → Expiry date: 30/06/2029
Lambda-cyhalothrin	II	91465-08-6	Acute tox 3 – H301, Acute tox 4 – H312, Acute tox 2 – H330 ADI: 0.0025 mg/kg bw/d, ARfD: 0.005 mg/kg bw, AOEL: 0.00063 mg/kg bw/d (Reg (EU) 2016/146 Potential ED cat.2 (JRC) (EC 2016)	Approved as PPP 00/80/EC, Reg. (EU) 2016/146, Reg. (EU) No 540/2011, Reg. (EU) 2018/155, Reg. (EU) No 2019/724 → Expiry date: 31/03/2024 Approved as BiPr T18 (Dir 2011/10/EU) → Renewal in progress expiry date postponed 31/10/2026

Systematic name	Type	CAS No.	Classification (EC1272/2008) and thresholds	Regulation
				Implementing Decision (EU) 2023/1087
Gamma-cyhalothrin	II	76703-62-3	No classification ADI: 0.0012 mg/kg bw/d, ARfD: 0.0025 mg/kg bw, AOEL: mg/kg bw/d (Reg (EU) No 1334/2014.	Approved as PPP Reg. (EU) No 1334/2014, Reg. (EU) 2020/1295 → Expiry date: 31/03/2025
Metofluthrin		240494-71-7	Acute tox 3 and 4, STOT SE 1 (nervous system), STOT RE 2	Approved as BiPr T18 (Dir. 2010/71/EU) → Renewal in progress expiry date postponed 31/10/2023 Not approved as BiPr T19 COMMISSION IMPLEMENTING DECISION (EU) 2022/2326
Prallethrin		23031-36-9	Acute tox 3 and 4	Under review as PB T18.
Tau-fluvalinate	II	102851-06-9	Acute tox 4 – H302, Skin Irrit 2 – H315. ADI: 0.005 mg/kg bw/d, ARfD: 0.05 mg/kg bw, AOEL: 0.0044 mg/kg bw/d Potential ED cat.3 (JRC) (EC 2016)	Approved as PPP Reg (EU) 2011/19/EU, Reg. (EU) No 540/2011, Reg. (EU) 2020/2007 → Expiry date: 31/08/2024
Tefluthrin	I	79538-32-2	Acute tox 2 – H300, Acute tox 2 – H310, Acute tox 1 – H330 ADI: 0.005 mg/kg bw/d, ARfD: 0.005 mg/kg bw, AOEL: 0.0015 mg/kg bw/dg (EFSA 10) Potential ED cat.3 (JRC) (EC 2016)	Approved as PPP Reg. (EU) No 800/2011, Reg. (EU) No 2019/291 → Expiry date: 31/12/2024
Tetramethrin	I	7696-12-0	Acute Tox. 4, Carc. 2, STOT SE 2 (nervous system, inhalation)	Not approved as PPP (2002/2076) Under review as BiPr T18
Transfluthrin		118712-89-3	Skin Irrit 2	Approved as BiPr T18, Reg (EU) 407/2014 → Expiry date: 31/10/2025
1R-trans-phenothrin (D-phenothrin, sumithrin)	I	26046-85-5		Approved as BiPr T18, Dir. 2013/41/EU → Expiry date: 31/08/2025
Resmethrin	I	10453-86-8	Acute Tox. 4 Aquatic Acute 1 Aquatic Chronic 1	Not approved as PPP Reg. (EC) No 2076/2002
Flucythrinate	II	70124-77-5	According to the classification provided by companies to ECHA in CLP notifications this substance is fatal if inhaled, toxic if swallowed, very toxic to aquatic life, very toxic to aquatic life with long lasting effects and is harmful in contact with skin. ADI 0.02 mg/kg bw/ (JMPR 1985)	Not approved as PPP Reg. (EC) No 2076/2002
Flumethrin	II	69770-45-2		No pesticide but biocide used in veterinary medicine.
Tralomethrin	II	66841-25-6	According to the classification provided by companies to ECHA in CLP notifications this substance is very toxic to aquatic life, is very toxic to aquatic life with long lasting effects, is harmful if	Not approved as PPP Reg. (EC) No 2076/2002

Systematic name	Type	CAS No.	Classification (EC1272/2008) and thresholds	Regulation
			swallowed, causes serious eye irritation and causes skin irritation.	

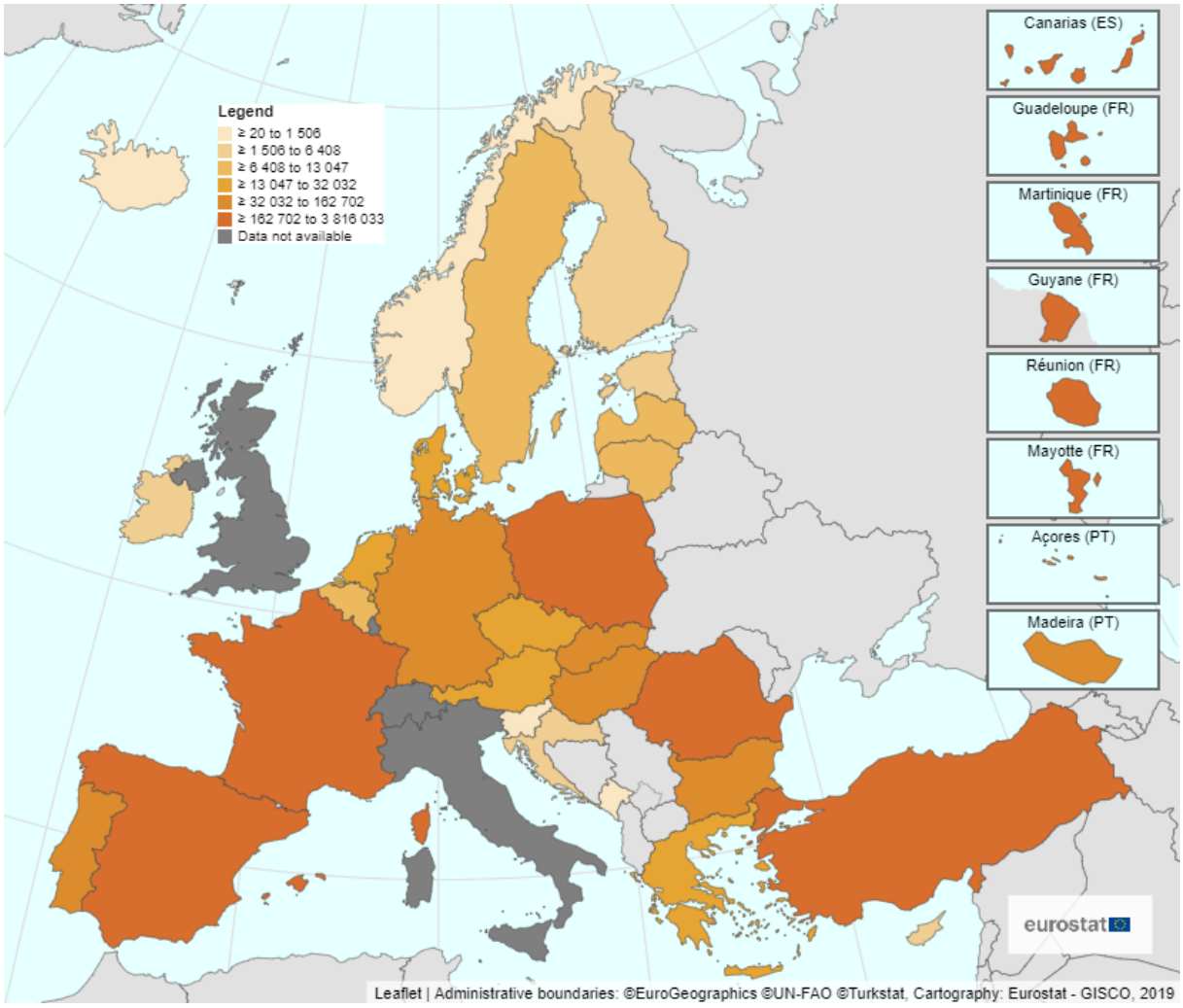
Note: Acceptable Daily Intake (ADI)

Source: HBM4EU scoping document pesticides (HBM4EU, 2020b) and ATSDR (Agency for Toxic Substances and Disease Registry (ATSDR), 2003)

4.1.2. Exposure characterization

The earliest year for which pyrethroid sales are available is 2012. France had the highest sales of pyrethroids (286 898 kg), followed by Germany (159 333 kg), Italy (140 254) and Romania (80 964). In 2016 France had again the highest sales (301 824 kg), followed by Spain (188 003 kg), Italy (151 036 kg), Germany (104 800 kg) and Romania (93 181 kg). In 2021 Turkey had the highest sales (3 816 033 kg), followed by France (417 356 kg), Spain (173 533 kg), Romania (172 538 kg) and Poland (169 393 kg). The annual sales of pyrethroid insecticides are shown in Figure 4.1. For Turkey and Italy no comparison between 2012, 2016 and 2021 is possible, since there were no data available for 2012 and 2016 for Turkey and no data for Italy in 2021. Except for Germany, all mentioned countries saw an increase in pyrethroids sales in 2021 compared to 2016 and 2012. Germany saw a decrease over the years, but an increase again in 2021. These quantities do not include the insecticides based on pyrethroids or the adjuvants that paired with pyrethroids in commercial insecticide products (Eurostat, 2023b). This observed increase in sales, which is expected to continue, is likely due to the fact that pyrethroid insecticides have replaced organophosphate and carbamate insecticides in biocides and to a lesser extent in agriculture (HBM4EU, 2022m).

Figure 4.1: Annual sales (in kg) of pyrethroid insecticides in the European territory for the year 2021

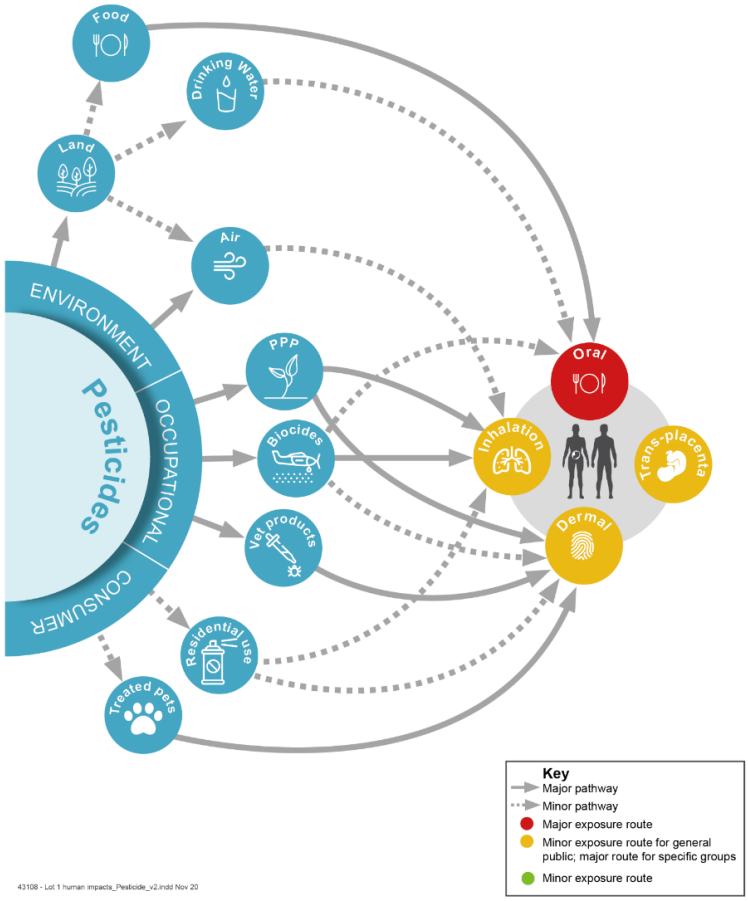


Source: Eurostat([1]).

As shown in Figure 4.2, different exposure routes for pesticides exist and the importance of these routes slightly differs between children and adults. The most important route for the general population is ingestion of residues on and in food. This route of exposure is even more important for children because they have higher food intake per kilogram body weight compared to adults. This is corroborated by human biomonitoring (HBM) studies (HBM4EU, 2020b, 2022l). Additionally, young children's frequent hand-to-mouth activity can increase exposure via ingestion (Xue et al., 2007). In homes where pesticides are frequently used, which often contain pyrethroids (e.g. floor wipe products, veterinary products for pets, scabies and head lice treatment) the inhalation and dermal exposure routes become important exposure routes for children and can even exceed exposure from ingestion (HBM4EU, 2020b). Pyrethroids can pass through the human placenta, prenatal exposure infants is therefore possible (Andersen et al., 2022).

([1])https://ec.europa.eu/eurostat/databrowser/view/AEI_FM_SALPEST09__custom_5991627/bookmark/map?lang=en&bookmarkId=3b608819-8ad3-4068-b04d-c1d5b6052a58

Figure 4.2: Overview of exposure sources, pathways and routes for pesticides for the general population



Source: HBM4EU Substance report Pesticides (HBM4EU, 2022m).

More than a dozen pyrethroid insecticides are approved for various uses both professionally and domestically and sales are high across Europe and human exposure to pyrethroids has been shown through HBM. Several biomarkers can be measured to determine the urinary concentration of pyrethroids. Table 4.2 gives an overview of urinary biomarkers to measure exposure to pyrethroids. 3-PBA, cis-DCCA, trans-DCCA, cis-DBCA and F-3-PBA are commonly used biomarkers in HBM studies. The HBM4EU project additionally measured CIF3CA (HBM4EU, 2020b).

3-PBA is a non-specific biomarker for exposure to many pyrethroid; it is now broadly detected in urine from the general population including pregnant women. 3-PBA concentration in urine increased the most in children from 2001 to 2012 in the National Health and Nutrition Examination Survey (NHANES), which reflects their higher exposure through diet compared to adults (Andersen et al., 2022).

3-PBA is an appropriate biomarker for the aggregated exposure to dietary pyrethroid mixtures in populations mainly exposed through diet, because the exposure is assumed to be more or less continuous. It may not however be an appropriate biomarker for peak exposures from for example indoor use. Detection of parent-compound specific biomarkers depends on recent exposure to those parent-compound pyrethroids; detection frequencies of pyrethroid-specific biomarkers will therefore be lower than for non-specific biomarkers and be more subject to intra-individual variation.

Table 4.2: Overview of urinary biomarkers to measure pyrethroid exposure

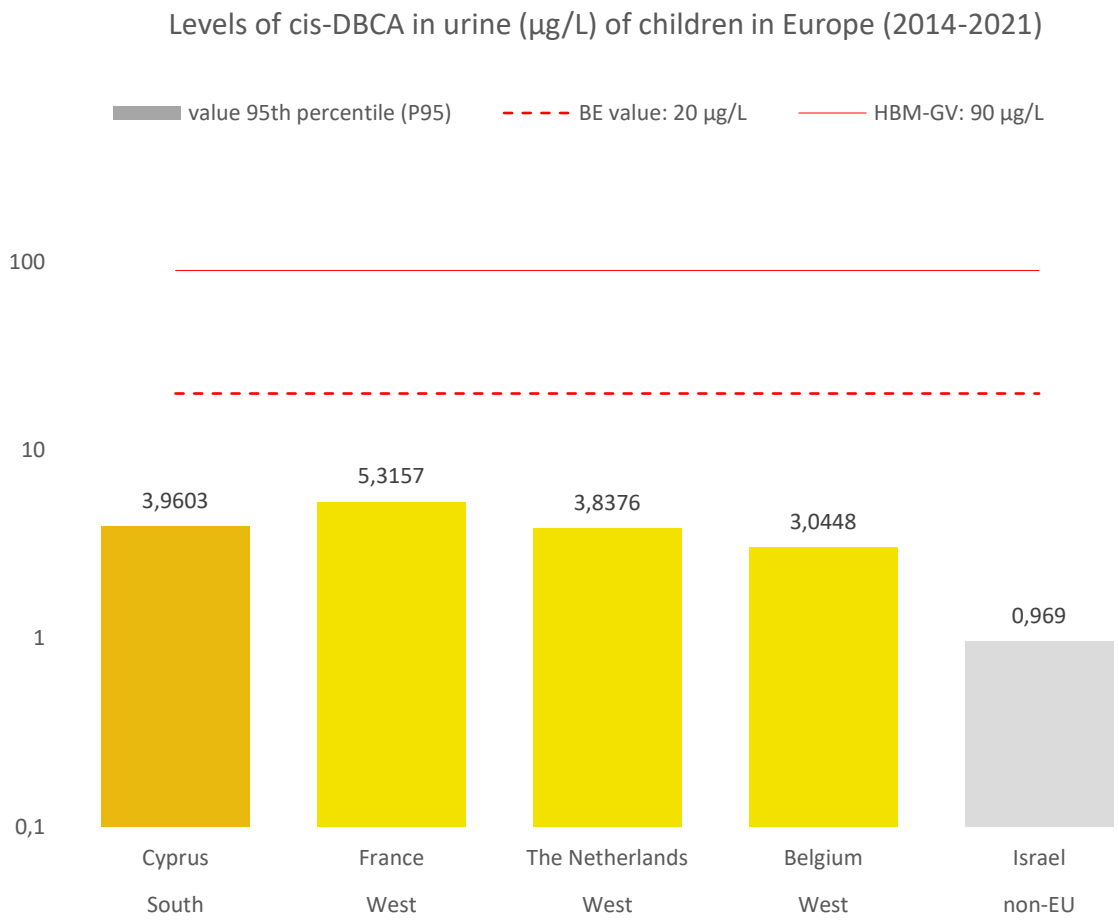
Biomarker name	Biomarker acronym	Description
3-phenoxybenzoic acid	3-PBA	Common metabolite of most pyrethroids (e.g., cyhalothrin, cypermethrin, deltamethrin, fenpropathrin, permethrin, tralomethrin) estimate for total exposure.
cis-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropane-1-carboxylic acid	cis-DCCA	Metabolites of the respective isomers of permethrin, cypermethrin and cyfluthrin.
trans-3(2,2-dichlorovinyl)-2,2-dimethylcyclopropane-1-carboxylic acid	trans-DCCA	Metabolites of the respective isomers of permethrin, cypermethrin and cyfluthrin
cis-3-(2,2-dibromovinyl)-2,2-dimethylcyclopropane-1-carboxylic acid	cis-DBCA	Specific metabolite of deltamethrin.
4-fluoro-3-phenoxybenzoic acid	F-3-PBA/F-PBA	Metabolite of cyfluthrin.
cis-3-(2-chloro-3,3,3-trifluoroprop-1enyl)-2,2-dimethylcyclopropanecarboxylic acid	CIF3CA/CFMP	Metabolite of bifenthrin, λ-cyhalothrin, tefluthrin.

Guidance values have been derived for several pyrethroid metabolites. The US Biomonitoring equivalents (BE) reflects the concentration of a biomarker of exposure in a human biological matrix such as blood and urine consistent with existing external exposure guidance values or reference toxicity value (e.g. reference doses and concentrations, minimal risk levels, daily tolerable intakes (TDIs)). The BE is a tool for interpreting biomonitoring exposure concentrations from a public health perspective (Hays et al., 2008). BE values for children were derived for cis-DBCA and F-3-PBA and are 20 µg/L and 46 µg/L, respectively. Two BE values were derived for 3-PBA since it is a non-specific biomarker for several pyrethroids of differing toxic potencies. This allows for a tiered interpretation of biomonitoring exposure concentrations in risk assessment. The Tier 1 values are based on the toxicological reference dose of cyhalothrin (the pyrethroid with the highest toxicity out of nine parent pyrethroids of 3-PBA) and a highly conservative screening value for assessment of population urinary 3-PBA data, while the Tier 2 is higher and based on weighting by relative exposure estimates in the US for the different parent compounds. Tier 2 should be used when the biomonitoring concentrations exceed Tier 1. The BE value Tier 1 is 1.7 µg/L for children and the BE value Tier 2 is 87 µg/L for children (Aylward et al., 2018).

The HBM guidance values (HBM-GVs) reflect the concentration of exposure in a human biological matrix such as blood and urine below which no risk for adverse health effects are expected based on the knowledge at the time of derivation. They can be based on human internal data (option 1), external toxicity reference values or on a defined occupational exposure limit (option 2) and critical effect in an animal toxicity study (option 3). When the HBM-GVs are based on existing external toxicity reference values, they correspond with the BE. The HBM-GVs are a tool for determining if exposure based on biomonitoring concentrations will pose a risk and require action. These values were derived under the HBM4EU project and national experts where extensively consulted to ensure a high degree of scientific integrity and acceptance. An HBM-GV for children was derived for both cis-DBCA and F-3-PBA and are 90 µg/L and 80 µg/L respectively (Apel et al., 2020). Tarazona et al. (2022) derived a HBM-GV for 3-PBA. The Tier 1, the most stringent value, equals 3.25 µg/L for children. All HBM-GVs were based on animal toxicity studies (animal studies with neurotoxicity as endpoint).

Figure 4.3, Figure 4.4, Figure 4.5 show the comparison of the urinary concentrations of cis-DBCA, 3-PBA and F-3-PBA of European children from the HBM4EU aligned studies with their corresponding guidance values. The indicator for cis-DBCA (Figure 4.3) shows that exposure of European children to the parent pyrethroid compounds of cis-DBCA did not exceed the BE value or HBM-GV value.

Figure 4.3: Levels of cis-DBCA in urine (µg/L) of children in Europe (2014-2021)



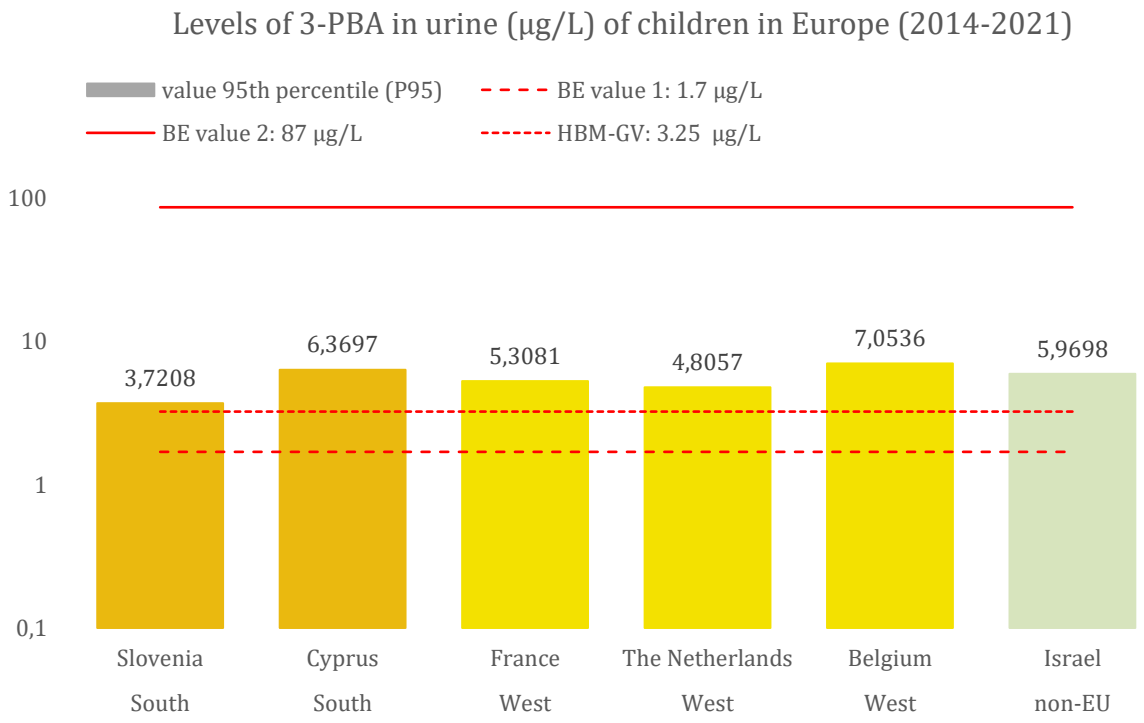
Notes: Indicator shows the p95 values of cis-DBCA in urine (µg/L) of European children (6-12 years) from 5 studies (HBM4EU aligned studies children: Cyprus ORGANIKO, France ESTEBAN, The Netherlands SPECIMEn, Belgium 3xG, Israel RAVMABAT) sampled between 2014 and 2021. The red dotted line represents the BE value for cis-DBCA (20 µg/L). The full red line represents the HBM-GV for cis-DBCA (90 µg/L). The indicator shows the comparison between the levels in children and both guidance values.

Source data: EU HBM Dashboard([2]).

The exposure of European children to pyrethroids in general, as shown by the indicator for 3-PBA (Figure 4.4), exceeded the conservative BE value Tier 1 and HBM-GV, but not the BE value Tier 2. Tarazona et al. (2022) noted that although no exceedances of the risk levels have been observed in the HBM4EU aligned studies for HBM-GV at higher tier (further refinement considering relative potency factors), the combined risk is below but close to the acceptability threshold, particularly for children. This means that risks for health effect cannot be excluded for high exposed children. This is worrying as the guidance values set for most pyrethroids are based on neurotoxicity observed in adult experimental animals, which may not sufficiently protect against developmental neurotoxicity.

([2]) https://www.hbm4eu.eu/what-we-do/european-hbm-platform/eu-hbm-dashboard/

Figure 4.4: Levels of 3-PBA in urine (µg/L) of children in Europe (2014-2021).

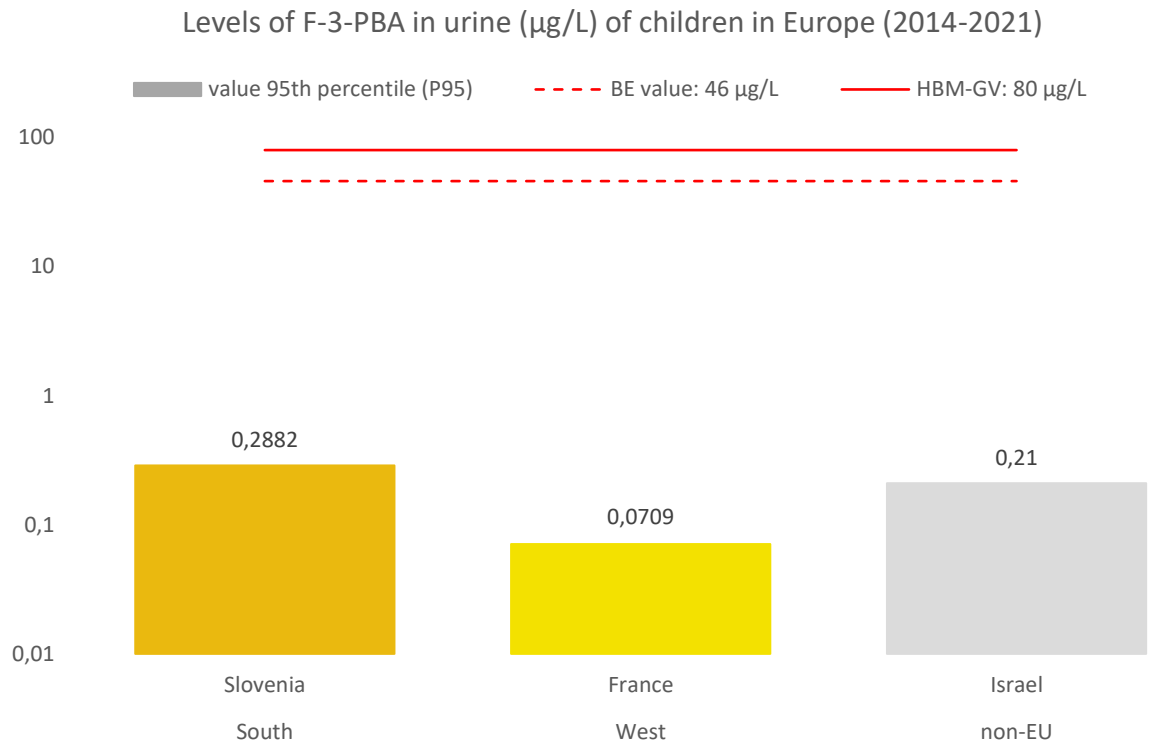


Notes: Indicator shows the p95 values of 3-PBA in urine (µg/L) of European children (6-12 years) from 6 studies (HBM4EU aligned studies children: Slovenia SLO CRP, Cyprus ORGANIKO, France ESTEBAN, The Netherlands SPECIMEn, Belgium 3xG, Israel RAVMABAT) sampled between 2014 and 2021. The bottom red dotted line represents the BE value tier 1 for 3-PBA (1.7 µg/L). The top red dotted line represents the proxy HBM-GV of 3.25 µg/L (lower tier; most stringent urinary excretion factor). The full red line represents the BE value tier 2 for 3-PBA (87 µg/L). The indicator shows the comparison between the levels in children and both guidance values.
Source data: EU HBM Dashboard([3]).

Similarly to cis-DBCA, the exposure of European children to cyfluthrin (parent-compound of F-3-PBA) did not exceed the two guidance values available for F-3-PBA.

([3]) https://www.hbm4eu.eu/what-we-do/european-hbm-platform/eu-hbm-dashboard/

Figure 4.5: Levels of F-3-PBA in urine (µg/L) of children in Europe (2014-2021)



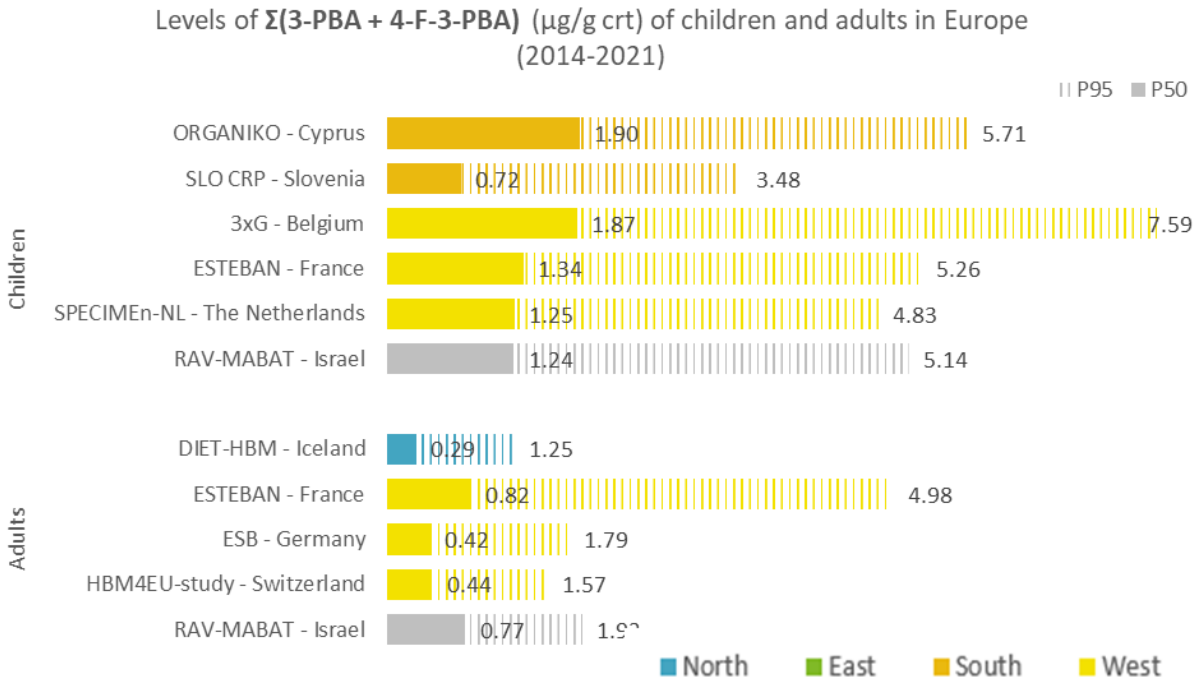
Notes: Indicator shows the p95 values of F-3-PBA in urine (µg/L) of European children (6-12 years) from 3 studies (HBM4EU aligned studies children: Slovenia SLO CRP, France ESTEBAN, Israel RAVMABAT) sampled between 2014 and 2021. The red dotted line represents the BE value for F-3-PBA (46 µg/L). The full red line represents the HBM-GV for F-3-PBA (80 µg/L). The indicator shows the comparison between the levels in children and both guidance values.

Source data: EU HBM Dashboard([4]).

Furthermore, similar data for European adults (available on the EU HBM Dashboard([5])) shows that children have a higher total exposure to pyrethroids than adults (see Figure 4.6). This is an additional point of attention. The geomean concentration of 3-PBA was in the combined Aligned Studies of HBM4EU equal to 1.24 µg 3-PBA/g creat in children where this was 0.39 µg 3-PBA/g creat in adults (Govarts et al., 2023) This means a factor of 3 difference in exposure for children and adults although measurements for adults and children were not always in identical countries.

([4]) https://www.hbm4eu.eu/what-we-do/european-hbm-platform/eu-hbm-dashboard/
([5]) https://www.hbm4eu.eu/what-we-do/european-hbm-platform/eu-hbm-dashboard/

Figure 4.6: Exposure indicator showing median (P50) value and P95 value of Σ(3-PBA + 4-F-3-PBA) from 6 studies in children (6-11 years) and 5 studies in adults (20-39 years) in Europe between 2014-2021. 3-PBA: 3 phenoxybenzoic acid; 4-F-3-PBA: 4-Fluoro-3-phenoxybenzoic acid



Although most guidance values were not exceeded, the data shows that exposure to pyrethroids of European children from HBM4EU is apparent and widespread. For 3-PBA detection rates of more than 90 % were observed. Data on adult exposure to pesticides from HBM4EU shows that children have higher internal exposure compared to adults. Based on the exposure data from HBM4EU there is little concern for pyrethroid exposure to the general population, however concern for highly exposed children cannot be neglected. Especially, since the ADIs used to determine the HBM-GV was based on neurotoxicity experiments in adult animals (HBM4EU, 2022a) and does not account for developmental neurotoxicity specifically.

4.1.3. Health effects

Exposure to pesticides has been associated with an increased risk of several adverse health effects. Effects differ between pesticides. The focus in this section is on health effects, therefore research on pyrethroids for which the use is not allowed in the EU is also included. Information on the regulation of different pesticides can be found in Table 4.1. In children the strongest evidence can be found for neurological disorders for organophosphates and pyrethroids. An association is suspected for childhood leukaemia, endocrine effects, immunotoxicity, reproductive effects and carcinogenicity. The acting active substances are often not identifiable, adverse health effects are therefore usually linked to pesticide groups. Children are particularly sensitive during specific developmental windows for exposure to chemicals (HBM4EU, 2022m).

Pyrethroids in particular have known or suspected toxic properties according to the harmonised classification under the CLP Regulation (Regulation (EC) No 1272/2008) as listed inTable 4.1. Research has linked pyrethroids to various health effects both in adults and children with varying degrees in strength of evidence.

The strongest evidence for an association between pyrethroids and health effects in children is found for behavioural disorders and adverse neurodevelopmental outcomes. Additionally, endocrine disruption, reproductive effects, childhood leukaemia and carcinogenicity are suspected as well (HBM4EU, 2022m).

Brain/neurological outcomes

Pyrethroids are neurotoxic, they target VGSCs and other ion channels. Animal studies have shown that pyrethroid exposure prenatally and early postnatally can cause long-lasting brain dysfunction. Neurochemical and neurobehavioral changes such as altered dopamine function, hyperactivity and learning and memory deficits have been demonstrated. Pyrethroids can directly or indirectly act as neurotoxins. For the direct mechanisms the concentration of pyrethroids in the brain determines effect. Blood flow to the brain and concentration of unbound pyrethroid in plasma determines the concentration in the brain. Due to faster breathing, higher food intake per kg body weight and larger relative body surface compared to adults, exposure of children is higher. Additionally, Cytochrome P450 enzymes and carboxylesterase only reach adults concentration at 10-15 years and 6 months respectively and the unbound fraction is higher in newborns because plasma levels of albumin and total proteins is lower. All these elements can contribute to a higher pyrethroid concentration in the brain in children compared to adults. Pyrethroids are suspected thyroid hormone (TH) disrupters. THs are essential for normal brain development and during the first trimester of pregnancy the fetus is dependent on maternal THs since the fetus does not produce THs yet. Even small alterations of maternal THs can impact fetal brain development.

