Annex A1.1: Overview of the evidence for the health effects associated with the selected chemicals

1 Overview of the health outcomes associated with lead (Pb) exposure

A comprehensive examination of official reports and systematic review analyses was carried out to determine the most important health outcomes associated with lead exposure. The European Chemicals Agency (ECHA) conducted a systematic review of the scientific literature, collecting data from epidemiological studies involving lead-exposed workers to evaluate the harmful health effects linked to occupational lead exposure (ECHA, 2019). The main sources used included i) recommendations from the Scientific Committee on Occupational Exposure to lead and its inorganic compounds (EC, 2002); ii) findings of the National Health and Medical Research Council (NHMRC) and a United Nations Environment Program (UNEP) working group that analysed scientific evidence concerning lead and human health by screening the literature for systematic reviews, publications, and reports publicly accessible on governmental, intergovernmental, and non-governmental organization websites (NHMRC, 2010; UNEP, 2015) and iii) insights from the Global Burden of Disease Study 2019 based on an analysis of 87 risk factors and their corresponding health effects across 204 different countries (Murray et al., 2020). A summary outlining the evidence-base of the most important health effects linked to lead exposure follows.

1.1 Neurological and cognitive effects (IQ loss)

Lead exposure has been associated with significant neurological and cognitive effects in both adults and children. The impact of lead exposure on children is particularly concerning, as it is linked to reduced IQ, behavioural issues, and learning disabilities, which have an effect on the whole life span (ECHA, 2019). While high levels of lead exposure, starting at blood lead levels of 100-120µg/dL in adults and 70-100µg/dL in children, have been linked to severe neurological impairments, long-term exposure at only around 40µg/dL has already led to minor neurological changes (Krieg et al., 2008; Seeber et al., 2002; Vlasak et al., 2019; NHMRC, 2015). Recently, cohort studies have revealed neurological impairments due to low lead exposure levels, as observed in the general population. There is evidence for such harm at levels below 10µg/dL, and even lower than 5µg/dL (Canfield et al., 2004; Lanphear et al., 2005), which were included for the calculations of the estimates in the GBD 2019 study (Murray et al., 2020). These findings were further supported, when the screening of scientific literature for threshold values eventually resulted in the conclusion that no "safe" level of lead exposure could be established for children or foetuses (UNEP, 2010).

1.2 Hypertension (high blood pressure)

Relatively high lead concentrations of 30µg/dL, as observed in study population working in a lead-related occupational environment, have been linked to increases of 0.5-2mmHg systolic or diastolic blood pressure (ECHA, 2019). Although occupational and animal studies have demonstrated lead's blood pressure effects, such associations in the general population are less pronounced. The evidence of a link between blood lead and blood pressure was found to be strongest for systolic blood pressure in adult males. A 1.25mmHg rise in systolic blood pressure for every 5µg/dL increase in blood lead has been found and supported by several studies (Schwartz, 1995; Fewtrell, 2003, Pirkle, 1985). Corresponding associations were less robust in women, though females with blood lead levels as low as 4µg/dL exhibited elevated diastolic and a moderately increased systolic blood pressure (Nash et al., 2003; UNEP, 2010).

1.3 Cardiovascular effects

Even though less researched than an increase in blood pressure, numerous studies have examined possible adverse cardiovascular effects of lead exposure (ECHA, 2019). Based on the findings of occupational studies, cardiovascular deaths appear to increase significantly at measured lead concentrations between 20-40µg/dL. However, adjustments for non-occupational risk factors possibly confounding this relationship have not been included (EC, 2002; Glenn et al., 2003, Hu et al. 1996). Recent research, particularly that comparing exposure levels, provides evidence of an association between historical lead exposure and cardiovascular mortality (Bertke et al., 2016; Chowdhurry et al., 2014; ECHA, 2019; Kim et al., 2015; McElvenny et al., 2015; Steenland et al., 2017). Based on large epidemiological studies, evidence for negative effects on cardiovascular health were found in the general population at blood lead level measured as low as 65µg/dL (UNEP, 2015). Cardiovascular disease was also included as one of the health effects associated with low-level lead exposure. Based on a series of cohort studies, a link between bone lead and systolic blood pressure was found, seemingly a linear relationship declining with age. While cardiovascular events were treated as secondary health outcome in the GBD 2019 study, other studies of the peer-reviewed literature were able to quantify direct adverse cardiovascular health effects, starting at low lead concentrations of 5-10µg/dL (Fewtrell et al., 2004; Landrigan et al., 2018; Schober et al., 2006).

