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Estimating the burden of disease due to lead, PFAS, phthalates, cadmium, pyrethroids and bisphenol A using HBM4EU data – test of feasibility and first results for selected countries

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Executive summary

Burden of disease analyses are progressively used in many thematic areas to quantify the population health impact of diseases, injuries and risk factors. In the last couple of years especially environmental factors were pushed stronger into the focus of such analyses. The increasing production amount and the further increased use of chemicals led to a continuous deposition of chemicals in the environment which in turn has led to a constant rise in exposure of the global population to hazardous chemicals. Therefore, the European Topic Centre "Human Health and the Environment" (ETC-HE) embarked on estimating the Environmental Burden of Disease (EBD) for chemicals to quantify their impact on the health of the European population.

This Eionet report summarizes the analyses performed in task 3.2.6.3 "Chemical burden of disease - Estimating the burden of disease of selected chemicals in Europe based on HBM4EU data" in the ETC-HE. This task followed the aim to test the feasibility of applying the EBD approach for chemicals. The report presents the first set of estimates on the environmental disease burden attributable to 6 chemicals/chemical groups for selected countries, where relevant human biomonitoring (HBM) and health data were available. For the selection of chemicals, we reviewed priority lists of institutions and projects (e.g. World Health Organization, WHO; Human Biomonitoring for the EU, HBM4EU; Partnership for the Assessment of Risks from Chemicals, PARC) to arrive at a relevant, but, in light of the resource and time constraints of this task, still manageable set of chemicals. Finally, we considered lead, per- and polyfluorinated alkyl substances (PFAS), phthalates, pyrethroids, cadmium and bisphenol A as chemicals of concern for population health in Europe and estimated where possible the Disability-Adjusted Life Years (DALYs) attributable to risk factor specific exposure in several (number of countries varies by chemicals considered) European countries for the year 2021. Data gathered in the recent European Human Biomonitoring Initiative, the so called HBM4EU-project, served as the basis for the exposure assessment. Some additional countries outside Europe (e.g. Israel) participated also in the HBM4EU-project and consequently it was possible to make burden of disease estimates here. In the aligned studies under HBM4EU-project, HBM samples were collected and statistically processed in a harmonized way but also existing HBM data prior to the HBM4EU-project were collected and statistically harmonized although measurements were not quality controlled. We applied the top-down approach to estimate the attributable disease burden. This approach is also known as the Comparative Risk Assessment (CRA), or specifically for environmental risks as the EBD approach. In the best case we aimed to estimate the DALYs which consists of the years of life lost due to death (YLLs) and the years lived with disability (YLD). Even though the efforts of the HBM4EU-project improved the coverage of harmonized HBM data in Europe, the data on HBM are still patchy (e.g. missing years, limited number of EU countries, etc.) and do not allow a full assessment of the disease burden for all countries in Europe. Nonetheless, we tried to estimate the attributable burden for 15 risk-outcome-pairs for the year 2021 and started from most recent HBM data. EBD estimates per considered chemical for different countries are described below.

Lead was not measured in the HBM4EU aligned studies but data on other existing HBM studies were collected. Lead attributable disease burden was estimated for 3 countries and the highest burden was found for all-cause mortality in Belgium with 986 deaths per 1,000,000 persons; it must be noted though, that the Belgian exposure data were the most dated (2004-2005) since more recent data are lacking and the age interval considered was larger compared to other countries. In recent Flemish HBM campaigns (FLEHS) it was observed that for adolescents blood lead concentrations dropped significantly over the last 20 years so the estimate of the burden attributable to lead presented in this report might probably be overestimated.

More recent HBM exposure data were available for PFAS. The number of countries with estimates of disease burden attributable to PFAS exposure varied by risk-outcome-pair. The focus for the EBD calculation was on PFOS (perfluorooctanesulfonic acid) and PFOA (perfluorooctanoic acid). A first estimate of the EBD showed that for hypertension, out of 5 countries, the highest burden was found

in Belgium with 89 DALYs per 1,000,000 persons. The state of newborns being small for gestational age and the resulting IQ loss was associated with about 437 DALYs (only YLDs) per 1,000,000 persons in France, where the highest DALYs attributable to this risk-outcome-pair were detected. Overall, the burden for this risk-outcome-pair was calculated for 9 countries. In addition, DALYs were also estimated for hospitalizations related to lower respiratory infections. The highest burden was found in Norway with 13 DALYs (only YLDs) per 1,000,000 persons attributable to the PFAS exposure. For other health outcomes related to PFAS exposure, estimates were not yet performed but for example for kidney cancer a review is ongoing to assess the weight of evidence.

For phthalates, here for the metabolites DEHP (di(2-ethylhexyl) phthalate) and MCOP (monocarboxyoctyl phthalate), we estimated the attributable burden for asthma, obesity and diabetes mellitus (only women). The attributable burden for asthma was estimated for 9 countries, with the highest burden found in Greece with 53 YLDs per 1,000,000 persons. The attributable burden for obesity was also highest in Greece with 11,324 obesity cases per 1,000,000 persons attributable to MCOP exposure. For diabetes mellitus, the highest burden attributable to DEHP was found in Polish women, amounting to 1,324 YLDs per 1,000,000 women.

For cadmium, the disease burden related to chronic kidney disease was calculated for 4 European countries, with Czechia showing the highest burden at about 142 YLDs per 1,000,000 persons. For osteoporosis, 10 European countries were considered with the highest burden attributable to cadmium exposure estimated for Poland with 2,025 DALYs per 1,000,000 persons.

The burden due to pyrethroids was estimated based on the marker 3-PBA (3-phenoxybezoic acid), to describe the exposure. The outcome selected was attention deficit hyperactivity disorder (ADHD) for which the weight of evidence for being associated with 3-PBA is increasing. We calculated the highest burden for Israel, with 35 DALYs (only YLDs) per 1,000,000 persons due to ADHD. The number of DALYs is relatively low due to the low disability weight for ADHD but it was estimated that on average 1 in 5 ADHD cases was attributable to pyrethroid exposure. When attributable costs for society would be calculated the impact would be relatively large seeing the prevalence of ADHD and associated costs.

Finally, we also estimated the disease burden resulting from bisphenol A. We calculated the obesity associated burden and quantified the highest attributable obesity prevalence for children in Germany with 954 prevalent cases per 1,000,000 persons, but it should be noted that only two countries were considered based on the available exposure data. For adults aged 20-44 years 5 countries with existing exposure data were considered. The highest burden was estimated for Poland, with 8,290 obesity cases per 1,000,000 persons.

Overall, we have identified many relevant challenges when estimating the burden attributable to the selected chemicals. Especially the missing data (e.g. HBM data for countries, age groups or sex or differences in exposure by socio-economic status) need to be tackled by adequate gap filing techniques in the next years. Currently we can only highlight the burden in countries where data is available and thus identify the countries with the highest burden according to this data. The disease burden might be higher in countries currently out of the scope of our estimation and this needs to be kept in mind when interpreting our results which are not representing all European countries. Here, also the European initiatives such as PARC can help to gather more HBM data to allow a more comprehensive assessment of the burden of disease.

Aiming at a comparable set of estimates, we witnessed that even using the same baseline method for all chemicals, the differences in input data were strong, not allowing direct comparisons of the final burden of disease results. For example, we could not retrieve the estimates for the same age groups, because either HBM data was missing or there was not enough evidence for the risk-outcome-pair combinations for specific age groups. We also could not assure the same level of evidence for the selected risk-outcome-pairs. This clearly indicates the need to improve the baseline input data for burden of disease assessments related to chemicals. Varying quality and availability of data hampers the comparability and the results should be interpreted with the right level of caution.

We see that a part of the disease burden of EU citizens is attributable to the 6 selected chemicals. For the metals lead and cadmium, exposure needs to be followed up. Where for lead the exposure and disease burden decreased over the last two decades in several EU countries, cadmium exposure is still relatively high especially in vegetarians. According to the European Food Safety Authority (EFSA) there is a need to reduce cadmium exposure. Also, for the man-made chemicals (phthalates, bisphenols, pyrethroids, PFAS) access to sustainable harmonized HBM exposure and health data covering the EU will improve estimates of the disease burden. Benefits of the use of these chemicals should be analyzed and regrettable substitution be avoided. Where chemical regulation is a slow process, exposure reduction through hygiene measures can already be stimulated. Seeing the expected significant increase in chemical production and diversity of chemicals in the EU towards 2050, the mixtures of chemicals to which we are exposed tends to increase and efforts should be taken to minimalize this considering the One Health principle.

1 Introduction and background

The contribution of environmental risk factors to the overall burden of disease (BoD) is relevant and evident, which was already shown in various studies all over the world. Landrigan and colleagues, as part of the Lancet commission on pollution and health, described in their publication that according to currently available BoD estimates around 16 % of all global deaths can be attributed to environmental pollution. They summarized that about 92 % of these deaths occurred in low- and middle income countries (Landrigan et al., 2018). The World Health Organization (WHO) estimated the Environmental Burden of Disease (EBD) and their estimates are in a comparable order of magnitude, with 23 % of global deaths and 22 % of global Disability-Adjusted Life Years (DALYs) attributable to environmental risk factors (Prüss-Ustün et al., 2017). The WHO analyses also identified low- and middle-income countries as more prone to the health effects of environmental risks. Here, especially communicable diseases were identified as an important driving force. This is also supported by the most up-to-date global estimates provided by the Global Burden of Disease (GBD) study, where in low income countries in 2019 about 32 % of deaths and 29 % of DALYs due to communicable, maternal, neonatal and nutritional conditions were attributable to environmental risk factors (GBD 2019 Risk Factors Collaborators, 2020; IHME, 2022).

These analyses mainly indicate the unmet need to improve basic living conditions particularly because risk factors such as inadequate sanitation, no access to clean drinking water or indoor air pollution due to cooking and heating with solid fuels, still cause a tremendous disease burden in these countries.

From a European perspective, where at least for a large share of the population basic living conditions have improved in the last decades, other environmental risk factors play a more important role. In Europe, especially ambient air pollutants are the environmental risk factor group causing the largest BoD (GBD 2019 Risk Factors Collaborators, 2020). A report published in 2022 by the European Environment Agency (EEA) states that exposure to air pollution, carcinogenic chemicals, radon, UV radiation and second-hand smoke together may contribute over 10 % of the cancer burden in Europe (EEA, 2022).

Because the global estimates from the GBD-study focus on the “classical” environmental risk factors, they, to a certain extent, do not meet the specific challenges in Europe, with respect to magnitude and type of environmental exposures. The exposure to various chemicals or chemical groups, such as phthalates, per- and polyfluoroalkyl substances (PFAS) or pesticides, is a growing challenge in Europe, posing a serious risk to population health of current and especially future generations. These chemicals can enter the body through various routes from which food consumption was shown to be the most relevant exposure source (Gibb et al., 2015, 2019).

Chemical pollution is a great and growing global threat. Effects of chemical pollution on human health are however poorly defined and quantified (Prüss-Ustün et al., 2011). Since 1950, more than 140,000 new chemicals have been synthesized. The production volume of synthetic chemicals is still increasing and is expected to triple in 2050 compared to 2010 (OECD, 2012).

Measuring the BoD attributable to chemicals remains critical especially because when using the Comparative Risk Assessment (CRA) as introduced by the GBD-study, many necessary parameters are not available or are uncertain or different approaches (top-down or bottom-up) are needed. This hampers the use of the CRA for chemicals, which consequently leads to missing quantitative estimates of the impact on population health. Thus, it remains challenging to feed such estimates into the relevant policy discussions. Already in 2011, Prüss-Üstün and colleagues indicated that estimating the disease burden due to chemicals is necessary but very complex and often results in an underestimation of the true population health impact (Prüss-Ustün et al., 2011). Estimates are often based on a limited set of exposure-response functions with lower levels of evidence as compared to risk factors better studied in human surveys. There are several assessments available that focus on single chemicals or

chemical groups. However, as methodologies and assumptions vary widely, a direct comparison of the estimates is limited (Trasande et al., 2016; Thomsen et al., 2022).

Generally, there is a need for a more standardized and comprehensive assessment of the disease burden due to chemicals. Therefore, the aim of the task "Chemical burden of disease - Estimating the burden of disease of selected chemicals in Europe based on HBM4EU data" is to estimate the EBD using a widely consistent methodology, in the best-case having estimates of DALYs. For the assessment of the exposure towards the selected chemicals it is aimed to use the data gathered within the HBM4EU-project to have, at least for some chemicals, a better comparable baseline data for the exposure of the European population.

The overarching aim of the underlying assessment was to test the feasibility of estimating the EBD due to chemicals using human biomonitoring (HBM) data as the basis for the exposure assessment. For a first assessment we prioritized lead (Pb) and cadmium (Cd) as more classical and historically important chemicals. Lead and cadmium still pose a threat to human health. The exposure of populations towards lead in many European countries is stagnating with no further significant reductions. There is also an increase in demand due to lead use in energy efficient vehicles, which might also pose an additional source for human exposure in the near future. In addition, in an occupational HBM study of European workers in the e-waste sector implemented in the scope of the HBM4EU-project, higher exposures were measured for lead, revealing clusters of high exposure in the European population (European Chemical Agency, 2020).

Recent studies on cadmium related BoD and costs have shown that the cost attributed to cadmium exposure related osteoporosis in women aged over 50 years is substantial (Ougier et al., 2021a). With further demographic change towards elderly populations, it is worthwhile to consider the impact of cadmium on these vulnerable groups. We additionally strived to estimate the BoD for phthalates, which are ubiquitous chemicals, and the PFAS (perfluorooctanesulfonic acid, PFOS, and perfluorooctanoic acid, PFOA) which are currently strongly debated in many European countries. We also included pyrethroids as an important segment of the pesticide group. Pesticides are still used in high volumes and the impact of restrictions might take time, with further increased exposures of the European populations. Estimating the population health impact of pesticides might support ongoing activities to reduce or ban pesticides, such as the proposed regulation on the sustainable use of plant protection products and other commitments under the Farm to Fork strategy and the Zero Pollution Action Plan. In addition, we also selected bisphenol A (BPA), because we consider the relevance of BPA to increase with the new tolerable daily intake (TDI) value published by the European Food Safety Authority (EFSA) (EFSA Panel on Food Contact Materials et al., 2023). Therefore, it was considered of great interest to quantify its impact on population health in Europe.

It is important to note, that this report describes the first set of estimates and the methodology is not entirely streamlined, as we needed to test the most suitable approaches for the different chemicals.

2 Environmental burden of disease methodology

The EBD methodology was developed by the WHO to focus BoD assessments on environmental risk factors (Prüss-Üstün et al., 2003). Generally, EBD is based on the CRA methodology which was developed during the first GBD-study (Murray et al., 2003). The CRA, also sometimes referred to as the "top-down approach", allows to estimate the share of the disease burden that can be attributed to the exposure towards a risk factor. With the DALY, and other burden of disease indicators, such as deaths, Years Lived with Disability (YLDs) and Years of Life Lost due to death (YLLs), the CRA uses the same outcome parameters as general BoD studies, before the attribution to risk factors. This enables direct comparisons of the results between selected risk factors as well as with diseases and injuries. Such comparisons are very useful for setting priorities for prevention and intervention measures. As EBD

follows the general idea of a CRA, a stepwise approach is taken for estimating the attributable disease burden (Plass et al., 2022).

The next section describes these steps and also explicitly specifies the assumptions that are used in the underlying analyses to arrive at EBD estimates for lead, PFAS, phthalates, cadmium, selected pyrethroids and BPA.

Before starting the stepwise CRA procedure, relevant risk factors must be selected. We therefore reviewed existing priority lists for chemicals already elaborated by other institutions. We consulted WHO documents and priority lists from the HBM4EU- and PARC-project. The selected chemicals should be of importance for the European population and the anticipated workload of estimating the attributable burden of disease should be within the resource and time constraints of the ETC-HE task. We selected on the one hand more "classical" or historically important chemicals such as lead and cadmium, but on the other hand also included chemicals which more recently were prioritized due to their negative effects on health. We also selected the chemicals based on their wide range of potential health effects including endocrine disrupting, neurologic or cardiovascular effects. It was aimed to include risk factors with different characteristics to be able to test the feasibility for a broad scope of possible features and varying input data. Generally, we were only able to estimate the effects of single chemicals on the respective health outcomes, not considering any combined effects.

Step 1: Definition of exposure

For the assessments in this report the population exposure to a certain chemical is defined as the internal concentrations of a chemical or its metabolite in human bodily fluids (e.g. blood, urine), as considered in the context of the HBM4EU-project.

Step 2: Exposure assessment

For all chemicals considered in this assessment, exposure data gathered in the HBM4EU-project form the basis for the exposure assessment. The HBM4EU-project was a joint project of 30 countries, the European Environment Agency and the European Commission. This initiative coordinated and advanced HBM activities in Europe. The HBM4EU-project has generated evidence regarding the exposure of citizens to chemicals and the potential health effects (for more information visit the HBM4EU-Website). Both aligned studies, where the chemicals and metabolites were measured following similar chemical-analytical protocols under a QA/QC program and using uniform statistics to generate statistical distributions, as well as concentration estimates outside of the aligned studies were used for the exposure assessment (e.g. occupational studies). When available the necessary data was extracted from the HBM4EU-dashboard.

Lead concentrations as measured in human blood samples were used to estimate the population-based exposure. Depending on the health outcomes PFAS concentrations in serum (in adults, teenagers and children) or cord-blood (newborns) were used. For phthalates, their metabolites or the summarized concentrations of certain phthalate metabolites were measured in urine samples. Cadmium was measured in blood samples. For pyrethroids, data on the marker 3-PBA was used to assess the pyrethroid concentration in urine. BPA was measured in urine samples.

Streamlining the exposure assessment is only realizable to a certain extent as e.g. not all chemicals and metabolites are measured in the same media. For this reason, considerable flexibility within the exposure assessment is necessary. Thus, the methods to assess the exposure and also to fill some existing gaps differ between the chemicals.

Step 3: Identification of risk-outcome-pairs

We reviewed the most recent peer-reviewed-literature and relevant reports from key institutions or projects to identify relevant health outcomes that showed consistent associations with the selected chemicals and for which burden of disease estimates could be calculated. The following health outcomes were identified for the 6 chemicals/chemical groups (Table 2.1). Ideally the evidence of the causal associations between the risk-outcome-pairs is evaluated using appropriate tools. For a first assessment and to test the feasibility of using HBM4EU data in EBD assessments we did not perform a formal evaluation and relied on the expertise of the ETC members and external experts. We compiled relevant information on the risk-outcome-pairs in the chapters on "mode of action and weight of evidence". In these sub-chapters the general biological/mechanistic associations between a chemical and outcome and the relevant underlying studies describing the evidence are presented. Additional information on the risk-outcome-pairs can also be found in Annex A1.1.

Table 2.1: Selected risk-outcome-pairs and considered population groups

Risk factor	Health outcome	Population group
	All-cause mortality	Adults
	Cardiovascular mortality	Adults
	Cancer mortality	Adults
	Hypertension	Adults
Lead	(Mild) intellectual disability	Children
	Hypertension	Adults
	Small for gestational age and IQ loss	Newborns
PFOS/PFOA	Hospitalization for lower respiratory infections	Children
	Asthma	Children/adolescents
	Obesity	Adults
Phthalates	Diabetes mellitus	Adult women
	Chronic kidney disease (CKD)	Adults
Cadmium	Osteoporosis	Adult women
Pyrethroids	Attention deficit hyperactivity disorder (ADHD)	Children
Bisphenol A	Obesity	Children/adolescents/adults

Step 4: Quantification of the association between risk exposure and outcome

To estimate the population attributable fraction (PAF) a quantitative exposure-response estimate is required. Generally, the formula to estimate the PAF requires a relative risk (RR) as the key input parameter. For many chemicals RRs are not available requiring hazard ratios (HR) or odds ratios (OR) to be used in the formula or the RR to be estimated based on the OR (Zhang and Yu, 1998). This limitation is crucial as e.g. OR can only be used as approximation for the RR under low prevalence assumption (prevalence less than 10 %).

The effect estimate can either follow a dichotomous, a categorical or a continuous exposure. For chemicals mostly categorical or continuous exposures were considered. Under a continuous exposure the RR, OR or HR can e.g. be estimated for a certain increase of exposure. Here, an exposure-response function (ERF) can be derived allowing to extrapolate the effect estimates to required exposures. The

effect estimates used for the analyses in this analysis are presented in the risk factor specific sections or in the supporting electronic files.

Generally, the attributable burden can be estimated in two ways, the bottom-up and the top-down approach. In the bottom-up approach the exposure-response relationships are exploited to estimate e.g. the additional number of cases from a certain disease that would occur when the exposure towards a risk factor is increased. Mostly these new cases are referred to as incident cases. Here, no total disease envelope is estimated and health data for the baseline burden of disease is not used. A disease envelope describes the total amount of burden e.g. total number of deaths due to a disease in a country as found in the vital statistics.

In the top-down approach, first the baseline burden of disease (envelope) is estimated by calculating e.g. YLLs, YLDs and DALYs for a certain disease. By using the PAF, a certain share of the baseline disease burden is then attributed to the risk factor. The analyses presented in this report follow the top-down approach. However, the estimation process for calculating the baseline burden of disease differs. In some cases, disease/death rates are combined with population data to estimate the overall number of prevalent cases or deaths. In other cases, data from national/international registries or population-based surveys are used as key information on the baseline burden of disease. If such data were not available, results from the GBD 2019 study were used to arrive at baseline burden of disease estimates(GBD 2019 Diseases and Injuries Collaborators, 2020). The general preference was to use data from existing European data bases to ensure transparency and reproducibility of our results.

Step 5: Calculating the PAF

Combining the population-based exposure estimates of step 2 with the quantitative estimates for the associations identified in step 4, the PAF can be estimated representing the share of disease burden that can be attributed to a certain risk factor. Depending on the exposure, different versions of the PAF formula can be applied (Plass et al., 2022). The simplest version of the PAF reads as follows:

$$[1]\ PAF = \frac{RR-1}{RR}$$

Step 6: Estimation of the EBD

In the final step the (cause specific) BoD-estimates (e.g. DALYs) are multiplied by the PAF which results in the burden attributable to a certain risk factor. This part is referred to as attributable burden (AB). For the estimation of the baseline BoD estimates no time-discounting or age weighting were used. To estimate the morbidity component (YLD) we used the prevalence-based approach.

$$[2]\ AB = BoD * PAF$$

Reference year for the estimates

For better comparability, all results were calculated for the reference year 2021. However, where health or exposure data were not available for the reference year, assumptions or adjustments were made: First we applied the most recent prevalence or death rates to the population of the reference year 2021. Second, with regard to exposure, data for 2021±5 years were partially used to improve data availability and spatial coverage (more countries considered).

3 Results

The following Table 3.1 provides a navigation through our results and summarizes which BoD-indicators were estimatied for the selected risk-outcome-pairs and countries. A summary table of all results can also be found in Annex A3.1.

Table 3.1: Summary of considered risk-outcome-pairs

Risk factor	Health outcome	Population group	Countries covered	Indicator covered
Lead	All-cause mortality	Adults	Belgium, Czechia, Slovenia	PAF, attributable deaths
	Cardiovascular mortality	Adults	Belgium, Czechia, Slovenia	PAF, attributable deaths
	Cancer mortality	Adults	Belgium, Czechia, Slovenia	PAF, attributable deaths
	Hypertension	Adults	Belgium, Czechia, Slovenia	PAF, attributable cases, YLDs
	(Mild) intellectual disability	Children	Belgium, Czechia, Germany	DALYs
PFOS/PFOA	Hypertension	Adults	Austria, Belgium, Czechia, Denmark, Norway, Spain	PAF, attributable deaths, attributable cases, DALYs
	Small for gestational age and IQ loss	Newborns	Belgium, Germany, Greece, France, Slovenia, Slovakia, Sweden, Norway, Spain	PAF, attributable cases, DALYs
	Hospitalization for lower respiratory infections	Children	Austria, Belgium, Czechia, Denmark, Norway, Spain	PAF, attributable cases, DALYs
Phthalates	Asthma	Children/adolescents	Belgium, Czechia, Germany, Greece, Poland, Slovakia, Slovenia, Spain, Sweden	PAF, YLDs
	Obesity	Adults	Belgium, Czechia, Denmark, France, Germany, Greece, Hungary, Netherlands, Norway, Poland, Slovakia, Slovenia, Spain, Sweden	PAF, attributable cases
	Diabetes mellitus	Adults (only women)	Belgium, Czechia, Denmark, France, Germany, Greece, Hungary, Netherlands, Norway, Poland, Slovakia, Slovenia, Spain, Sweden	PAF, YLDs
	Chronic kidney disease (CKD)	Adults	Czechia, Belgium, Slovenia, Norway	PAF, attributable cases, YLDs
Cadmium	Osteoporosis	Adult Women	Czechia, Belgium, Denmark, Germany, Hungary, Poland, Slovakia, Slovenia, Spain, Sweden	PAF, attributable cases, YLLs, YLDs, DALYs
Pyrethroids	ADHD	Children	Belgium, Cyprus, France, Germany, Iceland, Israel, Netherlands, Slovenia Switzerland	PAF, DALYs
Bisphenol A	Obesity	Children/adolescents/adults	Adults: Austria, Germany Children/Adolescnets: Czechia, Croatia, Finland, Poland, Portugal	PAF, attributable cases

3.1 Burden of disease due to lead

3.1.1 General information on lead and basic assumptions

Population exposure to lead has been a long-recognized challenge in low- and middle-income countries, where policies often fail to reduce hazardous sources of lead in the environment (Kordas et al., 2018; Ericson et al., 2021). However, lead exposure in European countries is still relevant, especially now that recent studies have revealed that health consequences may occur at lower exposure levels that previously were considered as safe (Bierkens et al., 2011; Apel et al., 2017; European Chemical Agency, 2020; Lermen et al., 2021). The most common sources of lead are lead-contaminated soil, water or utensils, electronic and electric waste, batteries, lead-based paint in old houses, dust from industrial emissions, imported ceramics, cosmetics, toys or traditional medicines (Obeng-Gyasi, 2019). Evidence of negative health effects and physiological changes due to lead are accumulating due to new studies investigating different exposure-response relationships. Blood lead concentrations have mostly been shown to negatively impact blood pressure, protective mechanisms against carcinogens and neurobehavioral functioning (Steenland and Boffetta, 2000; Nawrot et al., 2002; Virgolini and Aschner, 2021). Even though the influence of low blood lead concentrations is generally classified as mild, these pathways may progress into a serious health condition over the lifetime and result in a significant impact at the population level (Kim et al., 2015). While increased blood pressure may result in a variety of heart diseases such as cardiovascular, cerebrovascular or ischemic heart disease as a single entity from the group of cardiovascular diseases (Fewtrell et al., 2003). A loss in IQ points was shown to be especially problematic for young children because of its potential to increase the risk of mild intellectual disability (Lanphear et al., 2005).

Adverse health outcomes result from a toxic mechanism induced by elevated lead exposure. Thereby, lead ions (Pb^{2+}) are absorbed into the blood stream binding to circulating erythrocytes that distribute it throughout the body. Consequentially, lead accumulates in the brain, liver and kidney tissue and is eventually stored in the bone for up to 30 years (Virgolini and Aschner, 2021). Antioxidant reserves are depleted by the increased concentration of lead in the body due to the formation of reactive oxygen species (ROS), also known as oxidative stress (Kim et al., 2015). Glutathione (GSH) is one of the most important substances with an antioxidant capacity and available in almost every cell at high concentrations, usually up to 90 percent in a reduced form and to only 10 in an oxidative state (Ahamed and Siddiqui, 2007). However, due to the influence of lead, the defense mechanism of GSH is disturbed by oxidation induced through an accumulation of ROS. In addition, lead has the potential to deactivate important enzymes, which may lead to the destabilization of cell walls. In extreme cases, the cell membranes of the red blood cells are damaged to an extent that the hemoglobin escapes into the blood plasma. This may further result in an insufficient transport of oxygen to the organs, known as anemia. The sum of these processes results in higher vulnerability to oxidative stress and cell death (Patrick, 2006). Furthermore, neurological functions may be affected mainly due to the ion mimicry mechanism of Pb^{2+}. Already at relatively low levels of lead exposure, lead has the potential to compete with calcium ions (Ca^{2+}), zinc ions (Zn^{2+}) and iron ions (Fe^{2+}) for insertion sites and essential functions. Nutritional deficiencies even increase the lead susceptibility and gastrointestinal Pb^{2+} absorption. In contrast to calcium ions lead is able to cross the blood-brain barrier, leading to lead accumulation in the brain tissue. This may negatively influence the formation of the myelin sheath, which results in a reduced neurotransmitter activity and an impairment of brain function (Virgolini and Aschner, 2021). Furthermore, lead exposure has been identified as a risk factor for cardiovascular disease. Possible pathways resulting in an increased probability for the development of a thrombosis are lead-induced inactivation of nitric oxide, increased formation of hydrogen peroxide, inhibition of endothelial repair, or impairment of angiogenesis. All these factors have been linked to negative heart implications (Landrigan et al., 2018). Lead exposure in the general population is most commonly quantified via the biomarker blood lead (PbB), which was therefore employed in the HBM4EU data collection. This measurement method is best known for its high sensitivity to current lead exposure and has a mean

observation time characterized by an elimination half-life of approximately one month. Lead content in blood is the best validated biomarker, as it is clearly associated with environmental exposure (European Chemical Agency, 2020).

For the estimation of the EBD due to lead exposure in the general European population, the following criteria were applied to select which health outcomes to prioritize: evidence in the scientific literature confirming a robust ERF, availability of exposure and population data to perform disease burden calculations, and high political and public interest in quantifying the contribution of environmental lead exposure to disease cases. Therefore, the health effects (mild) intellectual disability due to an increased risk of IQ loss in children, hypertension morbidity as a primary health outcome as well as cardiovascular disease mortality as a secondary health outcome resulting from a higher risk of increased blood pressure, plus mortality due to the carcinogenic potential of lead were considered in this report (Fewtrell et al., 2003; Lanphear et al., 2005; Schober et al., 2006). Due to non-availability of survey data within the HBM4EU-project including measurements of lead in bones and according risk quantifications in the scientific literature morbidity was neglected here.

A further overview on relevant health effects related to lead exposure can be found in Annex A1.1.

3.1.2 All-cause, cardiovascular disease and cancer mortality in adults

Environmental lead exposure has been identified as a risk factor for a variety of diseases, mostly associated with high blood pressure or a carcinogenic effect. However, the evidence base has not yet been conclusively established for all lead-induced health outcomes. Therefore, all-cause mortality is used to estimate the number of deaths due to low-level lead exposure (Lanphear et al., 2018). The association between lead exposure and all-cause mortality has become evident due to studies in subpopulations exposed to high levels of lead resulting from occupational exposures. Miners were found to experience lead poisoning due to the coal and dust particles increasing their likelihood to develop cancer, famous painters were suffering from mental disorders due to the high concentrations in their lead-based paint or newspaper printers and typewriters who were exposed to lead in ink (Collis, 1923; Michaels et al., 1991; Cocco et al., 1994; Montes-Santiago, 2013).

Recent studies have found an association between all-cause mortality and low levels of blood lead concentrations, showing that the risk is still relevant at concentrations found today (Menke et al., 2006; Schober et al., 2006; Landrigan et al., 2018). A relationship between blood lead levels and all-cause and cancer mortality as well as cardiovascular disease mortality has been established based on data from the National Health and Nutrition Examination Survey (NHANES III), which specifically investigated a population with low lead exposure as it is observed in Europe (Schober et al., 2006). Today, cardiovascular diseases are the main cause of death and the health condition with the biggest share of the global burden of disease (GBD 2019 Diseases and Injuries Collaborators, 2020). On the other hand, there is a long history of occupational risk studies providing evidence for an association between lead and various cancer types in subgroups, which lead to follow-up investigations of the carcinogenic potential of lower lead levels in the general population (Steenland and Boffetta, 2000).

Exposure-response relationship

Based on the NHANES III-data an exposure-response relationship between the blood lead concentrations of participants 40 years of age or older (n = 9,757) and the mortality risk was established. Number of deaths due to cardiovascular diseases, cancer and all-causes is assumed to increase at a blood lead concentration of 50µg/L and to continuously worsen with higher lead levels (Schober et al., 2006). The figure displaying this ERF in detail can be found in Annex A2.1.

Additionally, multivariable adjusted relative risks were provided for 3 different lead concentrations (less than 50µg/L, 50-100µg/L, more than 100µg/L) and age groups (40-74 years, 75-84 years, older than 85 years) or as normalized measure that may be applied to all ages (Table 3.2).

Table 3.2: Multivariable adjusted relative risks for all-cause, cardiovascular disease and cancer mortality by blood lead level and age category

	Blood lead level	Relative risk (95 % CI) by age category years			
		40-74	75-84	>85	All
All-cause	<50µg/L	1	1	1	1
	50-100µg/L	1.30 (1.03-1.65)	1.38 (1.04-1.83)	0.98 (0.85-1.14)	1.24 (1.05-1.48)
	>100µg/L	1.73 (1.28-2.35)	1.39 (0.93-2.08)	1.67 (1.11-2.53)	1.59 (1.28-1.98)
Cardio-vascular	<50µg/L	1	1	1	1
	50-100µg/L	1.11 (0.79-1.56)	1.41 (0.87-2.28)	1.07 (0.87-1.31)	1.20 (0.93-1.55)
	>100µg/L	1.47 (0.93-2.33)	1.71 (0.94.3.09)	1.45 (0.85-2.48)	1.55 (1.16-2.07)
Cancer	<50µg/L	1	1	1	1
	50-100µg/L	1.44 (0.91-2.28)	1.46 (1.03-2.07)	1.44 (0.92-2.26)	1.44 (1.12-1.86)
	>100µg/L	2.27 (1.38-3.74)	0.80 (0.38-1.69)	2.2 (1.13-4.29)	1.69 (1.14-2.52)

Source: (Schober et al., 2006).

The analysis of all-cause, cardiovascular disease and cancer mortality is based on a sample of 9,757 adults (40 years and older) who provided a blood sample between 1988 and 1991 to the National Health and Nutrition Examination Survey (NHANES III) (Schober et al., 2006).

Mode of action and weight of evidence

Various mechanisms explain how lead may result in increased mortality, the most common being through oxidative stress or neurological impairment as previously described. Further disease-specific pathways are contributing factors leading to an overall increase of all-cause mortality.

For example, the generally recognized pathway of how blood lead results in an increased risk of dying from cardiovascular disease is through hypertension. Several studies have found evidence for a correlation between lead concentrations in blood and both systolic and diastolic blood pressure (Nawrot et al., 2002). However, the underlying mechanisms of this relationship are not completely clear yet. While some studies find an explanation in the metabolic and hemodynamic changes associated with diabetes, others claim oxidative stress is responsible (Kim et al., 2015). The lead-induced oxidation may result in an overproduction of ROS in the cardiovascular tissues, which can result in serious health consequences over time (Hu et al., 1996).

Evidence of lead potentially being a contributing factor in the process of cancer comes mostly from animal testing and only to a limited extent from human studies. Assumingly, it enhances the mutagenic power of other mutagens, possibly acting by inhibiting the mechanisms responsible for DNA repair (Steenland and Boffetta, 2000). An association between lead exposure and an increased risk of lung, stomach, and bladder cancer has been confirmed (International Agency for Research on Cancer, 2006). Based on the IARC's evaluation of the carcinogenic risk of lead in humans, inorganic lead compounds

were classified as probably carcinogenic to humans (Group 2A) and organic lead compounds are not classifiable in terms of their carcinogenic potential to humans (Group 3) (International Agency for Research on Cancer, 2006).

Exposure-, health-, population data

Data on lead exposure in the population were extracted from the estimates gathered for adults within HBM4EU and compiled in the HBM4EU aggregated data set (Table 3.3). The data on lead concentrations was not part of the aligned atudies. The data was retrieved from the HBM4EU dashboard: https://www.hbm4eu.eu/what-we-do/european-hbm-platform/eu-hbm-dashboard/ (05.07.2022).

Table 3.3: Lead concentrations (µg/L) in human blood samples of existing studies gathered in HBM4EU for adults (in percentiles; P)

Country	Data collection	Stratification value	P05	P10	P25	P50	P75	P90	P95	Number of participants	Sampling period
Belgium[(a)]	FLEHS 1 adults	Adults 40-59 years	16.18	19.92	26.89	37.55	53.31	73.73	86.40	980	2004-2005
	FLEHS 1 adults	Elderly 60 years and older	16.83	21.45	28.41	41.34	57.53	79.80	92.46	599	2004-2005
Slovenia	SLO-HBM-I	Adults 20-39 years	8.95	10.25	13.06	17.25	23.65	32.36	40.08	1,042	2008-2014
Czechia	CzechHBM-AE_2005	Adults 20-39 years	14.25	17.38	23.35	30.10	40.05	54.08	66.12	307	2005
	CzechHBM-AE_2005	Adults 40-59 years	12.80	18.70	24.30	32.00	39.35	54.30	73.75	91	2005
	CzechHBM-AE_2007	Adults 20-39 years	16.34	17.60	21.98	28.15	37.20	48.96	56.36	288	2007
	CzechHBM-AE_2007	Adults 40-59 years	16.62	18.79	22.77	32.30	42.475	58.56	74.10	114	2007
	CzechHBM-AE_2009	Adults 20-39 years	7.90	9.53	12.53	18.65	26.425	42.57	50.67	274	2009
	CzechHBM-AE_2009	Adults 40-59 years	10.50	12.60	15.90	22.40	33.10	49.20	92.80	121	2009
	CzechHBM-AE_2015	Adults 40-59 years	7.83	9.31	12.57	18.98	28.60	43.19	59.33	148	2015
	CzechHBM-AE_2015	Adults 20-39 years	6.85	7.95	10.47	14.57	19.76	26.01	44.08	140	2015
Norway[(b)]	MoBa	Adults 20-39 years (pregnant woman)	4.44	5.08	6.45	8.20	10.57	13.66	16.06	2,899	2002-2008

Country	Data collection	Stratification value	P05	P10	P25	P50	P75	P90	P95	Number of participants	Sampling period
	MoBa	Adults 40-59 years (pregnant woman)	5.60	6.78	7.87	9.30	11.53	15.86	18.48	53	2003-2008

Notes: Lead exposure data was available for 4 countries but was collected in different sampling years.

