The value of human toxicity

An explorative research for use in environmental prices

CE Delft

Committed to the Environment

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Content

Summary

Due to the increasing scale of production and consumption of hazardous chemicals since the 1950s, chemical pollution has evolved into a serious global health issue effecting hundreds of millions of people worldwide. The European Union has imposed regulations, such as REACH, which effectively addresses the issue of hazardous chemical emissions upon market access. However, despite these positive steps, substantial knowledge gaps still exist about the impact on human and environmental health as current knowledge is primarily limited about the disease risk of widely used chemicals. Therefore, the real cost of environmental pollution is hidden which hampers the possibility to frame economic arguments for the widespread control of chemical emissions.

Environmental prices, developed by CE Delft, have been used widespread to monetize and evaluate environmental risks to human health, ecosystems and buildings/materials from using certain materials or products. However, the human toxicity element is recognized as a particular area of great uncertainty in the construction of environmental prices. For the majority of the chemicals, the impacts to human health are not known precisely while the real impacts could be immense. The available figures are believed to be highly underestimated as the assessments have only considered chemicals with well characterized causal relationship and omit numerous hazardous substances due to the unavailability of human exposure data. Moreover, present figures neglect additional important subclinical dysfunctions where the health effects are more difficult to quantify.

Nevertheless, estimating the cost of disease burden from using chemicals can be a useful tool to support the formulation of public health strategies and environmental policies. This report therefore aims to develop a consistent framework based on epidemiological literature for valuation of impacts of chemical emissions on human toxicity. From the here applied methodology, it is possible to calculate human health damage costs from toxic substances, both for individual substances and for LCA-midpoint indicators. Nevertheless, epidemiological data still remains limited and exists only for a small proportion of potentially hazardous substances available on the market.

We focused in our study on epidemiological evidence in nine chemicals, (mercury, cadmium, chromium, arsenic, benzo[a]pyrene, bisphenol A, dibutyl phthalate, Chlorpyrifos and Glyphosate) which have been used in high quantities in the EU, their hazardous effects are well-know and these compounds have significant literature regarding their toxicity. We used relative risk from available epidemiological literature to calculate the population attributable fraction and estimate the disease burden of these nine chemicals in the EU28 and in the Netherlands. As a final step we derived unit cost for the eight compounds for the Netherlands and in the case of Chlorpyrifos for the US. We also combined our results with other valuation studies where different diseases were identified. Based these results, the unit costs were calculated to be the following: € 38,000-244,000/kg for mercury, € 168,500-207,000/kg for cadmium, € 297/kg for all chromium, € 208,000/kg for chromium (VI), € 867-938/kg for arsenic, € 15,460/kg for benzo[a]pyrene, € 822-46,000/kg for bisphenol A, € 80,500-107,000/kg for dibutyl phthalate, € 950-35,500/kg for Chlorpyrifos and € 0-2,160/kg for Glyphosate. On top of these result, we further calculated the unit cost for emission to different compartments and compared our results to USEtox comparative CTUhs.

Our approach can facilitate and open new avenues to a more rapid valuation of chemicals even in the case when limited epidemiological data is available. However, the method employed contains important uncertainties. The main impediment to our study results is that in many cases it is difficult to determine the correlation between exposure and disease and that it is difficult to derive from our method unit damage costs as these critically depend on the estimated emissions.

1 Introduction

1.1 Background

To date, pollution in its many forms is the largest environmental cause of disease and the main contributor to premature deaths worldwide. In 2012, environmental risks were responsible for 12.6 million deaths globally, which corresponded to the 23% of total death burden (Landrigan et al., 2018). The accountable proportion of deaths from pollution was even higher for children under five (26%) which highlights the vulnerability to environmental risk factors at young age (Prüss-Ustün et al., 2017). In the European Union approximately 13% of all deaths are accounted for environmental causes, and the highest proportion of deaths occur as a consequence of pollution (EEA, 2020). Environmental pollution also has negative implications on countries' economy as pollution related diseases contribute to a productivity loss of approximately 2% of global GDP and are responsible for up to 7% of total health expenditures (Landrigan et al., 2018). On top of this, welfare losses were estimated to be as high as $ 4.6 trillion per year corresponding to 6.2% of global economic output (Landrigan & Fuller, 2018).

The WHO (2013) has developed guidelines on how to monetize health costs of air pollution to consider in Cost-Benefit Analysis (CBA). This relates to the commonly known impacts from particulate matter, ozone and NO_2 pollution. However, so far chemical pollution has not been included in the WHO cost-benefit frameworks while it has evolved into a serious global issue in the last decades. Industrial chemical production and consumption are at a constant rise which most likely has led to elevated chemical pollution and associated human exposure levels globally. This is not only a story about the sheer scale of production and consumption. Since the 1950s, approximately 140,000 new chemicals and pesticides have been introduced and about 5,000 of them are widely used globally and have dispersed throughout the planet, while less than half of them went under appropriate toxicity and safety testing (Landrigan & Goldman, 2011). Many of these compounds are toxic, nevertheless their hazardous effects on humans have only been recognized after excessive use. This practice even continued with newer synthetic chemicals being introduced without proper safety evaluation until the last 15 years when stricter evaluation practices were introduced (Landrigan et al., 2018). In numerous cases identified hazardous chemicals have been removed from the market and replaced by new substances with similar chemical makeup without assessed toxicological profile just to be identified later with similar toxic effects (EEA, 2020).

In 2018, 314 million tonnes of chemicals were consumed in the European Union and over 70% of these chemicals have potentially hazardous health effects (Eurostat, 2020).[1] Moreover, many low- and middle-income countries are taking the lead in chemical manufacturing, processing and use nowadays but their health care and chemical monitoring systems are not prepared to handle the environmental and health burden of high levels of chemical emissions (Grandjean & Bellanger, 2017). In hand with emerging chemical production the export of chemical waste to low-income countries is constantly increasing. In the case of chemical exposure and other environmental risks the marginalized

[1] Noteworthy, that statistics only include substances which are used in high quantities and many pharmaceuticals and pesticides are not counted in these datasets (EEA, 2020).

communities are more prone to be affected and the highest burden already falls on the vulnerable Sub-Saharan African region (Prüss-Ustün et al., 2017).
This is in contrast with the situation in developed economies. Many developed countries have made solid progress in mapping industrial contamination, remediating hazardous waste sites and introducing stricter safety measures. Novel technologies such as satellite imaging allow us to map pollution levels and identify the main pollution sources. In addition, multi-year epidemiological studies provide further information and advances to identify long-term toxic effects of widely used chemical compounds (Landrigan et a., 2018; EEA, 2020). However, despite these positive steps, informational gaps still exist about the pollution's effect on human and environmental health and there is lack of knowledge about the human toxicity of widely used chemicals with scarce information about their exposure-response function and long-term impacts which could help to estimate disease risks. The real cost of pollution thus is hidden which hampers the possibility to frame economic arguments for the widespread control of chemical emissions (EEA, 2020).

1.2 Objective and delineation

CE Delft has published Environmental Prices Handbooks in 2017 and 2018 for the Netherlands and the EU28, respectively.[2] Within these handbooks, unit damage costs have been calculated for over 2,500 substances for emissions to air, water and soil. Damage costs have been calculated from impacts on the end-points of human health, ecosystems and man-made capital. These handbooks have been frequently used in Cost-Benefit Analysis (CBA), Life Cycle Assessment (LCA) (to derive a single score) and corporate social reporting.
CE Delft's Environmental Prices Handbooks are updated every 5-7 years to take into account new scientific developments and improvements in methods. Currently, human toxicity is recognized as a particular area of great uncertainty in the valuation of the Environmental Prices Handbook. The present study aims to improve the valuation of toxicity to take into account of future updates of the Environmental Prices Handbook. **The study aims to explore frameworks from which a valuation of the impact of emissions on human toxicity can be derived by calculating human health damage costs from toxic substances and express them as unit damage costs (cost per kg emission).** The present study only considers the human health impact from various chemicals. Eventually eco-toxicological impacts have not been addressed in this report – such could be subject of future analysis.

The study considers emissions from toxic substances to the environment. Our study does not explicitly address occupational hazards, like working with certain substances in a closed environment.[3] Intake fractions by humans from occupational hazards can be several hundred times higher than from pollution in the environment. Results from this study therefore should not apply to occupational hazards and cannot be used for that purpose.

[2] Environmental prices are prices for the social cost of pollution, expressed in Euros per kilogram pollutant. Environmental prices indicate the loss of economic welfare that occurs when one additional kilogram of the pollutant finds its way into the environment.

[3] In some cases we derived a value for environmental pollution from studies dealing with occupational hazards.

1.3 Human toxicity in the Environmental Prices Handbook

The Environmental Prices Handbook combines characterization models, impact pathway models and economic valuation methods to acquire a more precise estimate of external costs of emission both at midpoint and endpoint levels. These models identify physicochemical relationship of emissions and environmental themes, dispersion and concentration of pollutants and the health impacts at endpoint level which appears as the real cost (NEEDS, 2008; Goedkoop, et al., 2013).
For human toxicity, the environmental handbook considered four different approaches (based on toxicological models) and concluded that they differ fundamentally in assumptions and outcomes. It was decided to calculate unit damage costs from each of these four approaches for four emissions to air from four substances (mercury, cadmium, arsenic and lead) using the endpoint valuation developed in the handbook, and added IQ losses from Nedellec & Rabl (2016), valued at € 17,500/IQ point, to these estimates.[4]
A midpoint toxicity indicator as valued using the average value of these four substances, expressed as € per kg 1,4DB-equivalent and weight them by the emissions in the Netherlands.[5] The value of dioxins was based on NEEDS (2008).

This gave the following results for valuation:

Table 1 - Unit damage costs in the Environmental Prices Handbook for the EU28 in €$_{2015}$/kg emission to air and the midpoint indicator

Substance/indicator	Lower	Central	Upper
Cadmium	€ 371	€ 589	€ 869
Arsenic	€ 586	€ 862	€ 963
Lead	€ 3,631	€ 5,367	€ 5,761
Mercury	€ 24,680	€ 34,490	€ 52,920
Dioxin	€ 49,450,000	€ 67,650,000	€ 104,500,000
Midpoint: 1,4 DB-equivalent		€ 0.158	

Using the midpoint indicator with the ReCiPe (2009) characterisation factors, an individual estimate can be derived of the relative valuation of an individual substance.[6]

1.4 Reading guide

In Chapter 2 we distinguish various valuation frameworks that could be used to put a value on human toxicity. We also discuss limitation of the current GBD and WHO frameworks to estimate total disease burden. In this chapter we also explain the basic economics principles behind environmental pricing. In end of the chapter, we introduce current LCA models focusing on the aspects of human toxicity and the USEtox model.

4 Only IQ losses to arsenic, lead and mercury were included in the analysis.

5 As characterisation factor, ReCIPe (2009) was used with in the lower estimate the individualistic perspective, the hierarchistic perspective in the upper estimate and the average of the individualistic and hierarchistic perspectives in the central estimate.

6 The reader should be aware that in order to derive an indicator of external costs, one would use the individualistic perspective in ReCiPe. In order to derive a weighting factor, one would use the hierarchistic perspective in ReCiPe. For more information, see CE Delft (2018).

In Chapter 3, we introduce the nine chemicals included in the report, their general characteristics, emissions, environmental fate and human exposure. After we go into details regarding their toxicity and review the epidemiological literature. In the end of the sections the valuation literature is summarized regarding each substance.

In Chapter 4, we present the general framework used in current report, describe the methodology and the calculation methods applied. We also explain how we calculated the damage costs for specific substances. At the end of the chapter the main finding regarding total damage cost in the EU28 are presented.

In Chapter 5, as a continuation of Chapter 4, the methodology behind deriving unit costs is described, and the results are presented for the Netherlands. In this chapter our results are compared to other results from the valuation literature and to toxicity potential used in LCA models. The potential utility of the study in LCA or BCA is discussed and at the end of the section we also highlight potential the limitations of our calculations.

1.5 Acknowledgement

This report is produced as part of an internship at CE Delft that lasted from October 2020 to March 2021. Parts of this research have fed into the project 'Milieuprijzen afval' (Environmental prices for waste) that CE Delft will publish in the second half of 2021.

2 Valuation frameworks

2.1 Introduction

In this chapter we will describe the existing valuation frameworks that can be used to derive at a value of toxic substances. In Paragraph 2.2 we explore the general framework of the impact-pathway analysis that has been used frequently in valuation of the effects of pollution. Then in Paragraph 2.3 we describe the methods that valued the total global burden of disease from toxic compounds. Finally, in Paragraph 2.4 we discuss the LCA models and methods that in the future could be used to establish a value framework for estimating the costs of toxic substances.

2.2 General framework

The impact pathway framework is a general framework through which the emissions can be valued. Impact pathway models describe the relationships between emissions and human health impacts, by mapping environmental dispersion of emissions and the impacts of the resulting concentrations on humans. These impacts can subsequently be valued to derive a unit damage cost estimate from the emission of one pollutant. An extensive elaboration of the impact pathway framework in the context of valuing emissions can be found in the Environmental Prices Handbook by CE Delft (2017).

The impact pathway approach (IPA) in the context of valuation consists of three building blocks:

1. **Dispersion of pollutants** and human exposure that describe the pathway of emissions through the various environmental media and determine the relationship between emissions in one compartment to concentrations in another compartment.
2. **Exposure-response functions (ERFs)** describe the impact that a certain concentration of pollution, or the intake of a pollutant, has on human health. For each health impact and for each exposure compartment a different exposure-response function can be established.
3. **Valuation frameworks** value these health impacts. The valuation framework is mostly rooted in welfare economics in which both financial expenses (e.g., medical expenses), monetary impacts (e.g., working days loss) and non-monetary welfare losses (e.g., reduced life expectancy or disability) are calculated and included to derive an overall estimate of the welfare loss of a certain impact.

Dispersion of pollutants and human exposure

Toxic chemicals can disperse in the environment via various routes contaminating air, soil and water. Hazardous chemicals can sometimes be found concentrated on certain contaminated sites which are dangerous to both the environment and human health. Chemical exposure can also occur due to occupational activities or releases at the product's end stage as waste. These substances can be inhaled from the air or ingested through food or water (Hauschild, 2018). Occupational exposure is a noteworthy contributor to the global burden of disease and responsible for a high proportion of cancer cases worldwide (WHO, 2016; Landrigan et al., 2018). Chemicals enter the body via ingestion, inhalation or dermal absorption and can be passed via the umbilical cord to the unborn child or via breast milk to

new-borns (WHO, 2016). Water is an important compartment for chemical agents as industrial activity pollutes the drinking water and treatment cannot remove all toxic compounds from this medium. Air pollution is another leading factor to human toxicity. Particulate matter is formed from the mixture of water droplets, dust and various chemical substances including volatilized pesticides (WHO, 2016). Soil can be an important source for dietary exposure, as plants and animals take up the chemicals and accumulate it in different tissues in the body. After release, chemicals degrade to various metabolites which are very important causes of the toxic effects (EEA, 2020).

Exposure-response functions

Exposure-response functions attempt to measure the correlation between exposure to specific pollutants and potential health impacts (UN et al., 2005). The ERFs, or with another name, dose-response functions (DRFs) are widely used in health impact assessments (Nedellec & Rabl, 2016). ERFs can be used to estimate the damage costs per year due to exposure to various pollutants. The established relationship shows to what extent the pollution affects human and environmental health. Ideally the functions rely on epidemiological studies, but in most cases only toxicological data is available. The function has various characteristics such as linearity/non-linearity, and threshold/no-threshold effects (UN et al., 2005). The methodology generally differentiates between cancer and non-cancer endpoints. The carcinogenic potential is assumed to be linear without actual threshold effect, while for non-carcinogens usually a threshold is applied. Due to this, when exposure is above this threshold, the actual effects are difficult to quantify. With non-cancer cases usually LOAEL (lowest observed adverse effect level) or NOAEL (no observed adverse effect level) is used as threshold value. Many studies suggest non-linearity between exposure and effects; however, especially for cancer cases linearity is assumed for ERFs, which makes it independent of the background concentration and facilitates the calculation process (Rabl et al., 2014). Recently, non-cancer effect specific ERFs were created mainly relying on epidemiological studies, instead of on toxicological studies, which more realistically estimates the impacts. The ERFs can be constructed from the relative risk (RR) based on the following equation:

$$\mathrm{sERF} = \text{incidence rate} * \Delta\mathrm{RR} * \Delta\mathrm{E}$$

where ΔRR = RR− 1 and ΔE is the change in exposure (Nedellec & Rabl, 2016). The sERF is the slope factor of the function estimated from an epidemiological or toxicological study. It is mostly derived from a linearized model and expressed in units of mg intake/kg body mass/day (Rabl et al., 2014). Increase in RR and in exposure are expressed in the unit of (cases/year)/(mg/year). Within the model the timeframe is difficult to establish, and usually stationary conditions are assumed with 70 years of life-long exposure. For the ERFs, in the case of biomarker detection further extrapolation is necessary to estimate the real exposure level. The ERFs are essential elements of the impact pathway approach wherein the impact is quantified based on these functions (see above). The IRIS database is an important source to derive ERFs. Despite this, for many substances the slope factor is not yet determined and for non-cancer effects it is more challenging to define it as the estimated thresholds are rarely precise. The ER functions exist for various endpoints both for mortality and morbidity (Rabl et al., 2014). In the case of health risk calculations, there is high variability in ERFs, in the calculated unit risk factors and the oral slope factor for cancer outcomes, which increases the uncertainty of the results (EEA, 2021).

Valuation through the global burden of disease framework

According to the WHO's assessment, in 2016, the health impact of chemicals was estimated to be responsible for 2.7% of the total disease burden and 1.7% of total deaths globally (WHO, 2018). Despite the vast health burden, the figures are believed to be highly underestimated as the assessment only considers well characterized chemicals and omits numerous hazardous substances due to the unavailability of human exposure data. The Global Burden of Disease studies (GBD) provide comprehensive and comparative risk assessment and quantification of risk factors that increase human mortality and morbidity. The GBD utilizes the metric of Disability-Adjusted Life Year (DALY), which provides a universal comparison of diseases, encompassing changes in life duration and quality (GBD, 2015). According to the GBD estimates, the environmental burden of disease (BoD) adds up to 5.18% of total DALY cases globally. However, like the WHO estimates, this value is also underestimated as it only reflects the impact of pollutants with well characterized causal relationships and it neglects additional important subclinical dysfunctions where the health effects are not quantifiable (Grandjean & Bellanger, 2017).

A further dilemma with chemical toxicity evaluation is that the risks are assessed based on the effect of single substances while in reality, people are exposed to various chemicals simultaneously which together can lead to cumulative or synergistic effects (EEA, 2020). This also questions the regulation processes where only single chemical substances are considered (JRC, 2017). On top of this, certain demographic groups are more vulnerable to the toxic effects of chemicals, including children and pregnant women, as many toxic agents interfere with early phases of development which usually are also neglected in the assessments (Landrigan et al., 2018).

The lack of precise evaluation of environmental risk factors and exposure data hinders the possibility for realistic estimation of health burdens. Considering both assessments from WHO and GBD, the effects of numerous, mainly newer chemicals are not included due to our incomplete knowledge, while their negative impacts are certainly significant. Strong evidence has been established that chemical exposure to disregarded pesticides, heavy metals and environmental neurotoxicants are of big global concerns (Grandjean & Bellanger, 2017; Landrigan et al., 2018).

2.2.1 The cost of BoD

Estimating the cost of the disease burden can be a useful tool to support the formulation of public health strategies and environmental policies. In order to facilitate decision making, environmental chemical exposures can be assessed with the economic value of adverse health effects. The calculation of the burden in terms of costs has to be built on some assumptions. Therefore, it only grasps certain aspects which do not allow a systematic approach for a high precision calculation of global BoD. Nevertheless, studies which go beyond the GBD's scope reveal significant differences in the total burden, which shows that complete omission of disorders or substances leads to a serious underestimation of the costs (Grandjean & Bellanger, 2017).

To date, economic estimations of costs related to health impacts of toxic substances mainly rely on epidemiological data from long-term epidemiological studies. However, this data is very limited and exists only for a negligible proportion of compounds, considering the vast number of hazardous substances available on the market. Therefore, additional data included in the evaluation processes comes from animal toxicological studies as a surrogate for human toxicity (Prichystalova et al., 2017). Nevertheless, these extrapolation factors can be very arbitrary, and the two different approaches yield substantially different results which highly influences the estimated related health costs (Vermeire, 2009; Prichystalova

et al., 2017). Despite its problems, toxicological data is still widely accepted for human toxicological estimates as epidemiological data requires long-term observation of chemical exposure effects which is ethically better to avoid (Prichystalova et al., 2017).

Due to the aforementioned restrictions, the cost of the burden is known to be highly undervalued. Various authors have already identified divergent results from the GBD estimates. In some cases, more than 200 times higher costs were estimated for contaminants by including wider adverse effects in the estimation process in comparison to GBD (Attina & Trasande, 2013). Therefore, it is evident that widening the focus to include various dysfunctions, especially cognitive functional deficits and diseases such as obesity, would greatly add to the more accurate estimation of the total cost of the health burden (Trasande et al., 2016). Furthermore, integrating newly emerging chemicals and establishing stronger relationships to disabilities (based on epidemiological data) into future GBD studies could enhance estimation outcomes. This is especially relevant for certain pesticides, developmental neurotoxicants, polybrominated diphenyl ethers and endocrine disruptors which are the most undervalued chemical groups (Grandjean & Bellanger, 2017). Valuation of highly neglected neuropsychiatric disorders including childhood behaviour disorders would be an especially powerful contribution to estimating the BoD. These impacts are the most difficult to measure, but they are estimated to make a 12% share of all disorders attributed to environmental causes (including pollution) and being responsible for over 7 million DALYs and a total damage cost of € 12 billion worldwide (Prüss-Ustün et al., 2017).

Although adequate evaluation of BoD is essential for precise estimates, data on hazardous effects which do not meet all the requirements still need to be considered. Thus, a systematic approach with less restrictive criteria for establishing causal relationships would facilitate integration of these data. The underestimations could be further complemented with combining methods from health economics and toxicology. While there is proof that there are impediments hindering the valuation of attributable risk regarding causal relationships and exposure distribution these can be addressed and solved. The total cost attributed to environmental BoD potentially surpasses 10% of the global GDP. Therefore, environmental chemicals such as developmental neurotoxicants need to gain extensive recognition (Grandjean & Bellanger, 2017).

The European Environmental Agency (EEA) publishes on the cost of air pollution from European industrial facilities which reported to the European Pollutant Release and Transfer Register (E-PRTR). The total damage cost within the period of 2008-2012 was estimated to be between € 329 and 1,053 billion which can be as high as 8% of the total GDP in the EU. Information was taken from 14,325 industrial facilities across the EU. The E-PRTR collects information on 91 different pollutants to soil, air and water for 27EU countries as well as Liechtenstein, Norway, Iceland, Serbia and Switzerland. The external cost for individual pollutants were determined in monetary values per kilogram of emission (EEA, 2014). The report was updated in 2021 where a total cost of € 277–433 billion was estimated. This suggests a decrease in damage cost; however, the unit costs for heavy metals and organic compounds have significantly increased compared to the earlier report (EEA, 2021).

2.2.2 Valuation of toxic compounds

The known health burden of certain chemicals can also assist decision making based on the comparison of hazardous effects. Life Cycle Assessment integrates information about pollution effects, including chemical substances, and evaluates the overall costs attributed to the environmental exposure based on the characteristics of chemicals. The results of the

assessment can be used as a comparison of various chemical substances in the complete life cycle of products or services based on environmental impact including human toxicity.