1.4 Cancer

The link between lead exposure and cancer is complex and mostly indirect, with evidence suggesting its potential to inhibit DNA repair and enhance the genotoxic effects of other agents (ECHA, 2019; Silbergeld et al., 2000). Rodent studies have shown that high doses of lead induce kidney tumours in rats and mice, as well as brain cancer in rats (Hiasa et al., 1983; Kobayashi et al., 1974). Additionally, pooled data from lead-exposed workers in 3 cohorts from different countries, revealed potentially elevated risks for brain, lung and stomach cancer, particularly in a Finnish cohort (Steenland et al., 2017). Based on the occupational research, lead's involvement in the development of carcinogenicity has been confirmed for blood lead levels above 30µg/dL (EC, 2002). Epidemiological studies conducted within the general population mostly provide evidence for an indirect process of lead exposure causing cancer in humans via an impairment of the DNA repair mechanism. Associations between lead exposure and lung cancer, and to a lesser extent, stomach cancer have been found (Landrigan et al., 2005). As the evidence for an association between blood lead concentrations and individual cancer types remains limited and inconsistent across studies, the association between total cancer mortality and blood lead was examined in the NHANES II cohort, resulting in sex-specific discrepancies of the yet significant effect (Schober et al., 2006; UNEP, 2010).

1.5 Renal effects (kidney dysfunction)

Occupational studies have widely investigated the negative effects of lead exposure on kidney function, with lead in bone or teeth proving to be the most informative biomarker (ECHA, 2019). Cohort studies of lead-exposed workers that examined kidney function in relation to blood levels found mostly non-significant trends without evidence to suggest excess mortality from kidney disease (McElvenny, 2015; Neuberger, 2009, Steenland, 2017). Evidence for a higher risk of experiencing kidney toxicity was found in individuals with high lead exposure levels of 40-70µg/dL (EC, 2002; ECHA, 2019). Nevertheless, epidemiological studies conducted among the general population suggested abnormal kidney function in individuals with long-term lead exposure at blood lead concentrations of 10-20µg/dL. Even more severe renal effects were found to increasingly occur starting at blood lead levels of 40µg/dL (NHMRC, 2015). Studies investigating an association between blood lead and renal effects are still relatively rare, resulting in a restricted evidence-base (Buser et al., 2016; Jain et al., 2022).

1.6 Further health effects (anaemia, impaired fertility)

Other adverse health effects have been associated with lead exposure, however observed in populations with relatively high blood lead levels that exceed the typical lead concentrations measured in the general population of Europe. An abnormally high frequency of anaemia cases, a deficiency of haemoglobin in the blood, was

observed in adults as well as children with blood lead levels of approximately 40µg/dL or higher (NHMRC, 2015). Another association was found between lead exposure and fertility. Evidence of harmful effects on sperm quality have been identified at blood lead concentrations exceeding 40µg/dL in studies involving lead-exposed male workers (EC, 2000, ECHA, 2019). Conversely, an occupational study involving women showed an increased risk of miscarriages at blood lead concentrations exceeding 50µg/L (Paredes Alpaca et al., 2013). Below these threshold levels of blood lead findings of studies vary (U.S. ATSDR, 2020).