([a]) The lead exposure data as collected in the FLEHS study was assumed to be representative for the entire Belgium population in this report, even though only citizens from the Flemish region were surveyed.

([b]) Data from only a subset of the general population such as pregnant women were excluded.

The most recent exposure data was selected for the calculations (values in grey).

The increased mortality risk due to all-causes, cardiovascular disease and cancer was estimated with the population groups in (Table 3.4). The mortality rate was calculated based on the mean annual number of deaths due to the health outcome of interest (all-cause, cardiovascular disease and cancer mortality) and the mean number of persons per year during the time of blood lead data collection. This was necessary to account for the time lag between the estimates of population lead concentrations from the HBM4EU data and recent blood lead levels, which have been decreasing due to stricter policies and technical improvements.

Table 3.4: Population size in the selected age groups (data extracted for 2021)

Country	Age group	Population size in 2021	Mean annual population during time of HBM4EU data collection	Mean annual deaths due to *all-causes* during time of HBM4EU data collection	Mean annual deaths due to *cardiovascular disease* during time of HBM4EU data collection	Mean annual deaths due to *cancer* during time of HBM4EU data collection
Belgium	40-59 years	3,096,755	2,924,513 (2004-2005)	10,785	2,026	4,648
	>60 years	2,962,118	2,295,434 (2004-2005)	87,722	31,581	23,484
Czechia	20-39 years	2,571,076	2,987,160 (2015)	1,897	189	364
	40-59 years	3,136,723	2,879,226 (2015)	10,091	2,458	3,813
Slovenia	20-39 years	529,018	576,408 (2008-2014)	353	22	68

Notes: Number of population based on data Eurostat. https://ec.europa.eu/eurostat/databrowser/product/page/DEMO_PJAN__custom_2892906.

Mortality data based on IHME tool https://vizhub.healthdata.org/gbd-results/.

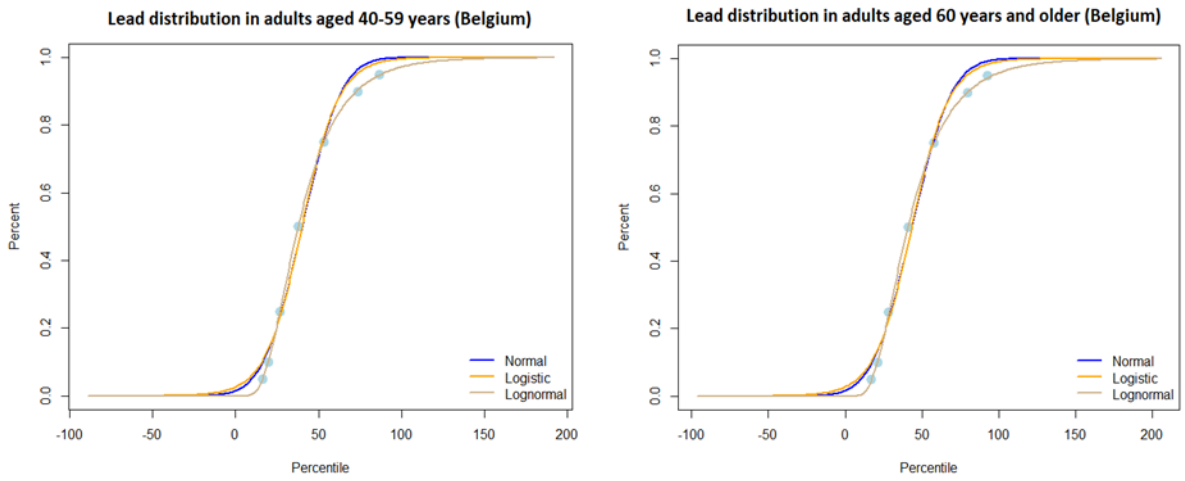
Attributable burden

The method applied to calculate deaths resulting from lead-induced all-cause, cardiovascular disease and cancer mortality is presented with the example of Belgium but has been used in the same way for Czechia and Slovenia.

The analysis was conducted using R software (R Core Team, 2022). The R package 'rriskDistributions' provides a collection of functions that allows to evaluate the distribution most representative for the measured lead concentrations in the European populations (Belgorodski et al., 2017). All continuous or discrete distributions are plotted simultaneously without the need to specify the distribution family in advance. The output then provides a diagnosis showing the sum of squared differences between the given percentiles from the HBM4EU data and the percentiles of each fitted distribution. The distribution with the smallest value, meaning the least deviation from the actual distribution of lead exposure in the population, is therefore the most appropriate distribution. The described fitting of a variety of different distributions was performed with the 3 functions rriskFitdist.perc, plotDiagnostics.perc and fit.results and revealed that the European blood lead concentrations follow a lognormal distribution. As an example, we show the lead distributions of two age groups (40-59 years, 60 years to elderly) in Belgium with the fitted functions in (Figure 3.1). Here, only the 3 distribution families that best model the lead exposure in the population are displayed. However, a

total of 17 different distributions were tested with the rriskFitdist.perc function, including a gamma or Weibull distribution.

Figure 3.1: Diagnostic plots for choosing the most appropriate distribution for the known percentiles of blood lead concentrations (light-blue dots) in the Belgium population for the age groups 40-59 years (left) and over 60 years (right)



Notes: Showing the 3 distribution family most appropriate to model the population lead exposure in Belgium out of the 17 tested distribution functions.

For each age group and European country with available lead data, the percentage of the population (f) with a blood lead concentration in a certain range or above a certain threshold was evaluated.

Table 3.5: Blood lead (Pb) concentrations (µg/L) in the Belgium population as collected in the FLEHS 1 study (in percentiles) and percentage of the population exposed to either 50-100µg/L or >100µg/L

Study (Country)	Age group	p05	p10	p25	p50	p75	p90	p95	% of pop. with blood lead conc. 50-100µg/L	% of pop. with blood lead conc. >100µg/L
FLEHS 1 adults (Belgium)	40-59 years	16.18	19.92	26.89	37.55	53.31	73.73	86.40	26.22 %	2.79 %
	>60 years	16.83	21.45	28.41	41.34	57.53	79.80	92.46	30.62 %	4.26 %

The population attributable fraction (PAF), the mortality rate (MR) and the attributable deaths (AD) were calculated with equations 1-3 as listed in Annex A2.1. To adjust for the recent changes of lead exposure, the MR was calculated with mortality and population data during the time of HBM4EU surveying and then projected to the current population. The estimates given in the tables below (Table 3.6, Table 3.7, Table 3.8) show the results for two age groups (40-59 years, older than 60 years) and two blood lead concentrations (50-100µg/L, higher than 100µg/L) in Belgium. The RRs from Table 3.2 provided for all ages were applied to these two age groups.

Table 3.6: Number of attributable deaths due to lead exposure resulting in all-cause mortality in Belgium (central estimate)

Lead-induced *all-cause mortality* in Belgium in 2021				
Age group	40-59 years	>60 years	40-59 years	>60 years
Blood lead concentration, Pb (µg/L)	50-100µg/L	50-100µg/L	>100µg/L	>100µg/L
Relative Risk RR[a]	1.24	1.24	1.59	1.59
% of pop. with blood lead conc.[b]	26.22 %	30.62 %	2.79 %	4.26 %
Mortality Rate[c]	0.004	0.038	0.004	0.038
Attributable Fraction	0.059	0.068	0.016	0.025
Number of deaths attributable to *all-causes* and lead exposure in 2021[d]	676	7,750	185	2,774
Total number of deaths attributable to *all-causes* and lead exposure in 2021				11,386

Notes: The calculation follows the approach taken by (Goldenman et al., 2019).

([a]) RRs extracted from Table 3.2.

([b]) percentage of the population (f) with a blood lead concentration in a certain range or above a certain threshold extracted from Table 3.5.

([c]) Mortality rates were calculated based on numbers in Table 3.4.

([d]) Population numbers were extracted from Table 3.4.

Table 3.7: Number of attributable deaths due to lead exposure resulting in cardiovascular disease mortality in Belgium (central estimate)

Lead-induced *cardiovascular disease mortality* in Belgium in 2021				
Age group	40-59 years	>60 years	40-59 years	>60 years
Blood lead concentration, Pb (µg/L)	50-100µg/L	50-100µg/L	>100µg/L	>100µg/L
Relative Risk RR[(a)]	1.20	1.20	1.55	1.55
% of pop. with blood lead conc.[(b)]	26.22 %	30.62 %	2.79 %	4.26 %
Mortality Rate[(c)]	0.001	0.014	0.001	0.014
Attributable Fraction	0.050	0.058	0.015	0.023
Number of deaths attributable to *cardiovascular disease* and lead exposure in 2021	107	2,352	32	933
Total number of deaths attributable to *cardiovascular disease* and lead exposure in 2021				3,424

Notes: The calculation follows the approach taken by Goldenman and colleagues (Goldenman et al., 2019).

([a]) RRs extracted from Table 3.2.

([b]) percentage of the population (f) with a blood lead concentration in a certain range or above a certain threshold extracted from Table 3.5.

([c]) Mortality rates were calculated based on numbers in Table 3.4.

Source: (Goldenman et al., 2019).

Table 3.8: Number of cancer deaths attributable to to lead exposure in Belgium (central estimate)

Lead-induced *cancer mortality* in Belgium in 2021				
Age group	40-59 years	>60 years	40-59 years	>60 years
Blood lead concentration, Pb (µg/L)	50-100µg/L	50-100µg/L	>100µg/L	>100µg/L
Relative Risk RR[(a)]	1.44	1.44	1.69	1.69
% of pop. with blood lead conc.[(b)]	26.22 %	30.62 %	2.79 %	4.26 %
Mortality Rate[(c)]	0.002	0.01	0.002	0.010
Attributable Fraction	0.103	0.119	0.019	0.029
Number of deaths attributable to lead exposure and *cancer* in 2021	509	3,599	93	865
Total number of deaths attributable to *cancer* and lead exposure in 2021				5,066

Notes: The calculation follows the approach taken by Goldenman and colleagues (Goldenman et al., 2019).

([a]) RRs extracted from Table 3.2.

([b]) percentage of the population (f) with a blood lead concentration in a certain range or above a certain threshold extracted from Table 3.5.

([c]) Mortality rates were calculated based on numbers in Table 3.4.

Source: (Goldenman et al., 2019).

Based on these calculations, a total of 11,386 deaths can be attributed to lead exposure in the Belgian population aged above 40 years in 2021 based on the all-cause mortality estimates. Using the cause-specific deaths a total of 3,424 result from cardiovascular diseases and 5,066 are from cancer were attributable to lead exposure. Estimates for other countries are given in Table 3.9 and Table 3.10. Attributable deaths that arise in different lead exposure categories were summed up to produce annual deaths per age group due to all-causes, cardiovascular disease or cancer and rounded to whole numbers. To calculate the attributable deaths per year for all adults with available lead data per country the values of the different age groups were added up and to adjust the value per 1,000,000 persons the average of all the values per age group was calculated.

Table 3.9: Lead-induced all-cause, cardiovascular disease and cancer mortality in 2021 (central) plus the upper and the lower limit of the 95 % confidence interval. All results were rounded to 3 digits.

		Number of deaths attributable to lead exposure in 2021								
		All-cause			Cardiovascular disease			Cancer		
Country	Age group	Central	Lower 95 %	Upper 95 %	Central	Lower 95 %	Upper 95 %	Central	Lower 95 %	Upper 95 %
	40-59 years	**861**	236	1,581	**139**	0	333	**602**	169	925
	>60 years	**10,525**	3,041	19,042	**3,285**	0	7,651	**4,464**	1,254	8,160
Belgium	Total	**11,386**	3,277	20,623	**3,424**	0	7,984	**5,066**	1,423	9,085
	20-39 years	**2**	0	3	**0**	0	0	**1**	0	1
	40-59 years	**158**	39	307	**33**	0	85	**104**	28	201
Czechia	Total	**160**	39	310	**33**	0	85	**105**	28	202
Slovenia	20-39 years	**1**	0	1	**0**	0	0	**0**	0	0

Table 3.10: Lead-induced all-cause, cardiovascular disease and cancer mortality/1,000,000 persons in 2021 (central) plus the upper and the lower limit of the 95 % confidence interval. All results were rounded to 3 digits.

		Number of deaths in 2021 attributable to lead exposure/1,000,000 persons in 2021								
		All-cause			Cardiovascular disease			Cancer		
Country	Age group	Central	Lower 95 %	Upper 95 %	Central	Lower 95 %	Upper 95 %	Central	Lower 95 %	Upper 95 %
	40-59 years	**75**	20	137	**12**	0	29	**52**	15	96
	>60 years	**911**	263	1,648	**284**	0	662	**386**	109	706
Belgium	Total	**986**	283	1,785	**296**	0	691	**438**	124	802
	20-39 years	**0**	0	0	**0**	0	0	**0**	0	0
	40-59 years	**15**	4	29	**3**	0	8	**10**	3	19
Czechia	Total	**15**	4	29	**3**	0	8	**10**	3	19
Slovenia	20-39 years	**0**	0	1	**0**	0	0	**0**	0	0

3.1.3 Hypertension in adults

Hypertension is a complex disease and a number of environmental as well as genetic factors may play a role with differing importance. Diet, lifestyle, obesity, exposure to toxins, including lead or other metals, are risk factors found in the environment that have been associated with the development of hypertension (Hu et al., 1996; Alghasham et al., 2011). The relationship between lead exposure and hypertension has been controversial, until data from the NHANES II cohort provided strong evidence for both elevated systolic and diastolic blood pressure in adults with higher blood lead concentrations (Pirkle et al., 1985). The biggest difficulty in quantifying the hypertension cases attributable to lead exposure was that salt intake functions as a major confounder in the disease progression. While 51 % of the global population were found to be sensitive to salt, which eventually means that their body reacts with a blood pressure increase when consuming salt, only 16 % were resistant to it and experienced no change in blood pressure (Weinberger et al., 1986). Furthermore, bone lead was found to be a much better indicator for the onset of hypertension compared to the blood lead level. While lead concentrations in the blood primarily reflect recent lead exposure, a measurement from the bone can give information about the cumulative lead exposure over a lifetime and thus better predicts the risk for high blood pressure (Yawen et al., 2001). All these findings have resulted in an improvement of establishing an accurate exposure-response relationship between lead exposure and hypertension, which was used for the following burden of disease estimates.

Exposure-response relationship

A first ERF between lead exposure and blood pressure with adjustments for confounders was described for adult men. An increase in blood lead from 5µg/dl to 10µg/dl was associated with an increase in systolic blood pressure by 1.25mmHg as found among the participants in NHANES I (Pirkle et al., 1985). In a second study NHANES II 20,322 male participants aged between 40 and 59 years were examined from 1976 to 1980. The systolic blood pressure was observed to be 2mmHg lower when blood lead was reduced from 20µg/dl to 15µg/dl or from 15µg/dl to 10µg/dL.

Following-up, a weaker relationship between blood lead level and blood pressure was found for women in an epidemiological study with 24,000 participants, estimating an increase of systolic blood pressure by only 0.8mmHg with a doubling of the blood lead concentrations (Nawrot et al., 2002). These results and additional study outcomes in the consecutive years until 2003 were then summarized in a meta-analysis. According to this analysis, the relationship between lead exposure and hypertension was assumed to be linear between 5 and 20mg/dl, with a constant increase in blood pressure for each additional 5mg/dl. From that, the relative risk was calculated for both males and females for different thresholds of lead exposure (Fewtrell et al., 2003). In order to apply these measures to the lead exposure data of the European population, relative risks irrespective of the sex for the respective blood lead levels were formulated by taking the mean of the provided female and male relative risks for the two blood lead categories 50-200µg/L and more than 200µg/L. Also, relative risks were adjusted to the age groups of the data that was compiled in the HBM4EU-project and 95 % confidence intervals were calculated by applying the proposed uncertainty from the study in the NHANES I cohort. The extracted numbers are summarized in Table 3.11.

Table 3.11: Relative risks for hypertensive disease for defined increases in blood pressure, blood lead level and age category

		Relative risk by age category years		
	Blood pressure increase Blood lead level	20-39 years	40-59 years	>60 years
	0.800mmHg			1.04 (0.73-1.35)
	50-200µg/L	1.16 (0.81-1.51)	1.08 (0.75-1.40)	
	2.400mmHg			1.13 (0.79-1.46)
Females	**>200µg/L**	1.56 (1.09-2.02)	1.25 (0.87-1.62)	
	1.125mmHg			1.06 (0.74-1.38)
	50-200µg/L	1.27 (0.89-1.65)	1.12 (0.79-1.46)	
	3.750mmHg			
Males	**>200µg/L**	2.00 (1.40-2.59)	1.41 (0.99-1.84)	1.20 (0.84-1.56)
Both	**50-200µg/L**	1.21 (0.85-1.58)	1.10 (0.77-1.43)	1.05 (0.74-1.37)
	>200µg/L	1.78 (1.24-2.31)	1.33 (0.93-1.73)	1.16 (0.82-1.51)

Notes: The analysis of hypertension is based on the collective findings from NHANES I and II that investigated 20,322 males. In a meta-analysis that included 31 studies providing population data of blood lead measurements. These findings were then extrapolated to females and finally further summarized and translated into risk relationships.

Source: (Fewtrell et al., 2003; Nawrot et al., 2002; Pirkle et al., 1985; Schwartz, 1988).

Mode of action and weight of evidence

Low-level lead exposure most likely leads to high blood pressure via oxidative stress. This results in an excess of ROS, as the antioxidant defense is weakened in the process, which would otherwise be responsible for the detoxification process. This may further lead to the damage of important proteins, lipids and even DNA and therefore negatively affects the cell membrane (Sirivarasai et al., 2015).

Exposure-, health-, population data

Data on lead exposure in the population was extracted from the estimates gathered for adults within HBM4EU and compiled in the HBM4EU aggregated data set. This data was retrieved from the HBM4EU dashboard: https://www.hbm4eu.eu/what-we-do/european-hbm-platform/eu-hbm-dashboard/ (05.07.2022).

The disease burden due to lead-induced hypertension was estimated with the population data in Table 3.12.

Table 3.12: Population size in the selected age groups (data extracted for 2021)

Country	Age group	Number of persons
Belgium	40-59 years	3,096,755
	>60 years	2,962,118
Czechia	20-39 years	2,571,076
	40-59 years	3,136,723
Slovenia	20-39 years	529,018

Source: Numbers based on data Eurostat (https://ec.europa.eu/eurostat/databrowser/product/page/DEMO_PJAN__custom_2892906).

Attributable burden

The method applied to calculate the YLDs resulting from lead-induced hypertension is presented for Belgium, and has been used in the same way for Czechia and Slovenia. As described in the methodology, a lognormal distribution was fitted to the population-based lead concentrations from HBM4EU, which was then used to calculate the percentage of the population (f) with a blood lead concentration in a certain range or above a certain threshold. Table 3.13 displays, the estimated proportion of the Belgium population falling into the two lead categories 50-200µg/L and more than 200µg/L for the two age groups 40-59 years and older than 60 years.

Table 3.13: Blood lead (Pb) concentrations (µg/L) in the Belgium population as collected in the FLEHS 1 study (in percentiles) and percentage of the population exposed to either 50-200µg/L or >200µg/L

Study (Country)	Age group	p05	p10	p25	p50	p75	p90	p95	% of pop. with blood lead conc. 50-200µg/L	% of pop. with blood lead conc. >200µg/L
FLEHS 1 adults (Belgium)	40-59 years	16.18	19.92	26.89	37.55	53.31	73.73	86.40	28.96 %	0.05 %
	>60 years	16.83	21.45	28.41	41.34	57.53	79.80	92.46	34.77 %	0.11 %

The attributable fraction (AF), the number of people in the particular age group exposed to the blood lead concentration in a certain range (No of exposed), the number of hypertension cases per year (No of cases) and the number of hypertension cases attributable to lead (AC) were calculated with equations 4-8 as listed in Annex A2.1. To do so, prevalence estimates as found in the scientific literature and disability weights as estimated by the GBD 2019 study were used (GBD 2019 Diseases and Injuries Collaborators, 2020). To perform EBD calculations for the reference year 2021, we applied the prevalence rates of 2019 to the population of 2021. Only YLDs were estimated as part of DALYs since hypertension is known to cause a significant amount of morbidity within Europe, however, usually progresses to a more serious health condition such as cardiovascular diseases before resulting in mortality.

Table 3.14 shows the results for two age groups (40-59 years, older than 60 years) and two blood lead concentrations (50-200µg/L, higher than 200µg/L) in Belgium. The RRs from Table 3.11 were applied to these age groups. For the individuals aged 40 to 59 years, the RRs of the age group were used and for the individuals aged 60 years and older mean RRs for the two age groups 60-69 years

and 70-79 years were calculated. As only the morbidity associated burden related to hypertension was calculated (thus only YLD) and the YLL were not accounted for, the calculation performed here is an underestimation of the real burden.

Table 3.14: Burden of disease in YLDs for lead exposure and hypertension in Belgium

Lead-associated hypertension in Belgium in 2021				
Age group	40-59 years	>60 years	40-59 years	>60 years
Blood lead concentration, Pb (µg/L)	50-200µg/L	50-200µg/L	>200µg/L	>200µg/L
Relative Risk RR[a]	1.10	1.05	1.33	1.16
Attributable Fraction	0.092	0.050	0.248	0.135
% of pop. with blood lead conc.[b]	28.96 %	34.77 %	0.05 %	0.11 %
Number of people with blood lead conc. in age group	896,823	1,029,909	1,658	3,339
Number of hypertension cases/year	882,575	844,204	882,575	844,204
Number of hypertension cases attributable to lead exposure in 2021[c]	23,394	14,608	117	135
YLDs 2021	5,404	3,374	27	31
Total YLDs 2021				8,836

Notes: ([a]) RRs extracted from Table 3.11.

([b]) percentage of the population (f) with a blood lead concentration in a certain range or above a certain threshold extracted from Table 3.13.

([c]) Population numbers were extracted from Table 3.12.

Source: (Goodman et al., 2014; Ougier et al., 2021a).

Based on the calculation for hypertension related to lead exposure, a total of 8,836 YLDs were estimated for Belgium in 2021. Estimates for other countries are given in Table 3.15 (rounded to whole numbers). YLDs for different lead exposure categories were summed up and to calculate a value for the total population adjusted per 1,000,000 persons the average of all measures per age group was estimated.

Table 3.15: Burden of disease measured as YLDs in 2021 hypertension attributable to lead. All results were rounded to 3 digits.

		YLDs in 2021			YLDs/1,000,000 persons in 2021		
Country	Age group	Central	Lower 95 %	Upper 95 %	Central	Lower 95 %	Upper 95 %
	40-59 years	**5,431**	0	17,828	**470**	0	1,543
	60 years-elderly	**3,405**	0	18,318	**295**	0	1,585
Belgium	Total	**8,837**	0	36,146	**765**	0	3,128
	20-39 years	**87**	0	287	**8**	0	27
	40-59 years	**793**	0	4,281	**74**	0	400
Czechia	Total	**880**	0	4,568	**82**	0	427
Slovenia	20-39 years	**39**	0	128	**18**	0	61

3.1.4 (Mild) intellectual disability in children

Lead-induced IQ loss does not necessarily manifest as a severe disease. However, children with a relatively low IQ score are at risk to suffer from intellectual disability due to additional IQ points being lost because of lead exposure. Per definition, an IQ below 70 is referred to as mild intellectual disability (MID), and an IQ between 50 and 70 points as intellectual disability (ID). The burden of disease related to lead-induced IQ loss results from the increased percentage of children at risk to develop MID or ID, which are the individuals who would usually fall into the IQ category just above 70 or 50 IQ points (Fewtrell et al., 2004). Recent studies have provided evidence for lead-induced intellectual deficits starting at low lead exposure. A Rochester longitudinal study, as well as a Boston cohort study, showed adverse consequences below 100µg/L blood lead concentrations (Bellinger and Needleman, 2003; Canfield et al., 2003). The following calculations are based on the findings of 7 prospective cohort studies, whereby intellectual performance and blood lead concentrations were investigated in children from infancy to 5-10 years of age (Lanphear et al., 2005).

Exposure-response relationship

The ERF between lead exposure and IQ loss, currently recognized as most valid, was extracted from the mentioned internationally pooled analysis. Inclusion and exclusion criteria such as, availability of a detailed methodology description or data approval from an institutional review board were applied to each cohort study. A full-scale IQ was calculated, which included both verbal and written performance as a measure of intelligence. An ERF describing the relationship between blood lead level and IQ score was identified for children between 0 and 10 years (Lanphear et al., 2005). From this curve, relative risks were calculated for 12 different lead exposure categories further translated into increments of IQ shift as shown in Table 3.16 (GBD 2019 Risk Factors Collaborators, 2020).

Table 3.16: Expected IQ shift for different blood lead concentrations

Blood lead exposure in HBM4 EU unit (in µg/L)	Blood lead exposure in GBD 2019 study (in µg/dL)	IQ shift (95 % CI)
20	2	0.0 (0.0-0.0)
40	4	3.15 (1.15-05.14)
60	6	3.80 (1.40-6.21)
80	8	4.30 (1.58-7.02)
100	10	4.69 (1.72-7.66)
120	12	5.01 (1.84-8.19)
150	15	5.42 (1.99-8.85)
200	20	5.95 (2.18-9.72)
250	25	6.37 (2.34-10.40)
300	30	6.71 (2.46-10.97)
350	35	7.01 (2.57-11.44)
400	40	7.26 (2.66-11.86)

Source: (GBD 2019 Risk Factors Collaborators, 2020).

Mode of action and weight of evidence

While, both the central and peripheral nervous systems (CNS/PNS) can be adversely affected by lead-induced toxicity, the CNS is most vulnerable especially during childhood when it is still developing (Kim et al., 2015). In relatively minor cases, headaches, irritability, muscular tremors, and loss of memory are common symptoms, whereas severe disease outcomes may result in delirium, convulsions, temporary or permanent brain damage such as encephalopathy, or even coma. Even at relatively low lead exposure levels, the neurobehavioral development may be impaired, resulting in a lowered IQ or ADHD-like symptoms (Mason et al., 2014).

When Pb2+-ions replace other essential metals such as Ca2+, Zn2+ and Fe2+ brain cells may be altered through interference with neuronal differentiation, myelination, and synapse formation. A disruption of the Ca2+-concentration in the cells results in an alteration of the mitochondrial functioning and energy metabolism, which may further lead to a redox imbalance. Other negative consequences of the observed Pb2+-ion mimicry are neuro-inflammation or neuro-toxicant manifestations (Virgolini and Aschner, 2021).

Exposure-, health-, population data

Data on population exposure to lead for children was extracted from data gathered with the HBM4EU-project and compiled in the HBM4EU aggregated data set. This data was retrieved from the HBM4EU dashboard: https://www.hbm4eu.eu/what-we-do/european-hbm-platform/eu-hbm-dashboard/ on 05.07.2022.

Table 3.17: Lead concentrations (µg/L) in human blood samples of existing studies gathered in HBM4EU for children and adolescents

Country	Data collection	Stratification value	P05	P10	P25	P50	P75	P90	P95	Number of participants	Sampling period
Belgium[a]	FLEHS 1 adolescents	Teenagers 12-19 years	7.91	9.93	14.48	22.00	31.70	45.35	57.60	1,659	2003-2004
	FLEHS 2 adolescents	Teenagers 12-19 years	7.42	8.63	11.14	14.47	18.83	24.97	29.64	210	2008-2009
	FLEHS 2 adolescents Genk	Teenagers 12-19 years	7.31	8.11	10.51	13.62	17.32	22.96	29.59		2010
	FLEHS 2 adolescents Menen	Teenagers 12-19 years	7.09	8.00	9.90	12.90	16.45	21.22	24.30		2010-2011
	FLEHS 3 adolescents	Teenagers 12-19 years	5.02	5.83	6.79	9.02	11.90	16.19	18.39	207	2013
	FLEHS 3 adolescents Ghent harbour	Teenagers 12-19 years	4.63	5.49	7.04	9.20	12.26	16.28	19.26		2013-2014
Germany	GerES IV	Children 3-5 years	8.95	10.59	14.73	20.15	26.78	34.43	40.22	330	2003-2006
	GerES IV	Children 6-11 years	7.80	9.90	12.98	16.90	22.10	28.37	33.29	804	2003-2006
	GerES IV	Teenagers 12-19 years	6.90	8.22	11.30	15.00	20.15	25.38	30.76	423	2003-2006
Czechia	CzechHBM-CE_2006	Children 6-11 years	17.00	19.00	23.00	29.00	34.00	41.00	46.90	363	2006
	CzechHBM-CE_2008	Children 6-11 years	7.00	9.00	14.00	20.00	25.00	30.00	37.60	195	2008
	CzechHBM-CE_2016	Children 3-5 years	7.28	8.30	9.97	12.96	17.05	22.67	28.59	159	2016-2017
	CzechHBM-CE_2016	Children 6-11 years	6.44	7.13	9.45	11.71	14.95	18.03	20.78	252	2016-2017

Notes: Lead exposure data was available for 3 countries but was collected in different sampling years. The most recent exposure data was selected for the calculations (values in grey).

([a]) The lead exposure data as collected in the FLEHS study was assumed to be representative for the entire Belgium population in this report, even though only citizens from the Flemish region were surveyed.

Table 3.18: Population size in the selected age groups (data extracted for 2021)

Country	Age group	Number of persons
Belgium	12-19 years	1,045,331
Czechia	3-5 years	342,987
	6-11 years	686,771
Germany	3-5 years	2,403,553
	6-11 years	3,854,844
	12-19 years	6,097,694

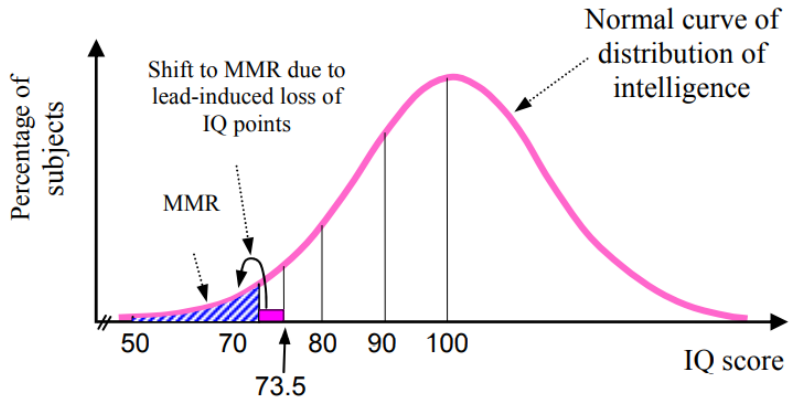
Source: Numbers based on data Eurostat (https://ec.europa.eu/eurostat/databrowser/product/page/DEMO_PJAN__custom_2892906).

Attributable burden

The method applied to calculate the DALYs resulting from lead exposure and the consequential IQ shift is shown with the example of Belgium in children aged 12 to 19 years but has been used in the same way for the children in Czechia and Germany.

Since the IQ of the global population follows a normal distribution with a mean of 100 and a standard deviation of 15 IQ points (Fewtrell et al., 2003), the percentage of children at risk to fall below the two critical thresholds (IQ score of 50 or 70) were calculated. Figure 3.2 is a graphical illustration of the IQ shift below 70 IQ points, which is assumed to results in mild intellectual disability (Fewtrell et al., 2003).

Figure 3.2: Shift to MMR as a result of lead-induced IQ loss. Mild mental retardation (MMR) is referred to as mild intellectual disability (MID) in the framework of this report.



Source: (Fewtrell et al., 2003).

To account for regional differences, validated national IQs and the within-country standard deviation of 15 was used to adjust the distribution of intelligence to each country (Lynn and Meisenberg, 2010). In the example of Belgium, the mean national IQ of 99 points was applied.

The percentage of individuals falling into the IQ-category above 70 was calculated with the suggested increments (GBD 2019 Risk Factors Collaborators, 2020) and named “population at risk for MID”(risk pop MID). The same calculation was performed for the individuals at risk to fall below 50 IQ points, respectively called “population at risk for ID” (risk pop ID).

Once again as previously described in the methodology, a *lognormal* distribution was fitted to the population lead data from HBM4EU. The percentage of the population (f) with a blood lead concentration in a certain range was estimated, in this example from the Belgium teenagers (12-19y).

Finally, an MID and ID rate were calculated by multiplying these two percentages according to equations 9 and 10 as listed in Annex A2.1. These two rates give information about the proportion of children at risk of developing lead-induced (mild) intellectual disability per blood lead level and IQ category.

Table 3.19 displays, the calculated percentages of the Belgium children between 12 and 19 years falling into the high-risk categories of developing lead-induced (mild) intellectual disability.

Table 3.19: Blood lead (Pb) concentrations (µg/L) in the Belgium population as collected in the FLEHS 1 study (in percentiles) and percentage of the population exposed to different lead levels and in high-risk IQ categories

Blood lead concentration in percentiles (12-19 years, Belgium)								
Study (Country)	**Age group**	**p05**	**p10**	**p25**	**p50**	**p75**	**p90**	**p95**
FLEHS 3 adolescents (Belgium)	12-19 years	5.02	5.83	6.79	9.02	11.90	16.19	18.39

Source: (Fewtrell et al., 2003; GBD 2019 Risk Factors Collaborators, 2020).

Table 3.20: Risk of MID and ID in lead exposure classes (adopted from Fewtrell et al., 2003).

		Mild intellectual disability (MID) calculation			Intellectual disability (ID) calculation		
Blood lead level	**% of pop. with blood lead level**	**IQ increment (MID risk)**	**Risk pop MID**	**MID rate**	**IQ increment (ID risk)**	**Risk pop ID**	**ID rate**
20-40µg/L	2.46 %	70-73.15	1.58 %	0.00039	50-53.15	0.06 %	<0.001
40-60µg/L	0.01 %	70-73.80	1.99 %	<0.001	50-53.80	0.08 %	<0.001
60-80µg/L	<0.001 %	70-74.30	2.32 %	<0.001	50-534.30	0.09 %	<0.001
80-100µg/L	<0.001 %	70-74.69	2.59 %	<0.001	50-54.69	0.10 %	<0.001
100-120µg/L	<0.001 %	70-75.01	2.83 %	<0.001	50-55.01	0.11 %	<0.001
120-150µg/L	<0.001 %	70-75.42	3.14 %	<0.001	50-55.42	0.13 %	<0.001
150-200µg/L	<0.001 %	70-75.95	3.56 %	<0.001	50-55.95	0.15 %	<0.001
200-250µg/L	<0.001 %	70-76.37	3.91 %	<0.001	50-56.37	0.17 %	<0.001
250-300µg/L	<0.001 %	70-76.71	4.21 %	<0.001	50-56.71	0.19 %	<0.001
300-350µg/L	<0.001 %	70-77.01	4.47 %	<0.001	50-57.01	0.20 %	<0.001
350-400µg/L	<0.001 %	70-77.26	4.70 %	<0.001	50-57.26	0.22	<0.001

Usually, DALYs are a composite measure of YLDs and YLLs as a consequence of a disease (Caravanos et al., 2014; Vasconcellos et al., 2018). The total number of cases attributable to IQ loss and lead exposure (AC), the total yearly IQ loss and related IQ costs have been estimated with the equations 11-13 as listed in Annex A2.1, plus the DALYs were derived for the blood lead levels and IQ increments with equation 15.

The results given in the Table 3.21 show the calculations for the Belgium teenagers aged between 12 to 19 years and 4 blood lead categories (20-40µg/L, 40-60µg/L, 60-80µg/L, 80-100µg/L). All results were rounded to 3 digits, meaning that the number 0 in the table not necessarily means no burden.

Table 3.21: Burden of disease in DALYs in 2021 for lead exposure and IQ loss in Belgium (central estimate) for the age group 12-19 years

Lead-induced (mild) intellectual disability in 2021						
Age group	12-19 years age group					
Blood lead concentration, Pb (µg/L)	20-40µg/L	40-60µg/L	60-80µg/L	80-100µg/L	100-120µg/L	120-150µg/L
IQ shift associated with blood lead conc.[a]	3.15	3.80	4.30	4.69	5.01	5.42
% of pop. with blood lead conc.	2.46 %	0.01 %	<0.001 %	<0.001 %	<0.001 %	<0.001 %
% of pop. at risk for MID[b]	1.58 %	1.99 %	2.32 %	2.59 %	2.83 %	3.13 %
% of pop. at risk for ID[b]	0.06 %	0.08 %	0.09 %	0.10 %	0.11 %	0.13 %
MID rate[b]	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
ID rate[b]	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Number of new MID cases associated with exposure to lead in 2021[b]	407	2	<0.5	<0.5	<0.5	<0.5
Number of new ID cases associated with exposure to lead in 2021	15	<0.5	<0.5	<0.5	<0.1	<0.5
Total number of new cases related to IQ loss and lead exposure in 2021	421	2	<0.5	<0.5	<0.5	<0.5
Total IQ loss	1,326	9	<0.5	<0.5	<0.5	<0.5
Euro/IQ point			16,458			
Costs/year (EUR)	21,823,742	9	<0.5	<0.5	<0.5	<0.5
Monetary value of 1 DALY (EUR)			45,000			
DALYs in 2021	485	3	<0.5	<0.5	<0.5	<0.5
Total DALYs 2021						488

Notes: The calculation follows the approach taken by (Goldenman et al., 2019; Ougier et al., 2021a).

([a]) numbers extracted from Table 3.20.

([b]) population numbers extracted from Table 3.20.

Source: (Goldenman et al., 2019; Ougier et al., 2021a).

Based on the calculations for (mild) intellectual disability related to lead exposure, a total of 488 DALYs in 2021 were estimated for Belgium (age group: 12-19 years). Estimates for other countries are given in Table 3.22 and Table 3.23. DALYs of different lead exposure categories were summed up to produce annual DALYs per age group and rounded to whole numbers. To calculate the DALYs per year for all the children with available lead data per country the values of all the age-groups were added up and to adjust it per 1,000,000 persons the average of all the values in one country was calculated.

Table 3.22: Burden of disease in DALYs in 2021 for exposure to lead and IQ loss (central) plus the upper and the lower limit of the 95 % confidence interval (95 % UL, 95 % LL). All results were rounded to 3 digits.