Andersen et al. (2022) reviewed scientific literature on prenatal and childhood exposure to pyrethroids and neurodevelopmental outcomes. Seventeen studies were considered for prenatal exposure, ten for childhood exposure and two investigated both. The studies were conducted between 2011 and 2021 in 12 countries. 12 of the 17 studies investigating prenatal exposure found associations with adverse effects on neurodevelopment, the other five found no significant associations. All the studies that investigated neurobehavioral outcomes found that increasing prenatal pyrethroid exposure was associated with worse scores for higher risk of autism spectrum disorder (ASD) diagnosis. A decreased cognitive function was also found to be associated with increasing prenatal pyrethroids exposure, but not across all studies. It was concluded based on a consistent reporting of adverse associations and an overall moderate quality of evidence across the studies that there was sufficiently strong evidence for an association between prenatal pyrethroid exposure and adverse neurodevelopmental effects. Evidence included results from large, well-conducted studies as well as indications in some studies for a loss of cognitive function with increasing prenatal pyrethroid exposure. Eight out of the ten studies investigating childhood exposure found significant associations. The majority of these studies strongly suggested the possibility of an association between childhood pyrethroid exposure and impaired neurodevelopment, although reverse causation cannot be ruled out. Based on the fact that all studies were cross-sectional and that effect estimates of adverse neurodevelopment were small to moderate, even though the majority of studies found significant associations and direction of effect was consistent across the studies, it was concluded that the strength of evidence for an association between childhood exposure to pyrethroids and adverse neurodevelopmental outcomes was limited. Experimental evidence suggests that pyrethroids can affects key events in established AOPs of neurodevelopment. Most evidence is reported for disturbances in TH function, but evidence has also been found that suggests interference with brain-derived neurotrophic factor (BDNF) expression and dopamine dynamics and dopamine transporter (DAT) expression. Only a limited number of pyrethroids have been investigated. The latter could be important in unravelling the relation between pyrethroid exposure and development of ADHD, because changes in dopaminergic and noradrenergic neurotransmission are suspected to be linked to ADHD pathophysiology. Andersen et al. (2022) concluded that enough mechanistic evidence exists that suggests there is a link between pyrethroid exposure during neurodevelopment and impaired neurodevelopment. Based on epidemiological and experimental studies as well as biological plausibility, Andersen et al. (2022) concluded that an

association between pyrethroid exposure during sensitive windows for neurodevelopment and adverse neurodevelopmental outcomes is plausible.

A narrative review on scientific evidence on the association between pyrethroid exposure and developmental toxicity conclude that current evidence suggests that both prenatal and childhood exposure could be associated with neurodevelopmental delay, decreased cognitive abilities and adverse behavioural outcomes (Elser et al., 2022).

Two more recent studies from 2022 investigated prenatal and childhood pyrethroid exposure on neurodevelopmental outcomes. Qi et al. (2022) investigated the association between prenatal pyrethroid exposure during all three trimesters and neurodevelopmental outcomes (assessed with the Bayley Scales of Infant and Toddler Development, third edition (BSID-III)) in one-year-old Chinese children. Prenatal exposure to pyrethroids during the first and second trimesters was inversely associated with BSID-III composite scores at one year old. Associations were stronger with high maternal pyrethroid concentration. In the first trimester cognition and motor scores were significantly inversely associated with maternal concentration of cis-DBCA (at the 90th percentile) and language score was significantly inversely associated with maternal concentration of 3-PBA (at the 90th percentile) also in the second trimester. Maternal concentration of cis-DBCA (at the 90th percentile) was significantly inversely associated with cognition and language scores in the second trimester (Qi et al., 2022). Lee et al. (2022) examined the association between prenatal and childhood pyrethroid exposure (at ages two and six) and ADHD symptoms in South-Korean children at six and eight years old (assessed via the ADHD Rating Scale IV (ARS). They found significant direct associations between both prenatal and childhood pyrethroid exposure and ARS scores. A doubling of 3-PBA concentrations during pregnancy and age two was associated with an increased ARS score at age six. Additionally, the concentration of 3-PBA at ages four and six were associated with and increased ARS score at age eight (Lee et al., 2022). Important to note is that concentrations in children are comparable across Europe, USA and Asia (Ye et al., 2017b, 2017a; Panuwet et al., 2009; Barr et al., 2010; Roca et al., 2014; Oates and Cohen, 2011; Winston et al., 2016).

A meta-analysis from 2023 on 19 studies (from before August 2022) investigating the association between prenatal pesticide exposure and ASD and ADHD found that prenatal pyrethroid exposure was significantly associated with a higher risk of ASD (Xu et al., 2023).

Childhood leukaemia and carcinogenicity

An association between childhood leukaemia and pyrethroid exposure is suspected, although studies on pyrethroids are limited and inconclusive. Several meta-analyses reported a positive association between residential pesticide exposure and childhood leukaemia (Vinson et al., 2011; Van Maele-Fabry et al., 2011; Turner et al., 2010; Chen et al., 2015; Van Maele-Fabry et al., 2019; Bailey et al., 2015). Pesticide products for residential use often contain pyrethroids, results of these meta-analysis could therefore be suggestive for pyrethroid exposure. A review of the molecular and cellular effects of pyrethroids reported that pyrethroids are genotoxic, can induce genetic alterations, can change gene expression and modify DNA. These changes potentially underly carcinogenic processes in hematopoietic cells (Navarrete-Meneses and Pérez-Vera, 2019).

A pooled analysis of data from multiple case-control studies (between 1988 and 2007) investigating the association between home pesticide exposure (often contains pyrethroids) and childhood leukaemia, found that exposure right before conception (based on five studies), during pregnancy (based on nine studies) and after birth (based on six studies) were significantly positively associated with a higher risk of acute lymphoblastic leukaemia (ALL). A higher risk for acute myeloid leukaemia (AML) was only significantly positively associated with home pesticide exposure shortly before conception (based on four studies) and during pregnancy (based on seven studies) (Bailey et al., 2015).

A systematic review and meta-analysis of 15 case-control studies (between 2009 and 2018) investigating the association between household pesticide exposure and risk of childhood leukaemia yielded similar results. The risk of ALL, AML and unspecified leukaemia was significantly increased with exposure during pregnancy, prenatal indoor exposure and prenatal exposure to insecticides. Risk was increased at all ages of diagnosis (≤2, ≤5, ≤15, ≤18 year) (Van Maele-Fabry et al., 2019).

Chen et al. (2015) performed a meta-analysis on 16 studies investigating the association between residential childhood exposure to pesticides and childhood cancers. They found that overall, the type of pesticide and place of use are a determining factor in cancer risk. Outdoor use of insecticides during childhood were not associated with cancer risk, but indoor residential exposure to insecticides was associated with an increased risk of childhood cancers, namely leukaemia, acute leukaemia (AL) and lymphoma. Childhood brain tumour (CBT) was not associated, although the four studies included in the meta-analysis studying CBT did not provide the exposure location which could have possibly weakened the associations. The risk estimates were largest for the association between indoor residential childhood insecticide exposure and AL, and risk of childhood hematopoietic malignancies increased with use frequency of insecticides (Chen et al., 2015).

The Brazilian Multi-institutional study of infant leukaemia observed significant associations between prenatal exposure to three type I pyrethroids (permethrin, imiprothrin and esbiothrin) and increased risk of childhood ALL (0-11 months). Similarly prenatal pyrethroid exposure was significantly associated with an increased risk of childhood AML (0-11 months for prallethrin, permethrin, tetramethrin, d-alletrhin and 12-24 months for esbiothrin and d-phenothrin). These results are similar to results reported for unspecified pesticide exposure but should however be interpreted with caution since no adjustment for multiple testing was done (Ferreira et al., 2013). Similar results were reported for an association between pyrethroid metabolites and ALL in children from Shanghai (Ding et al., 2012).

Research on associations between childhood leukaemia and general carcinogenicity and pyrethroid exposure specifically is very limited, especially meta-analyses are very scarce. Several meta-analyses have reported positive associations between residential pesticide exposure both during pregnancy and childhood, and childhood leukaemia. These results could be an indication for a link between pyrethroid exposure and childhood leukaemia. Research focussed specifically on pyrethroid exposure is needed to add and broaden current knowledge.

Endocrine system

Research has shown that pyrethroids can interfere with hormone signalling in fish and mammals. Pyrethroid metabolites are stronger endocrine disruptors (ED) then their parent compound(s), but strength of the endocrine activity is dependent on the enantiomer present. This might in part explain the nonmonotonic responses pyrethroids elicit (Brander et al., 2016).

The potential ability of pyrethroids to interfere with THs has already been discussed under neurological outcomes. Pyrethroids are suspected to be able to interfere with sex hormones, this is further discussed below under reproductive outcomes.

Reproductive outcomes

In terms of reproductive outcomes, epidemiological studies have observed disturbances in sperm quality, sperm DNA, reproductive hormones and pregnancy outcomes associated with pyrethroid exposure. Studies focused on pyrethroid exposure and reproductive outcomes in children are rather limited.

A systematic review on non-persistent pesticides and puberty timing found some studies investigating the association between pyrethroid exposure and puberty outcomes, where they found a puberty delay in girls and puberty acceleration in boys (Castiello and Freire, 2021). 3-PBA concentration was

significantly associated with a reduction in the odds of reaching breast development stage 3, later onset of pubic hair development stage 2 and later onset of menarche in 9-15 year old Chinese girls (n = 305) (Ye et al., 2017a). In 9-16 year old Chinese boys 3-PBA concentration was associated with increased luteinizing hormone (LH) and follicle stimulating hormone (FSH), higher risk of being in genitalia development stage 3 and 4 (Ye et al., 2017b). A recent study found that 3-PBA concentrations were associated with higher odd of genital development in boys, but only in overweight/obese boys (Castiello et al., 2023).

Evidence from experimental studies support these findings although less conclusively for the latter.

Animal studies in female rats exposed to fenvalerate showed delayed puberty, which is consistent with a peripheral antiestrogenic effect and lack of response from LH to gonadotropin releasing hormone (GnRH) stimulation. *In vitro* studies have shown that certain pyrethroids altered the expression of genes involved in steroidogenesis, which reduced the production of oestrogens, progesterone and prostaglandin 2. Male rats that were exposed to cypermethrin have shown early puberty via a pleiotropic effect on the hypothalamic-pituitary-gonadal (HPG) axis resulting in an increased testosterone, LH and FSH production. Findings from *in vitro* studies suggest an anti-androgenic effect of several pyrethroids and reduced testosterone production. This contrasts the increased level of testosterone in rats and the hypothesis that pyrethroids accelerate male puberty. This could be due to enantioselectivity of certain pyrethroid derived compounds. The endocrine activity could be different between pyrethroids, where certain enantiomers might have an accelerating impact while this ability might be much lower for other enantiomers (Castiello and Freire, 2021). Two studies found associations between pyrethroid metabolite concentration in adult men and hormone concentrations. LH was significantly positively associated with 3-BPA and FSH was additionally also positively associated with cis and trans-DCCA. This is consistent with a possibly accelerated puberty although one of the studies found an inverse association for testosterone. One of the studies found that 3-BPA and oestradiol were negatively associated (Koureas et al., 2012; Castiello and Freire, 2021).

Epidemiological research focussed on pyrethroid exposure and reproductive outcomes is rather limited. Observations in adults suggest a link with alterations in semen quality, decreased semen counts and aneuploidy. Positive associations between pyrethroid exposure and sex hormones, mainly LH and FSH, in male adults have been reported. Contrasting associations have been reported for testosterone. But these associations are less consistently reported than for sperm outcomes (HBM4EU, 2020b; Saillenfait et al., 2015). Both experimental and epidemiological research suggests that pyrethroids have the ability to interfere with reproductive outcomes, although evidence is not as conclusive for every outcome. In children the research is very limited and mainly focused on puberty outcomes. Here as well findings are inconclusive.

Evidence rating for health effects

The approach used to categorise evidence strength for each substance is based on HBM4EU (2022m). For some effects, the categorisation itself has been updated to reflect new evidence, based on expert judgement. Evidence can be for prenatal and/or childhood exposure.

Table 4.3: Evidence rating based on the assessment of relevant publications

Outcome	Evidence	References**
Neurodevelopmental impairment	Suspected	(Qi et al., 2022; Andersen et al., 2022; HBM4EU, 2022m; Xu et al., 2023; Abreu-Villaça and Levin, 2017; Viel et al., 2015; Fluegge et al., 2016; Xue et al., 2013; Watkins et al., 2016; Eskenazi et al., 2018; Furlong et al., 2017; Viel et al., 2017; Oulhote and Bouchard, 2013; Elser et al., 2022)
ASD	Suspected	(Andersen et al., 2022; Xu et al., 2023)
ADHD	Strong	(European Environment Agency, 2023a; Lee et al., 2022; Wagner-Schuman et al., 2015)
Leukaemia	Lacking*	(Vinson et al., 2011; Van Maele-Fabry et al., 2011; Turner et al., 2010; Chen et al., 2015; Van Maele-Fabry et al., 2019; Bailey et al., 2015; Ntzani et al., 2013)
Carcinogenicity	Lacking	(HBM4EU, 2022m; Chen et al., 2015)
Endocrine disruption	Suspected	Based on ECHA properties of concern (HBM4EU, 2022m; Zhu et al., 2020; Ye et al., 2017b; Castiello and Freire, 2021)
Puberty outcomes	Suspected	(Castiello et al., 2023; Castiello and Freire, 2021; Ye et al., 2017b, 2017a)

* Suspected for residential insecticides, but lacking for pyrethroids.
** Based on EEA policy brief on pesticides (https://www.eea.europa.eu/publications/how-pesticides-impact-human-health/) with HBM4EU as basis and extended with new evidence.

4.1.4. Prevention measures

Looking at policy, the Farm to Fork Strategy entails a.o. a 50 % cut in the use and risk of chemical pesticides and in the use of more hazardous pesticides in 2030 from a 2015 – 2017 baseline. Policy measures to reduce pesticide use are e.g. providing training and information to professional users, incentives for the transition to organic farming and precision farming and introducing higher taxes for more hazardous pesticides (European Environment Agency, 2023a). Impact on human health and environment can be mitigated through restriction or banning of pesticide use in public spaces (e.g. pesticide free towns), limitations on pesticide use by non-professional users and by applying appropriately-sized buffer strips around sensitive areas in which spraying is banned (Wiener, 2023). Protection by regulation (as described above) is a time-consuming process.

The setting of buffer strips to reduce pesticide drift and protect the citizen's health and nature will be an important discussion in future pesticide regulation (PAN Europe, 2023). The EU proposal for a Regulation on the Sustainable Use of Pesticides, contains following text: "*The use of all plant protection products is prohibited in all sensitive areas and within 3 metres of such areas. This 3-metre buffer zone shall not be reduced by using alternative risk-mitigation techniques.*" (European Commission and Directorate-General for Health and Food Safety, 2022). Different nature and environmental organizations are already contesting this buffer as it is not very ambitious according to them. Different scientific studies report higher human pesticide exposure near agricultural fields (e.g. PROPULPPP study Wallonia, review by Santé Publique France in 2020 confirming that residents living near sprayed

fields are exposed to higher quantities of pesticides compared to people living far from fields, Italian study in the province Bolzano-South Tyrol). PAN Europe asks for a 50 metre (m) buffer zone from the edge of the field, reducing it to 25 m if next to a neighbouring field. The report of the SUR (Sustainable Use Regulation) rapporteur in the ENVI Committee asks for a general width of buffer zones of 10 m and 50 m for sensitive areas used by vulnerable groups and for the use of the most hazardous pesticides (Wiener, 2023).

An intervention study in Bolzano, South Tyrol showed that regional measures to reduce pesticide exposure (buffer of 30 m or less in case of additional mitigation measures), stricter than those proposed by the EU Commission, are not enough to prevent exposure of children and the general public to substances that have the potential to cause cancer or harm to reproduction. A reduction of all pesticides and a significant expansion of the suggested buffer zones to at least 50 metres are urgently needed to protect health according to HEAL (HEAL, 2022; Aguiar et al., 2015).

As regulation takes some time, the environmental hygiene hypothesis may help to reduce exposure to pesticides already at young age. Pregnant women should be more informed on the prenatal exposure to pyrethroids. Intervention studies could be set up to analyse the result of different recommendations given by an expert group to reduce exposure (Bourguignon et al., 2018). Also, initiatives like limiting dietary exposure to pesticides in schools by ensuring that kids have access to organic food is a possibility (European Environment Agency, 2023b).

4.2. Lead

4.2.1. Chemical characterization and emission sources

Lead (Pb) is a chemical element and belongs to the group of heavy metals. It occurs naturally in the environment but is mostly introduced into environmental media through human activities such as smelting, mining or battery manufacturing. Generally, lead can occur in the three different forms, elemental, organic and inorganic. IARC classified lead in general as “possibly cancerogenic” to humans (Group 2B) and the inorganic form as “probably cancerogenic” to humans (Group 2A). However, there is no evidence for associations between lead and specific childhood cancers (International Agency for Research on Cancer (IARC), 1987, 2006). Due to insufficient evidence the organic form was classified as Group 3 (not classifiable) (International Agency for Research on Cancer (IARC), 2006). All forms show different toxicological potentials and are also associated with various health outcomes (HBM4EU, 2020a).

In addition to the indicated purposes, lead is also used in leaded fuels or in paints –both forbidden in the EU, though there is concern for stock of the latter- from where it can also be released into ambient outdoor and indoor air. Lead can further reach humans by drinking contaminated water, when water supply systems include lead-based pipes. Overall, the general population can be exposed to lead by contaminated food, drinking water, air, soil as well as dust and can be found in many products of daily use (Agency for Toxic Substances and Disease Registry (ATSDR), 2020; United States Environmental Protection Agency, 2013; World Health Organization, 2022b). Due to the generally high toxicity of lead it was phased out of many products globally which resulted in a continuous decrease in lead exposure. Nonetheless, the global lead mining production is still at a high level with about four to five million tons of lead produced globally per year between 2019 and 2022 (United States Geological Survey, 2023). It is expected that due to the increased production and use of electric cars the demand for lead might increase, also potentially leading to further intakes of lead into the environment (HBM4EU, 2020a).

4.2.2. Exposure characterization

Lead can reach the human body system though different exposure routes. Children, and especially the very young can have an increased exposure due to their specific behaviors like higher hand-to-mouth contacts (e.g. mouthing behavior) (Sachdeva et al., 2018). In case of lead loaded dust, toddlers can have a higher lead intake, which shows a considerable vulnerability of this population group (Agency for Toxic Substances and Disease Registry (ATSDR), 2020). Being exposed through the oral route, children may absorb 40-50 % of water-soluble lead. This results in a considerably higher uptake of lead as compared to adults with about 3-10 % (Agency for Toxic Substances and Disease Registry (ATSDR), 2020). In addition, lead can be transmitted from the mother to the unborn child and also by breast feeding (Agency for Toxic Substances and Disease Registry (ATSDR), 2020).

Because of the high volumes of lead used in the past, it can also be released into the environment through construction work, where e.g. lead containing paint is removed without taking the necessary precautionary measures. Due to the fact that there is no degradation of lead in the environment it remains a legacy contaminant which can leach into systems that might again become important for the human exposure (e.g. food) (Agency for Toxic Substances and Disease Registry (ATSDR), 2020). When using human biomonitoring to assess the internal exposure, lead is mostly measured in blood samples which reflect the exposure of the last few months. The cumulative long-term exposure is reflected by the concentration of lead in bone tissue (Agency for Toxic Substances and Disease Registry (ATSDR), 2020).

Once exposed to lead, the half-time elimination can vary from one week to two years in blood and can take up to one to two decades in bones(Agency for Toxic Substances and Disease Registry (ATSDR), 2020). However, bodily processes such as pregnancy in women can lead to considerable releases of lead from the bones back to the blood.

Despite the efforts of the HBM4EU-project, data on population exposure for Europe is still patchy and sometimes not comparable due to different measurement techniques or simply because different population groups were sampled in the human-biomonitoring studies. Studies reviewed for the HBM4EU Project showed that a considerable amount of studies measuring lead in blood is available, but the sampling years are very outdated. Most recent studies presented blood lead levels for Germany (data collection from 2014 to 2017), Spain (data collection from 2016-2017) and Poland (data collection in 2017). None of the mentioned studies however sampled the full range of the population, with the German and Polish studies focusing on children and the Spanish study investigating the exposure of pregnant women (HBM4EU, 2020a). Children aged 3-17 in Germany had an average blood lead concentration of 9.47 µg/L (GM, geometric mean) (95 % CI: 9.16-9.80) (Vogel et al., 2021). Kowalska and colleagues surveyed children in Silesia and found comparably higher concentrations in boys and girls with 25.4 and 23.9 µg/L blood. However, the sampling site was described as located in the vicinity of industrially contaminated sites, probably reflecting a higher environmental pollution as compared to other parts of the country and thus not being representative for Poland (Kowalska et al., 2017). The study in Spain measured blood lead levels in pregnant women showing an average concentration of 10 µg/L in the first trimester and 12 µg/L at delivery. In addition, cord blood concentrations were measured at delivery indicating a slightly lower concentration of 7.9 µg/L (Bocca et al., 2019). The available studies do not allow to draw clear trends but indicate that the most recently measured exposure levels seem to be around 10 µg/L (blood lead level) with huge variations depending on the sample and the site the sample was taken from. In addition, the EFSA collects data on the occurrence of lead in food products, however, there has been no dietary exposure assessment since 2012. This shows a need to further investigate the population exposure towards lead, a chemical without any safe level.

4.2.3. Health effects

The toxicity of lead is undisputed and especially studies on children show that there is no safe level for the effects. Generally, it was shown that especially children from low- and middle-income countries have a higher burden resulting in costs of about 977 billion US dollar (Attina and Trasande, 2013).

Historically, studies focused on high exposure occupational settings, where acute high levels of lead were associated with severe forms of poisoning (Agency for Toxic Substances and Disease Registry (ATSDR), 2020). However, in the last decades it was shown in many studies that health effects such as neurological, renal, cardiovascular, hematological, immunological, reproductive, and developmental are already observed at very low levels. Most epidemiological studies investigated neurological, cardiovascular and developmental effects (Agency for Toxic Substances and Disease Registry (ATSDR), 2020).

The Global Burden of Disease study considers lead in their analyses and the most recent estimates show that overall, about 21.7 million disability-adjusted life years (DALYs) were attributable to the exposure towards lead in 2019 globally. In Europe the highest burden was found for Bulgaria with about 214 DALYs per 100,000 persons. Most of the global disease burden was estimated to occur in countries with low socioeconomic status. The largest share of the disease burden relates to cardiovascular diseases in adults but however, 2.7 million DALYs are related to mental disorders (classified as "idiopathic developmental intellectual disability") with a peak of disease burden located in the age group of young children, indicating a considerable impact on the health of this age group. In the European Union "idiopathic developmental intellectual disability" accounts for about 50,500 DALYs (Institute for Health Metrics and Evaluation, 2023). In a very recent analyses by Larsen and Sánchez-Triana they estimated that about 765 million IQ points were lost by children younger than five years globally in 2019. Further they modelled 5,545,000 cardiovascular disease deaths attributable to global lead exposure in the population aged 25 years and older (Larsen and Sánchez-Triana, 2023). For both outcomes the highest burden was found in countries with low- or medium-income levels.

Lead can affect virtually every organ system of the human body because the toxicity of lead can impact all cell types and effects are documented at blood lead levels lower than 100 µg/L (Agency for Toxic Substances and Disease Registry (ATSDR), 2020). Children are prone to many neurological effects because their blood-brain barrier is not yet fully established. Lead exposure can lead to reduced cognitive functions that reduce learning abilities and hamper memory function (Agency for Toxic Substances and Disease Registry (ATSDR), 2020; Sachdeva et al., 2018). Children may also experience changes in behavior and mood (attention, hyperactivity, impulsivity, irritably, delinquency) (Agency for Toxic Substances and Disease Registry (ATSDR), 2020). A recent review of cohort studies showed that the exposure to lead was associated with an increased risk of attention deficit hyperactivity disorders in children (ADHD). The review found an increased relative risk of 2.37 (95 % CI: 1.28–4.40) (Bernardina Dalla et al., 2022).

Further, changes in neuromotor and neurosensory functions (visual-motor integration, dexterity, postural sway, changes in hearing and visual thresholds) were also observed after exposure to lead. Due to the fact, that neurological effects are mostly irreversible and thus remain throughout the lifetime they are seen as the greatest concern for children's health with a strong impact on the entire life span (Agency for Toxic Substances and Disease Registry (ATSDR), 2020). In the long run lead exposure can lead to relevant reductions of the IQ which remain lifelong (United States Environmental Protection Agency, 2013; Sachdeva et al., 2018; Bauer et al., 2020; Heidari et al., 2022). It was also confirmed that especially low levels of lead have introduced a profound IQ loss in children (Lanphear

et al., 2005). Also, as indicated by several studies there seems to be no threshold concentration for the neurological effects of lead (Centers for Disease Control and Prevention, 2012).

Several studies have shown hematological effects of lead in the general population but also in the subgroup of children at blood concentrations lower than 100 µg/L (Agency for Toxic Substances and Disease Registry (ATSDR), 2020). The results of the studies are mixed and partly related to changes in markers in blood, not indicating any resulting adverse health effects (Agency for Toxic Substances and Disease Registry (ATSDR), 2020).

Immunological effects were shown by several studies (Agency for Toxic Substances and Disease Registry (ATSDR), 2020). In a recent review Zheng and colleagues have summarized the immunological effects of lead, showing that even low levels of lead can lead to changes in the immune system of children. It was also shown that vaccine responses were suppressed, with children having higher blood lead levels observed to have lower antibody titers for e. g. measles, mumps or rubella (Zheng et al., 2023). It was further shown that the changes in the immune system are associated with an increased risk of allergic reactions in children (Zheng et al., 2023) which was however not supported by a recent quantitative meta-analyse (Wang et al., 2022).

Only few studies in children populations have shown associations between lead exposure and dental caries as well as reduced renal function, however, there is no clear link for these outcomes (Agency for Toxic Substances and Disease Registry (ATSDR), 2020).

In addition, lead was also shown to be associated with developmental effects resulting in outcomes such as low birth weight, decreased head circumference or a delayed onset of puberty(Agency for Toxic Substances and Disease Registry (ATSDR), 2020).

In both the children and adult populations associations between lead and genotoxic effects were observed. Lead exposures have led e.g. to damages in DNA repair systems from which it is not clear how they might affect future health (United States Environmental Protection Agency, 2013).

Recent literature reviews on the health effects of lead on children emphasize several important drivers of ill-health resulting from lead exposure. Zheng and colleagues investigated the body of evidence considering the renal effects of lead in children. Despite a non-conclusive evidence, several studies have shown associations between lead exposure, measured as blood lead levels, with markers of kidney damage, such as estimated glomerular filtration rate (eGFR), urine protein, or urine albumin (Zheng et al., 2017).

Table 4.4: Evidence rating based on the assessment of relevant publications

Outcome	Evidence	References
Reduced cognitive functions	Suspected	(Agency for Toxic Substances and Disease Registry (ATSDR), 2020; United States Environmental Protection Agency, 2013)
Mood and behavioural changes	Suspected	(United States Environmental Protection Agency, 2013)
Attention Deficit Hyperactivity Disorder	Suspected	(United States Environmental Protection Agency, 2013; Bernardina Dalla et al., 2022)
Visual-motor integration	Suspected	(Agency for Toxic Substances and Disease Registry (ATSDR), 2020; United States Environmental Protection Agency, 2013)
Dexterity	Suspected	(Agency for Toxic Substances and Disease Registry (ATSDR), 2020; United States Environmental Protection Agency, 2013)
Postural sway	Suspected	(Agency for Toxic Substances and Disease Registry (ATSDR), 2020)
Changes in hearing and visual thresholds	Suspected	(Agency for Toxic Substances and Disease Registry (ATSDR), 2020; United States Environmental Protection Agency, 2013)
IQ reduction	Strong	(Bauer et al., 2020; Heidari et al., 2022; United States Environmental Protection Agency, 2013; Sachdeva et al., 2018)
Genotoxic effects	Strong	(United States Environmental Protection Agency, 2013; HBM4EU, 2020a)
Hematological effects	Suspected	(Agency for Toxic Substances and Disease Registry (ATSDR), 2020)
Immunological effects	Suspected	(Agency for Toxic Substances and Disease Registry (ATSDR), 2020; United States Environmental Protection Agency, 2013; HBM4EU, 2020a)
Developmental effects	Suspected	(Bauer et al., 2020; Agency for Toxic Substances and Disease Registry (ATSDR), 2020; United States Environmental Protection Agency, 2013)
Dental caries	Lacking	(Agency for Toxic Substances and Disease Registry (ATSDR), 2020)
Reduced renal function	Lacking	(Agency for Toxic Substances and Disease Registry (ATSDR), 2020; Zheng et al., 2017)

4.2.4. Prevention measures

The highest exposure of the global population to lead resulted from its use in petrol. Since lead use in petrol was phased out in most countries of the world the exposure of the global population was reduced significantly (HBM4EU, 2022j; World Health Organization, 2019c). Nonetheless, after strong reductions have been observed there is a halt in the decreasing trends of the exposure as observed in

several human biomonitoring studies. This shows that there seems to be still a considerable amount of lead that is reaching the human bodies through various routes. Lead as a legacy chemical is stored in the environment for long time periods and can leach though different processes back to exposure routes that are relevant for humans. The exposure through food and drinking water still poses a relevant route making further measures necessary to reduce lead contaminations in e.g. water pipes, food packages or food processing (EFSA Panel on Contaminants in the Food Chain (CONTAM), 2010).

Even today in some Non-EU countries lead is still used in petrol or as an additive in paints, introducing an urgency to further restrict or ban the use of lead globally.

Further, lead should be recycled properly. If not recycled properly lead can reach environmental media and result in contaminated sites with considerable effects on the nature and the health of animals and humans.

EU Policies should aim at the reduction or ban of lead use in several processes and practices, such as the use of lead in bullets for e.g. hunting birds in wetlands (European Commission, 2021a, 2023).

The results from the HBM4EU-project indicated that since the phase out of lead many industrial processes the interest of measuring current human exposures to lead went down. This results in not appropriate monitoring of the lead exposure in the general population. With stagnating blood levels as indicated by some studies and with the most recent scientific evidence, indicating no safe-level for lead, monitoring of lead concentrations in the human body as well as in environmental media contributing to the exposure needs to be fostered (HBM4EU, 2022j).

4.3. Benzophenones

4.3.1. Chemical characterization and emission sources

Benzophenone (BP) belongs to the chemical group of organic compounds (aromatic ketones). BP and various derivates have the special property of filtering UV (ultraviolet) radiation, protecting human skin from sun damage. Therefore, they are most commonly used in sunscreens, cosmetics and other personal care products such as makeup, deodorants or body lotions. BP-3 in particular is used in these products. Other BP agents used as UV filters include BP-1, BP-2 or 4-methylbenzylidene camphor (4-MBC). To protect commercial products against photodegradation, BPs are also frequently added as UV blockers to plastics, coatings, food packaging, paints, varnishes, inks, furniture, textiles, detergents and many other products. In addition, BPs are used in the production of insecticides, agrochemicals and pharmaceuticals. They are used as flavouring agents or odour enhancers, yet also occur naturally in flowering plants (Mustieles et al., 2023; Mao et al., 2022; HBM4EU, 2022e; IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, 2013).

According to ECHA (2023a), ≥ 1,000t of BP are manufactured and/or imported per year in the European Economic Area. However, corresponding data on the use of derivatives such as BP-1 is less known. Moreover, there is growing concern about the potential effects of BPs on the environment and human health.

4.3.2. Exposure characterization

For the general population, the most relevant exposure route for BPs is dermal absorption through direct application of sunscreens, cosmetics or other personal care products containing BPs. To a lesser extent BPs are taken up via food, e.g. foods that naturally contain BPs, such as mangoes or muscat grapes, but also foods containing flavouring or colouring additives, BPs that have migrated from food packaging or consumption of contaminated drinking water. Inhalation of substances containing BP from paints or varnishes may also contribute to the overall exposure (HBM4EU, 2022e).

Regarding occupational exposure, BP uptake through inhalation of dusts, but also through absorption via the skin, plays the major role. Employees working with plastics, paints or in the chemical industry are particularly at risk in this regard (HBM4EU, 2022e).

The chemical group of BPs is included in the HBM4EU list of priority substances. Due to its widespread use and application, BP exposure can be widely detected in humans. It is rapidly metabolized in the body and excreted in the urine with a short half-life of about 16 hours (HBM4EU, 2022e; IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, 2013). Though, apart from urine, BP can also be found in many other biological samples, such as blood, breast milk or amniotic fluid (Mao et al., 2022).

Many HBM studies mainly measure BP-3 or its metabolite BP-1 in urine. Worldwide, however, there is less data available for children and adolescents than for adults (HBM4EU, 2020c). Within the HBM4EU project, results of aligned studies from six countries showed that BP-3 and BP-1 were measured in about 96 % of urine samples in adolescents (aged 12-18 years). HBM studies also showed that girls, and especially adolescent girls, had higher urinary BP-3 levels than boys up to 18 years of age, presumably due to more frequent use of personal care products (HBM4EU, 2022e; Tschersich et al., 2021). Spatial differences in exposure cannot be clearly identified but suggested. When comparing HBM4EU aligned studies, Govarts et al. (2023) found generally higher urinary BP-3 concentrations in Southern and Eastern Europe. One reason could be a higher need for sunscreen due to the prevailing climate. However, HBM results of the fifth German environmental survey (GerES V) showed that urinary BP-3 levels in children and adolescents were hardly affected by the use of sunscreens (Tschersich et al., 2021). Likewise, findings from HBM studies in Denmark showed that BP-3 levels in children were elevated not only in summer, but also in the colder season when the need for sunscreen use is low. This suggests that exposure in children and adolescents originates from additional sources such as personal care products (Frederiksen et al., 2013; Krause et al., 2017; Mao et al., 2022).

In terms of exposure levels in adolescents analysed in HBM4EU aligned studies, the provisional HBM-GV for BP-3 (340µg/g creatinine) was only exceeded in less than 1 % of the adolescents studied (Govarts et al., 2023). In principle, BP-3 exposure can therefore be considered low. Yet, there are various co-exposures with BP substitutes, e.g. BP-1, that are either not measured or cannot be assessed due to missing health-based guidance values. This makes a more realistic risk assessment challenging (Govarts et al., 2023).

4.3.3. Health effects

The widespread presence of BPs and its detection in various human bodily fluids has raised concerns about its potential health effects (HBM4EU, 2022e; Mao et al., 2022). Available studies suggest that exposure to BP or its derivatives can have various negative impacts on health. HBM4EU (2022e) identified three main health risks: a) maternal and reproductive toxicity and the impacts on thyroid hormones (BP-3), b) its potential carcinogenicity (BP) and c) effects on liver and kidneys (BP). Most of the study findings to date are primarily based on animal or in-vitro studies. However, associations are increasingly being investigated in epidemiological studies, many of them focussing on health effects related to BP-3 exposure. Nevertheless, study results are often controversial and therefore the strength of evidence for the respective associated health outcomes varies (Mustieles et al., 2023; Mao et al., 2022; Wnuk et al., 2022; HBM4EU, 2022e). Moreover, many study results on the three key health impacts from BP, but also on other potential health effects, refer to the adult population, with limited knowledge on the effects for children and adolescents. For this younger population group, potential health effects of BP and some of its derivates are described below, based primarily on findings from epidemiological studies. In Table 4.5, the evidence on the different risk-outcome pairs is rated based on the relevant literature.

There is some evidence that prenatal exposure, especially to BP-3, may have adverse developmental effects on the unborn child or neonate, though knowledge is controversial. Literature reviews by Mao et al. (2022), Mustieles et al. (2023) and Wnuk et al. (2022) reported several epidemiological studies showing that prenatal BP-3 exposure can affect foetal growth. Some studies also found associations with decreased length of gestation for male infants (Mao et al., 2022). Likewise, several human studies found that BP-3 exposure during pregnancy was related to lower birth weight in new-born girls, while higher birth weight was associated with BP-3 in the sample of boys (Mustieles et al., 2023; Mao et al., 2022). In general, however, Mustieles et al. (2023) and Wnuk et al. (2022) also cited epidemiological studies that could not confirm such associations or where study quality was insufficient to draw meaningful conclusions. Based on animal studies, there is further suspected evidence of a link between BP-3 and damage to the central nervous system of the foetus (HBM4EU, 2022e).