In order to make environmental impacts of various chemicals comparable they need to be translated into a common metric. Regarding the environment, monetization can be used for the comparison of various processes and toxicity of substances based on their health burden. Monetary valuation creates additional insight into the weighting of non-monetary items and can rank impacts regarding the welfare perspective. This can be further utilized to analyse the cost/benefit ratios of the application of various chemical compounds. It is important to note that weighting methods are always based on various assumptions which makes the results only indicative (Ahlroth, 2014). Monetary valuation techniques allow us to determine the value of non-market products. As part of the valuation, we mainly translate social and biophysical impacts into monetary terms. The environment as a non-value product provides numerous direct and indirect contributions to human well-being which are rarely priced in real life. Monetary valuation is based on welfare economics principles and estimates from marginal changes in a given resource or emission. This way, monetization enables us to compare the environmental impacts to each other, or to other already known costs of certain actions which can be utilized in decision supporting tools such as Cost-Benefit Analysis and LCA (Pizzol et al., 2015).

2.2.3 Pricing environmental pollution

The environment or environmental quality can be considered a product since it undoubtedly has a value to society, although it is not priced on any market. Environmental pollution, which leads to human toxicity, is manifested as a negative externality as it affects the health of communities outside the pollution source without granting any compensation for the adverse effects. Environmental prices aim to capture the welfare loss associated with pollution which provides the ground for monetary valuation, in this case the quantified damage caused by a given contaminant. The environmental quality changes as a consequence of emissions and related environmental alterations, therefore the environmental price can indicate the social marginal value of preventing emissions. Following this line of thinking, the price of the environment should be equal to the external costs of environmental pollution.

As the market for environmental quality is absent and the prices cannot be established based on market observation, it requires manual calculations (CE Delft, 2018). For LCA, choice experiments are believed to be the best approach when directly observable market prices are not available. In other cases, different approaches can be beneficial depending on the examined midpoints or endpoints (Pizzol et al., 2015). The calculation can be based on human preferences of avoiding the environmental impacts of emissions. In other words, the calculation identifies the price which society assigns to environmental quality. Studies frequently look at how much people are willing to pay on a hypothesized market for a certain good or service or the achievement of a goal and then use that information to determine its value (willingness to pay-WTP). The price is expressed as the social cost of pollution in €/kg emitted. Although it appears as a straightforward approach, willingness to pay studies have moderate precision for environmental pricing. Environmental quality remains an abstract term which is difficult to grasp and the existing methods possess many built-in biases. It is fairly challenging to design a questionnaire which encompasses all the aspects and importance of the environment and is able to directly link the costs to all environmental damages. Moreover, misinformation and the lack of comprehensive knowledge of individuals about the real impacts of pollution tend to further distort the results (CE Delft, 2018).

In 2017, CE Delft published the Environmental Prices Handbook which aimed to harmonize environmental price values at midpoint and endpoint levels and reach a consensus valuation for the pollution effects in the EU. The handbook identified monetary values for over 2,500 pollutants at three different levels, namely pollutant level (value of emission), midpoint level (value of environmental themes) and endpoint level, the last representing the damage to humans and the ecosystems. These environmental prices can be used in Social Cost-Benefit Analysis (SCBA) to determine the value of environmental impacts of policies or other measures. Additionally, the prices enable us to measure corporate social responsibility and benchmarking to provide transparency and overview of environmental impacts of companies' operations. Furthermore, it can be used in LCA where environmental prices are handy to provide a comparison of the impacts of various materials in the process of optimizing operations. Environmental prices calculated in the handbook have a degree of uncertainty and only represent average values for the EU and do not aim to conclude on site specific impact values. Therefore, the prices are only recommended to be used in specific contexts (CE Delft, 2018).

Valuation of human health and toxicity

Unfortunately, environmental prices related to human toxicity yield the highest uncertainty and for specific toxicity studies its application is not recommended (CE Delft, 2018). This report aims to provide potential updates and suggestions for the validity of the environmental prices for LCA focusing on human toxicity, based on damage cost caused by one kilogram of emitted pollutant. Epidemiological studies are used as a base to derive the disease incidence and the total disease burden in relation to the emission and exposure levels.

The contribution of a risk factor such as a chemical substance to a disease can be quantified by the population attributable fraction (PAF). This metric indicates the proportion of the population impacted by a substance as a result of environmental exposure. PAF evaluates the change in disease incidence in the absence (and presence) of the risk factor while all other factors remain constant, thus giving the fraction of disease cases which would be avoided with the reduction or elimination of the risk factor. It also helps to calculate the epidemiology for the entire population in question since only data of the exposed group is available (Wang et al., 2018; WHO, 2020). It is important to note that risk factors usually overlap, therefore the total fraction can exceed the actual attributable fraction. Nevertheless, methods exist to separate and partition the overlapping effects contributing to a disease and calculate the contribution of single factors (Lin et al., 2013). The PAF can be calculated by the prevalence of risk factor multiplied by the disease risk (Hanley, 2001). With the knowledge of PAF, the BoD also can be estimated by using the following equation:

Disease rate * Attributable Fraction * Population size (IoM, 1981).

The PAF approach, however, relies on data on exposure and disease distribution which is frequently absent. This is the valid reason why studies such as the GBD avoid including certain disorders and clinical dysfunctions in their assessments (Grandjean & Bellanger, 2017). The GRADE working group created epidemiological criteria to evaluate the available epidemiologic information that can assist and evaluate the reliability of PAF or BoD estimations (Atkins et al., 2004). To estimate the costs, the human capital approach is a transparent method which also provides opportunity to include costs related to subclinical dysfunctions that are not linked to medical expenditures and are based on indirect costs (Grandjean & Bellanger, 2017).

Value of human health burden

On top of the estimated attributable fraction the burden of the adverse effects per case determines the total costs. There are three types of health effects derived from pollution that can be differentiated: chronic mortality, which represents the reduction in life expectancy due to pollution (OECD, 2012); acute mortality, which is attributed to the increased risk of premature death; and morbidity, which marks the increased prevalence of illness in populations. Various indicators can be used to measure health impacts such as years of lives lost (YOLL), expressing mortality impact; quality-adjusted life year (QALY), which is a more suitable measurement for morbidity than of mortality (as it rather shows the changes in well-being) and disability-adjusted life year (DALY), which shares similarities with QALY, but it is a more widely accepted metric. DALY estimates adverse health effects with creating a uniform score and expresses life years lived in disability (Krewitt et al., 2002; CE Delft, 2018). The estimated conversion rate between the latter indicators is determined to be 1 DALY = 1.087 QALY. The impact of environmental pollution on human toxicity at midpoint level is well captured by the value of a life year (VOLY). VOLY is the most useful metric to estimate the costs of health impacts of environmental pollution as environmental pollution tends to influence mortality rather than morbidity. VOLY estimates differ among studies but the Handbook of Environmental Prices by CE Delft determined € 50,000 and € 110,000 as lower and upper values respectively, and € 70,000 as central value for VOLY. In the case of morbidity QALY was used instead of VOLY, which only differs in the upper value of € 100,000 instead of € 110,000 (CE Delft, 2018).

To evaluate both non-fatal and fatal cancer the cost of illness (CoI) is mostly used, in combination with the income loss during the disease course and the WTP to avoid suffering linked to the disease. In France, it was estimated for non-fatal cases that the CoI and the productivity loss were € 42,000 and € 21,000 respectively which equals € 63,000 per case. In the case of fatal cancer cases, the life loss is usually between six and fifteen years. Two different approaches assume € 2 million and € 1.12 million respectively. The CoI itself is estimated to be € 481,000 for a cancer case (Rabl et al., 2014).

2.3 LCA methods and models

LCA (life cycle assessment) is a standardized analysis technique employed to evaluate the overall environmental impacts of specific products, processes or measures throughout their whole life cycle. As part of the LCA, life cycle inventory (LCI) is prepared which covers all the inputs and outputs over the product's life cycle, such as production, materials used and emissions (Fantke et al., 2017). Life cycle impact assessment (LCIA) is an integral part of LCA which compiles the environmental impacts and provides a uniform score based on characterization factors throughout the total life cycle of a product or service, which is mainly derived from substance emission and resource extraction (RIVM, 2016). This enables comparison of products, raw materials or substances in the supply chain and eventually makes it possible to compare socioeconomic effects as a causality of environmental impacts (CE Delft, 2018). LCIA quantifies the impacts of chemical releases identified in the inventory stage and defines the compartments where the substances were emitted. LCIA models work at high spatial scale and time scales are usually avoided in the process (RIVM, 2016).

Characterization factors in LCA aid us to compare harmful chemical substances showing how a given quantity of pollutant leads to environmental or health effects. The midpoint level mainly includes mechanisms, where many different elements contribute to the effect, while the endpoint level rather affects everyday life (Ahlroth, 2014). The midpoint represents aggregated environmental themes of various emissions while a specific emission can

influence multiple midpoints simultaneously. Midpoint level characterization factors for different midpoints can be combined into a uniform score which further can be used to support policy decisions. Based on this framework we can gain information about the socio-economic consequences of the environmental impacts of pollutants and compare them to each other. The endpoint level is mainly concerned with damages to humans and to the environment. This gives the base for monetary valuation which provides the opportunity to weigh environmental impacts against one another (CE Delft, 2018). Midpoint level characterization has stronger connections to the environmental flows and is characterized by lower uncertainty, while endpoints highlight the environmental relevance of the impact but deliver higher uncertainty (Hauschild & Huijbregts, 2015). The human toxicity impact from chemical exposure is one of the characterization factors at midpoint level in LCA (Fantke et al., 2017). Characterization factors for human toxicity comprise fate in the form of environmental persistence, intake and accumulation of substances in humans and the final toxicity effect. Fate and exposure are derived from evaluative multimedia models while the effect factor uses the actual toxicity data mainly from laboratory animal studies (RIVM, 2016).

ReCiPe model

The ReCiPe model (Goedkoop et al., 2009) provides a harmonized life cycle assessment method at midpoint and endpoint levels. The complete assessment covers all phases of production, consumption and the end-cycle management of products which can help optimize production processes and waste management. The areas included in the LCIA at endpoint level are human health, natural environment and resource scarcity. ReCiPe considers three perspectives for human behaviour throughout the assessment: firstly individualistic, which is based on short-term interest and undisputed impacts; secondly hierarchist, where the time frame is based on scientific consensus and possibility of impact mechanisms; and lastly egalitarian, which focuses on long timeframes and all impact-pathways for which data is available (RIVM, 2016). There are currently two versions of the ReCiPe model active: the 2009 version (Goedkoop et al., 2009) that was last updated in 2013, and the 2016 version (RIVM, 2016). For human toxicity, ReCiPe 2009/2013 uses a toxicological model called USES-LCA (Huijbregts et al., 2005). In later versions the model Usetox was being used and adjusted (see below).

USEtox model

Various impact assessment methods exist which differ from each other with a wide range of characterization factors. Hence, they frequently yield very distinct results (Hauschild et al., 2012). USEtox is a scientific consensus model and characterization framework in LCIA recommended by the European Commission and supported by the UNEP/SETAC Life Cycle Initiative. USEtox focuses on the characterization of toxicological impacts of chemical emissions in comparative toxicity assessments (such as LCA). It is applied to identify and calculate characterization factors considering the fate, exposure and impact of chemical substances, linking chemical emission to damages on human health through a cause-effect chain. As a result, USEtox allows policy makers to consider their decisions by comparing the toxicity potential of products and product systems based on chemical substances involved in the processes. The USEtox model differentiates between three impact categories, namely human cancer effects, human non-cancer effects and ecotoxicity. USEtox follows the impact pathway from emission through dispersion to exposure and subsequent health effects which yields the characterization factor for human toxicity at midpoint level. This substance-specific characterization helps to identify the compound's potential toxicological impacts.

To model chemical fate and exposure, USEtox applies environmental compartments to represent the flow of chemical substances which can be transported, transformed or degraded in the environment. The model builds on three main factors. The fate factor [kg in the compartment/kg emitted] considers how the contaminant was dispersed in various environmental compartments. The exposure factor [kg intake/kg in the compartment] determines the human contact with the substance within a specific time period. Lastly, the effect factor [kg cases/kg intake] estimates the effect for a kg intake of the substance after exposure. These factors are compiled into a single score characterization factor of human toxicity impacts at midpoint level, called the Comparative Toxic Unit (CTUh) which represents the estimated increase in disease cases for every kg of chemical emitted. From this data further factors can be derived such as the intake fraction which is the fraction of the quantity emitted that reaches the human body. The weighting damage factor can be used to derive the DALY cases related to chemical emissions to reach impacts of environmental toxicity at endpoint level from the midpoint CTUh (Fantke et al., 2017). It is estimated after that the relationship for cancer effects is 11.5 DALYs per case while for non-cancer effects it is 2.7 DALYs per case (Huijbregts et al., 2005). The characterization factor is expressed as DALY/kg chemical emitted. Hence it represents the human health damage for a unit of emission in a single metric. This enables a comparison of the different disease types in the view of severity of different disabilities caused by chemical emission. This conversion is based on data from 2005 (Huijbregts et al., 2005) which is considered outdated and lacks differentiation between distinct health conditions. Some estimates for disease burden expressed in DALY were already proposed for different types of cancers (Zhou et al., 2015).

As many models, the USEtox model also has its limitations. Some important factors are the lack of physical and chemical data and the lack of data about chemical degradation mechanisms. In addition, due to the lack of scientific consensus some exposure pathways are excluded from the model. The compartments included in USEtox also lack high spatial resolution and the characterization factors involve considerable uncertainty, thus they are only deemed as indicative numbers (Fantke et al., 2018). Although USEtox is considered a consensus model for both human toxicity cancer and non-cancer effects, it is recommended to be applied with caution. Improvements are needed, especially in the case of midpoint to endpoint level characterization for non-cancer effects, which is labelled as interim. Despite the limitations, USEtox is still the most recommended model for human toxicity due to its multimedia coverage and large database of chemicals with the flexibility for modification and addition of new substances and compartments. However, the number of substances without any derived characterization factors is still way higher than what is included in the USEtox model (Hauschild et al., 2012).

Recent developments: addressing challenges in human toxicity evaluation

To improve human toxicity assessment challenges, a Toxicity Task Force was initiated to develop guidelines for the assessment of human toxicity impacts and human exposure in LCIA. In order to model human toxicity data, improvements are necessary for better characterised occupational exposure during manufacturing processes, higher differentiation between environmental compartments and integration of pulse emissions and long-term emissions into the model. There is a need for a consistent mass-balance model combining near and far field exposure into a common metric that incorporates all pathways. (Fantke et al., 2018). The literature is also very limited about the transformation processes of chemicals, which certainly requires more research. LCIA practice also assumes linearity and additivity in dose-response models, while co-exposure can exert higher risk than simple additivity through synergies (RIVM, 2009; Fantke et al., 2018). The models regularly use this

linearity in dose-response relationships which usually stands for cancer but to less extent for other disease endpoints, which consequently requires the application of a dose-response modifier. Diversification of endpoint toxicity impacts would also help to acquire more precise estimates in toxicity assessment. Nevertheless, this requires further research data. Moreover, LCIA models need a wider scope on capturing the impacts of exposure during product use, next to the impact during manufacturing and product afterlife stage (Fantke et al, 2016). Metals and heavy metals generally impose further challenges to LCIA, since certain elements are necessary for humans in lower dosage but toxic at higher doses. Therefore, a steady-state model is not suitable for these compounds. Human subgroups are also not differentiated in LCIA modelling, which accounts for further uncertainty of the outcomes (Fantke et al., 2018).

3 Literature review for nine toxic substances

3.1 Introduction

In this Chapter, a thorough literature review was conducted concerning the current state of chemical pollution. Specific attention was paid to emissions in the European Union and current approaches in assessing the global burden of diseases and monetary valuation practices. Nine compounds were selected as part of the project, more specifically four heavy metals: arsenic, mercury, chromium (chromium 0 and VI) and cadmium; two pesticides: Glyphosate and Chlorpyrifos; and three additional compounds: benzo[a]pyrene, dibutyl phthalate and bisphenol A. These nine compounds were selected based on their relevance, high environmental distribution, widespread use, and based on the fact that significant research has been conducted on them. Throughout the literature review the main characteristics, main uses, environmental fate and human exposure were addressed concerning all selected compounds. Epidemiological studies were also included in the review to highlight the toxic effect on human populations and to find the most relevant hazards of human exposure.

For the literature review various databases were searched. Studies that were covered included the US-EPA IRIS assessments, IARC monographs and toxicological and epidemiological reviews. In Paragraph 3.2 we discuss the studies for heavy metals, while in Paragraph 3.3 we discuss the findings for organic chemicals. For each substance we discuss the health impacts that can be expected from the substance, the routes that emissions can travel through the environment and the exposure to humans. Finally, we also investigate studies that directly valued damage costs estimates for these compounds.

3.2 Inorganic compounds - Heavy metals

3.2.1 Introduction

Heavy metals are a unique class of elements since several have essential roles in certain body functions and deficiency can lead to deterioration of human health. On the other hand, higher concentrations can exert major health risks to humans which highlights the importance of environmental pollution (Jaishankar et al., 2014). Heavy metals are classified based on their high density which reaches over 5g/cm^3 (Järup, 2003). The group embodies an increasing public health concern due to their growing industrial application aligned with growing human exposure levels (Tepanosyan et al., 2018). Heavy metals can be released to the environment as a consequence of natural events such as soil erosion and weathering of the earth's crust. Nonetheless, anthropogenic causes appear as major forms of emission including urban runoff, wastewater discharge, application as constituent in fertilizers and other chemicals in agriculture, industrial effluents, mining, manufacturing as well as transport and power generation (Morais et al., 2012; Li et al., 2016). Environmental contamination can also occur due to corrosion, atmospheric deposition and leaching (Cai et al., 2019). Heavy metal toxicity depends on the concentration, duration and route of exposure and they regularly affect and damage cellular organelles upon entering the human

body (Wang & Shi, 2001). Children are generally at much higher risks to these pollutants as heavy metals tend to have neurotoxic effects hence can interfere with normal development causing damage to the brain and other organ systems (Al osman et al., 2019). The aggregate damage cost for all heavy metals was determined to be €11.78 billion for the EU including As, Cr, Cd, Hg, Ni, Pb. The total damage was only calculated based on emissions from 11,655 industrial facilities (EEA, 2021).

In the remainder of this chapter, we will investigate the scientific literature of human health impacts from a variety of heavy metals including mercury (Chapter 3.2.2), cadmium (Chapter 3.2.3), chromium (VI) (Chapter 3.2.4) and arsenic (Chapter 3.2.5).

3.2.2 Mercury (Hg)

Mercury is a very toxic heavy metal which exists in the environment in three different forms: elemental, organic and other inorganic forms (Jaishankar et al., 2014). All three forms have different physicochemical properties and different toxicity profiles (Al osman et al., 2019). Mercury is used in the electrical industry as well as in cosmetics, paints, pesticides, medicines, switches, and thermometers (de Winter-sorkina et al., 2003). Thousands of tonnes of mercury are released into the environment yearly due to human activities and natural processes (Street, 2017). The main forms of mercury emissions are anthropogenic including wastewater discharge, disposal of industrial waste, incineration, mining activities and agriculture (Chen et al., 2012). Mercury is further released to the environment in the form of pharmaceutical waste, as an element of paper and pulp preservatives and soda production industry. However, the most important contributors to mercury release remain coal-fired power plants and residential coal burning processes (Jaishankar et al., 2014; WHO, 2017).

Environmental fate

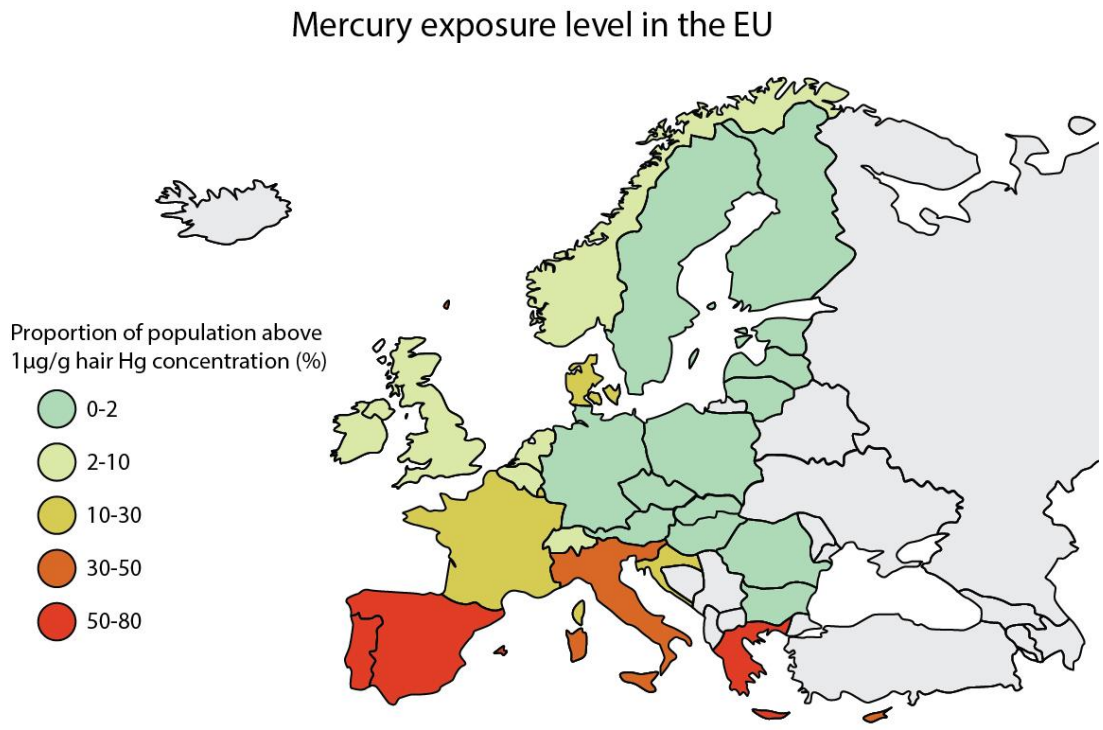
The chemical form of emitted mercury determines its deposition pattern. After emission mercury is primarily transported in vapour form until it transforms into a water-soluble form and disperses on the earth's surface. Mercury usually resides in the atmosphere in elemental form for up to a year and is transported over different continents. When it oxidizes and becomes soluble in water, it deposits rapidly on land and on water surfaces. If it is attached to other particles upon emission, it tends to deposit much faster and remains at a more local level. In Europe, 60% of mercury deposition is believed to occur due to human emissions (EC, 2017; EEA, 2018). The atmospheric mercury and the deposited mercury in the soil has a lower toxic potential. On the other hand, mercury that enters the water systems can be more harmful and potentially stored in the sediment for decades (EEA, 2018). Deep oceans can store mercury for centuries accumulating human emission products for the future (Lamborg et al., 2013). After deposition in the water, mercury is further converted into organic and highly toxic methylmercury (MeHg) which enters the aquatic food chain and due to its lipophilic nature accumulates in the fatty tissue of aquatic animals. In this environment it also tends to biomagnify at the top level of the food chain and reaches the highest concentrations in predatory fish (WHO, 2017; Al osman et al., 2019).

Human exposure

Oral intake is the prominent pathway for both organic and inorganic Hg forms while exposure cases via inhalation are considered negligible (de Winter-sorkina et al., 2003). The major sources of chronic low level mercury exposure are dental amalgams (which if present have shown relation with the mercury concentration of the adult brain) and dietary

fish (Tchounwou et al., 2012; EC, 2017). Seafood and freshwater fish are the main sources of MeHg and generally Southern European countries experience much higher exposure to mercury due to significantly higher fish consumption levels (EC, 2017; Figure X). Organic MeHg is considerably more bioavailable than the inorganic forms and mainly accumulates in the kidneys and in the human brain after exposure with a half-life ranging from 80 days up to 27.4 years in the human body (de Winter-sorkina et al., 2003; Rooney, 2014; Jo et al., 2015). Exposure to inorganic mercury mainly occurs through consumption of fish, shellfish, and inhalation of elemental mercury during occupational industrial processes (WHO, 2017). The elemental highly lipophilic form is efficiently absorbed in the lungs and enters the cells where it is oxidized and converted into a highly reactive Hg_2^+ form. After ingestion it can effectively cross the placental and the blood brain barriers. The highest proportion elemental mercury also tends to accumulate in the kidneys, neurological tissues and liver (Tchounwou et al., 2012).