Country	Age group	Central	Lower 95 % CI	Upper 95 % CI
Belgium	12-19 years	**488**	58	1,483
	3-5 years	**1,054**	125	3,188
	6-11 years	**922**	110	2,785
Czechia	Total	**1,976**	**235**	**5,973**
	3-5 years	**24,013**	2,820	73,283
	6-11 years	**25,630**	3,020	77,989
	12-19 years	**29,583**	3,486	90,005
Germany	Total	**79,226**	9,326	241,277

Table 3.23: Burden of disease in DALYs/1,000,000 persons in 2021 for exposure to lead and IQ loss. All results were rounded to 3 digits.

Country	Age group	Central	Lower 95 % CI	Upper 95 % CI
Belgium	12-19 years	**42**	4	127
	3-5 years	**99**	12	299
	6-11 years	**86**	10	260
Czechia	Total	**185**	**22**	**559**
	3-5 years	**290**	34	876
	6-11 years	**307**	36	927
	12-19 years	**356**	42	1,075
Germany	Total	**953**	112	2,878

3.2 Burden of disease due to PFAS (with focus on PFOS and PFOA)

3.2.1 General information on PFAS and basic assumptions

Exposure to the persistent PFAS (per- and polyfluorinated alkyl substances; 'forever chemicals') has been linked to several health effects such as kidney and testicular cancer, ulcerative colitis, pregnancy and fertility problems, liver diseases, thyroid diseases, and high levels of cholesterol (C8 Science Panel, 2012; ATSDR, 2018; Cordner et al., 2021). Exposure to PFAS is also associated with immunotoxic effects such as decreased antibody response to vaccination (Abraham et al., 2020) which was used by EFSA as a basis to set a health-based guidance value (safety threshold) for the tolerable weekly intake (external exposure) and was expressed as the sum of 4 PFAS: PFOS, PFOA, PFNA and PFHxS (European Food Safety Authority, 2020). Further, multiple studies have linked prenatal PFAS exposure with low birth weight, which is not trivial as it is associated with higher risk for cardiovascular disease, respiratory disease, diabetes in adulthood, impaired cognitive development and lower earnings throughout the person's life time (European Food Safety Authority, 2020; Cordner et al., 2021). A recent analysis of impacts due to PFAS exposure in Europe identified PFAS exposure attributable to annual external health related costs at EUR 52 to 84 billion per year (Goldenman et al., 2019). These costs are external costs as they are not reflected in the market price of PFAS but are borne by the general population (e.g. costs related to heath care, environmental degradation, etc.) and not by the polluter.

PFAS is a group consisting of more than 4,700 chemicals (OECD, 2018). Most famous ones and used for a long time are the long-chain chemicals PFOA (perfluorooctanoic acid; C8) and PFOS (perfluorooctane sulfonic acid; C8). These are also listed under the Stockholm Convention (PFOA in Annex A (elimination) and PFOS in Annex B (restriction))[1]. Most exposure (external and internal) studies so far have reported data on PFOS and PFOA and therefore most epidemiological studies looking at ERFs studied these two chemicals. More data are being gathered for other PFAS. They show that also short-chain PFAS are associated with health effects (Gomis et al., 2015; Kotthoff et al., 2015; Rosenmai et al., 2016). A further overview on relevant health effects related to PFAS exposure can be found in Annex A1.1.

In the following analyses, different health effects were considered for calculation of the EBD in the general population. Hypertension, for which already external costs for Europe were calculated by (Goldenman et al., 2019), small for gestational age (SGA) and hospitalizations for lower respiratory effects were studied. Other health effects considered were mortality, effect on total cholesterol, kidney disease and kidney cancer.

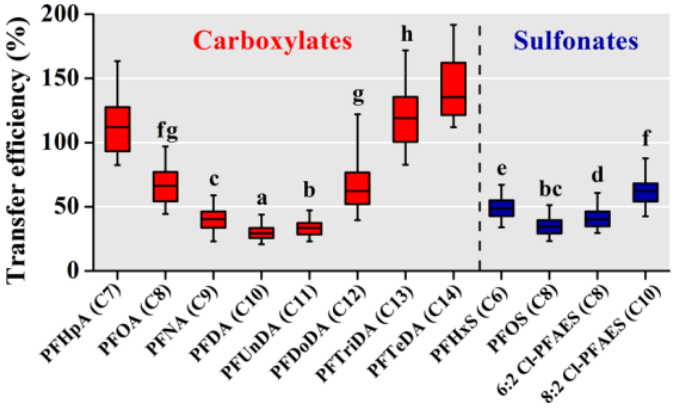
For PFAS, only serum levels in teenagers were recently measured in the HBM4EU aligned studies. Serum levels as acquainted within the HBM4EU aligned studies are high quality data from across Europe. Data from cohorts in different countries are comparable as they were generated using similar chemical-analytical protocols under a QA/QC program and using uniform statistics to generate statistical distributions. But as the considered health effects not only apply for adolescents but also for people of other age categories, in some cases extrapolations needed to be made. This mainly concerns extrapolations to younger ages seeing the accumulation potential of PFAS with ageing. To assess for example the SGA effect for newborns, data on serum PFAS concentrations in cord blood are necessary. Therefore, information on placental transfer efficiency (PTE) was searched. From the study of Pan and colleagues it could be derived that the PTE equals to around 40 % for PFOS and 60 % for PFOA (Figure 3.3) (Pan et al., 2017). PTE was determined using PFAS concentrations analyzed in 100 paired samples of human maternal sera collected in each trimester and cord sera at delivery (Pan et al., 2017). Similar estimates were observed in the studies by Zhang and colleagues and Gao and colleagues (Zhang et al., 2013; Gao et al., 2022). These PTE values were used to estimate fetus exposure (cord blood serum concentrations) to PFAS based on data of the aligned studies in teenagers. It is noted here that this

[1] https://ec.europa.eu/environment/pdf/chemicals/2020/10/SWD_PFAS.pdf

probably leads to an underestimate of PFAS exposure for the fetus as PFAS accumulate in the body over time and pregnancy takes mostly place a later age than adolescence.

Next to newly generated data in the HBM4EU aligned studies, also HBM4EU-independent existing data that were collected in databases within HBM4EU, were used in the calculations. For the current use they were used as displayed in the HBM4EU dashboard: https://www.hbm4eu.eu/what-we-do/european-hbm-platform/eu-hbm-dashboard/.

Figure 3.3: Transfer efficiencies of PFAS with increasing molecular chain length. PFAS with different letters indicate statistically significant differences in transfer efficiencies by Duncan's multiple range test at p<0.05



Notes: PFHpA and PFTeDA are excluded from Duncan's test due to their limited sample size (14 and 8 pairs for PFHpA and PFTeDA, respectively.

Source: (Pan et al., 2017).

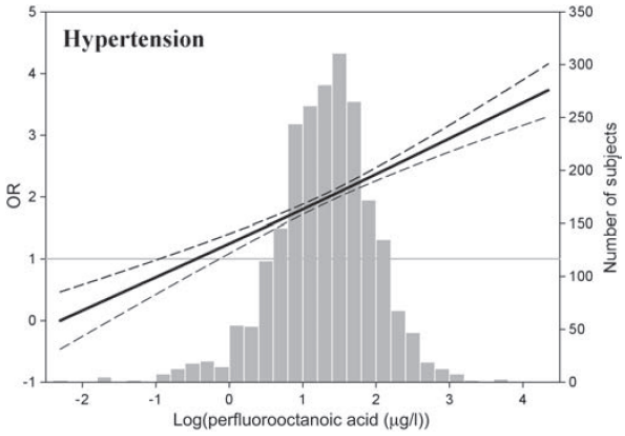
3.2.2 Hypertension in the adult population

Hypertension is a complex phenomenon and related to several possible physiological processes such as the generation of cholesterol, kidney disfunction and high salt intake. Goldenman and colleagues calculated external costs in the EU related to PFOA internal exposure and associated hypertension in the general population (Goldenman et al., 2019). The association between internal exposure (HBM levels) to PFOA and hypertension is based on data from NHANES (Min et al., 2012). However, according to the Agency for Toxic Substances and Disease Registry (ATSDR), there is only a suggestive association between hypertension during pregnancy and exposure to PFOS and PFOA and not for hypertension in the general population (ATSDR, 2021). There are some indications for an effect of PFOA exposure on the kidneys resulting in increased uric acid concentrations in blood (Steenland et al., 2010; Shankar et al., 2011; Geiger et al., 2013) which may influence blood pressure (Shankar et al., 2007; Bandaru and Shankar, 2011; Shankar et al., 2011; ATSDR, 2021). According to EFSA there is no clear association between exposure to PFOS and PFOA and cardiovascular effects like hypertension. Also, there was not enough evidence to suggest that PFOS and PFOA are associated with hypertension during pregnancy or the state of preeclampsia (European Food Safety Authority, 2020). The certainty on the association between this endpoint (hypertension) in the general population and exposure to PFOS and PFOA is thus rather limited (suggestive).

Exposure-response relationship

The ERF based on NHANES data shows that hypertension is associated with PFOA in blood of participants older than 20 years (n = 2,208). The adjusted OR for the 80th exposure percentile compared to the 20th percentile of log transformed PFOA concentrations is equal to 2.62 (95 % CI 2.09 to 3.14) (Figure 3.4).

Figure 3.4: Adjusted ORs for hypertension depending on the PFOA serum concentrations



Notes: Bold lines indicate the adjusted ORs, based on restricted cubic splines for log-transformed PFOA concentration with 3 knots.

Dashed lines present the 95 % CI.

OR was adjusted for age, sex, race/ethnicity, education, income, obesity, smoking, alcohol consumption, serum albumin, total ingestion of saturated fatty acids, physical activity, PFOS concentrations in blood, total cholesterol and kidney functioning.

The bar histogram presents the distribution of log-transformed PFOA concentrations in NHANES 2003-2004 and 2005-2006.

The blood pressure in the lowest quartile, lower than 2.6µg/L was used as reference, i.e. for that quartile, the OR was set to 1.

Source: (Min et al., 2012).

Below the OR for hypertension by increasing serum PFOA concentration is given in table format.

Table 3.24: Risk of developing hypertension as a function of exposure to PFOA

Serum PFOA concentration	Odds ratio (OR) (95 % CI)
Quartile 1 (<2.6µg/L)	1 (Reference)
Quartile 2 (2.7-3.9µg/L)	1.24 (0.89-1.74)
Quartile 3 (4.0-5.5µg/L)	1.63 (1.20-2.20)
Quartile 4 (>5.6µg/L)	1.80 (1.35-2.41)

Notes: The analysis of hypertension is based on a sample of 2,208 adults (20 years and older) who provided a blood sample between 2003 and 2006 to the National Health and Nutrition Examination Survey (NHANES).

Source: (Goldenman et al., 2019; Min et al., 2012).

Mode of action and weight of evidence

The mechanism by which PFOA could lead to hypertension is not clear but possibly increased oxidative stress plays a role influencing vasodilation by nitrogen monoxide (Ceriello, 2008). Another hypothesis is that exposure to PFAS would increase the production of aldosterone influencing the sodium uptake in the kidney (Kang et al., 2016). Based on reviews by ATSDR (ATSDR, 2018) and EFSA (European Food Safety Authority, 2020) the evidence for this effect in the general population is limited.

Exposure-, health-, population data

Data of the aligned studies of HBM4EU with PFAS concentrations in teenagers were not used but calculations were based on existing data for adults (Table 3.25). These were retrieved from the HBM4EU dashboard: https://www.hbm4eu.eu/what-we-do/european-hbm-platform/eu-hbm-dashboard/.

Values in *italic and* grey were selected for the calculations (Table 3.25). For each country for which data were available, one exposure dataset was chosen for estimating the burden in this proof of concept calculation. Data were available for 6 countries. Data are from different sampling years and some data sets include pregnant women.

Table 3.25: PFOA concentrations (µg/L) in serum of adults of existing studies gathered in HBM4EU

Country	Data collection	Sub-population	Stratification	P05	P10	P25	P50	P75	P90	P95	Cases per age category	Sample per year
Austria	*NEWDA*		*Adults 20-39 years*		*0.36*	*0.50*	*0.87*	*1.28*	*1.76*	*2.33*	*Adults 20-39 years, N = 125*	*2017, N = 55; 2018, N = 63; 2019, N = 7*
Spain	BIOAMBIENT.ES		Adults 20-39 years	0.79	1.00	1.29	1.83	2.64	3.66	4.35	Adults 20-39 years, N = 404	2009, N = 317; 2010, N = 87
Spain	*BIOAMBIENT.ES*		*Adults 40-59 years*	*0.82*	*1.02*	*1.36*	*1.98*	*2.96*	*4.32*	*5.52*	*Adults 40-59 years, N = 326*	*2009, N = 261; 2010, N = 65*
Norway	MoBa	Pregnant Women	Adults 20-39 years	1.04	1.28	1.76	2.41	3.19	4.03	4.69	Adults 20-39 years, N = 4128	2000, N = 33; 2001, N = 53; 2002, N = 344; 2003, N = 433; 2004, N = 1,229; 2005, N = 792; 2006, N = 661; 2007, N = 525; 2008, N = 58
Norway	*MoBa*	*Pregnant Women*	*Adults 40-59 years*	*1.12*	*1.28*	*1.57*	*2.11*	*2.82*	*3.96*	*4.82*	*Adults 40-59 years, N = 87*	*2001, N = 1; 2002, N = 8; 2003, N = 7; 2004, N = 31; 2005, N = 16; 2006, N = 12; 2007, N = 12*
Czechia	CzechHBM-AE_2015		Adults 20-39 years	0.18	0.32	0.49	0.78	1.12	1.83	3.52	Adults 20-39 years, N = 139	2015, N = 139
Czechia	CzechHBM-AE_2015		Adults 40-59 years	0.12	0.18	0.38	0.71	1.25	1.65	2.73	Adults 40-59 years, N = 147	2015, N = 147
Czech Republic	CzechHBM-AE_2018		Adults 20-39 years	0.48	0.81	1.08	1.42	1.96	2.59	3.11	Adults 20-39 years, N = 193	2018, N = 185; 2019, N = 8
Czechia	*CzechHBM-AE_2018*		*Adults 40-59 years*	*0.28*	*0.42*	*0.93*	*1.52*	*2.11*	*2.76*	*3.15*	*Adults 40-59 years, N = 189*	*2018, N = 185; 2019, N = 4*
Denmark	*Odense Child Cohort*	*Pregnant Women*	*Adults*	*0.67*	*0.78*	*1.10*	*1.66*	*2.34*	*3.19*	*4.01*	*Adults 20-39 years,*	*2010, N = 125; 2011, N = 349; 2012, N = 140; 2013, N = 2*

Country	Data collection	Sub-population	Stratification	P05	P10	P25	P50	P75	P90	P95	Cases per age category	Sample per year
			20-39 years								*N = 619*	
Denmark	DEMOCOPHES Denmark		Adults *20-39 years*	0.62	0.75	1.04	1.45	1.73	2.01	2.35	Adults 20-39 years, N = 50	2011, N = 50
Denmark	DEMOCOPHES Denmark		Adults 40-59 years	0.65	0.91	1.13	1.66	2.51	3.18	3.82	Adults 40-59 years, N = 93	2011, N = 93
Belgium	FLEHS 2 adults		Adults 20-39 years	1.23	1.65	2.50	3.50	4.50	5.80	6.30	Adults 20-39 years, N = 186	2008, N = 106; 2009, N = 80
Belgium	FLEHS 3 adults		Adults 40-59 years	1.18	1.50	1.98	3.00	3.86	5.08	6.65	Adults 40-59 years, N = 118	2014, N = 118
Belgium	*FLEHS 3 adults*		*60 years and older*	*1.42*	*1.78*	*2.32*	*2.86*	*3.59*	*4.60*	*5.48*	*60 years and older, N=87*	*2014, N = 87*

The calculation of external costs in the EU study by Goldman and colleagues was done for adults (older than 20 years) (Goldenman et al., 2019). In the calculation here of the EBD focus is also on persons older than 20 years. The incidence of hypertension in adults is estimated at 0.7 % (Wilkins et al., 2017; Goldenman et al., 2019). The increased risk of mortality because of hypertension is estimated at 1.2 % (Zhou et al., 2018b; Goldenman et al., 2019).

Population details are given in the Table 3.26 below. All input data, references, EBD calculation steps and results can also be found in Annex A2.2.

Table 3.26: Population size older than 20 years of age for the year 2021

Country	Population size
Belgium	8,978,799
Czechia	8,491,586
Denmark	4,549,795
Spain	38,201,070
Austria	7,211,927
Norway	4,153,579

Notes: Numbers based on data Eurostat.

Source: https://ec.europa.eu/eurostat/databrowser/product/page/DEMO_PJAN__custom_2892906

Attributable burden

The calculation is mainly based on the calculation done by (Goldenman et al., 2019) in which the number of attributable cases (deaths related to hypertension linked to exposure to PFOA) was calculated and to which a cost was applied. The calculation only focusses on YLL which is the main contributor to the impact and does not account for years lived with disability.

Table 3.27: Burden of disease in DALYs for PFOA exposure and hypertension in Belgium (central estimate)

Exposure percentile	P0-P10	P10-P25	P25-P50	P50-P75	P75-P90	P90-P95	>P95	Total
Estimated exposure to PFOA (µg/L)	1.42	2.05	2.59	3.23	4.09	5.04	5.48	
Odds ratio OR as proxy for Relative risk RR[(c)]	1.00	1.00	1.00	1.22	1.47	1.69	1.78	
Attributable fraction in the percentile	0.00	0.00	0.00	0.18	0.32	0.41	0.44	
Number of adults >20	897,880	1,346,820	2,244,700	2,244,700	1,346,820	448,940	448,940	

Exposure percentile	P0-P10	P10-P25	P25-P50	P50-P75	P75-P90	P90-P95	>P95	Total
years in the percentile								
Number of new hypertension cases/year[a]	6,285	9,428	1,5713	1,5713	9,428	3,143	3,143	
Number of hypertension cases associated with exposure to PFOA	0	0	0	2,855	3,023	1,282	1,374	8,534
Number of deaths[b]	0	0	0	34	36	15	16	102
DALYs[d]	0	0	0	340	360	150	160	1,020

Notes: The main methodology given in the table follows the approach made by (Goldenman et al., 2019).

([a]): for hypertension there is an incidence rate of 0.7 % in adults (Wilkins et al., 2017; Goldenman et al., 2019).

([b]): The extra mortality risk due to hypertension was estimated at 1.2 %

(Zhou et al., 2018b; Goldenman et al., 2019).

([c]): ERF based on (Min et al., 2012). Values below 2.6µg PFOA/L were used as reference.

([d]): Due to premature mortality related to hypertension or cardiovascular diseases there is (in Belgium) a loss of 10 years per case; Based on mortality statistics and life expectancy in Belgium. For other countries this can be different. 10 years was taken as a proxy for premature mortality related to hypertension.

The calculation follows the approach taken by (Goldenman et al., 2019).

Calculation checked by group of (Goldenman et al., 2019).

Based on this calculation for hypertension related to PFOA exposure, there is an estimate of 1,020 DALYs in 2021 year for Belgium. Estimates for other countries are given below (Table 3.28 and Table 3.29). As only the burden for premature mortality related to hypertension was calculated (thus only YLLs) and the YLDs were not accounted for, the calculation performed here is an underestimation of the real burden.

Table 3.28: Burden of disease in DALYs (YLL) in 2021 for exposure to PFOA and hypertension

Country	Central	Lower 95 % CI	Upper 95 % CI
Belgium	1,024	320	1,828
Czechia	100	1	227
Denmark	140	34	280
Spain	2,591	1,003	4,193
Austria	0		
Norway	243	77	416

Notes: 95 % CI: 95 % confidence interval.

Table 3.29: Burden of disease in DALYs (YLL)/1,000,000 persons in 2021 for exposure to PFOA and hypertension

Country	Central	Upper 95 % CI	Lower 95 % CI
Belgium	89	28	158
Czechia	9	0	21
Denmark	24	6	48
Spain	55	21	88
Austria	0		
Norway	45	14	77

Notes: 95 % CI: 95 % confidence interval.

3.2.3 Small for gestational age (SGA) and IQ-loss

Exposure to PFOA and PFOS is toxic for development. Decreased fetal growth was shown in human and animal studies (Lam et al., 2014). This may lead to IQ loss (Gabbert, 2018). The ERF used for this EBD calculation was based on a meta-analysis of 4 European birth cohorts and was described by Govarts and colleagues (Govarts et al., 2018). The health outcome (SGA) is defined, as newborns with a weight below the 10th percentile of a standard weight defined by the age at birth, the country and sex of the baby. Govarts and colleagues reported that the interquartile increase of PFOA concentrations in cord serum was associated with a higher risk for SGA with an OR of 1.64 (95 % CI 0.97 to 2.76; n = 662) (Govarts et al., 2018). This OR was borderline non-significant and remarkably larger than for the other analyzed chemicals in the study (e.g. PFOS, PCB153, HCB). The IQR for PFOA was equal to 900ng PFOA/L (=1,200-300 = 900ng/L). The 25th percentile from which effects were expected to occur was thus equal to 300ng PFOA/L or 0.3µg PFOA/L cord serum. In the calculation a value of 300ng/L was assumed as threshold.

The association between serum PFOA concentrations and increased ORs for SGA is consistent with a review including 14 studies (Bach et al., 2015). In utero exposure to PFOA was associated with decreased birth weight, even though the magnitude of the association differed between the studies and some were insignificant. In a meta-analysis of Johnson and colleagues, a significant decrease in birthweight (-18.9g, 95 % CI: -29.8 to -7.9g) was found for a 1µg/L increase in serum or plasma PFOA (studies analyzing PFOA in cord blood and maternal blood were combined assuming a placenta transfer efficiency of 100 %) (Johnson et al., 2014). In a more recent Scandinavian study, prenatal exposure to PFOA was associated with higher ORs for SGA (Lauritzen et al., 2016). The study of Meng and colleagues also showed an inverse association between birthweight and PFAS exposure (Meng et al., 2018).

SGA not only has direct consequences as an increased risk for premature death during development (Ludvigsson et al., 2018) but also an impaired cognitive development is likely. The association between SGA and cognitive development has been regularly described in different studies (Hollo et al., 2002; De Bie et al., 2010; Eves et al., 2020). In a recent publication by Eves and colleagues it was shown that newborns with SGA have an IQ retardation of 8 IQ points lower than newborns with normal weight for gestational age and this retardation was reduced to 3 points during the development until adulthood (Eves et al., 2020). When we weigh this by age there is a loss of IQ over life of 4.25 points per SGA case.

External costs (lifetime earning losses related to IQ loss and direct hospitalization costs) were already calculated for low birth weight (LBW) in the US by Malits and colleagues (Malits et al., 2018) based on the ERF derived by Johnson and colleagues (Johnson et al., 2014) (see above). LBW is defined as a birthweight lower than 2,500g and has been reported to be associated with an IQ loss of 4.98 points (Kormos et al., 2014). The reference level at which and below which no effects were calculated was set at 3.1µg PFOA/L in women of childbearing age, based on the study of Maisonet and colleagues (Maisonet et al., 2012) and in a sensitivity analysis at 1µg/L. However, according to Bach and colleagues (Bach et al., 2015) data are insufficient to determine a safe lower PFOA exposure level and more recent epidemiological studies may find lower levels than observed in the study of Maltis and colleagues (Malits et al., 2018). Each IQ point loss was valuated at USD 19,269 (Gould, 2009). The percentage of PFOA attributable LBW out of total LBW births was estimated between 0.4 and 5 % (varying between the year 2003 and 2014). Total costs across a 2-year period varied between USD 3 and 9.2 billion (reference level 1µg/L) for the studied period 2003 to 2014 (Malits et al., 2018). Loss of economic activity related to lower IQ were 90 % of total costs (direct hospitalization costs plus indirect costs as IQ loss). In the total costs only hospitalization costs and IQ loss were accounted for whereas there is also plenty of literature on LBW and cardiovascular diseases (Malits et al., 2018).

Mode of action and weight of evidence

PFOA is a PPARγ (Peroxisome proliferator- activated receptor gamma protein) ligand and promotes the differentiation of adipocytes (White et al., 2011; Yamamoto et al., 2015; Almeida et al., 2021). PPARγ has a regulatory function on the metabolism of the placenta and controls the amount of maternal nutrients going through the placenta to the fetus. By binding of PFOA to PPARγ, the growth of the fetus can be disturbed (Xu et al., 2007). Another hypothesis is that endocrine disruptors such as PFOA disturb the glucocorticoid and steroid hormones or estrogen receptors which in the end may influence the body energy regulation (Benninghoff et al., 2011; Harris and Seckl, 2011). EFSA concluded that there is possibly a causal association between exposure to PFOA and SGA (European Food Safety Authority, 2020). The effect is not large. This is in agreement with an earlier conclusion of EFSA (European Food Safety Authority, 2018). The effect may be confounded by pregnancy hemodynamics but only for a small part, see publication of (Wikström et al., 2020).

Exposure-, health-, population data

Two exposure data sources were used:

A first data source is the HBM4EU aligned studies. For the calculation starting from the aligned studies (adolescents) PFOA concentrations (Table 3.31) were reduced by 40 % to account for the placenta transfer efficiency. However, the estimate will probably still be an underestimate as pregnancy takes place later than adolescence and PFAS are accumulating in the body over time.

A second data source was measurements of PFAS in cord blood.

Table 3.30: PFOS concentrations (µg/L) in serum of adolescents of aligned studies HBM4EU

Country	Data collection[a]	N	P05	P10	P25	P50	P75	P90	P95	Mean	SD	Geomean	Sample per year
Germany	GerES V	300	1.27	1.55	1.96	2.605	3.4675	4.581	5.898	3.0416	1.9672	2.6637	2014, N = 28; 2015, N = 113; 2016, N = 132; 2017, N = 27
Norway	NEB II	177	1.4691	1.737	2.1815	2.7923	3.6828	5.2642	7.04	3.2476	1.7339	2.9107	2016, N = 162; 2017, N = 15
France	ESTEBAN	143	0.9762	1.132	1.5212	2.006	3.1243	5.2204	6.1553	3.2673	6.6799	2.2511	2014, N = 18; 2015, N = 107; 2016, N = 18
Slovakia	PCB cohort follow-up	292	0.4855	0.63	0.84	1.37	2.47	4.072	6.1455	2.4973	5.3299	1.5097	2019, N = 276; 2020, N = 16
Slovenia	SLO CRP	94	0.8255	0.949	1.17	1.645	2.7025	3.73	5.8185	2.313	2.0847	1.8287	2018, N = 94
Greece	CROME	52	1.2525	1.394	1.575	2.11	3.225	4.181	5.205	2.661	1.4172	2.371	2020, N = 22; 2021, N = 30
Sweden	Riksmaten adolescents	300	1.207	1.409	1.97	2.68	4.0825	6.282	8.229	3.5214	2.7332	2.8898	2016, N = 139; 2017, N = 161
Spain	BEA	299	0.5748	0.727	0.927	1.34	1.837	2.663	3.0647	1.5568	1.107	1.339	2017, N = 223; 2018, N = 76
Belgium	FLEHS IV	300	0.849	1	1.575	2.2	3.4	5.01	7.31	2.8093	2.0592	2.2899	2017, N = 77; 2018, N = 223

Notes: ([a]) data collections are not representative for the whole country.

Table 3.31: PFOA concentrations (µg/L) in serum of teenagers aligned studies HBM4EU

Country	Data collection[a]	N	P05	P10	P25	P50	P75	P90	P95	Mean	SD	Geomean	Sample per year
Germany	GerES V	300	<LOQ	<LOQ	0.81	1.255	1.795	2.7	3.12	1.4092	0.8275	1.173	2014, N = 28; 2015, N = 113; 2016, N = 132; 2017, N = 27
Norway	NEB II	177	0.7665	0.8667	1.0464	1.2813	1.5685	1.9497	2.0879	1.3596	0.4665	1.287	2016, N = 162; 2017, N = 15
France	ESTEBAN	143	0.8971	0.9567	1.2231	1.4741	1.7864	2.3486	2.6201	1.6287	0.8554	1.5044	2014, N = 18; 2015, N = 107; 2016, N = 18
Slovakia	PCB cohort follow-up	292	0.2455	0.32	0.48	0.71	0.96	1.18	1.3945	0.742	0.3501	0.6417	2019, N = 276; 2020, N = 16
Slovenia	SLO CRP	94	0.5295	0.63	0.74	0.86	1.06	1.2	1.442	0.9117	0.2929	0.8714	2018, N = 94
Greece	CROME	52	0.5655	0.621	0.7475	0.875	1.2425	1.787	2.193	1.0665	0.5141	0.9735	2020, N = 22; 2021, N = 30
Sweden	Riksmaten adolescents	300	0.55	0.69	0.8875	1.15	1.5125	2.03	2.3615	1.256	0.5585	1.1483	2016, N = 139; 2017, N = 161
Spain	BEA	299	0.3795	0.428	0.524	0.655	0.7975	0.9342	1.0324	0.6843	0.265	0.6463	2017, N = 223; 2018, N = 76
Belgium	FLEHS IV	300	0.609	0.738	0.88	1.1	1.4	1.6	1.8	1.1492	0.4044	1.085	2017, N = 77; 2018, N = 223

Notes: ([a]) data collections are not representative for the whole country.

Table 3.32: PFOA concentrations (µg/L) in serum of newborns (cord blood) of existing studies gathered in HBM4EU

Country	Data collection	Sub-population	Stratification	P05	P10	P25	P50	P75	P90	P95	Sample per year	Sample per year
Austria	*NEWDA*	*General population*	*Infants younger than 1 year*				*0.621345*	*0.964702*	*1.420639*	*1.843435*	*Infants younger than 1 year, N = 128*	*2017, N = 55; 2018, N = 68; 2019, N = 5*
Slovakia	*PRENATAL*	*General population*	*Infants younger than 1 year*	*0.133544*	*0.189943*	*0.501469*	*0.878533*	*1.474*	*2.220924*	*2.894 32*	*Infants younger than 1 year, N = 323*	*2010, N = 102; 2011, N = 196; 2012, N = 22*
Belgium	3xG	General population	Infants younger than 1 year	0.5235	0.567	0.77	1.045	1.37	1.933	2.2055	Infants younger than 1 year, N = 128	2011, N = 55; 2012, N = 73
Belgium	FLEHS 2 newborns	General population	Infants younger than 1 year	0.8	0.9	1.1	1.5	2	2.5	2.905	Infants younger than 1 year, N = 220	2008, N = 64; 2009, N = 156
Belgium	*FLEHS 3 newborns*	*General population*	*Infants younger than 1 year*	*0.48*	*0.64*	*0.89*	*1.27*	*1.57*	*2.14*	*2.4*	*Infants younger than 1 year, N = 269*	*2013, N = 14; 2014, N = 255*

Notes: Values in *italic* and grey were selected for the calculations. Data are from different sampling years.

The presence of SGA in the epidemiological study of (Govarts et al., 2018) varied between 7.0 and 13.6 %. By definition, at least 10 % of all newborns will be labeled SGA.

Table 3.33: Number of newborns in 2021

Country	Number
Belgium	114,216
Germany	769,380
Greece	85,228
Spain	340,976
France	690,466
Slovenia	18,734
Slovakia	57,110
Sweden	113,589
Norway	53,134
Austria	81,970

Notes: Numbers based on data Eurostat 2022.

Source: https://ec.europa.eu/eurostat/databrowser/product/page/DEMO_PJAN__custom_2892906.

All input data, references, EBD calculation steps and results can also be found in Annex A2.2.

Attributable burden

The calculation is given in Table 3.34 for Belgium.

Table 3.34: Burden of disease in DALYs in 2021 for exposure to PFOA associated with SGA and IQ loss. Example for Belgium

Exposure percentile	P0-P10	P10-P25	P25-P50	P50-P75	P75-P90	P90-P95	>P95	Sum
Number of newborns in percentile	11,422	17,132	28,554	28,554	17,132	5,711	5,711	
Estimated exposure adolescent (µg/L) HBM4EU	0.609	0.809	0.990	1.250	1.500	1.700	1.800	
Exposure newborns (µg/L)[(i)]	0.365	0.485	0.594	0.750	0.900	1.020	1.080	
Exposure (ng/L)[(a)]	365	485	594	750	900	1 020	1 080	
Odds ratio (OR)[(f)]	1.05[(b)]	1.13	1.21	1.32	1.43	1.51	1.55	

Exposure percentile	P0-P10	P10-P25	P25-P50	P50-P75	P75-P90	P90-P95	>P95	Sum
Relative risk (RR) (underestimation)	1.04[g]	1.12	1.18	1.28	1.37	1.44	1.47	
Attributable fraction in percentile	0.04	0.10	0.16	0.22	0.27	0.30	0.32	
Number of SGA-cases background[(c)]	1,142	1,713	2,855	2,855	1,713	571	571	
Total number of SGA-cases								11,422
Total number of SGA cases associated with PFOA exposure								2,111
Total IQ loss								8,973[(d)]
Euro/IQ point								16,458[(e)]
Costs/year (Euro)								1.48×10^8
DALYs								3,282[(h)]

Notes: ([a]): µg/L to ng/L.

([b]): effect per ng/L = 0.00071 per ng/L. Linear approximation. Log-linear ER function could be used but would marginally influence results in considered exposure range. No effect calculated under 300ng/L, assumed as threshold (Govarts et al., 2018).

([c]): Born SGA set at 10 % (see publication Govarts et al., 2018).

([d]): weighted IQ-loss over life is 4.25 points/SGA case based on (Eves et al., 2020).

([e]): Euro 2008 for Belgium based on (Bellanger et al., 2013); lifetime cost.

([f]): maximum set on OR (= 1.64 (95 % CI 0.97-2.76)) based on (Govarts et al., 2018).

([g]): relative risk estimated from OR based on formula of (Zhang and Yu, 1998); SGA in reference population without exposure set at 10 %.

([h]): EUR 45,000 per DALY for intellectual disability (see (Kassotis et al., 2020) and http://en.opasnet.org/w/DALY_to_money_conversion#:~:text=One%20DALY%20is%20estimated%20to,something%20between%2030-60k%E2%82%AC.).

([i]): this step is not necessary when starting from cord blood newborns.

Source: Exposure data from aligned studies as gathered in the HBM4EU-project.

Based on the calculation above exposure to PFOA results in 3,282 DALYs per year for Belgium in 2021. For other countries sampled in HBM4EU following estimate is made (Table 3.35).

Table 3.35: Burden of disease in DALYs in 2021 for exposure to PFOA and SGA and resulted IQ loss

Country	Central estimate	Lower 95 % CI	Upper 95 % CI
Belgium	3,282	0	6,390
Germany	22,923	0	41,516
Greece	1,677	0	3,298
Spain	2,722	0	6,231
France	29,552	0	52,971
Slovenia	267	0	565
Slovakia	471	0	1,000
Sweden	3,664	0	6,880
Norway	2,282	0	4,247

Notes: 95 % CI: 95 % confidence interval.

Source: Exposure based on aligned studies HBM4EU.

Table 3.36: Burden of disease in DALYs in 2021 for exposure to PFOA and SGA and resulted IQ loss. Results expressed per 1,000,000 persons

Country	Central estimate	Lower 95 % CI	Upper 95 % CI
Belgium	284	0	553
Germany	276	0	499
Greece	157	0	309
Spain	57	0	131
France	437	0	783
Slovenia	127	0	268
Slovakia	86	0	183
Sweden	353	0	663
Norway	423	0	788

Notes: 95 % CI: 95 % confidence interval. Results expressed per 1,000,000 persons.

Source: Exposure based on aligned studies HBM4EU.

Table 3.37: Burden of disease in DALYs in 2021 for exposure to PFOA and SGA and resulted IQ loss. Exposure based on existing data gathered during the HBM4EU-project

Country	Central estimate	Lower 95 % CI	Upper 95 % CI
Austria	2,099	0	3,819
Slovakia	1,230	0	2,133
Belgium	5,320	0	9,065

Notes: 95 % CI: 95 % confidence interval.

Exposure data based on direct measurement of PFOA in cord blood.

Table 3.38: Burden of disease in DALYs in 2021 for exposure to PFOA and SGA and resulted IQ loss. Results expressed per 1,000,000 persons

Country	Central estimate	Lower 95 % CI	Upper 95 % CI
Austria	235	0	428
Slovakia	225	0	391
Belgium	460	0	785

Notes: 95 % CI: 95 % confidence interval.

Exposure based on existing data gathered during the HBM4EU-project.

Exposure data based on direct measurement of PFOA in cord blood.

Based on estimates for 3 countries for which data in cord blood was available it can be seen that for Belgium and Slovakia estimates based on cord blood are higher than based on the corrected aligned study data taking into account TFE. However, study years differ. The estimates are in the same order of magnitude.

Alternative calculation

Where in the calculation above the loss of IQ is considered as a personal and economic loss over the entire IQ range, this may not be visible in the disease burden as for persons with for example an IQ higher than 100 who lose some IQ points, the loss may not result in a measurable health loss or clinical disease. This is a discussion going on for some time if the loss of IQ over the entire IQ range should be taken up in the calculation of the disease burden or not. An alternative approach was taken which was based on the percentage of the persons born SGA who would fall below the threshold of an IQ of 70 which would lead to mild mental retardation (MMR). The assumption made in the calculation below is that the IQ distribution with average 100 and standard deviation 15 is shifted to the left towards lower IQ by 4.25 IQ points for children born SGA. Compared to previous calculations no backward calculation from cost to DALYs is necessary.

Table 3.39: Burden of disease in DALYs in 2021 for exposure to PFOA associated with SGA and IQ loss. Example for Belgium

Exposure percentile	P0-P10	P10-P25	P25-P50	P50-P75	P75-P90	P90-P95	>P95	Sum
Number of newborns in percentile	11,422	17,132	28,554	28,554	17,132	5,711	5,711	
Estimated exposure adolescent (µg/L) HBM4EU	0.609	0.809	0.990	1.250	1.500	1.700	1.800	
Exposure new born (µg/L)[g]	0.365	0.485	0.594	0.750	0.900	1.020	1.080	
Exposure (ng/L)[a]	365	485	594	750	900	1,020	1,080	
Odds ratio (OR)[e]	1.05[b]	1.13	1.21	1.32	1.43	1.51	1.55	
Relative risk (RR) (underestimation)	1.04[f]	1.12	1.18	1.28	1.37	1.44	1.47	
Attributable fraction in percentile	0.04	0.10	0.16	0.22	0.27	0.30	0.32	
Number of SGA-cases background[c]	1,142	1,713	2,855	2,855	1,713	571	571	
Total number of SGA-cases								11,422
Total number of SGA cases associated with PFOA exposure								2,111
Attributable fraction SGA								18 %
Weighted IQ loss per SGA case								4.25[d]
Percentage of pop that would have IQ<70 due to loss of 4.25 points								=normdist(70+4.25;100;15;1)-normdist(70;100;15;1)=2 %
DALYs[i]								=11422x18%x2%x0.36x76=1,195

Notes: ([a]): µg/L to ng/L.