1.7 Summary

Based on the studies highlighted above, a strong evidence-base supports the link between lead exposure and neurological effects as well as hypertension. Less conclusive research has been conducted in the case of cardiovascular disease and cancer. The association with cardiovascular disease has often been treated as a secondary outcome of hypertension and therefore the quantification of the indirect relationship with lead exposure was more challenging. On the other hand, the association with cancer is complex due to the diverse mechanisms by which lead might contribute to the development of carcinogenicity depending on the different types of cancers. The link between lead exposure and kidney dysfunction has been most pronounced with biomarkers like lead in bone or teeth, but less so in blood. Elevated occurrences of anaemia or impaired fertility have been identified at levels higher than the typical exposures in the general population in Europe. Taking into account the prerequisites for conducting the burden of disease study using the European Human Biomonitoring Initiative (HBM4EU) blood data in Europe, as well as these research outcomes, the adverse health effects concerning neurological and cardiovascular functions, hypertension and all-type cancer have been included in this study. Conversely, renal dysfunction, anaemia, and impaired fertility have not been considered due to a relatively small and inconclusive evidence base.

2 Overview of health outcomes associated with cadmium (Cd) exposure

Secondary literature including systematic reviews, meta-analyses, and official reports was summarized to establish the effect relationships of the health effects resulting from low-level exposure to cadmium (Cd) and evaluate the evidence-base. Firstly, the adverse health effects linked to Cd mentioned in the European Union Risk Assessment Report, identified by the Scientific Committee on Occupational Exposure Limits (SCOEL) as well as evaluated by the Occupational Safety and Health Administration (OSHA) were considered, all 3 assessing the risks of Cd exposure in occupationally exposed populations (ECHA, 2008; Hartwig et al., 2017; OSHA, 2013). Secondly, the technical report, a risk assessment of effects of Cd, as published by the Chemistry and Human Health, Division VII of the International Union on Pure and Applied Chemistry (IUPAC) was used as guidance (Nordberg et al., 2018). Additionally, a meta-analysis, conducted by the European Food Safety Authority (EFSA), summarising the available data on urinary-Cd and resulting dose-response estimations was considered (Alexander et al., 2009), plus 2 documents provided by the Joint FAO/WHO Expert Committee on Food Additives as a contribution to the International Programme on Chemical Safety (IPCS) with the agenda of assessing the impact of chemicals on human health and the quality of the environment (JECFA, 2004a/b, WHO; 1992).

2.1 Renal effects (kidney dysfunction)

Extensive evidence, from both human studies and animal experiments, establishes a link between Cd exposure and kidney dysfunction (Hartwig et al., 2017). The kidney was identified as the primary organ at risk by the effects of Cd exposure in studies with both the general population and occupationally exposed individuals (Alexander et al., 2009; ECHA, 2008; OSHA, 2013). Investigations to pinpoint the toxic threshold for Cd exposure have been conducted in occupational and non-occupational settings. Various studies, including a meta-analysis by the EFSA and a joint committee of the UN's Food and Agriculture Organization (FAO) and WHO, have focused on urinary Cd levels (Nordberg et al., 2018). Some limited studies have explored the connection with blood Cd. In a representative sample of the general adult population of the United States (1999-2006 NHANES), the association between renal dysfunction and Cd levels in both blood and urine was examined. Although previous studies considered Cd in blood to be the less reliable marker of health effects of the 2 (ECHA, 2008), this study showed that the elevated risk to develop chronic kidney disease (CKD) can be better predicted by measuring the Cd concentrations in blood, especially because urinary Cd levels are likely to be influenced by the confounding factor smoking (Navas-Acien et al., 2009; Ferraro et al., 2010; Hartwig et al., 2017). Determining a threshold of Cd exposure below which no adverse renal effects are observed remains a challenge and therefore Cd-related renal dysfunction should be investigated at low Cd concentrations as measured in the general population (Nordberg et al., 2018).