Figure 1 - ***Differences in hair Hg level among countries in the European Union after Bellanger et al., 2013***



Human toxicity impacts

Mercury poisoning or acrodynia is usually referred to as pink disease while more severe mercury poisoning leads to the so-called Minamata disease (EC, 2017). Mercury intake can result in gastrointestinal lesions as well as kidney- and cardiovascular damages (de Winter-sorkina et al., 2003; Jaishankar et al., 2014). Its toxicity is connected to mitochondrial damage, lipid peroxidation, damage of the microtubules and interference with the intracellular calcium homeostasis which causes defects in muscles, kidneys and nerves (Patrick, 2002). Mercury is also a neurotoxic substance causing brain damage and influences the developing foetus prenatally through developmental neurotoxicity (de Winter-sorkina et al., 2003).

Elemental mercury and methylmercury are toxic to the central and peripheral nervous systems. After chronic inhalation, Mercury vapour is easily absorbed and can produce harmful effects leading to bronchitis, asthma and temporary respiratory problems but can damage various body organs such as lungs, kidneys, immune system, digestive system and nervous system with potentially fatal consequences (WHO, 2017). Moreover, Mercury also damages the hearing and vision (EC, 2017). Acute poisoning from inhalation usually leads to altered brain functions, shyness, tremors, memory problems, irritability, vomiting, diarrhoea, lung damage and increased blood pressure (Jaishankar, 2014). The inorganic salts of mercury are corrosive to the skin, eye and gastrointestinal tract, and may induce kidney toxicity if ingested (WHO, 2017).

Although methylmercury and mercuric chloride are potentially carcinogenic agents, the connection between mercury exposure and carcinogenesis remains controversial (Tchounwou et al., 2012, Jaishankar et al., 2014). Mercury inhibits intercellular communication and therefore could function as a cancer promoter. In addition, it can interfere with the antioxidant system and possibly act as an epigenetic carcinogen (Zefferino et al., 2017). Further evidence supports oxidative stress induction by mercury (Karimi et al., 2016). Overall, it is still classified as a group three carcinogen according to the IARC classification system as strong proof is lacking to confirm carcinogenic effects (IARC, 2018).

In epidemiological studies mercury has been associated with various disorders such as increased blood pressure (Dórea et al., 2005; Fillion et al., 2006; Genchi et al., 2017), elevated cardiovascular disease risk (Karagas et al., 2012), myocardial infarction (Roman et al., 2011), renal injury and elevated disease risk for aging kidney (Pollack 2014; Bridges & Zalups, 2017) as well as increased risk of metabolic syndrome (Fox et al., 2012; Eom et al., 2014; Roy et al., 2017). After in utero exposure, mercury causes impaired motor functions and verbal abilities, lower attention span (Grandjean et al., 1997), developmental delay corresponding to about 1.5 IQ points (Grandjean & Herz, 2011), impaired visuospatial processing and memory (Grandjean et al., 2012), as well as increased risk of autism and autism-related disorders (Grandjean & Landrigan 2014). On top of these effects, associations were found with increased body mass index, increased waist circumference and elevated cholesterol and triglyceride levels (Eom et al., 2014) as well as increased prevalence of diabetes and pancreatic disorders (He et al., 2013; Schumacher & Abbott, 2017).

Direct valuation

Foetuses are more sensitive to mercury exposure as mercury affects the neurological development (WHO, 2017). The negative effect on brain development can result in lifelong impacts which have significant economic implications. According to an estimate, 1,865 million babies are born yearly in Europe above the cut-off level of mercury exposure and 231,000 are born over the safety exposure limit identified by the WHO (Bellanger et al., 2013). The number of compromised births were shown to be much higher in countries where predatory fish consumption was more significant (Landrigan et al., 2018). Associated productivity loss from methylmercury can help to estimate the economic burden of health outcomes. The economic effects of prenatal MeHg exposure were calculated based on the loss of lifetime earnings per person. Exposure was estimated to cause 600,000 IQ points loss per year with a total economic loss of € 8-9 billion annually. This number is still believed to be an underestimation as other neurological effects and long-term risks were not included in the valuation. The cut-off level was also supposedly set too high and certain other costs such as direct medical costs were also omitted from the study (Bellanger et al., 2013).

Another study focusing on the IQ loss burden found that prenatal methylmercury exposure contributes to a total cost of $4.8 billion in the EU (Bartlett & Trasande, 2013). An earlier estimate calculated € 8,000/kg for mercury emission from coal power plants in Europe (Needs, 2008) while a different study estimated it at € 1,487/kg globally (Spadaro & Rabl, 2008) According to the estimate from emissions to air by E-PRTR
industrial facilities, the environmental price for mercury emission related to IQ loss was determined to be € 910/kg for the EU and € 2,860/kg at global level. This data relies solely on emissions to air which account for only the 36% of total emission (EEA, 2014). An updated assessment calculated € 16,903/kg emission from facilities from the same E-PRTR registry (EEA, 2021). This estimate relied on the methodology by Nedellec & Rabl (2016), where a unit cost of € 22,937 was calculated for mercury.

3.2.3 Cadmium (Cd)

Cadmium is another significant element in the group of heavy metals. It is mainly used in nickel-cadmium batteries, alloys of electronic compounds, electrodes, coatings, plastic stabilizers, detergents and mineral fertilizers (de Winter-sorkina et al., 2003; WHO, 2019). Cadmium is also present in natural mineral deposits, mostly in sedimentary phosphate rocks. It can be released to the environment by natural processes as a consequence of volcanic activities or weathering (Kazantzis, 2004; Jaishankar et al., 2014). Nevertheless, anthropogenic causes of atmospheric Cd emissions are more significant, in particular smelting of non-ferrous metal ores, fossil fuel combustion, mining, waste incineration, fertilizer manufacturing and smoking (IARC, 2012; Jaishankar et al., 2014; WHO, 2019).

Environmental fate

After emission cadmium can travel and reside in the atmosphere forming part of the particulate phase for up to a few weeks until it deposits on water surfaces and soil. Soil and water compartments are also polluted by direct emission such as discharge of industrial waste (WHO, 2000). The soil can be contaminated from fertilizers or atmospheric deposition as well as from water- and sewage contamination. Cadmium is highly soluble in water thus has higher mobility in water compartments and has high bioavailability in humans (WHO, 2019). Cadmium is taken up by various food crops where it accumulates. Carrot, spinach, tomato, lettuce, head lettuce and celery tend to accumulate high quantities of cadmium (Versluijs & Otte, 2001; Olympio et al., 2018). Besides the agricultural plants, molluscs are also potential sources of higher cadmium intake (Satarug et al., 2003).

Human exposure

Human exposure occurs through inhalation or ingestion. Cadmium can accumulate and reside in the human body for decades with an estimated half-life of 11.6 years, though certain estimates are as high as 35 years (Amzal et al., 2009; WHO, 2019). Smoking is one of the most important sources of exposure as tobacco plants also take up cadmium from the soil which is released during smoking activities (Jaishankar et al., 2014). For non-smokers food is the most important source of exposure and responsible for about 90% of total intake (Mudgal et al., 2010; Mahurpawar, 2015). Occupational exposure can also be significant for people working at contaminated sites (Tchounwou et al., 2012). Exposure from contaminated drinking water is negligible compared to dietary sources or occupational hazards (WHO, 2019).

Human toxicity impact

The main intracellular hazardous effects of Cd are interference with DNA repair mechanisms, stimulation of inflammation and cell death, induction of lipid peroxidation and production of reactive oxygen species (ROS) (Navas-Acien et al., 2004). Cadmium mainly impacts the kidneys, skeletal system and the respiratory system (Jaishankar et al., 2014; WHO, 2019). It alters the calcium metabolism which affects the bone minerals and can lead to the development of osteoporosis (de Winter-sorkina et al., 2003; Jaishankar et al. 2014). The main mechanism behind the adverse skeletal effects is believed to be the enhancement of osteoclast activity which breaks down the bone collagen matrix at a faster pace (Kazantzis, 2004). After exposure, cadmium tends to accumulate in the renal proximal tubule cells for long-term causing serious renal dysfunctions (Ginsberg, 2012; Safhi et al., 2016). Inhalation of high amounts of cadmium damages the lungs causing acute pneumonitis and longer exposure can result in the development of COPD (IPCS, 1992). Acute ingestion can lead to gastrointestinal tract irritation, pulmonary, hepatic or renal injury and coma (Baselt, 2000). High exposure during pregnancy influences the foetus and can result in premature birth (Henson & Chedrese, 2004), impaired neurological development (Rice et al., 2014) and mental retardation (Mahmud et al., 2016). There is also a relation between cancer cases and cadmium exposure levels (Hartwig, 2013). Cadmium is classified as group 1 carcinogen according to the IARC (IARC, 2018). There is strong evidence that Cd causes lung cancer (IARC, 1993; WHO, 2019) while epidemiological studies have shown strong correlation with renal cancer (Ilyasova & Schwartz, 2005; Song et al., 2015) and some causation was also established to prostate, testis, liver and stomach cancers (Waalkes et al., 1996; WHO, 2019).

An epidemiological study showed that cadmium had negative effects on bone mineral density already at low exposure level, most probably via increased bone resorption. This effect was further intensified after menopause (Åkesson et al., 2006). Moderate exposure similarly caused dose-dependent decrease in bone mineral density, higher incidence of bone fracturing in women and height loss in men both within the general populations and at occupational settings (Nordberg et al. 2002; Kazantzis, 2004; Engström et al., 2011). Other epidemiological studies have revealed early kidney damage and osteoporosis as a consequence of Cd exposure (Alfvén et al., 2000). Furthermore, Cd induced tubular and glomerular effects in the kidney causing renal dysfunctions both in children and adults already at low exposure level (Åkesson et al., 2005; Wang et al., 2016). For low doses of cadmium, a risk for stage III kidney disease (CKD III) increased significantly with higher exposure and with older age (Ginsberg, 2012). Moreover, it was demonstrated that cadmium further elevates risk of renal dysfunction for people with diabetes (Nordberg, 2009). Cadmium was also associated with elevated cardiovascular diseases risk and mortality including heart failure and stroke (Tellez-Plaza et al., 2013) and it was found to exert negative effects on IQ (Kippler et al., 2012). All these effects are worrying given the fact that the cadmium content of mineral fertilizers is still not controlled in the European Union (Ulrich, 2019). According to an estimate cadmium intake by children was 64% of the tolerable daily intake in the Netherlands (de Winter-sorkina et al., 2003) but the aforementioned low-level effects raise further concerns about the tolerable intake level.

Direct valuation

A monetary valuation of human health impacts was carried out in Denmark focusing on the impacts of soil pollution by cadmium, a natural constituent of phosphorus fertilizers. The effects were attributed to dietary intake of plants with cadmium content from the polluted soil. For each kilogram of cadmium emitted, €334 were calculated as an external human health cost which corresponds to €15.53/km^2 of danish agricultural soil (Pizzol et al., 2014).

The damage cost of heavy metals/kg emissions was also estimated based on the slope factor from the IRIS database. The results for cadmium were calculated to be €27/kg where a cost of €2 million/cancer case was used (Rabl et al., 2014). On top of this, an earlier estimate calculated €84/kg for cadmium emission from coal power plants (Needs, 2008).
According to the estimate from emissions to air by the E-PRTR industrial facilities the environmental price for Cadmium related cancer endpoint is determined to be €29/kg which was estimated to be €50/kg for the Netherlands. This data relies solely on emission to air which only accounts for the 13% of total emissions (EEA, 2014). An updated assessment calculated € 185,175/kg emission from facilities from the same E-PRTR registry (EEA, 2021). This estimate relied on the methodology by Nedellec & Rabl (2016), where a unit cost of € 138,969 was calculated for cadmium.

3.2.4 Chromium (Cr)

Chromium is an essential heavy metal which is present in many forms in the earth's crust although, chromium 0, III and VI are the most abundant oxidation forms in the environment. Chromium III is an essential nutritional supplement for certain physiological processes both in plants and humans (WHO, 1996; HHS, 2012). Furthermore, chromium is widely used in various metal industries such as manufacturing of metal alloys and found in numerous consumer products including tanned leather, stainless steel, kitchenware, fertilizers and treated wood (Ghani, 2011; HHS, 2012; Jaishankar et al., 2014). Most of the chromium emission and -pollution occur due to industrial waste discharge, metal processing, pigment production, electroplating, leather tanning, textile production, and manufacturing products containing chromium, while it is also released during coal, oil and gas burning processes. Approximately 29,000 tons of chromium is released to the environment every year globally (HHS, 2012).

Environmental fate

After emission chromium is deposited rapidly from the atmosphere and dissipates into soil and water phases. The physical and chemical conditions determine the partition and form of chromium in various compartments. Certain chromium compounds can possess high water solubility and they partition mainly into the water phase (Wolińska et al., 2013). The most stable trivalent form possesses low solubility and generally low reactivity (Barnhart, 1997). Chromium VI appears in various insoluble to highly soluble forms (Cole & Rodu, 2005). This hexavalent elemental form is very rare in nature and almost exclusively produced by industrial activities (Zhitkovich, 2011).

Human exposure

Chromium can enter the human body via all exposure pathways. Food is the main source of chromium exposure to the general population. Chromium enters the human body by consumption of fruits, vegetables and meat or contaminated drinking water (HHS, 2012). Workers can be exposed to much higher levels of chromium than the general population and in the occupational setting inhalation and skin absorption are the main causes of exposure (HHS, 2008; Al Osman et al., 2019). Inhalation can occur due to occupational hazards in metallurgy, tanning industries and chromite mining while cigarette smoke or the proximity to hazardous waste sites are also potential contributors to exposure. After inhalation, chromium can accumulate in the lungs for several years but most of the substance leaves the body within a week (HHS, 2012). Occupational exposure has the most important contribution to chromium VI related health issues. Chromium is essential to plants but in

excess amounts can be very destructive causing chlorosis and necrosis and after uptake can also expose humans to the highly toxic chromium VI (Ghani, 2011).

Human toxicity impact

The literature concerning chromium deficiency is scarce but it has been demonstrated to be associated with impaired metabolism (HHS, 2012). The adverse health effects of the compound depend on its oxidation state, the most oxidized form being the most hazardous (Tchounwou et al., 2012). The trivalent form has very low membrane permeability which makes it almost completely harmless while chromium VI is a strong oxidizing agent and can lead to the production of ROS (Zayed & Terry, 2003). Due to its high oxidizing potential, chromium VI is categorized as group 1 human carcinogen while chromium 0 and chromium III are classified as group 3 in the IARC classification system (Jaishankar et al., 2014; IARC, 2018). Most of the health issues are associated with the ingestion of chromium VI which can cause various cancers and can damage the reproductive system (HHS, 2012). Chromium VI can easily enter the cell via anion transport where it is converted to chromium III (Zhitkovich, 2011).

The main adverse effects of occupational exposure are related to the respiratory system including coughing, respiratory difficulties and impaired lung functions (Neghab et al., 2015; Hamzah et al., 2016). Moreover, ulcers of nasal septum, asthma and bronchitis are also common consequences of exposure (Rasoul et al., 2017). Carcinogenic risks are most often related to a group of chromium compounds rather than to a single substance as chromium VI is never present in elemental form but found in a very diverse array of compounds (Katz & Salem, 1993). Human epidemiological studies have reported strong association of lung cancer to occupational chromium VI exposure (Costa, 1997, Luippold et al., 2003; Halasova et al., 2009). Despite the strong evidence of relation between chromium exposure and lung cancer, the real mechanisms behind chromium toxicity are not that well understood (Tchounwou et al., 2012). As chromium VI is a strong oxidizing agent the main toxic effects are attributed to this characteristic. It induces the production of radical species which disrupts cellular functions and causes cellular reduction, chromosomal damage and DNA damage (Wise et al., 2002; O'Brian et al., 2003; Patlolla et al., 2008; Al osman et al., 2019). Epidemiological studies have mainly focused on occupational settings while studies assessing effects on general population are rather scarce. A meta-analysis of epidemiological studies showed causation between chromium VI exposure and lung cancer, but no other cancer effect could be linked to occupational exposure (Cole & Rodu, 2005). On the other hand, a further study in China revealed elevated incidence of stomach cancer besides the lung cancer effects (Beaumont et al., 2008) and a newer epidemiological study found statistically significant links to liver cancer, lung cancer, renal cancer and cancer of genitourinary organs as a consequence of chromium VI water contamination. Moreover, the study showed elevated incidence of pharynx, breast, stomach and prostate cancers and leukaemia with statistically non-significant results (Linos et al., 2011). A thorough meta-analysis of the epidemiological literature focusing on industry workers concluded that chromium VI might cause cancer to the respiratory system, pharynx, buccal cavity, prostate and stomach (Deng et al., 2019). Carcinogenicity of chromium VI also can be attributed to the induced changes in the epigenetic make-up (Sun et al., 2015). In addition to the cancer effects, chromium VI exposure can lead to immunological problems in sensitive individuals (HHS, 2012), skin ulcers and dermatitis (Buters & Biederman, 2017) and adverse gastrointestinal and haematological effects (Ray, 2016).

Direct valuation

The damage cost of chromium emission is most commonly estimated based on the slope factor from the IRIS database. The costs per kg of chromium VI was calculated to be € 177/kg (Rabl et al., 2014). In this valuation a € 2 million/cancer case was used. An earlier estimate derived a unit cost of € 66/kg for chromium VI emission from coal power plants in Europe (Needs, 2008). According to an estimate from emissions to air from the E-PRTR industrial facilities, the environmental price for Chromium (VI) related to cancer effects was determined to be € 38/kg which was estimated to be € 66.7/kg for the Netherlands. This data relies solely on emission to air which only accounts for the 22% of total emissions (EEA, 2014). An updated assessment calculated € 5,501/kg emission from facilities from the same E-PRTR registry (EEA, 2021).

3.2.5 Arsenic

Arsenic is an important heavy metal, also referred to as metalloid due to its semi-metallic properties. It is present in three main forms in the environment including inorganic, organic and arsin gas forms (IARC, 2012). The two inorganic forms, the trivalent arsenite and the pentavalent arsenate are highly toxic to living organisms and these are the main factors behind arsenic related human toxicity. Arsenic is found in nature in various mineral complexes, most abundantly in sedimentary manganese and iron ores and phosphate rock deposits (WHO, 2001). Arsenic is widely used in pharmaceuticals, veterinary medicine (interestingly effective against parasites and leukaemia), as agricultural agents in pesticides and fertilizers, wood preservatives, mining and metallurgical industries and manufacturing of metal alloys (Tchounwou et al., 1999; IARC, 2012). It is also an important component of various dyes, paints and soaps (Jaishankar et al., 2014). Natural environmental emissions occur due to volcanic activities, geological leaching and soil erosion which are responsible for about the third of all emissions (IARC, 2012). Due to chemical reactions, mainly through oxidative and reductive mechanisms, arsenic is released from the mineral deposits to the surrounding water systems (Argos et al., 2012). Nevertheless, industrial mining, smelting and fuel combustion are the major sources of emissions which highly contaminate air, drinking water and soil. The use of arsenic containing pesticides has also significantly contributed to the high level of soil contamination (Bencko & Yan Li Foong, 2017).

Environmental fate

After emission, arsenic resides in the air mainly in the inorganic forms as part of the particulate matter and stays in the close radius of emission sources (WHO, 2001). Water is possibly the most important compartment for arsenic compounds as the metal is mainly found and transported through the water systems. On top of the anthropogenic contributions such as chemical disposals or pesticide uses, the drinking water gets contaminated with the substance by natural sources leading to high local concentrations and exposure levels. This problem also affects certain European countries including Hungary, Italy, Spain and the UK (WHO, 2001; van Halem et al., 2009).

Human Exposure

Human exposure mainly occurs due to ingestion of drinking water or food products, while inhalation is a much less significant source of exposure for the general population. However, inhalation is the most important exposure pathway for occupational hazard. It was estimated that around 147,569 workers were exposed to higher levels of arsenic in the EU and most of them were employed in the metal industries. In the case of food, the

highest concentration is found in seafood products, but meats and cereals can also contain significant amounts of arsenic compounds. In the human body and in other organisms the inorganic arsenic is converted into organic methylated forms mainly monomethylarsenic acid and dimethylarsinic acid which are also the main biomarkers of arsenic exposure. The level of arsenic in the human body tends to be higher in men then in women (IARC, 2012). Arsenic can be transferred to the unborn child via the placenta, where it is able to cross the blood brain barrier and can cause hazardous effects on child development (Tolins et al., 2014).

Human toxicity impact

Certain arsenic compounds, especially the most reactive and toxic forms, already show hazardous effects at lower concentrations (Cohen et al., 2013). Chronic arsenic toxicity, which is referred to as arsenicosis, is mainly characterized by changes in pigmentation in skin and keratosis with skin lesions (Martin & Griswold, 2009). The carcinogenic potential was determined by various studies; however, less is known about the underlying mechanisms of arsenic carcinogenicity (IARC, 2012). Arsenic mainly exerts its carcinogenic or tumour promoter effect through oxidative stress, altered growth factor expression and via interference with the signal transduction pathway (Porter et al., 1999). Out of these, oxidative stress is the most probable mechanism behind the carcinogenic and developmental effects (Tchounwou et al., 2012). In the human body arsenic binds to thiol and sulfhydryl protein chains and it can inactivate numerous enzymes causing and oxidative phosphorylation and impaired cellular respiration (Goyer, 2001). The health effects of lower-level arsenic exposure are widespread. It causes pigmentation, hypertension, cardiovascular disease, diabetes, immunological problems and developmental effects (Jaishankar et al., 2014). More than 200 million people worldwide are believed to be chronically exposed to arsenic above the safety level mainly due to exposure to contaminated drinking water (Tolins et al., 2014).

Numerous epidemiological studies have revealed toxic effects of arsenic compounds and evaluated cancer risks for the trivalent and pentavalent inorganic forms. The evidence is reliable enough to assume a cause-effect relationship between arsenic exposure and elevated lung cancer risk. Furthermore, association with bladder and kidney cancers and elevated risk of skin cancer and potentially liver cancer have been demonstrated. IARC has considered the present evidence sufficient and solid enough for bladder, lung, and skin cancers, while correlations with the other types of cancers are weaker and require more evidence (US-EPA, 1998; IARC, 2012). A high scale epidemiological study in Taiwan showed increased mortality rates dose dependently for all liver, lung, bladder and kidney cancers for most age groups (Chen et al., 1992). Another epidemiological study found correlation with higher death rate for a wide range of cancer types such as liver, kidney, skin, lung, bladder, nasal-cavity, stomach, bone, larynx and colon cancers and lymphoma, with further increased risk of cardiovascular diseases (Tsai et al, 1999). Further epidemiological studies showed the association with bladder and lung cancers (Smith et al, 1998; Marshall et al., 2007) and urothelial, urinary and kidney cancers (Chiou, 2001; Huang et al., 2008; Chen et al., 2010). Another epidemiological study in Chile identified correlation with the incidence of renal diseases on top of the bladder, liver and laryngeal cancers (Smith et al., 2012).

Although the cancer effects are the best revealed impacts, arsenic exposure can also lead to developmental neurotoxicity. The neurodevelopment has been demonstrated to be affected in a wide range of epidemiological studies (Tolins et al., 2014). Exposure during the first trimester of pregnancy is proved to be the most vulnerable period to arsenic exposure (McDermott et al., 2012). An important cause is the adverse development of nerve

cells upon exposure (Rai et al., 2010). A meta-analysis of studies assessing high exposure levels has shown significant association with decreased cognitive functions and identified a 6.1-6.5-point decrease in IQ score compared to unexposed children (Dong et al., 2009), while another study demonstrated similarly high decline in IQ scores in Mexico (Rocha-Amador, 2007). However, a longitudinal study in Bangladesh only showed a significant effect on IQ for girls but not for boys (Hamadani et al., 2011). A thorough meta-analysis of available epidemiological studies found a correlation with neurodevelopmental deficit with arsenic exposure and determined that a 50% increase in urine arsenic level is associated with a 0.39 full scale IQ loss while the same 50% increase in water arsenic level leads to a 0.56 IQ-point decrease (Rodriguez-Barranco et al., 2013). Arsenic exposure in childhood also resulted in lower scores in neurobehavioral tests at adolescent age (Tsai et al., 2003) and impaired visuospatial abilities, memory and problem-solving abilities in children (Rosado et al., 2007). Long-term lower-level arsenic exposure was also found to be negatively associated with certain neuropsychological functions such as language and visuospatial skills, executive functioning, global cognition, processing speed and immediate memory (O'Bryant et al., 2011).