BP and some of its derivates may also have endocrine-disruptive properties (Mustieles et al., 2023; Mao et al., 2022; HBM4EU, 2022e; Fivenson et al., 2021; Danish Environmental Protection Agency, 2018; IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, 2013). Cell, animal and epidemiological studies on thyroid hormones biomarkers all provide strong evidence that prenatal exposure to 3-benzylidene camphor (3-BC) can lead to altered hormone production in the thyroid gland in the foetus or newborns, but also other BP derivates are suspected (HBM4EU, 2022e; Mustieles et al., 2023). Reproductive health could also be impaired. However, most of the findings come from animal studies, in which adverse effects mainly occurred in the high dose range. For example, animal and cell studies have shown that exposure to BP-3 and 4-MBC can have reproductive toxic effects in the foetus (HBM4EU, 2022e; Wnuk et al., 2022). There are only few epidemiological studies that show clear associations and even fewer studies that deal with the effects on children or adolescents. Mustieles et al. (2023) reported one observational study analysing data, where higher BP-3 exposure was associated with lower serum testosterone levels in male adolescents. More often, exposure influences on pubertal development in children are studied, but also controversially discussed. Many individual studies investigated in reviews (Mustieles et al., 2023; Wnuk et al., 2022; Mao et al., 2022) and one meta-analysis (Bigambo et al., 2020) suggest that there is no statistically significant effect of BP-3 or BP-2 exposure on pubertal timing, e.g. age at menarche, thelarche, pubarche or genital development, neither in girls nor in boys. In contrast, other researchers noticed a relationship between BP-3 exposure and some of the investigated outcomes (decreased testicular volume in boys or higher risk of an earlier puberty onset or delayed breast development in girls) (Mustieles et al., 2023; Mao et al., 2022; Wnuk et al., 2022).

The influence of BP-3 on the internal hormone balance, both before and after birth, may also lead to other clinical or subclinical health consequences later in life. For example, human observational studies have reported that BP-3 exposure in children and adolescents may be related to anthropometric parameters such as lower body mass index (BMI), body fat mass or waist circumference. However, the BMI-related results were only significant for girls in some studies and only for boys in others (Mustieles et al., 2023). Furthermore, impacts of BP-3 on behavioural problems, cognitive disorders or psychomotor development are also discussed. Though, findings from epidemiological studies on behavioural problems in children are inconsistent. Mustieles et al. (2023) reported that some individual studies observed an inverse relationship between prenatal BP-3 exposure and emotional symptoms in male infants or hyperactivity-inattention in early childhood, as well as a positive association with poorer prosocial behaviours in children at the age of ten. Yet, the authors also described one study that did not find any associations with behaviour in boys between three and five years of age. Some epidemiological studies also did not find a relationship between prenatal BP-3 exposure and cognitive functions, including the intelligence quotient. However, one individual study reported a statistically significant association between prenatal 4-hydroxybenzophenone (4-OH-BP) exposure and psychomotor development index scores for boys (Mao et al., 2022).

Apart from potential influences on physical, mental or motor development and hormone balance, exposure to BPs is also suspected to affect various organs in children and adolescents. On the one hand, the skin can be affected. Wearing or applying products containing BP-3 might lead to allergic or photoallergic contact dermatitis (HBM4EU, 2022e; Wnuk et al., 2022; Tschersich et al., 2021; Fivenson et al., 2021). Furthermore, possible alterations in liver and kidneys of infants or unborn children have been identified in relation to BP exposure, primarily based on animal studies (HBM4EU, 2022e).

In addition, BP is officially recognised in the EU as carcinogenic and categorised as group 2b (possibly carcinogenic to humans) according to the IARC classification. These findings also result mainly from animal experiments (European Chemicals Agency (ECHA), 2023a; HBM4EU, 2022e; IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, 2013). Therefore, it cannot be ruled out that there is an increased risk of cancer in children due to BP or 4-methyl-benzophenone (4-MBP) exposure. However, there are hardly any specific human studies for this age group, as cancer often appears in adulthood due to long latency periods. Even so, Mustieles et al. (2023) reported one cross-sectional study linking elevated BP-3 concentrations in children aged 6-14 years to oxidative DNA damage evaluated from urinary 8-hydroxy-deoxy-guanosine concentrations.

Finally, BP exposure at young age can also lead to health consequences in adulthood. There is initial suspicion that BP-3 exposure, especially during pregnancy, can lead to Alzheimer's, Parkinson's or Huntington's disease many years later in life (Wnuk et al., 2022).

Table 4.5: Evidence rating based on the assessment of relevant publications

Outcome	Substance	Evidence	References
Foetal growth	BP-3	Suspected	(HBM4EU, 2022e; Mao et al., 2022; Mustieles et al., 2023; Wnuk et al., 2022)
Damage to central nervous system	BP-3	Suspected	(HBM4EU, 2022e)
Decreased gestational length (males)	BP-3	Suspected	(Mao et al., 2022)
Birth weight	BP-3	Suspected	(HBM4EU, 2022e; Mao et al., 2022; Mustieles et al., 2023; Wnuk et al., 2022)
Endocrine disrupting effects on the thyroid gland	3-BC, BP, BP-1, BP-2, BP-3, 4-MBC, 4-HBP	Suspected to strong	(HBM4EU, 2022e; Mao et al., 2022; Mustieles et al., 2023; Wnuk et al., 2022)
Reproductive toxicity	BP-3, 4-MBC	Suspected	(HBM4EU, 2022e; Wnuk et al., 2022)
Lower serum testosterone levels	BP-3	Suspected	(Mustieles et al., 2023)
Pubertal development (e.g. decreased testicular volume, delayed breast development, earlier puberty onset)	BP-3	Suspected	(Mustieles et al., 2023; Mao et al., 2022; Wnuk et al., 2022)
Anthropometric parameters (e.g. lower BMI, waist circumference)	BP-3	Suspected	(Mustieles et al., 2023)
Hyperactivity-inattention	BP-3	Suspected	(Mustieles et al., 2023)
Emotional symptoms (males)	BP-3	Suspected	(Mustieles et al., 2023)
Poorer prosocial behaviour	BP-3	Suspected	(Mustieles et al., 2023)
Psychomotor development (males)	4-OH-BP	Suspected	(Mao et al., 2022)
Allergic or photoallergic contact dermatitis	BP-3	Suspected	(HBM4EU, 2022e; Wnuk et al., 2022; Tschersich et al., 2021; Fivenson et al., 2021)
Liver and kidneys toxicity	BP	Suspected	(HBM4EU, 2022e)
Cancer	BP, 4-MBP	Suspected	(HBM4EU, 2022e; European Chemicals Agency (ECHA), 2023a; IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, 2013)
Oxidative DNA damage	BP-3	Suspected	(Mustieles et al., 2023)
Alzheimer's disease (in adulthood)	BP-3	Lacking	(Wnuk et al., 2022)
Parkinson's disease (in adulthood)	BP-3	Lacking	(Wnuk et al., 2022)
Huntington disease (in adulthood)	BP-3	Lacking	(Wnuk et al., 2022)

4.3.4. Prevention measures

The EU has adopted several policy measures to prevent human exposure to BPs and potentially associated health risks. As part of HBM4EU, Johansen et al. (2020) prepared a detailed report on the relevant EU legislation related to BPs. The use of BP in the EU is regulated on the one hand under the Regulation (EC) No 1907/2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH), and on the other hand by Regulation (EC) No 1272/2008 on Classification, Labelling and Packaging of substances and mixtures (CLP Regulation). According to the updated Regulation (EC) No 1272/2008 of February 2022, BP is now classified as a category 1b carcinogen (may cause cancer). Thus, as of November 2023, cosmetic products containing BP may no longer be distributed and sold.

Furthermore, EU regulations restrict the use of BPs and other UV-filters in sunscreens and cosmetics (Cosmetics Regulation (EC) No 1223/2009) (HBM4EU, 2022e). According to Annex II of the cosmetics regulation, 3-BC, for example, is prohibited in cosmetics. Since 2022, the re-evaluation of BP-3 due to its potential endocrine disrupting properties has resulted in new maximum levels in cosmetics[1] under Regulation (EU) No 2022/1176. On behalf of the European Commission, the SCCS is currently also evaluating the use of BP-1 in view of potential endocrine disrupting effects.

To further protect consumers, EU regulations also restrict the use of BPs in materials intended to get into contact with food (Regulation (EC) No 2002/72) (HBM4EU, 2022e). Additionally, the EFSA has assessed the safety of BP as a flavouring substance in food. In 2017, the experts confirmed a tolerable daily intake (TDI) of 0.03mg/kg bodyweight/day and associated no safety concerns for the general population, including the possible carcinogenic potential of BP (EFSA Panel on Food Contact Materials et al., 2017). However, there are also voices calling for additional restrictions on different BPs. For example, the International Chemical Secretariat has listed BP, BP-2 and BP-3 on the SIN list, implying that these chemicals should be removed as soon as possible as they pose a risk to human health and the environment.

The general problem is that BPs are usually not used individually, but in mixtures. Although some BPs are already restricted in the EU, not all substances are currently regulated and their mode of action is not well understood (Govarts et al., 2023; Tschersich et al., 2021). Also, exposure to individual BP-containing products may still be low, yet simultaneous use of multiple products may potentially lead to additive effects. Therefore, on the one hand, human biomonitoring of BP and its derivates needs to be expanded to better reflect the body burden, and on the other hand, restrictions to further BPs should be continuously evaluated (Wnuk et al., 2022).

Beyond regulatory actions, prevention measures can also be taken at the individual level. Overall, health concerns about BPs should not lead to a general avoidance of sunscreens. The application of sunscreens is rather essential to protect the skin from harmful UV radiation and thus reduce the risk of skin damage or even skin cancer. Alternatively, sunscreens and cosmetics should be used that do not contain BPs but, for example, mineral UV filters. The population and healthcare providers should be better informed about such alternatives (Mustieles et al., 2023). In this respect, a more transparent ingredients labelling would be supportive, as would encouraging manufacturers to offer more BPs free products.

4.4. Per-/poly-fluorinated compounds

4.4.1. Chemical characterization and emission sources

PFAS are a group of man-made chemicals that contains thousands of compounds. In 2018 the OECD identified 4730 CAS numbers linked to PFAS and related substances (OECD, 2018). They were first made in the 1930s and have been commercially used since the 1950s. They have water, grease and oil

resistant properties that make them very useful to processes and for products that require these properties. PFAS are therefore used in a multitude of products including consumer products such as food containers, personal care products, non-stick cookware, and cleaning products (HBM4EU, 2022l). PFAS have a long half life, on average 2-5 years in humans, and bioaccumulate both in the environment and humans. The half lives in the human for perfluorooctanoic acid (PFOA) and Perfluorooctane sulfonic acid (PFOS) are 3.8 and 5.4 years respectively (Zhang et al., 2013). They can pass through the placenta; prenatal exposure is therefore possible (European Environment Agency, 2019).

PFAS are made up of a carbon chain that is partly or fully fluorinated with different possibly functional groups attached. The length of the chain as well as the number of fluorine atoms and the functional group are very varied, which is way the group of PFAS is so large and variation between PFAS is so varied. Perfluoroalkyl carboxylic acids (PFCAs) are PFAS with a carboxylic acid attached, examples are PFOA, PFNA, PFDA, etc. Perfluoroalkyl sulfonic acids (PFSAs) are PFAS with a sulfonic acid attached, examples are PFOS, perfluorohexane sulfonic acid (PFHxS), perfluorobutane sulfonate (PFBS), etc. PFAS are often classified as short or long-chain PFAS based on the length of the fluorinated carbon chain. PFCAs are considered long chain when the chain consists of seven or more fluorinated carbons, PFOA is an example of a long chain PFCAs and PFBA (four fluorinated carbons) is an example of a short chain PFCAs. PFSAs are considered long chain when the chain has six or more fluorinated carbons, with PFOS as an example and PFBS is an example of short chain PFSAs. Short chain PFAS were often used as a replacement to long chain PFAS that were banned (HBM4EU, 2022l).

Many PFAS precursors exist, which are generally not environmentally persistent, but they can degrade to PFAS. PFAS can also degrade itself to other PFAS (EFSA Panel on Contaminants in the Food Chain (EFSA CONTAM Panel) et al., 2020). Several PFAS are included in the candidate list of substances of very high concern for authorisation under the REACH regulation (Regulation (EC) No 1907/2006) on the basis of their very persistent and very bioaccumulative (vPvB) or persistent, bioaccumulative, toxic (PBT) properties or equivalent concern to vPvB/PBT or carcinogenic, mutagenic or reprotoxic (CMR) substances. PFOA, PFOS and PFNA are presumed reprotoxic substances (Repr. 1B), known specific target organ (liver) toxicants (STOT RE 1), know eye irritants (Eye Dam. 1) and suspected carcinogens (Carc. 2) according to the harmonized classification under CLP Regulation (EC) No 1272/2008 (HBM4EU, 2022l). Short chain PFAS are assumed to be less bioaccumulative than long chain PFAS, due to their higher water solubility and consequent quicker elimination from the body (Chambers et al., 2021). However, short chain PFAS have been found to accumulate in the environment (European Environment Agency, 2019; HBM4EU, 2022l). Moreover, a study found that short chain PFAS accumulated more in plants than the long chain PFOS and PFOA (Schulz et al., 2020). Due to their higher water solubility, short chain PFAS are more mobile and persistent in aquatic ecosystems than long chain PFAS (Chambers et al., 2021).

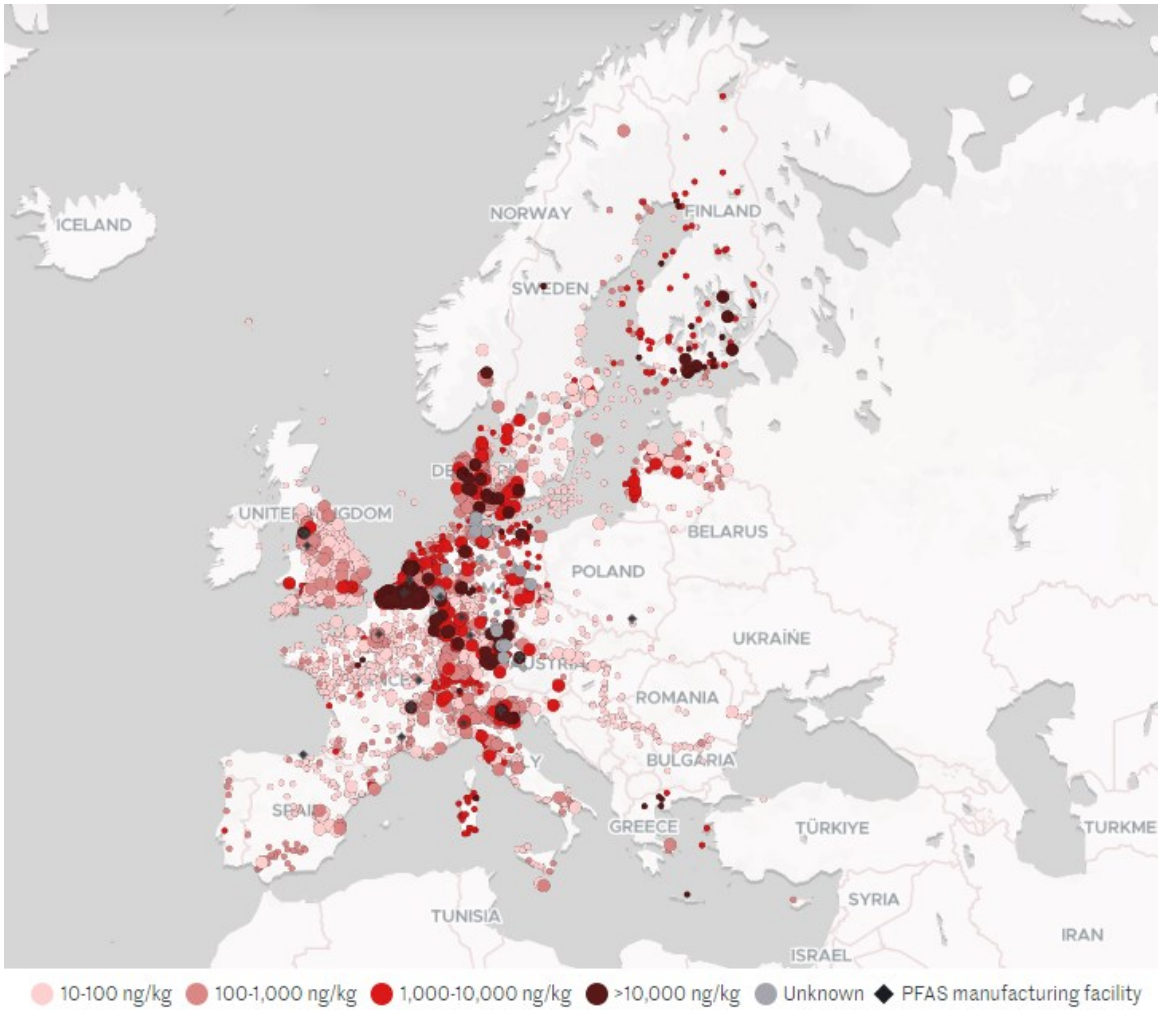
Some PFAS exist in two forms: linear and branched. PFAS used to be mainly produce via electrochemical fluorination (ECF), which resulted in 70-80 % of the desired linear form of PFOS, 80-85 % of PFOA and 95 % of PFHxS. The remaining percentage consisted of unwanted branched forms of these PFAS, which were a by-product. ECF was later replaced by telomerisation, which resulted in 100 % of the desired linear form. Even though branched isomers were a by-product and production level was lower, there presence in the environment is substantial, the distribution however is inconsistent in the environment. Geographic location is a determining factor in distribution of PFAS in environmental compartments, animals and humans. This is mainly due to how long ECF was used before telomerisation was implemented. Additionally, branched and linear isomers show different preferential accumulation in the environment, animals and humans. Linear isomers sorb preferentially to sediment and soil compared to branched isomers. Evidence in plants is limited, but linear isomers seem to be preferentially taken up by plants. Data in animals is also limited but suggests preferential accumulation of linear isomers. Mostly PFOA or PFOS, have been measured, which makes generalization to other PFAS difficult (Schulz et al., 2020).

Humans seem to have preferential accumulation of branched isomers, but also here geographical differences in isomer profiles are observed. Branched isomers can more easily pass through the placenta. Researchers hypothesise that this could be why pregnant women had lower concentrations of branched isomers than linear isomers compared to other human studies of the general population (Schulz et al., 2020).

4.4.2. Exposure characterization

Due to the worldwide production and use of PFAS they are released to the environment. Because PFAS are persistent and bioaccumulate they are very prevalent in the environment (HBM4EU, 2022l). The map below shows all production sites and locations where monitoring detected PFAS. Water, soil or living organism were sampled between 2003 and 2023 (see Figure 4.7). PFAS was detected at over 17,000 sites. Geographically neighbouring sampling locations were clustered together, which is represented by the circles. This allowed the identification of over 2100 hotspots (PFAS concentration >100 ng/l without notification of the medium or how this value was derived). Additionally, over 21,000 sites are presumed to be contaminated, because of past or current use and emission of PFAS. Monitoring needs to confirm whether these sites are contaminated (Dagorn et al., 2023).

Figure 4.7: Overview of production sites and locations where PFAS was detected by monitoring



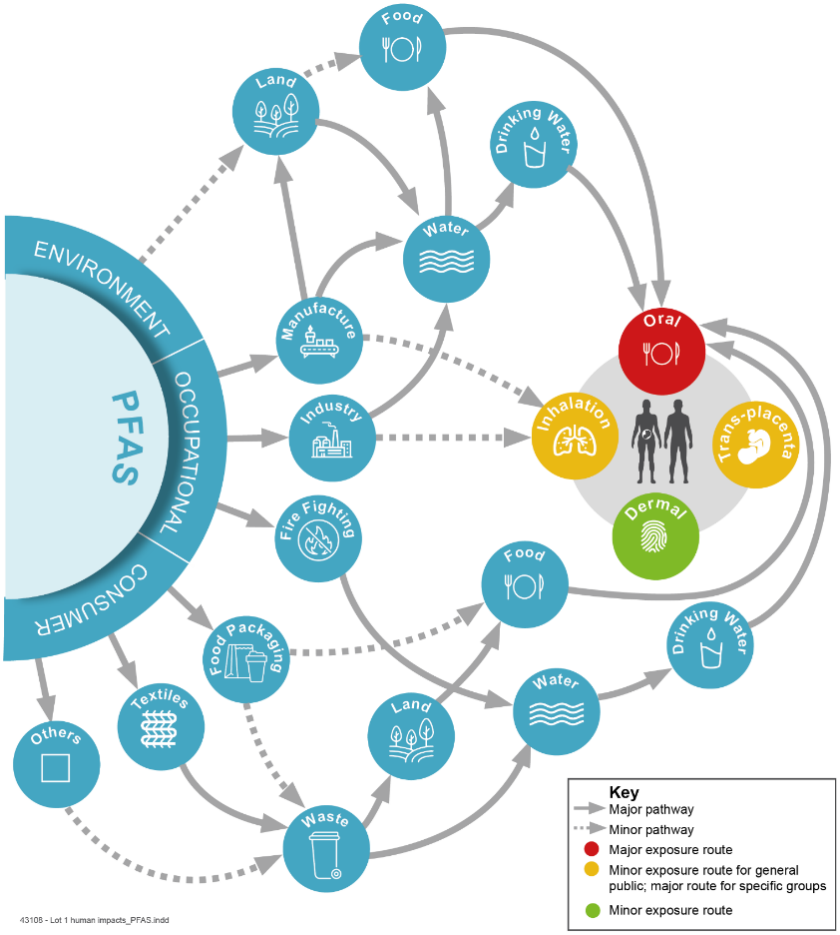
Notes: Every circle represents a cluster of neighbouring sampling locations.
Source: The Forever Pollution Map by Le Monde([6]) (Dagorn et al., 2023).

([6])https://www.lemonde.fr/en/les-decodeurs/article/2023/02/23/forever-pollution-explore-the-map-of-europe-s-pfas-contamination_6016905_8.html

People are exposed to PFAS via several major pathways as shown in Figure 4.8. The main routes of exposure for the general population are via ingestion of drinking water and food, contact with consumer products and inhalation of dust. Exposure to PFAS is complicated, as is clear below: drinking water and food can be contaminated with PFAS through many pathways. Directly from PFAS that has been deposited and accumulated in the environment, but also through consumer products that can contaminate drinking water and food. Young children will have an increased intake per kg bodyweight from food than adults, approximately a two-fold increase (HBM4EU, 2022l).

Consistent with the many production and contaminated sites as well as the very broad and widespread use, PFAS are now found across the world and extensively detected in the general population by monitoring studies. The levels of long chain PFAS are decreasing, however the short chain PFAS that replaced them are being increasingly detected (European Environment Agency, 2019). Data from the HBM4EU shows that the internal serum concentration of PFAS (sum of PFOS, PFHxS, PFOA and PFNA) of 14.26 % of European teenagers participating in HBM4EU exceeded the guideline value of 6.9 µg/L PFAS, which corresponds to 4.4 ng/kg tolerable weekly intake (TWI) of EFSA (EFSA Panel on Contaminants in the Food Chain (EFSA CONTAM Panel) et al., 2020). The highest median values are observed in studies from Northern and Western Europe (HBM4EU, 2022b).

Figure 4.8: Overview of exposure sources, pathways and routes for PFAS for the general population



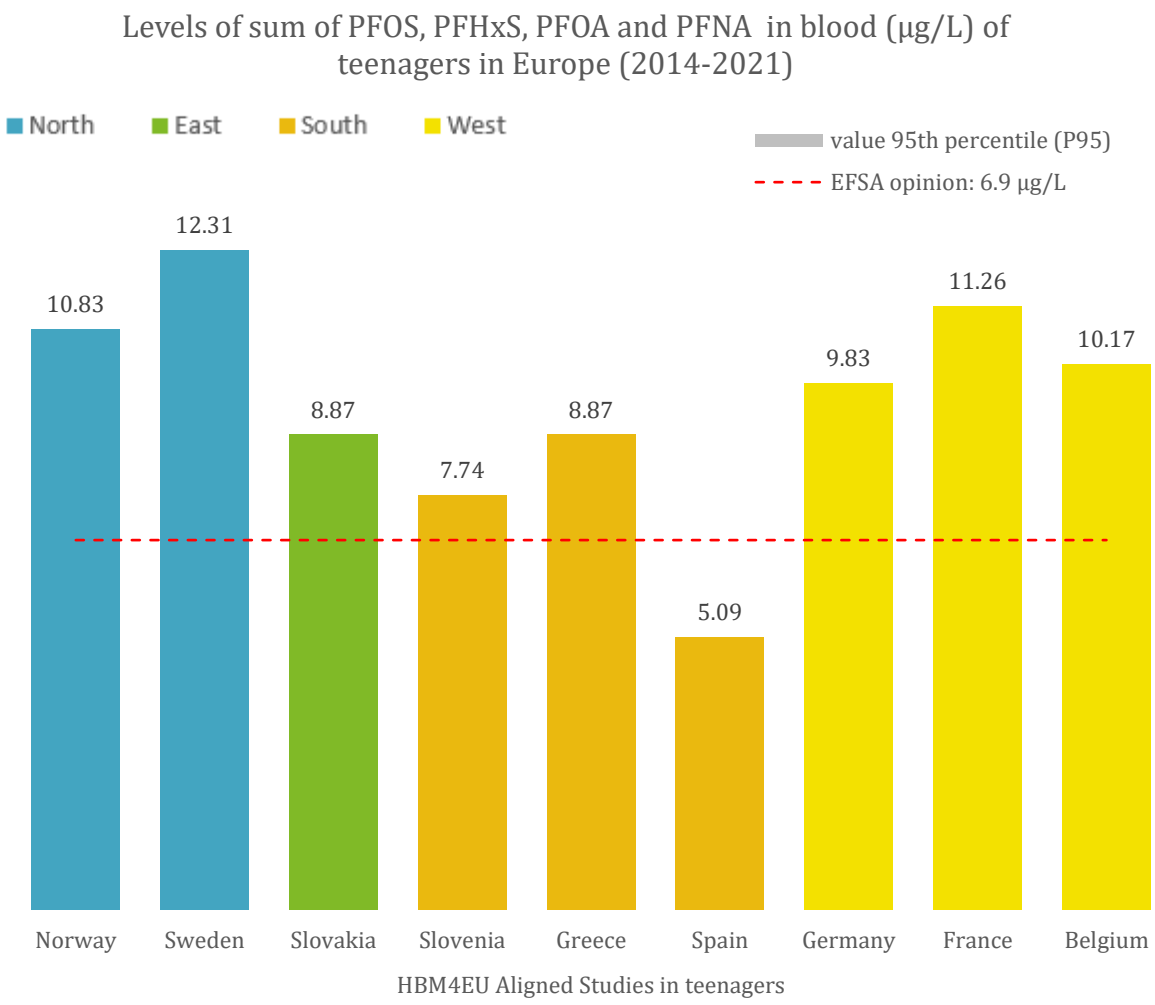
Source: HBM4EU Substance report Per- and polyfluoroalkyl substances (HBM4EU, 2022l).

The EFSA guideline value of 6.9 µg/L for the sum of PFOS, PFHxS, PFOA and PFNA in serum was calculated from the TWI of 4.4 ng/kg body weight. The TWI was based on reduced vaccination immune response in one year old children and EFSA states that this TWI also protects against other adverse effects in humans. The TWI corresponds to a serum level of 6.9 µg/L in mothers assuming 12 months

of breastfeeding. This guidance value should prevent breastmilk levels in mothers that can lead to decreased immune response in children (EFSA Panel on Contaminants in the Food Chain (EFSA CONTAM Panel) et al., 2020).

As previously mentioned, internal exposure data from teenagers across Europe from HBM4EU shows that the blood levels for the sum of PFOS, PFHxS, PFOA and PFNA exceeded the EFSA guidance of 6.9 µg/L. Only in Spain did the p95 of exposure not exceed this guidance value (Figure 4.9). Generally, concentrations are significantly higher in the North and West of Europe compared to the South and East (Richterová et al., 2023).

Figure 4.9: Levels of sum of PFOS, PFHxS, PFOA and PFNA in blood (µg/L) of teenagers in Europe (2014-2021)



Notes: Indicator shows the p95 values of the sum of PFOS, PFHxS, PFOA and PFNA in blood (µg/L) of European teenagers (12-18 years old) from 9 studies (HBM4EU aligned studies teenagers: Norway NEB II, Sweden Riksmaten Ungdom, Slovakia PCB cohort follow-up, Slovenia SLO CRP, Greece CROME, Spain BEA, Germany GerES V, France ESTEBAN and Belgium FLEHS IV) sampled between 2014 and 2021. The red dotted line represents the EFSA guideline value (6.9 µg/L). The indicator shows the comparison between the levels in teenagers and the EFSA guideline.

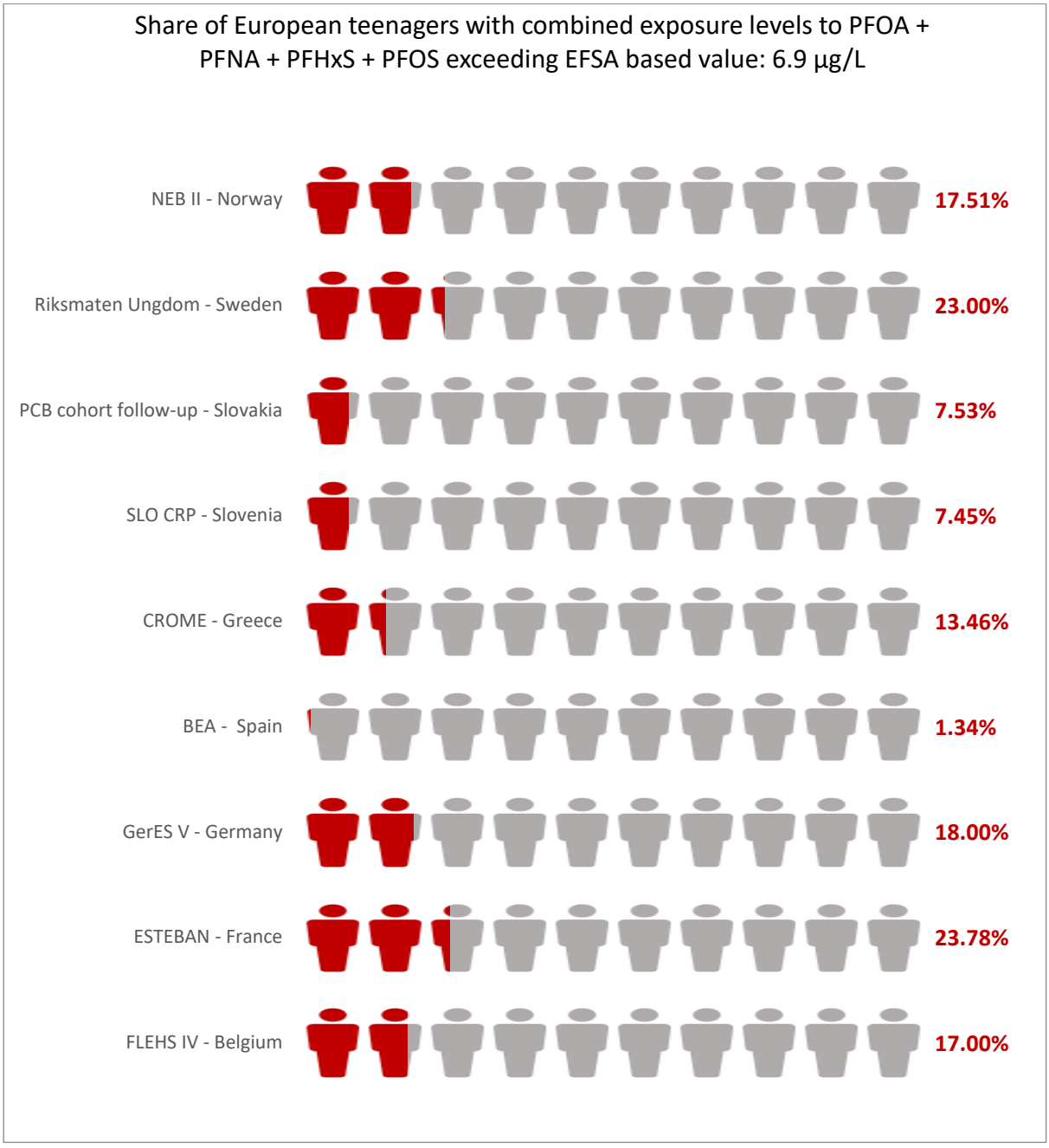
Source data: EU HBM Dashboard([7]).

Data on the percentage of teenagers that exceed the EFSA guidance value shows that in all countries except for Spain the p95 of the sum of PFOA, PFNA, PFHxS and PFOS above exceeds the EFSA guideline

([7]) https://www.hbm4eu.eu/what-we-do/european-hbm-platform/eu-hbm-dashboard/

value, with a maximum exceedance of 23.78 % for France. Figure 4.10 also shows that concentrations were higher in the North and West compared to the South and East.

Figure 4.10: Share of European teenagers with combined exposure levels to PFOA + PFNA + PFHxS + PFOS exceeding EFSA based value: 6.9 µg/L



Notes: Indicator shows the percentage of teenagers for whom the blood level of the sum of PFOS, PFHxS, PFOA and PFNA in blood exceeds the EFSA guideline value (6.9 µg/L). Data from the HBM4EU aligned studies teenagers (12-18 years old): Norway NEB II, Sweden Riksmaten Ungdom, Slovakia PCB cohort follow-up, Slovenia SLO CRP, Greece CROME, Spain BEA, Germany GerES V, France ESTEBAN and Belgium FLEHS IV.

Source data: EU HBM Dashboard([8]).

([8]) https://www.hbm4eu.eu/what-we-do/european-hbm-platform/eu-hbm-dashboard/

Data from HBM4EU and other studies confirm that populations across the world are exposed to PFAS (Fenton et al., 2021; HBM4EU, 2022b). This is of concern since they are persistent and bioaccumulative and several PFAS have been classified as toxic substances. Experimental and epidemiological research has linked PFAS exposure to multiple health effects, with confirmed reprotoxic (PFOA, PFOS, PFNA, PFDA), PBT (PFOA, PFOS, PFNA, PFDA, PFHxS), vPvB (PFUnDA, PFDoDA, PFTrDA, PFTeDA) and POP (PFOA, PFOS, PFHxS) concerns (HBM4EU, 2022l). HBM data shows that PFAS have been detected in infants and children (Fenton et al., 2021; European Environment Agency, 2019). Foetal and childhood development are very susceptible, vulnerable and sensitive periods for exposure to chemicals such as PFAS. Since PFAS exposure has been linked to several health effects, exposure during these sensitive periods could have negative implications on childhood health and later in life (Perlroth and Castelo Branco, 2017; HBM4EU, 2022l)

4.4.3. Health effects

Several PFAS, as mentioned above, have been classified as or are suspected to be toxic substances. Experimental and epidemiological research have studied the effects of PFAS exposure on human health. Numerous adverse health outcomes haven been investigated: effects on liver, cholesterol, endocrine and immune systems, reproduction, developmental and neurological effects as well as carcinogenicity. Associations have not been found for all these health effects, but for some the strength of evidence is sufficient to indicate a relation with PFAS exposure. Most evidence is available for PFOS and PFOA, since they are the most extensively studies PFAS (HBM4EU, 2022l). For several health effects the evidence for a link is inconclusive, this is in part due to the fact that different associations are observed for different PFAS on the same outcome. Long and short chain PFAS are suspected to elicit different responses in the body. Also, until recently studies generally made no differentiation between linear and branched PFAS isomers in analyses. Both isomers were thought to have the same health effect and if both isoforms were measured separately, they were treated as one mixture (Schulz et al., 2020). Health effects discussed primarily start with findings in HBM4EU and are extended with results found in recent literature.