2.2 Effects on bones

Cd exposure can lead to significant skeletal damages, either as a secondary consequence of kidney damage or as a direct effect on bone cells (Alexander et al., 2009; WHO, 1992). Some studies suggest that Cd disrupts calcium metabolism and thus can contribute to osteoporosis. A well-established association exists between Cd-induced osteoporosis and an elevated risk of fractures (ECHA, 2008; Nordberg et al., 2018). While high Cd concentrations have been linked in several studies to adverse effects on bone tissue in occupationally exposed populations of both sexes, it has been shown that increased bone resorption can be induced at even low levels of Cd exposure in the general female population. Indeed, this pathway seems to be enhanced by menopause (Åkesson et al. 2006; Hartwig et al., 2017). Based on available evidence, long-term Cd exposure, even at relatively low urinary Cd levels, have been associated with an increased risk of adverse bone effects, including osteoporosis and reduced bone mineral density (ECHA, 2008; Nordberg et al, 2018). Consequently, establishing the lowest exposure levels that result in adverse bone effects is not feasible yet (Hartwig et al., 2017). Furthermore, Ougier et al. (2021) showed that the cost of osteoporosis associated with Cd exposure in women over 50 years of age is significant, thus supporting the importance of reducing Cd exposure in the population.

2.3 Cancer

Cohort studies of Cd-exposed workers or evidence from animal studies show that Cd may play a role in the development of cancer (Hartwig et al., 2017). However, the findings of studies investigating carcinogenic effects at low Cd exposure in the general public, have been controversial. While human cancer-related mortality rates have not shown statistical significance in various countries, the International Agency for Research on Cancer (IARC) classifies Cd and its compounds as human carcinogens. Assessing the cancer risk in numerical terms proves challenging due to inconsistent relationships in epidemiological studies and complex interactions with factors like smoking and other co-carcinogenic elements (ECHA, 2008; Nordberg et al., 2018).

2.4 Further health effects (anaemia, diabetes, blood pressure, cardiovascular effects)

Slightly reduced haemoglobin concentrations have been observed in individuals exposed to Cd in occupational settings or in patients suffering from the most severe form of Cd poisoning. These manifestations of anemia are not evident in individuals exposed to low levels of Cd in uncontaminated areas, and thus should not be included for risk assessment purposes. Given the pronounced accumulation of Cd in the pancreas, investigations have been conducted to explore the potential role of Cd in the development of diabetes. However, as of now, conclusive evidence has only been established through experimental studies on laboratory animals (ECHA, 2008; Nordberg et al., 2018). Studies conducted in occupational settings have revealed a decrease in blood pressure among individuals with severe Cd-induced renal dysfunction. Nonetheless, it remains unclear whether mild Cd exposure can lead to hypertension (Hartwig et al., 2017; Nordberg et al., 2018).

2.5 Summary

Renal dysfunction has been identified as the most important Cd-induced adverse health effect, through an extensive body of evidence from epidemiological studies in the work environment or in the general population, as well as experimental studies in animals. Furthermore, it has been shown that Cd in blood is less affected by confounding factors compared to urinary Cd. Relatively low Cd exposures in the general population have been associated with skeletal damage, including osteoporosis and an increased risk of fractures, especially in women at older ages, because of the compounding effect of menopause. Although some studies suggest a possible role of Cd in carcinogenesis, the epidemiological evidence for low-level exposure in the general population is inconclusive. Furthermore, Cd exposures have been associated with decreased haemoglobin concentrations, diabetes, high blood pressure, and cardiovascular impairment, but these associations remain unclear.

3 Overview of outcomes associated with PFOS/PFOA exposure

Assessments of adverse health effects from environmental exposure to perfluorooctane sulfonic acid (PFOS) or perfluorooctanoic acid (PFOA) conducted by the European Food Safety Authority (EFSA), the U.S. Environmental Protection Agency (USEPA), and the Agency for Toxic Substances and Registers (ATSDR) were considered to summarise the evidence. However, knowledge of the metabolic pathways of PFOS/PFOA remains largely based on animal studies and a relatively small number of epidemiological studies (Deepika et al., 2022). Mechanistic information on how effects take place also remain unclear.