Arsenic exposure from drinking water was further found to be negatively correlated with birth weight, leading to a 29g average decrease in new-borns (Yang et al., 2003). Additional human toxicological impacts have been revealed such as the suppression of the immune system which can lead to the promotion of cancer and other infectious diseases (Haque et al., 2017). Arsenic exposure also has been associated with cardiovascular risk factors including hypertension, myocardial infarction, diabetes and carotid atherosclerosis (Medrano et al., 2010; D'Ippoliti et al., 2015). However, the findings about increased mortality connected to cardiovascular diseases are rather inconsistent (Smith et al., 2012; Stea et al., 2013).

Direct valuation

While exposure from arsenic contaminated drinking water is a significant health concern, it is still not included in the GBD studies. The main reason is that the data is not sufficient to estimate accurate costs and burden for arsenic from the available epidemiological literature (Grandjean & Bellanger, 2017). A study in the Netherlands estimated the benefits of arsenic water content reduction and the consequent decrease in lung cancer cases. A total cost of €10.7 million was determined in the study (Ahmad et al., 2020). In another valuation study, the damage cost of heavy metals for unit emissions was estimated based on the slope factor obtained from the IRIS database. The results for arsenic were determined to be € 130/kg (Rabl et al., 2014). An earlier estimate calculated € 530/kg for arsenic emission from coal power plants in Europe (Needs, 2008). According to an estimate based on emissions from the E-PRTR industrial facilities in the EU, the environmental price for arsenic related to cancer effects was determined to be € 349/kg. For the Netherlands it was estimated to be € 417/kg. This data relies solely on emissions to air which only accounts for the 12% of total emissions in the EU (EEA, 2014). An updated assessment calculated € 11,044/kg emission from facilities from the same E-PRTR registry (EEA, 2021). This estimate relied on the methodology by Nedellec & Rabl (2016), where a unit cost of € 5,713 was calculated for arsenic.

3.3 Organic chemicals

3.3.1 Introduction

Organic chemicals play an important role in the modern economy. These chemicals include substances as pharmaceuticals, pesticides, plastics, fuels, solvents, explosives, surface coatings, adhesives, disinfectants, fire retardants and numerous further important substances. Of the over 50 million chemicals that have been characterized so far, most are organic compounds. Some 100,000 chemicals are commercially produced in quantities large enough to raise concerns that they may become present in the environment and could potentially cause risks to the well-being of humans (Gama et al., 2012). Pesticides, developmental neurotoxicants and endocrine disruptors are mainly newly emerging but less characterized substances comprising of wide range of chemicals. For these reasons, they will be introduced shortly in this chapter.

Developmental neurotoxicants

Exposure to developmental neurotoxicants can lead to a wide range of hazardous effects including impaired cognition, IQ and executive functions as well as can cause attention deficit, learning disabilities, autism spectrum disorder and functional delays in brain development (Landrigan et al., 2018). Projected life-time earnings serve as a base for estimating productivity loss. Cognitive dysfunctions lead to long-term economic effects measured in decrease in IQ points. Avoiding IQ loss has a projected benefit of € 13,579 per IQ point per lifetime, although this figure may be an underestimation as it was calculated by neglecting certain costs (Bellanger et al., 2013). The foetus is exceptionally vulnerable to these chemicals as the developing brain and the developmental processes are extremely sensitive to exposure and injury (Grandjean & Landrigan, 2014). Important neurotoxicants are certain heavy metals such as lead and mercury, additionally pesticides, polycyclic aromatic hydrocarbons and brominated flame retardants are also noteworthy neurotoxic chemicals (Landrigan et al., 2018). Overall, there are twelve chemicals which have a strong cause-effect relationship with hazardous brain effects, while the real number of hazardous substances is undoubtedly much higher (Grandjean & Landrigan, 2014). According to an estimate, lead, methylmercury, polybrominated diphenyl ethers and organophosphate pesticides alone account for a total health burden that represents more than 2.5% of global GDP (Grandjean & Bellanger, 2017).

Endocrine disruptors (EDCs)

Endocrine disruptors are a group of chemical pollutants that are capable of blocking or altering the functions of various hormones, including reproductive and developmental hormones, by interfering their signalling nuclear hormone receptors (Swedenborg et al., 2009; WHO, 2017). Through this effect they can interfere with appropriate development at an early age (Attina et al., 2016). EDCs are widely used chemicals and abundant in numerous consumer products including soaps, shampoos, perfumes, plastics, and food containers. Exposure during early development can lead to chronic damages to organs and elevated disease risks. Notable examples are phthalates, bisphenol A, pesticides and brominated flame retardants. Many of the endocrine disruptors also have neurodevelopmental toxicity effects which makes them especially dangerous to children at an early age (Landrigan et al., 2018). The total cost of EDC exposures is estimated to be $ 557 billion for the EU and the US together being $ 217 billion for the EU alone. In this estimate only the effects of PBDEs, DDE, Organophosphate pesticides, BPA and Phthalates were evaluated using the cost of illness approach with health economic benefits. These

compounds only represent a small fraction of all EDCs thus the real costs can be considerably higher (Attina et al., 2016). Another study for Europe estimated that EDCs have economic costs of € 157 billion a year corresponding to the 1.23% of the total European GDP with high probability for significantly larger associated disease costs. This is equal to a per capita cost of € 322 in the EU (Trasande et al., 2016).

Pesticides (Herbicides, fungicides, insecticides)

The toxic characteristic of pesticides is embedded in their utility as this class of compounds is designed to cause harm to living organisms. Pesticides represent a very diverse group of formulations including various herbicides, insecticides, fungicides and rodenticides. To date, there are more than 20,000 different pesticides on the market which are released in millions of tonnes annually worldwide (Blair et al., 2014; Landrigan et al., 2018). Agricultural pesticides significantly increase the chemical burden both on humans and natural ecosystems (Nicolopoulou-Stamati et al., 2016). In 2007, around 2.4 million tonnes of pesticides were used for agricultural purposes and the metabolites of many of these chemicals are ubiquitous in human populations (Grube et al., 2011; Blair et al. 2014). In 2018, the total quantity of pesticide use was 4.12 million tonnes worldwide — almost half of this figure was applied in China (FAO, 2020). On top of the active ingredients, the pesticides contain other potentially toxic chemicals such as solvents and preservatives which appear as further risk factors to humans (Cox & Surgan, 2008). Rapidly industrializing countries are the biggest users of pesticide products globally. In many of these developing countries exposure data is lacking which embodies a big environmental risk for local populations (Landrigan et al., 2018).

The health impact of pesticides is determined by the type of pesticide, the duration and route of exposure and the health conditions of individuals (WHO, 1990). The accumulated data of genetic, biochemical and toxicological studies have demonstrated dose and context dependent effects and it is believed that the vast majority of pesticides alter cellular metabolism in various ways (Sabarwal et al., 2018). Although the emergence of pesticides has become a global issue, children and developing foetuses are believed to be especially vulnerable to the adverse effects as they consume higher quantities of substance per kilogram of body weight (RIVM, 2009). Environmental exposure is generally lower than occupational exposure; however, affects a much higher fraction of the population including more susceptible subgroups such as children and the elderly. In the Netherlands, a high proportion of the population could be at significant exposure to pesticides as the population lives densely in proximity to agricultural lands (Brouwer, 2018). Chronic exposure to pesticides can increase the risk of certain non-communicable diseases such as cancers, lung disease and neurodevelopmental disorders. Moreover, they can have damaging effects on the immune, nervous, respiratory, endocrine, gastrointestinal, and reproductive systems (WHO, 1990; Blair et al., 1990; Blair et al., 2014; Guyton et al., 2015; Landrigan et al., 2018). Childhood cancer has also been connected to occupational and environmental exposure of parents (Infante-Rivard & Weichenthal, 2007). Pesticides with similar modes of action can have cumulative effects but synergistic effects can also occur. As the global burden is not estimated for pesticides, the need arises for comprehensive research regarding the impact of these toxic substances (RIVM, 2009). In the case of pesticides epidemiological studies are considered to be inaccurate and difficult to execute as exposure levels are very uncertain. Thus, the attributed effects are difficult to be used for damage quantification. Generally, the damage cost of pesticides is estimated to be 0.17 €/person per year for the EU which accounts for a lifetime cost of € 12 (Fantke et al., 2012; Rabl et al., 2014).

3.3.2 Chlorpyrifos

Chlorpyrifos is an organophosphate insecticide which is proven to cause neurotoxicity and which is considered a developmental neurotoxicant. The main mode of action of organophosphate insecticides appears to be the inhibition of brain acetylcholinesterase enzyme (AChE) (RIVM, 2009). The inhibition of cholinesterase function interferes with the normal synapse formation role of acetylcholine during the brain development causing potentially irreversible changes in brain functions (Augusti-Tocco et al., 2006). As many pesticides, Chlorpyrifos is mainly used in the agricultural sector but occasionally for household pest control (Eaton et al., 2008).

Environmental fate and human exposure

After release, Chlorpyrifos quickly volatiles into the atmosphere or binds to particles in the soil due to its low water solubility. In the environment Chlorpyrifos undergoes an oxidation step where the most important toxic metabolite, the chlorpyrifos-oxon, is produced. Proximity to Chlorpyrifos contaminated areas such as farmland can lead to much higher concentrations compared to the background exposure of the general population (Eaton et al., 2008). There is probably only a low risk of chronic adverse effects from exposure, while acute health effects are more frequent (Phung et al., 2013). The main exposure pathways for Chlorpyrifos are inhalation, ingestion and dermal exposure wherein dietary intake is the largest source of non-occupational form of exposure. Inhalation mainly occurs due to residential pest control and acute exposure to farmers applying the substance (Eaton et al., 2008). The central and peripheral nervous systems are the primary targets for the chemical and evidence suggests that these are the only sites of action in the human body (Eaton et al., 2008). The developing foetus is especially vulnerable to the substance as Chlorpyrifos is able to cross the placenta from the mother to the foetus damaging the unborn child (Whyatt et al., 2005).

Human toxicity impact

Independent studies and industry supported studies have contradicting findings about the neurodevelopmental effects of Chlorpyrifos. These confronting results impede scientific society to draw a conclusion about the real toxicity impacts of the chemical. In the EU, the acceptable intake level was determined based on erythrocyte acetylcholine esterase activity from rat toxicological studies carried out by an industry supported research (Anon, 1998; Mie et al., 2018). However, newer independent epidemiological studies identified deleterious effects on neurodevelopment at current exposure levels, and at lower doses compared to the determined regulatory exposure level, causing decreased IQ at school age at the level of current exposure (Grandjean & Landrigan, 2014). Additionally, a new study pointed out various flaws in the experimental design of the industry sponsored studies in relation to human exposure modelling for the prenatal period which could lead to biases in the initial assessment (Mie et al., 2018).

Based on well-designed longitudinal observation studies initial evidence has emerged that Chlorpyrifos exposure may lead to cognitive dysfunctions at lower exposure levels than what is present in the EU (Engel et al., 2011; Rauh et al., 2006). Moreover, in other studies Chlorpyrifos exposure was linked to smaller head-circumference new-borns with further abnormalities including thinning of cerebral cortex (Rauh et al., 2011; 2012; Bouchard et al., 2011). Further evidence revealed negative impacts on mental development and pervasive development of children (Eskenazi et al., 2007) while upon postnatal exposure increased prevalence of attention problems and ADHD was also found in boys (Marks et al.,

2010). Prenatal exposure was also associated with decreased birth weight and birth length (Whyatt et al., 2005) impaired foetal growth, developmental delay and behavioural problems in children (Whyatt, 2004; Rauh et al., 2006b). Exposed children also underperformed in the Psychomotor Development and Mental Development Indexes (Rauh et al., 2006). Additional findings showed that Chlorpyrifos exposure particularly affected the hippocampal region in the brain of rats and subnormal hippocampal dopamine and 5HT levels were observed in humans too (Aldridge et al., 2005). On the other hand, some epidemiological studies reporting neurodevelopmental effects did not provide complete data to confirm their findings (Dourson et al., 2020) and certain studies did not find brain cholinesterase activity at established safe doses which questions if Chlorpyrifos actually hazardously affects the foetus (Marty et al., 2012).

On top of the neurodevelopmental effects, epidemiological studies have revealed compromised development of reproductive functions due to prenatal exposure. Chlorpyrifos performed weak reproductive toxicity with an anti-androgenic effect and led to hypothyroidism influencing the thyroid hormone signalling pathway which also has a crucial role in brain development (Jeong et al., 2006). Strong toxicological evidence was also found for endocrine disruption due to AChE activity (De Angelis et al., 2009). Although Chlorpyrifos is not listed by IARC as a potential carcinogen, studies have shown some evidence of its carcinogenicity. An epidemiological study found a correlation between Chlorpyrifos use and elevated breast cancer risk (Engel et al., 2017). Newer studies also found more evidence in rodents that exposure to Chlorpyrifos can increase tumour incidence and decrease latency time for tumour growth while inducing migration and invasion of cancer cells thus promoting breast cancer formation (Ventura et al., 2018; Lasagna et al., 2020). Some epidemiological studies have produced evidence establishing stronger connections with Chlorpyrifos and other cancer types such as lung cancer (Alavanja et al., 2004a; Lee et al., 2004a), and showed exposure related responses to rectal cancer (Lee et al., 2007).

Direct valuation

Organophosphate exposure, including also Chlorpyrifos, was assessed in the EU and estimated to be responsible for 59,300 intellectual disability cases and 13 million IQ point losses annually. This translates to a total cost of €146 billion (€46.8 billion - €195 billion) associated with the organophosphate exposure due to cognitive impairments (Bellanger et al., 2015).

3.3.3 Glyphosate

Glyphosate is considered to be a broad-spectrum non-selective herbicide. It has become one of the most widely used pesticides globally since its appearance on the market in the 1970s particularly as a consequence of the introduction of genetically engineered glyphosate-tolerant plants. Glyphosate is available on the market in a range of chemical forms and used in mixtures with other substances to form the Glyphosate-based herbicides which were used in 79 million kg worldwide in 2014 (Benbrook, 2016; Andreotti et al., 2018; FAO & WHO, 2019). Glyphosate is a member of the organophosphorus compounds and capable of the competitive inhibition of 5-enolpyruvylshikimate-3-phosphate synthase enzyme which is responsible for the synthesis of the three aromatic amino acids in plants. For a long time, the application of Glyphosate was considered safe to the environment; however more recently concerns arose about its potential carcinogenic and genotoxic effects (Andreotti et al., 2018).

Environmental fate and human exposure

The human exposure data of this widely used herbicide is very scarce and accurate risk assessments are still lacking (Gillezeau et al., 2019). Glyphosate and its main metabolites show low mobility after soil treatment and mainly remain at the site of application (EFSA, 2015). Exposure can occur via inhalation and ingestion, oral intake of food and drinking water being the most important sources affecting the general populations (OCSAPP, 2017). Occupational exposure is also an important source of exposure and among workers the dermal route is considered the main exposure pathway (Conolly et al., 2019). Glyphosate exposure can be measured based on the urine concentration of a metabolite Aminomethylphosphonic acid (AMPA). AMPA can be detected from all soil, water, plant, animal and food samples due to ubiquitous exposure. The average environmental exposure to Glyphosate can be as high as 7.6µg/L while occupational exposure can reach 10-fold higher levels (Gillezeau et al., 2019). Glyphosate and metabolites mainly accumulate in the kidney, liver and colon but only reside in the body for approximately 48 hours when it is mostly eliminated via faeces (Williams et al. 2000; Peillex & Pelletier, 2020).

Human toxicity impact

Generally, Glyphosate has only modest hazardous effects on humans and other mammals. However, conflicting results have been presented regarding its human toxicity impacts (Tarazona et al., 2017). As many epidemiological studies have found a correlation between non-Hodgkin lymphoma (NHL) and multiple myeloma, IARC classified Glyphosate as a probable carcinogen (Group 2A) which underlines the second strongest evidence to cancer (IARC, 2015). A meta-analysis of epidemiological studies has also found a correlation between the incidence of NHL and Glyphosate (Zhang et al., 2019). In contrast, other epidemiological studies produced conflicting results to these findings. A systematic review of the epidemiological studies found no clear causal relationship between Glyphosate exposure and the occurrence of cancer cases (Acquavella et al., 2016). Furthermore, it was also considered by the European Food Safety Authority (EFSA) as unlikely to have carcinogenic effects in humans (EFSA, 2015). A newer well-designed high-scale study did not show any statistically significant relation with NHL risk while a slight increase in risk was shown towards acute myeloid leukaemia when the highest exposure quartile was compared to the non-exposed population (Andreotti et al., 2018). This raises the possibility for carcinogenicity to a rarer type of cancer but not to NHL (Kogevinas, 2019). Additionally, another high-scale analysis of epidemiological data comprising millions of farmers also revealed no correlation with Glyphosate exposure and NHL risk (Léon et al., 2019). All these findings were further supported with results from another systematic epidemiological review which strongly questions the IARC group 2A classification of Glyphosate (Barukčić, 2020). It was further argued that incorporation of these newer studies (specifically Andreotti et al., 2018) to the meta-analysis by Zhang et al. (2019) would have resulted in non-significant correlation between NHL and Glyphosate exposure. Besides this, according to an analysis of the aforementioned study, Zhang et al. (2019) did not perform the meta-analysis appropriately thus Glyphosate should be marked as not likely to be carcinogenic (US-EPA, 2020). The IARC also defined Glyphosate as genotoxic due to its potential to induce oxidative stress. Nevertheless, a systematic review of epidemiological literature concluded that there is no linkage between Glyphosate formulations and genotoxicity (Brusick et al., 2016). Overall, it is very unlikely that glyphosate causes genotoxicity or carcinogenicity as a consequence of dietary exposure (FAO & WHO, 2016).

On top of the hypothesized cancer effects, Glyphosate has been mainly linked to hazardous impacts on the immune system by interfering with the complement cascade, phagocyte functions and lymphocyte response which can lead to cytotoxicity and oxidative stress in humans (Peillex & Pelletier, 2020). There is some evidence suggesting estrogenic effect

(Benachour et al. 2007) and cardiovascular effect of Glyphosate (Wang et al., 2019) based on cell and rodent studies while anxiety and depression was also associated with exposure in rodents, causing dysbiosis and leading to learning and memory impairments (Ait Bali et al., 2018). Exposure was also associated with inflammatory diseases (de Raadt et al., 2015) and airway inflammation such as asthma (Hoppin et al., 2017). Although there is strong evidence in animals for the toxic effects of Glyphosate and recent studies raise higher concerns, the human epidemiological effects are scarcer. Studies would hence need to provide more evidence to build a stronger causal relationship to human diseases (Vandenberg et al, 2017; Peillex & Pelletier, 2020).

3.3.4 Polycyclic aromatic hydrocarbons (PAHs) and benzo[a]pyrene

Polycyclic aromatic hydrocarbons are a group of organic compounds which are formed as a product of incomplete burning or heating of organic materials such as coal, oil and petrol (Abdel-Shafy et al., 2016). Their production and emission can originate from natural sources such as volcanic activities, seepage of aromatic hydrocarbon deposits and wildfires, but anthropogenic emissions remain the most prominent source. Main anthropogenic causes are residential heating, coal gasification, asphalt production, aluminium production, petroleum refining, emission of diesel exhaust and wood stoves (Abdel-Shafy et al., 2016; RIVM, 2018). First of all, PAHs can be formed by pyrogenic processes during burning, such that the highest concentrations are found around urban areas. Another process, the petrogenic formation can occur among others through crude oil maturation (Abdel-Shafy et al., 2016). BaP is frequently used as a reference for all PAH emissions and the toxicity is measured in BaP equivalent assuming additive effects of various PAHs (EEA, 2021).

Environmental fate

Benzo[a]pyrene (BaP) is a highlighted member of PAHs due to its early-known carcinogenicity (Verma et al., 2012). The BaP molecule contains five rings and has low vapour pressure. This leads it to be absorbed to particles forming part of particulate matter. The BaP molecules can reside in the atmosphere for a wide range of time spans depending on the emission source. It deposits on the earth surface by dry or wet deposition from nearby or distant sources. (Hussein et al., 2017). Atmospheric fallout is the prominent source of contamination (Ciecierska & Obiedzin, 2013). BaP is effectively insoluble in water but can deposit on the surface of water bodies where it can be absorbed to particles and form part of the sediment phase (Abdel-Shafy et al., 2016). Due to its low solubility, it partitions between soil and sediment in 99% of the cases (Hattemer-Frey & Travis, 1991). The mobility of the compound in the soil is highly influenced by the soil particle and pore size where the BaP molecules are bound to (Masih & Taneja, 2006).

Human exposure

PAHs are usually present in mixtures which makes it more complicated to assess their individual effects. BaP and other PAHs can enter the human body via inhalation, ingestion, or dermal contact. Exposure to PAHs mainly occurs via inhalation of tobacco smoke and other smoke sources. One of the major sources of contamination is food processing, mainly drying and smoking processes that directly expose humans. Breathing of fume exhaust can be another hazardous consequence of occupational exposure. PAHs and especially BaP are important constituents of tobacco smoke which are one of the main factors behind smoke related cancer cases (ACGIH, 2005). Although tobacco smoke is the prominent source, exposure to BaP via food has been gaining attention in the literature lately (Hilton et al., 2017). Dietary intake is responsible for most of the baseline exposure and constitutes an

important exposure pathway for non-smokers. Bakery products, cereals and grains contribute to 29% of BaP exposure, while grilled and barbecued meat contribute to 21% of total intake (Kazerouni et al., 2001). BaP disperses rapidly in the body and due to its high lipid solubility, it is highly bioavailable and tends to accumulate mainly in the adipose tissues (RIVM, 2018).

Human toxicity impact

The metabolites of BaP can cause damage to the DNA which in if unrepaired can lead to cancer formation affecting mainly the respiratory tract. BaP can further induce proliferation and migration of cells that contain the damaged DNA. This is the reason why BaP is considered as group 1 carcinogenic by IARC (RIVM, 2018). The carcinogenic effects are mainly attributed to epoxide and dihydrodiol metabolites of the compound (Armstrong et al., 2004). The health effects are widely researched, and exposure has been connected to many types of cancers. Around 60% of lung cancer mutations are believed to be caused by PAHs, especially by BaP (Verma et al., 2012). Further epidemiological studies have established strong correlation with increased lung cancer risk (Armstrong & Gibbs, 2009; Olsson et al., 2010; Friesen et al., 2009) while potential risks for bladder cancer were also shown (Armstrong et al., 2002; Gu et al., 2008). Other studies have demonstrated association with BaP exposure and elevated risk to cervical cancer (Gao et al. 2011) as well as its synergistic effect with human papillomavirus for cervical cancer progression was also observed (Alam et al., 2007). BaP also showed potential for breast carcinogenicity and elevated risks for prostate cancer formation (Perera et al., 1995; Venkateswaran & Klotz, 2010) while skin tumour induction was also observed in rodents (Sivak et al., 1997) and potentially humans (Costa et al., 2010). Besides these impacts, kidney tumour induction was also revealed in rats (Kroese et al, 2001).

The gene alteration effect of BaP in human cells can have immunosuppressive consequences (Kaarthik et al., 2008; Verma et al., 2012). Toxicity studies in rats showed increased immunosuppression and thereby was associated with increased susceptibility to cancer and other diseases (IPCS, 2010). Furthermore, rats experienced decreased serum IgM, IgA and B lymphocyte concentrations after exposure (De Jong et al., 1999). The immune toxicity is mainly expressed by the suppression of humoral and cell mediated immune responses (Verma et al., 2012).