Reduced birth weight

The EFSA (2018) Opinion on PFOS and PFOA concluded that an association between PFOS and PFOA exposure and birth weight is possible, with the general finding being a decrease in birth weight with increase in PFAS exposure. The EFSA (2020) scientific evaluation of the risk to human health related to the presence of PFAS in food reiterated the conclusion made in the EFSA (2018) Opinion and states that the majority of meta-analyses published before the 2020 evaluation reported similar results (EFSA Panel on Contaminants in the Food Chain (EFSA CONTAM Panel) et al., 2020). A meta-analysis of 23 studies from before March 2021 on the association between prenatal exposure to PFAS and birth outcomes observed significant associations between prenatal PFOS exposure and preterm birth and low birth weight and prenatal PFOA exposure and miscarriage (Yang et al., 2022b). Another meta-analysis (based on 46 studies([9]) from between 2007-2021 across the world) on the association between prenatal exposure to PFAS and birth outcomes concluded that overall the exposure to several PFAS (PFOS, PFHpS and PFDA) was inversely associated with birth weight and PFOS, PFOA and PFDoDA with birth length. Only PFHpS was inversely associated with gestational age. Only PFDA was associated with the risk of small for gestational age (SGA)([10]) (Gui et al., 2022). Wright et al. (2023) investigated the link between prenatal PFNA exposure and birth weight. They concluded based on their meta-analysis (on 27 studies from between 2012-2022 across the world) that prenatal PFNA exposure was inversely associated with birth weight (Wright et al., 2023). A smaller meta-analysis on six studies (2009-2017) from America, Spain and Asia (Taiwan and Korea) determined that prenatal PFOA exposure was not

([9]) Not all 46 studies were included in all the analysis.

([10]) Babies considered SGA have a smaller birth weight and/or length than average.

significantly associated with low birth weight, but that prenatal exposure to PFOS was significantly associated with low birth weight (Cao et al., 2021).

Some evidence has been reported for an association between PFAS exposure and preterm birth and SGA, however the EFSA (2020) scientific evaluation concluded that the evidence for this association is still limited (EFSA Panel on Contaminants in the Food Chain (EFSA CONTAM Panel) et al., 2020). The above discussed meta-analysis reported an association between PFNA and PFHpS and the risk of preterm birth (Gui et al., 2022). Gao et al. (2021) conducted a systematic review and meta-analysis on 29 studies on prenatal PFAS exposure and birth outcomes (up to February 2021). They found that prenatal exposure to PFOS, PFNA and PFOA were significantly associated with a higher risk of preterm birth (Gao et al., 2021b).

The association between exposure to PFAS and reduced birth weight was taken up in the proposal for a PFAS restriction (European Chemicals Agency (ECHA), 2023c). A study of 5446 newborns in seven European cohorts found an association between PFOA and SGA. PFOS concentration was positively associated with SGA in newborns that were exposed to smoking during pregnancy, but inversely associated with SGA in newborns not exposed to smoking during pregnancy (Govarts et al., 2018).

Immune effects

Strong evidence exists for an association between PFAS exposure and decreased vaccine response in children. The EFSA (2020) scientific evaluation of the risk to human health related to the presence of PFAS in food confirmed the conclusion from the EFSA (2018) Opinion on PFOS and PFOA that exposure to these PFAS is associated with impaired antibody response to vaccinations (EFSA Panel on Contaminants in the Food Chain (EFSA CONTAM Panel) et al., 2020). PFOA and PFHxS were found to be significantly inversely associated with the level of tetanus antibodies in children according to a recent meta-analysis (based on studies up to February 2022) (Zhang et al., 2022). Another meta-analysis including 14 studies between 2012 and 2022([11]) found that in children PFOA was significantly inversely associated with diphtheria and tetanus antibodies. PFOS and PFHxS were significantly inversely associated in children with rubella antibodies (Crawford et al., 2023). Von Holst et al. (2021) reviewed epidemiological studies on PFAS exposure and vaccine response from between 2010 and 2021. They found that PFAS exposure (prenatal and childhood) can lower the antibody response to diphtheria and tetanus vaccines. Strength of suppression depends on type of PFAS. Similar results were found for the measles, mumps and rubella (MMR) vaccine, though the strength of suppression depended on vaccine component (Von Holst et al., 2021). Based on the evidence it is probable that there is a relation between PFAS exposure and lowered vaccine response (Ehrlich et al., 2023).

The 2020 EFSA scientific evaluation concludes that there is some evidence available that suggest an association between PFAS exposure and increased risk for infection (EFSA Panel on Contaminants in the Food Chain (EFSA CONTAM Panel) et al., 2020). This further supports the evidence that PFAS exposure is linked to decreased vaccine response, which can be linked to a higher risk of infection (Ehrlich et al., 2023). The review of (Von Holst et al., 2021) states that the available evidence suggests a link between PFAS and infection. Studies into PFAS exposure and COVID-19 suggest a link, where exposed people have a higher risk for COVID-19 infection or more severe symptoms (Perkins, 2022; Ehrlich et al., 2023). This supports the hypothesis that PFAS have immunosuppression properties (Von Holst et al., 2021; EFSA Panel on Contaminants in the Food Chain (EFSA CONTAM Panel) et al., 2020; Ehrlich et al., 2023). The HBM-GV of 6.9 µg/L for the sum of 4 PFAS derived by EFSA was based on immunosuppression (study Abraham et al. 2020).

Studies investigating the relation between PFAS exposure and immune disorders report inconsistent results. The EFSA (2020) scientific evaluation determined that evidence is not sufficient to establish a

([11]) Some studies only investigated adults and some children and adults.

link between PFAS exposure (prenatal and childhood) (EFSA Panel on Contaminants in the Food Chain (EFSA CONTAM Panel) et al., 2020). Several cross-sectional studies have reported associations between PFAS exposure and increased risk of asthma and that existing asthma might be exacerbated in children (Ehrlich et al., 2023). Inverse and null associations between PFAS exposure and asthma have also been reported. A definitive conclusion on a relation cannot be drawn (Von Holst et al., 2021). Similar results have been reported for allergic disorders in children (e.g. eczema, wheezing, allergic rhino conjunctivitis). Research shows a tendency for an inverse association between PFAS exposure and allergic disorder, however evidence is too inconclusive to draw conclusions (Von Holst et al., 2021).

Although evidence is only mainly consistent for a link between PFAS exposure and vaccine response, research indicates that PFAS possibly display immunosuppressive and modulatory activity (Ehrlich et al., 2023).

Endocrine system

PFAS have been suggested to have endocrine disrupting properties. This has mainly been demonstrated in experimental studies, although some epidemiological studies have reported associations for endocrine disruption (Fenton et al., 2021; Mokra, 2021).

The EFSA (2018) Opinion on PFOS and PFOA concluded that there was insufficient evidence to establish a link between PFOS and PFOA exposure and thyroid function both in adults and children, which the EFSA (2020) scientific evaluation of the risk to human health related to the presence of PFAS in food reiterated. Most studies investigating thyroid function are conducted in adults or adolescents (EFSA Panel on Contaminants in the Food Chain (EFSA CONTAM Panel) et al., 2020). Research into the link between PFAS exposure and thyroid function or THs in children is very limited. A systematic review and meta-analysis on studies investigating prenatal exposure to endocrine disrupting chemicals and thyroid function in neonates (32 studies from between 2007-2021) found that PFAS was negatively associated with neonatal TT_4 concentrations (Sun et al., 2022).

In the C8 Health Project children (1–17-years old, *n* = 10,725) living in a PFAS contaminated area in Ohio, showed a positive association between childhood exposure to PFOA and hypothyroidism. Childhood exposure to PFOS and PFNA was associated with increased total thyroxine (TT_4) (Lopez-Espinosa et al., 2012). In NHANES 2011-2012 it was observed that serum PFOS and PFNA were significantly positively associated with TSH in male adolescents (12-19 years old, *n* = 158), and PFHxS and TT_4 borderline significantly inversely associated. PFOA was significantly inversely associated with TSH in female adolescents (same age range, *n* = 145), *b*orderline significant associations were observed between PFOA and PFNA and TT_4 (Lewis et al., 2015). More research has been conducted in adults. NHANES 2011-2012 showed some borderline significant positive associations in adult males (40 - <60 years old, *n* = 218) between PFAS and TT_4 and several significant positive associations in adult females (20 - <40 years old, *n* = 257 and 60-80 years old, *n* = 199) between PFAS and FT4 and free triiodothyronine (FT3) (Lewis et al., 2015). Data from across NHANES (1999-2000, 2003-2004, 2005-2006) showed that higher PFOA concentrations were significantly associated with higher risk of thyroid disease (unspecified) in adult females (Melzer et al., 2010). A recent meta-analysis including 13 studies (until July 2022 across the world) investigating the link between PFAS exposure and thyroid health in adults, reported a positive association between maternal PFOS, PFOA and PFDA exposure during pregnancy and maternal TSH. In subgroup analyses of studies in the same region, maternal PFOS and PFOA exposure was significantly positively associated with FT_4 in Europe (Zhang et al., 2023). A cross-sectional study in 1048 pregnant women reported a positive association between maternal PFOS, PFOA and PFNA concentrations and maternal FT_4 (Jensen et al., 2022).

In vitro and animal studies indicate that PFAS may have thyroid disrupting abilities, while human studies are much less conclusive about the disruption. Studies report contradicting directions of associations (e.g. positive and inverse associations between THs and PFAS have been reported).

Hypothyroidism has most consistently been reported to be associated with PFAS in research (Coperchini et al., 2021).

Even though evidence is not conclusive, it suggests that PFAS could have the ability to disturb normal thyroid functions in adults, definitive conclusions cannot be made yet for children. This has implications for children in terms of exposure during pregnancy. Good thyroid function is essential for the growth and neurodevelopment of foetuses and infants. During pregnancy the foetus is dependent on maternal THs since foetal THs production is not yet sufficient to support neurodevelopment. Changes in maternal THs could therefore have serious implications on the neurodevelopment. Hence why findings in female adults of reproductive age are important to note in terms of child health (Coperchini et al., 2021; Sun et al., 2022). It has been hypothesized that THs dysfunction could mediate early neurodevelopment impairment. There is some research that suggests a link between impaired maternal thyroid function during pregnancy and higher risk of ASD and other neurodevelopmental disorders. If PFAS can affect maternal THs levels during pregnancy this might potentially mediate impaired neurodevelopment in the child (Shin et al., 2022). A meta-analysis found an association between prenatal PFAS exposure and impaired neurodevelopment including psychomotor and comprehensive development and externalizing behaviour (Gao et al., 2023).

The EFSA (2018) Opinion on PFOS and PFOA concluded that evidence for a link between PFAS exposure and puberty was also insufficient (EFSA Panel on Contaminants in the Food Chain (EFSA CONTAM Panel) et al., 2020). In NHANES 2011-2012 borderline significant associations were found in adolescent females (12-19 years old, *n* = 145) between PFOA and PFNA and decreased total testosterone (Lewis et al., 2015). In a systematic review on PFAS childhood exposure and various outcomes including puberty it was reported that evidence for an association between PFAS exposure and sex hormones both in girls and boys was inconsistent and therefore inconclusive. Both in girls and boys null, inverse and positive associations were found according to timing and level of exposure, PFAS type and ages at sex hormone measurement (Lee et al., 2021). Overall research into PFAS exposure and sex hormones in children is limited. A recent cross-sectional study on HBM4EU data of 733 teenagers (age range 14-17 years) from three European cohorts investigated the association between PFAS exposure and sex hormones. The pooled analysis showed a significant positive association between PFOA, PFNA and PFOS concentrations and total testosterone (TT) in females, while in males only PFNA was significantly positively associated with TT. The PFAS mixture (PFOA, PFNA and PFOS) was also significantly positively associated with TT in females in the pooled analysis. In males the PFAS mixture was significantly negatively associated with FSH in the pooled analysis (Rodríguez-Carrillo et al., 2023). Another cross-sectional study with NHANES 2013-2016 data of 6–19-year-old children was recently conducted. In children (6-11 years old) the PFAS mixture was significantly inversely associated with TT. Only in boys the PFAS mixture was positively associated with sex hormone binding globulin (SHBG). Pubertal adolescents showed significant inverse associations between the PFAS mixture and estradiol (He et al., 2023).

Research into the association between PFAS exposure and sex hormones in children is rather limited and inconclusive and most research has been conducted in boys. Though the evidence suggests PFAS may alter sex hormone levels in children, which is plausible according to the endocrine disrupting properties that PFAS exhibit (Fenton et al., 2021; Mokra, 2021).

Evidence rating for health effects

The approach used to categorise evidence strength for each substance is based on HBM4EU (2022). For some effects, the categorisation itself has been updated to reflect new evidence, based on expert judgement.

Table 4.6: Evidence rating based on the assessment of relevant publications. Evidence is not found for each PFAS equally

Outcome	Evidence	References
Reduced birth weight	Suspected	(EFSA Panel on Contaminants in the Food Chain (EFSA CONTAM Panel) et al., 2020; Gui et al., 2022; Wright et al., 2023; Cao et al., 2021)
Preterm birth	Suspected	(EFSA Panel on Contaminants in the Food Chain (EFSA CONTAM Panel) et al., 2020; Gui et al., 2022; Gao et al., 2021b)
SGA	Suspected	(EFSA Panel on Contaminants in the Food Chain (EFSA CONTAM Panel) et al., 2020; Govarts et al., 2018)
Reduced vaccine antibody response	Strong	(EFSA Panel on Contaminants in the Food Chain (EFSA CONTAM Panel) et al., 2020; Von Holst et al., 2021; Zhang et al., 2022; Ehrlich et al., 2023; HBM4EU, 2022l; Rappazzo et al., 2017; National Toxicology Programme, 2016; Grandjean and Budtz-Jørgensen, 2013)
Increased infection risk	Suspected	(EFSA Panel on Contaminants in the Food Chain (EFSA CONTAM Panel) et al., 2020; Ehrlich et al., 2023; Von Holst et al., 2021; Rappazzo et al., 2017)
Immune disorders (e.g. asthma)	Lacking	(EFSA Panel on Contaminants in the Food Chain (EFSA CONTAM Panel) et al., 2020; Von Holst et al., 2021; Ehrlich et al., 2023; Rappazzo et al., 2017)
Endocrine disruption	Suspected	(EFSA Panel on Contaminants in the Food Chain (EFSA CONTAM Panel) et al., 2020; Lopez-Espinosa et al., 2012; Lewis et al., 2015; Coperchini et al., 2021; Lee et al., 2021; Rodríguez-Carrillo et al., 2023; He et al., 2023; Fenton et al., 2021; Mokra, 2021)

4.4.4. Prevention measures

Legislators globally and in the EU have taken concrete risk management measures starting more than a decade ago. Since then, a few PFAS (PFOS, PFOA, PFHxS) have been included in the international Stockholm Convention and/or added to the EU POP Regulation. The larger group of C9-C14 perfluorinated carboxylic acids in general have been restricted under REACH since this year (2023). In addition, several PFAS have been identified as REACH SVHC (Substances of Very High Concern) by adding them to the REACH Candidate List for authorisation. Furthermore, several restriction proposals have been submitted for a confined set of PFAS whereas notably. And last but not least, a restriction covering a wide range of PFAS uses has been proposed early 2023 (European Chemicals Agency (ECHA), 2023b).

According to the National Academies of Sciences (2022), there is only limited literature presenting recommendations for effective behaviour modifications to reduced internal PFAS levels. In places with water contamination, exposure can be reduced through water filtration. For places without water contamination or workplace exposure, diet is the primary exposure route to be tackled but there is

limited information on recommended diet interventions. No intervention study has examined exposure reduction and its impact on serum concentrations. To fully show the effectiveness of an intervention, it would have to be conducted over a long period of time to account for the long half-lives of PFAS.

Some steps can be taken by the public to limit their exposure based on common exposure routes. In regions with known drinking water contamination it is recommended to use appropriate filters (reverse osmosis filters in case of PFAS). If there is suspicion of PFAS contamination of drinking water, the supplier can be contacted. If they do not have this information available, people can opt to have the drinking water tested. This should be done by a certified laboratory. In case of the PFAS concentration exceeds guidelines, filters can be used. In case a well is used for drinking water, the well should be tested. In case the well is contaminated (concentrations exceed guidelines), a different water source should be considered if possible and in case this is not possible filters should be used. In terms of diet, people should take care with consuming vegetables and livestock grown and reared on land that is contaminated. In case of suspicion of contamination, the soil should be tested. If the soil concentration exceeds guidelines different measures can be taken based on the severity of contamination. The most severe measure is to stop consume home-grown vegetables and reared livestock. Other measures are to limit consumption (more specific examples below) and wash vegetables really well before consumption. If people consume home-grown products, a good rule of thumb is to have a balanced diet that contains a good mix of home-grown and store-bought products. Exposure to PFAS also occurs through products such as food packaging, care and other consumer products. Being attentive to buying products that contain less or no PFAS can also decrease exposure (Agency for Toxic Substances and Disease Registry (ATSDR), 2022a; United States Environmental Protection Agency, 2021; National Academies of Sciences et al., 2022). There is some literature available on the effectiveness of PFAS exposure preventing measures, but the data is too limited to make conclusion about the effectiveness and therefore also too limited to formulate recommendations that are known to be effective in reducing exposure (National Academies of Sciences et al., 2022).

In the framework of the road construction project the 'Oosterweel-connection' in Antwerp (Belgium), contamination of soil with PFAS was observed (related to the production site of 3M). It became clear that a broad approach was necessary given the spread of the contamination and the presence of PFAS over all of Flanders (Vlaamse overheid, 2021). Zones with known contamination or a presumed contamination were indicated and the mayors of the jurisdictions confronted with (possible) PFAS contamination were offered the below risk management measures. These are called the 'no-regret measures' in Flanders (they are expected to provide a benefit in any case). These measures are similar to those often implemented in other contamination cases such as dioxin or lead contamination.

The current no-regret measures in Flanders can be traced back to breaking the exposure chain, and are site-dependent compiled from the following list:

- Most vulnerable population (children < 12 years, immunocompromised persons, pregnant women, women who are breastfeeding, or wish to become pregnant) should not consume home-grown vegetables;
- General population: consume home-grown vegetables moderately, provided a good mix with purchased vegetables. Always wash vegetables well before consumption;
- Do not consume home-grown small livestock;
- Do not use groundwater as drinking water (consumption);
- Do not use groundwater from shallow wells to irrigate the vegetable garden;
- Do not use groundwater from shallow wells to fill the pool;
- Do not use compost composed of material from your own garden;
- Apply good hygiene:

    - Personal hygiene: wash your hands, especially before meals;
    - Indoor environment: wet cleaning is more efficient than dry cleaning to remove PFAS contaminated dirt;
- Avoid spraying of fallow land as much as possible;
- Consume a maximum of 1 egg of one's own chickens per person per week or do not consume eggs of one's own chickens;
- Healthy food is important for everyone: cf. the recommendations in the nutrition triangle. Use a mix of food from different sources (shop, home-grown, ...)

4.5. Other chemicals

4.5.1. Bisphenols

Chemical characterization and emission sources

Bisphenols are a group of synthetic organic compounds that are used as a building block in the production of polycarbonate plastics and epoxy resins. The most commonly used bisphenol is bisphenol A (BPA) which is among the highest volume of chemicals produced world-wide. Other bisphenols, such as bisphenol F (BPF) and bisphenol S (BPS), have become more widely used in recent years due to regulations on BPA. Polycarbonate plastics are used in a wide range of consumer goods, such as sports equipment, CDs, DVDs, reusable bottles and plastic tableware. Epoxy resins are used, for example, to line food and beverage cans and water pipes, and in the manufacture of thermal paper (HBM4EU, 2020d, 2022f).

Exposure characterization

Most exposure to bisphenols occurs through consumption of foods and beverages that have been in contact with materials containing bisphenols. Exposure can also occur via dermal absorption by handling thermal paper or contact with textiles and safety equipment containing bisphenols. Limited exposure occurs through inhalation of contaminated air and dust, e.g. at the workplace in production facilities (HBM4EU, 2022f, 2020d). Bisphenols have a short metabolic half-life, as they are conjugated within hours and excreted through the urine. But there is concern that bisphenols could be deconjugated at the tissue level (HBM4EU, 2020d). Human exposure to BPA, BPF and BPS is widespread. In a study in the United States, detectable levels of BPA were found in 93 % of urine samples (Calafat et al., 2008). A French cross-sectional study found detectable levels of BPA, BPF and BPS in almost all samples (99.9-100 %) (Balicco et al., 2019). Both studies were conducted with people six years and older.

Health effects

In the EU, BPA is classified as endocrine disruptor and toxic for reproduction (HBM4EU, 2022f). There is large amount of literature on the toxicity of BPA, even at low doses (Bergman et al., 2013; EFSA Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids (CEF), 2015; Gore et al., 2015; Vandenberg, 2014). Studies have indicated an association with increased risk for fetal development; reproductive and sexual dysfunctions; breast and prostate cancer; altered immune system activity; obesity, diabetes and cardiovascular disease in adults and cognitive and behavioural development in young children (HBM4EU, 2020d).

In 2015 a systematic review concluded that BPS and BPF are as hormonally active as BPA (Rochester and Bolden, 2015). Studies suggest that other bisphenols are likely to induce similar health effects (Den Braver-Sewradj et al., 2020; Mesnage et al., 2017; Rochester and Bolden, 2015).

The EFSA published a comprehensive assessment of BPA's exposure and toxicity in 2015, in which the experts suggested to reduce the TDI from 50 to 4µg/kg body weight (bw) per day. However, the EFSA concluded that there is low health concern from aggregated exposure and no health concern for any age group from dietary exposure as the exposition is well below the defined temporary TDI (EFSA Panel

on Food Contact Materials, Enzymes, Flavourings and Processing Aids (CEF), 2015). In April 2023, a new EFSA report re-evaluated the risks to public health of BPA and concluded that the TDI should be further reduced to 0.2ng/kg bw/day, taking into account the evidence from animal data and human observational studies. Dietary exposure estimates from the 2015 report exceed the newly established TDI by two to three orders of magnitude, especially for infants, toddlers and children (1450 to 4285 times the new TDI). Therefore, the experts concluded that there is a health concern from dietary exposure to BPA for all age groups (EFSA Panel on Food Contact Materials Enzymes and Processing Aids et al., 2023). In 1988, the U.S. Food and Drug Administration (FDA) set the still valid TDI at 50µg/kg bw, which is 250,000 times higher than the new European recommendation and makes it urgent for the FDA to re-evaluate its recommendation (Bienkowski, 2023).

Relevance for children

Studies show that the exposition of children to BPA is higher than in adults (Calafat et al., 2008; Balicco et al., 2019) and that the estimated dietary intake is highest in infants and toddlers whereas the aggregated exposure is highest in adolescents (EFSA Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids (CEF), 2015). Studies suggest that prenatal and early child exposure to bisphenols is associated with developmental and behavioural problems in children (Braun et al., 2009; Ejaredar et al., 2017; Jiang et al., 2020; Perez-Lobato et al., 2016). Due to their effect as endocrine disruptors, early exposure to bisphenols is also associated with obesity and metabolic disorders, reproductive disorders and hormone-sensitive cancer (Naomi et al., 2022; Rochester and Bolden, 2015; Sowlat et al., 2016; Trasande et al., 2015). Due to the evidence on the increased risks in children, there are stricter regulations for products that come into contact with children such as toddler bottles, food containers and toys (HBM4EU, 2022f; Den Braver-Sewradj et al., 2020).

In summary, the widespread exposure to bisphenols, known for their properties as endocrine disruptors and reproductive toxins, is particularly concerning given that children's exposure is notably higher than in adults, posing a significant risk to their health.

4.5.2. Cadmium

Chemical characterization and emission sources

Cadmium (Cd) is a heavy metal found in the earth’s crust. Most Cd is extracted as a by-product in the mining and production of other metals such as zinc, lead or copper. Cd is used in the manufacture of products like batteries, pigments, plastics, coatings, plating, alloys and photovoltaic devices (Agency for Toxic Substances and Disease Registry (ATSDR), 2012b). The anthropogenic emission sources of Cd can be grouped in following categories: mobilization of Cd impurities in raw materials such as zinc and copper ores, phosphate minerals and fossil fuels; releases of Cd used in products due to use, disposal, recycling and burning; and the anthropogenic mobilisation of historical cadmium deposited in sediments, soils, landfills and other sources (United Nations Environment Programme (UNEP), 2010). Natural activities such as weathering and erosion, river transport and volcano activity are other emission sources of Cd (World Health Organization, 2019b). Annual production and consumption of Cd remained steady over the past 20 years (International Cadmium Association, 2021; United Nations Environment Programme (UNEP), 2019a). Whereas in Europe battery manufacturing composed 80 % of Cd application in 2019, at world level 57 % is applied for jewellery, which is not authorised in the EU (International Cadmium Association, 2021).

Exposure characterization

Exposure to Cd occurs mainly through consumption of contaminated food and water, inhalation of tobacco smoke and inhalation of contaminated air, especially during occupational exposure or in highly contaminated regions due to anthropogenic activities. Cd can be taken up from water and soil by crops and aquatic organism and accumulate in the food chain. In the general population, food is the main environmental source of Cd for non-smokers. In case of heavy smokers the daily intake from inhalation

may exceed that from food (World Health Organization, 2019b). Cd might be found in leafy green vegetables, liver, kidney, chocolate, seafood, cereal products and potatoes (HBM4EU, 2022g). The average daily intake varies according to dietary habits, especially vegetarian diet showing an important increase in exposure with 35 % higher levels than in non-vegetarians (Snoj Tratnik et al., 2022; United Nations Environment Programme (UNEP), 2010). In the latest report of the Joint Expert Panel of the FAO and WHO (JECFA) in 2022, they concluded that the national exposure estimates were predominantly below the provisional Tolerable Monthly Intake (TMI) of 25 µg/kg bw established in 2011, with exceptions for young children and adults in China (Joint FAO/WHO Expert Committee on Food Additives (JECFA), 2022). However, in 2009 the European Food Safety Authority (EFSA) set a lower tolerable intake (2.5 µg/kg bw per week) and confirmed this after re-evaluation to ensure sufficient protection of all consumers (European Food Safety Authority (EFSA), 2011, 2012).

Cd accumulates in the body, mostly in kidneys and liver due to the limited capacity to excrete the metal and its long biological half-life in humans (10-35 years) (Schoeters et al., 2006; World Health Organization, 2019b, 2022a). Cumulative exposure to Cd can be monitored in blood and urine. While urinary Cd levels reflect the accumulated body burden, blood levels also reflect recent exposure to Cd (Schoeters et al., 2006). Elevated exposure has been associated with higher values for low molecular proteins in the urine as markers of renal tubular dysfunction (Cui et al., 2018; Jin et al., 2002; World Health Organization, 2019b). In a review by the HBM4EU project, which monitored Cd levels in adults across Europe from 2014-2020, 16 % of participants exceeded the age specific alert levels, with high variability across studies and locations (1.4 % to 42 %) (Snoj Tratnik et al., 2022).

Health effects

Cd has been identified by the WHO as one of the 10 chemicals of major public health concern. It is classified as carcinogenic to humans by the IARC and the ECHA (European Chemicals Agency (ECHA), 2023e; International Agency for Research on Cancer (IARC), 2012). In particular, inhalation of contaminated air from occupational exposure or highly polluted areas is associated with lung cancer. There is limited epidemiological evidence for an association with cancers of the kidneys and the prostate. Inhalation exposure can also lead to acute pneumonitis with pulmonary oedema and long-term to chronic lung changes (World Health Organization, 2019b). Cd primarily accumulates in the kidneys, which can lead to renal tubular degeneration and dysfunction, kidney stones, disturbances in calcium, phosphorous and vitamin D metabolism and decreased bone mineral density and osteoporosis (Schaefer et al., 2022; World Health Organization, 2019b). For the year 2015, it was estimated that foodborne Cd resulted in about 12’000 new severe and end-stage chronic kidney disease cases, about 2’000 deaths and 70’000 DALYs worldwide (Gibb et al., 2019; Zang et al., 2019).

Relevance for children

Cd exposure and accumulation may start early in life due to transplacental transfer, food intake, second-hand tobacco smoke, house dust and contact to plastics, toys and inexpensive jewellery and has long term adverse consequences (Agency for Toxic Substances and Disease Registry (ATSDR), 2012b; Trzcinka-Ochocka et al., 2004; United Nations Environment Programme (UNEP), 2010; World Health Organization, 2019b; Lamkarkach et al., 2021). Also, disposal and recycling of e-waste has been identified as a particularly important exposure to children (World Health Organization, 2019b). The placenta partially provides a barrier to Cd and limits prenatal exposure. However, the barrier's capacity can be impaired, resulting in significant prenatal exposure. (Dong et al., 2023; Lauwerys et al., 1978). Prenatal and childhood exposure to Cd from e-waste is significantly linked with negative birth outcomes, DNA-damage, impaired immune function (i.e. vulnerability to common infections and susceptibility to allergies and autoimmune diseases) and some chronic diseases in later life (cancer and cardiovascular disease) (World Health Organization, 2021a). Further, recent studies observed that prenatal exposure was associated with impaired neurodevelopment in boys (Ma et al., 2021), decreased birth weight (Huang et al., 2019) and increased risk of congenital heart disease (Li et al., 2022).

In summary, the early childhood exposure to Cd is a significant public health concern due its adverse effects on children's health, particularly at sensitive developmental stages, and its bioaccumulative properties, which lead to organ damage and chronic disease later in life.

4.5.3. Chromium VI

Chemical characterization and emission sources

Chromium is a naturally occurring element found in rocks, animals, plants and soil, where it forms various compounds with other elements (Agency for Toxic Substances and Disease Registry (ATSDR), 2012c). It can exist in different oxidation states, but is mainly found in its trivalent (+3) and hexavalent (+6) form. In this report we focus on the hexavalent oxidation state, which is the most toxic form and is commonly abbreviated as Cr(VI) (HBM4EU, 2020d; World Health Organization, 2022a).

Natural occurrence of Cr(VI) is rare, most Cr(VI) compounds are manufactured (products or by-products) and contamination is a result of industrial emissions. Cr(VI) compounds are mainly used in electroplating, leather tanning, wood preservation, refractory production and the manufacture of pigments, dyes and corrosion inhibitors. Moreover, fossil fuel combustion and waste incineration are sources of chromium in the environment (Blade et al., 2007; HBM4EU, 2020d; World Health Organization, 1988).

Exposure characterization

For the general population exposure to Cr(VI) occurs primarily by ingestion of contaminated soil, food and water. Moreover, cigarette smoking represents an important exposure source (HBM4EU, 2020d; World Health Organization, 2022a). The most significant exposure to Cr(VI) via inhalation of contaminated air, dust, fumes or mist occurs at the workplace in a variety of sectors that use chromium compounds (Blade et al., 2007; HBM4EU, 2022h; International Agency for Research on Cancer (IARC), 2012; Santonen et al., 2022). Moreover, Cr(VI) can enter the body via dermal absorption in small amounts when being in direct contact with products containing chromium such as paint pigments and coatings (Agency for Toxic Substances and Disease Registry (ATSDR), 2012c; HBM4EU, 2022h). Cr(VI) can also be present in certain consumer goods such as leather, toys, cosmetics and tattoo inks (Blade et al., 2007; Bocca et al., 2018; HBM4EU, 2022h; Kolarik et al., 2019).

Cr(VI) is absorbed best by the respiratory tract, followed by the gastrointestinal tract and then by dermal absorption (International Agency for Research on Cancer (IARC), 2012). After absorption Cr(VI) is distributed in nearly all tissues and can enter body cells through carriers. The body reduces Cr(VI) into its trivalent form (III) which can create reactive intermediates and cause cellular damage. Cr is predominantly excreted in urine. Exposure to chromium can result in increased concentrations in blood, serum and red blood cells, urine, expired air, hair, and nails (Agency for Toxic Substances and Disease Registry (ATSDR), 2012c). The Cr levels in urine, blood and red blood cells as well as in exhaled respiratory condensate are reliable indicators of exposure and should be used complementarily for biomonitoring (Agency for Toxic Substances and Disease Registry (ATSDR), 2012c; Barceloux, 1999; Caglieri et al., 2006; HBM4EU, 2022h; Santonen et al., 2022).

Health effects

Chromium VI is classified as carcinogen by inhalation by the ECHA and the IARC (European Chemicals Agency (ECHA), 2022; HBM4EU, 2022h; International Agency for Research on Cancer (IARC), 2012). It is associated with increased risk for lung cancer, cancer of nose and nasal sinuses among workers in certain industries (HBM4EU, 2020d; World Health Organization, 2022a). Animal studies suggest that Cr(VI) compounds may cause intestinal cancer but data is lacking for carcinogenicity for humans via oral route (Agency for Toxic Substances and Disease Registry (ATSDR), 2012c; World Health Organization, 2022a). Further, Cr(VI) is classified as skin sensitising substance (European Chemicals Agency (ECHA), 2022) as it can lead to various skin reactions such as contact dermatitis and ulceration

when there is a direct contact with products or consumer goods containing Cr(VI) (Gibb et al., 2000; HBM4EU, 2022h; Shelnutt et al., 2007). Repeated and prolonged exposure to Cr(VI) especially at higher levels measured at worksites has different adverse effects. It can lead to nasal septum alterations, respiratory irritation, breathing problems (asthma, cough and shortness of breath) renal effects and allergic reactions (Agency for Toxic Substances and Disease Registry (ATSDR), 2012c; Hamzah et al., 2016; HBM4EU, 2022h; Neghab et al., 2015). Further, damage to the male reproductive system, sperm, red blood cells and the intestine have been observed in animal studies (Agency for Toxic Substances and Disease Registry (ATSDR), 2012c; Ray, 2016). Overall, as knowledge of Cr(VI) levels in the European population is limited, further data are needed to improve the understanding of current health risks (HBM4EU, 2022h).

Relevance for children

Cr(VI) can be transferred to the foetus through the placenta and to infants via breast milk. Animal studies suggest that high exposure in pregnancy may cause miscarriage, low birth weight and adverse developmental effects (Agency for Toxic Substances and Disease Registry (ATSDR), 2012c). In a systematic review published in 2022, maternal exposure to chromium was correlated with an elevated risk for preterm birth (Wu et al., 2022). Further, postnatal chromium exposure has been associated with negative effects on neuropsychological development (Caparros-Gonzalez et al., 2019). Several studies were conducted in a heavily chromium-polluted region in China with numerous e-waste recycling facilities to assess the exposition and health effects on children. Correlations were found between higher exposure to chromium and DNA damage (Li et al., 2008; Ni et al., 2014), increased body weight and chest circumference (Xu et al., 2015), reduced lung function (Zheng et al., 2013) and increased respiratory symptoms like cough and wheeze (Zeng et al., 2016) in children.

In summary, although Cr(VI) exposure and its health impacts have been primarily studied in occupational settings, there is growing evidence from animal and epidemiological studies of the adverse effects of Cr(IV) on birth outcomes and neurodevelopment, especially in regions with heightened Cr(VI) exposure.

4.5.4. Flame retardants

Chemical characterization and emission sources

Flame retardants (FRs) are chemical compounds or mixtures added to manufactured materials to reduce flammability and improve product safety. A range of inorganic and organic FRs are used, with the synthetic organic FRs being of particular health concern. They are categorised in brominated FRs (BFRs), chlorinated FRs (CFRs) and organophosphorus FRs (OPFRs) and are often used as mixtures (HBM4EU, 2020d; United Nations Environment Programme (UNEP), 2023a). Since the 1970s, FRs have been widely used in building materials and consumer products, such as electronics, textiles, plastics, furniture, automobiles and insulation (HBM4EU, 2022i; United Nations Environment Programme (UNEP), 2023a, 2023b). Due to concerns about persistence, toxicity and bioaccumulation several FRs have been defined by the UNEP as Persistent Organic Pollutants (POPs) and are regulated under the Stockholm Convention (HBM4EU, 2020d; Sharkey et al., 2020; United Nations Environment Programme (UNEP), 2023a). However, the global FRs production is still increasing and replacement compounds have emerged in recent years, which are currently being investigated for their hazardous properties (De Boer and Stapleton, 2019; HBM4EU, 2020d; United Nations Environment Programme (UNEP), 2023b). Information on the production and usage of FRs is extremely limited due to various challenges to provide the data from the industry and high variability in compounds (HBM4EU, 2022i).