3.1 Hypertension

The EFSA CONTAM Panel conducted a review of 9 studies, encompassing five cross-sectional and 4 longitudinal investigations. These studies explored various cardiovascular outcomes, including mortality, coronary heart disease, stroke, hypertension, and atherosclerosis. In summary, the collective findings from these studies did not provide conclusive evidence of a clear association between PFOS/PFOA and cardiovascular disease (EFSA CONTAM Panel, 2020). However, the longitudinal studies did suggest a slight increase in relative risk to develop cardiovascular disease and associations of PFOS/PFOA exposure with hypertension as well as blood pressure was statistically significant (Bao et al., 2017). Nevertheless, an analysis of data from the NHANES cohort failed to confirm such link between PFOA/PFOS levels and hypertension in both unadjusted and multivariable-adjusted analyses (USEPA, 2016). Thereby, establishing whether mild PFAS exposure can lead to hypertension remains challenging.

3.2 Small for gestational age and IQ loss

The EFSA CONTAM Panel conducted a comprehensive examination, incorporating 13 prospective studies and 4 cross-sectional studies, to investigate potential associations between PFOS/PFOA and birth weight. These studies collectively revealed relatively modest yet consistent inverse associations between both compounds and birth weight. However, it's important to note that not all studies provided clear evidence for such associations. Subsequent studies published after 2018 have suggested a plausible causal link between PFOS and PFOA and birth weight, a conclusion supported by most meta-analyses conducted to date (EFSA CONTAM Panel, 2020). Exposure to PFOS/PFOA has been linked to impaired foetal growth in both human and animal studies (Lam et al., 2014). This exposure may also result in a reduction of IQ, as a meta-analysis of 4 European birth cohorts showed (Gabbert, 2018). Additionally, there is a higher risk of developing the condition small for gestational age (SGA) associated with PFOS/PFOA exposure, a finding supported by research including 14 studies and a recent Scandinavian study (Bach et al., 2015; Lauritzen et al., 2016; Govarts et al. 2018). SGA not only increases the risk of premature death during childhood development but also has implications for the cognitive development (Ludvigsson et al, 2018). Various studies have consistently reported an association between SGA and impaired cognitive development (Hollo et al., 2002; De Bie et al., 2010). Recent research has shown that new-borns that are SGA are prone to IQ loss (Eves et al., 2020).

3.3 Hospitalization for lower respiratory infections

Hospitalization resulting from lower respiratory infections (LRTI) may be linked to a weakened immune response attributed to exposure to PFOS/PFOA. According to EFSA, exposure to PFAS may potentially increase the risk of infections, although the presence of more objective parameters is needed to confirm such infections (EFSA, 2020). A cohort study involving Danish children found a connection between elevated PFOS/PFOA levels and an increased risk of LRTI (Dalsager et al., 2021).

3.4 Further health effects (kidney/testicular cancer, ulcerative colitis, pregnancy, developmental toxicity, weight gain, fertility problems, liver diseases, thyroid diseases, elevated cholesterol levels)

Exposure to PFAS/PFAO has been linked to a range of health effects, including kidney and testicular cancer, ulcerative colitis, pregnancy, developmental toxicity, weight gain and fertility problems, liver diseases, thyroid diseases, and elevated cholesterol levels (C8 Science Panel, 2012; ATSDR, 2018; Cordner et al., 2021, Gaballah et al., 2020; Mitro et al., 2020; Ashley-Martin et al., 2016). Moreover, there is evidence of an association between PFAS exposure and adverse immunotoxic effects, such as a reduced antibody response to vaccination (Abraham et al., 2020). Several studies have also established a connection between prenatal PFAS exposure and low birth weight, which, in turn, has been associated with an increased risk of cardiovascular disease, respiratory disease, adult-onset diabetes, and impaired cognitive development (European Food Safety Authority, 2020; Cordner et al., 2021).