Neurotoxicity and developmental toxicity are other important characteristics of BaP. Epidemiological studies found that BaP exposure decreased birth weight and birth length (Duarte-Salles et al., 2012). It was also associated with increased incidence of abortion (Wu et al., 2010), long-term memory loss (Zhang et al., 2008), decreased head circumference due to developmental delay, and a loss of 4.31-4.67 IQ points for highly exposed children (Perera et al., 2009). BaP also interferes with reproductive functions showing decreased epididymal sperm count, testicular lesions (Chen et al., 2011), lowered foetal survival, lower number of pups and decreased weight of thymus (Kroese et al, 2001; Archibong et al., 2012). An extensive collection of studies including other numerous human and animal studies are summarized by the US-EPA (2017).

Direct valuation

A study in New York showed that a slight decrease in ambient PAH concentration could lead to an increase in IQ points and consequently lifetime earnings of $ 215 million (~€ 328.5 million in $€_{2015}$) for a single year cohort in New York City (Perera et al., 2014). According to the estimate (which was based on emissions to air from the E-PRTR industrial facilities) the

environmental price for PAHs (BaP equivalent) related to cancer effects was determined to be € 1,279/kg. This emissions from industrial facilities account for only 6% of total PAH emissions, meaning the real damage costs could be significantly higher (EEA, 2014). An updated assessment calculated a cost of € 11,965/kg based on facilities from the same E-PRTR registry (EEA, 2021).

3.3.5 Bisphenol A (BPA)

BPA is a widely used compound in consumer products, frequently present in polycarbonate-based food packaging materials and in the epoxy resin lining of aluminium cans, which are the most important sources of dietary exposure. Besides these items, BPA is used in toys, cosmetics, thermal paper, and medical devices. Overall, BPA is produced in about 6,800 tonnes a year worldwide (Vandenberg, 2013).

Environmental fate and human exposure

BPA leaches into the environment from consumer products during everyday human use while human exposure is still believed to be far under the daily tolerable intake in Europe (Vandenberg et al., 2012; RIVM, 2018b). Nonetheless, BPA was ranked as a substance of very high concern by the European Union in 2017 (ECA, 2017). The exposure of the general population almost exclusively occurs via ingestion while BPA can be detected in water, air, dust samples, soil and in every human being on earth (Groff, 2010; RIVM, 2018b). Dermal absorption and inhalation also occur, but these pathways are much less relevant for the general population (HCON, 2019). Working with manufacturing and handling of BPA rich products, however, can lead to higher exposure via inhalation and skin absorption (Li et al., 2010). Assessing the exposure to BPA is complicated since the adult liver rapidly metabolizes the compound which has an approximate half-life of 6 hour and the body completely eliminates it through the urine within a day. The rapid elimination can easily lead to the underestimation of toxicity risks related to BPA due to the absence of chronic exposure data (Stahlhut et al., 2009; Grandjean & Landrigan, 2014; Braun, 2016).

Human toxicity impact

Exposure to BPA can cause allergic reactions and respiratory irritations as well as it potentially causes liver and kidney toxicity and endocrine disruption (RIVM, 2018b; HCON, 2019). BPA's main mode of action in the human body is manifested in affecting oestrogen receptor (ER) related mechanisms (vom Saal et al., 2007) but the substance also interferes with other pathways such as thyroid hormone receptor, androgen receptor and peroxisome proliferator receptor pathways (Vandenberg et al., 2012). Allegedly, BPA also has a low dose non-monotonic effect which is not predicted by high dose toxicological studies (Vandenberg et al., 2012; Vandenberg, 2014; HCON, 2019). However, there are mixed findings regarding this potential effect (Vandenberg et al., 2012).

The foetus is particularly susceptible to BPA exposure during the developmental phase (Mustieles et al., 2015). Although BPA is one of the most studied ECDs, strong epidemiological relationships still need to be confirmed as the links to various physiological effects are not well understood. What is known, is that BPA surely multiple steroid hormones and alters normal brain development mostly leading to behavioural disorders (Nesan et al., 2018). Perinatal exposure to BPA can lead to neurobehavioral disturbances and disruption of normal maternal care patterns in rats. Human epidemiological and animal toxicity studies have shown clear results of impaired cognitive and behavioural effects such as a positive correlation with the prevalence of anxiety, depression, hyperactivity,

problems with emotional control and behavioural inhibition especially in the case of girls. This is attributed to the impact of BPA on endocrine or neurotransmitter pathways which disrupts brain differentiation and affects behaviour. The results highlight a different sensitivity of men and women to BPA during the gestational period (vom Saal et al., 2007; Braun et al., 2011).

Since BPA functions as a weak oestrogen, it influences the ER function which has effect on pubertal development (Howdeshell et al., 1999), while it also interacts with androgen and thyroid receptors (Nesan et al., 2018). During the foetal brain development BPA also interferes with various factors which among others affect brain regionalization (Haubst et al., 2004) and reduces ER expression in the hippocampus (Xu et al., 2010). Additionally, BPA exposure was linked to activated changes in cellular morphology and dendritic growth, (Mathisen et al., 2013). It further led to impaired spatial learning memory in humans (Liu et al., 2016) and caused alteration of the dopaminergic system in rodents (Zhou et al, 2011). Parental behaviour is also found to be vulnerable to perinatal exposure to BPA supposedly because BPA disrupts normal organization of the brain and alters steroid hormone production which can impair social interactions of the upcoming generations (Rosenfeld, 2015). Adverse nursing behaviour of rodents has been assessed by a wide range of studies demonstrating decrease in nursing time (Palanza et al., 2002), disrupted maternal care (Della Seta et al., 2005) and impaired dishabituation (Wolstenholme et al., 2013). Human epidemiological studies have also revealed differences in neurodevelopmental behaviour such as increased externalizing and aggressivity in boys (Perera et al., 2012; Evans et al., 2014) and girls (Braun et al., 2009) while another study showed decreased levels of aggression in girls as a consequence of perinatal BPA exposure (Perera et al., 2012). Adverse immune effects can also arise due to exposure during the developmental phase (Hessel et al., 2016). One of the most significant impacts of BPA is increased adiposity, body mass index and risk for being overweight (Valvi et al., 2013; Harley et al, 2013; Hoepner et al, 2016). Overall, the body of evidence seems solid about the obesogenic nature of BPA (Braun, 2016).

Direct valuation

The association with childhood obesity has a strong toxicological correlation but lower epidemiological correlation. The total probability of causation is estimated at 20-69%, leading to an estimated annual health cost of € 1.54 billion in the EU (Legler et al., 2015; Tasande et al., 2016).

3.3.6 Phthalates and Dibutyl phthalate (DBP)

Phthalates are a group of widely used compounds with the function to enhance plasticity of rigid materials such as PVC, but are also important components of lubricants, solvents, adhesives, detergents, air fresheners, antifoam agents, food packaging and toy materials. Phthalates also form active and inert ingredients of certain pesticides and excipients of pharmaceutical products (Schettler, 2006; Engel et al., 2010; EEA, 2020). Phthalates are classified as toxic substances to human fertility acting as endocrine disruptors, but they are also associated with increased risk of obesity, insulin resistance, ADHD, asthma, cognitive disparities and behavioural problems (Braun, 2016; EEA, 2020). Phthalates are usually present as a mixture of chemicals which antagonistically affect both androgen and thyroid receptors (Prichystalova et al., 2017).

Environmental fate and human exposure

Phthalate esters can easily leak into the environment as they are not bound covalently to the products they are used in (Schettler, 2006). The vapour pressure of phthalates is generally low which makes them lipophilic in nature and further determines their partitioning in the environment. Dietary intake from contaminated food is the most prominent source of exposure and can be especially high among regular users of pharmaceutical products. (Schettler, 2006; Ahern et al., 2019). Dibutyl phthalate is the main phthalate ester compound and hence the main factor behind human phthalate exposure (Blount et al., 2000). DBP is extensively used as scent retainant in personal care products, fragrances, additives in pharmaceuticals, cellulose plastics and adhesives (Miodovnik et al., 2011; Braun, 2016). Exposure to phthalates is basically ubiquitous (Ahern et al., 2019). Environmental exposure can occur via inhalation ingestion and dermal contact. After absorption, phthalates rapidly metabolize and disperse widely in the human body (NRC, 2008). As phthalates have noticeably short residence time in humans, effects of long-term constant exposures are more difficult to assess (Miodovnik et al., 2011). Inhalation can occur via exposure to household air and dust but baking of polymer clays can result in a high single dose exposure. Skin absorption also occurs to a lower extent through clothing and cosmetics (Schettler, 2006). Importantly, higher phthalate exposure significantly affects people with lower social status which was also observed in the Netherlands (Ye et al., 2008; Navaranjan et al., 2019).

Human toxicity impact

Although DBP is used in disproportionally higher amounts than any other phthalate, its effect on gene expression is indistinguishable from other toxic phthalate esters which makes the attributed effects difficult to separate (Benson, 2009). DBP has been associated with numerous human disorders. It mainly acts as an endocrine disruptor and developmental neurotoxicant during the perinatal period. Epidemiological studies have identified a causal relationship with attention deficit and hyperactivity in children (Engel et al., 2010), and a possible association with autism spectrum disorders (Miodovnik et al., 2011). A significant share of these disorders could be related to DBP with an estimated attributable fraction of 8.88% of the population (Bellanger et al., 2015). Exposure to DBP during the foetal period further interferes with male reproductive development and leads to decreased masculinity of boys due to its anti-androgenic activity (Swan et al., 2010). A systematic review of epidemiological studies found a further correlation between anomalous semen parameters, decreased fecundity, and decreased testosterone levels in boys (Radke et al., 2018). Epidemiological studies also showed an association with impaired intellectual development of children after prenatal exposure to DBP which resulted in a significant 6.7 points decrease in IQ (Factor-Litvak et al., 2014). Moreover, adverse effects of mental, motor and behavioural development were observed (Whyatt et al., 2012).

Exposure to DBP in the adult population occurs due to presence in pharmaceuticals. Accompanying exposure levels can already interfere with the thyroid system (Nassan et al., 2019) causing lower serum T4 (Huang et al., 2007). High levels of cumulative DBP exposure were furthermore associated with increased risk of breast cancer in a nationwide study in Denmark (Ahern et al., 2019). In rats, DBP and other phthalates were demonstrated to lead to pregnancy loss upon exposure, while in humans, according to one study, evidence was not found that DBP could be associated with this kind of hazardous effect (Messerlian et al., 2016).

Direct valuation

While evidence is growing about phthalate related endometriosis, the probability of causation is estimated to be only 20-39% (Hunt et al., 2016). The total attributable cases were estimated to be 145,000 leading to a total cost of € 1.25 billion in the EU (Hunt et al., 2016). The costs were also estimated for male fertility and the total cost of benzyl and butyl phthalates on male reproductive system were identified to be € 4.71 billion with 618,000 additional assisted reproductive technology procedures. Moreover, it was estimated that there is a 40-69% probability that phthalate exposure lowers the body's testosterone concentration. With 24,800 deaths annually this is estimated to lead to an economic productivity loss of € 7.96 billion. The total costs of phthalate-attributable mortality due to testosterone reduction are potentially higher than calculated since indirect costs were not included in the valuation (Hauser et al., 2015; Trasande et al., 2016). Furthermore, total phthalate related obesity and adult diabetes were estimated to equal € 15.4 billion and € 607 million respectively (Trasande et al., 2016). Lastly, EDCs including phthalates showed an additional burden of € 199 million connected to autism (Bellanger et al., 2015).

4 Total damage costs from epidemiological studies

4.1 Introduction

In this chapter the methodological framework of our effort to derive at a total cost and unit damage cost value for human toxicity will be discussed. Our methodological framework will be based on an epidemiological estimate of the total costs of the heavy metals (arsenic, mercury, chromium (VI) and cadmium), pesticides (Glyphosate and Chlorpyrifos) and chemical compounds (benzo[a]pyrene, dibutyl phthalate and bisphenol A) that were discussed in Chapter 3. From these studies we took the estimates of the relative risks, calculated the population attributable fraction and applied them to calculate our estimate of the total damage in the EU28 and for the Netherlands.

In the remainder of the chapter, we will outline first the building stones of our framework in Paragraph 4.1. Then we will elaborate in Paragraph 4.2 all the necessary calculations undertaken to derive at an estimate of the total damage from emissions of the investigated substances. Finally, in Paragraph 4.3 we will present the results from our calculation and compare this with results in the literature.

4.2 Methodology: five building blocks

The method used to establish an estimate of total damage costs is grounded in the epidemiological literature. This contrasts with the approach that is used in the Environmental Prices Handbook which largely is based on toxicological information. Knowing the toxicological impacts is helpful in calculating the potential health effects and in determining the toxicological value of the chemicals. It is being used in characterisation models like Uses-LCA (Huijbregts et al., 2005) or USEtox (Frantke, 2016). However, it reveals less about the actual health impacts when a substance is emitted into the environment from various sources and disperses widely through various pathways. Additionally, toxicological data is mostly derived from only one impact, whereas epidemiological data suggests other diseases can also be attributed to exposure of the chemical at hand. Finally, epidemiological data can be especially useful to determine the effect of low levels of chronic exposure to specific compounds, as is typically with environmental pollution, which are often difficult to reveal in toxicological studies that are more associated with direct (acute) effects. This resembles very much the situation with tobacco smoke: while toxicological evidence of the adverse health consequences were small or absent, epidemiological studies revealed overwhelming evidence of the negative impact of smoking, actively and later passively (Samet, 2016).

The main challenge in epidemiological studies is that in many cases it is difficult to determine the correlation between exposure and disease. Moreover, it can take many years and long-term exposure to develop a disease which makes the epidemiological approach much slower to prove adverse health effects of chemicals. Therefore, valuation using epidemiological literature tends to increase over time, as more impacts from pollution become apparent.

The method we employ here consists of five building blocks[7]:

1. Establishing the relative risk (RR) from exposure to a substance from epidemiological literature. The relative risk is a measure of the strength of an association between an exposure and disease, and can be used to assess whether an observed association is likely to be casual.
2. Calculating the population attributable fraction (PAF). The population-attributable fraction is a measure of how much of the population burden of disease could be eliminated if a specific risk factor (like exposure to chemical pollution) was removed from the population. The attributable fraction reflects the fraction of disease cases that would disappear if the population was not exposed to the substance at hand and is easily calculated based on the exposure-response relationship for the identified percentile ranges (Prychistalova et al., 2017).
3. Calculate the total physical burden of disease from exposure to pollution. Physical measures like the Disability Adjusted Life Years (DALY) that expresses the total impact from pollution on mortality and morbidity.
4. Monetize the impacts to express the burden of disease in a financial metric (e.g., billion Euros) using the human capital approach.
5. Compare this figure to other studies that have calculated the total burden of disease to investigate if our approach yields similar results and to discuss differences.

The method was employed on the nine substances that have been discussed in Chapter 3. Epidemiological studies for each of the nine substances were included. From these studies relative risks and population attributable fractions were gathered. Based on these RR values and PAF's, we calculated the environmental prices using the so-called *human capital approach*. This approach was previously used by Bellanger et al. (2015), Trasande et al., (2015) and Prichystalova et al. (2017) and will be explained in more detail in the next paragraph. The studies which reported relative risk or provided sufficient data to calculate the relative risk were selected for the current report.[8]

Below these will be elaborated in more detail in the subparagraphs.

4.2.1 Relative risks

The relative risk (or risk ratio; RR) shows the difference in incidence rate between different exposure groups in the population. It thus compares the exposed population to the non-exposed population. Determining the RR was an essential part of our project because it is needed to determine the attributable fraction. In epidemiology of air pollution, the RR expresses the chance that people develop, e.g., lung cancer from inhalation of cadmium compared to the chance of lung cancer from people that have not been exposed to cadmium. The Attributable Fraction (AF) calculated with the help of the RR then expresses

[7] The followed approach for valuation thus is based on quantification of the attributable fraction related to exposure — a method that was originally formulated by the Institute of Medicine (IoM, 1981). Calculating the PAF starts with identifying the available epidemiological literature with exposure-response relationships. These studies are screened, and the most relevant studies are selected and subjected to the further valuation steps.

[8] From a scientific perspective one may argue that there has been a selection bias towards studies which made it possible to calculate the relative risks and studies which found positive correlation. On the other hand, there has been a negative selection bias towards studies that have proven effects through epidemiological data, which tend to be a limited subset of the potential impacts from chemical pollution. In the case of Glyphosate we did explicitly also include studies that did not find a statistically significant relationship and give an upper and lower estimate.

the percentage of lung cancer cases that would not occur if cadmium exposure was zero in the entire population.

The relative risk was derived from selected epidemiological studies included in Chapter 3. We employed three ways to calculate the relative risks:

1. In many instances the RR was determined in the epidemiological studies, thus it was directly used in our calculations.
2. If the RR was not determined or reported directly in the studies, it could sometimes be calculated from the reported cases, following the formula adopted from Rabl et al. (2014) as follows:

$$RR = \frac{\%\ exposed\ cases\ in\ population}{\%\ of\ non-exposed\ cases\ in\ the\ poplation}$$

In the case of ubiquitous exposure or when the epidemiological studies divided the exposure groups based on exposure levels, the reference exposure group (or non-exposed group) was established to be the exposure group without elevated incidence rates of disease outcomes. To calculate the RR, this no-effect group was compared to the higher exposure groups displaying statistically significant elevated incidence rates from the general population. In case of occupational exposure, the incidence rate among the worker group was compared to the general population to gain the specific RR of occupational exposure. In case only hazard ratios (HRs) were available we substituted the RR with the HR values which is mainly useful for short-term cohort studies (Crowson et al., 2009).

3. In other cases, the relative risks could be estimated from the odds ratio (OR). In cohort studies, the OR can be used to approximate the RR. However, substituting the RR with OR is only applicable when certain conditions are met. In cases when the incidence rate in the population is low the OR is closer to RR. However, as the prevalence increases the OR will overestimate the RR. More specifically, using the OR rather than the RR will lead to over estimation if the correlation between exposure and diseases is positive and underestimation in the case of negative correlation. Certain methods can be used to derive a closer estimation to the RR from OR. For instance, adjustments can be made by a modified logistic regression, calculation is possible with the Mantel-Haenszel equation or by using and alternative and simpler equation by Zhang & Yu (1998):

$$RR = \frac{OR}{(1 - P_0 + OR * P_0)}$$

In this equation P_0 represents the incidence rate of the disease in the non-exposed population. This equation can be used to correct the adjusted OR by logistic regression in case the Mantel-Haenszel method is not applicable (Zhang & Yu, 1998). In our calculations, in the end, we did not use the odds ratio and relied exclusively on RR values derived or calculated from the epidemiological studies.

4.2.2 Population attributable fraction

The contribution of a risk factor such as contribution of a chemical substance to a disease can be further quantified by the population attributable fraction (PAF). The metric indicates the percentage of people with the disease that would not have developed the disease had they not been exposed to the substance. Or to look it from another way, it basically determines the reduction in death or disease cases if the specific risk factor is removed or reduced to a desired level (Prüss-Ustün et al., 2017). The total PAF for various

substances can surpass 1 as a total as numerous risk factors can lead to the development of a certain diseases (Lin et al., 2013). In this study we did not adjust the PAF to further risk factors other than the ones used in the epidemiological studies for adjustments. In one way, PAF can be calculated based on the below equation:

$$PAF = C_e * \frac{RR - 1}{RR}$$

In this formula, called Miettinen's formula, RR refers to the aforementioned relative risk calculated (or adopted) from the epidemiological studies. The C_e corresponds to the case fraction which is the proportion of exposed cases among all cases within the total population.[9] Besides this approach, a different method, the Levin's formula exists which also can be used to determine the PAF. In principle the two equations attain the same results and the choice between the two mainly depends on the availability of data in specific studies. The Miettinen's formula is mostly used in case-control studies, while the Levin's formula is applied mostly in cohort studies (Lin & Chen, 2019). The Levin's formula is also based on the same RR values with the relation as follows:

$$PAF = \frac{P_e * (RR - 1)}{P_e * (RR - 1) + 1}$$

In this equation P_e stands for the exposed population fraction.[10] In our report the P_e values were determined from the same epidemiological studies that were used to calculate the RR. It is important to note that unless data for exposed population fraction was explicitly mentioned in the studies, in our calculation P_e was chosen to be the proportion of population, which was compared to the other, higher exposure segment of the population (1-P_e) in the epidemiological study to calculate the potential relative risk. This value was used to calculate the PAF in case elevated risk was found. Consequently, in our study we considered exposure level of P_e as excess exposure and 1-P_e as the 'optimal' level of exposure. Thus, this fraction does not capture precisely the real P_e value but can be seen as a reasonable estimate based on the available data. In case multiple exposure groups with elevated RRs were identified, the AFs were calculated to all separate exposure groups based on Hanley (2001) before summing them up to derive the total PAF. In the case of meta-analyses, the P_e was estimated from the studies used for deriving the RR value by taking the average population exposure.

4.2.3 Occupational exposure and population attributable fractions

In some cases, we used studies where evidence of the relative risks was obtained through occupational use of the substance (e.g., chromium VI in paint). Occupational exposure studies compare the risk of a disease upon occupational exposure with the incidence rate in the general population. Therefore, the P_e or C_e (to calculate PAF) were determined based on EU worker statistics or statistics for the Netherlands. The worker statistics were taken from Eurostat. Reports about the total EU or Dutch population with occupational exposure to cadmium were not available. Instead, it was assumed that workers in the following categories face cadmium exposure during their job: Manufacture of basic metals and

[9] Thus, it compares, for example, the number of people that gotten lung cancer in a certain period from exposure to cadmium compared to all people that have gotten lung cancer during that period.

[10] For example: the number of people exposed to a certain concentration of cadmium over the sum of the number of people exposed to this concentration of cadmium plus the number of people in the population that were not exposed to cadmium.

fabricated metal products, except machinery and equipment; Manufacture of other transport equipment; Manufacture of computer, electronic and optical products; Manufacture of electrical equipment; Manufacture of machinery and equipment; and Repair and installation of machinery and equipment. This led to the estimate that 325,000 workers in the Netherlands face occupational exposure to cadmium. For Chlorpyrifos the US agricultural worker statistics were used from https://www.ers.usda.gov. For chromium (VI) statistics for exposed worker population were taken from a European Commission report and it was assumed that the effected population fraction in the Netherlands is similar to the European average (EC, 2017).
In the case of BaP, asphalt worker statistics were taken from https://eapa.org/asphalt, aluminium worker statistics from https://aluminiumandalloys.com and coke industry worker statistics for the Netherlands and for the EU were taken from Eurostat. As only EU worker statistics were available, the population proportions were assumed similar for the Netherlands. The exposed population fraction was calculated by dividing the number of industry workers by the total population which resulted in relatively low PAF. These numbers are particularly important for certain substances such as chromium (VI) where occupational exposure data is almost the only source of human toxicity.

4.2.4 Burden of disease

To estimate the disease burden, we first derived the disease incidence for the total population at a specific age group. To obtain the necessary information, the GBD-results tool was used (http://ghdx.healthdata.org/gbd-results-tool — GBD, 2019). We gained the number of cases for the whole EU and for the Netherlands for specific diseases at specific age groups (the age groups enrolled in the epidemiological studies where the PAF was calculated from). To calculate the attributable cases for specific substances the Incidence was multiplied by the PAF.

DALY's were also acquired through the GBD results tool. Subsequently, the DALYs attributable to the environmental exposure could be calculated for the EU28 countries by multiplying the PAF with the DALYs for the specific diseases (GBD, 2019). For eight out of nine compounds, the total EU28 incidences (only used for cancers) and DALYs were taken for the specific diseases and for the specific age groups to establish the lower bound of the total environmental costs. The upper bound was estimated based on the assumption that the relative risk is the same for the whole general population as the determined RR for the specific age group (for occupational exposures, no upper bound was calculated as this assumption would be flawed). In the case of Chlorpyrifos the total incidences and DALYs were obtained for the US population and this data was used for the ultimate monetization step. Accordingly, we calculated the total costs and unit costs for the US. The reason behind the decision was that the EU did not renew the market authorization of the compound from 2021 January (EUR-Lex, 2020). Moreover, the emission for Chlorpyrifos in the EU and the Netherlands was already low in the last years, hence the monetization step would yield overestimated results while in the US Chlorpyrifos is still used in high quantities. Finally, the vast majority of epidemiological studies were implemented in the US which further supported our choice. The emissions data for Chlorpyrifos was taken from https://water.usgs.gov in pounds (lbs) with taking and average of the lower and upper values of the emission range. This average value was converted to kg for the calculations.