Exposure characterization

Human exposure to FRs can occur via several routes, including inhalation, ingestion, dermal contact and transplacental transfer. For the general population the primary route of exposure is though diet, whereas for babies and toddlers the primary pathway is through ingestion of house dust through the

mouthing of toys and other objects (HBM4EU, 2022i). Higher exposure is associated with high-income regions with more consumer products and electronic devices at home (Demirtepe et al., 2019), higher flammability standards (Dodson et al., 2017), and more time spent indoors or in vehicles (Reddam et al., 2020) as many FRs are found in indoor dust (Lucattini et al., 2018). Further, occupational exposures need to be considered, especially in electronics and chemical manufacturing, e-waste recycling and for firefighters and aircraft staff (Estill et al., 2020; Gravel et al., 2019; Leslie et al., 2016; Wu et al., 2020b; Xiong et al., 2019).

FRs defined as POPs are highly persistent substances that are widely distributed in the environment, accumulate in living organisms and are toxic to humans and wildlife (United Nations Environment Programme (UNEP), 2019c). Many other FRs are found in various concentrations in the environment and in human matrices (Chupeau et al., 2020; Lucattini et al., 2018; Xiong et al., 2019) but there is a lack of systematic monitoring and risk assessments (De Boer and Stapleton, 2019). There is no standard for biomonitoring FRs due to the numerous compounds and their different chemical and physical properties. Highly lipophilic FRs are found in their original form in human matrices, most commonly in serum and breast milk. Other FRs, such as OPFRs and some novel BFRs are metabolised and can be monitored using urinary metabolites as biomarkers. However, many compounds of emerging concern have no identified biomarkers (HBM4EU, 2020d).

Health effects

Legacy BFRs have been identified to have a range of potential health effects, including adverse neurological, immunological, endocrine, reproductive and carcinogenic effects (Chevrier et al., 2010; Feiteiro et al., 2021; HBM4EU, 2020d; Herbstman et al., 2010; Lai et al., 2015; Wang et al., 2010; Wu et al., 2020b). There is concern that the hazard profiles of novel FRs may not have been accurately characterised. Early evidence suggests that some CFRs, OPFRs and novel BFRs may have similar health concerns but there is insufficient evidence to assess human toxicity for many of these FRs (Castorina et al., 2017; Chupeau et al., 2020; Dishaw et al., 2011; Meeker and Stapleton, 2010; Springer et al., 2012; Xiong et al., 2019; HBM4EU, 2020d). Further, FRs are often used as mixtures and cumulative effects need to be considered. For example a mixture called Firemaster 550®, containing various FRs, is widely used in commercial products and there is evidence that it may be obesogenic, an endocrine disruptor and impact neurodevelopment (HBM4EU, 2022i; Patisaul et al., 2013). Further research is needed, particularly on cumulative effects, chronic toxicity, carcinogenicity, reproductive health and endocrine disruption (HBM4EU, 2022i).

Relevance for children

Children are identified as a vulnerable target group due to the combined effects of higher exposure and sensitive developmental periods. The body burden of FRs is higher in young children due to transplacental transfer, breastfeeding and child behaviour (e.g. hand-to-mouth behaviour) (Ghassabian et al., 2022; HBM4EU, 2022i; Sugeng et al., 2017). Children are more exposed to high levels of household dust, which represents an important exposure indoors (Feiteiro et al., 2021). Exposure to some FRs at an early age has been associated with adverse neurodevelopmental effects (Castorina et al., 2017; Czerska et al., 2013; Lam et al., 2017; Moore et al., 2022). In particular, the FRs identified as POPs pose a health threat to children due to their high persistence, bioaccumulation and endocrine disrupting properties. Exposure of children to endocrine disruptors early in life can have serious adverse developmental effects (Ghassabian et al., 2022).

In conclusion, FRs pose a health concern for children because of the higher body burden of FRs in children and the associated health risks, which are confirmed for legacy BFRs and suspected for newer FRs.

4.5.5. Arsenic

Chemical characterization and emission sources

Arsenic is a naturally occurring element that is widely distributed in the earth's crust, especially in minerals and ores containing copper or lead. It is defined as a metalloid, having both properties of both a metal and a non-metal. Arsenic is commonly found in the environment in its organic (combined with carbon and hydrogen) or inorganic (combined with elements such as oxygen and chlorine) form, with the inorganic form posing the greatest risk to the environment and human health (Agency for Toxic Substances and Disease Registry (ATSDR), 2007; HBM4EU, 2022d). Regarding the exposure and health effects, we focus on inorganic arsenic in this report. Arsenic is emitted to the environment from both natural and anthropogenic sources, with the anthropogenic sources playing a major role in the global exposure (United Nations Environment Programme (UNEP), 2020b). Natural activities such as weathering and erosion of rocks, volcanic activity, dissolution of minerals (especially in groundwater) and exudates from vegetation release arsenic (International Agency for Research on Cancer (IARC), 2012; World Health Organization, 2019a). Mining, metal smelting, fossil fuel combustion and activities related to the use, disposal and recycling of products are the main human sources of environmental contamination (International Agency for Research on Cancer (IARC), 2012; United Nations Environment Programme (UNEP), 2020b). Arsenic is persistent for at least 15 years and accumulates in the environment (HBM4EU, 2022d; United Nations Environment Programme (UNEP), 2020b). Arsenic and arsenic compounds are used in wood preservatives, pesticides, animal feed additives, glass production, alloy manufacturing, electronics, semiconductor manufacturing and pharmaceuticals (Grund et al., 2008; HBM4EU, 2020d; International Agency for Research on Cancer (IARC), 2012; United Nations Environment Programme (UNEP), 2020b). The use of arsenic in some products has been restricted or forbidden in certain countries (United Nations Environment Programme (UNEP), 2020b).

Exposure characterization

The primary route of arsenic exposure for the general population is through ingestion of contaminated food and water, while exposure via inhalation and dermal absorption is usually much lower (HBM4EU, 2020d; International Agency for Research on Cancer (IARC), 2012; United Nations Environment Programme (UNEP), 2020b; World Health Organization, 2019a). The main food products of concern are milk, wheat bread, fruit, vegetables, rice, soft drinks, beer, crustaceans and molluscs (European Food Safety Authority (EFSA), 2014; National Research Council, 2013; Xue et al., 2010). Further, arsenic can pass though the placenta and lead to foetal exposure (World Health Organization, 2019a). In the occupational setting, inhalation of particles is the primary exposure, but ingestion and dermal exposure may also be significant in certain settings (International Agency for Research on Cancer (IARC), 2012; United Nations Environment Programme (UNEP), 2020b). The WHO has established a provisional guideline value for arsenic in drinking water (10µg/L), but not in air or through dietary exposure (United Nations Environment Programme (UNEP), 2020b; World Health Organization, 2022a). In 2002, an estimated 140 million people worldwide were drinking water with arsenic at levels above the WHO guideline (Ravenscroft et al., 2009; World Health Organization, 2023, 2019a), which may be an underestimate as some countries did not screen for arsenic or used a different threshold (United Nations Children's Fund (UNICEF) and World Health Organization, 2018). A recent statistical model suggests that between 94 and 220 million people worldwide are currently at risk of exposure above the guidelines in groundwater, of whom 94 % live in Asia (Podgorski and Berg, 2020). As arsenic is the most significant chemical contaminant in drinking-water globally (World Health Organization, 2023), public health interventions are needed to reduce exposure to arsenic, particularly in areas with naturally high levels in groundwater (United Nations Environment Programme (UNEP), 2020b; World Health Organization, 2019a). Arsenic is generally well absorbed via the oral and inhalation routes, with low absorption via dermal contact. In part, enzymes in the liver or other tissues methylate arsenic. Most arsenic is promptly excreted in the urine in different oxidation states and metabolites, but some arsenic may remain bound to tissues for months or longer (Agency for Toxic Substances and Disease Registry (ATSDR), 2007; National Research Council, 2013). The preferred biomarkers for exposure to

inorganic arsenic are the determination of arsenic and its chemical forms in urine (HBM4EU, 2020d; Lauwerys and Hoet, 2001; National Research Council, 2013).

Health effects

Arsenic has been identified by the WHO as one of the 10 chemicals of major public health concern as the contamination of soil and drinking water by arsenic is globally threatening human health (HBM4EU, 2020d; United Nations Environment Programme (UNEP), 2020b; World Health Organization, 2019a). Inorganic arsenic compounds are classified as carcinogenic to humans by the IARC (International Agency for Research on Cancer (IARC), 2012). While lung cancer is associated to exposure for the inhalation and ingestion routes, bladder and skin cancer are associated to arsenic in drinking-water. Further there is evidence for an association with kidney, liver and prostate cancer (Di Giovanni et al., 2020; HBM4EU, 2020d; International Agency for Research on Cancer (IARC), 2012; Jaafarzadeh et al., 2022; Kasmi et al., 2023; Yang et al., 2022a). Chronic oral exposure to inorganic arsenic can lead to chronic arsenic poisoning (arsenicosis) which is associated to a range of adverse health effects such as skin lesions, peripheral neuropathy, diabetes, gastrointestinal symptoms, cardiovascular disease as well as reproductive and developmental toxicity (HBM4EU, 2020d; National Research Council, 2013; World Health Organization, 2019a, 2022a). For the year 2015, it was estimated that foodborne arsenic resulted in about 240,000 illnesses, including bladder, lung and skin cancer, about 50,000 deaths and about 1,400,000 DALYs worldwide (Gibb et al., 2019).

Relevance for children

Children were identified to be the most vulnerable and sensitive group to the adverse effect of arsenic (HBM4EU, 2022d). The dietary exposure to inorganic arsenic in the European population was found highest in young children, about 2 to 3-fold higher than in adults relative to body weight (European Food Safety Authority (EFSA), 2014). There is growing evidence that prenatal and early-life exposure to arsenic in drinking water is associated with adverse developmental and neurodevelopmental effects in children and adverse health outcomes later in life such as cardiovascular disease, chronic pulmonary disease and cancer (Agency for Toxic Substances and Disease Registry (ATSDR), 2016; Farzan et al., 2013; Li et al., 2022; Liu et al., 2010; Nachman et al., 2017; National Research Council, 2013; Rodríguez-Barranco et al., 2013; Tolins et al., 2014; World Health Organization, 2019a; Young et al., 2018).

In summary, arsenic poses an important health risk to children and their health in later life due to the higher exposure of children and their increased susceptibility to adverse health effects.

4.5.6. Mercury

Chemical characterization and emission sources

Mercury (Hg) is a naturally occurring heavy metal in the earth's crust and can exist in three main forms: elemental (metallic), inorganic, and organic (HBM4EU, 2022k). Elemental mercury is a liquid at room temperature that can evaporate at low temperatures (Agency for Toxic Substances and Disease Registry (ATSDR), 2022c; World Health Organization, 2021b). Once released in the environment, mercury can be transported over large distances, undergoes a series of complex transformations between the various forms and can cycle between atmosphere, ocean, sediments, soil and living organisms. The conversion into methylmercury (organic mercury compound) in water is of particular importance and concern for public health due to its higher membrane permeability and greater capacity for tissue fixation that can lead to bioaccumulation and magnification in the food chain (HBM4EU, 2022k; World Health Organization, 2021b).

Emission sources of mercury can be both natural and anthropogenic, whereby natural sources are of minor importance and anthropogenic activities have cumulatively increased atmospheric mercury concentrations by 300-500 % over the past century (HBM4EU, 2022k; United Nations Environment

Programme (UNEP), 2019b). The primary sectors responsible for air emissions are artisanal and small scale gold mining (ASGM), where gold is extracted from ore using mercury amalgamation, followed by combustion of fossil fuels (mainly coal), non-ferrous metal production and cement production. Releases into the water are mainly due to non-ferrous metal production, municipal sewage, mercury-added products, coal-fired power plants and coal washing (United Nations Environment Programme (UNEP), 2019b). Further, remobilization of legacy sources in the environment and recycling of products can cause emissions to the environment (United Nations Environment Programme (UNEP), 2019a; World Health Organization, 2021b).

Elemental mercury has been commonly used in electrical, medical and laboratory equipment, fluorescent-lighting and dental amalgams but its use has been increasingly regulated (Agency for Toxic Substances and Disease Registry (ATSDR), 2022c, p. 2; HBM4EU, 2022k; United Nations Environment Programme (UNEP), 2019a). Nevertheless, elemental mercury is still used in large amounts in some countries, for example in the industrial production of chlorine gas and caustic soda (HBM4EU, 2022k; Sakamoto et al., 2018). Inorganic mercury compounds are used in the production of polyvinyl chloride (PVC), batteries and pigments. Organic mercury compounds have been historically used in pesticides, fungicides, antiseptics and disinfectants, but have mostly been phased out. Ethylmercury is still used in small amounts in vaccines and pharmaceuticals as preservative due to its antiseptic properties. However, the toxicity profile of ethylmercury is considerably lower than that of methylmercury due to its shorter blood half-life, distribution and elimination time (Dórea et al., 2013; Centers for Disease Control and Prevention U.S. (CDC), 2020; HBM4EU, 2022k).

Between 2010 and 2015, anthropogenic emissions of mercury increased overall by about 20 % with regional differences. While in Europe and North America emissions decreased, there was an increase in other regions, especially in Asia, which contributes to 49 % of all mercury emissions (United Nations Environment Programme (UNEP), 2019b, 2019a). Globally, efforts are made to reduce emissions and regulate the use of mercury. For example, the Minamata Convention on Mercury (including 141 parties), which entered into force in 2017, includes a ban on new mercury mines, the phase-out of existing ones, the phase-out and phase-down of mercury use in products and processes, control measures on emissions and the regulation of ASGM (Minamata Convention on Mercury, 2021). Newer trends of global mercury emissions show a slow decline with regional differences (United Nations Environment Programme (UNEP), 2019a; Zhang et al., 2016).

Exposure characterization

The primary route of exposure for the general population is to organic mercury (typically methylmercury) from dietary exposure such as fish, seafood and rice and to a minor degree to elemental mercury from dental amalgams (Agency for Toxic Substances and Disease Registry (ATSDR), 2022c; HBM4EU, 2022k; United Nations Environment Programme (UNEP), 2019b). Transplacental transfer to the foetus has also been identified as major exposure route to organic mercury (HBM4EU, 2022k).

Occupational exposure is primarily to elemental mercury by inhalation of vapours in industrial processes and in dentistry (HBM4EU, 2022k; Agency for Toxic Substances and Disease Registry (ATSDR), 2022c). The various forms of mercury have distinct toxicokinetics and dynamics. For the purpose of this summary, we focus on elemental and organic mercury, as evidence on inorganic mercury exposure and its health effects for humans is limited (Agency for Toxic Substances and Disease Registry (ATSDR), 2022c). Elemental mercury is mainly absorbed as mercury vapour by inhalation and distributes throughout the body with highest concentrations in the kidneys. Most Mercury is then rapidly oxidized by enzymes and excreted through urine and faeces with an estimated terminal half-time of 30 to 90 days. Organic mercury (mostly methylmercury) is absorbed nearly to 100 % by the gastrointestinal tract and distributes throughout the body with highest concentrations in liver, kidneys and brain. When exposed chronically, methylmercury can accumulate due to the limited capacity of

demethylation and excretion (mainly through faeces, urine and hair). The terminal half-time of methylmercury has been estimated to be 64-97 days (Agency for Toxic Substances and Disease Registry (ATSDR), 2022c). Mercury exposure can be monitored by measuring the concentration of mercury in hair, urine, blood, and umbilical cord blood. While hair concentration mainly reflects the exposure to organic mercury, urine levels mainly reflect the exposure to inorganic and elemental mercury and blood samples provide information about exposure to organic and inorganic mercury. In the general population, the concentration of mercury in blood and hair is most commonly used as biomarker for exposure. The combination of different biomarkers together with surveys about behaviour and diet provide a deeper assessment of mercury in its various forms (Agency for Toxic Substances and Disease Registry (ATSDR), 2022c; United Nations Environment Programme (UNEP), 2019b).

Health effects

The WHO has identified mercury as one of the ten chemicals of major public health concern. It is highly toxic and poses a significant global threat to human health and the environment having effects even at low levels (HBM4EU, 2022k; World Health Organization, 2021b). The IARC classified methylmercury as possibly carcinogenic to humans (Group 2B) as there is evidence of an association with cancer in lung, liver and kidneys. Elemental mercury and inorganic compounds are not classifiable as carcinogenic to humans (Group 3) (HBM4EU, 2022k; International Agency for Research on Cancer (IARC), 1993).

Elemental mercury, inorganic mercury and organic mercury have distinct properties and toxicities but for all forms, neurological and renal effects have been observed (World Health Organization, 2021b; Agency for Toxic Substances and Disease Registry (ATSDR), 2022c). Exposition to elemental mercury vapour can lead to various neurological effects in humans such as tremor, impaired nerve conduction, fine motor coordination, cognitive performance and subjective symptoms like irritability and mood swings. Moreover, animal studies suggest effects on neurodevelopment. Elemental mercury vapour can also lead to a decreased renal function and renal tubular damage. There is strong evidence of neurological and neurodevelopmental effects of oral exposure to organic mercury. Further, studies in humans and animals provide evidence for renal, reproductive, cardiovascular, immune and developmental effects of oral exposure to organic mercury (Agency for Toxic Substances and Disease Registry (ATSDR), 2022c). However, the use of ethylmercury in vaccines is supported by human toxicity studies, which show that even cumulative doses of vaccines do not lead to toxic levels of ethylmercury. Furthermore, there is no robust epidemiological evidence regarding the potential health effects of ethylmercury use in vaccines (WHO Global Advisory Committee on Vaccine Safety (GACVS), 2012; Centers for Disease Control and Prevention U.S. (CDC), 2020). For the year 2015, it was estimated that foodborne methylmercury resulted in about 226’000 new cases of mild or moderate intellectual disability and nearly 2 million DALYs worldwide (Gibb et al., 2019).

Relevance for children

Mercury poses a particular threat to the development of children in utero and early in life, as they are especially sensitive to the adverse effects of mercury (HBM4EU, 2022k; World Health Organization, 2021b). Mercury can be transferred to the foetus through the placenta and to the infant through breast milk. (Agency for Toxic Substances and Disease Registry (ATSDR), 2022c). Epidemiological studies show an association of maternal exposure during pregnancy to mercury with adverse health outcomes, especially for the neuronal system. Observed developmental effects include congenital malformations, mental retardation, vision and hearing loss, seizures, memory loss, delayed development and language disorders (Agency for Toxic Substances and Disease Registry (ATSDR), 2022c; Gibb et al., 2019; World Health Organization, 2021b; HBM4EU, 2022k; World Health Organization, 2010).

The developmental neurotoxicity has been studied best for methylmercury. Outbreaks of severe neurodevelopmental disorders have been linked to the consumption of wheat contaminated with a methylmercury fungicide in Iraq and to maternal ingestion of methylmercury in contaminated seafood

in Minamata (Japan), later termed congenital Minamata disease (Agency for Toxic Substances and Disease Registry (ATSDR), 2022c; Harada, 1978). In infants and young children, a condition called acrodynia has been observed as a consequence of chronic mercury exposure. It is characterised by red and painful extremities with local swelling and intense itching, which can be accompanied by insomnia, irritability, and sensitivity to light (World Health Organization, 2021b).

In conclusion, children, especially during their developmental stages, are highly susceptible to the adverse effects of mercury exposure and therefore require special attention in exposure monitoring and prevention measures.

4.5.7. Polycyclic aromatic hydrocarbons

Chemical characterization and emission sources

Polycyclic aromatic hydrocarbons (PAHs) constitute a large group of organic compounds containing only carbon and hydrogen and consisting of two or more fused aromatic rings (International Agency for Research on Cancer (IARC), 2010). There are more than 100 different PAHs and their physicochemical properties can vary substantially (United Nations Environment Programme (UNEP), 2020d; Jameson, 2019). PAHs can occur naturally in coal, crude oil, and petrol, but are mainly formed as by-products of the incomplete combustion of coal, oil, petrol, wood, garbage, tobacco and other organic materials (HBM4EU, 2022o; Agency for Toxic Substances and Disease Registry (ATSDR), 1995). They generally occur as complex mixtures rather than as single compounds (Agency for Toxic Substances and Disease Registry (ATSDR), 1995). Emissions of PAHs are predominantly from anthropogenic activities such as residential, commercial and industrial combustion, road traffic, metal production, waste incineration and cigarette smoke (HBM4EU, 2022o; World Health Organization Regional Office for Europe, 2021).

Depending on their physicochemical properties, some PAHs emitted to the atmosphere remain in the gas mixture, while others get bound to particulates in air, soil, sediments and other matrices (HBM4EU, 2022o; Jameson, 2019). A few PAHs are used in medicines, and to make dyes, plastics or pesticides, but most have no use and occur as by-products of manufacturing processes (Agency for Toxic Substances and Disease Registry (ATSDR), 1995; United Nations Environment Programme (UNEP), 2020d).

Exposure characterization

PAHs are ubiquitous in the environment and exposures are always to a mixture of PAHs. This result in measurable background levels of PAHs metabolites in the general population (International Programme on Chemical Safety (IPCS), 1998; United Nations Environment Programme (UNEP), 2020d). Human exposure to PAHs can occur by ingestion, inhalation and dermal absorption. For non-smoking population the main exposure routes are diet and the inhalation of polluted ambient and indoor air, with dietary sources being a major exposure route, which can contribute up to 90 % of the daily intake (HBM4EU, 2022o; Rengarajan et al., 2015; Sampaio et al., 2021). The main dietary sources of PAHs are meat, seafood, fats, oils and cereal products. The way food is processed and cooked has a significant impact on the PAHs levels, as smoking, drying, grilling, roasting and frying, especially at high temperatures, can contaminate food with PAHs (Joint FAO/WHO Expert Committee on Food Additives (JECFA), 2005; European Food Safety Authority (EFSA), 2008). For smokers, tobacco smoke can represent a major route of exposure (International Agency for Research on Cancer (IARC), 2010). In addition, PAHs may be present in consumer products made of rubber or elastomers due to the use of PAH-containing plasticizers, oil extenders or carbon black, which can lead to PAHs entering the body via dermal absorption (United Nations Environment Programme (UNEP), 2020d, 2023a; HBM4EU, 2022o). Workers in several occupational settings are exposed to higher levels of PAHs than the general population. These include facilities working with materials such as asphalt, aluminium, coke, petroleum, cement and waste (HBM4EU, 2022o; Rengarajan et al., 2015).

The absorption of PAHs varies depending on the chemical compound, the route of exposure and the carrier particles. Once in the body, PAHs distribute to all tissues of the body, with a tendency to localise in body fat, kidneys and liver and to a lesser extend in the spleen, adrenal glands and ovaries. The metabolism of PAHs can vary and is influenced by the mixture of PAHs entering the body, sometimes forming harmful intermediates. Most PAHs leave the body within a few days, mostly in faeces and urine (Agency for Toxic Substances and Disease Registry (ATSDR), 1995; Abdel-Shafy and Mansour, 2016). To assess the human exposure to PAHs, mono-hydroxylated PAHs in the urine are commonly used as biomarkers (HBM4EU, 2022o).

Health effects

UNEP has identified PAHs as a risk to human health and the environment (United Nations Environment Programme (UNEP), 2019a). Exposure to PAHs has been associated with a range of health risks including cancer, respiratory disease, cardiovascular disease, immune dysfunction, organ damage, and developmental and reproductive toxicity (HBM4EU, 2022o; World Health Organization Regional Office for Europe, 2021). Particular public health concern applies to the contribution of PAHs in the emergence of cancer. The exposure to PAHs has been associated with cancers of the skin, lung, bladder, breast and the gastrointestinal tract, with the strongest evidence for non-melanoma skin cancers and lung cancers in the occupational setting (HBM4EU, 2022o; International Agency for Research on Cancer (IARC), 2010; Jameson, 2019; World Health Organization Regional Office for Europe, 2021). The latest report of the IARC assessed the evidence for the carcinogenicity of 60 PAHs, of which one compound was classified as carcinogenic to humans (Group 1), three as probably carcinogenic to humans (Group 2A) and eleven as possibly carcinogenic to humans (Group 2B). In addition, the IARC has classified several occupations associated with high exposure to PAHs, such as coal gasification, coke production, coal-tar distillation, chimney sweeping, and aluminium production, as carcinogenic to humans (Jameson, 2019; International Agency for Research on Cancer (IARC), 2010, 2012). The European Chemicals Agency has identified eight PAHs with presumed carcinogenicity based on animal data (Group 1B) (HBM4EU, 2022o). Benzo[a]pyrene is the most hazardous among all PAHs and has been classified as carcinogenic, mutagenic, skin sensitising and toxic to reproduction (HBM4EU, 2022o).

Epidemiological studies have indicated various health effects, linking PAHs with reduced lung function, exacerbation of asthma, increased rates of obstructive lung diseases and cardiovascular diseases (World Health Organization Regional Office for Europe, 2021). Furthermore, many PAHs have potent immunosuppressive properties, affecting the development and function of the immune system (HBM4EU, 2022o; Laupeze et al., 2002). Due to their toxic properties, the European Union has restricted eight PAHs by limiting the level of PAHs level in consumer products such as toys, clothing and household utensils (HBM4EU, 2022o).

Relevance for children

PAHs can be transferred to the foetus through the placenta and to the infant through breast milk (HBM4EU, 2022o; Agency for Toxic Substances and Disease Registry (ATSDR), 1995). Various studies demonstrate that exposure to PAHs during pregnancy is harmful to the developing foetus, especially for neurodevelopment and lung development. Prenatal exposure to PAHs is negatively correlated with birth weight, birth length and head circumference and is associated with preterm births and respiratory symptoms soon after birth (Huo et al., 2019; Suzuki et al., 2010; Choi et al., 2006, 2008; World Health Organization Regional Office for Europe, 2021). Moreover, prospective cohort studies in New York City and Krakow indicate an association of prenatal exposure with developmental delay, lower IQ scores and height growth, and an increase of symptoms of anxiety, depression, and attention problems in children (Perera et al., 2006, 2009, 2012; Jedrychowski et al., 2015, 2015). Further, epidemiological studies have shown that exposure to PAHs in childhood is associated with asthma onset and increasing asthmatic symptoms in children (World Health Organization Regional Office for Europe, 2021).

Evidence from six case-control studies conducted in the United States suggests that prenatal and postnatal exposure to PAHs is associated with the development of several childhood cancers, including leukaemia, nephroblastoma, brain tumours, neuroblastoma and retinoblastoma. However, the level of evidence for the association with childhood cancers and the effect on cognitive or behavioral function in children is limited, and more studies are needed (World Health Organization Regional Office for Europe, 2021).

In summary, there is a pressing need for closer monitoring and regulation of PAHs due to the widespread human exposure to mixtures of PAHs, with varying properties and health effects. Evidence from epidemiological studies associates prenatal und early life exposure with adverse birth outcomes, impaired lung development and neurodevelopmental issues.

4.5.8. Phthalates

Chemical characterization and emission sources

Phthalates form a family of synthetic organic compounds. They are used in a wide variety of industrial and consumer products as plasticizers to make plastics, such as polyvinyl chloride (PVC), more flexible and durable. (European Chemicals Agency (ECHA), forthcoming; HBM4EU, 2022n; United Nations Environment Programme (UNEP), 2023a). Phthalates are produced in high volumes for products such as vinylflooring, adhesives, wires and cables, sport equipment, toys, packaging, coated textiles, footwear, personal care products and others (United Nations Environment Programme (UNEP), 2020c; HBM4EU, 2022n). They accounted for 65 % of global use of plasticizers in 2017 and an estimated 6 to 8 million tonnes of phthalates are consumed every year (United Nations Environment Programme (UNEP), 2023a, 2020c). Since phthalates are additives and not chemically bound to the (plastic) materials, some phthalates can leach into the environment during manufacturing and use and disposal and can therefore be found ubiquitously in the environment, including air, water, sediment, soil, dust and living organisms (HBM4EU, 2022n; United Nations Environment Programme (UNEP), 2023a, 2020c). However, the omnipresence of phthalates in the environment is due to their continuous release rather than bioaccumulation, as phthalates persist for a short time due to degradation and rapid metabolism in organisms. (United Nations Environment Programme (UNEP), 2020a).

Phthalates can be differentiated into low molecular weight ortho-phthalates (LMW) and high molecular weight phthalates (HMW) with distinct physical and chemical properties in the environment and in the human body. (HBM4EU, 2022n; United Nations Environment Programme (UNEP), 2020a).

Exposure characterization

Phthalate metabolites have been detected in a high percentage of study populations in HBM studies conducted in the Europe, North America and Asia. The metabolites were sometimes even measured in each urine sample, indicating the ubiquitous and continuous exposure of the general population to phthalates (HBM4EU, 2022n; United Nations Environment Programme (UNEP), 2020a).

Human exposure to phthalates can occur via ingestion, inhalation and dermal absorption. For HMW the main source of exposure is through diet, especially through contamination via food contact materials. For LMW, inhalation of indoor air, exposure via ingestion of house dust and dermal contact with phthalate-containing material or dust are the main exposure routes (HBM4EU, 2022n). In certain cases, exposure of phthalates through medical devices (e.g. for blood transfusion or artificial ventilation) can lead to a significant exceedance of the tolerable daily intake (Scientific Committee on Emerging and Newly-Identified Health Risks (SCENIHR), 2016).

To reduce the exposure, the use of certain phthalates has been restricted in many countries, including the EU, Brazil, Israel, China, Canada and the United States. The restrictions mainly focus on toys, childcare products and other consumer goods with prolonged contact with human skin (United Nations Environment Programme (UNEP), 2023a; HBM4EU, 2022n). In 2016, the EU restricted seven phthalates

under the REACH regulation (European Chemicals Agency (ECHA), 2016b, 2016c). Due to legal restrictions, the exposure to those compounds decreased in various countries in Europe, while the exposure to substitutes has increased in recent years. Nevertheless, the European population will presumably still be exposed to restricted phthalates in the future due to remaining uses of those phthalates, long lifetime of articles and recycled PVC products. Results from HBM4EU aligned studies conducted between 2014 and 2021 demonstrate that children in Europe continue to be exposed to multiple phthalates, with some concerning phthalates exceeding biomonitoring guidance values in 2-4 % of cases (HBM4EU, 2022n). However, cumulative risk assessments of exposure to mixtures of phthalates are crucial to accurately determine the health risk, as the adverse health effects of phthalates can act in an additive manner (HBM4EU, 2022n; European Chemicals Agency (ECHA), 2016a; United Nations Environment Programme (UNEP), 2023a; Howdeshell et al., 2017).

Health effects

Phthalates were identified as an emerging risk for human health in the UNEP Global Chemicals Outlook II report in 2019 (United Nations Environment Programme (UNEP), 2019a). Also, the EU has identified 17 phthalates or phthalate mixtures as substances of very high concern (United Nations Environment Programme (UNEP), 2020a). Phthalates can cause a variety of adverse health effects, the most prominent of which are the endocrine disrupting effects and their toxicity for reproduction (HBM4EU, 2022n).

Several phthalates show anti-androgenic effects, which have been extensively studied in animals and are considered to be biologically relevant to humans. Prenatal exposure to certain phthalates is associated with male reproductive abnormalities such as decreased foetal testosterone, malformation of genitals, reduced semen quality, infertility and others. However, not all phthalates have these endocrine disrupting effects causing these reproductive abnormalities (European Chemicals Agency (ECHA), 2016a; HBM4EU, 2022n). Epidemiological studies suggest an association of phthalates exposure with overweight, insulin resistance and other cardiometabolic risk factors, asthma, neurodevelopment and attention deficit hyperactivity disorder (ADHD). However, there is a need for more robust epidemiological studies as there is inconclusive evidence in some systematic reviews (e.g. for ADHD and adiposity) (HBM4EU, 2022n; Ribeiro et al., 2019; Wu et al., 2020a; Praveena et al., 2020; Golestanzadeh et al., 2019; Li et al., 2017; Ejaredar et al., 2015; Gao et al., 2021a).

Current evidence indicates that the potential carcinogenicity of phthalates is of minor concern compared to other health effects. IARC classifies only two phthalates: Di(2-ethylhexyl) phthalate (DEHP) is classified as possibly carcinogenic to humans (Group 2B), while Butyl benzyl phthalate (BBzP) has been defined as not classifiable as to its carcinogenicity to humans (Group 3) (International Agency for Research on Cancer (IARC), 2013, 1999).

Relevance for children

Children are particularly vulnerable to the harmful effects of phthalates (HBM4EU, 2022n; United Nations Environment Programme (UNEP), 2023a). Exposure of children to endocrine disruptors in utero and early in life can have serious adverse developmental effects (Ghassabian et al., 2022).

Biomonitoring studies generally find higher levels of phthalate metabolites in children than in adults (HBM4EU, 2022n). Some phthalates can be transferred to the foetus in utero and to infants through breast milk (Agency for Toxic Substances and Disease Registry (ATSDR), 2022b; Mose et al., 2007). Moreover children may be directly exposed to phthalates found in toys or other consumer goods through mouthing, skin contact, inhalation of volatile compounds and ingestion of food (United Nations Environment Programme (UNEP), 2023a; HBM4EU, 2022n). Exposure levels for foetuses, infants and children can exceed the guidance values, exposing them to a significant health risk. ECHA reported in 2016 that more than 5 % of children were at risk from combined exposure to four hazardous phthalates in 14 out of 15 member states. Furthermore, ECHA estimated that in 2014 about

5 % of male newborns were at risk due to in utero exposure and about 15 % of boys were at risk from direct exposure (European Chemicals Agency (ECHA), 2016a).

Systematic reviews have identified associations of prenatal and postnatal exposure to phthalates and adverse cognitive and behavioural outcomes in children, including lower IQ, poorer social communication and problems with attention and hyperactivity, and childhood asthma (Ejaredar et al., 2015; Li et al., 2017).

In summary, the scientific evidence indicates widespread exposure to various hazardous phthalates, with children experiencing higher exposure levels than adults. Given that endocrine disruptors are particularly detrimental to children's health, it is crucial to recognize phthalates as a significant health threat for children.

4.5.9. Acrylamide

Chemical characterization and emission sources

Acrylamide is a highly water-soluble, colourless and odourless organic compound and is considered as non-persistent in the environment and non-bioaccumulative in living organisms (Agency for Toxic Substances and Disease Registry (ATSDR), 2012a; HBM4EU, 2022c). In the chemical industry and research laboratories, acrylamide is mainly used for the production of polyacrylamides which can be used as flocculants in different processes. Acrylamide and polyacrylamides are used in the treatment of wastewater and in the production of organic chemicals, dyes, textiles, pulp, paper, contact lenses, cosmetics and toiletries. Furthermore, acrylamide is used in the oil industry as flow control agent to enhance oil production from wells and in building and construction as grouting agent and soil stabilizer for big infrastructure (e.g. tunnels and sewers). Direct releases of acrylamide to the environment can occur during all of these processes, resulting in measurable levels in the environment, especially in water and soil (Agency for Toxic Substances and Disease Registry (ATSDR), 2012a; HBM4EU, 2020d, 2022c).

In addition to its commercial use, it was discovered in 2002 that acrylamide can be formed unintentionally during everyday food preparation, leading to public health concerns. Acrylamide is formed in certain foods when processed at high temperature (<120°C) under low moisture conditions, e.g. frying, roasting and baking. These foods are generally high in carbohydrates, such as potatoes, bread and cereals but acrylamides could also be found in roasted coffee and nuts, olives in brine, prunes, dates and baby food. Levels of acrylamide increase with higher temperatures and longer cooking times (HBM4EU, 2020d; European Food Safety Authority (EFSA), 2015; Agency for Toxic Substances and Disease Registry (ATSDR), 2012a)

Exposure characterization

Acrylamide exposure is assumed to be widespread in the general population (Agency for Toxic Substances and Disease Registry (ATSDR), 2012a; HBM4EU, 2020d). According to a study conducted by the Centers for Disease Control and Prevention (CDC) in the United States, measurable levels of acrylamide were detected in 99.9 % of the 14’000 samples representative of the national population (Centers for Disease Control and Prevention U.S. (CDC), 2021). Human exposure to acrylamide can occur via ingestion of food and drinking water, via inhalation of cigarette smoke or contaminated dust and vapour and via dermal absorption. Transplacental transfer as exposure to foetuses should also be considered but further evidence in humans is needed (HBM4EU, 2022c; Agency for Toxic Substances and Disease Registry (ATSDR), 2012a).