3.5 Summary

While the collective findings from various epidemiological studies did not conclusively establish a clear association between PFOS/PFOA exposure and cardiovascular disease, a statistically significant association was found for hypertension, which was further analysed and quantified within the NHANES cohort. PFOS/PFOA concentrations were also strongly linked to impaired foetal growth, measured as SGA, and lower IQ scores, as findings of several studies and meta-analyses showed. Furthermore, a weakened immune response and a higher risk for hospitalization due to LRTI was connected to PFOS/PFOA exposure. On the contrary, the evidence for the role of PFAS/PFOA in the development of disease outcomes such as kidney and testicular cancer, ulcerative colitis, pregnancy-related issues, developmental toxicity, weight gain, fertility problems, liver diseases, thyroid diseases, elevated cholesterol levels, and adverse immunotoxic effects remains to be clarified.

4 Overview of outcomes associated with phthalates exposure

The evaluation of the evidence base about the adverse health effects linked to phthalate exposure was mainly based on the updated risk assessment of the European Commission, the EFSA Panel on Food Contact Materials, Enzymes and Processing Aids (CEP Panel) as requested of the European Commission (EFSA, 2019), as well as the precedent review conducted by the European Chemicals Agency (ECHA, 2017). Additionally, human epidemiological studies provide evidence for associations between the exposure to phthalates and health effects. However, most of the research establishing how exposure to phthalates may result in adverse health effects comes from animal studies.

4.1 Asthma

The EFSA's human health hazard assessment indicates that exposure to phthalates, potentially even at relatively low levels, may increase the risk of various immunological disorders, including asthma (EFSA, 2019). According to the assessment of ECHA (2017), this conclusion aligns with the findings of several epidemiological studies which also provided evidence for adverse health effects due to phthalate exposure (Braun et al. 2013; Bornehag et al., 2004; Kolarik et al., 2008; Hsu et al., 2012). Additionally, there is a suggested link between environmental phthalate exposure and an increased sensitivity to allergens, potentially exacerbating asthma severity (Guo et al., 2012; You et al., 2014). Recent reports, systematic reviews, and meta-analyses have further reinforced the potential connection between phthalate exposure and asthma risk in the general population (Jaakkola and Knight, 2008; Li et al., 2017, the European Human Biomonitoring Initiative, 2020; Wu et al., 2020; Mattila et al., 2021). However, the understanding of the underlying mechanisms is still incomplete since the results of these epidemiological studies have not always been consistent. Some studies have reported positive associations, while others have shown negative or non-significant associations (Wu et al., 2020). Possible factors contributing to these variations include different types of phthalates studied, varying exposure time frames, and diverse sources of exposure data (Li et al., 2017). These variations also hamper conducting a meta-analysis.

4.2 Obesity/Diabetes mellitus

Animal studies with rodents provide evidence for an association between phthalate exposure and body weight (Majeed et al., 2017). In addition, several plausible pathways have been suggested on how phthalate exposure may contribute to the development of obesity or diabetes mellitus (Benjamin et al., 2017; Muscogiuri et al., 2017). Many studies conducted within the general population report statistical associations between urinary phthalate concentrations and increased risk of obesity, insulin resistance or type 2 diabetes mellitus (Song et al., 2016; Muscogiuri et al., 2017; Benjamin et al., 2017). In recent years, systematic reviews indicate an overall positive association between phthalate exposure and obesity, primarily for adults (Ribeiro et al., 2019, 2020). Since, these studies are limited in sample size, studied time periods, and mostly have a cross-sectional or retrospective design and are not designed to address specifically the effects of phthalate exposure on obesity or diabetes mellitus, the specifics of this exposure-response relationship are still uncertain (EFSA, 2019). However, based on the assessment of ECHA (2017a), the findings of several epidemiological, in vitro and animal studies confirm an obesogenic effect induced by phthalate exposure.

4.3 Fertility effects

Most of the available evidence regarding fertility effects and reproductive disorders linked to phthalates exposure comes from animal studies, making an application of these findings to calculate the burden of disease in human populations challenging. According to EFSA, the reproductive effects related to phthalates exposure were not permanent and did not result in reduced sexual function, fertility, or impaired development in animal studies (EFSA, 2019).