In the case of osteoporosis (consequence of cadmium exposure) we could not set the context in the research tool as cause, therefore we gained information for injuries (instead of causes) including fractures of hand, ankle, tibia, fibula, vertebrae, femur, hip, patella. For these injuries we only could obtain the value of Years Lived in Disability (YLD) which is only one part of the DALYs. However, since we could not derive further data for DALYs, in

this study we assumed that the fractures do not lead to mortality. The YLD data was thus used in combination with the PAF to estimate the attributable DALYs. In the case of obesity (consequence of BPA), the risk of high BMI was used to estimate the attributable DALYs by changing the context to risk from causes in the GBD research tool.

If the attributable cases were already determined in another study, we did not estimate the PAF using our own method. Instead, we took a different approach to determine the attributable DALYs. For example, Guerreiro et al. (2016) estimated the number of lung cancer cases which are attributable to BaP exposure in Europe. In this case we could calculate the DALYs based on the relationship of 13.6 DALYs/lung cancer cases estimated by Zhou et al. (2015). Based on our data regarding DALY cases this number seems to be an underestimation especially if we take into account the rise in life expectancy in the EU in the last five years. We hence derived the number of DALYs per lung cancer case based on the GBD data (17.6 for the Netherlands and 18.7 for the EU) (GBD, 2019).

In case of occupational exposure where no average age for commencing the job was determined, we worked with DALY cases from the age fraction of over twenty. We assumed that that the average number of years of exposure was fifteen.

4.2.5 Monetization using the human capital approach

The human capital approach is a method to estimate the monetarized losses that result from various diseases and dysfunctions. A large benefit of the human capital approach over other methodologies is that costs can be also attributed to subclinical dysfunctions or consequences that are not tied to any specific DALY or disease cluster. For instance, on top of the impairments, this method also can account for social cost, such as IQ losses which remain in the normal range without compromising human health conditions (Grandjean & Bellanger, 2017). The valuation can also incorporate direct costs which cover medical expenses, costs of rehabilitation and indirect costs such as projected lifetime earnings or loss of economic productivity due to premature death or progression of the of disability (Trasande et al., 2015). To estimate the effects on lifetime earnings or loss of productivity, future earnings are converted to present day earnings using a discount rate and by taking Purchasing Power Parity (PPP) into account.

Values used in this research.

The valuation follows the framework of the Environmental Prices Handbook by CE Delft (2018):

- For a DALY or VOLY we used € 70,000.
- Additionally, a Cost of Illness (CoI) value of 0.481 million/ cancer case was added to the total costs following Rabl et al. (2014).[11] This cost is an average CoI/case for cancer cases.
- Finally, the costs for IQ losses was estimated as € 17,500/IQ point as in CE Delft (2018).

All price levels are in $€_{2015}$.

[11] We did not adjust this cost to the 2015 price levels because technological improvement may lower such costs over time.

4.3 Comparison with other economic valuation studies

As a final step we compared the results with other studies. Available economic valuation studies were also integrated into our assessment to estimate the total costs in €/kg emission. We needed to take a different approach for the inclusion of various economic valuation studies as they can estimate multiple costs such as productivity loss, benefits of abatement and CoI. As a first step we converted the prices from other valuation studies to $€_{2015}$ prices. Three of the estimates relied on the slope factors from the IRIS database which USEtox also relies on. Other estimates followed the human capital approach for valuation. The studies usually determined the total cost of chemicals and rarely estimated costs/kg emission. In these cases, we calculated the share of costs based on the population proportion of the Netherlands (if data for the EU28 was available) and divided the number with the total emission from the Netherlands from 2017. The valuation studies were integrated into our final estimates in case we could not estimate the cost for a specific disease; while they served as comparison when prices were also calculated by us. Data for cancer cases (mainly from heavy metals) were gathered from Rabl et al. (2014), EEA (2014), Nedellec & Rabl (2016), EEA (2021) while non-cancer effects such as endocrine disruption and neurodevelopmental toxicity were derived from Bellanger et al. (2013); Bartlett & Trasande (2013); Pizzol et al. (2014); Perera et al. (2014); Bellanger et al. (2015); Legler et al. (2015); Hunt et al. (2016); Trasande et al. (2016), Hauser et al. (2016), Nedellec & Rabl (2016) and EEA (2021).

To combine our results with other non-overlapping valuation studies we added the values to the lower bound if the total costs were specifically calculated for the EU28. For mercury, results from CE Delft were available for the Netherlands in the form of unit costs related to IQ loss. Since we also could derive unit costs for mercury from two other studies (Bellanger et al., 2013; Bartlett et al., 2013) the average of the three was added to the combined total cost and unit cost. For the EU total costs, we used the results from Bellanger et al., 2013. In the case of BPA related obesity, we took the cost from Legler et al. (2015). Concerning the other substances (DBP, Chlorpyrifos and BaP) the valuations did not have compound specific total cost estimates for the EU. We calculated the total burden ourselves based on various assumptions (see details in the following paragraphs). For these compounds we only incorporated the damage costs to the upper bound of the combined results. The following paragraphs will describe in detail how we derived the total and unit costs from other valuation studies when additional calculation steps were necessary. The paragraphs also entail methodological description for chemicals and diseases where different approach was taken to calculate our results compared to the general methodology.

Dibutyl phthalate

We estimated the potential productivity loss due to IQ point loss upon phthalate exposure based on Factor-Litvak et al. (2014). The study determined a 6.6-point lower IQ for the highest exposure group at the age of seven in a New York City based cohort study. We estimated the total cost of exposure from the relationship defined for the EU as one point IQ loss = € 13,579 (Bellanger et al., 2013). The mean value of Monobutyl phthalate (metabolite of DBP) is lower in the EU population than in the corresponding US cohort. In the study a mean 37.6 g/L maternal urinary phthalate concentration was measured while for Europe an average of 23.9 g/L was measured (Schwedler et al., 2017). Thus, we applied an adjustment factor of 0.636 for calculating the total costs (we assumed a linear dose-response relationship). The total cost was calculated by multiplying the total number of children in the age group up to seven by the proportion of high exposure in the population. Subsequently, the result was multiplied by the number of IQ points lost and the price of one

point IQ loss. This yielded a total cost of € 73,662,730,063. Assuming a uniform emission distribution in the EU, the total cost in the Netherlands were calculated to be € 2,499,507,100 Combining this figure with the Dutch emission data yielded a unit cost of € 826,830/kg. This estimate is calculated with high uncertainty as we believe the IQ loss points are significantly overestimated. We did not include this figure in our final cost estimate due to the fact that other valuation studies concerning phthalates estimated significantly lower costs than the € 73.7 billion calculated for DBP only. Moreover, the underlying toxicity profile of DBP in USEtox also suggests lower impacts from exposure. Therefore, we considered this estimate as an outlier and did not include this calculation into the results. The reason behind the high costs is the high estimated IQ-loss for a large fraction of the population. The 6.6 points decrease affecting 25% of all new-borns due to DBP emission seems an unrealistic assumption and further investigation would be necessary to identify and confirm the real health impacts.

Many studies have estimated the burden of phthalate exposure connected to numerous diseases, however few performed estimations for specific phthalate compounds. For this reason, we derived the specific cost for DBP based on its contribution to total phthalate emissions. The dibutyl phthalate costs were calculated from the Dutch emission data (http://www.emissieregistratie.nl) The total phthalate emissions in the Netherlands equalled 101,933 kg and the DBP emission equalled 3,387 kg. The total share DBP was hence determined to be 3.32%. As DBP accounts for 3.32% of total phthalate emission, we calculated all attributable costs for DBP by multiplying the total burden of phthalates by 0.0332. In the case of male infertility, we assumed a 10 times higher exposure (33.2%) since the costs were estimated only for benzyl and butyl phthalates. From this, the total cost related to DBP was estimated to be € 2,636,242,400. Using a factor of ten is an arbitrary decision and needs to be considered with caution. Nevertheless, this decision was made due to the lack of data availability on benzyl and butyl phthalate emissions. Until further scientific contribution, this value will remain in the calculations.

Benzo[a]pyrene

Perera et al. (2014) estimated that in New York City alone, prenatal BaP exposure caused a a loss of lifetime earnings of $ 215 million. In this study the authors valued a reduction of the BaP concentration of 0.25 ng/m^3. We assumed that after this reduction, the remaining concentration would no longer lead to incremental IQ point losses. The reference concentration in New York is slightly above 1 ng/m^3 which is the target level in the European Union. We thus assumed that the same concentration reduction would also be sufficient in the European Union to eliminate incremental IQ point losses. According to an EEA study, 17% of the urban population lives above the 1 ng/m^3 BaP level (especially in Poland) (EEA, 2019). In 2018, the European urban population was 70.9% of the total population, which corresponds to 363,717,000 people (pre-Brexit) (Eurostat, 2020). We applied this percentage to the affected population to calculate the total births impacted by BaP which equals to 564,019 births/year if we assume that the birth rate is the same in cities and rural areas. In the original study a total birth count of 63,462 was identified as the number of new-borns at risk in New York. Expressed in €$_{2015}$, the total costs in New York equalled € 328.45 million. To account for the different birth numbers, a conversion factor of 8.888 was applied. This led to total cost in the EU equalling € 2,919,228,000. In the case of the Netherlands, we did not consider any cases of cognitive dysfunction arising from BaP exposure as the air BaP content is under the WHO reference level of 0.12 ng/m^3 including cities (EEA, 2019). Guerreiro et al. (2016) estimated the lung cancer cases in the EU due to BaP exposure. We could not assume that the lung cancer cases are distributed evenly (this would result in overestimation for the Netherlands due to

the same reason). As the Dutch BaP concentration lies in the first 16th percentile, we applied a division factor of 6.25 to calculate the attributable cases in the Netherlands after adjusting to population size (EEA, 2019).

Chlorpyrifos and organophosphate insecticides

Bellanger et al. (2015) estimated the total cost of cognitive dysfunction related to organophosphate pesticide emission in the EU to € 159.4 billion (€ 146 billion converted to €$_{2015}$). In 2018, according to Eurostat 39,489 tonnes of insecticides were used, 11.7% of which were organophosphate based insecticides (Eurostat, 2020). Thus, we estimated the total organophosphate consumption to equal 4,620,213 kg. From this we estimated the cost of 1 kg organophosphate insecticide by dividing the 159.4 billion by the pesticide consumption. The calculation yielded a unit cost of € 34,500 per kg of organophosphate pesticides. We assume that these substances are similarly toxic therefore this value was applied to Chlorpyrifos as well and included in the upper bound of the valuation. The total US cost for Chlorpyrifos was estimated by comparing the total organophosphate consumption in the EU to the Chlorpyrifos consumption in the US. The Chlorpyrifos consumption in the US is approximately 73.6% of the European organophosphate consumption (3,401,943/4,620,213). Therefore, we estimated the total costs by multiplying the € 159.4 billion by 73.6%, which yields € 117.37 billion.

Concerning the epidemiological studies on Chlorpyrifos, most of them focused on exposure of farmers and their spouses. We estimated the P_e (exposed population fraction – see Chapter 4.2.2) from statistics on number of farmers in the population (https://www.ers.usda.gov; NCFH, 2020). However, only including farmers and not their spouses would lead to an underestimation. Therefore, a factor of 1.2 was applied to account for a supposed 20% fraction of spouses who work in different sector but can be highly exposed due to the proximity of farmlands. This adjusted value was only used in the upper bound of our valuation as it is based on an assumption. Until further data this number will be used.

Arsenic

Arsenic is a tricky substance as environmental exposure is strongly connected to local concentration in the environment and it mostly affects people in specific locations in the proximity of volcanic rocks where it contaminates the drinking water. Such, local concentrations cannot be used as a proxy for all European countries since in many countries the exposure level is much lower. Countries in with significant arsenic exposure were identified for the European Union include Italy, Hungary, Poland, Croatia, France, Spain, the UK, Romania, Germany and Greece (van Halem et al., 2009). In Italy it was estimated that 1.7% of the population is exposed to more than the EU recommended level of 10 µg/L (D'Ippoliti et al., 2015). In Spain similar results were produced which revealed that 2.1% of the population is exposed to arsenic contaminated drinking water above the 10 µg /L level (Medrano et al., 2010). As exposure data is scarce, we estimate the adverse effects of arsenic exposure from the Italian and the Spanish exposure data and relative risks. This estimate is deemed indicative as we needed to take numerous assumptions about population exposure. By taking the average of the two studies, we gain a population fraction estimate of 1.89% over 10 µg/L exposure level from drinking water. The total population of the arsenic affected EU countries was 402,747,000 in 2020 including the population of the UK (Eurostat, 2020). Based on this, we assume that 7,611,918 people are exposed to higher-than-recommended arsenic levels. We used this number as the exposed population fraction (P_e). The risks were identified for long-term, 40 years of exposure. As

the exposure came from natural sources we do not account for the change in arsenic exposure in these countries. Based on the study from Italy, around 43.4% of the examined population was exposed to arsenic between 10 and 20 µg/L and the remaining 56.6% was exposed to higher levels. Thus, we applied the relative risk of both exposure groups compared to the non-exposed group. This same estimate for exposed population fraction was also used to estimate diabetes related costs based on a Serbian study (Jovanovic et al., 2013).

For arsenic exposure in the Netherlands a different approach was taken as the level of exposure is under the WHO safety level. A study estimated the health benefits of reducing As exposure from drinking water. This would mean a reduction from the average 1.2 µg/L level to under 1 µg/L. The total benefit was determined to be € 10.7 million/year for arsenic related lung cancer cases which included € 1 million for health care cost (Ahmad et al., 2020). We adjusted the estimate to current year by accounting for an increase in population and applying a different price value/DALY (more specifically € 70,000 instead of € 60,000). Additionally, we added a cost of illness for each cancer case. In the calculation we used a factor of 1,045 to address the population increase in the country which resulted in a case increase up to 53.295 and DALY increase up to 790/µg/L drinking water arsenic concentration. The reduction to under 1 µg/L thus can be calculated by multiplying by a factor 0.2 (reduction in drinking water As concentration) which results in 10.66 cases and 158 DALYs per year. This equals to € 16,187,460 of total costs (€ 13,189,785-€ 19,185,135) (158*70,000+10.66*481,000). The unit costs were calculated by dividing by total arsenic emissions in the Netherlands and yielded € 191/kg (€155-226).

On a final note, we mentioned that epidemiological studies on arsenic rely on specific locations where due to the proximity of volcanic rocks the population is exposed to toxic levels of the substance via drinking water. Thus, it is challenging to derive an EU-wide estimate from these locations. An additional consequence is that occupational studies or studies on the general population are less consistent in determining correlations with hazardous effects. This case also highlights the importance of toxicological studies which can determine the potential toxicity in the absence of epidemiological data. Therefore, when only sporadic environmental exposures occur from nature, Nation or EU wide unit costs estimates relying on toxicological potential of the substance could provide more accurate estimates.

Ischaemic heart disease (mercury, cadmium)

For myocardial infarction we were only able to get data for the larger class of ischaemic heart disease from the GBD tool. To correct for overestimation, we used the following approach. First, we estimated the prevalence of myocardial infarction which equals 45.3% of the total prevalence for ischaemic heart disease. This follows from considering that in the general population over twenty years of age the prevalence is 6.4% for all ischaemic heart disease, while for myocardial infarction is 2.9% (Ferreira-González, 2014). This, however, still does not provide us with a viable estimate as not all the ischaemic heart disease cases have the same health outcome (some are more mild than myocardial infarction). The five-year hazard ratio is almost twice as large for myocardial infarction than for angina (the other prevalent ischaemic heart disease type — frequently the two are strongly connected). The hazard rates equal 6.8 and 3.5 respectively (Jones et al., 2006). Hence, we assume that 62.2% of ischaemic heart disease related DALYs are caused by myocardial infarction which is responsible for 45.3% of the ischaemic heart disease incidence.

4.4 Results

Table 2 shows the results from Steps 1-4 of our building framework that has calculated the total damage costs for the EU28 from the exposure of the nine substances and reveals the specific costs calculated for the various health impacts. The reference studies were used for the calculation of damage costs. When more than one reference study was used, we calculated the impacts as the average of the studies.

We report a lower and upper value. For the *lower* bound values, we used the costs calculated for the relevant age group and the related RR from the reference studies. For the *upper* values we used the incidence rates for the total population assuming that the RR from the relevant age group actually is the same for every age group. This on one hand helps to attribute to disease cases which occur due to elevated risk from exposure in other age groups, while on the other hand it can also lead to overestimation as we assume similar risk for the whole population which is rarely the case.

This recalculation with relevant age groups significantly changed the cost range of mercury which has a proportionally much smaller lower bound compared to the upper bound value. The readjustment was much less significant for other compounds mainly because the studies determined the RR for most of the age groups or analysed occupational studies where the risk is not dependent on age group but on exposure at workplace. Thus, in most of the cases the lower and upper bounds are identical. We did not extend the calculation to other age groups in case of increased risk during childhood exposure, as it only effects children during the developmental phase and cannot be extended to the adult population.

Table 2 - ***Total damage cost of various chemical and related diseases in the EU28***

Chemical	Diseases, disfunctions	Total cost EU28 lower bound (€)	Total cost EU28 upper bound (€)	Reference
Mercury	Myocardial infarction	17.49 bln	111.95.5 bln	Virtanen et al., 2005; Wennberg et al., 2012
Cadmium	Chronic kidney disease	201.3 mln	615.8 mln	Ginsberg, 2012
	Renal cancer	3.16 bln	3.16 bln	Illyasova & Schwartz, 2005; Song et al., 2015
	Bone-mineral density and fractures (osteoporosis)	6.55 bln	32.3 bln	Engström et al., 2011
	Lung cancer	53.59 bln	53.6 bln	Cheng et al., 2016
	Myocardial infarction	37.75 bln	37.76 bln	Tellez-Plaza et al., 2013
Chromium (all)	Lung cancer	785 mln	785 mln	Luippold et al., 2003
	Respiratory systems cancers	393 mln	393 mln	Deng et al., 2019
	Oral cavity cancer	33.8 mln	33.8 mln	Deng et al., 2019
Arsenic	Lung cancer	2.05 bln	2.05 bln	D'Ippoliti et al., 2015
	Ischemic heart disease	1.29 bln	1.29 bln	
	Stroke	350.9 mln	350.9 mln	
	COPD	2.01 bln	2.01 bln	
	Cardiovascular mortality	597.5 mln	597.5 mln	
	Cerebrovascular diseases	35.3 mln	35.3 mln	Medrano et al., 2010; D'Ippoliti et al., 2015
	Diabetes	467.3.5 mln	2.74 bln	Jovanovic et al., 2013; D'Ippoliti et al., 2015

Chemical	Diseases, disfunctions	Total cost EU28 lower bound (€)	Total cost EU28 upper bound (€)	Reference
Benzo[a]pyrene	Lung cancer	1.71bln	1.71 bln	Armstrong et al., 2004; Olsson et al., 2010; Armstrong & Gibbs, 2009; Guerreiro et al., 2016
	Bladder cancer	23.9 mln	23.9 mln	Armstrong et al., 2002
Bisphenol A	Anxiety disorder	15 mln	15 mln	Braun et al., 2011
	Obesity	377.9 mln	377.9 mln	Trasande et al., 2012
Dibutyl phthalate	Breast cancer	6.89 bln	6.89 bln	Ahern et al., 2019
Chlorpyrifos	ADHD	15.2 mln*	15.2 mln*	Rauh et al., 2006 Marks et al., 2010 Rauh et al., 2006
	PDD	45.7 mln*	45.7 mln*	
	Breast cancer	707.8 mln*	849.3 mln*	Engel et al., 2017
	Lung cancer	330 mln*	396 mln*	Lee et al., 2004a
	Rectal cancer	1.97 bln*	2.36 bln*	Lee et al., 2007
Glyphosate	Non-Hodgkin lymphoma	0	2.23 bln	Zhang et al., 2019

*Value for the United States

For Glyphosate, a lower bound of 0 has been suggested by us as recent empirical evidence fails to find a significant impact of Glyphosate on non-Hodgkin's lymphoma. The upper bound is formed by earlier studies that did report an elevated cancer risk from the substance.

In Table 3, the results for the EU28 are summarized comparing our results and results from other valuation studies that used the similar attributable fraction approach. The table shows the total costs in the EU28 connected to the nine substances.

Table 3 - ***Total costs in the EU28 from other valuation studies and our valuation***

	Other valuation studies		Our valuation	
Chemical	**Total cost adjusted to the EU28 (€)**	**Reference**	**Total cost EU28 lower bound (€)**	**Total cost EU28 upper bound (€)**
Mercury	10.3 bln	Bellanger et al., 2013	17.5 bln	111.95 bln
Cadmium	-		101.24 bln	127.4 bln
Chromium (all)	-		801 mln	801 mln
Arsenic	-		6.92 bln	10.62 bln
Benzo[a]pyrene	2.4 bln	Perera et al., 2014	1.55 bln	1.55 bln
Bisphenol A	1.68 bln	Legler et al., 2015	392.9 mln	392.9 mln
Dibutyl phthalate	2.64 bln	Bellanger et al., 2015; Legler et al., 2015; Hunt et al., 2016; Hauser et al., 2016; Trasande et al., 2016	6.89 bln	6.89 bln
Chlorpyrifos (USA)	117.37 bln*	Bellanger et al., 2015	3.23 bln*	3.83 bln*
Glyphosate	-		0	2.23 bln

*Value for the United States

This table shows that the total damage costs from our report are mostly higher than what was estimated in other valuation studies. Nevertheless, they are still very similar in magnitude to our estimates. However, the higher bound of the total mercury cost is ten times higher than what was calculated by Bellanger et al. (2013). This value also seems too high in the view of that we calculated the damage costs for myocardial infarction as consequence of exposure and not for IQ loss.

Our results show that the total loss in economic welfare from exposure to these 9 substances is equal to € 138 to 265 billion annually in the EU28.

4.5 Conclusions

Using a methodology based on epidemiology we have calculated total damage costs due to exposure to chemical pollution in the EU28. Our approach showed that total welfare economic loss due to chemical pollution in the EU28 from nine often used substances could equal between € 138 to 265 billion annually.

We showed that our approach could be used to estimate welfare losses for a wide range of chemicals. Unfortunately, the epidemiological literature on many of these substances is limited. This is an obstacle as for deep economic valuations more substantial evidence may be desirable. On the other hand, deep economic valuation studies would hinder the possibility of rapid pricing of a high number of substances. Our approach can facilitate and open new avenues to a more rapid valuation of chemicals even in the case when limited epidemiological data is available. Relying on the limited epidemiological evidence makes our results scientifically less robust and requires a more pragmatic look on the relationship between exposure and effect.

We believe this pragmatic approach based on best-available knowledge is justified as the alternative is a situation is which substances are effectively undervalued, leading to potential hazardous effects on human health. We tend to accept positive correlations between chemical exposures and diseases to calculate an environmental price even when the evidence is only moderately strong. Thus, our damage costs are rather indicative, and they can be considered reasonable but uncertain point estimates that can help inform decision makers until more robust estimates become available.

5 Unit damage cost estimates for the Netherlands

5.1 Introduction

Based on the analysis in Chapter 4, we will now derive unit damage cost estimates for the Netherlands and compare these with values from the literature for the nine substances.

The calculation of unit damage costs implies that we relate exposure to emissions. Because we have better information available on emissions for the Netherlands, we decided to conduct this analysis at the level of the Netherlands. First, in Paragraph 5.2 we will outline the method used to derive at a unit damage cost estimate for the Netherlands. Then in Paragraph 5.3 we will present our unit damage cost estimates and, in Paragraph 5.4, compare this with other results in the literature. Finally, in Paragraph 5.5 we will discuss our results in terms of uncertainty and potential uses.