The diet is the main source of exposure for the general population, with variations observed in different age groups and in accordance to the dietary habits and the cooking methods employed. The main dietary sources of acrylamide are fried potato products, such as French fries and chips, as well as coffee, soft and crispy bread, biscuits and cereals (European Food Safety Authority (EFSA), 2015;

HBM4EU, 2022c; Joint FAO/WHO Expert Committee on Food Additives (JECFA), 2011). The uptake of contaminated water is a minor exposure source for the general population (HBM4EU, 2022c). Furthermore, cigarette smoke represents a significant source of exposure, with smokers experiencing up to 50 % greater overall exposure than non-smokers (HBM4EU, 2022c; Agency for Toxic Substances and Disease Registry (ATSDR), 2012a). Occupational exposure may be significant for workers in specific industries. Workers can be exposed by inhalation of dust and vapours, as well as dermal absorption through direct skin contact (HBM4EU, 2020d, 2022c).

Acrylamide is highly water-soluble, therefore facilitating absorption in the gastrointestinal tract and distribution to all organs. Within body, acrylamide is extensively metabolised, among others creating glycidamide, which is considered to represent the major route underlying the genotoxicity and carcinogenicity of acrylamide. Acrylamide does not bioaccumulate and is mostly excreted through urine, to a lesser extent through faeces, exhaled air and breast milk. (European Food Safety Authority (EFSA), 2015, 2022; Agency for Toxic Substances and Disease Registry (ATSDR), 2012a)

To date, there are only few human biomonitoring studies and further research is needed to assess current exposure levels for the general population and associated health risks, to provide a dose-response assessment for acrylamide and to establish robust health-based guidance values for humans (HBM4EU, 2022c; European Food Safety Authority (EFSA), 2015).

Health effects

Acrylamide is considered to be a public health concern, especially since the identification of acrylamide in processed foods and its the widespread exposure. In experimental animal studies, acrylamide has been shown to be carcinogenic, genotoxic, neurotoxic and reproductive toxic, as well as suspected immunotoxic and developmental toxic (European Food Safety Authority (EFSA), 2015; Agency for Toxic Substances and Disease Registry (ATSDR), 2012a; HBM4EU, 2020d). Due to strong evidence in animal studies, acrylamide have been classified as probably carcinogenic to humans (Group 2A) by IARC and as a substance which is presumed to have carcinogenic and mutagenic potential for humans (Carc 1B) by ECHA. Furthermore, acrylamide has been classified by ECHA as skin sensitising and suspected to be toxic to reproduction (HBM4EU, 2022c; European Chemicals Agency (ECHA), 2023d; International Agency for Research on Cancer (IARC), 1994). However, in human there is limited epidemiological evidence concerning health impacts caused by acrylamide and further investigation is needed.

In the occupational setting, effects on the neuronal system, such as muscle weakness and peripheral numbness, have been reported in workers in close and continuous contact with acrylamide. However, the general population is not exposed to levels of acrylamide high enough to cause these effects (Agency for Toxic Substances and Disease Registry (ATSDR), 2012a; Joint FAO/WHO Expert Committee on Food Additives (JECFA), 2011). Carcinogenic and mutagenic effects of acrylamide compose the most important public health concern. While in animal studies acrylamide has caused several types of cancer in animals, epidemiological studies do not provide consistent evidence of an association with cancer in humans. Although some studies suggest an association with some tumour types, more evidence is needed to confirm the correlation (Agency for Toxic Substances and Disease Registry (ATSDR), 2012a; European Food Safety Authority (EFSA), 2022, 2015; Joint FAO/WHO Expert Committee on Food Additives (JECFA), 2011; HBM4EU, 2020d). Nevertheless, in the latest European Food Safety Authority (EFSA) report on acrylamide, the experts concluded that there is substantial evidence for the genotoxicity of acrylamide through dietary exposure (European Food Safety Authority (EFSA), 2022).

Relevance for children

Infants, toddlers, children and pregnant women were identified as the most vulnerable groups for the possible adverse effect of acrylamide exposure. Children might be more vulnerable during their sensitive developmental stages, especially in utero and early in life during brain development (HBM4EU, 2022c, 2020d). Moreover, based on limited data on children's exposure to acrylamide,

children had up to twice the dietary exposure of adults, expressed on a body weight basis (Joint FAO/WHO Expert Committee on Food Additives (JECFA), 2011; HBM4EU, 2022c). Various developmental effects, such as reduced body weight and delayed motor development, have been observed in animals when exposed before and after birth. However, there is no evidence of acrylamide causing developmental effects in humans (Agency for Toxic Substances and Disease Registry (ATSDR), 2012a).

In summary, acrylamide represents an important public health concern due to strong evidence of adverse health effects in animal studies and widespread exposure of the general population. However, there are important gaps in our knowledge of exposure levels in children and adults, due to a lack of human biomonitoring studies, and epidemiological evidence of human health effects that need to be addressed.

4.6. Regulations on childhood exposure to chemicals

Children are a vulnerable group within society. There are concerns for exposure to certain chemicals and related health effects. Only for PFAS a TWI is available based on studies in children (see Section 4.4). The TDI of pyrethroids and benzophenones was derived based on animal studies and there is no limit value below which lead would not cause neurotoxic effects. Some protection measures specifically targeting children are in place at EU level. The most known Directive is the Toy Safety Directive 2009/48/EC (European Commission, 2009). Toys are subject to the EU legislation and migration limits for certain metals (e.g. lead), BPA and certain phthalates are regulated. In 2018, Directive 2018/725 was published with limits for chromium VI in appendix C of the Toy Safety Directive. In 2019 the EU decided to work on limit values for aluminium and formaldehyde in toys (ANEC, 2023). In 2021, Directive 2021/903 amending the Toy Directive was published with specific limits for aniline in toys. In 2021 ANEC([12]) wrote a position paper on the Toy Safety Directive evaluation and Chemicals Strategy for Sustainability (CSS): Which way forward? (ANEC, 2021). Recommendations were given.

The European commission adopted some regulations regarding safety of childcare products other than toys:

- 2010: Decision 2010/9/EU on safety requirements to be met by European standards for specific childcare products, namely bath rings, bathing aids, bath tubs and stands. For the chemical requirement, these three products shall comply with relevant EU legislation. Since there is no such a children specific legislation, the chemical safety aspect of Decision 2010/9/EU is not specific for children (2010/9/EU: Commission Decision of 6 January 2010 on the safety requirements to be met by European standards for bath rings, bathing aids and bath tubs and stands for infants and young children pursuant to Directive 2001/95/EC of the European Parliament and of the Council (notified under document C(2009) 10290) Text with EEA relevance, 2010).
- 2010: Decision 2010/376/EU on safety requirements to be met by European standards for childcare products in the sleeping environment of children. The chemical requirement for cot mattresses and bumpers, suspended baby beds, duvets, sleeping bags shall comply with EU legislation. Similarly to Decision 2010/9/EU, the chemical safety of this Decision is not specific for children. The use of chemical flame retardant substances should be kept to the minimum. If chemical flame retardant substances are used, their toxicity during use and end-of-life disposal should not endanger the health of the users, carers and the environment (2010/376/: Commission Decision of 2 July 2010 on the safety requirements to be met by European

([12]) **ANEC is the European consumer voice in standardisation.** We represent the European consumer interest in the creation of technical standards, especially those developed to support the implementation of European laws and public policies. (https://www.anec.eu/)

standards for certain products in the sleep environment of children pursuant to Directive 2001/95/EC of the European Parliament and of the Council, 2010).

- 2013: Decision 2013/121/EU on safety requirements to be met by European standards for seats for children. Regarding the chemical requirements, the products should comply with relevant EU legislation, which is not specific for children similar to the above Decisions. The use of chemical flame retardant substances should be kept to the minimum. If chemical flame retardant substances are used, their toxicity during use and their end-of-life disposal should not endanger the health of the user, the child's carers or the environment (2013/121/EU: Commission Decision of 7 March 2013 on the safety requirements to be met by European standards for certain seats for children pursuant to Directive 2001/95/EC of the European Parliament and of the Council on general product safety Text with EEA relevance, 2013).

Currently, no regulation is implemented that targets products meant for children in general. In that respect a new proposal regarding the safety of children's products excluding toys was drafted. This regulation would be in accordance with Directive 2001/95/EC on general product safety but specifically focused on children's products. The draft states that children's products shall have no adverse health effects as a result of exposure to chemical substances/mixtures contained in the products. The products must comply with all relevant EU legislation and standards shall reflect the latest chemical and scientific knowledge regarding the safety and health of children (including mouthing, inhalation and absorption). To determine safety requirements such as limit values, relevant guidelines, regulatory provisions and most recent scientific data for similar products will be taken into account, as well as the intended use and corresponding factors such as exposure duration. The draft act has been composed and gone through the required feedback period. The original adoption by the Commission was planned in the fourth quarter of 2021, however the feedback period was only closed in September of 2022. A new planned adoption date has not been announced yet (European Commission, 2022).

Childcare articles (baby carrier, diapers, etc.) and playground equipment are not subject to a specific regulation and they fall under Directive 2001/95/EC on General Product Safety. The French Agency for Food, Environmental and Occupational Health and Safety (ANSES) carried out a study on chemicals in diapers and found that 90 % of babies have been exposed to chemicals contained in diapers which are hazardous to their health. For now, there is no law regulating the use of chemicals in diapers (Bauer-Babef, 2022).

The use of cutlery and feeding utensils intended to be used by children from the age of 6 months to 3 years old is regulated under the EU standard EN 14372([13]) for CEN Members (CEN: Comité Européen de Normalisation). There is a limit for the migration of antimony (Sb), arsenic (As), barium (Ba), Cd, Pb, Cr, Hg, selenium (Se), the content of phthalates and the release of formaldehyde, nickel (Ni) and BPA (EU, 2004). For baby bottles there is an EU restriction on the use of BPA in feeding bottles (European Commission, 2011).

For textiles in particular, the OEKO-TEX® standard 100 is a world-wide recognized voluntary label that has been tested for a series of harmful substances. Every process step in the production of the textile is tested and clothing will only receive the OEKO-TEX® standard 100 label when each production step successfully passes the standard 100 limit values of 350 substances (including but not limited to pesticides, plasticizers, PAHs, flame retardants, PFAS, heavy metals, etc.) (number of substances at the time of the writing of this report, substances are added over time). These values go beyond many national and international requirements for textiles. Moreover, the OEKO-TEX® catalogue of substances is updated yearly to reflect new scientific knowledge and regulatory requirements. The requirements that textiles must meet to receive the OEKO-TEX® standard 100 label depends on the product class of the textile. OEKO-TEX® distinguishes four product classes of which the first applies

([13]) https://www.pcbase.cn/wp-content/uploads/2020/04/EN14372-2004.pdf

specifically to textiles for babies. This product class has to meet the strictest requirements. Although the other three product classes do not specifically mention children, they do also apply to children as these classes include products used by children. Clothing and other textile products are not legally required to have an OEKO-TEX® standard 100 label. This label does however inform consumers about the safety of their textiles and enables them to make more informed choices about the textiles they are buying for their children([14]).

4.6.1. Risk assessment

For risk assessment of chemicals in products, there is often no structured or harmonized approach to include a separate children's exposure scenario (OECD, 2019). There is a gap in exposure assessment methodologies aimed at children (OECD, 2013). The OECD document of 2019 creates awareness for the lack of child specific exposure scenarios and gives some guidance. Chemicals for which child-specific exposure assessment was performed in scientific literature are polybrominated diphenyl ethers (PBDEs) (Ionas et al., 2016), BPA (Healy et al., 2015), diethylhexylphthalate (DEHP) (Ginsberg et al., 2016) and parabens (Gosens et al., 2014). Children's exposure differs from that of adults and are considered a more sensitive group for chemical exposure than the general population. Additionally, there is a gap in risk assessment methodologies for children, this means that children's specific characteristics are often overlooked in risk assessment (OECD, 2019). This also entails that they are often also overlooked as a separate entity in regulations regarding chemical safety, protection and prevention. As stated above even legislation focused on children refers to relevant legislation regarding chemical safety which is not child specific. Legislation should therefore treat children as a separate group from adults when it comes to assessment of exposure of children and make explicit mention of children in regulations were relevant and/or necessary (i.e., legislation for the general population might already consider elements that adequately cover the risk to children and taking into account children specific characteristics would therefore not be needed). An exception is the guidance for the Testing of Cosmetic Ingredients and Their Safety Evaluation, which was reviewed in May of 2023. One of the updates of the guidance is the explicit inclusion of exposure of children to different cosmetic product categories according to age. Children are consistently mentioned to be included in safety assessment of products that can be used by children according to age. It mentions that when a cosmetic ingredient is suspected of having a potential endocrine activity, safety assessment for children according to age need to be done taking into consideration the relevant cosmetic categories to which children of different ages are usually exposed to (SCCS, 2023).

5. Conclusions and Outlook

As a result of the industrial lifestyle, more than 140,000 new chemicals and pesticides have been synthesised since 1950 (Landrigan et al., 2018) and the production volume is still increasing (OECD, 2012). Along with this, the diversity of physicochemical properties of synthesized chemicals is increasing. Around 5,000 of the 140,000 have been produced in large quantities and are widely distributed in the environment. Less than half of these chemicals have been tested for toxicity. As some synthetic chemicals have been restricted in recent years due to confirmed adverse human health effects, new related compounds have emerged for which the toxicity and health effects have to be re-evaluated. In several instances, these related compounds have demonstrated similar health effects (also called regrettable substitution), again requiring an extensive political process before policies are implemented to restrict their use. This situation is a challenge for assessing the health risk of the population and especially of children and adolescents.

In general, epidemiological studies are scarce, in particular for emerging compounds as well as studies with a special focus on children, although for several chemicals it was demonstrated that concentrations in blood or urine in children is higher than in adults. The scarcity of health studies is a

([14]) https://www.oeko-tex.com/en/our-standards/oeko-tex-standard-100

challenge when evaluating the impact for children. On the one hand, lack of data could be because the a priori chance for detrimental health effects has been considered to be low. On the other hand, lack of data could also just reflect research challenges and cannot be considered as evidence for absence of risk. For instance, a common challenge for many chemicals is the assessment of long-term exposure in large population samples, which is a requirement for epidemiological research on real life exposure situations. In summary, the monitoring of human exposure to mixtures of chemicals and the assessment of cumulative health effects represents important challenges.

Despite limited exposure knowledge, current scientific studies demonstrate health risks for several chemicals. Various health outcomes are proven or suspected to be associated with chemical exposures such as cognitive development, neurobehavioral effects (ADHD), endocrine disruptions, impaired immune system, reproduction and cancer. These findings are backed up by toxicity studies and mechanistic evidence by adverse outcome pathways. Thereby both, exposure during childhood and of the mother during pregnancy are of concern.

Future policies should consider to address vulnerable populations like children in an adequate manner. This review has found that for the protection of children from chemicals policy gaps exist in the EU framework and at national level. Protection by regulation is a time-consuming process and there is a delay of several decades before effective protection of the public including children. The regulatory management of chemicals addresses hundreds of different chemicals. Prenatal and early postnatal life is a high vulnerable exposure window and is a priority period for exposure reduction. There are some recommendations for pregnant women in place aiming to protect against different health hazards, however these are not validated by intervention studies. Therefore, implementable measures to reduce exposure to chemicals should be developed by an expert panel and their efficacy to reduce exposure in the critical time windows should be evaluated by biomonitoring. 'Environmental hygiene' is proposed, next to regulation, as a global strategy to effectively protect pregnant women, unborn children and infants against chemical exposure (Bourguignon et al., 2018).

For the future there is a growing concern for diffuse chemical pollution. Thus, one needs to develop solutions to mitigate the health risks from particular chemicals as well as effects from mixtures. HBM is a useful tool for assessing the integrated exposure to complex mixtures of chemicals and geographical and temporal variations in exposure to chemicals. Such EU harmonized data are useful for risk assessment and risk mitigation and should be complemented with high quality etiological research and intervention studies.

List of abbreviations

Abbreviation	Name	Reference
AChE	AcetylCholinestEsterase	
ADHD	Attention Deficit Hyperactivity Disorder	
ADI	Acceptable Daily Intake	
AL	Acute leukaemia	
ALL	Acute lymphoblastic leukaemia	
AML	Acute myeloid leukaemia	
ANEC	European consumer voice in standardisation	
ANSES	French Agency for Food, Environmental and Occupational Health and Safety	https://www.anses.fr/en
AOEL	Adverse Observed Effect Level	
AOP	Adverse Outcome Pathway	
ARfD	Acute Reference Dose	
ARS	ADHD Rating Scale IV	
As	Arsenic	
ASD	Autism Spectrum Disorder	
ASGM	Artisanal and Small Scale Gold Mining	
ATSDR	Agency for Toxic Substances and Disease Registry	www.atsdr.cdc.gov/index.html
Ba	Barium	
BBzP	Butyl Benzyl Phthalate	
3-BC	3-benzylidene camphor	
BDNF	Brain-derived neurotrophic factor	
BE	Biomonitoring Equivalent	
BFRs	Brominated Flame retardants	
BiPr	Biocidal product	
BMI	Body mass index	
BP	Benzophenone	
BPA	Bisphenol A	
BPF	Bisphenol F	
BPS	Bisphenol S	
BSID-III	Bayley Scales of Infant and Toddler Development, third edition	
bw	Body Weight	
Carc	Carcinogenic	
CBT	Childhood brain tumour	
Cd	Cadmium	
CDC	U.S. Centers for Disease Control and Prevention	www.cdc.gov/index.htm
CEN	Comité Européen de Normalisation	
CFRs	Chlorinated Flame retardants	
CI	Confidence interval	

Abbreviation	Name	Reference
CLP	Classification, Labelling and Packaging of substances and mixtures	
Cr(VI)	Hexavalent Chromium	
DALYs	Disability-Adjusted Life Years	
DAT	Dopamine transporter	
DEHP	Di(2-ethylhexyl)Phthalate	
DNA	Deoxyribonucleic acid	
EC	European Commission	
ECF	Electrochemical fluorination	
ECHA	European Chemicals Agency	https://echa.europa.eu/
ED	Endocrine Disruptor	
EEA	European Environment Agency	www.eea.europa.eu
EFSA	European Food Safety Agency	www.efsa.europa.eu/en
eGFR	Estimated glomerular filtration rate	
ETC HE	European Topic Centre on Human Health and the Environment	www.eionet.europa.eu/etcs/etc-he
EU	European Union	
FAO	Food and Agriculture Organisation	www.fao.org/home/en
FDA	U.S. Food and Drug Administration	www.fda.gov/
FRs	Flame retardants	
FSH	Follicle stimulating hormone	
GerES V	German Environmental Survey for Children and Adolescents 2014-2017	https://www.umweltbundesamt.de/en/topics/health/assessing-environmentally-related-health-risks/german-environmental-surveys/german-environmental-survey-2014-2017-geres-v#undefined
GM	Geometric mean	
GnRH	Gonadotropin releasing hormone	
GRADE	Grading of recommendations, assessment, development and evaluation	
HBM	Human biomonitoring	
HBM4EU	Human Biomonitoring for Europe	www.hbm4eu.eu/
HBM-GV	Human biomonitoring guidance value	
Hg	Mercury	
HMW	High Molecular Weight Phthalates	
HPG	Hypothalamic-pituitary-gonadal	
4-OH-BP	4-Hydroxy-benzophenone	
IARC	International Agency for Research on Cancer	www.iarc.who.int/
IPCS	International Programme on Chemical Safety	
IQ	Intelligence quotient	

Abbreviation	Name	Reference
IRAC	Insecticide Resistance Action Committee	https://irac-online.org/
JECFA	Joint Expert Panel of the FAO and WHO	www.who.int/groups/joint-fao-who-expert-committee-on-food-additives-(jecfa)/about
JMPR	Joint Meeting on Pesticides Residues	
L	Litre	
LH	Luteinizing hormone	
LMW	Low Molecular Weight Ortho-Phthalates	
m	Metre	
4-MBP	4-Methyl-benzophenone	
4-MBC	4-Methyl-benzylidene camphor	
MoA	Mode of Action	
NHANES	National Health and Nutrition Examination Survey	
Ni	Nickel	
OECD	Organisation for Economic Cooperation and Development	www.oecd.org/
OPFRs	Organophosphorus Flame retardants	
PAHs	Polycyclic Aromatic Hydrocarbons	
PARC	Partnership for the Assessment of Risks from Chemicals	www.eu-parc.eu/
Pb	Lead	
3-PBA	3-PhenoxyBenzoic Acid	
PFAS	Per/Polyfluorinated Alkyl Substances	
PFCA	Perfluoroalkyl carboxylic acids	
PFOA	Perfluorooctanoic acid	
PFOS	Perfluorooctane sulfonic acid	
PFSA	Perfluoroalkyl sulfonic acids	
POPs	Persistant Organic Pollutants	
PPP	Plant Protection Product	
PVC	Polyvinyl Chloride	
REACH	Registration, Evaluation, Authorisation and Restriction of Chemicals	https://environment.ec.europa.eu/topics/chemicals/reach-regulation_en
Sb	Antimony	
SCCS	Scientific Committee on Consumer Safety	https://health.ec.europa.eu/scientific-committees/scientific-committee-consumer-safety-sccs_en
Se	Selenium	
SGA	Small for Gestational Age	
SIN	Substitute it now	
TDI	Tolerable Daily Intake	
TH	Thyroid hormone	
TWI	Tolerable weekly intake	
UNICEF	United Nations Children's Fund	www.unicef.org/

Abbreviation	Name	Reference
UNEP	United Nations Environment Programme	www.unep.org/
US-EPA	United States – Environmental Protection Agency	www.epa.gov/
UV	Ultraviolet	
VGSC	Voltage-Gated Sodium Channel	
WHO	World Health Organization	www.who.int/
µg	Microgram	

References

Abdel-Shafy, H. I. and Mansour, M. S. M., 2016, 'A review on polycyclic aromatic hydrocarbons: Source, environmental impact, effect on human health and remediation', *Egyptian Journal of Petroleum* 25(1), pp. 107-123 (DOI: 10.1016/j.ejpe.2015.03.011).

Abreu-Villaça, Y. and Levin, E. D., 2017, 'Developmental neurotoxicity of succeeding generations of insecticides', *Environment International* 99, pp. 55-77 (DOI: 10.1016/j.envint.2016.11.019).

Agency for Toxic Substances and Disease Registry (ATSDR), 1995, *Toxicological Profile for Polycyclic Aromatic Hydrocarbons*, Atlanta (https://www.atsdr.cdc.gov/ToxProfiles/tp69.pdf).

Agency for Toxic Substances and Disease Registry (ATSDR), 2003, *Toxicological profile for Pyrethrins and Pyrethroids.*, U.S. Department of Health and Human Services, Public Health Service., Atlanta, GA (https://www.atsdr.cdc.gov/toxprofiles/tp155.pdf) accessed 8 May 2023.

Agency for Toxic Substances and Disease Registry (ATSDR), 2007, *Toxicological Profile for Arsenic*, U.S. Department of Health and Human Services, Public Health Service, Atlanta (https://www.atsdr.cdc.gov/ToxProfiles/tp2.pdf).

Agency for Toxic Substances and Disease Registry (ATSDR), 2012a, *Toxicological Profile for Acrylamide*, U.S. Department of Health and Human Services, Public Health Service, Atlanta (https://www.atsdr.cdc.gov/ToxProfiles/tp203.pdf).

Agency for Toxic Substances and Disease Registry (ATSDR), 2012b, *Toxicological Profile for Cadmium*, U.S. Department of Health and Human Services, Public Health Service, Atlanta.

Agency for Toxic Substances and Disease Registry (ATSDR), 2012c, *Toxicological Profile for Chromium*, U.S. Department of Health and Human Services, Public Health Service, Atlanta.

Agency for Toxic Substances and Disease Registry (ATSDR), 2016, *Addendum to the Toxicological Profile for Arsenic*, U.S. Department of Health and Human Services, Public Health Service, Atlanta (https://www.atsdr.cdc.gov/toxprofiles/Arsenic_addendum.pdf).

Agency for Toxic Substances and Disease Registry (ATSDR), 2020, *Toxicological Profile for Lead* (https://wwwn.cdc.gov/TSP/ToxProfiles/ToxProfiles.aspx?id=96&tid=22).

Agency for Toxic Substances and Disease Registry (ATSDR), 2022a, 'PFAS chemical exposure' (https://www.atsdr.cdc.gov/pfas/health-effects/exposure.html) accessed 18 August 2023.

Agency for Toxic Substances and Disease Registry (ATSDR), 2022b, *Toxicological profile for Di(2-ethylhexyl)phthalate (DEHP)*, Atlanta.

Agency for Toxic Substances and Disease Registry (ATSDR), 2022c, *Toxicological Profile for Mercury (Draft for Public Comment)*, U.S. Department of Health and Human Services, Public Health Service, Atlanta (https://www.atsdr.cdc.gov/ToxProfiles/tp46.pdf).

Aguiar, T. R., et al., 2015, 'Riparian buffer zones as pesticide filters of no-till crops', *Environmental Science and Pollution Research* 22(14), pp. 10618-10626 (DOI: 10.1007/s11356-015-4281-5).

Andersen, H. R., et al., 2022, 'Pyrethroids and developmental neurotoxicity - A critical review of epidemiological studies and supporting mechanistic evidence', *Environmental Research* 214(Pt 2), p. 113935 (DOI: 10.1016/j.envres.2022.113935).

ANEC, 2021, 'Toy Safety Directive evaluation and Chemicals Strategy for Sustainability (CSS): Which way forward?' (https://anec.eu/images/Publications/position-papers/Child/ANEC-CHILD-2021-G-055.pdf).

ANEC, 2023, 'Child Safety' (https://www.anec.eu/priorities/child-safety) accessed 20 March 2023.

Apel, P., et al., 2020, 'Human biomonitoring initiative (HBM4EU) - Strategy to derive human biomonitoring guidance values (HBM-GVs) for health risk assessment', *International Journal of Hygiene and Environmental Health* 230, p. 113622 (DOI: 10.1016/j.ijheh.2020.113622).

Attina, T. M. and Trasande, L., 2013, 'Economic Costs of Childhood Lead Exposure in Low- and Middle-Income Countries', *Environmental Health Perspectives* 121(9), pp. 1097-1102 (DOI: 10.1289/ehp.1206424).

Aylward, L. L., et al., 2018, 'Screening-level Biomonitoring Equivalents for tiered interpretation of urinary 3-phenoxybenzoic acid (3-PBA) in a risk assessment context', *Regulatory Toxicology and Pharmacology* 92, pp. 29-38 (DOI: 10.1016/j.yrtph.2017.11.002).

Bailey, H. D., et al., 2015, 'Home pesticide exposures and risk of childhood leukemia: Findings from the childhood leukemia international consortium', *International Journal of Cancer* 137(11), pp. 2644-2663 (DOI: 10.1002/ijc.29631).

Balicco, A., et al., 2019, *Imprégnation de la population française par les bisphénols A, S et F*, Programme national de biosurveillance, Esteban 2014-2016 No 2609-2174, Santé publique France.

Barceloux, D. G., 1999, 'Chromium', *Journal of Toxicology: Clinical Toxicology* 37(2), pp. 173-194 (DOI: 10.1081/CLT-100102418).

Barnes, J. H., et al., 2019, 'Emissions vs exposure: Increasing injustice from road traffic-related air pollution in the United Kingdom', *Transportation Research Part D: Transport and Environment* 73, pp. 56-66 (DOI: 10.1016/j.trd.2019.05.012).

Barr, D. B., et al., 2010, 'Urinary Concentrations of Metabolites of Pyrethroid Insecticides in the General U.S. Population: National Health and Nutrition Examination Survey 1999–2002', *Environmental Health Perspectives* 118(6), pp. 742-748 (DOI: 10.1289/ehp.0901275).

Bauer, J. A., et al., 2020, 'Associations of metals and neurodevelopment: a review of recent evidence on susceptibility factors', *Current epidemiology reports* 7(4), pp. 237-262 (DOI: 10.1007/s40471-020-00249-y).

Bauer-Babef, 2022, EURACTIV: European Commission urged to eliminate chemicals in toxic nappies, (https://www.euractiv.com/section/chemicals/news/european-commission-urged-to-eliminate-chemicals-in-toxic-nappies/).

Bergman, Å., et al., 2013, *State of the science of endocrine disrupting chemicals 2012*, World Health Organization.

Bernardina Dalla, M. D., et al., 2022, 'Environmental pollution and attention deficit hyperactivity disorder: A meta-analysis of cohort studies', *Environmental Pollution* 315, p. 120351 (DOI: 10.1016/j.envpol.2022.120351).

Bienkowski, B., 2023, 'Europe seeks drastic cut to BPA exposure'.

Bigambo, F. M., et al., 2020, 'Association between phenols exposure and earlier puberty in children: A systematic review and meta-analysis', *Environmental Research* 190, p. 110056 (DOI: 10.1016/j.envres.2020.110056).

Blade, L. M., et al., 2007, 'Hexavalent Chromium Exposures and Exposure-Control Technologies in American Enterprise: Results of a NIOSH Field Research Study', *Journal of Occupational and Environmental Hygiene* 4(8) (DOI: 10.1080/15459620701463183).

Bocca, B., et al., 2018, 'Hexavalent chromium in tattoo inks: Dermal exposure and systemic risk', *Contact Dermatitis* 79(4), pp. 218-225 (DOI: https://doi.org/10.1111/cod.13051).

Bocca, B., et al., 2019, 'Human biomonitoring to evaluate exposure to toxic and essential trace elements during pregnancy. Part A. concentrations in maternal blood, urine and cord blood.', *Environmental Research* 177, p. 108599 (DOI: 10.1016/j.envres.2019.108599).

Bourguignon, J.-P., et al., 2018, 'Rationale for Environmental Hygiene towards global protection of fetuses and young children from adverse lifestyle factors', *Environmental Health* 17(1), p. 42 (DOI: 10.1186/s12940-018-0385-y).

Brander, S. M., et al., 2016, 'Pyrethroid Pesticides as Endocrine Disruptors: Molecular Mechanisms in Vertebrates with a Focus on Fishes', *Environmental Science & Technology* 50(17), pp. 8977-8992 (DOI: 10.1021/acs.est.6b02253).

Braun, J. M., et al., 2009, 'Prenatal bisphenol A exposure and early childhood behavior', *Environ Health Perspect* 117(12), pp. 1945-1952 (DOI: 10.1289/ehp.0900979).

Caglieri, A., et al., 2006, 'The Effect of Inhaled Chromium on Different Exhaled Breath Condensate Biomarkers among Chrome-Plating Workers', *Environmental Health Perspectives* 114(4), pp. 542-546 (DOI: 10.1289/ehp.8506).

Calafat, A. M., et al., 2008, 'Exposure of the U.S. population to bisphenol A and 4-tertiary-octylphenol: 2003-2004', *Environ Health Perspect* 116(1), pp. 39-44 (DOI: 10.1289/ehp.10753).

Cao, T., et al., 2021, 'The relationship between maternal perfluoroalkylated substances exposure and low birth weight of offspring: a systematic review and meta-analysis', *Environmental Science and Pollution Research* 28(47), pp. 67053-67065 (DOI: 10.1007/s11356-021-15061-4).

Caparros-Gonzalez, R. A., et al., 2019, 'Childhood chromium exposure and neuropsychological development in children living in two polluted areas in southern Spain', *Environmental Pollution (Barking, Essex: 1987)* 252(Pt B), pp. 1550-1560 (DOI: 10.1016/j.envpol.2019.06.084).

Castiello, F., et al., 2023, 'Childhood exposure to non-persistent pesticides and pubertal development in Spanish girls and boys: Evidence from the INMA (Environment and Childhood) cohort', *Environmental Pollution* 316, p. 120571 (DOI: 10.1016/j.envpol.2022.120571).

Castiello, F. and Freire, C., 2021, 'Exposure to non-persistent pesticides and puberty timing: a systematic review of the epidemiological evidence', *European Journal of Endocrinology* 184(6), pp. 733-749 (DOI: 10.1530/EJE-20-1038).

Castorina, R., et al., 2017, 'Current-Use Flame Retardants: Maternal Exposure and Neurodevelopment in Children of the CHAMACOS cohort', *Chemosphere* 189, pp. 574-580 (DOI: 10.1016/j.chemosphere.2017.09.037).

Castro, A., et al., 2022, 'Environmental health risks to children and adolescents: an umbrella review on indoor and outdoor air pollution', *European Topic Centre on Human Health and the Environment* Eionet Report – ETC HE 2022/22.

Centers for Disease Control and Prevention, 2012, *CDC response to Advisory Committee on Childhood Lead Poisoning Prevention. Recommendations in "Low level lead exposure harms children: A renewed call for primary prevention"*., Atlanata, GA (https://www.cdc.gov/nceh/lead/acclpp/cdc_response_lead_exposure_recs.pdf).

Centers for Disease Control and Prevention U.S. (CDC), 2020, 'Thimerosal and Vaccines - Vaccine Safety' (https://www.cdc.gov/vaccinesafety/concerns/thimerosal/index.html) accessed 27 September 2023.

Centers for Disease Control and Prevention U.S. (CDC), 2021, 'Acrylamide Factsheet' (https://www.cdc.gov/biomonitoring/Acrylamide_FactSheet.html) accessed 19 September 2023.

Chambers, W. S., et al., 2021, 'A Review of Per- and Polyfluorinated Alkyl Substance Impairment of Reproduction', *Frontiers in Toxicology* 3.

Chen, M., et al., 2015, 'Residential Exposure to Pesticide During Childhood and Childhood Cancers: A Meta-Analysis', *Pediatrics* 136(4), pp. 719-729 (DOI: 10.1542/peds.2015-0006).

Chevrier, J., et al., 2010, 'Polybrominated Diphenyl Ether (PBDE) Flame Retardants and Thyroid Hormone during Pregnancy', *Environmental Health Perspectives* 118(10), pp. 1444-1449 (DOI: 10.1289/ehp.1001905).

Choi, H., et al., 2006, 'International Studies of Prenatal Exposure to Polycyclic Aromatic Hydrocarbons and Fetal Growth', *Environmental Health Perspectives* 114(11), pp. 1744-1750 (DOI: 10.1289/ehp.8982).

Choi, H., et al., 2008, 'Prenatal Exposure to Airborne Polycyclic Aromatic Hydrocarbons and Risk of Intrauterine Growth Restriction', *Environmental Health Perspectives* 116(5), pp. 658-665 (DOI: 10.1289/ehp.10958).

Chupeau, Z., et al., 2020, 'Organophosphorus Flame Retardants: A Global Review of Indoor Contamination and Human Exposure in Europe and Epidemiological Evidence', *International Journal of Environmental Research and Public Health* 17(18), p. 6713 (DOI: 10.3390/ijerph17186713).

Coperchini, F., et al., 2021, 'Thyroid Disrupting Effects of Old and New Generation PFAS', *Frontiers in Endocrinology* 11, p. 612320 (DOI: 10.3389/fendo.2020.612320).

Crawford, L., et al., 2023, 'Systematic review and meta-analysis of epidemiologic data on vaccine response in relation to exposure to five principal perfluoroalkyl substances', *Environment International* 172, p. 107734 (DOI: 10.1016/j.envint.2023.107734).

Cui, X., et al., 2018, 'Cadmium exposure and early renal effects in the children and adults living in a tungsten-molybdenum mining areas of South China', *Environmental Science and Pollution Research International* 25(15), pp. 15089-15101 (DOI: 10.1007/s11356-018-1631-0).

Czerska, M., et al., 2013, 'Effects of polybrominated diphenyl ethers on thyroid hormone, neurodevelopment and fertility in rodents and humans', *International Journal of Occupational Medicine and Environmental Health* 26(4), pp. 498-510 (DOI: 10.2478/s13382-013-0138-7).

Dagorn, G., et al., 2023, '"Forever pollution": Explore the map of Europe's PFAS contamination', *Le Monde.fr*, 23 February 2023 (https://www.lemonde.fr/en/les-decodeurs/article/2023/02/23/forever-pollution-explore-the-map-of-europe-s-pfas-contamination_6016905_8.html) accessed 10 May 2023.

Danish Environmental Protection Agency, 2018, *Substance evaluation conclusion as required by REACH Article 48 and evaluation report for benzophenone* (https://echa.europa.eu/documents/10162/5a195cc0-82f3-cd0a-8fa3-65c400911515) accessed 30 July 2023.

De Boer, J. and Stapleton, H. M., 2019, 'Toward fire safety without chemical risk', *Science* 364(6437), pp. 231-232 (DOI: 10.1126/science.aax2054).

Demirtepe, H., et al., 2019, 'Linking past uses of legacy SVOCs with today's indoor levels and human exposure', *Environment International* 127, pp. 653-663 (DOI: 10.1016/j.envint.2019.04.001).