([b]): effect per ng/L = 0.00071 per ng/L. Linear approximation. Log-linear ERF could be used but would marginally influence results in considered exposure range. No effect calculated under 300ng/L, assumed as threshold (Govarts et al., 2018).

([c]): SGA set at 10 %.

([d]): weighted IQ-loss over life is 4.25 points/SGA case based on (Eves et al., 2020).

([e]): maximum set on OR (1.64, 95 % CI 0.97-2.76) based on (Govarts et al., 2018).

([f]): relative risk estimated from OR based on formula of (Zhang and Yu, 1998); SGA in reference population without exposure set at 10 %.

([g]): this step is not necessary when starting from cord blood newborns.

([h]): disability weight of 0.36 and duration of 76 years from Hänninen and colleagues (Hänninen et al., 2014).

([i]): the calculation assumes that the IQ distribution with average 100 and stdev 15 is shifted to the left towards lower IQ by 4.25 IQ points for children born SGA.

Exposure data from aligned studies as gathered in the HBM4EU-project.

Only cases of mild mental retardation taken into account.

Following results are obtained for other countries (see Table 3.40, Table 3.41, Table 3.42, Table 3.43).

Table 3.40: Burden of disease in DALYs in 2021 for exposure to PFOA and SGA and resulted IQ loss

Country	Central estimate	Lower 95 % CI	Upper 95 % CI
Belgium	1,195	0	2,328
Germany	8,988	0	16,278
Greece	762	0	1,498
Spain	1,204	0	2,756
France	10,205	0	18,292
Slovenia	134	0	284
Slovakia	282	0	598
Sweden	1,280	0	2,403
Norway	682	0	1,270

Notes: Exposure based on aligned studies HBM4EU.

Endpoint Mild Mental Retardation.

Table 3.41: Burden of disease in DALYs in 2021 for exposure to PFOA and SGA and resulted IQ loss. Results expressed per 1,000,000 persons

Country	Central estimate	Lower 95 % CI	Upper 95 % CI
Belgium	103	0	201
Germany	108	0	196
Greece	71	0	140
Spain	25	0	58
France	151	0	270
Slovenia	64	0	135
Slovakia	52	0	110
Sweden	123	0	232
Norway	126	0	236

Notes: Exposure based on aligned studies HBM4EU.

Endpoint Mild Mental Retardation.

Table 3.42: Burden of disease in DALYs in 2021 for exposure to PFOA and SGA and resulted IQ loss. Exposure based on existing data gathered during the HBM4EU-project

Country	Central estimate	Lower 95 % CI	Upper 95 % CI
Austria	785	0	1,427
Slovakia	735	0	1,274
Belgium	1,938	0	3,302

Notes: Exposure data based on direct measurement of PFOA in cord blood.

Endpoint Mild Mental Retardation.

Table 3.43: Burden of disease in DALYs in 2021 for exposure to PFOA and SGA and resulted IQ loss. Results expressed per 1,000,000 persons

Country	Central estimate	Lower 95 % CI	Upper 95 % CI
Austria	88	0	160
Slovakia	135	0	233
Belgium	168	0	286

Notes: Exposure based on existing data gathered during the HBM4EU-project.

Exposure data based on direct measurement of PFOA in cord blood.

Endpoint Mild Mental Retardation.

When results of this alternative calculation for MMR are compared to the initial one, the burden is a factor 2 to 3 lower and thus still in the same order of magnitude.

3.2.4 Hospitalization of children due to lower respiratory infections

Exposure-response relationship

Hospitalization due to lower respiratory infections can be related to a lower immune response associated with exposure to PFOS/PFOA. According to EFSA, exposure to PFAS may be associated with an increased odds for infections but more objective parameters to confirm the infection (next to self-reporting) are necessary (European Food Safety Authority, 2020).

The ERF used is described in (Dalsager et al., 2021) studying the Odense Child cohort in Denmark. The HR for hospitalization of children (followed up from 0-4 years) for (LRTI) was equal to 1.54 (95 % CI 1.11-2.15) for a doubling of the PFOS concentration in the blood of the mother. Also, for PFOA the association was significant; HR equal to 1.27 for a doubling of PFOA in mothers' blood. In the paper there is no threshold mentioned below which effects would not take place. For the calculation of the health impact the 0-10th exposure percentile of the Odense Child cohort (4µg PFOS/L) could be used as reference. The median concentration of PFOS in the mothers of the Odense child cohort was equal to 7.52µg/L and the P95 15.08µg/L (Dalsager et al., 2021).

Mode of action and weight of evidence

Exposure to PFAS influence the immune system (European Food Safety Authority, 2020). Through reduction of the immune response reaction this could lead to an increasing change on infections like LRTI in children. The effect on the immune system can also be induced by effects on the hormonal system (thyroid). According to EFSA there is some evidence that exposure to PFAS is associated with infections but more evidence is necessary (European Food Safety Authority, 2020).

Exposure-, health-, population data

In Belgium (Flanders) there is an incidence of 4 % for hospitalization of children (0-4 years) because of LRTI (ICD-10 code J09-J22). For European children (0-4 years) in New Zealand it is estimated that the hospitalization rate for lower respiratory tract infections in children equals 2 % (https://www.ehinz.ac.nz/assets/Factsheets/Released-2017/Lower-respiratory-tract-infections-children.pdf). Similar rough estimates of 1 to 3 % were estimated for admissions related to respiratory tract infections based on the paper of Reeves and colleagues (Reeves et al., 2020). Exposure data for the calculation are based on concentrations in blood of adults reported in studies before HBM4EU but gathered in the HBM4EU dashboard.

Table 3.44: PFOS (µg/L) in blood of adults in existing studies for which data was gathered within HBM4EU

Country	Data collection	Sub-population	P05	P10	P25	P50	P75	P90	P95	Cases per age category	Sample per year
Austria	*NEWDA*				*0.656*	*1.012*	*1.381*	*1.911*	*2.463*	*Adults 20-39 years, N = 125*	*2017, N = 55; 2018, N = 63; 2019, N = 7*
Spain	*BIOAMBIENT.ES*		*2.375*	*3.232*	*4.541*	*6.451*	*9.185*	*13.828*	*16.211*	*Adults 20-39 years, N = 404*	*2009, N = 317; 2010, N = 87*
Spain	BIOAMBIENT.ES		2.847	3.718	5.595	8.118	11.427	16.077	18.971	Adults 40-59 years, N = 326	2009, N = 261; 2010, N = 65
Norway	MoBa	Pregnant Women	6.296	7.388	9.705	12.858	16.663	21.382	25.172	Adults 20-39 years, N = 4,128	2000, N = 33; 2001, N = 53; 2002, N = 344; 2003, N = 433; 2004, N = 1,229; 2005, N = 792; 2006, N = 661; 2007, N = 525; 2008, N = 58
Norway	*MoBa*	*Pregnant Women*	*6.095*	*7.188*	*9.030*	*12.762*	*17.256*	*21.306*	*24.492*	*Adults 40-59 years, N = 87*	*2001, N = 1; 2002, N = 8; 2003, N = 7; 2004, N = 31; 2005, N = 16; 2006, N = 12; 2007, N = 12*
Czechia	CzechHBM-AE_2015		0.509	0.923	1.406	2.088	3.456	5.196	6.284	Adults 20-39 years, N = 139	2015, N = 139
Czechia	CzechHBM-AE_2015		0.492	0.666	1.561	2.582	3.958	5.951	11.476	Adults 40-59 years, N = 147	2015, N = 147
Czechia	CzechHBM-AE_2018		0.855	1.227	1.891	2.879	4.479	8.726	11.530	Adults 20-39 years, N = 193	2018, N = 185; 2019, N = 8
Czechia	*CzechHBM-AE_2018*		*0.482*	*0.846*	*1.456*	*2.525*	*4.368*	*9.758*	*13.921*	*Adults 40-59 years, N = 189*	*2018, N = 185; 2019, N = 4*
Denmark	*Odense Child Cohort*	*Pregnant Women*	*3.813*	*4.502*	*5.961*	*7.985*	*11.011*	*13.249*	*15.599*	*Adults 20-39 years, N = 619*	*2010, N = 125; 2011, N = 349; 2012, N = 140; 2013, N = 2*
Denmark	DEMOCOPHES Denmark		2.646	2.941	3.390	4.166	5.724	7.113	9.141	Adults 20-39 years, N = 50	2011, N = 50

Country	Data collection	Sub-population	P05	P10	P25	P50	P75	P90	P95	Cases per age category	Sample per year
Denmark	DEMOCOPHES Denmark		2.739	3.256	4.380	5.778	7.606	10.183	12.067	Adults 40-59 years, N = 93	2011, N = 93
Belgium	FLEHS 2 adults		5.200	6.700	9.150	12.600	16.975	25.650	32.550	Adults 20-39 years, N = 186	2008, N = 106; 2009, N = 80
Belgium	*FLEHS 3 adults*		*2.928*	*3.415*	*5.153*	*7.200*	*10.295*	*15.944*	*17.932*	*Adults 40-59 years, N = 118*	*2014, N = 118*

Notes: Values in *italic* and grey were selected for the calculations. Data are from different sampling years.

Table 3.45: Number of 0-4 year olds in 2021

Country	Number of children (0-4 years)
Belgium	600,245
Czechia	567,262
Denmark	309,850
Spain	1,926,253
Austria	433,755
Norway	282,960

Source: (Eurostat, 2022) for the year 2021.

All input data, references, EBD calculation steps and results can also be found in Annex A2.2.

Attributable burden

The calculation is shown in Table 3.46 below.

Table 3.46: DALYs for lower respiratory infections for exposure to PFOS and hospitalization children for acute infections lower respiratory tract (LRTI). Example for Belgium in 2021

Percentile for exposure	P0-P10	P10-P25	P25-P50	P50-P75	P75-P90	P90-P95	>P95	
Estimated exposure (µg/L)	2.93	4.28	6.18	8.75	13.12	16.94	17.93	
Exposure ln2 scale	1.55	2.10	2.63	3.13	3.71	4.08	4.16	
HR infection[(c)]	1.00	1.04	1.31	1.63	2.10	2.46	2.55	
AF in percentile	0.00	0.04	0.24	0.39	0.52	0.59	0.61	
Children (0-4y) in percentile	60,025	90,037	150,061	150,061	90,037	30,012	30,012	
AF weighted								=sumproduct (children in the percentile; AF in the percentile) /total number of children = 0.30
Number of hospitalizations LRTI/year[(a)]	1,218	1,828	3,046	3,046	1,828	609	609	

Percentile for exposure	P0-P10	P10-P25	P25-P50	P50-P75	P75-P90	P90-P95	>P95	
Hospitalizations related to PFOS exposure	0	76	722	1,175	956	361	370	
Total number hospitalizations related to PFOS								3,661
DALYs[(b)]								91

Notes: ([a]): 2 % hospitalizations LRTI infections/year.

([b]): disability weight (0.65) and duration (14 days) from 'Verloren gezonde levensjaren (DALYs) door blootstelling aan fijn stof' en 'Externe gezondheidskosten door fijn stof' which is based on the publication of de Hollander and colleagues (de Hollander et al., 1999). Study focusses on hospitalization (YLD) and does not include mortality which underestimates the real impact.

([c]): based on Dalsager and colleagues (Dalsager et al., 2021). HR = 1.54 for risk of hospitalization per doubling PFOS concentration mother.

Based on this calculation for hypertension related to PFOS exposure, there is an estimate of 90 DALYs/year for Belgium. Estimates for other countries are given below.

Table 3.47: Burden of disease (DALY) for lower respiratory infection hospitalization due to exposure to PFOS in 2021

Country	Central	Lower 95 % CI	Upper 95 % CI
Belgium	91	27	134
Czechia	28	8	41
Denmark	52	15	77
Spain	253	74	376
Austria	0	0	0
Norway	71	22	98

Notes: 95 % CI: 95 % confidence interval.

Table 3.48: Burden of disease (DALY) for lower respiratory infection hospitalization per 1,000,000 persons due to exposure to PFOS in 2021

Country	Central	Lower 95 % CI	Upper 95 % CI
Belgium	7	2	12
Czechia	3	1	4
Denmark	9	3	13
Spain	5	2	8
Austria	0		
Norway	12	4	17

Notes: 95 % CI: 95 % confidence interval.

3.2.5 Kidney disease and kidney cancer

Kidney disease

Several studies reported an association between exposure to PFOA, PFOS and kidney dysfunction (based on estimated glomerular filtration rate) (e.g. (Shankar et al., 2011; Wilkins et al., 2017; Kataria et al., 2015; Dhingra et al., 2016).

According to the The Panel on Contaminants in the Food Chain (CONTAM), there is insufficient evidence to conclude that exposure to PFAS decrease glomerular filtration rate in the kidney or leads to an increase in uric acid in serum. The possibility of reverse causality is relevant. Epidemiological studies provide insufficient evidence for associations between exposure to PFAS and changes in kidney function (European Food Safety Authority, 2020).

Due to a current lack of evidence for this endpoint the calculation was not made.

Kidney cancer

One study reported an association between PFOA exposure (estimated based on residence location) for persons living near the US C8 plant (West-Virginia) and increased change for kidney cancer (Vieira et al., 2013). No HBM data were available.

Studies provided insufficient support for carcinogenicity of PFOS and PFOA in humans (European Food Safety Authority, 2020). This is in line with the conclusion of IARC, which concluded that there was limited evidence for carcinogenicity (IARC, 2017).

Due to a current lack of evidence the calculation for this endpoint was not made.

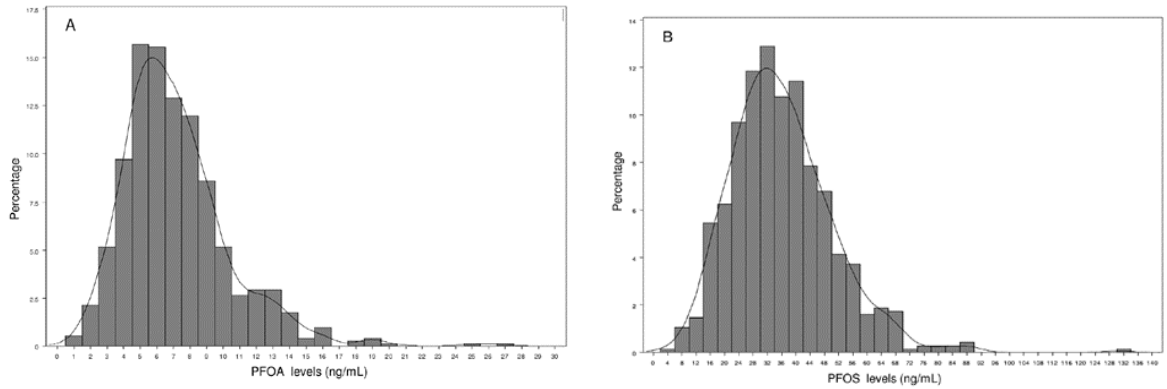
3.2.6 Cholesterol and cardiovascular mortality

Exposure-response relationship

A statistically significant positive association was found between both perfluorinated compounds (PFOS and PFOA) and total cholesterol in a Danish study (DCH cohort 1993 to 1997) (Eriksen et al., 2013). A higher cholesterol level may increase the risk of cardiovascular diseases. PFOA concentrations in the study of (Eriksen et al., 2013) ranged between 1 and 30µg/L and PFOS concentrations between 4 and 132µg/L (Figure 3.5). Mean plasma PFOA and PFOS levels were 7.1µg/L and 36.1µg/L respectively (Eriksen et al., 2013).

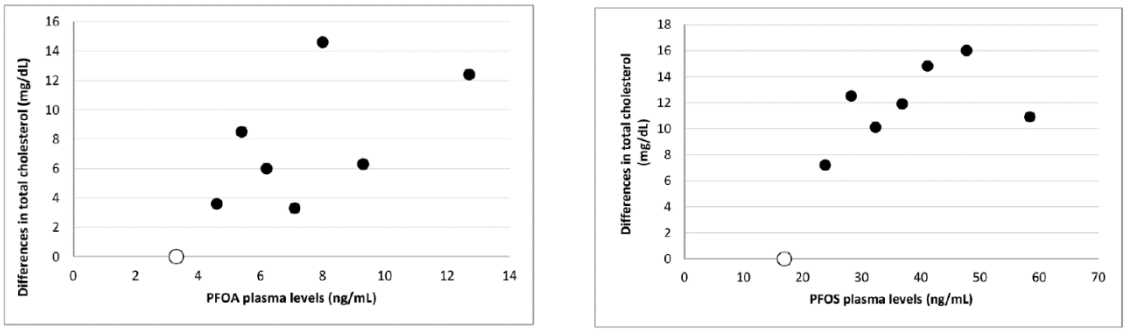
A 4.4 (95 % CI 1.1-7.8) higher concentration of total cholesterol (mg/dL) per interquartile range of PFOA was observed. For PFOS this was an increase of 4.6 total cholesterol (mg/dL) (95 % CI 0.8-8.5) per IQR change. Associations between change in total cholesterol and PFOS or PFOA concentrations are given in Figure 3.6. Literature data show that findings are not consistent.

Figure 3.5: PFOS and PFOA concentrations in blood observed in Danish adults.



Source: (Eriksen et al., 2013).

Figure 3.6: Associations between PFOA/PFOS and change in total cholesterol in Danish adults.



Source: (Eriksen et al., 2013).

Mode of action and weight of evidence

In 2018 EFSA considered the increase of serum total cholesterol in adults and the decrease in antibody response at vaccination in children as critical effects (European Food Safety Authority, 2018).

The CONTAM Panel derived tolerable weekly intakes (TWI) for PFOS and PFOA based on serum cholesterol. These TWI are protective for other potential critical endpoints. In 2020 EFSA based the TWI on decreased antibody response (European Food Safety Authority, 2020). Although the association with increased cholesterol was observed in a large number of studies, the CONTAM panel considered in 2020 the uncertainty regarding causality to be larger. This is primarily due to a postulated biological process around the enterohepatic cycling of both PFAS and bile acids, the latter affecting serum cholesterol levels. This should be further investigated.

The exact mechanism is unknown, possibly PPAR-α (Peroxisome proliferator- activated receptor alpha), although this peroxisome proliferation is much less apparent in humans than in animals, may play a role.

Exposure-, health-, population data

Blood concentrations for PFOS in adults are given in Table 3.44 and for PFOA in Table 3.31 and Table 3.32. Highest observed P95 in selected studies was equal to 5 to 6µg/L for PFOA and 24µg/L for PFOS. These concentrations lie at the lower end of the observed ERF (Figure 3.5). Concentrations are thus lower in the more recent exposure data gathered under HBM4EU than in the study in which the ERF was derived.

Attributable burden

No calculations were performed here because concentrations identified in the ERF are higher than data gathered under HBM4EU for adults.

3.2.7 All-cause mortality

Exposure-response relationship

The ERF was described recently by Wen and colleagues based on NHANES data (1999-2014) (Wen et al., 2022). However, an overlap with other endpoints (e.g. hypertension) describing diseases related with premature mortality is possible. Participants in a high-exposure group had an increased risk of all-cause mortality (HR 1.38, 95 % CI 1.07-1.80) compared to participants in low-exposure group for a mixture of PFOS and PFOA. In single PFAS analysis, PFOS was associated with all-cause mortality (third vs first tertile (HR 1.57, 95 % CI 1.22-2.07). For heart disease mortality this was HR=1.65 (95 % CI 1.09-2.57) and cancer mortality HR=1.75 (95 % CI 1.10-2.83). PFOS concentrations in high exposed group (tertile) were higher than 17.1µg/L. PFOA exposure had no significant association with mortality.

Mode of action and weight of evidence

No consistent conclusion on the link with mortality are made yet.

Exposure-, health-, population data

Exposure data for PFOS in EU are for the P95 in general less than 17.1µg/L. Only for Norway there was an exceedance (P95 = 24.4µg/L) (see Table 3.44).

Attributable burden

The concentration observed for the exposure effect association was in general higher than observed in the EU; the calculation was not made.

3.2.8 Reduced immune response

At the moment the TWI set by EFSA for the sum of 4 PFAS is based on reduced immune response after vaccination (tetanus, diphtheria) (European Food Safety Authority, 2020). A reduced immune function will not only have an effect seen as a reduced vaccination response but in general it may influence our reaction to exposure to viruses, bacteria, chemicals etc.

Therefore, it is difficult to quantify what a reduced immune response exactly means for our health. Therefore, this calculation is hard to make at the moment and will be further investigated under the EU PARC-project.

3.2.9 Overall Environmental burden of disease related to PFOS and PFOA

DALYs were calculated for effects on small for gestational age and related IQ loss, hospitalization and hypertension associated with exposure to PFOA and PFOS. A summary is given in table

Table 3.49. Per million persons the DALYs for PFOA and PFOS exposure are presented in Table 3.50. It should be considered that estimates for PFOA and SGA are probably an underestimate as data for adolescents were used as a proxy for pregnant mothers in some calculations.

Table 3.49: Summary of burden of disease attributable to PFOS and PFOA in 2021

Country	Hypertension and mortality DALY/year	Small for gestational age and IQ loss DALY	SGA and IQ loss (alternative calculation considering MMR)	Hospitalization LRTI DALY	Total DALY/year	Total based on alternative calculation for SGA
Belgium	1,024	3,282 or 5,320(*)	1,195 or 1,938(*)	91	4,397 or 6,435(*)	2,310 or 3,053(*)
Czechia	100			28		
Denmark	140			52		
Spain	2,591	2,722	1,204	253	5,566	4,048
Austria	0	2,099	785	0	2,099	785
Norway	243	2,282	682	71	2,596	996
Germany		22,923	8,988			
Greece		1,677	762			
France		29,552	10,205			
Slovenia		267	134			
Slovakia		471 or 1,230(*)	282 or 735(*)			
Sweden		3,664	1,280			
Norway		2,282	682			

Notes: (*): depending on exposure data used (adult blood and transfer factor or cord blood).

Table 3.50: DALYs/1,000,000 persons in 2021 estimated in this study

Country	Hypertension	Small for gestational age and IQ loss	SGA and IQ loss (alternative calculation considering MMR)	Hospitalization LRTI	Total	Total based on alternative calculation for SGA
Belgium	**89**	**284 or 460(*)**	**103 or 168(*)**	**8**	**381 or 557(*)**	**200 or 265(*)**
Czechia	**9**			**3**		
Denmark	**24**			**9**		
Spain	**55**	**57**	**25**	**5**	**117**	**85**
Austria	**0**	**235**	**88**	**0**	**235**	**88**
Norway	**45**	**423**	**126**	**13**	**481**	**185**
Germany		**276**	**108**			
Greece		**157**	**71**			
France		**437**	**25**			
Slovenia		**127**	**64**			
Slovakia		**86 or 225(*)**	**52 or 135(*)**			
Sweden		**353**	**123**			
Norway		**423**	**126**			

Notes: (*): depending on exposure data used (adult blood and transfer factor or cord blood).

3.3 Burden of disease due to phthalates

3.3.1 General information on phthalates and basic assumptions

Phthalates are chemicals that are produced in high volumes worldwide. They are used as plasticizers and in personal care products. Phthalates easily leach from products and thus can enter the human body though various exposure routes. Due to their ubiquitous occurrence phthalates and their metabolites can be found in many human samples. According to their different physico-chemical characteristics they can be split into high molecular weight (HMW) and low molecular weight (LMW) phthalates (European Human Biomonitoring Initiative, 2020).

The health effects of phthalates were shown to be linked with their endocrine disruptive characteristics and reproductive toxicity. Especially animal studies indicated reproductive malformations that might e.g. lead to reduced fertility. Human epidemiological studies also indicated a considerable variety of associations between the exposure to phthalates and health effects. Among others it was shown that increased exposure to phthalates is linked with higher risks of overweight, asthma, attention deficit disorders, attention deficit hyperactivity disorders and preliminary stages of diabetes mellitus (Engel et al., 2010; Hatch et al., 2010; Wang et al., 2015; Franken et al., 2017).

Asthma, obesity and diabetes mellitus were taken into consideration. Fertility effects and associations with reproductive consequences were not considered because on the one hand the burden of disease due to infertility might be low in children and adolescents as they might not be aware of their status. Further, most of the evidence on fertility effects and reproductive disorders is based on animal studies which hamper the use of these estimates for calculating the burden of disease for humans.

Mode of action and weight of evidence

Most of the evidence related to the mode of action for phthalates was established in animal studies. Overall it has been shown that phthalates induce oxidative stress, estrogenicity, antagonism to androgens and are associated with expressions of peroxisome-proliferator activated receptors playing an important role in the metabolism of lipids and carbohydrates (Gourlay et al., 2003; Jepsen et al., 2004; Desvergne et al., 2009; Desdoits-Lethimonier et al., 2012; Chen et al., 2014; Meeker and Ferguson, 2014; Woodward et al., 2020). It can be assumed that interferences of phthalates into the human homeostasis mechanisms might be the cause of such health effects (Hatch et al., 2010). However, the evidence for the causality with respect to many health effects is still limited (Begum and Carpenter, 2022). A further overview on relevant health effects related to phthalate exposure can be found in Annex A1.1.

Phthalates are increasingly covered by HBM-studies where concentrations of the phthalate metabolites are measured in urine or blood serum samples. Generally, phthalates are metabolized very fast, with most metabolites leaving the body withing 24 hours. Mostly, urine samples are used for analyses as they provide an integrative measure including all phthalate exposure pathways (Franken et al., 2017).

For the underlying analyses, data gathered in both the aligned studies and other studies collected within the HBM4EU-project are used to estimate the exposure. Due to missing or limited data the estimates are only performed for selected countries. Also, selected case studies indicate where calculation might be possible, considering the limitations resulting from selective assumptions.

3.3.2 Asthma in children/adolescents

Asthma is characterized by long-term airway inflammation. The Global Initiative for Asthma further states that asthma describes the presence of disease symptoms such as wheeze, shortness of breath, chest tightness and cough. These symptoms can vary both over time and also in their intensity. All symptoms go along with different levels of expiratory airflow limitation (Reddel et al., 2015). In most cases, the disease develops during early childhood, however, it may also develop any time later in life (Asher et al., 2018). In recent years, several reports, systematic reviews and meta-analyses have indicated a suggestive association between exposure to phthalates and asthma risk in the general population (Jaakkola and Knight, 2008; Li et al., 2017; European Human Biomonitoring Initiative, 2020; Wu et al., 2020a; Mattila et al., 2021). Though, the processes in the human body are not yet fully understood. Moreover, the findings of the respective epidemiological studies reviewed were not always consistent. There are studies showing both a positive and a negative association between phthalate exposure and asthma, as well as studies reporting non-significant associations (Wu et al., 2020a). As possible reasons Li and colleagues point at the variety of different phthalates that have been studied, different exposure time frames, and different sources of exposure data (Li et al., 2017).

Exposure-response relationship

For EBD calculations, there were no pooled effect measures for the ERF from recent meta-analyses available. Therefore, we searched for eligible single epidemiological studies. One criterion was the potential comparability of the phthalate (metabolite) exposure data with HBM4EU exposure data, preferably from the aligned studies. The study by Franken and colleagues was selected, which was also considered in the HBM4EU scoping document on phthalates associations with asthma (Franken et al., 2017; European Human Biomonitoring Initiative, 2020).

In Franken and colleagues, the ERF was based on two cohort studies in Flanders, the Flemish Environment and Health Study FLEHS II and III (n = 418) (Franken et al., 2017). Pooled data showed that self-reported doctor-diagnosed asthma in adolescents aged 14-15 years was significantly associated with phthalate metabolites measured in urine (µmol/L, adjusted for specific gravity) with an exposure increase from percentile 25 to 75: DEHP (sum of MEHP[2], MEHHP[3] and MEOHP[4]) OR 1.94 (95 % CI 1.07-3.51), and MnBP[5] OR 1.84 (95 % CI 1.02-3.32). In our analysis, the EBD calculations were only performed for DEHP[6]. The value 0.07µmol/L adjusted for specific gravity was used as reference, acknowledging that health effects might also be suspected below this concentration.

Exposure-, health-, population data

Regarding asthma prevalence, data from the GBD 2019 study were used (IHME, 2022). These were available in 5-year age groups. To perform EBD calculations for the reference year 2021, we applied the prevalence rates of 2019 to the population of 2021. Input data for the DW were obtained from the same data source and for the same age groups. The respective DWs were calculated by dividing the annual YLDs by the number of prevalent asthma cases for the WHO European Region (IHME, 2022).

We did not calculate mortality indicators (e. g. YLLs) for this risk-outcome-pair, because the selected ERF only applied to asthma prevalence for adolescents aged 14-15 years. Applying the same effect estimate to mortality data may lead to over- or underestimation of the disease burden.

[2] Mono-2-ethylhexyl phthalate
[3] Mono-2-ethyl-5-hydroxyhexyl phthalate
[4] Mono-2-ethyl-5-oxohexyl phthalate
[5] Mono-n-butyl phthalate
[6] Di(2-ethylhexyl) phthalate

Regarding exposure data, phthalate concentrations of DEHP (sum of MEHP, MEHHP and MEOHP) from the aligned studies of HBM4EU in adolescents (12-18 years) were used. Only data sets with a number of 50 or more study participants were selected. Exposure data were available for different sampling years. Accordingly, data from 2021±5 years were used. If there were two data sets for a country in this period available, the most recent one was selected. Values in grey were selected for the calculations (Table 3.51). In total, 9 countries were considered in the estimation process.

Table 3.51: DEHP concentrations (µmol/L, adjusted for specific gravity) in urine of adolescents (12-18 years) of studies gathered in HBM4EU

Country	Data collection	Year	Age group (years)	N	P05	P10	P25	P50	P75	P90	P95
Belgium	T_VITO_FLEHS IV	2017	13-15	77	0.016	0.022	0.027	0.039	0.053	0.089	0.129
Belgium	T_VITO_FLEHS IV	2018	13-16	223	0.013	0.017	0.025	0.040	0.065	0.110	0.136
Czechia	T_MU_Pilot school children	2019	12-17	299	0.033	0.042	0.059	0.085	0.126	0.224	0.301
Germany	T_UBA_GerES V	2015	12-18	105	0.028	0.032	0.041	0.060	0.086	0.138	0.183
Germany	T_UBA_GerES V	2016	12-18	118	0.020	0.029	0.037	0.055	0.079	0.116	0.176
Germany	T_UBA_GerES V	2017	12-17	70	0.023	0.028	0.034	0.049	0.064	0.115	0.135
Greece	T_AUTH_CROME	2020	12-18	72	0.028	0.035	0.063	0.123	0.232	0.359	0.416
Greece	T_AUTH_CROME	2021	12-18	78	0.028	0.036	0.061	0.102	0.172	0.446	0.888
Norway	T_NIPH_NEB II	2016	12-14	166	0.024	0.026	0.033	0.050	0.082	0.120	0.151
Poland	T_NIOM_POLAES	2017	12-14	281	0.032	0.040	0.063	0.099	0.162	0.237	0.329
Slovakia	T_SZU_PCB cohort follow-up	2019	15-17	270	0.054	0.069	0.116	0.196	0.329	0.508	0.823
Slovenia	T_JSI_SLO CRP	2018	12-15	96	0.023	0.031	0.047	0.074	0.109	0.164	0.195
Spain	T_ISCIII_BEA	2017	13-17	224	0.028	0.036	0.048	0.070	0.105	0.166	0.215
Spain	T_ISCIII_BEA	2018	13-17	76	0.028	0.031	0.046	0.066	0.099	0.130	0.172
Sweden	T_NFA_Riksmaten Ungdom	2016	12-17	139	0.025	0.030	0.037	0.050	0.082	0.125	0.233
Sweden	T_NFA_Riksmaten Ungdom	2017	12-17	161	0.025	0.028	0.037	0.051	0.079	0.120	0.166

Notes: DEHP is the sum of MEHP, MEHHP and MEOHP.

Regarding population information for the above selected countries, data from Eurostat (1-year age groups) as of January 2021 was used (Eurostat, 2022).

All input data, references, EBD calculation steps and results can also be found in Annex A2.3.

Attributable burden

For this risk-outcome-pair, the PAF as well as the YLDs were calculated for the age group 10-19 years, the latter differentiated by sex. The age range represents a compromise, since the age groups considered were different in the respective input data (ERF: 14-15 years, exposure data: 12-18 years, and health data: 10-14, or 15-19 years).

The DEHP-related proportion of asthma in children and adolescents aged 10-19 years ranged between 4.2 % (Belgium) and 20 % (Poland). Accordingly, the total maximum of 1,825 (95 % CI 212-3,082) YLDs were attributable to asthma in Poland. The highest rates were estimated for Greece with 53 (6-88) YLDs per 1,000,000 persons. Regarding YLDs for boys, a slightly higher attributable disease burden was identified compared to girls in all countries considered. These differences exclusively resulted from higher asthma prevalence cases in boys. The exposure and derived PAF were not evaluated stratified by sex due to low case numbers and thus did not contribute to sex differences in the calculated YLD results. Estimates for other countries are listed in (Table 3.52).

Table 3.52: Asthma disease burden attributable to DEHP for children and adolescents (10-19 years) for different European countries in 2021

		Males		Females		Total(*)	
Country	PAF (95 % CI) (%)	YLDs (95 % CI)	YLDs per 1,000,000 (95 % CI)	YLDs (95 % CI)	YLDs per 1,000,000 (95 % CI)	YLDs (95 % CI)	YLDs per 1,000,000 (95 % CI)
Belgium	4.2 (0.4-8.4)	68 (6-136)	12 (1-24)	57 (5-114)	10 (1-19)	125 (12-251)	11 (1-22)
Czechia	15.7 (1.8-26.9)	131 (15-225)	25 (3-43)	106 (12-181)	19 (2-33)	237 (27-407)	22 (3-38)
Germany	4.3 (0.4-8.7)	354 (33-706)	9 (1-17)	326 (30-649)	8 (1-15)	680 (64-1,355)	8 (1-16)
Greece	21.2 (2.5-35.1)	290 (35-480)	56 (7-92)	277 (33-460)	51 (6-84)	567 (68-940)	53 (6-88)
Poland	20.0 (2.3-33.8)	971 (113-1,640)	53 (6-90)	854 (99-1,442)	44 (5-74)	1,825 (212-3,082)	48 (6-81)
Slovakia	34.8 (4.4-54.5)	138 (17-217)	52 (7-81)	109 (14-170)	39 (5-61)	247 (31-387)	45 (6-71)
Slovenia	11.6 (1.2-21.1)	25 (3-46)	24 (3-44)	20 (2-36)	19 (2-35)	45 (5-83)	21 (2-39)
Spain	8.7 (0.9-16.8)	527 (52-1,013)	23 (2-44)	415 (41-798)	17 (2-33)	942 (93-1,811)	20 (2-38)
Sweden	5.8 (0.6-10.8)	135 (14-252)	26 (3-48)	122 (12-228)	24 (2-44)	257 (26-480)	25 (2-46)

Note: DEHP is the sum of MEHP, MEHHP and MEOHP;

(*) Due to rounding, there may be small deviations in the total results.

3.3.3 Obesity in adults

Increasing scientific evidence suggests that phthalates as endocrine disrupting chemicals may affect metabolic processes that control fat accumulation and lipogenesis. Hence, phthalate exposure is suspected to contribute to the development of obesity (Ribeiro et al., 2020, 2019). In recent years, systematic reviews indicate an overall positive association between phthalate exposure and obesity, primarily for adults (Ribeiro et al., 2020, 2019). Though, the results of the individual studies in adults as well as in children were mostly statistically not significant, inconsistent or biased and therefore hardly generalizable. Consequently, the evidence is rather evaluated as uncertain or suggestive (Goodman et al., 2014; Ribeiro et al., 2019; European Human Biomonitoring Initiative, 2020; Gao et al., 2022).

Exposure-response relationship

For EBD calculations, there were no pooled effect measures for the ERF from recent meta-analyses available. For this reason, we examined the individual studies in the meta-analysis by Ribeiro and colleagues. The authors summarized study results for many phthalate metabolites with respect to associations with obesity (Ribeiro et al., 2019). However, the review rarely described the definition of obesity used in the individual studies.

Our study selection criteria for each metabolite were that suitable exposure data should be available within HBM4EU for each age group (children and adults). Further, the exposure-effect associations of all identified studies (per age group) should be statistically significant and not inversely associated. Lastly, most recent studies with comparable exposure levels to Europe were preferred.

Based on these criteria, only the phthalate metabolite mono-(carboxy-isooctyl) phthalate (MCOP) was selected as a risk factor from the meta-analysis. In fact, the metabolite mono-methyl phthalate (MMP) was also included in the shortlist. However, the only available study by Dong and colleagues was conducted in China, hampering the extrapolation to the European region (Dong et al., 2017). In addition, the study found a significant protective effect of phthalate exposure in relation to obesity. For both reasons, we excluded the study for disease burden calculations.

Regarding the metabolite MCOP, the identified epidemiological studies by Buser and colleagues and Zhang and colleagues both performed analyses using NHANES data (Buser et al., 2014; Zhang et al., 2019). However, Zhang and colleagues evaluated more recent data (2013-2014), so this study was finally selected (Zhang et al., 2019). Multivariable logistic regression analyses showed that ln-transformed MCOP concentrations measured in urine (µg/L) were significantly associated with general obesity, defined as BMI of equal to or more than 30kg/m² in adults aged 20 years or older, in the upper two quartiles (Table 3.53). The analysis was based on a sample of 1,269 participants (Zhang et al., 2019).

Table 3.53: Association between MCOP concentrations and general obesity

Urinary MCOP concentration (µg/L)	Adjusted OR (95 % CI)
Quartile 1 (<7.55µg/L)	1 (Reference)
Quartile 2 (7.55-17.80µg/L)	1.20 (0.83-1.72)
Quartile 3 (17.80-48.35µg/L)	1.74 (1.20-2.51)
Quartile 4 (>48.35µg/L)	1.80 (1.22-2.65)

Notes: 95 % CI: 95 % confidence interval.