5.2 Method

From the total costs calculated in Chapter 4, one can derive an estimate of the unit costs for the Netherlands. For the studies that reported relative risks, we just took the relative risk from the studies mentioned in Table 2 and applied this relative risk to the Netherlands. The total damage was then calculated for the Netherlands using the methodology outlined in Chapter 4.

For the total cost studies in Table 3 we took the Dutch share of population in the EU28 to derive an estimate of the total damage that would apply in the Netherlands.[12]
took a two step routine:

The total damage was in the end confronted with emissions to derive a unit cost estimate.

[12] The share of the Netherlands in the EU28 damages was based on the per capita share. In other words: the population share of the Netherlands in the EU28 was taken as a proxy for the damage share. Of course, this is a very rough proxy as the intake of heavy metals in humans is not evenly distributed across Europe. In general, people living in countries in Eastern Europe tend to have a higher intake, especially in the past, as much of the soils in Poland, Czech Republic and former German Democratic Republic, have been contaminated with heavy metals (Anderberg et al., 2000). Intake may also depend on natural occurrence of certain materials, like in the case of arsenic in drinking water in Italy. On the other hand, the concentration of economic activities and agriculture in the Netherlands plus the inflow of toxics from rivers may result in a higher intake for people living in the Netherlands. Without further research we cannot state to what extent this assumption is influencing our results.

Emissions

Data on emissions was determined relying for the year 2017 and obtained from Emissiegeistratie, which is the Dutch equivalent of the E-PRTR (www.emissieregistratie.nl). In the case of Chlorpyrifos, US data were used from 2017 (https://water.usgs.gov). In both the US and the Dutch cases, we calculated the cost/kg by dividing the total costs by total emissions – where we summed up the emissions to air, water and soil.

Accumulation adjustment *(mercury, cadmium)*

Certain heavy metals including cadmium and mercury are known to reside in the body for a long time and exposure can hence lead to accumulation which can be responsible for the diseases. Due to this reason, environmental prices for cadmium, chromium and mercury emissions need to take these accumulation effects into account. Cadmium is estimated to have a half-life of 10-35 years (WHO, 2019) in the human body, whereas mercury has an estimated half-life of 69 days to 27.4 years. For our calculations we used 11.6 years as a point-estimate for cadmium based on Amzal et al. (2009) and 5 years for mercury based on a review by Rooney (2014). We did not consider accumulation factor for chromium as only occupational studies were available where environmental accumulation does not influence workplace exposure. The results were adjusted with the accumulated emissions from the past. We used the study year as the reference year and estimated the accumulation based on the half-life from earlier emissions. This is necessary as without this we would overestimate the unit costs since the health effect are also attributable to the earlier emission and not only to this year's emissions. We also accounted for the accumulation effects in the future as this year's emission still will have further health impacts. Based on these two readjustments we can calculate the real unit costs for the compounds. A more detailed explanation of the methodology can be found in Annex A.

Averaging and summing up disease impacts

By calculating the population share and dividing by total emissions, we derived at a €/kg price per study that was included in Table 2 (Chapter 4). The study prices were subsequently averaged in case similar diseases could be attributed to exposure and summed up if multiple disorders or dysfunctions were identified for a specific compound. Like in Chapter 4 we have used an upper and lower value for unit damage costs.[13]

5.3 Results: unit damage costs

5.3.1 General results

First, we estimated the disease impact of Table 2 in Paragraph 4.3 for the Netherlands, following the routine outlined in Paragraph 5.2. This is: we calculated the total cost for the Netherlands based on the population share of the Netherlands within the EU28 and divided the results by the emissions (and for mercury and cadmium the cumulative emissions, see Annex A for methods) for the Netherlands.

[13] For the lower bound values, we used the costs calculated for the relevant age group and the related RR from the reference studies. For the upper values we used the incidences for the total population assuming that the RR is the same for every age group.

In our selection of studies we applied the following routines:[14]
When more study identified correlation with one specific disease type the average of the two calculations were taken for the final results.

The results are given in Table 4.

Table 4 - *Total damage cost and unit costs of various chemical and related diseases in the Netherlands, expressed in €2015*

Chemical	Diseases, disfunctions	Total cost NL lower bound (€)	Unit cost NL lower bound (€/kg)	Total cost NL upper bound (€)	Unit cost NL upper bound (€/kg)	Reference
Mercury	Myocardial infarction	326.5.3 mln	35,594	2.08 bln	226,876	Virtanen et al., 2005; Wennberg et al., 2012
	Cognitive disfunctions (IQ loss)	4.9 mln	2,325	4.9 mln	2,325	CE Delft, 2018
Cadmium	Chronic kidney disease	6.8 mln	1,251	17 mln	3,129	Ginsberg, 2012
	Renal cancer	66.1 mln	13,381	66.4 mln	13,443	Illyasova & Schwartz, 2005; Song et al., 2015
	Bone-mineral density and fractures (osteoporosis)	161.5 mln	11,411	683.4 mln	48,297	Engström et al., 2011
	Lung cancer	2.11 bln	92,022	2.11 bln	92,026	Cheng et al., 2016
	Myocardial infarction	701.6 mln	50,436	701.6 mln	50,447	Tellez-Plaza et al., 2013
Chromium (all)	Lung cancer	51.8 mln	440	51.8 mln	440	Luippold et al., 2003
	Respiratory system cancers	15.3 mln	130	15.3 mln	130	Deng et al., 2019
	Oral cavity cancer	0.84 mln	7	0.84 mln	7	Deng et al., 2019
Chromium (VI)	Lung cancer	51.8 mln	297,895	51.8 mln	297,907	Luippold et al., 2003
	Respiratory system cancers	15.3 mln	87,788	15.3 mln	87,816	Deng et al., 2019
	Oral cavity cancer	0.84 mln	4,821	0.84 mln	4,830	Deng et al., 2019
Arsenic	Lung cancer	13.2 mln	155	19.5 mln	226	Ahmad et al., 2020
	Cognitive disfunctions (IQ	60.5 mln	712	60.5 mln	712	CE Delft, 2018

[14] In addition, the reader should notice that our results were already framed by the fact that we only selected epidemiological studies where the relative risk was reported or was possible to calculate it from the provided data and that we were prone to select studies which found positive correlation between chemical exposure and disease to account for all the possible effects. The reader should also be aware that we did not evaluate the quality of the scientific literature during study selection due to the limited amount of literature.

Chemical	Diseases, disfunctions	Total cost NL lower bound (€)	Unit cost NL lower bound (€/kg)	Total cost NL upper bound (€)	Unit cost NL upper bound (€/kg)	Reference
	loss)					
Benzo[a]pyrene	Lung cancer	31.4 mln	15,066	31.4 mln	15,066	Armstrong et al., 2004; Olsson et al., Armstrong & Gibbs, 20092010
	Bladder cancer	0.87 mln	394	0.87 mln	395	Armstrong et al., 2002
Bisphenol A	Anxiety disorder	0.64 mln	509	0.64 mln	509	Braun et al., 2011
	Obesity	0.39 mln	312	0.39 mln	312	Trasande et al., 2012
Dibutyl phthalate	Breast cancer	272.5 mln	80,465	272.5 mln	83,539	Ahern et al., 2019
Chlorpyrifos	ADHD	15.18. mln*	23.42*	15.18. mln*	23.42*	Rauh et al., 2006; Marks et al., 2010
	PDD	45.7 mln*	13.4*	45.7 mln*	13.4*	Rauh et al., 2006
	Breast cancer	707.8 mln*	208*	849.3 mln*	250*	Engel et al., 2017
	Lung cancer	330 mln*	97*	396 mln*	116.4*	Lee et al., 2004a
	Rectal cancer	1.97 bln*	579*	2.36 bln*	695*	Lee et al., 2007
Glyphosate	Non-Hodgkin lymphoma	0	0	88.9 mln	2,162	Zhang et al., 2019

*Value for the United States.

On the basis of this Table, we derived at an estimate of the aggregated unit damage costs of the 9 substances investigated, which is given in Table 5. In calculating this new table, we applied the following routine:

* For each separate disease for a specific chemical, but for different occupations, the results were summed up.
* The final result includes various type of diseases. The two most important outcomes from exposure to these nine compounds seems to be lung cancer and Ischaemic heart disease (myocardial infarction).
* We also indicate the combined results where we combined our results, and results from other valuation studies, adding values for diseases that were not covered by our estimates, and averaging them if both studies identified it but from different source.

Table 5 - *Unit damage cost for the Netherlands in €$_{2015}$/kg* emission

	Our valuation results			Combined valuation results*	
Chemical	**Unit cost lower bound**	**Unit cost upper bound**	**Unit cost from literature added to our results**	**Unit cost lower bound**	**Unit cost upper bound**
Mercury	37,919	229,201	17,505	53,100	244,382
Cadmium	168,502	207,342	-	168,502	207,342
Chromium (all)	297	297	-	297	297
Chromium (VI)	208,089	208,118	-	208,089	208,118
Arsenic	867	938	-	867	938
Benzo[a]pyrene	15,460	15,461	-	15,460	15,461
Bisphenol A	822	822	22,835	23,344	23,344
Dibutyl	80,465	83,539	26,409	80,465	109,948

	Our valuation results			Combined valuation results*	
Chemical	Unit cost lower bound	Unit cost upper bound	Unit cost from literature added to our results	Unit cost lower bound	Unit cost upper bound
phthalate					
Chlorpyrifos	950	1,127	34,500	950	35,627
Glyphosate	0	2,162	-	0	2,162

* Additional costs were calculated from the average unit costs derived from the valuation literature: we used results from Bellanger et al. (2013), Bartlett et al. (2013) and CE Delt (2018) for mercury; the average derived from Legler et al. (2015) and our results (based on Trasande et al. [2012]) for BPA; we used Bellanger et al. (2015), Hunt et al. (2016), Hauser et al. (2016), Legler et al. (2015) for DBP; and we included Bellanger et al. (2015) for Chlorpyrifos.

Unit costs for the Netherlands are especially high for cadmium € 168,500-207,300/kg emissions, for dibutyl phthalate (€ 80,500-83,500/kg emission) and for chromium (VI) € 208,100/kg emission. Regarding the high costs of phthalates, more recent results concerning damage costs of phthalates and BPA suggests that high unit cost for endocrine disruptors are very likely (Trasande et al., 2015). We also derived € 41,538/kg emission as a unit cost for BPA for the Netherlands based on Legler et al., 2015. This suggests a very similar range of €/kg that we calculated for EDCs (endocrine disruptors), especially if we take into consideration that we used a higher VOLY than any other study for EDCs (see also Paragraph 5.4).

Our results for Cr (all) and Cr (VI) are based on certain assumptions which makes our result less robust. With Cr (all) we considered all effects from chromium compounds for the total chromium emissions which is a realistic estimate for all chromium. However, scientific literature suggests that most of the health impacts are attributed to Cr (VI) thus, these unit costs are overestimations for Cr (0, III) and underestimation for Cr (VI). On the other hand, when calculating unit costs for Cr (VI) we attributed all chromium related health impacts to Cr (VI) which is suspected to be an overestimation as other chromium compounds also influence human health (see also Paragraph 5.4 for a further discussion). For Glyphosate, the lower bound value is considered to be 0 as most of the new studies did not find correlation to NHL, which strongly questions the actual contribution of Glyphosate to elevated cancer risks.

In Annex C we also compare our results to per capita results in the EU28, to give a bit more insight into the differences we observe with EU28 values.

5.3.2 Results further differentiated to environmental compartments and uptake routes

Results fromFigure 2 are in principle for the total average load of these compounds into the environment and exposure to the human body. However, the damage these substances inflict on humans is dependent on the environmental medium where exposure occurs. Intake fractions differ widely between the various compartments, as can be observed from models like USEtox (see Annex E).

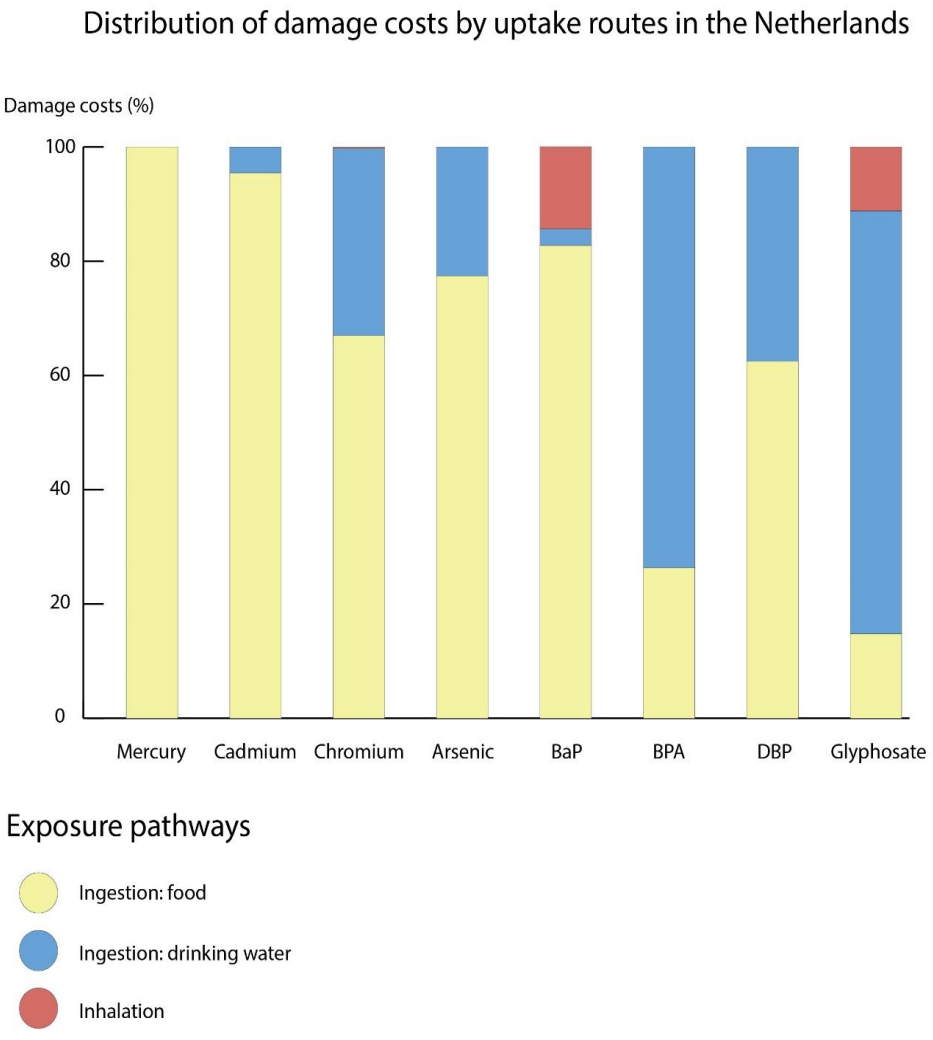
In this study we have made various attempts to derive at a unit damage cost differentiated to the compartment of emission:

a Through the ReCiPe (2008) individualistic characterization factors.
b Through the USEtox intake fractions.

However, none of these results seem to give a good approximation of the differentiation of our results into the various compartments. In general, one can state that emissions to air tend to be more damaging than our average values and emissions to water are less damaging. The extent to which this differs should be addressed by future research.

However, using information from USEtox, we can further differentiate the unit damage costs to uptakes if we look at intake fractions. We calculated intake fractions on the basis of USEtox (see Annex E). Applying those intake fractions, it can be observed that the majority of uptakes takes place through food. For BPA and Glyphosate, contamination of drinking water can be an important route as well, while emissions of BaP and Glyphosate tend to be distributed by inhalation as well. Inhalation of heavy metals only forms a very small proportion of total damage.

Figure 2 - Distribution of health damage cost among different uptake routes



Source: Own calculations based on UseTox (Fantke et al., 2016).

Use of our results to derive at specific damage cost estimates differentiated per environmental medium is further discussed in Paragraph 5.5.

5.4 Comparison with other approaches

An interesting question is of course to what extent our results are comparable to other results in the literature. We compare here our results with three different approaches:

1. Studies that present unit damage cost estimates.
2. Studies that present total damage cost estimates.
3. Toxicological models like USEtox.

5.4.1 Unit damage cost estimates

Table 6 reports values on unit damage costs for often used substances in the literature over the last 13 years. From this Table it can be observed that over time unit damage costs tend to be increased. This is largely due to the fact that more impacts have been taken into account plus the fact that, on average, higher VOLY's have been used.

Table 6 - Calculated unit cost from other valuation studies for emissions to various compartments (€/kg)

Valuation	Price base	Compartments	Country	Mercury	Cadmium	Chromium (VI)	Arsenic	Benzo [a]pyrene	VOLY (€/yr)
Needs, 2008	€2005	Air	EU27	8,000	84	66	530	-	40,000
Spadaro & Rabl, 2008	$2000	Total	Global	1,487	-	-	-	-	-
EEA, 2014	€2005	Air	EU28*	910	50	66.7	417	1,298	57,000†
Rabl et al., 2014	€2010	Air	Europe	-	27	177	130	-	
Pizzol et al., 2014	€2010	Soil	Denmark	-	334	-	-	-	40,000
Nedellec & Rabl, 2016	€2013	Air	Europe	22,937	138,969	-	5,713	-	126,000
EEA, 2021	€2019	Air	EU27**	16,903	185,175	5,501	11,044	11,965	101,000
Our results^	€2015	Total	NL	53,100	168,502	208,089	867	15,460	70,000

Notes: †A value of € 57,000 is stated in the report but they did not use it for heavy metals, there they used an VSL of € 0.5 million/cases for non-fatal and € 2 million/case for fatal cancers.

* EU28 and additional countries in Europe including Switzerland, Iceland Norway and Serbia.

** EU27 and additional countries in Europe including the UK, Switzerland, Iceland Norway and Serbia.

^ Low estimate from our combined results.

Comparing these results with our results (in the last row of Table 6) for the low estimate, one can conclude that our results resemble to some extent the results by the most recent study of EEA (2021) that identifies € 185,000 for cadmium as a unit cost which is remarkably similar to our findings.[15] Also the damage cost calculated for benzo(a)pyrene is very similar. Until 2015, most studies would identify mercury as the substance with the highest damage costs. Only more recently, damage costs reported for cadmium have been higher. Most of these studies use the impact pathway approach which estimates the damage from emission through the quality changes in environmental compartments. The following impacts based on the toxicological potential of the chemicals. The toxicological potential is derived from animal toxicological or human epidemiological studies.

[15] The reader should be reminded here that our unit costs reflect total cadmium, while their unit costs reflect the costs of emissions to air. One could argue that air emissions are more damaging because of the higher intake fractions.

Finally, we can suggest some reasons why our results are on general higher than that of other studies:

- Our results contain a complete treatment of potential diseases from the substances that we could find in the literature and that could explain why are coverage of diseases is higher than that of other studies (see also Subparagraph 5.4.4 for a further discussion).
- Our results may also be higher than of other studies as we were prone to accept positive correlations for various disease and disfunctions which can lead to the higher total and unit costs.
- Additionally, we also need to consider that our estimates for DALYs is higher (€ 70,000) than in other studies which can lead to 75% higher damage costs compared to studies where a VOLY of € 40,000 was used. On the other hand, the new EEA report (2021) used a higher VOLY value of € 101,000.

In Subparagraph 5.4.4 a more elaborate comparison with the EEA (2021) study can be found.

5.4.2 Total damage cost estimates

Another way to compare our results is to find similar studies on the total damage costs from one pollutant, and assume similar per capita costs for the Netherlands and the study and divide the total cost by emissions to obtain a per unit cost. Table 7 summarizes the results of other economic valuation studies focusing on the compounds investigated in current report. We adjusted the total costs derived from the studies to $€_{2015}$ values and to the EU28 and the Netherlands. For the Netherlands, the population proportion was used to derive the total costs in relation to the whole EU population. The unit costs were then calculated based on the Dutch emissions from 2017 (http://www.emissieregistratie.nl). In the case of cadmium and mercury the accumulation adjustments were used to derive the final unit costs (see Annex A).

Table 7 - Total costs and unit costs derived from other valuation studies for the EU28 and the Netherlands

Study reference	Chemical	Total damage costs (in euros, unless stated otherwise)	Total cost adjusted to the EU28 (€ 2015)^	Total cost adjusted to the Netherlands ^^	Unit cost adjusted to the Netherlands (€/kg)
Bellanger et al., 2013	Mercury	9 bln	10.3 bln	333.33 mln	36,342
Bartlett et al., 2013	Mercury	4.8 bln (USD)	3.74 bln	127.02 mln	13,849
Bellanger et al., 2015	Organophosphate pesticides (incl. Chlorpyirifos)	146 bln	117.37 bln**	0	34,500 (USA)
Bellanger et al., 2015	Phthalates	199 mln	7.22 mln*	0.24 mln	72.26
Perera et al., 2014	Benzo[a]pyrene	215 mln** (USD)	2.92 bln	0	0
Hunt et al., 2016	Phthalates	1.25 bln	45.32 mln*	1.54 mln	453.95
Hauser et al., 2016	Phthalates; benzyl & butyl phthalates	12.67 bln	1.99 bln*	67.73 mln	19,999
Legler et al., 2015	Phthalates	16.2 bln	587.2 mln*	19.91 mln	5,883
Legler et al., 2015	Bisphenol A	1.54 bln	1.68 bln	57.1 mln	45,357
Trasande et al., 2016	EDCs	157 bln	171 bln	5.82 bln	0
Attina et al., 2016;	EDCs	178.6 bln	194 bln	6.62 bln	0

* Adjusted to DBP; ** Value for the United States. ^Calculated on the basis of adjustment to $€_{2015}$ price level ^^ Calculated on the basis of population in the NL in relation to the EU28.

If we look at the unit costs in Table 6 and Table 7 the difference is clear as the values in Table 7 are significantly higher than the earlier estimates in Table 6. These results can be explained by the different approach used in the valuation studies. The earlier studies in Table 6 used the impact pathway approach using toxicological data while newer studies including Nedellec & Rabl (2016) and EEA (2021) took a different direction in the impact pathway approach and mainly relied on unit risks calculated from epidemiological data. This allows a more precise estimation of damage costs then basing the results on extrapolation from toxicological data. Studies in Table 7 calculated the costs from relative risks based on epidemiological studies and population attributable fraction. Therefore, we can conclude that there is increasing number of epidemiological studies that identify more and more impacts related to chemical exposure which also increases the related damage costs.

The attributable fraction approach calculates the correlation between disease and exposure and estimates the cost without taking the environmental fate into account — therefore such 'total estimate studies' may be an upper bound. Bellanger et al. (2015) estimated for example € 146 billion as a total damage cost for organophosphate pesticides which is higher than any of our estimate.

In Table 8, the results for EU28 are summarized comparing our results and results from other valuation studies using the similar attributable fraction approach. The table shows the total costs in the EU28 connected to the nine substances.

Table 8 - Total costs in the EU28 from other valuation studies and our valuation, in Euros

	Other valuation studies	Our valuation	
Chemical	**Total cost adjusted to the EU28**	**Total cost EU28 lower bound**	**Total cost EU28 upper bound**
Mercury	10.3 bln	17.5 bln	111.95 bln
Cadmium	-	101.24 bln	127.4 bln
Chromium (all)	-	801 mln	801 mln
Arsenic	-	6.92 bln	10.62 bln
Benzo[a]pyrene	2.4 bln	1.55 bln	1.55 bln
Bisphenol A	1.68 bln	392.9 mln	392.9 mln
Dibutyl phthalate	2.64 bln	6.89 bln	6.89 bln
Chlorpyrifos	117.37 bln*	3.23 bln*	3.83 bln*
Glyphosate	-	0	2.23 bln

*value for the United States.

The total damage costs from our studies are mostly higher than what was estimated in other valuation studies. Nevertheless, they are still very similar in magnitude to our estimates. Although the higher bound of the total mercury cost is ten times higher than what was calculated by Bellanger et al. (2013), this value also seems too high in the view of that we calculated the damage costs also including myocardial infarction as consequence of exposure.