Den Braver-Sewradj, S. P., et al., 2020, 'Substitution of bisphenol A: a review of the carcinogenicity, reproductive toxicity, and endocrine disruption potential of alternative substances', *Critical Reviews in Toxicology* 50(2), pp. 128-147 (DOI: 10.1080/10408444.2019.1701986).

Di Giovanni, P., et al., 2020, 'Arsenic Exposure and Risk of Urothelial Cancer: Systematic Review and Meta-Analysis', *International Journal of Environmental Research and Public Health* 17(9), p. 3105 (DOI: 10.3390/ijerph17093105).

Ding, G., et al., 2012, 'Pyrethroid pesticide exposure and risk of childhood acute lymphocytic leukemia in Shanghai', *Environmental Science & Technology* 46(24), pp. 13480-13487 (DOI: 10.1021/es303362a).

Dishaw, L. V., et al., 2011, 'Is the PentaBDE replacement, tris (1,3-dichloro-2-propyl) phosphate (TDCPP), a developmental neurotoxicant? Studies in PC12 cells', *Toxicology and Applied Pharmacology* 256(3), pp. 281-289 (DOI: 10.1016/j.taap.2011.01.005).

Dodson, R. E., et al., 2017, 'Flame Retardant Chemicals in College Dormitories: Flammability Standards Influence Dust Concentrations', *Environmental Science & Technology* 51(9), pp. 4860-4869 (DOI: 10.1021/acs.est.7b00429).

Dong, X., et al., 2023, 'Placental Barrier on Cadmium Transfer from Mother to Fetus in Related to Pregnancy Complications', *International Journal of Women's Health* 15, pp. 179-190 (DOI: 10.2147/IJWH.S393067).

Dórea, J. G., et al., 2013, 'Toxicity of ethylmercury (and Thimerosal): a comparison with methylmercury', *Journal of applied toxicology: JAT* 33(8), pp. 700-711 (DOI: 10.1002/jat.2855).

Dourson, M., et al., 2004, 'Differential Sensitivity of Children and Adults to Chemical Toxicity', *Human and Ecological Risk Assessment: An International Journal* 10(1), pp. 21-27 (DOI: 10.1080/10807030490280927).

EFSA Panel on Contaminants in the Food Chain (CONTAM), 2010, 'Scientific Opinion on Lead in Food', *EFSA Journal* 8(4), p. 1570 (DOI: 10.2903/j.efsa.2010.1570).

EFSA Panel on Food Contact Materials Enzymes and Processing Aids, et al., 2023, 'Re-evaluation of the risks to public health related to the presence of bisphenol A (BPA) in foodstuffs', *EFSA Journal* 21(4), p. e06857 (DOI: https://doi.org/10.2903/j.efsa.2023.6857).

EFSA Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids (CEF), 2015, 'Scientific Opinion on the risks to public health related to the presence of bisphenol A (BPA) in foodstuffs', *EFSA Journal* 13(1), p. 3978 (DOI: 10.2903/j.efsa.2015.3978).

EFSA Panel on Contaminants in the Food Chain (EFSA CONTAM Panel), et al., 2020, 'Risk to human health related to the presence of perfluoroalkyl substances in food', *EFSA Journal* 18(9) (DOI: 10.2903/j.efsa.2020.6223).

EFSA Panel on Food Contact Materials, E., Flavourings and Processing Aids (CEF), et al., 2017, 'Safety of benzophenone to be used as flavouring', *EFSA Journal* 15(11), p. e05013 (DOI: 10.2903/j.efsa.2017.5013).

Ehrlich, V., et al., 2023, 'Consideration of pathways for immunotoxicity of per- and polyfluoroalkyl substances (PFAS)', *Environmental Health* 22(1), p. 19 (DOI: 10.1186/s12940-022-00958-5).

Ejaredar, M., et al., 2015, 'Phthalate exposure and childrens neurodevelopment: A systematic review', *Environmental Research* 142, pp. 51-60 (DOI: 10.1016/j.envres.2015.06.014).

Ejaredar, M., et al., 2017, 'Bisphenol A exposure and children's behavior: A systematic review', *J Expo Sci Environ Epidemiol* 27(2), pp. 175-183 (DOI: 10.1038/jes.2016.8).

Elser, B. A., et al., 2022, 'A narrative review of converging evidence addressing developmental toxicity of pyrethroid insecticides', *Critical Reviews in Toxicology* 52(5), pp. 371-388 (DOI: 10.1080/10408444.2022.2122769).

Eskenazi, B., et al., 2018, 'Prenatal Exposure to DDT and Pyrethroids for Malaria Control and Child Neurodevelopment: The VHEMBE Cohort, South Africa', *Environmental Health Perspectives* 126(4), p. 047004 (DOI: 10.1289/EHP2129).

Estill, C. F., et al., 2020, 'Worker exposure to flame retardants in manufacturing, construction and service industries', *Environment International* 135, p. 105349 (DOI: 10.1016/j.envint.2019.105349).

EU, 2004, EU standard EN 14372.

EU, 2022, Directive 2009/48/EC of the European Parliament and of the Council - on the safety of toys, (https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:02009L0048-20221205).

European Chemicals Agency (ECHA), 2016a, *Proposal for a restriction: four phthlates (DEHP, BBP, DBP, DIBP) - Annex XV restriction report*, Helsinki.

European Chemicals Agency (ECHA), 2016b, Substances restricted under REACH, entry Nr.51 - Diisobutyl phthalate (DIBP); Dibutyl phthalate (DBP); Benzyl butyl phthalate (BBP); Bis(2-ethylhexyl) phthalate (DEHP), (https://echa.europa.eu/documents/10162/aaa92146-a005-1dc2-debe-93c80b57c5ee) accessed 16 September 2023.

European Chemicals Agency (ECHA), 2016c, Substances restricted under REACH, entry Nr.52 - Di-'isononyl' phthalate (DINP) Di-'isodecyl' phthalate (DIDP) Di-n-octyl phthalate (DNOP), (https://echa.europa.eu/documents/10162/0923c10f-5495-16ee-5c0f-dd3613fbde6d) accessed 16 September 2023.

European Chemicals Agency (ECHA), 2022, 'Substance Information - Chromium (VI)' (https://echa.europa.eu/substance-information/-/substanceinfo/100.132.559) accessed 24 May 2023.

European Chemicals Agency (ECHA), 2023a, 'Benzophenone', Brief Profile (https://echa.europa.eu/de/brief-profile/-/briefprofile/100.003.943) accessed 23 May 2023.

European Chemicals Agency (ECHA), 2023b, 'Perfluoralkylchemikalien (PFAS)' (https://echa.europa.eu/de/hot-topics/perfluoroalkyl-chemicals-pfas) accessed 24 November 2023.

European Chemicals Agency (ECHA), 2023c, 'Restriction proposal Per- and polyfluoroalkyl substances (PFAS)' (https://echa.europa.eu/registry-of-restriction-intentions/-/dislist/details/0b0236e18663449b) accessed 12 September 2023.

European Chemicals Agency (ECHA), 2023d, 'Substance Information - Acrylamide' (https://echa.europa.eu/substance-information/-/substanceinfo/100.001.067) accessed 19 September 2023.

European Chemicals Agency (ECHA), 2023e, 'Substance Information - Cadmium' (https://echa.europa.eu/substance-information/-/substanceinfo/100.028.320?_disssubsinfo_WAR_disssubsinfoportlet_backURL=https%3A%2F%2Fecha.europa.eu%2Fhome%3Fp_p_id%3Ddisssimplesearchhomepage_WAR_disssearchportlet%26p_p_lifecycle%3D0%26p_p_state%3Dnormal%26p_p_mode%3Dview%26_disssimplesearchhomepage_WAR_disssearchportlet_sessionCriteriaId%3D) accessed 8 May 2023.

European Chemicals Agency (ECHA), 'Phthalates' (https://echa.europa.eu/hot-topics/phthalates) accessed 16 September 2023.

European Commission, 2009, 'Toy Safety Directive 2009/48/EC' (https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A02009L0048-202212052009/48/EC).

European Commission, 2011, *COMMISSION DIRECTIVE 2011/8/EU of 28 January 2011 amending Directive 2002/72/EC as regards the restriction of use of Bisphenol A in plastic infant feeding bottles*.

European Commission, 2020, *COMMUNICATION FROM THE COMMISSION TO THE EUROPEAN PARLIAMENT, THE COUNCIL, THE EUROPEAN ECONOMIC AND SOCIAL COMMITTEE AND THE COMMITTEE OF THE REGIONS - Chemicals Strategy for Sustainability Towards a Toxic-Free Environment*, No COM(2020) 667 final (https://eur-lex.europa.eu/resource.html?uri=cellar:f815479a-0f01-11eb-bc07-01aa75ed71a1.0003.02/DOC_1&format=PDF).

European Commission, 2021a, *Commission Regulation (EU) 2021/57 of 25 January 2021 amending Annex XVII to Regulation (EC) No 1907/2006 of the European Parliament and of the Council concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) as regards lead in gunshot in or around wetlands*.

European Commission, 2021b, 'Statement by President von der Leyen on delivering the European Green Deal' (https://ec.europa.eu/commission/presscorner/detail/en/statement_21_3701) accessed 22 September 2023.

European Commission, 2022, 'Safety of children's products (excluding toys) - requirements to be met by European standards', European Commission - Have your say (https://ec.europa.eu/info/law/better-regulation/have-your-say/initiatives/12841-Safety-of-childrens-products-excluding-toys-requirements-to-be-met-by-European-standards_en) accessed 25 May 2023.

European Commission, 2023, 'New rules banning hunting birds with lead shot in wetlands take full effect' (https://environment.ec.europa.eu/news/new-rules-banning-hunting-birds-lead-shot-wetlands-take-full-effect-2023-02-16_en) accessed 23 November 2023.

European Commission and Directorate-General for Health and Food Safety, 2022, Proposal for a REGULATION OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL on the sustainable use of plant protection products and amending Regulation (EU) 2021/2115.

European Environment Agency, 2019, 'Emerging chemical risks in Europe — "PFAS"' (https://www.eea.europa.eu/publications/emerging-chemical-risks-in-europe) accessed 9 August 2023.

European Environment Agency, 2023a, How pesticides impact human health and ecosystems in Europe, (https://www.eea.europa.eu/publications/how-pesticides-impact-human-health) accessed 26 April 2023, European Environment Agency.

European Environment Agency, 2023b, 'Reducing children's exposure to pesticides by providing organic food in Cypriot schools' (https://www.eea.europa.eu/publications/how-pesticides-impact-human-health/reducing-childrens-exposure-to-pesticides).

European Food Safety Authority (EFSA), 2008, 'Polycyclic Aromatic Hydrocarbons in Food - Scientific Opinion of the Panel on Contaminants in the Food Chain', *EFSA Journal* 6(8), p. 724 (DOI: 10.2903/j.efsa.2008.724).

European Food Safety Authority (EFSA), 2011, 'Statement on tolerable weekly intake for cadmium', *EFSA Journal* 9(2), p. 1975 (DOI: 10.2903/j.efsa.2011.1975).

European Food Safety Authority (EFSA), 2012, 'Cadmium dietary exposure in the European population', *EFSA Journal* (2012;10(1):2551) (DOI: 10.2903/j.efsa.2012.2551).

European Food Safety Authority (EFSA), 2014, 'Dietary exposure to inorganic arsenic in the European population', *EFSA Journal* 12(3), p. 3597 (DOI: 10.2903/j.efsa.2014.3597).

European Food Safety Authority (EFSA), 2015, 'Scientific Opinion on acrylamide in food', *EFSA Journal* 13(6) (DOI: 10.2903/j.efsa.2015.4104).

European Food Safety Authority (EFSA), 2022, 'Assessment of the genotoxicity of acrylamide', *EFSA Journal* 20(5) (DOI: 10.2903/j.efsa.2022.7293).

Eurostat, 2019, 'More than 95% of children in the EU considered to be in good or very good health',.

Eurostat, 2023a, 'EU sales of pesticides rebounded in 2021' (https://ec.europa.eu/eurostat/web/products-eurostat-news/w/ddn-20230510-1) accessed 15 August 2023.

Eurostat, 2023b, 'Pesticide sales', Statistics | Eurostat (https://ec.europa.eu/eurostat/databrowser/view/AEI_FM_SALPEST09__custom_5991627/bookmark/table?lang=en&bookmarkId=3b608819-8ad3-4068-b04d-c1d5b6052a58) accessed 9 May 2023.

Farzan, S. F., et al., 2013, 'In utero and early life arsenic exposure in relation to long-term health and disease', *Toxicology and applied pharmacology* 272(2), pp. 384-390 (DOI: 10.1016/j.taap.2013.06.030).

Feiteiro, J., et al., 2021, 'Health toxicity effects of brominated flame retardants: From environmental to human exposure', *Environmental Pollution* 285, p. 117475 (DOI: 10.1016/j.envpol.2021.117475).

Fenton, S. E., et al., 2021, 'Per- and Polyfluoroalkyl Substance Toxicity and Human Health Review: Current State of Knowledge and Strategies for Informing Future Research', *Environmental toxicology and chemistry* 40(3), pp. 606-630 (DOI: 10.1002/etc.4890).

Ferreira, J. D., et al., 2013, 'In Utero Pesticide Exposure and Leukemia in Brazilian Children < 2 Years of Age', *Environmental Health Perspectives* 121(2), pp. 269-275 (DOI: 10.1289/ehp.1103942).

Fivenson, D., et al., 2021, 'Sunscreens: UV filters to protect us: Part 2-Increasing awareness of UV filters and their potential toxicities to us and our environment', *International Journal of Women's Dermatology* 7(1), pp. 45-69 (DOI: 10.1016/j.ijwd.2020.08.008).

Fluegge, K. R., et al., 2016, 'Effects of simultaneous prenatal exposures to organophosphate and synthetic pyrethroid insecticides on infant neurodevelopment at three months of age', *Journal of environmental toxiology and public health* 1, pp. 60-73 (DOI: 10.5281/zenodo.218417).

Frederiksen, H., et al., 2013, 'Urinary excretion of phthalate metabolites, phenols and parabens in rural and urban Danish mother–child pairs', *International Journal of Hygiene and Environmental Health* 216(6), pp. 772-783 (DOI: 10.1016/j.ijheh.2013.02.006).

Furlong, M. A., et al., 2017, 'Prenatal Exposure to Pyrethroid Pesticides and Childhood Behavior and Executive Functioning', *Neurotoxicology* 62, pp. 231-238 (DOI: 10.1016/j.neuro.2017.08.005).

Gao, H., et al., 2021a, 'Association between phthalate exposure and insulin resistance: a systematic review and meta-analysis update', *Environmental Science and Pollution Research* 28(40), pp. 55967-55980 (DOI: 10.1007/s11356-021-16252-9).

Gao, X., et al., 2021b, 'Per- and polyfluoroalkyl substances exposure during pregnancy and adverse pregnancy and birth outcomes: A systematic review and meta-analysis', *Environmental Research* 201, p. 111632 (DOI: 10.1016/j.envres.2021.111632).

Gao, X.-X., et al., 2023, 'Association between prenatal exposure to per- and polyfluoroalkyl substances and neurodevelopment in children: Evidence based on birth cohort', *Environmental Research* 236(Pt 2), p. 116812 (DOI: 10.1016/j.envres.2023.116812).

Ghassabian, A., et al., 2022, 'Endocrine-Disrupting Chemicals and Child Health', *Annual Review of Pharmacology and Toxicology* 62(1), pp. 573-594 (DOI: 10.1146/annurev-pharmtox-021921-093352).

Gibb, H. J., et al., 2000, 'Clinical findings of irritation among chromium chemical production workers', *American Journal of Industrial Medicine* 38(2), pp. 127-131 (DOI: 10.1002/1097-0274(200008)38:2<127::AID-AJIM2>3.0.CO;2-Q).

Gibb, H. J., et al., 2019, 'Estimates of the 2015 global and regional disease burden from four foodborne metals – arsenic, cadmium, lead and methylmercury', *Environmental Research* 174, pp. 188-194 (DOI: 10.1016/j.envres.2018.12.062).

Ginsberg, G., et al., 2016, 'Approaches to Children's Exposure Assessment: Case Study with Diethylhexylphthalate (DEHP)', *International Journal of Environmental Research and Public Health* 13(7), p. 670 (DOI: 10.3390/ijerph13070670).

Golestanzadeh, M., et al., 2019, 'Association of exposure to phthalates with cardiometabolic risk factors in children and adolescents: a systematic review and meta-analysis', *Environmental Science and Pollution Research* 26(35), pp. 35670-35686 (DOI: 10.1007/s11356-019-06589-7).

Gore, A. C., et al., 2015, 'EDC-2: The Endocrine Society's Second Scientific Statement on Endocrine-Disrupting Chemicals', *Endocrine Reviews* 36(6), pp. E1-E150 (DOI: 10.1210/er.2015-1010).

Gosens, I., et al., 2014, 'Aggregate exposure approaches for parabens in personal care products: a case assessment for children between 0 and 3 years old', *Journal of Exposure Science & Environmental Epidemiology* 24(2), pp. 208-214 (DOI: 10.1038/jes.2013.33).

Govarts, E., et al., 2018, 'Prenatal exposure to endocrine disrupting chemicals and risk of being born small for gestational age: Pooled analysis of seven European birth cohorts', *Environment International* 115, pp. 267-278 (DOI: 10.1016/j.envint.2018.03.017).

Govarts, E., et al., 2023, 'Harmonized human biomonitoring in European children, teenagers and adults: EU-wide exposure data of 11 chemical substance groups from the HBM4EU Aligned Studies (2014–2021)', *International Journal of Hygiene and Environmental Health* 249, p. 114119 (DOI: 10.1016/j.ijheh.2023.114119).

Grandjean, P. and Budtz-Jørgensen, E., 2013, 'Immunotoxicity of perfluorinated alkylates: calculation of benchmark doses based on serum concentrations in children', *Environmental Health* 12(1), p. 35 (DOI: 10.1186/1476-069X-12-35).

Gravel, S., et al., 2019, 'Assessment of Occupational Exposure to Organic Flame Retardants: A Systematic Review', *Annals of Work Exposures and Health* 63(4), pp. 386-406 (DOI: 10.1093/annweh/wxz012).

Grund, S. C., et al., 2008, 'Arsenic and Arsenic Compounds', in: *Ullmann's Encyclopedia of Industrial Chemistry*, Wiley.

Gui, S.-Y., et al., 2022, 'Association Between Exposure to Per- and Polyfluoroalkyl Substances and Birth Outcomes: A Systematic Review and Meta-Analysis', *Frontiers in Public Health* 10, p. 855348 (DOI: 10.3389/fpubh.2022.855348).

Hamzah, N. A., et al., 2016, 'Metal dust exposure and lung function deterioration among steel workers: an exposure-response relationship', *International Journal of Occupational and Environmental Health* 22(3), pp. 224-232 (DOI: 10.1080/10773525.2016.1207040).

Harada, M., 1978, 'Congenital Minamata disease: Intrauterine methylmercury poisoning', *Teratology* 18(2), pp. 285-288 (DOI: 10.1002/tera.1420180216).

Hays, S. M., et al., 2008, 'Guidelines for the derivation of Biomonitoring Equivalents: Report from the Biomonitoring Equivalents Expert Workshop', *Regulatory Toxicology and Pharmacology* 51(3, Supplement), pp. S4-S15 (DOI: 10.1016/j.yrtph.2008.05.004).

HBM4EU, 2016, 'Human Biomonitoring for Europe (HBM4EU) project' (https://www.hbm4eu.eu/) accessed 21 November 2023.

HBM4EU, 2020a, *Scoping document on lead* (https://www.hbm4eu.eu/wp-content/uploads/2019/03/HBM4EU_D4.9_Scoping_Documents_HBM4EU_priority_substances_v1.0-Lead.pdf).

HBM4EU, 2020b, *Scoping document on Pesticides* (https://www.hbm4eu.eu/wp-content/uploads/2019/03/HBM4EU_D4.9_Scoping_Documents_HBM4EU_priority_substances_v1.0-Pesticides.pdf) accessed 26 April 2023.

HBM4EU, 2020c, *Scoping document on UV filters*, European Human Biomonitoring Initiative (https://www.hbm4eu.eu/wp-content/uploads/2021/02/HBM4EU_D4.9_Scoping_Documents_HBM4EU_priority_substances_v1.0-UF-filters.pdf) accessed 6 June 2023.

HBM4EU, 2020d, *Scoping documents for 2021 for the first and second round HBM4EU priority substances*, HBM4EU.

HBM4EU, 2022a, 'HBM4EU Policy Brief Pesticides' (https://www.hbm4eu.eu/wp-content/uploads/2022/07/HBM4EU_Policy-Brief-Pesticides.pdf) accessed 15 August 2023.

HBM4EU, 2022b, 'HBM4EU Policy Brief PFAS' (https://www.hbm4eu.eu/wp-content/uploads/2022/06/HBM4EU_Policy-Brief-PFAS.pdf) accessed 9 August 2023.

HBM4EU, 2022c, *Substance report - Acrylamide* (https://www.hbm4eu.eu/wp-content/uploads/2022/07/Acrylamide_Substance-report.pdf).

HBM4EU, 2022d, *Substance report - Arsenic* (https://www.hbm4eu.eu/wp-content/uploads/2022/07/Arsenic_Substance-report.pdf).

HBM4EU, 2022e, *Substance report - Benzophenones* (https://www.hbm4eu.eu/wp-content/uploads/2022/07/Benzophenones_Substance-report.pdf).

HBM4EU, 2022f, *Substance report - Bisphenols* (https://www.hbm4eu.eu/wp-content/uploads/2022/07/Bisphenols_Substance-report.pdf).

HBM4EU, 2022g, *Substance report - Cadmium* (https://www.hbm4eu.eu/wp-content/uploads/2022/07/Cadmium_Substance_report.pdf).

HBM4EU, 2022h, *Substance report - Chromium VI* (https://www.hbm4eu.eu/wp-content/uploads/2022/07/ChromiumVI_Substance_report.pdf).

HBM4EU, 2022i, *Substance report - Flame retardants* (https://www.hbm4eu.eu/wp-content/uploads/2022/07/Flame-Retardants_Substance-report.pdf).

HBM4EU, 2022j, *Substance report - Lead* (https://www.hbm4eu.eu/wp-content/uploads/2022/07/Lead_Substance-report.pdf).

HBM4EU, 2022k, *Substance report - Mercury* (https://www.hbm4eu.eu/wp-content/uploads/2022/07/Mercury_Substance-report.pdf).

HBM4EU, 2022l, *Substance report - Per- and polyfluoroalkyl substances (PFAS)* (https://www.hbm4eu.eu/wp-content/uploads/2022/07/PFAS_Substance-report.pdf).

HBM4EU, 2022m, *Substance Report - Pesticides* (https://www.hbm4eu.eu/wp-content/uploads/2022/07/Pesticides_Substance-report.pdf) accessed 26 April 2023.

HBM4EU, 2022n, *Substance report - Phthalates and Hexamoll DINCH* (https://www.hbm4eu.eu/wp-content/uploads/2022/07/Phthalates_Substance-report-1.pdf).

HBM4EU, 2022o, *Substance report - Polycyclic Aromatic Hydrocarbons (PAHs)* (https://www.hbm4eu.eu/wp-content/uploads/2022/07/PAHs_Substance-report.pdf).

He, Y., et al., 2023, 'Association of perfluoroalkyl and polyfluoroalkyl substances with sex hormones in children and adolescents 6-19 Years of age', *Environmental Pollution (Barking, Essex: 1987)* 329, p. 121707 (DOI: 10.1016/j.envpol.2023.121707).

HEAL, 2022, 'Current pesticide reduction measures fail to protect vulnerable groups from pesticide pollution, new study from Italy shows' (https://www.env-health.org/current-pesticide-reduction-measures-fail-to-protect-vulnerable-groups-from-pesticide-pollution-new-study-from-italy-shows/).

Healy, B. F., et al., 2015, 'Bisphenol A exposure pathways in early childhood: Reviewing the need for improved risk assessment models', *Journal of Exposure Science & Environmental Epidemiology* 25(6), pp. 544-556 (DOI: 10.1038/jes.2015.49).

Heidari, S., et al., 2022, 'The effect of lead exposure on IQ test scores in children under 12 years: a systematic review and meta-analysis of case-control studies', *Systematic Reviews* 11(1), p. 106 (DOI: 10.1186/s13643-022-01963-y).

Herbstman, J. B., et al., 2010, 'Prenatal Exposure to PBDEs and Neurodevelopment', *Environmental Health Perspectives* 118(5), pp. 712-719 (DOI: 10.1289/ehp.0901340).

Holland, P., et al., 2000, 'Life course accumulation of disadvantage: childhood health and hazard exposure during adulthood', *Social Science & Medicine* 50(9), pp. 1285-1295 (DOI: 10.1016/S0277-9536(99)00375-5).

Howdeshell, K. L., et al., 2017, 'Cumulative effects of antiandrogenic chemical mixtures and their relevance to human health risk assessment', *International Journal of Hygiene and Environmental Health* 220(2, Part A), pp. 179-188 (DOI: 10.1016/j.ijheh.2016.11.007).

Huang, S., et al., 2019, 'The association between prenatal cadmium exposure and birth weight: A systematic review and meta-analysis of available evidence', *Environmental Pollution* 251, pp. 699-707 (DOI: https://doi.org/10.1016/j.envpol.2019.05.039).

Huo, X., et al., 2019, 'Maternal urinary metabolites of PAHs and its association with adverse birth outcomes in an intensive e-waste recycling area', *Environmental Pollution* 245, pp. 453-461 (DOI: 10.1016/j.envpol.2018.10.098).

IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, 2013, *Some chemicals present in industrial and consumer products, food and drinking-water*, IARC monographs on the evaluation of carcinogenic risks to humans No 101, International Agency for Research on Cancer (https://publications.iarc.fr/_publications/media/download/3116/9feb6c7a7913e3cb4abafc95eeb2fa4d62c72c59.pdf) accessed 22 May 2023.

Institute for Health Metrics and Evaluation, 2023, '2019 GBD Compare' (https://vizhub.healthdata.org/gbd-compare/) accessed 28 July 2023.

International Agency for Research on Cancer (IARC), 1987, *ARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Supplement 7: Overall Evaluations of Carcinogenicity: An Updating of IARC Monographs Volumes 1 to 42, IARC*, Lyon, France (https://publications.iarc.fr/Book-And-Report-Series/Iarc-Monographs-Supplements/Overall-Evaluations-Of-Carcinogenicity-An-Updating-Of-IARC-Monographs-Volumes-1%E2%80%9342-1987).

International Agency for Research on Cancer (IARC), ed., 1993, *Beryllium, cadmium, mercury and exposures in the glass manufacturing industry: this publication represents the views and expert opinions of an IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, which met in Lyon, 9-16 February 1993*, World Health Organization, Geneva.

International Agency for Research on Cancer (IARC), 1994, *Some industrial chemicals*, IARC, Lyon.

International Agency for Research on Cancer (IARC), ed., 1999, *Some chemicals that cause tumours of the kidney or urinary bladder in rodents and some other substances*, IARC, Lyon.

International Agency for Research on Cancer (IARC), 2006, *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Volume 87. Inorganic and Organic Lead Compounds* (https://publications.iarc.fr/105).

International Agency for Research on Cancer (IARC), ed., 2010, *Some non-heterocyclic polycliclic aromatic hydrocarbons and some related exposures: this publication represents the views and expert opinions of an IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, which met in Lyon, 11 - 18 October 2005*, IARC, Lyon.

International Agency for Research on Cancer (IARC), ed., 2012, *A review of human carcinogens. Part C: Arsenic, metals, fibres and dusts*, International agency for research on cancer (IARC), Lyon.

International Agency for Research on Cancer (IARC), ed., 2013, *Some chemicals present in industrial and consumer products, food and drinking-water*, International agency for research on cancer, Lyon.

International Cadmium Association, 2021, 'Cadmium applications' (https://www.cadmium.org/) accessed 9 May 2023.

International Programme on Chemical Safety (IPCS), 1998, *Selected Non-Heterocyclic Polycyclic Aromatic Hydrocarbons - Environmental Health Criteria 202*,.

Ionas, A. C., et al., 2016, 'Children's exposure to polybrominated diphenyl ethers (PBDEs) through mouthing toys', *Environment International* 87, pp. 101-107 (DOI: 10.1016/j.envint.2015.11.018).

Jaafarzadeh, N., et al., 2022, 'Arsenic in drinking water and kidney cancer: a systematic review', *Reviews on Environmental Health* (DOI: 10.1515/reveh-2021-0168).

Jameson, C. W., 2019, 'Polycyclic aromatic hydrocarbons and associated occupational exposures', in: Baan, R. A. et al. (eds), *Tumour Site Concordance and Mechanisms of Carcinogenesis*, IARC Scientific Publications, International Agency for Research on Cancer, Lyon (FR).

Jedrychowski, W. A., et al., 2015, 'Prenatal exposure to polycyclic aromatic hydrocarbons and cognitive dysfunction in children', *Environmental Science and Pollution Research International* 22(5), pp. 3631-3639 (DOI: 10.1007/s11356-014-3627-8).

Jensen, R. C., et al., 2022, 'Higher free thyroxine associated with PFAS exposure in first trimester. The Odense Child Cohort.', *Environmental Research* 212, p. 113492 (DOI: 10.1016/j.envres.2022.113492).

Jiang, Y., et al., 2020, 'Prenatal exposure to bisphenol A and its alternatives and child neurodevelopment at 2 years', *Journal of Hazardous Materials* 388, p. 121774 (DOI: https://doi.org/10.1016/j.jhazmat.2019.121774).

Jin, T., et al., 2002, 'Cadmium biomonitoring and renal dysfunction among a population environmentally exposed to cadmium from smelting in China (ChinaCad)', *Biometals* 15(4), pp. 397-410 (DOI: 10.1023/a:1020229923095).

Johansen, R., et al., 2020, 'Legislative mapping benzophenones - summary document' (https://www.hbm4eu.eu/wp-content/uploads/2019/03/benzophenones-310120.pdf) accessed 30 July 2023.

Joint FAO/WHO Expert Committee on Food Additives (JECFA), 2005, *Evaluation of certain food additives and contaminants: Sixty-fourth meeting of the Joint FAO/WHO Expert Committee on Food Additives*, Rome (http://www.fao.org/3/at877e/at877e.pdf).

Joint FAO/WHO Expert Committee on Food Additives (JECFA), 2011, 'Evaluation of certain contaminants in food: seventy-second [72nd] report of the Joint FAO/WHO Expert Committee on Food Additives', , p. 105.

Joint FAO/WHO Expert Committee on Food Additives (JECFA), 2022, *Evaluation of certain food additives and contaminants: ninety-first report of the Joint FAO/WHO Expert Committee on Food Additives*, World Health Organization and Food and Agriculture Organization of the United Nations, Geneva.

Kasmi, S., et al., 2023, 'Carcinogenic effect of arsenic in digestive cancers: a systematic review', *Environmental Health: A Global Access Science Source* 22(1), p. 36 (DOI: 10.1186/s12940-023-00988-7).

Kolarik, B., et al., 2019, Chromium VI and cobalt in leather goods -Control of chromium and risk evaluation of cobalt, The Danish Environmental Protection Agency.

Koureas, M., et al., 2012, 'Systematic review of biomonitoring studies to determine the association between exposure to organophosphorus and pyrethroid insecticides and human health outcomes', *Toxicology Letters* 210(2), pp. 155-168 (DOI: 10.1016/j.toxlet.2011.10.007).

Kowalska, M., et al., 2017, 'The determinants of lead and cadmium blood levels for preschool children from industrially contaminated sites in Poland', *International Journal of Occupational Medicine and Environmental Health* 31(3), pp. 351-359 (DOI: 10.13075/ijomeh.1896.01153).

Krause, M., et al., 2017, 'Exposure to UV filters during summer and winter in Danish kindergarten children', *Environment International* 99, pp. 177-184 (DOI: 10.1016/j.envint.2016.11.011).

Kutanzi, K. R., et al., 2016, 'Pediatric Exposures to Ionizing Radiation: Carcinogenic Considerations', *International Journal of Environmental Research and Public Health* 13(11), p. 1057 (DOI: 10.3390/ijerph13111057).

Lai, D. Y., et al., 2015, 'Tetrabromobisphenol A (TBBPA): Possible modes of action of toxicity and carcinogenicity in rodents', *Food and Chemical Toxicology: An International Journal Published for the British Industrial Biological Research Association* 80, pp. 206-214 (DOI: 10.1016/j.fct.2015.03.023).

Lam, J., et al., 2017, 'Developmental PBDE Exposure and IQ/ADHD in Childhood: A Systematic Review and Meta-analysis', *Environmental Health Perspectives* 125(8), p. 086001 (DOI: 10.1289/EHP1632).

Lamkarkach, F., et al., 2021, 'Human biomonitoring initiative (HBM4EU): Human biomonitoring guidance values (HBM-GVs) derived for cadmium and its compounds', *Environment International* 147, p. 106337 (DOI: 10.1016/j.envint.2020.106337).

Landrigan, P. J., et al., 2018, 'The Lancet Commission on pollution and health', *The Lancet* 391(10119), pp. 462-512 (DOI: 10.1016/S0140-6736(17)32345-0).

Landrigan, P. J. and Garg, A., 2002, 'Chronic Effects of Toxic Environmental Exposures on Children's Health', *Journal of Toxicology: Clinical Toxicology* 40(4), pp. 449-456 (DOI: 10.1081/CLT-120006747).

Lanphear, B. P., et al., 2005, 'Low-Level Environmental Lead Exposure and Children's Intellectual Function: An International Pooled Analysis', *Environmental Health Perspectives* 113(7), pp. 894-899 (DOI: 10.1289/ehp.7688).

Larsen, B. and Sánchez-Triana, E., 2023, 'Global health burden and cost of lead exposure in children and adults: a health impact and economic modelling analysis', *The Lancet Planetary Health* 7(10), pp. e831-e840 (DOI: 10.1016/S2542-5196(23)00166-3).

Laupeze, B., et al., 2002, 'Polycyclic Aromatic Hydrocarbons Affect Functional Differentiation and Maturation of Human Monocyte-Derived Dendritic Cells1', *The Journal of Immunology* 168(6), pp. 2652-2658 (DOI: 10.4049/jimmunol.168.6.2652).

Lauwerys, R., et al., 1978, 'Placental transfer of lead, mercury, cadmium, and carbon monoxide in women: I. Comparison of the frequency distributions of the biological indices in maternal and umbilical cord blood', *Environmental Research* 15(2), pp. 278-289 (DOI: 10.1016/0013-9351(78)90104-4).

Lauwerys, R. R. and Hoet, P., 2001, *Industrial Chemical Exposure: Guidelines for Biological Monitoring, Third Edition*, CRC Press.

Lee, K.-S., et al., 2022, 'The association of prenatal and childhood pyrethroid pesticide exposure with school-age ADHD traits', *Environment International* 161, p. 107124 (DOI: 10.1016/j.envint.2022.107124).

Lee, Y. J., et al., 2021, 'Early-Life Exposure to Per- and Poly-Fluorinated Alkyl Substances and Growth, Adiposity, and Puberty in Children: A Systematic Review', *Frontiers in Endocrinology* 12, p. 683297 (DOI: 10.3389/fendo.2021.683297).

Leslie, H. A., et al., 2016, 'Propelling plastics into the circular economy — weeding out the toxics first', *Environment International* 94, pp. 230-234 (DOI: 10.1016/j.envint.2016.05.012).

Lewis, R. C., et al., 2015, 'Serum Biomarkers of Exposure to Perfluoroalkyl Substances in Relation to Serum Testosterone and Measures of Thyroid Function among Adults and Adolescents from NHANES 2011–2012', *International Journal of Environmental Research and Public Health* 12(6), pp. 6098-6114 (DOI: 10.3390/ijerph120606098).

Li, M.-C., et al., 2017, 'Phthalate esters and childhood asthma: A systematic review and congener-specific meta-analysis', *Environmental Pollution* 229, pp. 655-660 (DOI: 10.1016/j.envpol.2017.06.083).

Li, S., et al., 2022, 'Relationship between maternal heavy metal exposure and congenital heart defects: a systematic review and meta-analysis', *Environmental Science and Pollution Research* 29(37), pp. 55348-55366 (DOI: 10.1007/s11356-022-21071-7).