4.4 Further health effects (attention deficit disorder/attention deficit hyperactivity disorder)

Phthalate exposure has been associated with various health effects, including an increased risk of developing attention deficit disorder/attention deficit hyperactivity disorder (ADHD) (Engel et al., 2010; Hatch et al., 2010; Franken et al., 2017). Additionally, phthalates have been found to induce metabolic reactions, such as oxidative stress, exhibit estrogenic and androgen antagonistic properties, all of which play a crucial role in lipid and carbohydrate metabolism possibly further resulting in a variety of health outcomes (Gourlay et al., 2003; Jepsen et al., 2004; Woodward et al., 2020). Nevertheless, the evidence regarding causality for many of these health effects remains limited.

4.5 Summary

Epidemiological studies and systematic reviews provide strong evidence connecting phthalate exposure to asthma, and the variations in findings may be attributed to differences in phthalate types, exposure durations, and data sources. Both animal and epidemiological research suggest a link between phthalate exposure and body weight, potentially leading to obesity and diabetes mellitus, which is supported by systematic reviews. However, most evidence concerning fertility effects and reproductive disorders comes from animal studies, making it challenging to apply these findings to humans. Phthalate exposure has also been examined in relation to an increased risk of developing ADHD and has been associated with metabolic reactions like oxidative stress and hormonal disruptions. Nevertheless, the evidence for causality remains limited.

5 Overview of outcomes associated with pyrethroids exposure

The Scientific Committee on Occupational Exposure Limits (SCOEL) provided recommendations informing about the adverse health effects associated with pyrethroid exposure in occupational settings (SCOEL, 2003). Furthermore, the metabolic mode of action of pyrethroid (EFSA, 2022) plus a risk assessment related to neurodevelopmental health outcomes (EFSA, 2021) was investigated by the European Food Safety Authority (EFSA). All 3 documents were considered to establish the state of the evidence base related to health effects resulting from pyrethroids exposure and also the findings of epidemiological studies.

5.1 Attention deficit hyperactivity disorder (ADHD)

There is strong evidence that exposure to pyrethroids during pregnancy is a significant risk factor for the development of attention deficit hyperactivity disorder (ADHD) and thus has the potential to adversely affect neurodevelopmental disorders in children (Kian et al., 2022). Recent epidemiological studies have demonstrated an association between exposure to pyrethroids, even at low exposure level, and diagnosis of ADHD in children (Fritsche et al., 2018). Mechanistic evidence through the Adverse Outcome Pathways (AOP) platform and experimental animal studies support these findings (Anderson et al., 2022; Richardson et al., 2015). Based on EFSA's evaluations, both prenatal and postnatal exposure to pyrethroids has been associated with increased risk of ADHD diagnosis. However, the strongest evidence is for the association between pyrethroid exposure in utero and adverse neurodevelopmental effects, including ADHD symptoms (EFSA, 2021). Several epidemiological and cohort studies confirm this link (An et al., 2022; Dalsager et al., 2019; Lee et al., 2022). The European Environment Agency (EEA) also supports the link between pyrethroids and behavioural disorders (EEA, 2023). Overall, the evidence suggests a significant association between pyrethroid exposure during pregnancy and ADHD-related symptoms during development. More focused epidemiological studies (with information on prenatal pyrethroid exposure and clinical diagnosis of ADHD) are needed that confirm toxicity tests and mechanistic information.

5.2 Further health effects (liver damage, skin/respiratory inflammation, genotoxicity)

The role of pyrethroids in the development of health disorders such as liver damage, skin or respiratory inflammation has been studied. However, no conclusive evidence of such adverse health effects was found at low levels of pyrethroid exposure, which is common in the general European population (SCOEL, 2004). Various studies have investigated gene mutations or chromosome damage in relation to pyrethroid exposure, once again most research stems from animal and in vitro studies (EFSA, 2022).