Source: adopted from (Zhang et al., 2019).

Exposure-, health-, population data

Within all aligned data sets gathered within HBM4EU, current MCOP exposure data for adults are not included. Most recent data are only available for selected countries for 2011-2012 and older years. For the age group of children and adolescents, on the other hand, there are current data for various countries, the most recent ones from 2020-2021. Therefore, as an approximation of adult exposure, a conversion factor (CF) was considered to infer adult exposure from child/adolescent exposure. To obtain a CF we used the study by Buser and colleagues, reporting urinary MCOP concentrations for both children/adolescents (aged 6-19 years) and adults (aged 20 years or older) from NHANES data 2007-2008 (Table 3.54) (Buser et al., 2014). The CF represents the ratio of the MCOP geometric mean concentration for adults to the one of children/adolescents . Accordingly, the derived exposure CF was 0.691.

Table 3.54: Urinary MCOP concentrations in children and adults in NHANES 2007-2010

Age group	MCOP geometric mean (µg/L)
All children/adolescents (aged 6-19 years)	12.43
All adults (aged ≥20 years)	8.59

Source: (Buser et al., 2014).

Regarding exposure data, HBM4EU aligned studies from 2021±5 years were used. Only data sets with a sample size bigger than 50 participants were selected. If there were two data sets for a country available in this period, the most recent one was selected. Where possible, the calculations were additionally differentiated according to the age group used for the exposure CF, i.e. children (age 6-12 years) or adolescents (age 12-18 years). Table 3.55 shows the urinary MCOP concentrations, multiplied by the exposure CF, which approximate exposure levels for adults aged 20 years or older. Values in grey were selected for the calculations. In total, 14 countries were considered in the estimation process.

Table 3.55: Converted urinary MCOP concentrations (µg/L) in adults (≥20 years) based on children and adolescents (6-18 years) exposure data of aligned studies under HBM4EU (N≥50)

Country	Data collection	Year	Age group (years in survey)	N	P05	P10	P25	P50	P75	P90	P95
Belgium	T_VITO_FLEHS IV	2017	13-15	77	0.42	0.60	0.89	1.38	2.64	4.51	6.87
Belgium	T_VITO_FLEHS IV	2018	13-16	223	0.27	0.44	0.75	1.13	1.71	2.95	4.86
Belgium	C_VITO_3xG	2019	6-8	112	<LOQ	<LOQ	<LOQ	0.18	0.42	0.79	1.05
Czechia	T_MU_Pilot school children	2019	12-17	299	1.09	1.43	2.15	3.57	6.46	13.27	24.18
Denmark	C_SDU_OCC	2018	7	97	0.58	0.80	1.40	2.61	4.51	7.05	10.74
Denmark	C_SDU_OCC	2019	6-7	203	0.49	0.82	1.68	2.87	4.92	8.48	11.74
France	T_ANSP_ESTEBAN	2015	12-17	215	2.31	3.07	4.60	7.67	12.99	31.00	74.49

Country	Data collection	Year	Age group (years in survey)	N	P05	P10	P25	P50	P75	P90	P95
France	T_ANSP_ESTEBAN	2016	12-17	54	2.42	3.30	4.21	6.17	10.04	23.78	37.57
France	C_ANSP_ESTEBAN	2015	6-12	205	1.87	2.78	4.36	7.05	12.78	25.69	42.88
Germany	T_UBA_GerES V	2015	12-18	105	1.11	1.31	1.93	3.39	6.08	13.41	23.02
Germany	T_UBA_GerES V	2016	12-18	124	0.77	1.04	1.71	3.07	5.01	7.93	15.26
Germany	T_UBA_GerES V	2017	12-17	71	0.86	1.17	1.87	2.76	4.28	5.74	6.94
Germany	C_UBA_GerES V	2015	6-12	70	1.79	2.19	3.25	5.63	8.29	16.58	26.06
Germany	C_UBA_GerES V	2016	6-12	160	1.24	1.52	2.21	3.46	5.74	9.27	14.28
Germany	C_UBA_GerES V	2017	6-12	70	1.17	1.58	2.59	3.66	7.01	12.10	14.01
Greece	T_AUTH_CROME	2020	12-18	72	1.47	1.94	2.79	3.86	5.83	9.08	13.14
Greece	T_AUTH_CROME	2021	12-18	78	1.57	1.91	2.85	4.64	7.60	19.62	26.86
Greece	C_AUTH_CROME	2020	6-11	84	1.70	2.16	2.92	4.21	6.19	9.21	15.59
Greece	C_AUTH_CROME	2021	6-11	77	1.70	2.10	3.10	4.88	11.60	21.01	27.36
Hungary	C_NPHI_InAirQ	2017	8-11	100	0.39	0.71	1.16	2.01	3.90	6.98	8.04
Hungary	C_NPHI_InAirQ	2018	8-11	162	0.27	0.37	0.78	1.55	2.72	6.00	7.49
Netherlands	C_RIVM_SPECIMEn-NL	2020	6-11	89	1.21	1.39	1.99	3.10	5.76	8.87	11.75
Norway	T_NIPH_NEB II	2016	12-14	166	3.46	3.74	4.81	6.56	10.86	16.94	27.56
Norway	C_NIPH_NEB II	2016	7-11	290	3.50	3.97	5.00	7.20	10.75	20.66	32.16
Poland	T_NIOM_POLAES	2017	12-14	281	0.79	0.97	1.62	2.42	3.74	6.75	8.46
Poland	C_NIOM_POLAES	2017	7-10	300	0.87	1.11	1.92	2.90	4.35	7.29	9.71
Slovakia	T_SZU_PCB cohort follow-up	2019	15-17	271	1.02	1.88	2.82	4.63	8.26	15.27	23.04
Slovenia	T_JSI_SLO CRP	2018	12-15	96	1.24	1.60	2.16	3.97	6.35	8.26	11.01
Slovenia	C_JSI_SLO CRP	2018	7-10	149	1.30	1.67	2.80	4.76	8.43	12.46	18.55
Spain	T_ISCIII_BEA	2017	13-17	224	0.88	1.40	2.65	4.51	7.88	12.26	16.09
Spain	T_ISCIII_BEA	2018	13-17	76	1.32	1.70	2.43	5.00	8.16	20.12	35.68
Sweden	T_NFA_Riksmaten Ungdom	2016	12-17	139	1.04	1.23	2.47	4.50	8.79	16.16	52.95
Sweden	T_NFA_Riksmaten Ungdom	2017	12-17	161	0.97	1.26	2.05	3.82	8.51	20.84	31.29

Notes: LOQ = level of quantification;

P = percentile.

Data on obesity prevalence in adults were derived from the European Health Interview Survey (Eurostat, 2023a). These were available for the year 2019 in a mix of 5- and 10-year age groups. Analogue to Zhang and colleagues, obesity was defined as BMI of equal or more than 30kg/m². Mortality data were not available for this disease (Zhang et al., 2019). To perform EBD calculations for

the reference year 2021, the prevalence rates of 2019 were applied to the population of 2021. However, since there is no DW available for this health state, only the PAF and the sex specific attributable prevalence for the adult population was estimated.

Regarding population information, data from Eurostat (1-year age groups) as of January 2021 was used (Eurostat, 2022).

All input data, references, EBD calculation steps and results can also be found in Annex A2.4 and Annex A2.5.

Attributable burden

Due to missing mortality data and no DW, only the PAF and sex specific attributable prevalence for the adult population 20 years or older were calculated for this risk-outcome-pair (Table 3.56).

For Belgium as well as Germany (based on adolescent's HBM data), no results were estimated, because the exposure level was below the counterfactual value of 7.55µg/L. Regarding the other European countries, the MCOP-related proportion of obesity was lowest in Poland (0.2 %, 95 % CI 0.0-1.5 %) and highest in Norway (9.2 %, 95 % CI 1.5-17.5). The total attributable prevalence ranged from 4,123 (95 % CI 0-9,807) cases in Slovenia to 681,929 (95 % CI 146,426-1,306,582) cases in France. The lowest and highest rates per 1,000,000 persons, however, were estimated for Poland (333, 95 % CI 0-2,283) and Greece (11,324, 95 % CI 1,929-22,391), respectively. Gender-specific differences in attributable prevalent cases were not identified.

However, it must be noted that the selected HBM4EU exposure data, depending on the age groups, had an impact on the final results. In the exposure datasets where both children and adolescents were examined for the same sampling year, it is evident that the concentration levels of urinary MCOP were higher in children than in adolescents (see Table 3.55). This has the corresponding effect for the conversion to adult exposure, depending on whether the exposure of children or adolescents was taken as a basis. Accordingly, converted adult exposure levels based on children's exposure levels resulted in a higher PAF and attributable prevalence as compared to exposure based on adolescents' data.

Table 3.56: Obesity disease burden attributable to MCOP in adults (≥20 years) in 2021

		Males		Females		Total(*)		Exposure input data	
Country	PAF (95 % CI) (%)	Attributable prevalence (95 % CI)	Attributable prevalence per 1,000,000 (95 % CI)	Attributable prevalence (95 % CI)	Attributable prevalence per 1,000,000 (95 % CI)	Attributable prevalence (95 % CI)	Attributable prevalence per 1,000,000 (95 % CI)	Year	Age group (years in survey)
Belgium	0.0	0	0	0	0	0	0	2019	Children
Czechia	4.7 (0.7-9.0)	43,390 (6,370-82,648)	8,226 (1,208-15,668)	37,708 (5,536-71,825)	6,949 (1,020-13,236)	81,099 (11,907-154,473)	7,578 (1,113-14,434)	2019	Adolescents
Denmark	3.9 (0.2-8.2)	14,213 (833-29,465)	4,893 (287-10,143)	15,282 (895-31,680)	5,206 (305-10,793)	29,495 (1,728-61,145)	5,050 (296-10,470)	2019	Children
France	8.7 (1.9-16.6)	307,909 (66,115-589,956)	9,411 (2,021-18,032)	374,020 (80,311-716,626)	10,705 (2,299-20,511)	681,929 (146,426-1,306,582)	10,079 (2,164-19,312)	2016	Adolescents
Germany	3.4 (0.0-7.6)	221,835 (1,118-489,941)	5,407 (27-11,942)	232,622 (1,172-513,763)	5,522 (28-12,195)	454,457 (2,290-1,003,704)	5,465 (28-12,070)	2017	Children
Germany	0.0	0	0	0	0	0	0	2017	Adolescents
Greece	8.2 (1.4-16.2)	57,910 (9,867-114,510)	11,145 (1,899-22,038)	63,010 (10,736-124,594)	11,493 (1,958-22,725)	120,920 (20,602-239,104)	11,324 (1,929-22,391)	2021	Children
Greece	6.6 (0.9-11.3)	46,805 (6,551-79,338)	9,008 (1,261-15,269)	50,927 (7,128-86,325)	9,289 (1,300-15,745)	97,732 (13,680-165,663)	9,152 (1,281-15,513)	2021	Adolescents
Hungary	1.2 (0.0-2.8)	11,391 (0-27,120)	2,442 (0-5,815)	11,605 (0-27,630)	2,290 (0-5,453)	22,996 (0-54,751)	2,363 (0-5,672)	2018	Children
Netherlands	4.4 (0.2-8.8)	40,478 (2,250-80,231)	4,660 (259-9,236)	50,815 (2,825-100,721)	5,782 (321-11,460)	91,293 (5,075-180,952)	5,224 (290-10,355)	2020	Children
Norway	9.2 (1.5-17.5)	30,577 (4,922-58,375)	11,245 (1,810-21,467)	24,416 (3,930-46,612)	9,137 (1,471-17,444)	54,993 (8,851-104,987)	10,200 (1,642-19,473)	2016	Children
Norway	8.1 (0.9-16.3)	26,879 (3,153-54,164)	9,885 (1,159-19,919)	21,462 (2,517-43,249)	8,032 (942-16,185)	48,341 (5,670-97,414)	8,966 (1,052-18,068)	2016	Adolescents

		Males		Females		Total(*)		Exposure input data	
Country	PAF (95 % CI) (%)	Attributable prevalence (95 % CI)	Attributable prevalence per 1,000,000 (95 % CI)	Attributable prevalence (95 % CI)	Attributable prevalence per 1,000,000 (95 % CI)	Attributable prevalence (95 % CI)	Attributable prevalence per 1,000,000 (95 % CI)	Year	Age group (years in survey)
Poland	0.7 (0.0-2.2)	21,052 (0-64,984)	1,150 (0-3,550)	20,698 (0-63,891)	1,060 (0-3,271)	41,749 (0-128,875)	1,103 (0-3,406)	2017	Children
Poland	0.2 (0.0-1.5)	6,356 (0-43,553)	347 (0-2,379)	6,250 (0-42,821)	320 (0-2,192)	12,606 (0-86,374)	333 (0-2,283)	2017	Adolescents
Slovakia	5.6 (0.7-10.1)	25,253 (3,046-45,510)	9,471 (1,142-17,068)	24,439 (2,948-44,043)	8,749 (1,055-15,767)	49,692 (5,994-89,553)	9,101 (1,098-16,402)	2019	Adolescents
Slovenia	4.5 (0.3-8.9)	8,375 (643-16,431)	7,902 (606-15,502)	7,376 (566-14,472)	7,032 (540-13,795)	15,752 (1,209-30,903)	7,469 (573-14,653)	2018	Children
Slovenia	1.2 (0.0-2.8)	2,192 (0-5,214)	2,068 (0-4,919)	1,931 (0-4,592)	1,841 (0-4,378)	4,123 (0-9,807)	1,955 (0-4,650)	2018	Adolescents
Spain	7.2 (1.3-11.8)	227,690 (41,651-373,094)	9,803 (1,793-16,063)	223,424 (40,870-366,104)	9,243 (1,691-15,146)	451,114 (82,521-739,198)	9,517 (1,741-15,595)	2018	Adolescents
Sweden	7.2 (1.3-11.8)	44,043 (7,842-72,422)	8,433 (1,502-13,866)	45,064 (8,024-74,102)	8,739 (1,556-14,371)	89,107 (15,866-146,524)	8,585 (1,529-14,117)	2017	Adolescents

Notes: (*) Due to rounding effects, there may be small deviations in the total results.

3.3.4 Diabetes mellitus in adults (women)

In recent years, it has been suggested that environmental endocrine disruptors such as phthalates might be a risk factor for the development and progression of diabetes mellitus. Most of the literature identified in the systematic review by Zhang and colleagues reported positive associations between phthalates and diabetes (Zhang et al., 2022). Two of the 7 individual studies evaluated type 2 diabetes mellitus (T2DM). In the 5 other studies the type was not defined. The authors also specified the phthalate metabolites mono-methyl phthalate (MMP), mono-isobutyl phthalate (MiBP), mono(3-carboxypropyl) phthalate (MCPP), MnBP and DEHP with a particular risk potential for diabetes mellitus. These associations have been indirectly supported by coherent results for phthalate exposure associated with insulin resistance. However, the small number of epidemiological studies and partially contradictory results for different metabolites reduces the confidence in the association between phthalates and diabetes mellitus (Radke et al., 2019).

Exposure-response relationship

Pooled exposure-effect associations from meta-analyses were not eligible as in the calculations for the outcomes asthma and obesity. Accordingly, individual studies were searched for in the recent systematic review by Zhang and colleagues (Zhang et al., 2022). From the perspective of a comparable exposure level to Europe, 3 epidemiological studies were identified that conducted investigations in the USA (James-Todd et al., 2012; Sun et al., 2014) and Sweden (Lind et al., 2012). Lind and colleagues investigated T2DM prevalence in relation to phthalate biomarker concentrations in sera of the elderly population (older than 70 years) and derived statistically significant results on the associations between phthalate exposure and diabetes mellitus. However, these ERF could not be applied in this analysis due to the lack of suitable exposure data within HBM4EU (Lind et al., 2012). Here, only concentrations in urine were measured.

Using NHANES data James-Todd and colleagues found statistically significant associations between concentrations of various phthalate metabolites in urine with prevalent diabetes in women (James-Todd et al., 2012). However, the effect estimates for the corresponding quartiles lack information on the related phthalate metabolite concentrations. Thus, the reported ERF was not suitable for our EBD calculations.

The study by Sun and colleagues was a nested case-control study using data from the US Nurses' Health Studies (NHS and NHSII) (Sun et al., 2014). The authors reported a positive association between the incidence of T2DM related to various phthalate metabolites in urine specifically in women. Hence, this study was selected for the EBD estimations. The summary phthalate parameter DEHP (MEHP, MHHP, MEOHP and mono(2-ethyl-5-carboxypentyl) phthalate (MECPP)) was chosen as the risk factor. Note, in contrast to the estimation regarding asthma in children/adolescents, DEHP is defined slightly differently for this risk-outcome-pair, i.e. it additionally includes the metabolite MECPP. The corresponding association between DEHP and T2DM in women (32 years or older) is shown in Table 3.57. These refer to associations within the NHSII study only, as all corresponding ORs of the NHS study were not significant. For the EBD quantifications, model 2 was chosen because the additional consideration of the BMI in model 3 resulted in a non-significant p-trend with no considerable changes in the ORs.

Table 3.57: Association between urinary DEHP concentrations (nmol/L) and T2DM in women (≥32 years of age, N = 1,154), NHSII

	DEHP median (nmol/L)	Adjusted OR(*) (95 % CI)
Quartile 1	123.2	1 (Reference)
Quartile 2	223.0	1.67 (1.12-2.49)
Quartile 3	376.8	1.47 (0.96-2.24)
Quartile 4	869.7	1.89 (1.20-2.98)

Notes: 95 % CI: 95 % confidence interval;
DEHP metabolites included MEHP, MEHHP, MEOHP, MECPP;
(*) model 2.

Source: adopted from (Sun et al., 2014).

Exposure-, health-, population data

In the aligned studies gathered within HBM4EU, DEHP exposure data (in urine) for adults are not included. Only data for children and adolescents for various EU countries are available. Therefore, comparably to the procedure for the risk-outcome pair MCOP and obesity, a CF was derived to approximate the exposure of adults (aged 20 years or older) from the exposure of children or adolescents (aged 6-19 years). We thus also assumed the same exposure for the female and male population. The study results by Buser and colleagues were again used to calculate the CF (Table 3.58) (Buser et al., 2014). Though, it must be acknowledged that the study's primary objective was to investigate the association between phthalates and obesity and not diabetes mellitus. This may have had an influence on the selection of study participants and thus the calculated geometric means. However, we suspect this bias is not relevant, as both conditions are often linked, and similar covariates have to be considered in the models. Hence, a CF of 0.75 was calculated by dividing the DEHP geometric mean concentration of adults by that of children/adolescents.

Table 3.58: Urinary DEHP concentrations (µmol/mL) in children and adults in NHANES 2007-2010

Age group	DEHP geometric mean (µmol/mL)
All children/adolescents (aged 6-19 years)	0.24
All adults (aged ≥20 years)	0.18

Notes: DEHP metabolites included MEHP, MEHHP, MEOHP, and MECPP.

Source: (Buser et al., 2014).

The final selection of urinary DEHP exposure data was analogous to the process for the obesity calculations: HBM4EU data were selected for 2021±5 years. Only samples bigger than 50 participants were used. If multiple datasets were available for a country, the most recent one was selected. Finally, were possible, EBD estimations were furthermore stratified by age group used to apply the CF to, i.e. children (age 6-12 years) or adolescents (age 12-18 years). Table 3.59 shows the DEHP concentrations for adults (20 years or older) derived from HBM4EU aligned studies on children/adolescents. Values in

grey were selected for the calculations. In total, 14 European countries were considered in the estimation process.

Table 3.59: Converted urinary DEHP concentrations (nmol/L) in adults (≥20 years) based on children and adolescents (6-18 years) exposure data of aligned studies under HBM4EU (N≥50)

Country	Data collection	Year	Age group (years in survey)	N	P05	P10	P25	P50	P75	P90	P95
Belgium	T_VITO_FLEHS IV	2017	13-15	77	23.33	30.98	42.98	59.40	90.90	122.18	161.48
Belgium	T_VITO_FLEHS IV	2018	13-16	223	19.80	26.78	41.25	62.85	92.25	139.43	174.23
Belgium	C_VITO_3xG	2019	6-8	112	28.95	35.03	60.08	101.18	174.23	272.55	360.83
Czechia	T_MU_Pilot school children	2019	12-17	299	21.60	27.98	46.20	74.63	114.98	201.98	318.68
Denmark	C_SDU_OCC	2018	7	97	11.03	14.03	21.83	37.58	63.15	108.75	163.43
Denmark	C_SDU_OCC	2019	6-7	203	12.30	14.85	25.58	39.45	58.50	95.48	149.93
France	T_ANSP_ESTEBAN	2015	12-17	215	40.50	51.53	71.63	113.63	179.78	285.68	462.38
France	T_ANSP_ESTEBAN	2016	12-17	54	26.85	29.63	48.38	77.55	127.50	204.68	272.25
France	C_ANSP_ESTEBAN	2015	6-12	205	35.25	55.20	72.23	119.78	208.43	285.83	350.93
Germany	T_UBA_GerES V	2015	12-18	105	24.90	30.38	39.00	67.28	108.08	163.65	219.53
Germany	T_UBA_GerES V	2016	12-18	123	18.90	23.18	37.58	60.38	103.13	148.50	216.30
Germany	T_UBA_GerES V	2017	12-17	71	19.88	25.50	40.05	55.88	86.55	138.98	205.05
Germany	C_UBA_GerES V	2015	6-12	70	37.13	43.13	72.60	113.85	163.95	197.85	248.78
Germany	C_UBA_GerES V	2016	6-12	158	24.98	30.00	51.15	79.35	122.10	190.73	255.30
Germany	C_UBA_GerES V	2017	6-12	70	33.23	38.48	51.53	75.45	115.13	225.68	308.03
Greece	T_AUTH_CROME	2020	12-18	72	28.58	37.28	54.23	81.08	144.83	207.30	294.98
Greece	T_AUTH_CROME	2021	12-18	78	26.25	30.30	46.88	82.20	127.05	210.83	359.03
Greece	C_AUTH_CROME	2020	6-11	84	30.60	45.00	64.28	93.00	144.45	243.60	308.93
Greece	C_AUTH_CROME	2021	6-11	77	37.88	45.83	73.80	122.55	222.53	331.43	396.90
Hungary	C_NPHI_InAirQ	2017	8-11	100	16.50	24.68	39.90	74.78	137.25	226.95	349.73
Hungary	C_NPHI_InAirQ	2018	8-11	162	11.18	16.20	38.63	70.73	117.60	168.83	222.75
Nether-lands	C_RIVM_ SPECIMEn-NL	2020	6-11	89	24.75	25.65	41.10	58.05	87.90	188.93	238.95
Norway	T_NIPH_NEB II	2016	12-14	166	34.88	38.63	51.75	83.25	127.20	202.35	253.80
Norway	C_NIPH_NEB II	2016	7-11	290	31.05	41.55	58.65	90.90	147.23	269.63	413.18
Poland	T_NIOM_POLAES	2017	12-14	281	19.50	30.00	49.73	74.70	127.35	187.43	238.95
Poland	C_NIOM_POLAES	2017	7-10	300	31.65	41.10	62.18	99.00	157.88	232.20	275.78
Slovakia	T_SZU_PCB cohort follow-up	2019	15-17	271	32.85	46.13	84.00	144.00	266.70	408.83	554.78
Slovakia	C_SZU_PCB cohort	2015	10-12	151	87.08	116.33	171.30	243.53	365.03	534.75	770.33
Slovakia	C_SZU_PCB cohort	2016	11-12	94	56.25	84.83	123.15	181.95	323.63	490.95	548.33
Slovenia	T_JSI_SLO CRP	2018	12-15	96	22.20	26.63	48.45	81.98	136.13	244.13	284.25

Country	Data collection	Year	Age group (years in survey)	N	P05	P10	P25	P50	P75	P90	P95
Slovenia	C_JSI_SLO CRP	2018	7-10	149	36.45	47.78	65.18	116.55	187.28	294.23	430.50
Spain	T_ISCIII_BEA	2017	13-17	224	17.18	21.60	45.68	76.88	116.03	213.90	271.13
Spain	T_ISCIII_BEA	2018	13-17	76	19.88	27.23	44.03	64.65	88.50	171.23	221.33
Sweden	T_NFA_Riksmaten Ungdom	2016	12-17	139	14.10	20.18	33.98	51.38	85.50	136.65	212.03
Sweden	T_NFA_Riksmaten Ungdom	2017	12-17	161	14.48	22.95	32.18	49.58	83.63	136.50	182.33

Notes: DEHP metabolites included MEHP, MEHHP, MEOHP, and MECPP.

The corresponding health data on diabetes mellitus for women were taken from the EHIS study for 2019 (Eurostat, 2023b). These were prevalence data for diabetes mellitus (type 1 and type 2 combined, ICD-10 E10-14) in women. Data was available in 10-year age groups. To perform EBD calculations for the reference year 2021, the 2019 prevalence rates were applied to the population in 2021. Input data for the DW for women were obtained from the GBD 2019 study and for the same age groups. The respective DWs were calculated by dividing the 2019 annual YLDs by the number of prevalent diabetes mellitus cases in women for the WHO European Region (IHME, 2022). Again, the assumption was that the DWs are applicable to 2021.

We did not calculate mortality indicators (e.g. YLLs) for this risk-outcome-pair, because the selected ERF only applied to diabetes morbidity. Applying the same effect estimate to mortality data may lead to over- or underestimation of the disease burden. All input data, references, EBD calculation steps and results can also be found in Annex A2.6 and Annex A2.7.

Attributable burden

For this risk-outcome-pair, the PAF as well as the YLDs were calculated for women aged 25 years or older in 14 different European countries (Table 3.60). This age group represents a compromise between the available age groups in the health data and the selected ERF.

Comparable with the obesity calculations, the choice of age group for the basic exposure data (children or adolescents) to extrapolate to adult exposure values influenced the level of PAFs and YLDs. Adolescents generally had lower urinary DEHP concentrations than children. Consequently, calculations based on survey exposure data of adolescents resulted in lower PAF and YLD values for women in all countries investigated.

Overall, the DEHP-related proportion of diabetes mellitus in women aged 25 years or older ranged between 16.5 % (Denmark) and 24.1 % (Slovakia). The lowest and highest rates were estimated for Denmark and Poland, with 527 (2-1,052) YLDs per 1,000,000 women in Denmark and 1,324 (95 % CI 49-2,476) YLDs per 1,000,000 women in Poland. However, highest absolute YLDs of 47,001 (95 % CI 1,381-89,015) or 42,804 (95 % CI 525-83,480) were estimated for women in Germany – depending on the selected baseline exposure age group. The corresponding lowest values were estimated for Slovenia accounting for 1,149 (95 % CI 38-2,169) or rather 1,273 (95 % CI 72-2,327) YLDs.

Table 3.60: Diabetes mellitus (type 1 and type 2) disease burden attributable to DEHP in women (≥25 years) for different European countries in 2021

				Exposure input data	
Country	PAF (95 % CI) (%)	YLDs (95 % CI)	YLDs per 1,000,000 women (95 % CI)	Year	Age group (years in survey)
Belgium	21.1 (1.0-39.1)	4,690 (226-8,679)	801 (39-1,483)	2019	Children
Czechia	19.3 (0.5-36.8)	6,381 (180-12,132)	1,176 (33-2,236)	2019	Adolescents
Denmark	16.5 (0.1-33.0)	1,547 (7-3,088)	527 (2-1,052)	2019	Children
France	19.4 (0.5-37.0)	29,377 (792-55,818)	841 (23-1,598)	2016	Adolescents
Germany	19.6 (0.6-37.2)	47,001 (1,381-89,015)	1,116 (33-2,113)	2017	Children
Germany	17.9 (0.2-34.9)	42,804 (525-83,480)	1,016 (12-1,982)	2017	Adolescents
Greece	22.6 (1.4-40.9)	7,183 (451-13,022)	1,310 (82-2,375)	2021	Children
Greece	19.8 (0.7-37.4)	6,306 (212-11,898)	1,150 (39-2,170)	2021	Adolescents
Hungary	18.6 (0.3-35.8)	5,852 (110-11,276)	1,155 (22-2,225)	2018	Children
Netherlands	18.4 (0.4-35.5)	5,635 (113-10,891)	641 (13-1,239)	2020	Children
Norway	20.9 (1.0-38.7)	1,727 (79-3,206)	646 (30-,1200)	2016	Children
Norway	19.6 (0.5-37.2)	1,623 (42-3,079)	607 (16-1,152)	2016	Adolescents
Poland	20.5 (0.8-38.4)	25,852 (952-48,371)	1,324 (49-2,476)	2017	Children
Poland	19.2 (0.4-36.6)	24,163 (550-46,138)	1,237 (28-2,362)	2017	Adolescents
Slovakia	24.1 (2.1-42.7)	3,683 (314-6,519)	1,319 (112-2,334)	2019	Adolescents
Slovenia	22.0 (1.2-40.1)	1,273 (72-2,327)	1,214 (69-2,218)	2018	Children
Slovenia	19.8 (0.7-37.4)	1,149 (38-2,169)	1,095 (37-2,067)	2018	Adolescents
Spain	18.3 (0.3-35.5)	22,668 (382-43,867)	983 (16-1,815)	2018	Adolescents
Sweden	17.5 (0.2-34.3)	3,233 (33-6,346)	627 (6-1,231)	2017	Adolescents

3.4 Burden of disease due to cadmium

3.4.1 General information on cadmium and basic assumptions

Cadmium (Cd) is a pervasive environmental pollutant that continues to be a concern in Europe, despite various efforts to reduce its presence and mitigate associated risks. The European Union (EU) has implemented several regulatory measures to control cadmium emissions, such as the Registration, Evaluation, Authorization and Restriction of Chemicals (REACH) regulation, the Industrial emissions Directive (IED), the Restriction of Hazardous Substances (RoHs) or the EU soil strategy (European Commission, 2021; European Parliament and Council, 2006, 2010, 2011). Cadmium in Europe is naturally present in the environment, as well as increases in its natural concentration due to human activities such as industrial emissions, urban pollution, and cadmium-containing fertilizers (Tratnik et al., 2022). This can lead to increased levels of cadmium in the soil, especially through the use of phosphate fertilizers containing cadmium. Over longer periods, the slow degradation of cadmium in soil, as well as other factors such as air pollution, sewage sludge, and compost, can contribute to its accumulation in agricultural lands (Park et al., 2021). Since cadmium can be taken up by plants, this can lead to increased cadmium levels in food. The main source of cadmium exposure in humans is the consumption of crops grown on cadmium-contaminated soils, especially in regions with high rice or

cereal consumption (Nordberg et al., 2018). In farm animals, organ meats such as kidneys and livers can also accumulate cadmium (EFSA, 2012). Furthermore, smoking is a significant source of cadmium exposure, as tobacco plants tend to accumulate cadmium in their leaves (Ganguly et al., 2018).

Environmental cadmium exposure is associated with several adverse health effects, with kidney damage and effects on bones being the most common in the general population. Over time, cadmium accumulates in the kidneys, leading to impaired kidney function and renal tubular dysfunction resulting in decreased kidney filtration and increased excretion of essential minerals like calcium and magnesium (Ferraro et al., 2010; Järup, 2000). Additionally, cadmium disrupts the calcium metabolism, affecting the balance between bone formation and resorption. Consequently, long-term exposure weaken the bone tissues, raising the risk of fractures and osteoporosis (Scimeca et al., 2017; Svedbom et al., 2013). Furthermore, occupational exposure to high cadmium levels increases the risk of lung cancer. Inhalation of cadmium-containing particles or fumes irritates the respiratory system, causing symptoms such as coughing, shortness of breath, and lung inflammation (Chen et al., 2016a). High cadmium exposure has also been associated with cardiovascular diseases like hypertension and heart disease due to its impairment of blood vessel function and promotion of atherosclerosis (Messner and Bernhard, 2010). Negative health effects on reproduction and development have also been discussed related to cadmium exposure. High cadmium levels have been linked to decreased fertility, hormonal disturbances, growth restrictions, developmental abnormalities and impaired fetal development. The relationship between cadmium exposure and the risk of certain types of cancer, including lung prostate and kidney cancer is controversial (Borné et al., 2014; Dutta et al., 2022; Waalkes, 2000).

Cadmium exposure can lead to adverse health effects through various pathways. It accumulates in renal tubular cells, disrupting kidney function by interfering with filtration and reabsorption processes. This induces oxidative stress through the generation of reactive oxygen species (ROS) that harm cellular structures like DNA, proteins, and lipids, causing oxidative stress and triggers multiple health issues (Yan and Allen, 2021). Cadmium also disrupts calcium homeostasis, affecting calcium absorption, storage, release from bones, and tissue regulation. This disruption leads to bone demineralization, weakened bone structures, and increased risk of osteoporosis (Ciosek et al., 2023). The endocrine system is affected as cadmium interferes with hormone production, release and signalling, causing hormonal imbalances and disturbances, impacting reproductive function, growth and metabolism (Guarnotta et al., 2022). Furthermore, cadmium has genotoxic potential, meaning it may damage DNA, induce mutations, and disrupt DNA repair and cell cycle regulation. Inflammatory responses and immune dysfunction are set off by cadmium exposure, leading to tissue damage, impaired immune function, and increased susceptibility and autoimmune disorders (Luevano and Damodaran, 2014; Kay et al., 2019). Prolonged exposure to high levels of cadmium is associated with an elevated risk of kidney dysfunction, possibly lung, prostate or kidney cancer related to the identified genotoxic effects of cadmium, oxidative stress, inflammation, and disruption of cellular signaling pathways (Peana et al., 2023). A further overview on relevant health effects related to cadmium exposure can be found in Annex A1.1.

Biomarkers within the HBM4EU study include cadmium concentrations in blood, urine, and other biological samples. They provide valuable insights into the extent of cadmium exposure and aid in assessing relevant health risks in Europe. For the estimation of the environmental burden of disease (EBD) due to cadmium exposure in the general European population, the following criteria were applied to select which health outcomes to prioritize: evidence in the scientific literature confirming a robust ERF, availability of exposure and population data to perform disease burden calculations, and high political and public interest in quantifying the contribution of environmental cadmium exposure to disease cases. Therefore, the health effects chronic kidney disease (CKD) in adults as well as osteoporosis in women older than 55 years were considered in this report.

3.4.2 Chronic kidney disease (CKD) morbidity in adults

Environmental cadmium exposure has been identified as a risk factor for chronic kidney disease (CKD), with evidence stemming from both occupational studies and population-based investigations. The prevalence of tubular proteinuria, characterized by an excessive presence of protein in urine due to impaired kidney function, varied from 5 % in individuals at lowest exposure to cadmium to as high as 50 % in the most heavily exposed group (Järup, 2002). While CKD has traditionally been observed in individuals with significant cadmium exposure, recent research has confirmed that even relatively low levels of cadmium exposure can increase the risk of CKD development (Thijssen et al., 2007). Studies have demonstrated that cadmium tends to accumulate in the kidneys, particularly in the renal proximal tubules, resulting in structural and functional impairments such as reduced glomerular filtration rate (GFR) and tubular dysfunction. Approximately 50 % of the total body burden of cadmium is found in the kidneys.

Since both blood cadmium as well as urinary cadmium have been suggested as biomarkers, the relationship between cadmium concentrations in blood and urine with kidney dysfunction has been investigated to determine which one is more informative (Akerstrom et al., 2013; Ferraro et al., 2010). The association between CKD and blood cadmium was found to be stronger based on data involving a representative sample of the general United States adult population that participated in the National Health and Nutrition Examination Survey (NHANES) conducted between 1999 and 2006.

Exposure-response relationship

The ERF based on the NHANES data shows that CKD is associated with an increase in blood cadmium concentrations in adults aged 20 years or older (n = 5,426). Individuals with blood cadmium higher than 1mcg/L showed a higher association with CKD (OR 1.48, 95 % CI: 1.01-2.17, p = 0.046).

Mode of action and weight of evidence

Cadmium-induced kidney disease involves a complex interplay of mechanisms including oxidative stress, inflammation, apoptosis, disruption of calcium homeostasis, and alterations in renal transport systems. Upon absorption through the lungs or gastrointestinal tract, cadmium binds to serum albumin and undergoes accumulation in the liver. Subsequently, it forms a protein complex that reaches the kidneys, where it is filtered and accumulated in the proximal tubules, leading to interference with their normal function. This interference gives rise to cadmium nephropathy, which is characterized by low molecular weight proteinuria. Importantly, tubular dysfunction persists until renal failure eventually ensues. Since cadmium has a biological half-time ranging from 10-30 years, cadmium concentrations persistently increase with age (Järup, 2000; Yang and Shu, 2015).

Exposure-, health-, population data

Data on cadmium exposure in the population was extracted from the estimates gathered for adults within HBM4EU and compiled in the HBM4EU aggregated data set (Table 3.61). This data was retrieved from the HBM4EU dashboard: https://www.hbm4eu.eu/what-we-do/european-hbm-platform/eu-hbm-dashboard/ (05.06.2023).

Table 3.61: Cadmium (Cd) concentrations (µg/L) in human blood samples of existing studies gathered in HBM4EU for adults

Country	Data collection	Stratification value	P05	P10	P25	P50	P75	P90	P95	Number of participants	Sampling period
Czechia	CZECHHBMAE2005	Adults 20-39 years	<LOD	<LOD	0.400	0.600	1.00	1.800	2.370	307	2005
	CZECHHBMAE2005	Adults 40-59 years	<LOD	0.300	0.400	0.600	1.100	1.700	2.300	91	2005
	CZECHHBMAE2007	Adults 20-39 years	<LOD	<LOD	0.300	0.400	0.600	1.500	2.200	288	2007
	CZECHHBMAE2007	Adults 40-59 years	<LOD	<LOD	0.300	0.400	0.800	1.400	2.100	114	2007
	CZECHHBMAE2009	Adults 20-39 years	0.120	0.160	0.220	0.325	0.520	1.262	2.303	274	2009
	CZECHHBMAE2009	Adults 40-59 years	0.160	0.220	0.290	0.370	0.570	0.950	1.280	121	2009
	CZECHHBMAE2015	Adults 20-39 years	0.221	0.248	0.366	0.511	0.709	1.467	1.880	140	2015
	CZECHHBMAE2015	Adults 40-59 years	0.279	0.310	0.435	0.565	0.718	1.120	1.457	148	2015
Belgium [a]	FLEHS1REFADULT	Adults 40-59 years	<LOD	0.160	0.290	0.480	0.773	1.281	1.530	980	2004-2005
	FLEHS2REFNB	Adults 20-39 years	0.136	0.156	0.209	0.287	0.430	0.676	1.003	235	2008-2009
Norway	MOBA	Adults 20-39 years	<LOQ	<LOQ	0.112	0.154	0.218	0.321	0.450	2,899	2002-2008
	MOBA	Adults 40-59 years	<LOQ	0.114	0.141	0.188	0.269	0.393	0.720	53	2003-2008
Slovenia	SLOHBM	Adults 20-39 years	<LOD	<LOD	<LOD	0.291	0.460	0.713	0.998	1,041	2008-2014

Notes: Cadmium exposure data was available for 4 countries, but was collected in different sampling years.