Li, Y., et al., 2008, 'The hazard of chromium exposure to neonates in Guiyu of China', *The Science of the Total Environment* 403(1-3), pp. 99-104 (DOI: 10.1016/j.scitotenv.2008.05.033).

Liu, Y., et al., 2010, 'The relationship between mental retardation and developmental delays in children and the levels of arsenic, mercury and lead in soil samples taken near their mother's residence during pregnancy', *International Journal of Hygiene and Environmental Health* 213(2), pp. 116-123 (DOI: 10.1016/j.ijheh.2009.12.004).

Lopez-Espinosa, M.-J., et al., 2012, 'Thyroid function and perfluoroalkyl acids in children living near a chemical plant', *Environmental Health Perspectives* 120(7), pp. 1036-1041 (DOI: 10.1289/ehp.1104370).

Lucattini, L., et al., 2018, 'A review of semi-volatile organic compounds (SVOCs) in the indoor environment: occurrence in consumer products, indoor air and dust', *Chemosphere* 201, pp. 466-482 (DOI: 10.1016/j.chemosphere.2018.02.161).

Ma, C., et al., 2021, 'Association of prenatal exposure to cadmium with neurodevelopment in children at 2 years of age: The Japan Environment and Children's Study', *Environ Int* 156, p. 106762 (DOI: 10.1016/j.envint.2021.106762).

Makri, A., et al., 2004, 'Children's Susceptibility to Chemicals: A Review by Developmental Stage', *Journal of Toxicology and Environmental Health, Part B* 7(6), pp. 417-435 (DOI: 10.1080/10937400490512465).

Mancini, A. J., 2004, 'Skin', *Pediatrics* 113(4 Suppl), pp. 1114-1119.

Mao, J. F., et al., 2022, 'Assessment of human exposure to benzophenone-type UV filters: A review', *Environment International* 167, p. 107405 (DOI: 10.1016/j.envint.2022.107405).

Meeker, J. D. and Stapleton, H. M., 2010, 'House Dust Concentrations of Organophosphate Flame Retardants in Relation to Hormone Levels and Semen Quality Parameters', *Environmental Health Perspectives* 118(3), pp. 318-323 (DOI: 10.1289/ehp.0901332).

Melzer, D., et al., 2010, 'Association between serum perfluorooctanoic acid (PFOA) and thyroid disease in the U.S. National Health and Nutrition Examination Survey', *Environmental Health Perspectives* 118(5), pp. 686-692 (DOI: 10.1289/ehp.0901584).

Mesnage, R., et al., 2017, 'Editor's Highlight: Transcriptome Profiling Reveals Bisphenol A Alternatives Activate Estrogen Receptor Alpha in Human Breast Cancer Cells', *Toxicological Sciences: An Official Journal of the Society of Toxicology* 158(2), pp. 431-443 (DOI: 10.1093/toxsci/kfx101).

Minamata Convention on Mercury, 2021, 'About Us - Minamata Convention on Mercury' (https://mercuryconvention.org/en/about) accessed 7 June 2023.

Mokra, K., 2021, 'Endocrine Disruptor Potential of Short- and Long-Chain Perfluoroalkyl Substances (PFASs)—A Synthesis of Current Knowledge with Proposal of Molecular Mechanism', *International Journal of Molecular Sciences* 22(4), pp. 1-36 (DOI: 10.3390/IJMS22042148).

Moore, S., et al., 2022, 'The Association between ADHD and Environmental Chemical - A Scoping Review', *International Journal of Environmental Research and Public Health* 19(5), p. 2849.

Mose, T., et al., 2007, 'Transplacental Transfer of Monomethyl Phthalate and Mono(2-ethylhexyl) Phthalate in a Human Placenta Perfusion System', *International Journal of Toxicology* 26(3), pp. 221-229 (DOI: 10.1080/10915810701352721).

Mustieles, V., et al., 2023, 'Benzophenone-3: Comprehensive review of the toxicological and human evidence with meta-analysis of human biomonitoring studies', *Environment International* 173, p. 107739 (DOI: 10.1016/j.envint.2023.107739).

Nachman, K. E., et al., 2017, 'Mitigating dietary arsenic exposure: Current status in the United States and recommendations for an improved path forward', *The Science of the total environment* 581-582, pp. 221-236 (DOI: 10.1016/j.scitotenv.2016.12.112).

Naomi, R., et al., 2022, 'Bisphenol A (BPA) Leading to Obesity and Cardiovascular Complications: A Compilation of Current In Vivo Study', *Int J Mol Sci* 23(6) (DOI: 10.3390/ijms23062969).

National Academies of Sciences, 2022, *Guidance on PFAS Exposure, Testing, and Clinical Follow-Up*,.

National Academies of Sciences, E., et al., 2022, 'PFAS Exposure Reduction', in: *Guidance on PFAS Exposure, Testing, and Clinical Follow-Up*, National Academies Press (US).

National Research Council, 2013, *Critical Aspects of EPA's IRIS Assessment of Inorganic Arsenic: Interim Report*, The National Academies Press, Washington, DC.

National Toxicology Programme, 2016, NTP Monograph Immunotoxicity Associated with Exposure to Perfluorooctanoic Acid (PFOA) or Perfluorooctane Sulfonate (PFOS), (https://ntp.niehs.nih.gov/ntp/ohat/pfoa_pfos/pfoa_pfosmonograph_508.pdf) accessed 24 March 2023, National Toxicology Program.

Navarrete-Meneses, M. D. P. and Pérez-Vera, P., 2019, 'Pyrethroid pesticide exposure and hematological cancer: epidemiological, biological and molecular evidence', *Reviews on Environmental Health* 34(2), pp. 197-210 (DOI: 10.1515/reveh-2018-0070).

Neghab, M., et al., 2015, 'Acute and Chronic Respiratory Effects of Chromium Mists', *Journal of Health Sciences & Surveillance System* 3(3), pp. 119-124.

Ni, W., et al., 2014, 'Associations of neonatal lead, cadmium, chromium and nickel co-exposure with DNA oxidative damage in an electronic waste recycling town', *The Science of the Total Environment* 472, pp. 354-362 (DOI: 10.1016/j.scitotenv.2013.11.032).

Ntzani, E. E., et al., 2013, 'Literature review on epidemiological studies linking exposure to pesticides and health effects', *EFSA Supporting Publications* 10(10), p. 497E (DOI: 10.2903/sp.efsa.2013.EN-497).

Oates, L. and Cohen, M., 2011, 'Assessing Diet as a Modifiable Risk Factor for Pesticide Exposure', *International Journal of Environmental Research and Public Health* 8(6), pp. 1792-1804 (DOI: 10.3390/ijerph8061792).

OECD, 2012, *Environmental outlook to 2050: The Consequences of Inaction* (http://www.oecd-ilibrary.org/environment/oecd-environmental-outlook-to-2050_9789264122246-en).

OECD, 2013, *Assessing the risk of chemicals to children's health: an OECD-wide survey, OECD [ENV/JM/MONO(2013)20]*.

OECD, 2018, *Global database of per-and polyfluoroalkyl substances* (https://view.officeapps.live.com/op/view.aspx?src=https%3A%2F%2Fwww.oecd.org%2Fchemicalsafety%2Frisk-management%2Fglobal-database-of-per-and-polyfluoroalkyl-substances.xlsx&wdOrigin=BROWSELINK) accessed 18 August 2023.

OECD, 2019, *CONSIDERATIONS WHEN ASSESSING CHILDREN'S EXPOSURE TO CHEMICALS FROM PRODUCTS*.

Oulhote, Y. and Bouchard, M. F., 2013, 'Urinary metabolites of organophosphate and pyrethroid pesticides and behavioral problems in Canadian children', *Environmental Health Perspectives* 121(11-12), pp. 1378-1384 (DOI: 10.1289/ehp.1306667).

PAN Europe, 2023, 'We need effective buffer zones - against a cloud of pesticides' (https://www.pan-europe.info/blog/we-need-effective-buffer-zones-against-cloud-pesticides).

Panuwet, P., et al., 2009, 'Urinary pesticide metabolites in school students from northern Thailand', *International Journal of Hygiene and Environmental Health* 212(3), pp. 288-297 (DOI: 10.1016/j.ijheh.2008.07.002).

Patisaul, H. B., et al., 2013, 'Accumulation and Endocrine Disrupting Effects of the Flame Retardant Mixture Firemaster® 550 in Rats: An Exploratory Assessment', *Journal of biochemical and molecular toxicology* 27(2), pp. 124-136 (DOI: 10.1002/jbt.21439).

Perera, F. P., et al., 2006, 'Effect of Prenatal Exposure to Airborne Polycyclic Aromatic Hydrocarbons on Neurodevelopment in the First 3 Years of Life among Inner-City Children', *Environmental Health Perspectives* 114(8), pp. 1287-1292 (DOI: 10.1289/ehp.9084).

Perera, F. P., et al., 2009, 'Prenatal Airborne Polycyclic Aromatic Hydrocarbon Exposure and Child IQ at Age 5 Years', *Pediatrics* 124(2), pp. e195-e202 (DOI: 10.1542/peds.2008-3506).

Perera, F. P., et al., 2012, 'Prenatal Polycyclic Aromatic Hydrocarbon (PAH) Exposure and Child Behavior at Age 6–7 Years', *Environmental Health Perspectives* 120(6), pp. 921-926 (DOI: 10.1289/ehp.1104315).

Perez-Lobato, R., et al., 2016, 'Exposure to bisphenol A and behavior in school-age children', *Neurotoxicology* 53, pp. 12-19 (DOI: 10.1016/j.neuro.2015.12.001).

Perkins, T., 2022, 'Higher levels of PFAS exposure may increase chance of Covid, studies say', *The Guardian*, 10 March 2022 (https://www.theguardian.com/environment/2022/mar/10/pfas-covid-infection-forever-chemicals-studies) accessed 17 August 2023.

Perlroth, N. H. and Castelo Branco, C. W., 2017, 'Current knowledge of environmental exposure in children during the sensitive developmental periods', *Jornal de Pediatria* 93(1), pp. 17-27 (DOI: 10.1016/j.jped.2016.07.002).

Podgorski, J. and Berg, M., 2020, 'Global threat of arsenic in groundwater', *Science (New York, N.Y.)* 368(6493), pp. 845-850 (DOI: 10.1126/science.aba1510).

Praveena, S. M., et al., 2020, 'Phthalates exposure and attention-deficit/hyperactivity disorder in children: a systematic review of epidemiological literature', *Environmental Science and Pollution Research* 27(36), pp. 44757-44770 (DOI: 10.1007/s11356-020-10652-z).

Qi, Z., et al., 2022, 'Effects of prenatal exposure to pyrethroid pesticides on neurodevelopment of 1-year- old children: A birth cohort study in China', *Ecotoxicology and Environmental Safety* 234, p. 113384 (DOI: 10.1016/j.ecoenv.2022.113384).

Rappazzo, K. M., et al., 2017, 'Exposure to perfluorinated alkyl substances and health outcomes in children: A systematic review of the epidemiologic literature', *International Journal of Environmental Research and Public Health* 14(7) (DOI: 10.3390/ijerph14070691).

Ravenscroft, P., et al., 2009, *Arsenic pollution: a global synthesis*, Wiley-Blackwell, Chichester.

Ray, R. R., 2016, 'Adverse hematological effects of hexavalent chromium: an overview', *Interdisciplinary Toxicology* 9(2), pp. 55-65 (DOI: 10.1515/intox-2016-0007).

Reddam, A., et al., 2020, 'Longer commutes are associated with increased human exposure to tris(1,3-dichloro-2-propyl) phosphate', *Environment International* 136, p. 105499 (DOI: 10.1016/j.envint.2020.105499).

Rengarajan, T., et al., 2015, 'Exposure to polycyclic aromatic hydrocarbons with special focus on cancer', *Asian Pacific Journal of Tropical Biomedicine* 5(3), pp. 182-189 (DOI: 10.1016/S2221-1691(15)30003-4).

Ribeiro, C., et al., 2019, 'Association between the exposure to phthalates and adiposity: A meta-analysis in children and adults', *Environmental Research* 179, p. 108780 (DOI: 10.1016/j.envres.2019.108780).

Richterová, D., et al., 2023, 'PFAS levels and determinants of variability in exposure in European teenagers - Results from the HBM4EU aligned studies (2014-2021)', *International Journal of Hygiene and Environmental Health* 247, p. 114057 (DOI: 10.1016/j.ijheh.2022.114057).

Roca, M., et al., 2014, 'Biomonitoring exposure assessment to contemporary pesticides in a school children population of Spain', *Environmental Research* 131, pp. 77-85 (DOI: 10.1016/j.envres.2014.02.009).

Rochester, J. R. and Bolden, A. L., 2015, 'Bisphenol S and F: A Systematic Review and Comparison of the Hormonal Activity of Bisphenol A Substitutes', *Environ Health Perspect* 123(7), pp. 643-650 (DOI: 10.1289/ehp.1408989).

Rodríguez-Barranco, M., et al., 2013, 'Association of arsenic, cadmium and manganese exposure with neurodevelopment and behavioural disorders in children: A systematic review and meta-analysis', *Science of The Total Environment* 454-455, pp. 562-577 (DOI: https://doi.org/10.1016/j.scitotenv.2013.03.047).

Rodríguez-Carrillo, A., et al., 2023, 'PFAS association with kisspeptin and sex hormones in teenagers of the HBM4EU aligned studies', *Environmental Pollution* 335, p. 122214 (DOI: 10.1016/j.envpol.2023.122214).

Rojas-Rueda, D., et al., 2019, 'Environmental Burden of Childhood Disease in Europe', *International Journal of Environmental Research and Public Health* 16(6), p. 1084 (DOI: 10.3390/ijerph16061084).

Röösli, M., 2011, 'Non-cancer effects of chemical agents on children's health', *Progress in Biophysics and Molecular Biology* 107(3), pp. 315-322 (DOI: 10.1016/j.pbiomolbio.2011.08.006).

Sachdeva, C., et al., 2018, 'Lead: Tiny but Mighty Poison', *Indian journal of clinical biochemistry: IJCB* 33(2), pp. 132-146 (DOI: 10.1007/s12291-017-0680-3).

Saillenfait, A.-M., et al., 2015, 'Pyrethroids: Exposure and health effects – An update', *International Journal of Hygiene and Environmental Health* 218(3), pp. 281-292 (DOI: 10.1016/j.ijheh.2015.01.002).

Sakamoto, M., et al., 2018, 'Mercury as a Global Pollutant and Mercury Exposure Assessment and Health Effects', *Nippon Eiseigaku Zasshi (Japanese Journal of Hygiene)* 73(3), pp. 258-264 (DOI: 10.1265/jjh.73.258).

Sampaio, G. R., et al., 2021, 'Polycyclic Aromatic Hydrocarbons in Foods: Biological Effects, Legislation, Occurrence, Analytical Methods, and Strategies to Reduce Their Formation', *International Journal of Molecular Sciences* 22(11), p. 6010 (DOI: 10.3390/ijms22116010).

Santonen, T., et al., 2022, 'HBM4EU chromates study - Overall results and recommendations for the biomonitoring of occupational exposure to hexavalent chromium', *Environmental Research* 204(Pt A) (DOI: 10.1016/j.envres.2021.111984).

SCCS, 2023, *SCCS Notes of Guidance for the Testing of Cosmetic Ingredients and Their Safety Evaluation* (https://www.cir-safety.org/sites/default/files/ADMIN_SCCSNotes.pdf).

Schaefer, H. R., et al., 2022, 'A systematic review of adverse health effects associated with oral cadmium exposure', *Regulatory Toxicology and Pharmacology* 134, p. 105243 (DOI: https://doi.org/10.1016/j.yrtph.2022.105243).

Schoeters, G., et al., 2006, 'Cadmium and children: Exposure and health effects', *Acta Paediatrica* 95(s453), pp. 50-54 (DOI: https://doi.org/10.1080/08035320600886232).

Schulz, K., et al., 2020, 'Distribution and effects of branched versus linear isomers of PFOA, PFOS, and PFHxS: A review of recent literature', *Science of The Total Environment* 733, p. 139186 (DOI: 10.1016/j.scitotenv.2020.139186).

Scientific Committee on Emerging and Newly-Identified Health Risks (SCENIHR), 2016, *Opinion on the safety of medical devices containing DEHP- plasticized PVC or other plasticizers on neonates and other groups possibly at risk*, Publications Office.

Sharkey, M., et al., 2020, 'Phasing-out of legacy brominated flame retardants: The UNEP Stockholm Convention and other legislative action worldwide', *Environment International* 144, p. 106041 (DOI: 10.1016/j.envint.2020.106041).

Shelnutt, S. R., et al., 2007, 'Dermatological toxicity of hexavalent chromium', *Critical Reviews in Toxicology* 37(5), pp. 375-387 (DOI: 10.1080/10408440701266582).

Shin, H.-M., et al., 2022, 'Prenatal Exposure to Per- and Polyfluoroalkyl Substances, Maternal Thyroid Dysfunction, and Child Autism Spectrum Disorder', *Endocrinology and Metabolism (Seoul, Korea)* 37(6), pp. 819-829 (DOI: 10.3803/EnM.2022.1598).

Sly, P. D. and Flack, F., 2008, 'Susceptibility of Children to Environmental Pollutants', *Annals of the New York Academy of Sciences* 1140(1), pp. 163-183 (DOI: 10.1196/annals.1454.017).

Snoj Tratnik, J., et al., 2022, 'Cadmium exposure in adults across Europe: Results from the HBM4EU Aligned Studies survey 2014–2020', *International Journal of Hygiene and Environmental Health* 246, p. 114050 (DOI: https://doi.org/10.1016/j.ijheh.2022.114050).

Sowlat, M. H., et al., 2016, 'The association between bisphenol A exposure and type-2 diabetes: a world systematic review', *Environ Sci Pollut Res Int* 23(21), pp. 21125-21140 (DOI: 10.1007/s11356-016-7525-0).

Springer, C., et al., 2012, 'Rodent thyroid, liver, and fetal testis toxicity of the monoester metabolite of bis-(2-ethylhexyl) tetrabromophthalate (tbph), a novel brominated flame retardant present in indoor dust', *Environmental Health Perspectives* 120(12), pp. 1711-1719 (DOI: 10.1289/ehp.1204932).

Sugeng, E. J., et al., 2017, 'Toddler exposure to flame retardant chemicals: Magnitude, health concern and potential risk- or protective factors of exposure: Observational studies summarized in a systematic review', *Chemosphere* 184, pp. 820-831 (DOI: 10.1016/j.chemosphere.2017.06.041).

Sun, M., et al., 2022, 'Prenatal exposure to endocrine-disrupting chemicals and thyroid function in neonates: A systematic review and meta-analysis', *Ecotoxicology and Environmental Safety* 231, p. 113215 (DOI: 10.1016/j.ecoenv.2022.113215).

Suzuki, Y., et al., 2010, 'Prenatal exposure to phthalate esters and PAHs and birth outcomes', *Environment International* 36(7), pp. 699-704 (DOI: 10.1016/j.envint.2010.05.003).

Tarazona, J. V., et al., 2022, 'A Tiered Approach for Assessing Individual and Combined Risk of Pyrethroids Using Human Biomonitoring Data', *Toxics* 10(8), p. 451 (DOI: 10.3390/toxics10080451).

Tolins, M., et al., 2014, 'The developmental neurotoxicity of arsenic: cognitive and behavioral consequences of early life exposure', *Annals of Global Health* 80(4), pp. 303-314 (DOI: 10.1016/j.aogh.2014.09.005).

Trasande, L., et al., 2015, 'Estimating burden and disease costs of exposure to endocrine-disrupting chemicals in the European union', *J Clin Endocrinol Metab* 100(4), pp. 1245-1255 (DOI: 10.1210/jc.2014-4324).

Trasande, L., et al., 2016, 'Burden of disease and costs of exposure to endocrine disrupting chemicals in the European Union: an updated analysis', *Andrology* 4(4), pp. 565-572 (DOI: 10.1111/andr.12178).

Trzcinka-Ochocka, M., et al., 2004, 'The effects of environmental cadmium exposure on kidney function: the possible influence of age', *Environmental Research* 95(2), pp. 143-150 (DOI: 10.1016/j.envres.2003.10.003).

Tschersich, C., et al., 2021, 'Bisphenol A and six other environmental phenols in urine of children and adolescents in Germany – human biomonitoring results of the German Environmental Survey 2014–2017 (GerES V)', *Science of The Total Environment* 763, p. 144615 (DOI: 10.1016/j.scitotenv.2020.144615).

Turner, M. C., et al., 2010, 'Residential Pesticides and Childhood Leukemia: A Systematic Review and Meta-Analysis', *Environmental Health Perspectives* 118(1), pp. 33-41 (DOI: 10.1289/ehp.0900966).

United Nations Children's Fund (UNICEF) and World Health Organization, 2018, *Arsenic Primer - Guidance on the Investigation & Mitigation of Arsenic Contamination*, New York (https://www.unicef.org/media/91296/file/UNICEF-WHO-Arsenic-Primer.pdf).

United Nations Environment Programme (UNEP), 2010, *Final review of scientific information on cadmium*, UNEP.

United Nations Environment Programme (UNEP), 2019a, *Global Chemicals Outlook II - From Legacies to Innovative Solutions*,.

United Nations Environment Programme (UNEP), 2019b, *Global Mercury Assessment 2018* (https://mercuryconvention.org/sites/default/files/2021-06/GMA2018.pdf).

United Nations Environment Programme (UNEP), 2019c, 'What are POPs?', UNEP Stockholm Convention (http://www.pops.int/TheConvention/ThePOPs/tabid/673/Default.aspx) accessed 23 May 2023.

United Nations Environment Programme (UNEP), 2020a, *An Assessment Report on Issues of Concern: Chemicals and Waste Issues Posing Risks to Human Health and the Environment*.

United Nations Environment Programme (UNEP), 2020b, 'Arsenic - Assessment Report on Issues of Concern',.

United Nations Environment Programme (UNEP), 2020c, 'Phthalates - Assessment Report on Issues of Concern',.

United Nations Environment Programme (UNEP), 2020d, 'Polycyclic Aromatic Hydrocarbons (PAHs) - Assessment Report on Issues of Concern',.

United Nations Environment Programme (UNEP), 2023a, *Chemicals in Plastics - A Technical Report*.

United Nations Environment Programme (UNEP), 2023b, 'Flame Retardants' (http://www.unep.org/explore-topics/chemicals-waste/what-we-do/persistent-organic-pollutants/flame-retardants) accessed 22 May 2023.

United States Environmental Protection Agency, 2013, *Integrated Science Assessment for Lead.*, North Carolina.

United States Environmental Protection Agency, O., 2021, 'Meaningful and Achievable Steps You Can Take to Reduce Your Risk' (https://www.epa.gov/pfas/meaningful-and-achievable-steps-you-can-take-reduce-your-risk) accessed 18 August 2023.

United States Geological Survey, 2023, *Statistics and information on the worldwide supply of, demand for, and flow of the mineral commodity lead.* (Retrieved 04.05.2023, from https://www.usgs.gov/centers/national-minerals-information-center/lead-statistics-and-information.).

Valent, F., et al., 2004, 'Burden of disease attributable to selected environmental factors and injury among children and adolescents in Europe', *The Lancet* 363(9426), pp. 2032-2039 (DOI: 10.1016/S0140-6736(04)16452-0).

Van Maele-Fabry, G., et al., 2011, 'Residential exposure to pesticides and childhood leukaemia: A systematic review and meta-analysis', *Environment International* 37(1), pp. 280-291 (DOI: 10.1016/j.envint.2010.08.016).

Van Maele-Fabry, G., et al., 2019, 'Household exposure to pesticides and risk of leukemia in children and adolescents: Updated systematic review and meta-analysis', *International Journal of Hygiene and Environmental Health* 222(1), pp. 49-67 (DOI: 10.1016/j.ijheh.2018.08.004).

Vandenberg, L. N., 2014, 'Chapter Five - Low-Dose Effects of Hormones and Endocrine Disruptors', in: Litwack, G. (ed.), *Vitamins & Hormones*, Academic Press, pp. 129-165.

Veras, M. M., et al., 2017, 'Before the first breath: prenatal exposures to air pollution and lung development', *Cell and Tissue Research* 367(3), pp. 445-455 (DOI: 10.1007/s00441-016-2509-4).

Viel, J.-F., et al., 2015, 'Pyrethroid insecticide exposure and cognitive developmental disabilities in children: The PELAGIE mother–child cohort', *Environment International* 82, pp. 69-75 (DOI: 10.1016/j.envint.2015.05.009).

Viel, J.-F., et al., 2017, 'Behavioural disorders in 6-year-old children and pyrethroid insecticide exposure: the PELAGIE mother-child cohort', *Occupational and Environmental Medicine* 74(4), pp. 275-281 (DOI: 10.1136/oemed-2016-104035).

Vinson, F., et al., 2011, 'Exposure to pesticides and risk of childhood cancer: a meta-analysis of recent epidemiological studies', *Occupational and Environmental Medicine* 68(9), pp. 694-702 (DOI: 10.1136/oemed-2011-100082).

Vlaamse overheid, 2021, *Aanpak PFAS-problematiek* (https://www.vlaanderen.be/pfas-vervuiling/).

Vogel, N., et al., 2021, 'Lead, cadmium, mercury, and chromium in urine and blood of children and adolescents in Germany – Human biomonitoring results of the German Environmental Survey 2014–2017 (GerES V)', *International Journal of Hygiene and Environmental Health* 237, p. 113822 (DOI: 10.1016/j.ijheh.2021.113822).

Von Holst, H., et al., 2021, 'Perfluoroalkyl substances exposure and immunity, allergic response, infection, and asthma in children: review of epidemiologic studies', *Heliyon* 7(10), p. e08160 (DOI: 10.1016/j.heliyon.2021.e08160).

Wagner-Schuman, M., et al., 2015, 'Association of pyrethroid pesticide exposure with attention-deficit/hyperactivity disorder in a nationally representative sample of U.S. children', *Environmental Health* 14, p. 44 (DOI: 10.1186/s12940-015-0030-y).

Wang, H., et al., 2010, 'Examining the relationship between brominated flame retardants (BFR) exposure and changes of thyroid hormone levels around e-waste dismantling sites', *International Journal of Hygiene and Environmental Health* 213(5), pp. 369-380 (DOI: 10.1016/j.ijheh.2010.06.004).

Wang, J., et al., 2022, 'Exposure to Heavy Metals and Allergic Outcomes in Children: a Systematic Review and Meta-analysis', *Biological Trace Element Research* 200(11), pp. 4615-4631 (DOI: 10.1007/s12011-021-03070-w).

Watkins, D. J., et al., 2016, 'Urinary 3-phenoxybenzoic acid (3-PBA) levels among pregnant women in Mexico City: Distribution and relationships with child neurodevelopment', *Environmental Research* 147, pp. 307-313 (DOI: 10.1016/j.envres.2016.02.025).

WHO Global Advisory Committee on Vaccine Safety (GACVS), 2012, *Weekly epidemiological record - WHO*.

Wiener, S., 2023, 'DRAFT REPORT on the proposal for a regulation of the European Parliament and of the Council on the sustainable use of plant protection products and amending Regulation (EU) 2021/2115 | ENVI_PR(2023)742368 | European Parliament' (https://www.europarl.europa.eu/doceo/document/ENVI-PR-742368_EN.html) accessed 18 August 2023.

Winston, J. J., et al., 2016, 'Hypospadias and maternal exposure to atrazine via drinking water in the National Birth Defects Prevention study', *Environmental Health: A Global Access Science Source* 15(1), p. 76 (DOI: 10.1186/s12940-016-0161-9).

Wnuk, W., et al., 2022, 'Benzophenone-3, a chemical UV-filter in cosmetics: is it really safe for children and pregnant women?', *Advances in Dermatology and Allergology/Postępy Dermatologii i Alergologii* 39(1), pp. 26-33 (DOI: 10.5114/ada.2022.113617).

World Health Organization, 1988, *Environmental Health Criteria 61 - Chromium*, Geneva.

World Health Organization, 2010, 'Children's exposure to mercury compounds', , p. 105.

World Health Organization, 2019a, *Exposure to Arsenic: A Major Public Health Concern*, Geneva.

World Health Organization, 2019b, 'Exposure to Cadmium: A Major Public Health Concern', , p. 6.

World Health Organization, 2019c, *Exposure to Lead: A Major Public Health Concern*, Geneva.

World Health Organization, 2021a, *Children and digital dumpsites: e-waste exposure and child health*.

World Health Organization, 2021b, *Exposure to Mercury: A Major Public Health Concern*, Geneva (https://apps.who.int/iris/rest/bitstreams/1341885/retrieve).

World Health Organization, 2022a, *Guidelines for drinking-water quality: fourth edition incorporating the first and second addenda*, WHO, Geneva.

World Health Organization, 2022b, *Lead in drinking-water: Health risks, monitoring and corrective actions* (https://www.who.int/publications-detail-redirect/9789240020863) accessed 24 July 2023.

World Health Organization, 2023, 'Arsenic' (https://www.who.int/news-room/fact-sheets/detail/arsenic) accessed 26 May 2023.

World Health Organization Regional Office for Europe, 2021, *Human health effects of polycyclic aromatic hydrocarbons as ambient air pollutants: report of the Working Group on Polycyclic Aromatic Hydrocarbons of the Joint Task Force on the Health Aspects of Air Pollution.*, Copenhagen.

Wright, J. M., et al., 2023, 'Systematic review and meta-analysis of birth weight and PFNA exposures', *Environmental Research* 222, p. 115357 (DOI: 10.1016/j.envres.2023.115357).

Wu, W., et al., 2020a, 'Association between phthalate exposure and asthma risk: A meta-analysis of observational studies', *International Journal of Hygiene and Environmental Health* 228, p. 113539 (DOI: 10.1016/j.ijheh.2020.113539).

Wu, Y., et al., 2022, 'Maternal exposure to endocrine disrupting chemicals (EDCs) and preterm birth: A systematic review, meta-analysis, and meta-regression analysis', *Environmental Pollution (Barking, Essex: 1987)* 292(Pt A), p. 118264 (DOI: 10.1016/j.envpol.2021.118264).

Wu, Z., et al., 2020b, 'Exposure pathways, levels and toxicity of polybrominated diphenyl ethers in humans: A review', *Environmental Research* 187, p. 109531 (DOI: 10.1016/j.envres.2020.109531).

Xiong, P., et al., 2019, 'A Review of Environmental Occurrence, Fate, and Toxicity of Novel Brominated Flame Retardants', *Environmental Science & Technology* 53(23), pp. 13551-13569 (DOI: 10.1021/acs.est.9b03159).

Xu, X., et al., 2015, 'E-waste environmental contamination and harm to public health in China', *Frontiers of Medicine* 9(2), pp. 220-228 (DOI: 10.1007/s11684-015-0391-1).

Xu, Y., et al., 2023, 'Maternal exposure to pesticides and autism or attention-deficit/hyperactivity disorders in offspring: A meta-analysis', *Chemosphere* 313, p. 137459 (DOI: 10.1016/j.chemosphere.2022.137459).

Xue, J., et al., 2007, 'A Meta-Analysis of Children's Hand-to-Mouth Frequency Data for Estimating Nondietary Ingestion Exposure', *Risk Analysis* 27(2), pp. 411-420 (DOI: 10.1111/j.1539-6924.2007.00893.x).

Xue, J., et al., 2010, 'Probabilistic Modeling of Dietary Arsenic Exposure and Dose and Evaluation with 2003–2004 NHANES Data', *Environmental Health Perspectives* 118(3), pp. 345-350 (DOI: 10.1289/ehp.0901205).

Xue, Z., et al., 2013, 'Effect of synthetic pyrethroid pesticide exposure during pregnancy on the growth and development of infants', *Asia-Pacific Journal of Public Health* 25(4 Suppl), pp. 72S-9S (DOI: 10.1177/1010539513496267).

Yang, Y., et al., 2022a, 'Arsenic exposures and prostate cancer risk: A multilevel meta-analysis', *Journal of trace elements in medicine and biology: organ of the Society for Minerals and Trace Elements (GMS)* 72, p. 126992 (DOI: 10.1016/j.jtemb.2022.126992).

Yang, Z., et al., 2022b, 'Associations between exposure to perfluoroalkyl substances and birth outcomes: A meta-analysis', *Chemosphere* 291, p. 132909 (DOI: 10.1016/j.chemosphere.2021.132909).

Ye, X., et al., 2017a, 'Association of pyrethroids exposure with onset of puberty in Chinese girls', *Environmental Pollution* 227, pp. 606-612 (DOI: 10.1016/j.envpol.2017.04.035).

Ye, X., et al., 2017b, 'Relationships of Pyrethroid Exposure with Gonadotropin Levels and Pubertal Development in Chinese Boys', *Environmental Science & Technology* 51(11), pp. 6379-6386 (DOI: 10.1021/acs.est.6b05984).

Young, J. L., et al., 2018, 'Impact of Prenatal Arsenic Exposure on Chronic Adult Diseases', *Systems biology in reproductive medicine* 64(6), pp. 469-483 (DOI: 10.1080/19396368.2018.1480076).

Zang, Y., et al., 2019, 'Global burden of late-stage chronic kidney disease resulting from dietary exposure to cadmium, 2015', *Environmental Research* 169, pp. 72-78 (DOI: 10.1016/j.envres.2018.10.005).

Zeng, X., et al., 2016, 'Heavy metals in PM2.5 and in blood, and children's respiratory symptoms and asthma from an e-waste recycling area', *Environmental Pollution (Barking, Essex: 1987)* 210, pp. 346-353 (DOI: 10.1016/j.envpol.2016.01.025).

Zhang, L., et al., 2023, 'Contact to perfluoroalkyl substances and thyroid health effects: A meta-analysis directing on pregnancy', *Chemosphere* 315, p. 137748 (DOI: 10.1016/j.chemosphere.2023.137748).

Zhang, X., et al., 2022, 'Effects of exposure to per- and polyfluoroalkyl substances on vaccine antibodies: A systematic review and meta-analysis based on epidemiological studies', *Environmental Pollution (Barking, Essex: 1987)* 306, p. 119442 (DOI: 10.1016/j.envpol.2022.119442).

Zhang, Y., et al., 2013, 'Biomonitoring of Perfluoroalkyl Acids in Human Urine and Estimates of Biological Half-Life', *Environmental Science & Technology* 47(18), pp. 10619-10627 (DOI: 10.1021/es401905e).

Zhang, Y., et al., 2016, 'Observed decrease in atmospheric mercury explained by global decline in anthropogenic emissions', *Proceedings of the National Academy of Sciences of the United States of America* 113(3), pp. 526-531 (DOI: 10.1073/pnas.1516312113).

Zheng, G., et al., 2013, 'Association between lung function in school children and exposure to three transition metals from an e-waste recycling area', *Journal of Exposure Science & Environmental Epidemiology* 23(1), pp. 67-72 (DOI: 10.1038/jes.2012.84).

Zheng, K., et al., 2023, 'Epidemiological evidence for the effect of environmental heavy metal exposure on the immune system in children', *Science of The Total Environment* 868, p. 161691 (DOI: 10.1016/j.scitotenv.2023.161691).

Zheng, L. Y., et al., 2017, 'Environmental exposures and pediatric kidney function and disease: A systematic review', *Environmental research* 158, pp. 625-648 (DOI: 10.1016/j.envres.2017.06.029).

Zhu, Q., et al., 2020, 'Synthesis, insecticidal activity, resistance, photodegradation and toxicity of pyrethroids (A review)', *Chemosphere* 254, p. 126779 (DOI: 10.1016/j.chemosphere.2020.126779).

2010, 2010/9/EU: Commission Decision of 6 January 2010 on the safety requirements to be met by European standards for bath rings, bathing aids and bath tubs and stands for infants and young children pursuant to Directive 2001/95/EC of the European Parliament and of the Council (notified under document C(2009) 10290) Text with EEA relevance (OJ L).

2010, 2010/376/: Commission Decision of 2 July 2010 on the safety requirements to be met by European standards for certain products in the sleep environment of children pursuant to Directive 2001/95/EC of the European Parliament and of the Council (OJ L).

2013, 2013/121/EU: Commission Decision of 7 March 2013 on the safety requirements to be met by European standards for certain seats for children pursuant to Directive 2001/95/EC of the European Parliament and of the Council on general product safety Text with EEA relevance (OJ L).

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