5.3 Summary

Evidence stemming from epidemiological studies, mechanistic research and comprehensive assessments by EFSA and EEA linked pyrethroid exposure to an increased risk of ADHD and neurodevelopmental disorders in children. However, evidence for other adverse health effects such as liver damage, skin and respiratory inflammation, or genotoxicity were not conclusively associated with low level pyrethroid exposure.

6 Overview of outcomes associated with bisphenol A (BPA) exposure

Based on a risk assessment by the European Food Safety Authority (EFSA) and an evaluation by the European Chemicals Agency (ECHA), both summarizing potential adverse health consequences linked to bisphenol A (BPA), a comprehensive review of the adverse health effects associated with BPA exposure was conducted. In addition, this knowledge base was supplemented with findings from animal studies, long-term epidemiological studies, meta-analyses and systematic reviews.

6.1 Obesity

A growing body of scientific evidence suggests that BPA, as an endocrine disruptor, may interfere with metabolic processes that control fat accumulation and lipogenesis. Overall, recent systematic reviews, meta-analyses or BoD assessments indicate a positive association between BPA exposure and obesity, not only in adults but also in children (Wu et al., 2020; Kim et al., 2019; Rancière et al., 2015; Ribeiro et al., 2020; Rojas-Rueda et al., 2021). However, the results of the individual assessments in adults as well as in children were often based on a small number of studies, partly statistically not significant or biased and therefore hardly generalizable. Consequently, the strength of evidence from studies on humans is evaluated rather medium to low, though the strength of toxicological evidence is evaluated as strong (Rojas-Rueda et al., 2021). In the framework of the EFSA's risk assessment a total of 22 cross-sectional studies investigating the association between BPA exposure and obesity. While 21 of them found evidence for a statistically significant positive relationship, only 1 prospective study found that higher BPA concentration in maternal urine during pregnancy was linked with lower obesity rates in female offspring. These results give reason to believe that BPA may be obesogenic (EFSA, 2014).

6.2 Reproductive and developmental effects

Prospective studies provide evidence that environmental exposure to BPA during pregnancy may lead to impaired foetal growth or even decreased thyroid function in both mother and child. However, there is a possibility that these results were confounded by diet or other exposure factors. The associations found in the human studies are therefore insufficient to draw firm conclusions about the influence of BPA exposure on reproduction and childhood development (EFSA, 2014).

6.3 Further health effects

Evidence from numerous toxicological, animal and epidemiological studies further linked BPA exposure to health effects, such as developmental disorders, neurobehavioral conditions, asthma, diabetes mellitus, cardiovascular diseases or cancer (Rochester, 2013; Healy et al., 2015; Ma et al., 2019; Colorado-Yohar et al., 2021). However, the findings stemming from this research attempting to quantify these risk-outcome relationships is still inconclusive. According to EFSA's latest opinion on the potential health risk of dietary BPA intake, there is evidence from animal data that BPA exposure may cause adverse effects on the immune system (EFSA Panel on Food Contact Materials et al., 2023). Furthermore, animal studies with rodents linked BPA exposure to adverse health effects in kidney and liver, which may not yet be applied to the human population due to large physiological differences (EFSA, 2014).

6.4 Summary

A strong evidence base has been established for an association between BPA exposure and an increased risk of obesity, both in adults and children, supported by systematic reviews, meta-analyses, and assessments of official authorities indicating a positive association, even though the strength of evidence from human studies varies. Less conclusive are the results of prospective cohort studies that investigated the relationship BPA exposure during pregnancy and foetal growth and potentially or thyroid function in both mothers and children. These associations are possibly confounded by other factors, making firm conclusions about the influence of BPA on reproduction and childhood development challenging. Furthermore, BPA exposure has been linked to various other health effects, including developmental disorders, neurobehavioral conditions, asthma, diabetes mellitus,

cardiovascular diseases, and cancer, based on evidence from toxicological, animal, and epidemiological studies. Nevertheless, the quantification of these risk-outcome relationships remains inconclusive, especially since findings from animal studies may not directly be applied to humans due to physiological differences.

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