The most recent exposure data was selected for the calculations (values in grey).

Comparable to study population in (Ferraro et al., 2010).

([a]) The cadmium exposure data as collected in the FLEHS study was assumed to be representative for the entire Belgium population in this report, even though only citizens from the Flemish region were surveyed.

Source: (Ferraro et al., 2010).

The increased CKD risk due to cadmium exposure was estimated with the population groups in Table 3.62. The prevalence was averaged for the respective age group based on the available data on the IHME online tool during the time of blood cadmium data collection. This was necessary to account for the time lag between the estimates of population cadmium concentrations from the HBM4EU data and recent blood cadmium levels, which have been decreasing due to stricter policies and technical improvements.

All input data, references, EBD calculation steps and results can also be found in Annex A2.8.

Table 3.62: Population size in the selected age groups

Country	Sampling period	Age group	Population size in 2021[a]	Mean CKD prevalence during time of HBM4EU[b] data collection (central)	Mean CKD prevalence during time of HBM4EU data collection (lower)	Mean CKD prevalence during time of HBM4EU data collection (upper)
Czechia	2015	Adults 20-39 years	2,571,076	5.630 %	4.283 %	7.128 %
		Adults 40-59 years	3,136,723	10.580 %	8.395 %	13.160 %
Belgium	2004-2005	Adults 40-59 years	3,096,755	6.623 %	5.240 %	8.235 %
	2008-2009	Adults 20-39 years	2,917,768	3.559 %	2.706 %	4.505 %
Norway	2002-2008	Adults 20-39 years	1,444,431	3.465 %	2.642 %	4.346 %
	2003-2008	Adults 40-59 years	1,433,754	6.344 %	5.018 %	7.906 %
Slovenia	2008-2014	Adults 20-39 years	500,379	5.489 %	4.189 %	6.904 %

Notes: Data extracted for 2021.

([a]) Number of population based on Eurostat data (https://ec.europa.eu/eurostat/databrowser/product/page/DEMO_PJAN__custom_2892906).

([b]) Prevalence data based on IHME tool (https://vizhub.healthdata.org/gbd-results/).

Source: (IHME, 2022)

Attributable burden

The method applied to calculate the YLDs resulting from cadmium-induced CKD is presented for the example of Czechia, and has been used accordingly for Belgium, Slovenia and Norway. As previously described in the methodology of the BoD estimates associated with lead exposure, a lognormal distribution was fitted to the population-based cadmium concentrations from HBM4EU, which was

then used to calculate the percentage of the population (f) with a blood cadmium concentration above a certain threshold. Table 3.63 displays, the estimated proportion respective population groups falling into the cadmium category higher than 1µg/L for the two age groups 20-39 years and 40-59 years.

Table 3.63: Cadmium (Cd) concentration in blood (µg/L) as extracted from the HBM4EU data. Percentage of the population with cadmium concentrations in blood >1µg/L estimated with rriskFitdist.perc function

Country	Sampling period	Age group	p05	p10	p25	p50	p75	p90	p95	% of pop. with Cd conc. in blood >1µg/L (f)
Czechia	2015	20-39 years	0.221	0.248	0.366	0.512	0.709	1.467	1.880	11.928 %
		40-59 years	0.279	0.310	0.435	0.565	0.718	1.120	1.457	9.758 %
Belgium	2008-2009	20-39 years	0.136	0.156	0.209	0.287	0.430	0.676	1.003	1.252 %
	2004-2005	40-59 years	<LOD	0.160	0.290	0.480	0.773	1.281	1.530	16.186 %
Slovenia	2008-2014	20-39 years	<LOD	<LOD	<LOD	0.291	0.460	0.713	0.998	3.759 %
Norway	2002-2008	20-39 years	<LOQ	<LOQ	0.112	0.154	0.218	0.321	0.450	0.063 %
	2003-2008	40-59 years	<LOQ	0.114	0.140	0.188	0.269	0.393	0.720	0.032 %

The limit of quantification (LOQ) or the limit of detection (LOD) was replaced with the value given in the aggregated HBM4EU dataset for the specific age group and country.

The relative risk (RR), the attributable fraction (AF), the number of people in the particular age group exposed to the blood cadmium concentration above a certain threshold (No. exp), the number of CKD cases per year (No CKD cases) and the number of CKD cases attributable to cadmium (AC) were calculated with equations 1-7 as listed in Annex A2.8. To do so, prevalence estimates as displayed in Table 3.62 and disability weights based on the GBD 2013 study were used (Salomon et al., 2015). To perform EBD calculations for the reference year 2021, we applied the prevalence rates of the year of HBM4EU data collection to the population of 2021. Only YLDs were estimated as part of DALYs since CKD is known to cause a significant amount of morbidity within Europe, however, usually progresses to a more serious health condition before resulting in mortality.

Table 3.64 shows the results for the part of the population within the two age groups (20-39 years, 40-59 years) and with a blood cadmium concentration above 1µg/L in Czechia. All results were rounded to 3 digits, meaning that the number 0 in the table does not necessarily means no burden. Only the morbidity of CKD was accounted for and calculated as YLD (central; 95 % CI), which only represents one part of the total DALYs.

Table 3.64: Burden of disease in YLDs for cadmium (Cd) exposure and CKD in Czechia

	Central	Lower 95 %	Upper 95 %	Central	Lower 95 %	Upper 95 %
Age group		20-39 years			40-59 years	
Odds Ratio	1.48	1.01	2.17	1.48	1.01	2.17
Attributable Fraction	0.306	0.010	0.501	0.290	0.009	0.468
% of pop. with blood lead conc. >1µg/L		11.928 %			9.758 %	
Number of people with blood Cd conc. in age group		306,678			306,081	
Number of CKD cases/year	144,752	110,119	183,266	331,865	263,328	412,793
Number of CKD cases attributable to Cd exposure in 2021	5,285	124	10,946	9,392	233	18,860
YLDs 2021	550	9	1,609	977	16	2,772
YLDs 2021 per 1,000,000 persons	51	1	150	91	2	259

Notes: The calculation follows the approach taken by (Goodman et al., 2014; Ougier et al., 2021a).

Source: (Goodman et al., 2014; Ougier et al., 2021a).

Based on the calculation for CKD related to cadmium exposure, the total YLDs per year were estimated for Czechia, Belgium, Slovenia and Norway. Estimates are given in Table 3.65 (rounded to whole numbers). Adjusted YLDs per 1,000,000 persons were also calculated for comparison reasons.

Table 3.65: Burden of disease in YLDs, YLDs per 1,000,000 persons and PAFs in 2021 due to exposure to cadmium and CKD

Country	Age group	YLDs in 2021 (95 % CI)	YLDs/1,000,000 persons in 2021 (95 % CI)	PAFs (95 % CI) (%)
Czechia	20-39 years	550 (9-1,609)	51 (1-150)	5.0 (0.1-10.7)
	40-59 years	977 (16-2,772)	91 (2–259)	3.8 (0.1-7.9)
	Total	1,526 (25-4,381)	142 (3-409)	8.8 (0.2-18.6)
Belgium	20-39 years	42 (1-125)	4 (0-11)	0.6 (0.0-1.3)
	40-59 years	1,046 (17-3,002)	90 (1-260)	6.6 (0.2-13.7)
	Total	1,088 (18-3,127)	94 (1-271)	7.1 (0.2-15.0)
Slovenia	20-39 years	1 (0-3)	0 (0-1)	0.0 (0.0-0.1)
Norway	20-39 years	1 (0-3)	0 (0-0)	0.0 (0.0-0.0)
	40-59 years	33 (1-96)	16 (0-45)	1.6 (0.0-3.7)
	Total	34 (1-98)	16 (0-45)	1.6 (0.0-3.7)

3.4.3 Osteoporosis in women above 55 years

Osteoporosis is a systemic bone disease associated with decreased bone mineral density, destruction of bone microstructure, and elevated risk of fragility fractures. Because osteoporosis greatly reduces the quality of life and is associated with high morbidity, this disease is gradually becoming a major public health concern (Svedbom et al., 2013). Bone health depends heavily on a balance of concentrations of various metals in the body, so environmental exposure to heavy metals is an important risk factor for degenerative diseases such as osteoporosis (Scimeca et al., 2017). Since cadmium is present in the air, soil, water, and in various consumer products, and has a half-life of up to 30 years, this metal is heavily researched in connection with the manifestation of osteoporosis. After several animal studies found an effect of cadmium on bone density (Chen et al., 2012), epidemiological studies began to accumulate. However, results of first attempts to quantify the relationship between cadmium and human bone health varied widely (Li et al., 2020; Songprasert et al., 2015; Trzcinka-Ochocka et al., 2010).

After reviewing the existing body of literature, a distinction between studies investigating the link between osteoporosis and urinary cadmium concentrations versus blood cadmium seems necessary. The association between urinary cadmium and osteoporosis was found to be significant, whereas blood cadmium has a smaller impact. When only looking at study results using urinary cadmium data, the exposure-response relationship was consistent whereby 17 studies provided evidence that the urinary cadmium concentration is a reliable bioindicator for the risk of osteoporosis (Li et al., 2021). Finally, a strong increase in the risk to develop osteoporosis was discovered in Swedish women older than 55 years with high urinary cadmium levels, which may be applied to the female population of Europe (Ougier et al., 2021a).

Exposure-response relationship

The risk of osteoporosis related to cadmium exposure was analyzed in a study with 2,680 women between the ages 56 and 69, enrolled in the Swedish Mammography cohort. The women were categorized into 3 groups based on their urinary cadmium concentrations (less than 0.50µg Cd/g of creatinine, 0.50-0.75µg Cd/g of creatinine, higher than 0.75µg Cd/g of creatinine). The study found that urinary cadmium concentrations of 50µg Cd/g of creatinine and above were associated with lower bone mineral density (BMD) and an increased risk of osteoporosis and fractures. The OR and 95 % CIs were calculated to determine the associations. For women aged 56-69 years, the ORs for hip or spine BMD-defined osteoporosis were 1.61 (1.20-2.16) for urinary concentrations of 0.50-0.75µg Cd/g of creatinine and 1.95 (1.30-2.93) for urinary concentrations above 0.75µg Cd/g of creatinine (Engström et al., 2012).

Mode of action and weight of evidence

Cadmium has the potential to act as a cumulative toxicant, thereby disrupting several cellular processes, including calcium metabolism, vitamin D metabolism, and bone remodelling. Evidence linking cadmium exposure to osteoporosis is growing, with studies providing consistent results regarding the adverse effects of cadmium on bone health (Buha et al., 2019; Youness et al., 2012). Cadmium can disrupt the normal process of bone remodelling, in which there is a balance between bone formation and resorption. Cadmium has an inhibitory effect on osteoblasts, the cells responsible for bone formation, and a stimulatory effect on osteoclasts, the cells involved in bone resorption. Thus, increased exposure to cadmium can result in an imbalance of osteoblasts and osteoclasts, which can lead to a net loss of bone density and contribute to the development of osteoporosis (Ciosek et al., 2023).

Exposure-, health-, population data

Data on cadmium exposure in the population was extracted from the estimates gathered for adults within HBM4EU and compiled in the HBM4EU aggregated data set. This data was retrieved from the HBM4EU dashboard: https://www.hbm4eu.eu/what-we-do/european-hbm-platform/eu-hbm-dashboard/ (05.06.2023).

Table 3.66: cadmium concentrations (µg/g creatinine) in human urinary samples of existing studies gathered in HBM4EU for adults

Country	Data collection	Stratification value	P05	P10	P25	P50	P75	P90	P95	Number of participants	Sampling period
Czechia	DEMOCOPHESCZ	Adults 20-39 years and female	0.102	0.118	0.163	0.209	0.278	0.430	0.469	88	2011-2012
Belgium[(a)]	DEMOCOPHESBE	Adults 40-59 years and female	0.076	0.093	0.135	0.208	0.274	0.393	0.472	67	2011-2012
Denmark	DKDEMOCOPHES	Adults 40-59 years and female	<LOQ	0.047	0.078	0.139	0.247	0.320	0.389	94	2011
Germany	DEMOCOPHESDE	Adults 40-59 years and female	<LOQ	0.100	0.136	0.198	0.247	0.344	0.527	53	2011
Hungary	DEMOCOPHESHU	Adults 20-39 years and female	<LOQ	<LOQ	0.101	0.170	0.239	0.302	0.442	89	2011-2012
Poland	DEMOCOPHESPL	Adults 20-39 years and female	0.093	0.137	0.251	0.390	0.543	0.729	1.107	88	2011-2012
Slovakia	DEMOCOPHESSK	Adults 20-39 years and female	0.103	0.120	0.165	0.220	0.290	0.384	0.447	91	2011-2012
Slovenia	SLODEMOCOPHES	Adults 40-59 years and female	<LOQ	0.119	0.186	0.276	0.347	0.516	0.542	57	2011-2012
Spain	DEMOCOPHESSPAIN	Adults 40-59 years and female	0.084	0.095	0.134	0.211	0.334	0.517	0.655	75	2011-2012
Sweden	DEMOCOPHESSE	Adults 40-59 years and female	0.055	0.076	0.107	0.151	0.194	0.260	0.369	50	2011-2012

Notes: cadmium exposure data was available for 10 countries but was collected in different sampling years. The most recent exposure data was selected for the calculations. Only data from the oldest age groups with available urinary data was used in order to project the osteoporosis burden on women above the age of 55 years.

BoD only calculated for oldest age groups with available urinary data to apply age standardization method from Ougier and colleagues (Ougier et al., 2021a).

([a]) The cadmium exposure data as collected in the FLEHS study was assumed to be representative for the entire Belgium population in this report, even though only citizens from the Flemish region were surveyed.

Source: (Ougier et al., 2021a).

To extend the found association between osteoporosis and urinary cadmium levels of women aged between 56 and 69 years, "alert" values of urinary cadmium concentrations can be used to determine the risk for other age groups. Previous modelling efforts have shown that urinary cadmium concentrations increase linearly over a lifetime until reaching a plateau at around 55 years of age. This follows the assumption that a constant cadmium intake and zero urinary cadmium at birth. Table 3.67 displays the estimated "alert" values of urinary cadmium per age for which it is assumed that the critical values of 0.50µg Cd/g creatinine or of 0.75µg Cd/g creatinine will be reached at an older age.

Table 3.67: PBPK modelled alert values of U-Cd (µg/g creatinine) according to age, assuming lifetime constant cadmium intakes (0.36µg/kg bw/d) and zero U-Cd concentration at birth as proposed by Ougier et al. (2021a)

		Median U-Cd (µg/g crea) alert level according to age				Median U-Cd (µg/g crea) alert level according to age				Median U-Cd (µg/g crea) alert level according to age	
Age (year)	Body weight (kg)	For reaching 0.50µg Cd/g crea (at age over 55 years)	For reaching 0.75µg Cd/g crea (at age over 55 years)	Age (year)	Body weight (kg)	For reaching 0.50µg Cd/g crea (at age over 55 years)	For reaching 0.75µg Cd/g crea (at age over 55 years)	Age (year)	Body weight (kg)	For reaching 0.50µg Cd/g crea (at age over 55 years)	For reaching 0.75µg Cd/g crea (at age over 55 years)
1	8	0.01	0.02	22	64	0.12	0.19	43	72	0.37	0.55
2	12	0.03	0.04	23	65	0.13	0.19	44	72	0.38	0.57
3	16	0.04	0.06	24	66	0.14	0.20	45	72	0.40	0.60
4	20	0.04	0.07	25	67	0.14	0.21	46	72	0.41	0.62
5	24	0.05	0.08	26	68	0.15	0.22	47	72	0.43	0.64
6	27	0.06	0.08	27	69	0.16	0.24	48	71	0.44	0.66
7	31	0.06	0.09	28	69	0.16	0.25	49	71	0.45	0.68
8	34	0.06	0.10	29	70	0.17	0.26	50	71	0.47	0.70
9	37	0.07	0.10	30	71	0.18	0.27	51	71	0.48	0.71
10	40	0.07	0.11	31	71	0.19	0.29	52	70	0.48	0.73
11	42	0.07	0.11	32	71	0.20	0.31	53	70	0.49	0.73
12	45	0.08	0.12	33	72	0.22	0.32	54	70	0.49	0.74
13	47	0.08	0.12	34	72	0.23	0.34	55	70	0.50	0.75
14	50	0.09	0.13	35	72	0.24	0.36	56	69	0.50	0.75
15	52	0.09	0.14	36	73	0.26	0.38	57	69	0.50	0.75
16	54	0.09	0.14	37	73	0.27	0.41	58	69	0.50	0.75
17	56	0.10	0.15	38	73	0.29	0.43	59	69	0.50	0.74
18	58	0.10	0.15	39	73	0.30	0.45	60	69	0.49	0.74
19	59	0.11	0.16	40	73	0.32	0.48	61	69	0.49	0.74
20	61	0.11	0.17	41	73	0.33	0.50	62	69	0.49	0.74
21	62	0.12	0.18	42	73	0.35	0.52				

Source: (Ougier et al., 2021a).

Urinary cadmium "alert" values to avoid exceedance of 0.50µg cadmium/g creatinine and 0.75µg Cd/g creatinine at latter age for the different age categories of women from the selected HBM4EU studies were determined by calculating an average "alert" value corresponding to the median of the respective age interval (based on Table 3.66).

Table 3.68: Median urinary cadmium "alert" values of U-Cd (µg/g creatinine) per age group

Age group	Median U-Cd (µg/g creatinine) alert level according to age	
	For reaching 0.50µg Cd/g creatinine at age over 55 years	For reaching 0.75µg Cd/g creatinine at age over 55 years
20-39 years	0.189	0.2835
40-59 years	0.4395	0.6585
≥55 years	0.5	0.75

Notes: based on Table 3.66.

The increased osteoporosis risk due to cadmium exposure was estimated for women aged between 55 to 70 years old by using the age-specific "alert" values of urinary cadmium concentrations for the age groups with available urinary cadmium data and projecting this onto the population groups in Table 3.68.

Table 3.69: Population size in the selected age groups (data extracted for 2021)

Country	Age group	Number of persons
Czechia	55-70 years	1,084,261
Belgium	55-70 years	1,159,253
Denmark	55-70 years	570,230
Germany	55-70 years	9,408,730
Hungary	55-70 years	1,069,494
Poland	55-70 years	4,206,393
Slovakia	55-70 years	585,056
Slovenia	55-70 years	231,282
Spain	55-70 years	4,833,066
Sweden	55-70 years	926,978

Source: Numbers based on Eurostat population data (https://ec.europa.eu/eurostat/databrowser/product/page/DEMO_PJAN__custom_2892906)

All input data, references, EBD calculation steps and results can also be found in Annex A2.8.

Attributable burden

The method applied to calculate the DALYs resulting from cadmium induced osteoporosis is presented for the example of Czechia and has been used in the same way for the other 9 countries with available urinary cadmium concentrations. As described in the methodology of the BoD calculations related to lead, a lognormal distribution was fitted to the population-based cadmium concentrations from HBM4EU, which was then used to calculate the percentage of the population (f) with a blood cadmium concentration in a certain range or above a certain threshold. Table 3.70 displays, the estimated proportion of the European populations falling into the two cadmium categories 0.5-0.75µg/g creatinine at an age above 55 years and higher than 0.75µg/g creatinine at age above 55 years.

Table 3.70: Cadmium (Cd) concentration in urine (µg/g creatinine) in the pooled European population

Country	Sampling period	Age group	p05	p10	p25	p50	p75	p90	p95	% of pop. with urinary conc. 0.50-0.75µg Cd/g creat. at age over 55 years (f)	% of pop. with urinary conc. >0.75µg Cd/g creat. at age over 55 years (f)
Czechia	2011-2012	20-39 years	0.102	0.118	0.163	0.209	0.278	0.430	0.469	34.168 %	26.004 %
Belgium	2011-2012	40-59 years	0.076	0.093	0.135	0.208	0.274	0.393	0.472	5.901 %	25.670 %
Denmark	2011	40-59 years	<LOQ	0.047	0.078	0.139	0.247	0.320	0.389	4.328 %	16.832 %
Germany	2011	40-59 years	<LOQ	0.100	0.136	0.198	0.247	0.344	0.527	3.412 %	19.682 %
Hungary	2011-2012	20-39 years	<LOQ	<LOQ	0.101	0.170	0.239	0.302	0.442	20.835 %	17.852 %
Poland	2011-2012	20-39 years	0.093	0.137	0.251	0.390	0.543	0.729	1.107	19.481 %	67.130 %
Slovakia	2011-2012	20-39 years	0.103	0.120	0.165	0.220	0.290	0.384	0.447	33.328 %	31.270 %
Slovenia	2011-2012	40-59 years	<LOQ	0.119	0.186	0.276	0.347	0.516	0.542	11.966 %	43.810 %
Spain	2011-2012	40-59 years	0.084	0.095	0.134	0.211	0.334	0.517	0.655	9.257 %	33.362 %
Sweden	2011-2012	40-59 years	0.055	0.076	0.107	0.151	0.194	0.260	0.369	1.021 %	8.474 %

Notes: Percentage of the population with urinary cadmium concentrations >1µg/L estimated with rriskFitdist.perc function

According to (Tratnik et al., 2022), the limit of quantification (LOQ) as measured in the HBM4EU populations ranged between 0.0016µg/L and 0.1µg/L. Because the average of all mean values of the country-specific sample population was slightly higher with 0.218µg/L when measuring urinary cadmium concentrations compared to 0.194µg/g creatinine when measuring creatinine concentration

instead, all values with the label <LOQ were replaced with 0.0268µg/g creatinine to calculate the following BoD estimates.

The RR, the attributable fraction (AF), the number of people in the particular age group exposed to the blood cadmium concentration above a certain threshold or in between a certain range (No exp), the number of osteoporosis cases per year (No osteoporosis cases) and the number of osteoporosis cases attributable to cadmium (AC) were calculated with equations 2-9 as listed in Annex A2.8. To do so, an osteoporosis prevalence of 19.8 % was assumed as calculated for the European population (Salari et al., 2021) and a DW of 0.286 (Bae et al., 2019). To perform EBD calculations for the reference year 2021, we applied the prevalence to the population of 2021. YLDs and YLLs were summed up to estimate the DALYs for osteoporosis burden associated with environmental cadmium exposure in Europe.

Table 3.71 shows the results for the female population aged between 55 and 70 years (in this case "alert" values for 20-39 year olds have been used to project the disease burden for when these women reach an older age). The following two categories have been investigated: urinary cadmium concentrations 0.5-0.75µg/g creatinine at age above 55 years and urinary cadmium concentrations above 0.75µg/g creatinine at age above 55 years. All results were rounded to 3 digits, meaning that the number 0 in the table not necessarily means no burden. The following table shows the methodology how DALYs (central; 95 % CI) were calculated on the example of osteoporosis and cadmium in Czechia for women above 55 years.

Table 3.71: Burden of disease in DALYs for cadmium (Cd) exposure (left table: 0.5-0.75µg/g creatinine at age over 55 years, right table: >0.75µg/g creatinine at age over 55 years) and osteoporosis in Czechia

	Osteoporosis burden for population with U-Cd 0.5-0.75µg/g creatinine at age over 55 years			Osteoporosis burden for population with U-Cd >0.75µg/g creatinine at age over 55 years		
	Central	Lower 95 %	Upper 95 %	Central	Lower 95 %	Upper 95 %
Age group with available U-Cd data	20-39 years					
U-Cd alert values (µg/g creatinine)	**0.189-0.2835**			**0.2835**		
Age group with osteoporosis burden	55-70 years					
Odds Ratio	1.61	1.20	2.16	1.95	1.30	2.93
Attributable Fraction	0.304	0.134	0.431	0.391	0.185	0.528
% of pop. with urinary Cd conc. >0.75µg/g at age over 55 years	34.168 %			26.004 %		
Number of people with blood cd conc. in age group	370,470			281,951		
Number of osteoporosis cases/year	214,684			214,684		
Number of osteoporosis cases attributable to cd exposure in 2021	22,289	9,805	31,593	21,812	10,332	29,492
YLDs 2021	6,375	2,804	9,036	6,238	2,955	8,435

	Osteoporosis burden for population with U-Cd 0.5-0.75µg/g creatinine at age over 55 years			Osteoporosis burden for population with U-Cd >0.75µg/g creatinine at age over 55 years		
	Central	Lower 95 %	Upper 95 %	Central	Lower 95 %	Upper 95 %
YLDs 2021 per 1,000,000 persons	596	262	844	583	276	788
YLLs 2021	5	2	6	4	2	6
YLLs 2021 per 1,000,000 persons	0	0	1	0	0	1
DALYs 2021	**6,379**	**2,806**	**9,042**	**6,243**	**2,957**	**8,441**
DALYs 2021 per 1,000,000 persons	**596**	**262**	**845**	**583**	**276**	**789**

Notes: The calculation follows the approach taken by (Goodman et al., 2014; Ougier et al., 2021a).

Source: (Goodman et al., 2014; Ougier et al., 2021a).

Based on the calculation for osteoporosis related to cadmium exposure, the total DALYs per year were estimated for Czechia, Belgium, Denmark, Germany, Hungary, Poland, Slovakia, Slovenia, Spain and Sweden. Estimates are given in Table 3.72 (rounded to whole numbers). DALY-rates per 1,000,000 persons were also calculated for comparison reasons.

Table 3.72: Burden of disease in DALYs in 2021 resp. DALYs per 1,000,000 persons in 2021 due to exposure to cadmium and osteoporosis in women aged between 55 and 70 years

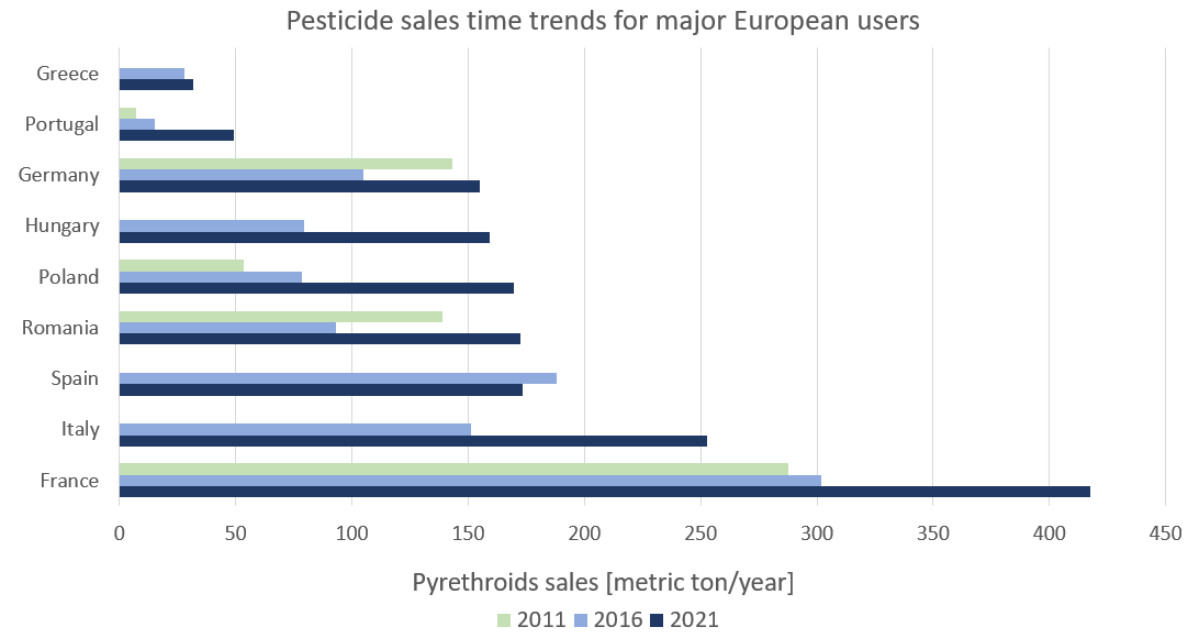
Country	DALYs in 2021			DALYs/1,000,000 persons in 2021		
	Central	Lower 95 %	Upper 95 %	Central	Lower 95 %	Upper 95 %
Czechia	12,622	5,763	17,483	1,179	539	1,634
Belgium	7,767	3,639	10,578	672	315	915
Denmark	2,550	1,194	3,476	437	204	595
Germany	46,530	21,854	63,273	560	263	761
Hungary	8,064	3,690	11,154	829	379	1,146
Poland	76,632	35,823	104,535	2,025	947	2,763
Slovakia	7,408	3,396	10,236	1,357	622	1,875
Slovenia	2,720	1,272	3,709	1,290	603	1,759
Spain	43,405	20,300	59,190	916	428	1,249
Sweden	1,902	896	2,583	183	86	249

3.5 Burden of disease due to pyrethroids

3.5.1 General information on pyrethroids and basic assumptions

In recent years, efforts have been made to phase out the more notorious organophosphate pesticides (e.g. chlorpyrifos) in the EU and replace these with safer alternatives, key among these being the pyrethroids. While pyrethroids are generally regarded as safer and less persistent substitutes of organophosphates in terms of human toxicity, it should be noted that their use is not entirely risk-free either (Thammachai et al., 2022). Moreover, a growing body of evidence suggests that prenatal exposure to pyrethroids adversely impacts the neurodevelopment of the offspring, with ADHD and autism-spectrum disorder (ASD) often being implicated as associated diseases (Oulhote and Bouchard, 2013; Andersen et al., 2022; Xu et al., 2023). An overview on relevant health effects related to pyrethroid exposure can be found in Annex A1.1. While pyrethroid sales in the EU have increased in recent years (Figure 3.7), it is not entirely clear how this has impacted exposure trends in European citizens. HBM programs worldwide have provided evidence of increasing exposure to pyrethroids. For instance, the Centers for Disease Control and Prevention (CDC) reported a rise in urinary 3-phenoxybenzoic acid (3-PBA), a non-specific biomarker for pyrethroids, from a geometric mean (GM) of 0.292µg/L to 0.418µg/L between 1999-2000 and 2009-2010 (CDC, 2015). Similar trends were observed in Canadian HBM programs (CHMS, Canadian Health Measures Survey) with urinary 3-PBA levels in the general population having increased from a GM of 0.25µg/L (2007-2009) to 0.43µg/L (2009-2011) (Health Canada, 2013). However, there is a lack of European data to establish clear-cut time trends, although HBM4EU time pattern data on 3-PBA do indicate higher urinary concentrations in recent years compared to a decade earlier[7] (Figure 3.8). It is nevertheless important to note that these EU data are from different campaigns, regions, and study populations, making it challenging to draw definitive conclusions, though they can provide an indication.

Figure 3.7: Pyrethroid sales in different EU countries



Notes: Results adapted from Eurostat.

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

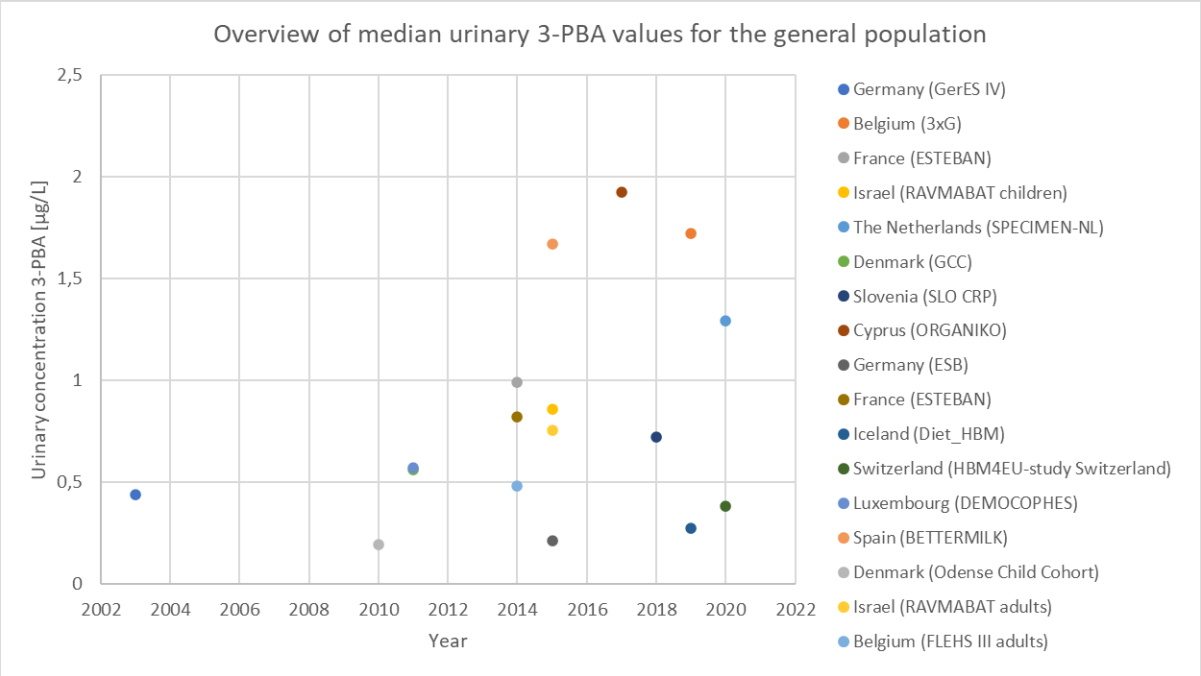
3.5.2 Attention deficit hyperactivity disorder (ADHD)

Aside from the lack of clear-cut time patterns regarding pyrethroid exposure in the EU, even less quantitative information exists on the health effects that are exerted on the European population. In this context, the BoD approach provides a robust framework for assessing the health impact associated with pyrethroid exposure. One of the neurodevelopmental diseases most implicated with pesticide exposure is ADHD. ADHD is a disease (ICD-10 F90) most observed in children and is characterized by difficulties regarding problem-solving abilities, paying attention, and hyperactivity (Kian et al., 2022). ADHD is estimated to affect around 5 % of the global population (Sayal et al., 2018a), which according to the IHME would correspond to approximately 1 million DALYs (GBD, 2019). In Europe, the estimated total annual national costs of ADHD for children and adolescents are equal to EUR 2,546 million (Olesen et al., 2012). Moreover, in Europe the prevalence of ADHD has also increased by 6 % between 1990 and 2019 (Castelpietra et al., 2022).

ADHD is one of the neurodevelopmental diseases with the highest heritability rates, with estimates ranging from 54 % to 70 % (Kian et al., 2022). Even so, 10 % to 40 % of the variance associated with ADHD is said to be explained by environmental, pre- or postnatal risk factors. The most commonly implicated studied risk factors linked to ADHD are maternal smoking, drinking, and substance misuse during pregnancy, maternal stress, and birth complications (i.e. premature birth, low birth weight) (Sciberras et al., 2017; Kian et al., 2022). Thus, the effects of environmental factors in ADHD etiology cannot be understated. Moreover, recent epidemiological studies show associations between pesticide exposure and diagnosis of ADHD in children even at body burdens far below health-advisory threshold values (e.g. health-based guidance values, HBM-GVs[8]). This might be caused by the insensitivity of animal models used in the derivation of such health-advisory values towards neurodevelopmental effects and thus regulatory thresholds may not be protective enough for developmental neurotoxicity (Fritsche et al., 2018).

[8] Associations between pyrethroids-ADHD already found at body burdens below most stringent HBM-GV of 1.7µg 3-PBA/L, while less stringent HBM-GV was derived at 87µg 3-PBA/L (Aylward et al., 2018).

Figure 3.8: Overview of urinary 3-PBA time patterns in (mostly) European countries



Notes: Results adapted from the HBM4EU dashboard (https://www.hbm4eu.eu/what-we-do/european-hbm-platform/eu-hbm-dashboard/)

Mode of action and weight of evidence

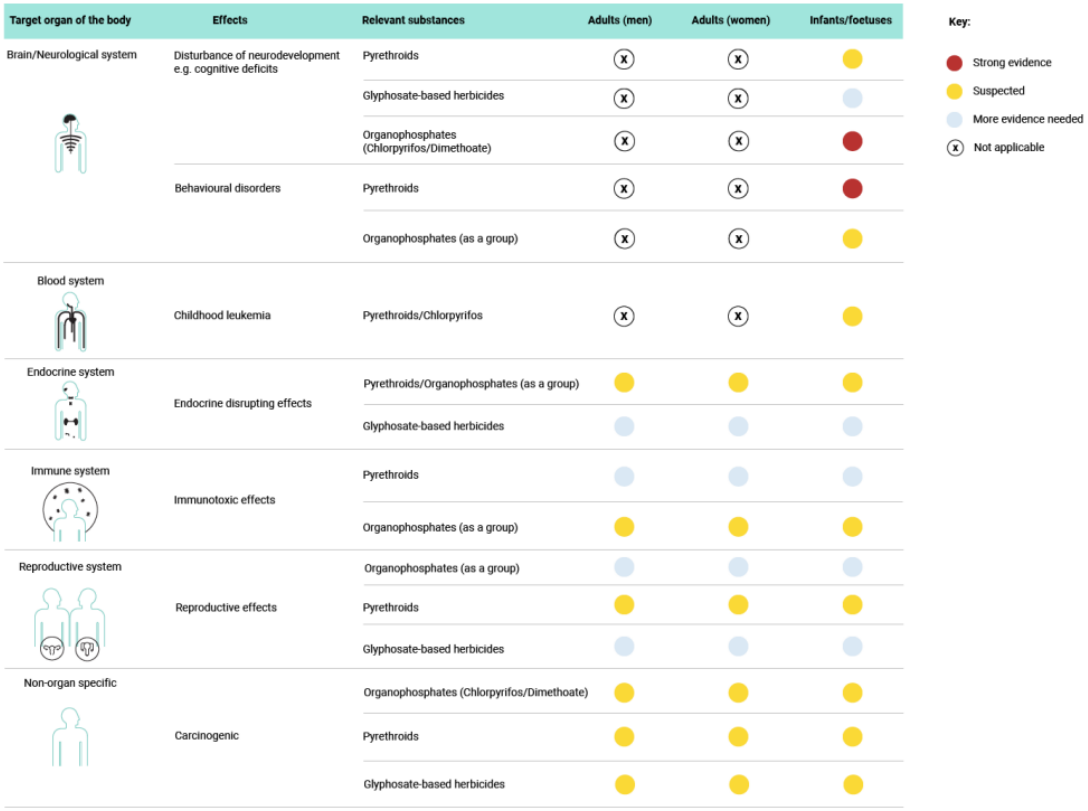
From a mechanistic point of view, pyrethroids exert their toxicological action by directly binding to Na^+ voltage-gated (Nav) channels, resulting in a net increase in Na^+-influx, and conversely, in excitotoxicity. In insects, this causes paralysis and mortality, however, due to the high evolutionary conservation between the Nav-channels in insects and humans, pyrethroids are also able to modify human Nav-channels in a similar way. The disruption of these Nav-channels in humans has been associated with a variety of neuropsychiatric diseases, including ADHD (Tapia et al., 2020). Other adverse effects caused by pyrethroids, which can be (in)directly linked to psychiatric diseases, include disturbance of thyroid hormone function, neuroinflammation and altered levels of brain-derived neurotrophic factor (Andersen et al., 2022). Mechanistic evidence for these neurotoxic effects is provided through the OECD-supported Adverse Outcome Pathways (AOP) platform by (Andersen et al., 2022). Additionally, current data provide a mechanistic basis to suggest that developmental pyrethroid exposure is a significant risk factor for ADHD (Richardson et al., 2015; EFSA, 2021).

Further evidence of neurodevelopmental effects of pyrethroids are provided by experimental animal studies, in which evidence of ADHD-like features or developmental neurotoxicity was found in rodents (Richardson et al., 2015; Pitzer et al., 2021). Similar evidence is also provided by epidemiological studies, with cohort studies (Dalsager et al., 2019; Lee et al., 2022; An et al., 2022) finding associations between prenatal maternal pyrethroid exposure and the development of ADHD or behavioral problems in the offspring.

According to EFSA, experimental findings provide support to epidemiological evidence indicating that either prenatal or postnatal exposure to pyrethroids, assessed by urinary non-specific pyrethroid metabolites, is associated with an increased risk of ADHD diagnosis (EFSA, 2021).

However, according to Andersen and colleagues the strength of evidence is only deemed to be sufficient for a link between in utero pyrethroid exposure and adverse neurodevelopmental effects (Andersen et al., 2022). This rating was given based on an overall moderate quality of evidence across multiple studies, in which adverse neurodevelopmental effects were consistently linked to pyrethroid exposure, combined with some evidence for reduced cognitive function with increased prenatal pyrethroid exposure (although not consistently found over all studies), and consistent findings for neurobehavioral outcomes. This conclusion is further corroborated within the HBM4EU-project and by the EEA in a recent briefing on the health and ecosystem impacts of pesticides, in which an overview of the health effects related to pesticide exposure and the evaluation of the weight of evidence based on findings from the European biomonitoring studies (HBM4EU) was recently published (Figure 3.9). In this, sufficient evidence was said to exist for the association between pyrethroids and behavioral disorders. The focus will be on prenatal exposure and the association with ADHD symptoms during development, given that in utero exposure is considered to be the most sensitive window of exposure, for which the evidence for adverse neurodevelopmental effects (e.g. ADHD) is strongest compared to other life stages.

Figure 3.9: Overview of health effects associated with exposure to HBM4EU priority pesticides



Source: (EEA, 2023).

Exposure-, health-, population data

Exposure data collected in the sligned studies of HBM4EU show the following results (µg/L) for the non-specific pyrethroid biomarker 3-PBA in urine of children and adults. Concentrations are lower in adults compared to children.

Table 3.73: Urinary concentrations (µg/L) of 3-PBA in children in the aligned studies collected under HBM4EU

Country	P05	P10	P25	P50	P75	P90	P95
France[(a)]	0.268	0.397	0.629	0.990	1.715	3.396	5.308
Slovenia	<LOD	<LOD	0.348	0.723	1.338	2.008	3.721
The Netherlands	0.436	0.521	0.882	1.290	2.531	3.942	4.806
Belgium	0.384	0.540	0.976	1.724	2.887	4.747	7.054
Cyprus	0.667	0.817	1.276	1.926	3.213	5.104	6.370
Israel[(a)]	0.242	0.342	0.493	0.857	1.793	3.997	5.970

Notes: ([a]) The studies of France (ESTEBAN) and Israel (RAV-MABAT) are representative for the entire respective country.

Source: HBM4EU Dashboard.

Table 3.74: Urinary concentrations (µg/L) of 3-PBA in adults in the aligned studies collected under HBM4EU

Country	P05	P10	P25	P50	P75	P90	P95
France	0.197	0.251	0.438	0.819	1.341	2.015	2.773
Iceland	<LOQ	<LOQ	0.148	0.270	0.546	1.188	1.650
Switzerland	<LOQ	0.110	0.190	0.380	0.680	1.220	1.932
Germany	<LOQ	-3.000	0.128	0.210	0.363	0.544	0.770
Israel	0.142	0.187	0.360	0.754	1.358	2.338	2.874

Notes: The studies of France (ESTEBAN), Israel (RAV-MABAT), Iceland (DIET-HBM) and Switzerland (HBM4EU study) are representative studies for the whole country.

Source: HBM4EU Dashboard.

Levels of the pesticide biomarkers were higher in children than in adults. This confirms earlier observations of 3-PBA levels measured in Poland (Wielgomas and Piskunowicz, 2013). Exposure differences by sex are small (see Table 3.75) and there is no clear trend for exposure being different between males or females.

Table 3.75: Urinary concentrations of 3-PBA (µg/L) stratified by sex

Country	Sex	N	P05	P10	P25	P50	P75	P90	P95
France	Male	61	0.203	0.241	0.414	0.858	1.263	2.126	2.745
France	Female	83	0.165	0.277	0.499	0.797	1.345	1.901	2.764
Iceland	Male	88	<LOQ	<LOQ	0.131	0.28	0.548	0.931	1.579
Iceland	Female	106	<LOQ	<LOQ	0.159	0.27	0.535	1.349	1.902
Switzerland	Male	162	<LOQ	0.112	0.213	0.39	0.723	1.217	1.931
Switzerland	Female	137	<LOQ	0.106	0.18	0.36	0.67	1.264	1.746
Germany	Male	90	<LOQ	<LOQ	0.133	0.23	0.368	0.531	0.709
Germany	Female	90	<LOQ	<LOQ	0.12	0.19	0.35	0.581	0.903
Israel	Male	36							
Israel	Female	47							

Source: HBM4EU Dashboard.

Global ADHD prevalence is indicated to be on average around 5 % (2-7 %), with at least a further 5 % of children having substantial difficulties with overactivity, inattention, and impulsivity that are just under the threshold for clinically diagnosable ADHD (Sayal et al., 2018a). This figure is supported (Bellanger et al., 2015; Coghill et al., 2021). Furthermore, ADHD prevalence is reported to have been increasing over time according to Sayal and colleagues and Castelpietra and colleagues (Sayal et al., 2018a; Castelpietra et al., 2022).

Data on prevalence were obtained from the IHME for ADHD for different age categories for the HBM4EU countries for which HBM pyrethroid exposure data are available. European data on the occurrence of ADHD in the different EU countries for which HBM data are available, were searched for in international scientific literature and in Eurostat databases but were not found.

Exposure-response relationship

Although numerous associations are reported in literature between pyrethroids exposure and increased ADHD symptoms, the focus in this paragraph will be on prenatal exposure and the association with ADHD symptoms during development. The reason for this, as stated in earlier, is that *in utero* exposure is considered to be the most sensitive window of exposure, for which the evidence for adverse neurodevelopmental effects (e.g. ADHD) is strongest compared to other life stages. Additionally, a preference is given to cohort studies compared to cross-sectional studies. The best described cohort studies that were found, focusing on prenatal exposure to pyrethroids and the development of ADHD or behavioral dysfunction during infancy, are the ones found in several studies (Dalsager et al., 2019; Lee et al., 2022; An et al., 2022). The ERFs found in these studies are summarized in Table 3.76.

Table 3.76: Overview of exposure-response functions found for prenatal pyrethroid exposure and ADHD onset during child development

Study	Body burden (µg/L)[(a)]	Exposure-response function
(Dalsager et al., 2019)	P50 = 0.21 P95 = 1.96	Doubling prenatal maternal 3-BPA associated with 3 % increase in ADHD-scores and 13 % higher odds of ADHD-score ≥P90 which is a predictor of later ADHD diagnosis (Aebi et al., 2010)
(Lee et al., 2022)	GM = 0.65 P50 = 0.77 P95 = 4.14	Doubling prenatal maternal 3-BPA associated with 2,7 % increased odds of ADHD at age 6
(An et al., 2022)	GM = 1.1	*In utero* log-unit increase in 3-BPA associated with increased risk of externalizing behavior (β = 0.82, RR = 1.35)

Notes: ([a]) P50 and P95 represent the 50th and 95th percentiles, while GM represents the geometric mean. All values reflect maternal urine 3-PBA values during pregnancy.

The OR value derived by the European study of Dalsager and colleagues for prenatal exposure and ADHD was used to calculate the burden of disease associated with pyrethroids in this report (Dalsager et al., 2019). The reason for this choice is that the study by Dalsager and colleagues is a European study and the exposure concentrations are closer to what is observed in the HBM4EU-project than the South Korean study (Dalsager et al., 2019). Moreover, a clear link between prenatal exposure and ADHD diagnosis is described, and a continuous ERF is reported.

All input data, references, EBD calculation steps and results can also be found in Annex A2.9.

Attributable burden

The most recent data on the burden of disease (measured through DALYs) per age category for ADHD from the IHME are presented in Table 3.77 below. These numbers date back to 2019. It is assumed that the burden associated with ADHD did not change a lot compared to present years.

Table 3.77: DALYs/year given by IHME for the global burden of disease on ADHD for the year 2019. Prevalence based DALYs

Country	Age (years)				
	<5	**5-14**	**5-9**	**0-14**	**0-19**
France	172	4,260	1,926	4,432	5,886
Slovenia	2	61	27	64	88
The Netherlands	34	854	370	888	1,250
Belgium	21	523	233	544	735
Cyprus	3	56	25	58	78
Israel	39	792	372	830	1,104
Iceland	1	21	9	22	29
Switzerland	18	411	186	429	589
Germany	72	1,615	722	1,687	2,311

Source: https://vizhub.healthdata.org/gbd-results/.

For the calculation of the EBD associated with pyrethroid exposure and ADHD is based on prevalence rates from IHME (IHME, 2022) and population data from Eurostat (Eurostat, 2022).

Population data applied in the calculation are exhibited below. These data are retrieved from Eurostat.

Table 3.78: Number of persons 0-19 years of age for the year 2021

Country[(a)]	Number of persons aged between 0-19 years
Belgium	2,575,968
Germany	15,334,574
France	16,150,779
Cyprus	191,886
Netherlands	3,743,466
Slovenia	411,678
Iceland	91,292
Switzerland	1,726,301
Israel	3,360,000

Notes: [a] Data retrieved form Eurostat except for Israel for which data were retrieved from: https://www.statista.com/statistics/1286953/total-population-of-israel-by-age-group/.

The calculation shown below is based on the top-down approach for estimating the ADHD disease burden associated with pyrethroid exposure. As illustrated earlier, the greatest weight of evidence was found for gestational exposure to pyrethroids and ADHD development in the offspring. Therefore, the time period in which pyrethroids were beginning to be used more extensively in Europe is an important

factor in determining which age category should be included in the disease burden estimation. However, there is little data on when and to what extend exactly pyrethroids were used in Europe the last decades.

In order to get a sensible BoD estimation, the age category of 0-19 years will be considered, which is an extrapolation compared to the age category for which the ERF was derived (namely for children aged 2-4 years). The reason for expanding the age category is because ADHD is less routinely tested and more difficult to assess at an age of 2-4 years (Dalsager et al., 2019). This is because ADHD symptoms in younger children are often perceived by the parents as normal developmental behavior (Sayal et al., 2018a). Moreover, any gestational exposure to pyrethroids that may lead to ADHD development is likely to persist throughout late adolescence (Franke et al., 2018), thereby justifying the inclusion of all non-adults. The reason why adulthood was not included is because ADHD symptoms tend to be more manageable during adult life, with a fraction of the ADHD cases diagnosed in early life potentially becoming asymptomatic during adulthood (approximately 33-50 %) (Rivas-Vazquez et al., 2023) or may even be remitted altogether (with 55-70 % remission by early adulthood, up to 80 % in later adulthood) (Sudre et al., 2018).

By considering the age category of 0-19 years there is a chance of both over- as well as underestimating the BoD. The HBM studies that were used in this report were conducted between 2014 and 2021. This implies that by expanding the age category until the age of 19, we assume that the exposure values measured in these fairly recent HBM campaigns are applicable from the year 2001 onwards, which may inflate the BoD estimations. On the other hand, by excluding the adult population based in the BoD estimation, there is realistic chance of underestimating the true disease burden. Given all the aforementioned reasons, limiting the population to all non-adults seems like the most safe and sensible approach for disease burden estimation.

Table 3.79: Calculation DALYs (prevalence based) for ADHD in persons 0-19 years associated with exposure to pyrethroids in 2021. The calculation is shown for France for the central estimate

Exposure percentile	<P05	P5-P10	P10-P25	P25-P50	P50-P75	P75-P90	P90-P95	>P95	Sum
Percent children in category	5 %	5 %	15 %	25 %	25 %	15 %	5 %	5 %	
Exposure adults (µg/L)	0.197	0.224	0.345	0.628	1.080	1.678	2.394	2.773	
OR as proxy for RR[(a)]	1.13	1.16	1.25	1.39	1.52	1.65	1.75	1.80	
AF in percentile	0.11	0.13	0.20	0.28	0.34	0.39	0.43	0.44	
Total DALYs for ADHD[(b)]	298	298	895	1,492	1,492	895	298	298	5,968
DALY attributed to pyrethroid exposure	34	40	177	415	513	352	128	133	**1,792**

Notes: ([a]) A relative risk of 1 was set at an exposure of 0.1µg/L. Each doubling in maternal 3-PBA concentration was associated with 13 % higher odds of having an ADHD score ≥90th percentile (OR: 1.13 (1.04,1.38)).

([b]) Based on prevalence rate of IHME (2019) and population data of Eurostat (2021). Age category considered 0-19 years.

Table 3.79 gives an overview of the different estimates made to calculate the DALYs associated with pyrethroid-related ADHD for France. Moreover, the proportion of DALYs attributable to pyrethroid exposure compared to the total number of DALYs for ADHD can be estimated by dividing the central

estimate by the total DALY estimates. The PAF thus reflects the amount of ADHD cases that are attributable to pyrethroid exposure. For France, this would lead to an estimate of 30 %, meaning that almost one in 3 cases of ADHD in France is associated with pyrethroid exposure. For all other countries, the results are summarized in Table 3.80. When the PAF values are averaged out for all countries listed in Table 3.80, a value of 18.3 % is obtained.

Table 3.80: DALYs (prevalence based) for ADHD in persons aged 0-19 years associated with exposure to pyrethroids for the year 2021. Countries are those for which data on pyrethroid exposure in adults is available in HBM4EU

DALY/year prevalence based	Central estimate	95 % LL	95 % HL	Total DALY ADHD/year prevalence-based[(a)]	PAF
France	1,792	640	3,532	5,968	30.0 %
Iceland	5	2	11	30	17.2 %
Switzerland	120	42	249	584	20.7 %
Germany	293	97	642	2,256	13.0 %
Israel	322	115	634	1,119	28.8 %
Average					18.3 %

Notes: 95 % LL: 95 % lower limit based on uncertainty (95 % CI) of the OR.

95 % HL: 95 % higher limit based on uncertainty (95 % CI) of the OR.

Studies analyzing exposure data in adults conducted in 2014-2016 for France, 2019-2021 for Iceland, 2020 for Switzerland, 2015-2020 for Germany, and 2015-2016 for Israel.

([a]) Based on prevalence data IHME and population data of Eurostat (2021).

The disease burden results per 1,000,000 persons for DALYs based on prevalence are given below.

Table 3.81: DALYs (prevalence based) for ADHD in persons 0-19 years associated with exposure to pyrethroids per 1,000,000 persons for the year 2021

DALY/year prevalence based	Central estimate	95 % LL	95 % HL
France	26	9	52
Iceland	14	5	29
Switzerland	14	5	29
Germany	4	1	8
Israel	35	12	68

Notes: 95 % LL: 95 % lower limit based on uncertainty (95 % CI) of the OR.

95 % HL: 95 % higher limit based on uncertainty (95 % CI) of the OR.

Countries are those for which data on pyrethroid exposure in adults is available.

From the results shown above, a large variation in disease burden between the different countries can be observed, with Israel (35 DALYs per 1,000,000 persons) and France (26 per 1,000,000 persons) exhibiting markedly higher BoD-estimates than Iceland (14 per 1,000,000 persons), Switzerland (14 per 1,000,000 persons) and Germany (4 per 1,000,000 persons). When considering the fraction of ADHD cases attributable to pyrethroid exposure, France exhibits the highest PAF of 30 %, followed by Israel (28.8 %), Switzerland (20.7 %), Iceland (17.2 %), and finally, Germany (13.0 %). The reason why France and Israel exhibit greater BoD- and PAF-estimates is due to the fact that their populations are more significantly exposed to pyrethroids.

It should be noted that the disease burden, as expressed through DALYs, does not the capture the true extent of the (health) impact associated with pyrethroid exposure. The relatively low DALY-estimates are due to the low DW of 0.045 attached to ADHD, whereas the true impact of ADHD would be better reflected through the associated economic cost related to health care expenditure, lost productivity and psychosocial consequences among others.

Pyrethroid use has also increased significantly in the last couple of years, implying that the body burdens measured during the aligned studies under HBM4EU might no longer reflect the actual exposures in the EU. This could lead to theunderestimation of the real burden of disease caused by pyrethroids. Another point that contributes to the underestimation of the actual BoD for pyrethroids is the fact that only ADHD is considered as possible disease outcome. Besides ADHD, significant associations between pyrethroid exposure and ASD and cognitive effects were also found in epidemiological studies (e.g. (Kim et al., 2021; Miani et al., 2021). However, the focus of this report was ADHD and other effects were not considered. Finally, the biomarker 3-PBA for which an association was found with a change in ADHD spectrum, does not cover the entirety of pyrethroid exposure. More precisely, this biomarker exclusively reflects exposure to cyhalothrin, cypermethrin, deltamethrin, fenpropathrin, fenvalerate, and permethrin, and may therefore underestimate the true total exposure to pyrethroids (USEPA, 2019). Mixture effects with other neurotoxic pesticides or chemicals are also not covered here.

Uncertainty

A major source of uncertainty arises from the ERFs used to estimate the BoD of pyrethroid-induced ADHD. More specifically, the child cohort study by Dalsager and colleagues was used, in which every doubling of prenatal maternal 3-PBA was associated (at offspring age 27 months) with 13 % higher odds of exhibiting ADHD scores above the 90th percentile (Dalsager et al., 2019). This association was considered to have an OR of 1.13 for explicitly having ADHD, while the actual outcome of the behavioral assessment indicates more severe ADHD symptoms. More specifically, in this study the Child Behavior Checklist for ages 1.5-5 years (CBCL:1.5-5) was used, which required the parents or guardians to answer a questionnaire consisting of 100 questions regarding behavioral, emotional, and social problems on a scale ranging from 0 (not true), 1 (sometimes) to 2 (often true). Though the CBCL:1.5-5 is reported to be well-established and stable over time, its outcome (ADHD scores above P90) is only a predictor of future ADHD diagnosis, not an explicit clinical diagnosis. Moreover, completion of the questionnaire is based on parental or guardian report rather than medical records or appropriate neuropsychological assessment (Dalsager et al., 2019). Thus, there is a potential for misclassification of ADHD (symptoms) due to systematic under- or overestimation of the severity of symptoms. In addition to this, the BoD estimation was based on a reported OR from a single scientific study. Preferably, multiple OR- or RR-values are reported by different scientific studies, so that meta-analysis can be performed to quantitatively summarize these exposure-response associations.

Another aspect of uncertainty is the fact that 3-PBA exposure data are based on a single spot urine sample in most studies. Since pyrethroids are metabolized and excreted from the body within hours to days, serial urine sampling would provide a more accurate estimation of the actual exposure. Although in populations continuously exposed to low amounts of pyrethroids through food residues,

it is assumed that exposure levels reach (quasi) steady state and thus remain relatively stable, thus justifying the use of single spot urine samples (Dalsager et al., 2019).

The 3-PBA exposure data that was used was based on the adult population from the aligned studies performed within HBM4EU. Exposure data for women of child-bearing age (20-40 years of age) would have been more realistic. However, research suggests that gender-specific differences in pyrethroid exposure are not significant, and that location of residency or occupation could be more decisive determinants of exposure differences.

The risk of reverse causality can also not be excluded. More specifically, children with ADHD may become more exposed because of their higher activity levels, thus leading to higher body burdens of pyrethroid metabolites. Though, it is likely that reverse causation will be less of an issue in cohort studies in which maternal body burdens are related to childhood health compared to cross-sectional studies performed postnatally.

Another source of uncertainty is the fact that the body burden of 3-PBA does not solely reflect exposure to pyrethroids. A part of the body burdens does indeed arise due to metabolization of pyrethroids, but a smaller part can be due to intake of environmentally formed 3-PBA, which arises during the environmental break-down of pyrethroids on food stuffs (Lee et al., 2020). This implies that pyrethroid exposure, as measured via the marker 3-PBA, may overestimate the actual intake of pyrethroids. Moreover, the metabolite 3-PBA is intrinsically less toxic than the pyrethroid parent-compounds. This is reflected by the Acceptable Daily Intake (ADI)-value of 1mg/kg bw/d for 3-PBA, which is several orders of magnitude greater than the ADI of relevant pyrethroids (EFSA, 2022). This thus implies that the real pyrethroid intake (i.e. corrected for environmental 3-PBA intake) would exert even higher levels of toxicity than the effects that are observed in epidemiological studies.

The calculated burden in this report is based on persons aged 0-19 years. Since there is little data on when and to what extend exactly pyrethroids were used in Europe the last decades, as mentioned earlier, the results may be both underestimated (by excluding adults in the BoD estimation) as well as overestimated (by extrapolating the exposure values measured between 2014 and 2021 to the entire time period of 2001 onwards).

Finally, only ADHD was considered as a pyrethroid-related health outcome for which BoD estimates were determined. Yet pyrethroid exposure is also associated with other health outcomes such as ASD and cognitive issues (Xu et al., 2023).

Because of the paucity in literature, it is warranted to conduct future studies to more accurately determine the neurotoxic effects of pyrethroids and the associated disease burden. In this context, cohort studies focusing on prenatal exposure to pesticides in critical exposure windows followed by clinical ADHD assessment in children are especially warranted. In addition to this, studies focusing on geospatial variability of ADHD would also be highly valuable, especially if geospatial risk factors such as living in close proximity to agricultural fields and the influence thereof on ADHD prevalence could be investigated. Toxicity studies and mechanistic data already provide ample prove for the possibility of ADHD effects due to pyrethroids occurring in children, but more epidemiological studies are needed.

Conclusion

In this report, the burden of disease of ADHD related to pyrethroid-exposure was estimated for several European countries. More and more evidence is found for the link between *in utero* exposure to pyrethroids and adverse neurodevelopmental effects in the offspring, among which ADHD is often implicated. For several countries that participated in the HBM4EU aligned studies (i.e. France, Iceland, Switzerland, Germany, and Israel), it was possible to estimate the ADHD disease burden associated

with pyrethroid exposure for children and adolescents (0-19 years). These countries were the only ones that measured urinary 3-PBA concentrations in adults during the aligned studies under HBM4EU. Countries that only measured urinary 3-PBA in children were not included given that the strongest evidence for ADHD development is linked to *in utero* exposure to pyrethroids, therefore, adult biomarker concentrations are preferred.

The highest disease burden estimates per 1,000,000 persons were found for Israel (35 DALYs), followed by France (26 DALYs), Iceland (14 DALYs), Switzerland (14 DALYs) and lastly, Germany (4 DALYs). When considering the fraction of ADHD cases attributable to pyrethroid-exposure, France exhibits the highest PAF of 30 %, followed by Israel (28.8 %), Switzerland (20.7 %), Iceland (17.2 %), and finally, Germany (13.0 %).

3.6 Burden of disease due to bisphenol A

3.6.1 General information on bisphenol A and basic assumptions

Bisphenols are man-made chemicals that are the principal component in the production of plastics such as polycarbonates and epoxy resins. Among the best known is bisphenol A (BPA). It is used in a wide range of products, e.g., electronic devices, CDs/DVDs, paints, flame retardants or medical devices. In addition, BPA is found in numerous consumer products which get in contact with food, such as reusable bottles, plastic tableware or food containers. It is also used to coat the inside of food and beverage cans.

Due to the large area of application, BPA is ubiquitous and thus can be found in many environmental media, especially in industrialized countries (EFSA, 2015; Ougier et al., 2021b). Accordingly, median levels of urinary BPA are increased in the European population although the framework for the use of BPA becomes increasingly stringent and substitutes such as BPS or BPF are increasingly used. For the general population, the most relevant exposure route and source of BPA is the consumption of food and beverages containing BPA that has been released from food packaging materials or feeding bottles. Another important exposure route is via dermal absorption (EFSA, 2015; Ougier et al., 2021b).

BPA was identified to be a potential risk to human health and the environment. The EU classifies BPA as an endocrine disrupting chemical that is associated with toxic health effects on fertility (HBM4EU, 2022; ECHA, 2023). In addition, there is further evidence from numerous toxicological, animal and epidemiological studies that this substance is linked to a variety of other conditions, such as developmental disorders, neurobehavioral conditions, asthma, diabetes mellitus, obesity, cardiovascular diseases or cancer (Rochester, 2013; Healy et al., 2015; Ma et al., 2019; Colorado-Yohar et al., 2021). Children are particularly at risk for exposure to endocrine disruptors such as BPA, as these substances can disrupt various stages of development and therefore pose a significant health risk. Yet, despite these ample suggestions of possible health outcomes associated with BPA exposure, no clear causal relationships involving epidemiologic evidence can be concluded from the study basis. A further overview on relevant health effects related to BPA exposure can be found in Annex A1.1.

The EFSA reevaluated the potential risk of BPA dietary intake in a comprehensive assessment in 2023 and proposed a new TDI at 0.2ng per kg bodyweight per day of total BPA (EFSA Panel on Food Contact Materials et al., 2023). This value is 20,000 times lower than the previous temporary TDI of 4,000ng per kg bodyweight per day set in 2015. Therefore, all HBM4EU measurements on BPA are well above the recommended HBM-GV that can be derived from the new TDI (HBM4EU, 2022). Thus, the risk for consumers related to dietary BPA exposure is of increased health concern, and even more targeted protective measures need to be taken. At the same time, the safety of BPA substitutes such as BPS and BPF as well as of mixtures remains unclear and will not be covered by the following analyses.

3.6.2 Obesity in children, adolescents and adults

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., 2020b; Kim et al., 2019; Rancière et al., 2015; Ribeiro et al., 2020; Rojas-Rueda et al., 2021; Trasande et al., 2016). However, the results of the individual assessments in adults as well as in children were often based on a small number of epidemiological 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; Trasande et al., 2016).

Exposure-response relationship

For EBD calculations, several meta-analyses have been available investigating the association between obesity risk and BPA exposure (Wu et al., 2020b; Kim et al., 2019; Rancière et al., 2015; Ribeiro et al., 2020). Based on the selection criteria timeliness, number of studies considered, non-binary exposure assessment, (subgroup) evaluation for different age groups and heterogeneity, the meta-analysis by Wu and colleagues was selected for our EBD calculations (Wu et al., 2020b).

The authors investigated a total of 10 individual studies and derived esposure-response functions for the association between obesity risk and BPA urine levels with a linear shape. It was shown that 1µg/L BPA increase is associated with an OR of 1.171 (95 % CI 1.136-1.206) for children/adolescents and an OR of 1.149 (95 % CI 1.113-1.186) for adults. However, the study did not report the concentrations of the respective counterfactual values. To determine these values, the urinary BPA concentrations for OR = 1 mentioned in the 10 individual studies were extracted. For a conservative BoD estimate, the highest reported concentration value was used, with a counterfactual value of 1.5µg/L for children/adolescents and 1.1µg/L for adults. For children, 1 study was not considered because it only assessed a binary BPA exposure (greater or less than 2µg/L).

Furthermore, it should also be noted that the definition of obesity in both children/adolescents and adults differed to some extent between the individual studies. Most studies on children/adolescents followed the US CDC definition, where childhood obesity is defined as sex and age specific BMI levels greater than or equal to the 95th percentile. Yet, 1 study also included overweight and selected a BMI equal to or higher than the 90th percentile for age and gender. For adults, most studies used the WHO obesity definition, which defines obesity as a BMI equal to or more than 30kg/m². 1 study used the BMI cut-off value of 28kg/m².

Exposure-, health-, population data

Regarding exposure data, total urinary BPA concentrations measured in HBM4EU studies in children (6-11 years), adolescents (12-18 years) and adults (20-39 years) were used. aligned studies covered only the adult population. Data sets with equal to or more than 50 study participants were selected. Exposure data were available for different sampling years. Accordingly, data from 2021±5 years were used. If there were two data sets for a country in this period available, the most recent one was selected. Values in grey were selected for the calculations (Table 3.82). In total, 7 countries were considered in the analyses for the different age groups. The study from Denmark was not considered, as it only investigated male adolescents. Furthermore, the exposure data from Israel and Switzerland could not be used either, as the relevant prevalence data were not available.

In addition, exposure and prevalence data were available in different age groups and had to be combined to calculate the EBD. This was done as follows:

- BPA exposure of 6-11 year olds was assumed to be equivalent for 5-9 year olds
- BPA exposure of 12-18 year olds was assumed to be equivalent for 10-19 year olds
- BPA exposure of 20-39 year olds was assumed to be equivalent for 20-45 year olds

Table 3.82: Total BPA concentrations (µg/L) in urine of children, adolescents and adults in studies gathered in HBM4EU between 2016 and 2021

Country	Data collection	Year	Age group (years)	N	P05	P10	P25	P50	P75	P90	P95
Children											
Austria	KS	2020	6-11	85	NA	NA	0.3	0.7	1.3	1.7	4.00
Germany	GerES V	2016	6-11	80	NA	0.6	1.0	1.8	3.0	5.0	6.44
Adolescents											
Denmark	Danish Young Men study	2017	12-19	76	NA	NA	0.5	1.1	2.1	4.6	7.00
Germany	GerES V	2016	12-19	71	NA	0.8	1.2	1.8	3.3	5.2	6.44
Adults											
Czechia	IELSPAC: YA	2019	20-37	290	0.2	0.4	1.0	1.6	3.0	5.2	8.74
Croatia	HBM survey in adults in Croatia	2019	20-39	206	0.09	0.5	1.2	2.2	3.71	6.63	8.58
Croatia	HBM survey in adults in Croatia	2020	20-39	94	0.5	0.6	1.1	1.8	3.0	4.9	7.08
Finland	FinHealth	2017	25-39	300	NA	0.2	0.4	0.9	1.8	3.7	5.65
Israel	Diet_HBM	2020	20-39	166	0.1	0.2	0.6	1.6	3.0	5.0	7.33
Poland	POLAES	2017	20-39	228	0.5	0.6	1.0	1.9	3.4	6.5	9.94
Portugal	INSEF-ExpoQuim	2019	28-39	247	0.5	0.7	1.1	1.9	3.5	8.0	11.9
Switzerland	HBM4EU-study Switzerland	2020	20-39	300	NA	NA	NA	0.5	0.9	1.8	2.52

Scenario analysis

HBM4EU studies gathered in recent years have primarily examined adults aged 20-39 years. However, these data cannot be used to estimate the burden of disease associated with BPA for older adults. Due to the lack of recent HBM data for this age group, we performed a scenario analysis for 2021 based on 2014 BPA concentration data from Belgium (FLEHS 3 adults). This study included both 40–59-year-olds and those aged 60 years and older (Table 3.83). These exposure values were applied to the age groups of 45-64 years and 65 years or older, respectively.

Table 3.83: Total urinary BPA concentrations (µg/L) in adults from Belgium 2014 gathered in HBM4EU

Country	Data collection	Year	Age group (years)	N	P05	P10	P25	P50	P75	P90	P95
			40-59	111	0.28	0.33	0.61	1.14	2.10	3.97	4.91
Belgium	FLEHS 3 adults	2014	≥60	83	NA	0.42	0.66	1.06	1.83	2.77	5.05

Prevalence rates of obesity among children (5-9 years) and adolescents (10-19 years) were derived from the WHO Global Health Observatory data repository (GHO). These are modelled data based on 2,416 pooled population-based studies worldwide, measuring height and weight of people older than 5 years of age (NCD Risk Factor Collaboration, 2017). Rates are available for 200 countries for the years 1975 to 2016. To obtain prevalence rates for the reference year 2021, a linear trend was derived based on age group and country-specific data from 2007 to 2016.

Furthermore, the prevalence rates are based on the WHO's definition of childhood obesity, where children and adolescents aged 5 to 19 are considered obese if their sex and age specific BMI is greater than two standard deviations above the WHO growth reference median (equivalent to the 97th percentile). This definition differs from the one mainly used in the individual studies of the meta-analysis by Wu and colleagues to derive the ERF. These mainly refer to the CDC childhood obesity definition (Wu et al., 2020b).

Corresponding prevalence data on obesity for adults were derived from the EHIS (Eurostat, 2023a). These were available for the year 2019 in a mix of 5- and 10-year age groups. Obesity was defined as BMI of equal to or more than 30kg/m² as in most studies included in (Wu et al., 2020b). To perform EBD calculations for the reference year 2021, the prevalence rates for 2019 were applied to the population of 2021.

No mortality indicators were calculated because no mortality data are available for this disease. Moreover, since there is no DW available for this health state, only the PAF and the sex specific attributable prevalence for the children, adolescent and adult populations was estimated.

Regarding demographic information for the selected countries, population data from Eurostat (1-year age groups) as of January 2021 was used (Eurostat 2022). All input data, references, EBD calculation steps and results can also be found in Annex A2.10 to Annex A2.14.

Attributable burden

Table 3.84 shows the calculated sex specific EBD indicators for this risk-outcome-pair. Regarding children aged between 5 and 9 years, the BPA-related PAF for obesity was considerably lower in Austria (2.7 %, 95 % CI 2.2-3.1) than in Germany (13.6 %, 95 % CI 11.4-15.5). This also resulted in substantially lower attributable obesity rates per 1,000,000 persons in Austria (191, 95 % CI 158-220) compared to Germany (954, 95 % CI 802-1,089).

Estimates for adolescents aged 10-19 years were only calculated for Germany, as only few BPA exposure datasets were available overall. Compared to the assessments for German children, the PAF for adolescents was slightly higher at 14.8 % (95 % CI 12.4-16.9) as well as the attributable prevalence rates per 1,000,000 persons.

Comparable estimates for adults between 20 and 44 years of age were calculated for 5 other European countries. The PAF was lowest in Finland (8.6 %, 95 % CI 6.9-10.1) and highest in Portugal (21.1 %, 95 % CI 17.5-24.1). The total attributable prevalence ranged from 23,367 (95 % CI 18,755-27,600) cases in

Finland to 313,685 (95 % CI 257,490-363,130) cases in Poland. The lowest and highest rates per 1,000,000 persons were also estimated for these two countries.

Regarding the overall attributable prevalence for the male population, higher attributable cases were almost always identified compared to the female population. This sex difference was due to a higher obesity prevalence in men.

Scenario analysis

To calculate EBD estimates for population groups 45 years or older, only older HBM4EU data from 2014 for Belgium were available. These were used in a scenario analysis under the assumption that the BPA exposure at that time corresponded to the exposure in the reference year 2021.

The PAF for the age groups 45-64 years and 65 years and older was 9.2 % (95 % CI 7.3-10.9) and 7.2 % (95 % CI 5.7-8.5), respectively (Table 3.85). Regarding the attributable prevalence cases, it was also shown that the older age group had a slightly lower overall burden than the 45–64-year-olds. A comparison of the scenario results with the main analysis shows that the values for the PAF and attributable prevalence are mostly lower in older people than in younger adults.

Table 3.84: Obesity prevalence attributable to BPA in children, adolescents and adults in 2021

			Males		Females		Total[a]	
Age group (years)	Country	PAF (95 % CI) (%)	Attributable prevalence (95 % CI)	Attributable prevalence per 1,000,000 (95 % CI)	Attributable prevalence (95 % CI)	Attributable prevalence per 1,000,000 (95 % CI)	Attributable prevalence (95 % CI)	Attributable prevalence per 1,000,000 (95 % CI)
		2.7	838	191	491	108	1,329	149
	Austria	(2.2-3.1)	(697-967)	(158-220)	(408-566)	(90-125)	(1,105-1,533)	(124-172)
Children		13.6	39,124	954	24,402	579	63,526	764
(5-9)	Germany	(11.4-15.5)	(32,919-44,671)	(802-1,089)	(20,532-27,862)	(487-661)	(53,451-72,532)	(643-872)
Adolescents		14.8	62,363	1,520	34,239	813	96,602	1,162
(10-19)	Germany	(12.4-16.9)	(52,483-71,191)	(1,279-1,735)	(28,815-39,086)	(684-928)	(81,298-110,277)	(978-1,326)
		16.1	41,910	7,945	32,410	5,972	74,319	6,945
	Czechia	(13.1-18.8)	(34,150-48,836)	(6,474-9,258)	(26,409-37,766)	(4,867-6,959)	(60,560-86,601)	(5,659-8,092)
		16.0	17,934	9,127	11,988	5,836	29,922	7,445
	Croatia	(12.9-18.8)	(14,469-21,084)	(7,364-10,730)	(9,672-14,093)	(4,709-6,862)	(24,140-35,178)	(6,007-8,753)
		8.6	11,613	4,248	11,754	4,198	23,367	4,223
	Finland	(6.9-10.1)	(9,321-13,717)	(3,410-5,017)	(9,434-13,883)	(3,369-4,958)	(18,755-27,600)	(3,389-4,987)
		19.6	191,381	10,454	122,304	6,262	313,685	8,290
	Poland	(16.1-22.7)	(157,096-221,547)	(8,581-12,101)	(100,394-141,583)	(5,140-7,249)	(257,490-363,130)	(6,805-9,596)
Adults		21.1	40,221	8,278	39,751	7,308	79,972	7,766
(20-44)	Portugal	(17.5-24.1)	(33,413-46,083)	(6,877-9,485)	(33,022-45,544)	(6,071-8,373)	(66,434-91,627)	(6,451-8,897)

Notes: [a]Due to rounding effects, there may be small deviations in the total results

Table 3.85: Obesity disease burden in adults from Belgium in 2021 attributable to BPA exposure in 2014

		Males		Females		Total[a]	
Age group	PAF (95 % CI) (%)	Attributable prevalence (95 % CI)	Attributable prevalence per 1,000,000 (95 % CI)	Attributable prevalence (95 % CI)	Attributable prevalence per 1,000,000 (95 % CI)	Attributable prevalence (95 % CI)	Attributable prevalence per 1,000,000 (95 % CI)
45-64	9.2 (7.3-10.9)	30,229 (24,145-35,865)	5,303 (4,236-6,292)	25,546 (20,405-30,309)	4,364 (3,485-5,177)	55,775 (44,550-66,174)	4,827 (3,856-5,727)
≥65	7.2 (5.7-8.5)	14,363 (11,448-17,079)	2,520 (2,008-2,996)	16,374 (13,051-19,470)	2,797 (2,229-3,326)	30,737 (24,499-36,549)	2,660 (2,120-3,163)

Notes: ([a]) Due to rounding effects, there may be small deviations in the total results.

4 Discussion

4.1 Chemical specific discussion

For a better overview of the discussion, we split this section into on the one hand a specific discussion of the single chemicals followed by a more general discussion indicating the potentials and limitations of such estimates and their value for policy making.

4.1.1 Lead

The evaluation of blood lead concentrations in various European populations provides evidence that environmental lead exposure is not yet a problem of the past. In the HBM4EU dashboard, data on blood lead exposure (µg/L) was available for the 5 countries Belgium, Czechia, Slovenia, Norway and Germany covering the following 6 age groups: 3-5 years, 6-11 years, 12-19 years, 20-39 years, 40-59 years, 60 ears and older. Most data covered age groups between 20 and 59 years and data availability were low for children between the ages 3 and 11.

To confirm that the relationship between lead and health implications as causal with certainty, co-exposures with other chemicals, various environmental or socio-economic risk factors, and individual-level differences must be taken into account. However, to provide consistency throughout this report, the interaction with other chemicals has not been included in the estimation of the disease burden. Negative health effects linked to lead concentrations in the blood might have resulted from another chemical exposure or even from a combination of several, leading to an overestimation of the impact of environmental lead. Despite all that, the negative effects of high blood lead concentrations on blood pressure and intellectual development are well established. While high blood pressure may lead to cardiovascular complications in adults, children may suffer from IQ loss which may further result in intellectual disability (Fewtrell et al., 2003; Lanphear et al., 2005). Futher connections between lead exposure and adverse health effects with a less solid evidence base have been found various times. Lead exposure has also been linked to various types of cancer (Menke et al., 2006). As a reaction to these findings, the Panel on Contaminants in the Food Chain (CONTAM Panel) of the European Food Safety Authority (EFSA) developed Benchmark Dose Levels (BMDLs) in 2010 to effectively reduce the lead exposure. Children were expected to be at risk for neurological impairments with blood levels above 5µg/dL and blood lead concentrations exceeding 15µg/dL were considered to negatively affect the systolic blood pressure in adults (European Food Safety Authority, 2010; Moore et al., 2022; Andersen et al., 2022). A re-evaluation based on the results of the German HBM studies GerES III to IV showed that even these reference values were not sufficiently protecting the public health. Limits of 4µg/dL for men and 3µg/dL for women were therefore proposed for adults, and exposure levels of more than 3.5µg/dL were considered to be dangerous for children (Umweltbundesamt, 2019). Recent studies show that even very low blood lead concentrations, such as 2µg/dL in children, may potentially result in disease (Lanphear et al., 2005). Even so, the analyzed HBM4EU data shows that some European countries have a relatively large fraction of the population with higher lead concentrations than the proposed guidelines. The highest levels were identified among the elderly (older than 60 years) in Belgium.

DALYs per 1,000,000 persons were calculated for lead and IQ loss in children, whereby Germany with 953 (95 % CI 122-2,878) annual DALYs in children between 3 and 19 years was the clear front runner. DALYs adjusted per 1,000,000 persons were considerably lower for children in Belgium aged between 12-19 with 42 (95 % CI 4-127) annual DALYs, respectively Czech children between 3 and 11 years old with 185 (95 % CI 22-559) annual DALYs. Related to lead and hypertension, the highest number of YLDs per 1,000,000 persons was found in the Belgian population above 40 years old with 765 (95 % CI 0-

3,128) annual YLDs. Among the people in the age group 20-39 years of Czechia and Slovenia the YLDs only summed up to 26 (95 % CI 0-88). The number of deaths (all-causes) attributable to lead exposure were calculated for Belgium (age: older than 40 years), Czechia (age: 20-59 years) and Slovenia (20-39 years) as a basis for further DALY estimates. The highest disease burden was found in Belgium with a total of 986 (95 % CI 283-1,785) yearly deaths per 1,000,000 persons, whereby 296 (95 % CI 0-691) were cardiovascular-related and 438 (95 % CI 124-802) due to cancer. Noticeably lower numbers were calculated for Czechia with 15 (95 % CI 4-29) annual lead-related deaths per 1,000,000 persons and close to 0 deaths in Slovenia.

It must be noted that data availability between age groups differed depending on the country, leading to an underestimation of the lead burden in countries with unavailable data for certain age groups. Consequently, certain ERFs found in the scientific literature stemming from a specific age group were then applied to different age groups for which blood lead concentrations were available in the HBM4EU database. This discrepancy was particularly evident in the assessment of attributable deaths resulting from lead exposure associated with cardiovascular disease, cancer, and all-cause mortality. While the study presenting RRs focused on adults aged 40 and above, blood lead data in this particular age group was only accessible in Belgium. Conversely, in Czechia the ERF was applied to adults aged 20-59 years and in Slovenia to 20-40 year olds. Furthermore, the association identified between lead levels in the blood of 0-10 year old children and IQ loss was extrapolated to European children up to 19 years old. This extrapolation likely resulted in an overestimation of the disease burden attributed to lead-induced intellectual disability. This limitation necessitates consideration when making cross-country comparisons. While results within identical age groups can be compared well, the total burden of disease of different countries often lack comparability.

Another limitation is the restricted data coverage of blood lead data in Europe, especially in countries from the Southern region. Due to low data availability, the HBM4EU data on lead exposure as measured in the Flemish population of Belgium was extrapolated to the entire country, possibly introducing an error in the estimation of the total Belgian lead burden. To make a more accurate estimate of the total European burden of disease due to environmental lead exposure, more detailed and timely data across all age groups and regions are needed. An overestimation of the disease burden is possible because most of the HBM4EU sampling periods for lead exposure are rather outdated (i.e. 2002-2016) and most likely have been greatly reduced in recent years. Among the adolescent populations (12-19 years), Belgium had the highest reduction of blood lead concentrations compared to Germany and Slovenia between 2003 and 2013. This indicates that blood lead concentrations in the older age groups probably was also reduced which was however not captured due to no additional surveys in more recent years. However, an underestimation may also be likely as it has been shown that neurological disabilities may occur at low blood lead concentrations which may also be the case for other health consequences (Lanphear et al., 2005). Blood concentrations of different age groups showed that lead accumulates in the body, therefore future thresholds should be of dynamic nature to adjust for different population groups.

Blood anemia (hematocrit value below 35 %) was shown to be associated with lead exposure in children. A cross-sectional prevalence study examined lead levels in children living near a lead ore smelter in Kellogg, Idaho, in 1974, and provided evidence for a relationship between lead and anemia (Schwartz, 1988). However, measured blood lead levels of children in the European populations are not high enough to fall into the high-risk categories, which is why no DALY calculations are provided for this health outcome. Other health outcomes may result from lead exposure over a lifetime. However, in the framework of this report, only a few have been selected based on several prioritization criteria as previously described. There is the possibility to include others in the continuation of this work.

4.1.2 PFOS and PFOA

A first estimate of the EBD for exposure to PFOS and PFOA was performed. There were already some studies that did some analysis on the external costs related to PFAS. Goldenman and colleagues calculated the costs for PFOA related hypertension at EU level and in the study of Malits and colleagues costs for low birth weight in the US were estimated (Goldenman et al., 2019; Malits et al., 2018)). A recent publication by Chemsec showed that for external costs (remediation and health costs), these were a factor 615 times higher than the revenues coming from PFAS (CHEMSEC, 2023). Estimates on the burden of disease are currently lacking for PFAS. Exposure to PFAS is linked to several health effects. When the weight of evidence is considered, for hypertension this is low according to ATSDR and EFSA. For effects on birth weight, EFSA mentioned that a causal effect can be possible. The effects on SGA could be confounded by hemodynamics in pregnancy but this consideration can only partly explain the observed associations (Wikström et al., 2020). In this study DALYs were calculated for hypertension, small for gestational age and articipated for lower respiratory tract infections. The latter was considered based on recent findings from the Odense child cohort. It has been shown that PFAS exposure influences the immune system which may possibly result in increased infections but according to EFSA more data are necessary. Based on these preliminary estimates it can be seen that the order of magnitude of the burden falls in the range of risk factors such as lead and dioxins and is higher than the burden for volatile substances like formaldehyde and benzene (based on (Hänninen et al., 2014)). Only a small selection of health effects of PFAS was considered yet which means current estimate is probably an underestimate. For example, for effects of PFAS on kidney cancer, a review is ongoing to assess the weight of evidence. Next to the link with health effects, PFAS are persistent in nature and both aspects should be considered when considering the use of these substances. This calculation shows that already for exposure to PFOS and PFOA only and for a limited amount of disease-outcome pairs (3) the estimate of the environmental burden of disease is not negligible. Seeing that around 4,800 PFAS substances are know, the burden here is an underestimate of the true burden. In a subsequent analysis under PARC more emphasis will be on the burden of disease related to immunosuppression effects caused by PFAS exposure.

4.1.3 Phthalates

We estimated the health impacts of phthalates on population level for up to 14 European countries in 2021. However, we could only estimate the YLDs, as a component of the DALYs, for asthma and diabetes mellitus and attributable prevalent cases for obesity due to several shortcomings regarding data availability and quality. Overall, the level of evidence for a causal relationship between phthalates and many health outcomes is rather uncertain. Thus, the interpretation of the results should be done carefully, as for many studies the effects of co-exposures to other chemicals and further environmental risk factors cannot be ruled out. Phthalates can cause significant changes to the hormone systems of humans, but sometimes the initial effects are subclinical, leading to development of health outcomes later in life and after a long continuous exposure. Not many longitudinal epidemiological studies covering these long-term effects are currently available. These studies and the related ERF are necessary to fully estimate the disease burden for phthalates. Furthermore, in our assessments, fertility effects or reproductive consequences were not considered in the context of phthalate exposure. We are aware that this probably leads to an underestimation of the related burden of disease, especially for the adult population. On the other hand, taking these effects into account might also lead to overestimation. For example, infertility, both in childhood and later in adulthood, does not automatically imply a bodily burden for the person concerned.

In a first step we were able to estimate asthma YLDs for children and adolescents aged 10 to 19 years in 9 European countries in 2021. Our main goal was to use the data gathered by the HBM4EU-project. Despite the incomplete coverage of phthalate data in Europe with many missing countries, also the

choice of the measured metabolites differed largely. Further, the identified systematic reviews of phthalate effects on asthma only provided ERF for a limited set of phthalate metabolites, which not always overlapped with the metabolites captured by the studies included in the HBM exposure dashboard provided by HBM4EU. Not all relevant input data was available for the selected reference year 2021, making several adjustments of the data necessary. This might have led to an over or underestimation of the asthma disease burden due to phthalate exposure in the selected European countries. Also, in some cases the relevant data was not available with the necessary stratification options, which hampered detailed analyses by certain age groups or by sex.

For obesity (BMI equal to or higher than 30kg/m²) we only estimated the share of obesity cases attributable to MCOP exposure in the adult population 20 years of age or older, because no disability weight is available for obesity. Also, because exposure data for adults were not included in the HBM4EU aligned studies, a CF was derived to calculate the adult population exposure from the exposure of children and adolescents. The choice of age group to extrapolate the exposure data (children or adolescents), however, influenced the final results. According to the study by Buser and Colleagues, adults have a lower MCOP burden compared to children or adolescents (Buser et al., 2014). Furthermore, HBM4EU exposure data showed that adolescents have lower concentration levels compared to children. Reasons for this could be that children have, among others, a higher food intake, a larger body surface area to body weight ratio (i.e. more surface area for intake) and a more pronounced mouthing behavior in infancy. Similarly, differences in metabolism may have an influence and also the socioeconomic status or eating behaviors. Consequently, the estimation of adult exposure resulted in lower exposure values if adolescent exposure was used as a basis for the conversion factor. This ultimately also led to lower PAFs or attributable cases compared to when children's exposure was used as the baseline concentration. However, from a toxicological point of view, such an extrapolation of exposure comes with considerable uncertainties, since factors influencing exposure levels are not necessarily constant over the course of a lifetime. In particular, increased phthalate intake through food, dust or products that can be put into the mouth is strongly dependent, among other things, on the respective behavior of the children and their parents. To possibly get a better approximation of a constant CF, further phthalate exposure data from different age groups should be assessed to see if differences between age groups are comparably similar in magnitude. Regarding these limitations, the extrapolated exposure results can certainly only be seen as a rough approximation. Nevertheless, without such an approach, no BoD estimates for adults could otherwise be realized.

The disease burden of diabetes mellitus attributable to DEHP exposure was estimated for women aged 25 years or older in 14 European countries. Again, challenges arose due to the lack of matching input data. For example, Sun and colleagues derived the effect estimate for incident T2DM (Sun et al., 2014). EHIS health data, on the other hand, were only available for prevalent diabetes mellitus (type 1 and 2) cases. However, since T2DM has the higher overall share, the ERF was still used for the EBD calculation. The application of an ERF based on incidence data to prevalent health data is also associated with uncertainties. Yet, there is often no alternative for this approach. This is mainly related to the fact that e.g. in cohort studies only incident events and not prevalent cases are used to model the effects estimates. Lastly, again no HBM4EU exposure data for adults were available and a CF was derived to extrapolate from the exposure of children/adolescents to that of adults. This led to the same effects on the EBD results as already described for the obesity calculations above.

Overall, awareness of the importance of phthalates for public health and the introduction of guidelines or implementation of precautionary measures is growing in European countries and worldwide. To better protect public health though, (Dueñas-Moreno et al., 2023) stress in their risk assessment on phthalates and BPA that guidelines and public policies need to be updated in light of increasing evidence of adverse effects even at low doses. This is supported by several studies that highlight estimated BoD costs for various outcomes related to endocrine disrupting chemical exposure, including phthalates. In the study by Trasande and colleagues, for example, an expert panel identified a 40-69 % probability that DEHP contributes to adult obesity and adult diabetes and further estimated

the associated economic costs in the EU (Trasande et al., 2016). However, there are hardly any other EBD studies that provide quantitative estimates in terms of DALYs on asthma, obesity or diabetes mellitus due to phthalate exposure. One such example is the study by Liu and colleagues who calculated DALYs due to indoor phthalate pollution in China (Liu et al., 2022). According to the results, about 57 % of asthma cases in children aged 0-17 years were due to DEHP exposure. Yet, a comparison with the results of this study is difficult, as the exposure level in Europe is much lower. The highest proportion in the countries analyzed here was about 35 % (see Table 3.52).

4.1.4 Cadmium

This study represents an initial assessment of the disease burden in Europe associated with low-level cadmium exposure. The focus of the analysis was on the relationship between cadmium in blood and chronic kidney diseases, as well as urinary cadmium levels in women above 55 years of age linked to osteoporosis. Data on blood cadmium concentrations (µg/L) were available for the 4 countries Belgium, Czech Republic, Slovenia, and Norway in the HBM4EU dashboard, while female urinary data (µg/g creatinine) were obtained for 10 countries, including Belgium, Czech Republic, Denmark, Germany, Hungary, Poland, Slovakia, Slovenia, Spain, and Sweden. The dataset provided sufficient coverage for adults aged between 20 and 50 years, while only limited data were available for the elderly European population.

Despite efforts to estimate the health impacts of cadmium exposure in selected European countries in 2021, several challenges regarding data availability and quality were encountered. In many cases, the lowest percentiles were labelled with limit of detection (LOD) or limit of quantification (LOQ), which made a proper estimation of the actual population distribution of cadmium difficult. Consequently, assumptions were made to account for these missing values, which may introduce bias into the estimations of the disease burden due to cadmium. Additionally, the estimation of the disease burden related to environmental cadmium exposure in the European population must be interpreted cautiously, considering the time difference between HBM4EU sampling and the present. Environmental cadmium concentrations generally exhibit a declining trend over time, which suggests a potential overestimation of the YLD/DALY estimates. Furthermore, it is important to acknowledge that the evidence for a causal relationship between cadmium exposure and various health outcomes remains uncertain. The possibility of concurrent exposure to other chemicals and environmental risk factors cannot be disregarded, introducing further complexity to the assessment. To make a more accurate estimate of the total European burden of disease due to environmental lead exposure, more detailed and timely data across all age groups and regions are needed.

Related to cadmium and CKD, the highest number of YLDs per 1,000,000 persons was found in the Czech as well as Belgian adult population above 40 years old with more than 90 YLDs per 1,000,000 persons. In total, the YLDs of the two age groups 20-39 years and 40-59 years only summed up to 94 (95 % CI 1-172) per 1,000,000 persons in the Belgian population and was exceeded by the Czech population with total YLDs of 142 (95 % CI 3-409) per 1,000,000 persons. Slovenia was the country with the lowest disease burden with only 0 (95 % CI 0-1) YLDs per 1,000,000 persons among adults aged 20 to 39 years old and were slightly surpassed by the YLD estimates of the Norwegian population between 20 and 59 years with 16 (0-45) YLDs. DALYs per 1,000,000 persons were calculated for cadmium and osteoporosis in women above 55 years, whereby Poland with 2,025 (95 % CI 947-2,763) DALYs in the elderly female population was the clear front runner. DALYs adjusted per 1,000,000 persons were considerably lower for women in Sweden with 183 (95 % CI 86-249) DALYs, Denmark with 437 (95 % CI 204-595) DALYs and Germany with 560 (95 % CI 263-761) DALYs.

4.1.5 Pyrethroids

According to the most recent insights, several authors consider there to be ample evidence for the link between *in utero* exposure to pyrethroids and the onset of neurodevelopmental pathologies later in life, such as ADHD (Andersen et al., 2022; EEA, 2023; Moore et al., 2022).

From a risk assessment perspective, where exposure levels throughout the population are compared to toxicological reference values (based on animal studies), the health risks associated with pyrethroid exposure are considered to be more limited compared to epidemiological studies. Even so, Tarazona and colleagues noted that although no exceedances of risk levels related to pyrethroid-induced toxicity have been observed in the HBM4EU aligned studies, the combined risk to different pyrethroids is below yet close to the acceptability threshold, particularly for children (Tarazona et al., 2022). When the low tier most stringent HBM-GV screening value of 1.7µg/L urine developed by Aylward and colleagues is used for risk assessment, a far greater population is at risk for developing pyrethroid-related illnesses (Aylward et al., 2018).

When findings from epidemiological studies are considered, behavioral dysfunction and ADHD appear to already be developing at exposure levels far below the most stringent HBM-GV value of 1.7µg/L urine (persons older than 6 years). This is shown by several studies including, but not limited to Dalsager and colleagues (increased odds of ADHD observed at maternal body burdens of 0.133µg/L), Lee and colleagues (increased odds of ADHD observed in a population where the maternal 3-PBA GM was 0.65µg/L), and An and colleagues (externalizing behavioral problems observed in a population in which the maternal 3-PBA GM was 1.11µg/L) (Dalsager et al., 2019; Lee et al., 2020; An et al., 2022). Since epidemiological studies indicate the occurrence of neurodevelopmental problems at exposure levels commonly encountered by most European populations and given the mechanistic evidence provided by AOPs and toxicological evidence for behavioral changes provided by animal studies, it is sensible to quantify the associated burden of disease. In this report, the burden of disease of ADHD related to pyrethroid-exposure was estimated for France, Iceland, Switzerland, Germany, and Israel. These countries were the only ones that measured urinary 3-PBA concentrations in adults during the aligned studies under HBM4EU. Countries that only measured urinary 3-PBA in children were not included given that the strongest evidence for ADHD-development is linked to *in utero* exposure to pyrethroids, therefore, adult biomarker concentrations are preferred. Also of note, is that only children and adolescents aged 0-19 years were included in the burden of disease calculation given that the dose-effect association (OR of 1.13, 95 % CI: 1.04, 1.38) used in this report was also derived for children overlapping with that age group (Dalsager et al., 2019). The burden of disease was estimated for France, Iceland, Switzerland, Germany, and Israel. The average pyrethroid-related ADHD disease burden for these countries is estimated to be 19 prevalence-based DALYs per 1,000,000 persons for children and adolescents aged 0-19 years for the year 2021. Additionally, it was estimated that an average of 18.3 % of all ADHD cases in these countries are caused by pyrethroid exposure. This number is similar to estimates of exposure to organophosates and ADHD (Bellanger et al., 2015).

4.1.6 Bisphenol A

The widespread use of BPA in Europe resulted in exposures of the European population in all age groups well above the guideline values. Also, BPA intakes are generally higher than the recommendations for the TDI. This clearly emphasizes the potential risk of BPA to human health. Accordingly, (Dueñas-Moreno et al., 2023) underline in their risk assessment of phthalates and BPA the importance of updating current guidance and public policies. However, the epidemiological evidence for many of the associations with health outcomes is still considered rather suggestive, including for example obesity in children and adults. Quantitative EBD estimates for obesity due to BPA exposure therefore need to be interpreted with caution.

In the course of our EBD assessments for Europe, data availability was identified as one major stumbling block. On the one hand, urinary BPA exposure data in the HBM4EU-dashboard was very patchy. There were not many studies with suitable data for the reference year 2021, so we included exposure data from 5 years before 2021 until present as an approximation. Still, the data was limited to a few age groups. Basically, there is little data available on children and adolescents. Regarding adults, only 20-39 year-olds were studied during this period. This means that we could not make any statements about the share of obesity in older people that is associated with urinary BPA exposure. This was only possible in a scenario analysis with exposure data from Belgium dating back to 2014. Furthermore, suitable exposure data was only available for 9 European countries (Austria, Germany, Czechia, Croatia, Finland, Israel, Poland, Portugal and Switzerland). However, data on obesity prevalence was not available for two of these countries (Israel and Switzerland). Therefore, the main analyses were limited to 7 countries. This hampers European-wide comparisons and calls for more recent and comprehensive data on the exposure of populations towards BPA as well as on health data. For more spatially and temporally comprehensive EBD estimates, the development of data gap filling methods would be of great interest. A first rough approximation could be to transfer exposure data and prevalence rates to neighboring countries with missing data. Yet, such an approach would ignore the fact that BPA exposure depends to a considerable extent on the diet, which differs between neighboring countries. Here, also other covariates would need to be considered to correct for country specific characteristics.

Regarding the EBD analyses for the 7 countries considered, results were difficult to compare. The PAF or the attributable prevalence for children were only modelled for 1 country, for adolescents only for two countries and for adults for 5 other countries. In addition, with respect to the studies analyzing the association between exposure and health effects, not all studies used the same definition of obesity. Some used the definition as proposed by the WHO, while others used the one from CDC, which allowed only a limited pooling of the effect estimates. In some cases, also overweight was included in the class of obesity which in turn can lead to an overestimate of the effect measure. When comparing the results of the main analysis with the scenario analysis, it became apparent that a lower PAF and attributable prevalence values were estimated for older adults (45 years of age or older) from Belgium than for younger adults (aged 20-44 years). It is conceivable that the age difference is an influencing factor here. However, since the exposure data for Belgium from 2014 were somewhat older, it could have been assumed that the BPA exposure was higher at that time, leading to a higher disease burden. Though, urinary BPA data from Belgium did not show this. Yet, differences in exposure may also be due to different sampling conditions.

To our knowledge, there are hardly any other calculations of the BPA-related EBD related to obesity for Europe. In Germany, a corresponding study was conducted on children and adolescents. According to this study, in 2016 about 28 % of obesity cases in children and adolescents aged 7-17 years were due to BPA exposure (Plaß et al., in press). This value appears very high as it is about twice as high as the results modelled in this analysis for Germany (see Table 3.84). A study by Trasande and colleagues estimated the costs associated with BoD from the exposure to endocrine disrupting chemicals such as BPA for the EU, also considering childhood obesity (Trasande et al., 2016). However, other classical BoD indicators were not provided by the authors. Furthermore, no comparable results are known for adults. It was therefore hardly possible to evaluate our results on BPA-related PAF and attributable prevalent cases.

Other limitations of this study were that only BPA was investigated and no other substitutes such as BPS or BPF, which are also identified as endocrine disruptors (Chen et al., 2016b; Mustieles et al., 2020; Rochester and Bolden, 2015) and might be associated with similar health effects. Further, only obesity was studied. Therefore, the disease burden identified in the current study is probably underestimated.

4.2 Overall discussion of the strengths and limitations

The general value of burden of disease estimates has already been shown in numerous studies. For environmental risk factors air pollutants remain the most studied risk factors which also resulted in a large number of existing EBD assessments. Just recently, burden of disease estimates were part of the documents that accompanied the draft of the updated air quality directive and will help guiding environmental policy making.

For chemicals, which have been identified as a potential major threat to population health, the evidence for the association between the exposure and the health effect is much lower as compared to the one found in air pollution research. Nonetheless, the evidence for their harmful effects was shown by toxicological and increasingly also by epidemiological studies. Our assessment of the environmental burden of disease summarized the currently available evidence on 6 selected chemicals and estimated for countries where relevant HBM data was available the population health impact. We were able to use the HBM data gathered in the HBM4EU-project that allowed us to have a highly standardized data source for the exposure. Such HBM data are of great value, because with increasing availability and quality, more comprehensive EBD studies for a bigger set of countries can be performed. Currently our estimates only include a smaller set of countries, because the relevant HBM data is not available for all countries in Europe or, at least in many cases not for recent years. But no data should not be misinterpreted as no burden. It is simply that in our case we were not able to properly assess the exposure.

The countries included in the assessment can use the results to see the impact of the chemicals on population health to highlight the relevance of these chemicals for health. Countries that lack such HBM data should invest in gathering data to be able to shed light on the effects of chemicals in their countries. A further increase of the HBM data availability and the further use of standards introduced in the HBM4EU-project would foster EBD analysis and help to achieve a comprehensive and comparable overview of the population health impact of chemicals in Europe. EBD analyses provide an added value to HBM data because they not only focus on the exposure and probable exceedances of e.g. HBM-GVs but allow to estimate the quantitative impact of chemicals on health. Such estimates can support and guide policy decision making processes. Further, EBD analyses can also form the basis for health impact assessments, providing pathways of how the disease burden might develop in case prevention or intervention measures to reduce chemical exposure are introduced. Such analyses are fundamental to show how policy measures can protect populations from adverse health effects resulting from chemical exposure. At the currents stage our estimates only present a fragmented picture of the burden of disease and the comparability, which is generally the strength of EBD analyses is limited. This results from the challenge that for the chemicals selected in our analyses the HBM data gathered in the HBM4EU-project was only available for a small group of countries or only for single reference years, which were additionally outdated. Further, sometimes only specific age groups or only male or female populations were covered due to limitations of the underlying studies. Here, sometimes only the vulnerable groups, such as children, pregnant women or older populations were covered. Such samples are not representative for the overall population and thus hamper the estimation of the EBD for the country. This is one of the factors that reduces the comparability of our estimates. Nonetheless, the results show the relevance of the chemicals for the countries, but they do not allow to formulate general conclusions for Europe.

ERFs play a critical role in the assessment of the EBD. In the best case such a parameter is based on an evaluated summary of the evidence. For many chemicals, summaries of especially epidemiological assessment are not available. In our assessments, the exposure-response functions are not based on the same level of evidence, which hampers the general comparison. In some cases we were able to rely on available systematic reviews, where else in other cases only single studies reporting the associations between exposure and outcome were used due to limited availability of epidemiological studies. However, this is also often the case in others assessments, such as GBD. Even though, the

results of this global comparative risk assessment are presented in a comparative picture, the level of evidence for the risk factor-outcome combinations also differs. In this case it is necessary to clearly state on the one hand the sources used for the exposure-response-functions and on the other hand to highlight that there is a considerable level of uncertainty when interpreting the results. The alternative would be to leave out risk-outcome-pairs with more limited evidence, which in turn could result in an underestimation of the population health impact.

Our aim was to consider the comprehensive impact of chemicals on population health. However, burden of disease studies are only able to capture the impact of manifested diseases, for which a disability weight is available. Chemicals have been shown to interact with bodily systems and, for example, disturb the correct functioning of endocrine processes. Such processes which were clearly documented for phthalates of bisphenol A in toxicological studies do not necessarily lead to acute or short-term health impacts that can be clinically confirmed and diagnosed. Such effects can however initiate processes that may result in diseases at a later stage of life. Here, especially longitudinal environmental epidemiological studies need to be used to identify the associations between e.g. early age exposure to chemicals and health effects over the life course.

Despite the uncertainty in our results introduced by various sources we were able to show that the 6 chemicals /chemical groups resulted in a considerable burden which could be avoided by introducing adequate reduction measures. In addition to the impact of chemicals measured by mortality and morbidity effects, other assessments have shown that also a non-negligible monetary impact is associated with the exposure to chemicals. Here, especially conditions such as IQ loss, which might not have a profound impact on physical health can reduce the overall economic achievements of individuals and societies.

5 Conclusions

We presented a series of case studies estimating the disease burden attributable to a selected set of 6 chemicals or chemicals groups for different European countries (including some non-EU countries which participated in the HBM4EU-project) for the reference year 2021. The general prerequisite, and also mandate from the EEA, was to use wherever possible the human biomonitoring data gathered within the HBM4EU-project. Within the task we opted to find the best approaches and most suitable input data to estimate the disease burden. We used the top-down approach knowing its strengths and limitations. The HBM4EU-project led to an increase of the availability and quality of human biomonitoring data in Europe. However, the coverage with regard to countries, sex and age groups was still not complete and did not allow a full range of European estimates. Therefore, sustainable HBM campaigns covering the whole EU are needed. This is also the reason, why an overall comparison of EBD results is not justifiable at the current stage of the estimates. Simply adding up the chemical specific estimates for the countries would lead to skewed interpretations because mostly not the same amount of risk-outcome-pairs are considered. However, we clearly highlighted with the case studies that the EBD approach is generally applicable to chemicals and HBM data, where available, is valuable source for the assessment of exposure. Nonetheless, for a full set of European estimates the baseline data on HBM need to be improved. The golden standard would be to have similar HBM campaigns in all EU countries, comparable to the US NHANES model covering the US States. Until results from such studies are not available for Europe adequate gap filling techniques should be considered and evaluated to overcome the patchy structure of the currently available data sets. Also, where possible, more harmonization between environmental disease burden estimates is necessary.

The presented analyses are a first step towards a comprehensive and comparable assessment of the disease burden attributable to chemicals in Europe. Generally, the experience from the 6 case-studies supported the feasibility to use HBM data for the assessment of the population exposure in EBD

studies. Nonetheless, we have also experienced that for many countries, years and age groups data was missing. With this is mind the next steps of our assessment will be to identify and evaluate techniques that will help us to fill the gaps in relevant input data which hopefully will allow to expand the number of countries considered. This lack of data identified for many countries should in addition also be seen as a spark for these countries to initiate HBM studies, because besides the general value of HBM data the co-benefit would be to be able to perform EBD assessments generating policy relevant indicators that can support policy actions to improve population health and further strive to meet the EU's zero pollution ambition.

List of abbreviations

Abbreviation	Name
µg	Microgram, 1E-6 grams
AC	Attributable cases
AD	Attributable deaths
ADHD	Attention deficit hyperactivity disorder
ADI	Acceptable daily intake
AF	Attributable fraction
AOP	Adverse outcome pathway
ASD	Autism-spectrum disorder
ATSDR	Agency for Toxic Substances and Disease Registry
BMI	Body mass index
BMD	Bone mineral density
BMDL	Benchmark dose levels
BoD	Burden of disease
BPA	Bisphenol A
CBCL	Child behavior checklist
Cd	Cadmium
CDC	Center for Disease Control and Prevention
CF	Conversion factor
CKD	Chronic kidney disease
CNS	Central nervous systems
CONTAM	The Panel on Contaminants in the Food Chain
CRA	Comparative risk assessment
CVD	Cardiovascular disease
DALY	Disability-adjusted life year
DEHP	Di(2-ethylhexyl) phthalate
DW	Disability weight
DNA	Deoxyribonucleic acid
EBD	Environmental burden of disease
EEA	European Environment Agency
ECHA	European Chemical Agency
EFSA	European Food Safety Authority
EHIS	European Health Interview Survey
EMR	Excess mortality rate
ETC-HE	European Topic Centre on Human Health and the Environment
EU	European Union
FLEHS	Flemish Environment and Health Study
GBD	Global burden of disease

Abbreviation	Name
GHO	Global Health Observatory data repository
GM	Geometric mean
GSH	Glutathione
HBM	Human biomonitoring
HBM4EU	The European Human Biomonitoring Initiative
HCB	Hexachlorobenzene
HMW	High molecular weight
HR	Hazard ratio
IARC	International Agency for Research on Cancerr
ID	Intellectual Disability
IHME	Institute for Health Metrics and Evaluation
IQ	Intelligence quotient
IQR	Inter quartile range
L	Liter
LMW	Low molecular weight
ln	Natural logarithm
LOD	Level of detection
LOQ	Level of quantification
LRTI	Lower Respiratory Tract Infection
MCOP	Mono-(carboxy-isooctyl) phthalate
MCPP	Mono(3-carboxypropyl) phthalate
MECPP	Mono(2-ethyl-5-carboxypentyl) phthalate
MEHHP	Mono(2-ethyl-5-hydroxyhexyl) phthalate
MEHP	Mono(2-ethylhexyl) phthalate
MEOHP	Mono(2-ethyl-5-oxohexyl) phthalate
MiBP	Mono-isobutyl phthalate
MID	Mild intellectual disability
MMP	Mono-methyl phthalate
MMR	Mild mental retardation
MnBP	Mono-n-butyl phthalate
MoA	Mode of action
MR	Mortality rate
n	Number
ng	nanogram
NHANES	National Health and Nutrition Examination Survey
OR	Odds ratio
P	Percentile

Abbreviation	Name
PBPK	Physiologically based pharmacokinetic modelling
PCB	Polychlorinated biphenyls
PAF	Population attributable fraction
PPARγ	Peroxisome proliferator- activated receptor gamma protein
PARC	Partnership for the Assessment of Risks from Chemicals
Pb	Lead
PFAS	Per- and polyfluoroalkyl substances
PFOA	Perfluorooctanoic acid
PFNA	Perfluorononanoic acid
PFHxS	Perfluorohexanesulfonic acid
PNS	Peripheral nervous systems
PTE	Placental transfer efficiency
QA/QC	Quality assurance/Quality control
ROS	Reactive Oxygen Species
RR	Relative risk
SGA	Small for gestational age
TDI	Tolerable daily intake
TWI	Tolerable weekly intake
US	United States
US EPA	U. S. Environmental Protection Agency
WHO	Worl Health Organization
WoE	Weight of evidence
YLD	Years lived with disability
YLL	Years of life lost due to death

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Annex 1 Evidence overview for the health effects associated with the selected chemicals

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

The document is attached as separate PDF file available together with this report.

Annex 2 Burden of disease calculations

Annex A2.1: Burden of disease due to lead
The calculations are attached as separate excel file available together with this report.

Annex A2.2: Burden of disease due to PFAS
The calculations are attached as separate excel file available together with this report.

Annex A2.3: Burden of disease due to phthalates-asthma (adolescents)
The calculations are attached as separate excel file available together with this report.

Annex A2.4: Burden of disease due to phthalates-obesity (adults_c)
The calculations are attached as separate excel file available together with this report.

Annex A2.5: Burden of disease due to phthalates-obesity (adults_a)
The calculations are attached as separate excel file available together with this report.

Annex A2.6: Burden of disease due to phthalates-diabetes (women_c)
The calculations are attached as separate excel file available together with this report.

Annex A2.7: Burden of disease due to phthalates-diabetes (women_a)
The calculations are attached as separate excel file available together with this report.

Annex A2.8: Burden of disease due to cadmium
The calculations are attached as separate excel file available together with this report.

Annex A2.9: Burden of disease due to pyrethroids
The calculations are attached as separate excel file available together with this report.

Annex A2.10: Burden of disease due to bisphenol A-obesity (children)
The calculations are attached as separate excel file available together with this report.

Annex A2.11: Burden of disease due to bisphenol A-obesity (adolescents)
The calculations are attached as separate excel file available together with this report.

Annex A2.12: Burden of disease due to bisphenol A-obesity (adults_1)
The calculations are attached as separate excel file available together with this report.

Annex A2.13: Burden of disease due to bisphenol A-obesity (adults_2)
The calculations are attached as separate excel file available together with this report.

Annex A2.14: Burden of disease due to bisphenol A-obesity (adults_scenario)
The calculations are attached as separate excel file available together with this report.

Annex 3 Summary burden of disease results

Annex A3.1: Summary burden of disease results table

The Table is attached as separate excel file available together with this report.

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