5.4.3 Comparison with CTUh values in USEtox

Finally, we could compare our results to the results obtained in USEtox. USEtox is a scientific consensus model on toxicological impacts of substances used in life cycle analysis and recommended by the European Commission and supported by the UNEP/SETAC Life Cycle Initiative (see Paragraph 2.3). USEtox uses a comparative unit to express relative toxicity: CTUh (Comparable Toxicity Unit-humans) that reflects the number of cases/kg

emissions at midpoint level of a certain disease and the DALYs/kg emissions at endpoint level. The comparison of our calculated CTUh values and the CTUhs from USEtox are presented in Table 12. For the calculation of the CTUh values we used the incidence and DALY numbers attributed to the diseases. We divided the total incidences with the emissions to gain the CTUh at midpoint level and we divided the total DALYs with the emissions to calculate the CTUh at endpoint level.

Table 9 - CTUh values from USEtox and values based on our results, based on estimated emissions (to all compartments^) in the Netherlands

	USEtox		Our results	
	Total midpoint all emissions (cases/kg)	Total endpoint all emissions (DALYs/kg)	Total midpoint all emissions (cases/kg)	Total endpoint all emissions (DALYs/kg)
Mercury	9.69	23.42	1.0-7.38**	2.21-22.76**
Cadmium	0.58	1.75	1.96-9.8	7.02-9.88
Chromium (VI)	0.26	1.83	0.12	2.04
Arsenic	0.36	1.26	0.0001	0.002
Benzo[a]pyrene	0.34	3.89	0.009	0.16
Bisphenol A	0.00005	0.0001	0.30	0.01
Dibutyl phthalate	0.00001	0.00003	0.53-0.55	0.9-0.93
Chlorpyrifos	0.006*	0.017*	0.02	0.008
Glyphosate	0.00002	0.00005	0.002	0.017

Notes:
* Chlorpyirifos-methyl was used in the table as a proxy because Chlorpyrifos is not available in USEtox in this form.
** Excluding cognitive disfunctions. ^Our results were thus calculated by dividing the attributable cases/DALYs with the total emissions in kg (summed up to air, water and soil) in the Netherlands.

The results are not strictly comparable, as our calculation is based on DALYs and incidence rates from the Netherlands while USEtox uses a European average. Moreover, while USEtox calculates disease cases from the slope factor and estimates the DALYs with the use of a damage factor (2.7 for non-cancer cases, and 11.5 for cancer cases) we used epidemiological data to determine the disease incidences and DALYs.[16] However, the results in terms of CTUh are relatively similar across both studies.

In the case of chromium (VI), the USEtox CTUh value is very similar to our calculated CTUh both at midpoint and endpoint levels. Many valuation studies calculated the highest toxicity potential for mercury which is also true for our CTUh values. USEtox for instance, assigns 10 times higher CTUh value to mercury than to any other substances assessed in our study. The CTUh values derived from our results follow similar pattern than in USEtox. However, our lower estimate for mercury is considerably lower than that of USEtox, which is mainly due to the fact that we only accounted for one disease (myocardial infarction) in the CTUh, as only for this outcome the potential cases and DALYs are known from the GBD data (GBD, 2019). Cognitive disfunctions were not included in this CTUh estimate (but have been included in the unit damage cost estimates), which is a very important consequence of mercury exposure, but we could not estimate the attributable incidences and DALYs for it.[17] In the case of pesticides and DBP, cancer cases are not considered in the USEtox CTUh,

[16] CTUh values were calculated separately for cancer and non-cancer cases by dividing the total number of cases (midpoint level) and DALYs (endpoint level) with the kilogram emissions from 2017.
[17] We also noticed that USEtox accounts for cancer cases to the CTUh value which is slightly unusual.

while we have identified potential increased risks for various cancers types in our report. Moreover, according to USEtox, phthalates and BPA have very low CTUh value, while new valuation studies reveal significant toxicity especially upon exposure at the crucial phase of child development. According to our estimate, cadmium has a very high CTUh value (1.8 to 6.5 times higher than in USEtox) which could be the cause of the five different disorders determined for cadmium exposure in our report. Concerning the number of disease types that we attributed to cadmium, the difference in cadmium toxicity seems realistic. On the other hand, we calculated significantly lower CTUh both numerically and proportionally for arsenic and BaP. The main reason behind could be that although arsenic emissions are high in the Netherlands in comparison to other substances, exposure barely occurs among the Dutch population which results in lower number of attributable incidences and DALYs. For BaP the reason is similar. The exposure is relatively low as the air quality concerning BaP content is the best in the Netherlands among the EU28 countries, therefore the attributable cases also become lower (EEA, 2019). Furthermore, mainly occupational studies were used for BaP which provide more limited overview of the exposure level of the general population.

5.4.4 Comparison with the EEA (2021) study

Finally, it is interesting to compare our findings to those of the recent EEA (2021) report in more depth.

Methodology of the EEA report

In the EEA assessment the impact pathway approach was used to identify connection between pollutant emissions and health impacts. The IPA provides a complete overview from emission to impacts and quantification of damage costs. It starts from quantifying the emissions and environmental fate, taking into account the dispersion patterns, transformation of chemicals in the environment and the scale of human exposure. For impacts the IPA uses an exposure-response function as an input to the economic valuation. This approach is especially effective if one exposure route is assessed; however, for instance for heavy metals it is more complicated as for these compounds multiple exposure routes exist. In the report the focus was on emissions to air including 11,655 industrial facilities which are reported to the E-PRTR registry. From these, 1,572 industrial facilities contribute to approximately 90% of the total damage cost.

One of the main updates in the 2021 report compared to 2014 is the improved dispersion and exposure modelling of organic pollutants and heavy metals. In the updated dispersion modelling the latest EMEP source receptor matrices were applied (EEA, 2021). In the case of toxic heavy metals, the assessment relied on the *uniform world model* applied for the whole EU28 (Rabl et al., 2014). The pollutant specific intake fractions were estimated for both inhalation and ingestion after Rabl et al. (2014). Based on the *uniform world model* the concentration of pollutants was spatially averaged, and the dietary intake is considered uniform for the EU28. In the multimedia model the transport of the pollutants in water and soil compartments was modelled by a methodology developed by the US-EPA (US-EPA, 2005). The significant difference between unit costs in 2021 compared to 2014 is mainly attributed to the updated VOLY values and the adjusted euro price base. In the 2014 report, a $€_{2005}$ price base was used which had increased with 28% in real prices for $€_{2019}$, the price base of the new report. On top of this, further health impacts were attributed to heavy metals mainly including mortality impacts and other morbidity effects (EEA, 2021). The valuation of fatal and non-fatal cancer damage has also changed compared to 2014 where € 2 mln and € 0.5 mln were used respectively (EEA, 2014). In the current report more

specific damage cost estimates were applied for different types of cancers and non-cancer cases.

In the new assessment, the damage costs were separately calculated for the emitting country and uniformly for Europe. The environmental fate was calculated by also considering the physical location of the emission sources, atmospheric dispersion and deposition patterns, accumulation, transport, uptake to plants and human intake. The health impacts from the change in exposure were calculated based on the compound specific ERFs. Incidence data was used to calculate the attributable fraction of impacts. The future incidences were adjusted to income growth and were discounted to the future. During the valuation of heavy metals, the impacts from increasing exposure were estimated by the RiskPoll model. To calculate the marginal damage of atmospheric emission, the health economic impact assessment methodology was used, developed by Nedellec and Rabl (2016). In the assessment, first the average marginal costs per ton of each pollutant was quantified by country and facilities from the E-PRTR. Further factors were accounted for, such as potential exposure of people or ecosystems from specific sources which affect dispersion and exposure (type of facility, geographic location etc.). Finally, the emissions for each facility were multiplied by national average marginal damage costs for each pollutant.

The main difference in the EEA report compared to our estimates that the report fully used the impact pathway approach relying on ERFs from epidemiological data. In contrast to this, we did not include environmental fate and exposure modelling and in our study the population attributable fractions were calculated based on relative risk and the exposure level of the study population. Another significant difference is found in the number of diseases and disfunctions attributed to chemical emissions (listed in Table 10): although many diseases are investigated by us and by EEA (2021), our scope is slightly more expansive. Furthermore, the EEA report used € 101,000 as a VOLY value while we calculated with a VOLY of € 70,000. Our results still remain higher than the unit costs in the new EEA report as we generally covered a broader variety of health impacts. In the case of cadmium, the results are surprisingly close in the two reports but the aforementioned two parameters (difference in VOLY and the number of attributable diseases) highlight the actual differences in environmental prices. For inhalation dose modelling the EEA report assumed that Cr (VI) is 20% of all Cr emitted in the EU. This is an overestimation compared to our results as in the Netherlands Cr (VI) only constitutes to 0.14% of total Cr emissions (http://www.emissieregistratie.nl, 2017). This explains why we attribute a much higher cost to a kg emission of Cr (VI) than the EEA study does.

Table 10 - Comparison of our results (€/kg emission inrrespective of compartment of release) with the EEA (2021) results (in €/kg air pollution)

	Our results 2021					EEA results, 2021		
	Diseases, Disfunctions	**Unit cost NL lower bound (€/kg)**	**Unit cost NL upper bound (€/kg)**	**Aggregated unit costs NL lower bound (€/kg)**	**Aggregated unit costs NL upper bound (€/kg)**	**Diseases, Disfunctions**	**Aggregated unit costs EU lower bound (€/kg)**	**Aggregated unit costs EU upper bound (€/kg)**
Mercury	Myocardial infarction	35,497	226,876	37,919	229,201	Cardiovascular mortality	15,099	16,904
	Cognitive disfunctions (IQ loss)	2,325	2,325			Cognitive disfunctions (IQ loss)	1,805	
Cadmium	Chronic kidney disease	1,251	3,129	168,502	207,342	All-cause mortality	182,457	185,174
	Renal cancer	13,381	13,443					
	Bone-mineral density and fractures (osteoporosis)	11,411	48,297					
	Lung cancer	92,022	92,026			Non-fatal hip-fractures	2,106	
	Myocardial infarction	50,436	50,447					
Chromium (all)	Lung cancer	440	440	297	297	Cancer mortality (lung)	5,501*	5,501*
	Respiratory system cancers	130	130			Non-fatal cancer		
	Oral cavity cancer	7	7					
Chromium (VI)	Lung cancer	297,895	297,907	208,089	208,118	Cancer mortality (lung)	5,501*	5,501*
	Respiratory system cancers	87,788	87,816			Non-fatal cancer		
	Oral cavity cancer	4,821	4,830					
Arsenic ***(*EU costs also include cardiovascular***	Lung cancer	155	226	867	938	Cancer mortality (bladder, kidney,	2,950	11,044

	Our results 2021					EEA results, 2021		
	Diseases, Disfunctions	**Unit cost NL lower bound (€/kg)**	**Unit cost NL upper bound (€/kg)**	**Aggregated unit costs NL lower bound (€/kg)**	**Aggregated unit costs NL upper bound (€/kg)**	**Diseases, Disfunctions**	**Aggregated unit costs EU lower bound (€/kg)**	**Aggregated unit costs EU upper bound (€/kg)**
mortality, ischemic heart disease, stroke, COPD, diabetes, cerebrovascular disease)						skin, lung)		
						Cognitive dis-functions (IQ *loss*)	983	
						Non-cancer mortality	2,887	
	Cognitive disfunctions (IQ loss)	712	712			Chronic bronchitis	126	
						Diabetes	4,098	
Benzo[a]pyrene *(*EU costs also include IQ loss)*	Lung cancer	5,763	5,763	15,460	15,461	Cancer mortality (Lung)	11,965*	11,965*
	Lung cancer	1,594	1,594					
	Lung cancer	5,174	5,174					
	Lung cancer	2,535	2,535					
	Bladder cancer	394	395					

*Specific value for the Netherlands.

The new EEA report (2021) and Nedellec & Rabl (2016) are unique among other valuation studies as they accounted for multiple health impacts in determining the unit costs. For mercury, the EEA report as well as our report included cardiovascular impacts and IQ loss in the calculation. The EEA report also used anaemia for mercury, but it seems to be and error as the report sometimes considers it as an impact of lead, while in other cases as an impact of mercury. Compared to earlier studies, the cadmium unit costs have increased significantly in the new EEA report which is mainly due to the increased all-cause mortality and fractures (osteoporosis) accounted for the heavy metal. The latter impact is also included in our study while we determined more specific health impacts as the cause of mortality in contrast to the EEA report. According to the EEA report, the unit costs for benzo[a]pyrene also increased more than 10 times compared to the earlier report from 2014. The new result of € 11,965/kg (figure for the Netherlands) is very close to our estimate of € 15,460/kg

5.5 Implications and use

The unit damage cost estimates in our study can be used in Cost-Benefit Analysis but they are subject to very large uncertainties. In this paragraph we list the main uncertainties and discuss the uses of the figures.

5.5.1 Uncertainty of valuation

In this study we have investigated the damage costs of nine substances on human health based on an extensive review of the literature. Compared to other studies, we have investigated more diseases reported in the literature than previous studies that only considered mortality or toxicological impacts from these substances. It proves that using an epidemiological framework results in valuation that easily result in values being a factor 10-500 higher than previously reported. This suggests that human toxicity presently is undervalued in the Handbook of Environmental Prices.

However, an important question is how robust these results are. There are a number of observations to be made in this respect. First of all, our results are probably an overestimation as we may have had a positive selection bias in this study: we did not perform a meta-analysis, or qualitative ranking of studies and our selection of studies may have been biased towards selection of studies that did evidence impacts from pollution. On the other hand, our results may be an underestimation, as the results were primarily obtained through European studies. As the Netherlands is much more densely populated, it is possible that intake fractions of emissions spread out over the Netherlands can be higher. However, there are no specific studies available from which Dutch intake fractions could be calculated.

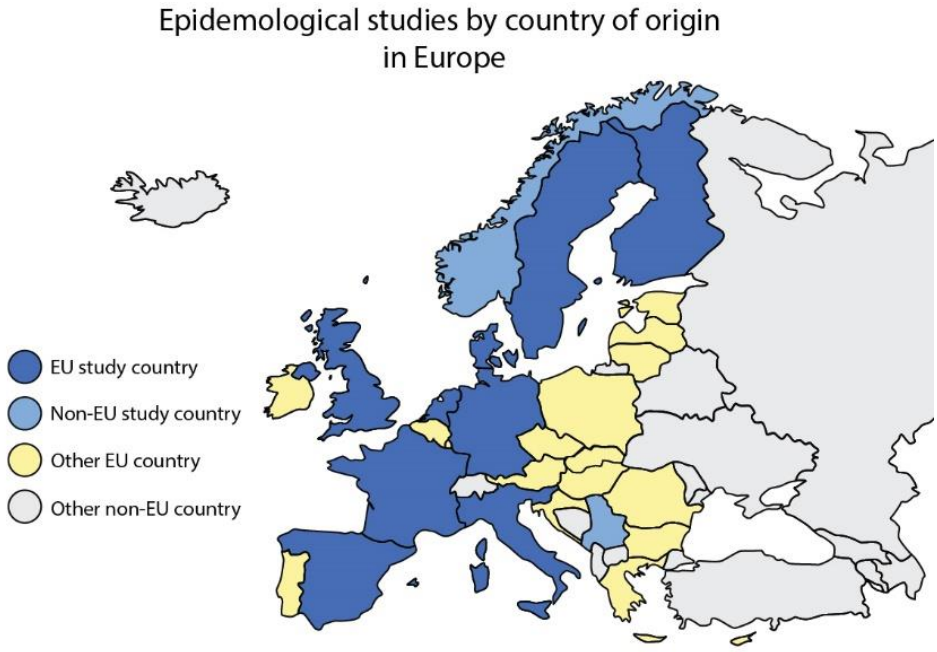
In our study a similar approach was used as described by Bellanger et al. (2015), Trasande et al. (2015) and Prithystalova et al. (2017) but some differences apply. The first decision we need to make with the economic valuation is that we need to assume causal relationship between the exposure and impact. Moreover, further assumptions are taken on distribution of exposures to the risk factors in the population and the contribution to the disease. (Grandjean & Bellanger, 2017). As we can observe, the valuation studies are based on numerous assumptions and it is not considered a systematic approach. This is the reason why these studies are able to provide additional information on top of the GBD estimates which have stricter criteria. A further difference from the methodology of valuation studies and our results is that they mostly worked with experts for evaluating the literature and epidemiological studies. Evaluation of confidence of epidemiological studies used in the calculations was not in the scope of our report and we did not have the capacity for it.

Thus, inclusion of certain studies might yield biased results leading to over or underestimation of the real external costs. This is something which could be improved in further valuation projects. Additionally, in our report, we tend to accept positive correlation beyond systematic evaluation of literature probably to higher extent than other valuation studies did. One reason is that the effects of most chemicals are certainly not zero, thus we believe that attributing for potential but not widely accepted causal relationships is favoured over ignoring the possibility of the hazardous outcome. Throughout this project we did not calculate with biomonitoring data which would support a more precise calculation of the population attributable fraction. Therefore, in our calculation we did not use new exposure-response functions to estimate the attributable cases in the population based on exposure levels. As of this reason, our results can be considered less accurate as we did not account for the real exposure levels in various countries. In the view of this, our methodology also could be improved and include biomonitoring data and evaluation of epidemiological literature which would help us to filter out lower quality studies. Economic valuation literature regarding toxic chemicals is generally scarce and only few studies have attempted to assess environmental prices of chemical exposures and human toxicity.

We can also see from the MeHg exposures levels In the EU (Figure 3) that the population can be exposed at very distinct levels which we would need to consider during cost estimates. We, however assumed uniform distribution of the compounds, and many occasions used the RR from one study only. For this reason, we suggest using our costs only as a proxy for the compounds and not for very specific cases where the damages can be significantly different from the results, based on a simple epidemiological study. Arsenic is also a good example where hazardous effects usually occur due to exposure from natural sources when it contaminates the drinking water. Higher exposure thus only occurs at a limited location in few countries. Data acquired from the specific locations can help to calculate toxicity potential of the compound while it is challenging to derive more universal cost estimates for emissions.

Due to limited availability of Europe wide epidemiological studies, the RR, P_e and C_e values were regularly determined based on single studies covering only one country from the EU. In our calculations this country specific value was used as a proxy for all EU28 countries, for the Netherland, and for the disease cases. This can lead to both over and underestimation of the emission related external total costs and costs/kg, as emissions and exposure to chemicals can be significantly higher or lower for specific countries than the EU28 average. Moreover, single epidemiological studies which were used in our calculation were mainly available from Northern and Western Europe which are less representative for the Eastern European countries (Figure 6).

Figure 3 - Studies used in our assessment by country of origin



Ideally studies from all countries could be included for more precise estimates but here our decision was simply based on study availability. The same is true for the US where we estimated costs for Chlorpyrifos. The application of the substance throughout the US is far from uniform, therefore this data could over and underestimate the results. In certain instances, third countries were used to calculate costs such as Canada or Japan which can also have specific differences compared to EU countries.

Another limiting factor is that the vast number of chemicals we are exposed to are barely characterized and are not accounted for as co-factors in disease aetiologies. It is evident that economic valuation studies and epidemiological studies do not have the capacity to include them and adjust the results for all possibilities mostly as literature is only available for a small fraction of chemicals.

Adjustment for accumulation (Mercury, Cadmium)

Although our adjustment is based on numerous assumption it is very necessary to achieve more accurate price estimates. Numerous factors such as environmental fate of compounds outside the human body were not taken into account as it is over the capacity of current study. We relied on past emissions and accumulation half-life based on median age of the study population while we need to understand that the correlation is not that straightforward. We can be exposed to a compound long after it was emitted but accumulated in the soil or sediment for decades. Also, if we take the example mercury accumulation in fish for a year, which later reaches humans and represents the most important exposure pathway in the majority of the countries, is the remainder of older emissions than what we calculate with. However, we do not have the knowledge of the source of the mercury: it can be released from the sediment after decades long accumulation or can be the result of more recent emissions. Adjusting for all the possibilities would really complicate the calculation and would not necessarily lead to more

accurate estimates from our side. We still believe that this adjustment is necessary and supports a more adequate estimate for substances which tend to accumulate for long term in the human body.

Omitted diseases and disfunctions

We did not include certain diseases and disfunction in the calculations which were identified in the epidemiological literature. The reason mainly was that the relative risk was not possible to calculate from the information given. These health impacts are metabolic syndrome for mercury, further renal effect in relation to cadmium exposure, emotional reactivity, aggressivity, defiant disorder, externalizing and internalizing behavior and somatic problem in the case of bisphenol A, neurobehavioral deficit for Chlorpyrifos, ADHD and lower scores in psychomotor development and motoric development indexes for DBP, and many diseases related to arsenic including urinary tract cancer, bladder cancer, skin cancer, laryngeal cancer, liver cancer, bone cancer, nasal cavity cancer, stomach cancer, colon cancer, kidney cancer, chronic kidney disease, neuropsychological functioning and reduced visuospatial abilities. These additional health impacts could significantly increase the damage costs if further research confirms the contribution of chemical substances to disease progression and identifies the risk.

5.5.2 Uncertainty of environmental fate and intake fractions

Our unit damage costs apply to an emission of a substance to the environment. It therefore is based on a generalized estimate of how emissions end up in the human body taking damage. However, the environmental fate and thus the toxicity of individual substances highly depends on the environmental medium in which the emissions are being released. An emission to soil may not be equally dangerous as an emission to air, especially when the adverse health effects are primarily realized through inhalation (e.g., in the case of lung cancers). It is also highly dependent on the chemical and physical properties of the substances which influence its behaviour in the environment. Thus, after emissions it is only possible to predict with high uncertainty what is the quantity which reaches the human body and how. We attempted to aggregate the intake fractions to gain uniform fraction for emissions to soil, water and air separately which required further assumptions to be taken.

Therefore, our results are by definition imprecise if the exact compartment is known through which an emission is being released. We have attempted to further differentiate our findings to emissions from specific compartments, but this proved to be rather difficult and not entirely fruitful. Therefore, our results cannot be used to value specific emissions, e.g., emissions released to water or air.

5.5.3 Use of results

Our results give an impression of the total damage costs that are associated with the use of certain chemicals in our economy. In this matter they could be helpful in Cost-Benefit Analysis that wants to estimate the burden of chemical pollution attributed to the use of certain materials.

The results of our study could also contribute to improve databases, such as the USEtox database, and update the characterization factors in them with accounting for additional diseases and dysfunction which are revealed by more recent epidemiological literature. Moreover, the USEtox approach in midpoint to endpoint characterization could be updated from the GBD database. USEtox uses a factor of 2.7 for non-cancer cases and a factor of 11.5 for cancer cases which was estimated in 2005 and it is considered outdated (Huijbregts

et al., 2005). Calculating the DALYs/case from the GBD data by using the online tool can give more precise estimate for specific diseases which the USEtox model could benefit from.

Also, our methodology for adjusting the cost in the case of accumulation can serve as a basis for future valuation literature also expanding the scope to adjusting for long-time exposures.

6 Conclusions

Our study confirms that it is possible to estimate unit costs for toxic substances using solely epidemiological results. However, at this point epidemiological data on toxic substances is sparse, which means that environmental prices related to human toxicity yield high uncertainty as the high differences in estimated unit costs also demonstrate. Further studies on the relationship between toxic emissions and disease outcomes can decrease this uncertainty. The epidemiological data we use shows less about the toxic potential of substances, but rather captures the real health effect arising from emissions to the environment. Nevertheless, we can also conclude that toxicological studies still remain an important pilar of environmental prices, as for many substances only toxicological data exists. Therefore, in a complete database of environmental prices and for future valuations both methods need to be considered. Using epidemiological data yields much higher estimates than the toxicological approach which also shows that extrapolation factors between humans and rodents require updating and more substance specific functions could be applied for the calculation. Although our results may very well be overestimates, the difference is so large that it seems likely that toxic emissions have been substantially undervalued so far. This large difference is also supported by newer studies calculating unit costs. Our results are also comparable with results by studies that estimate total costs in the EU28.

With increasing knowledge about epidemiological effects and accounting for additional diseases and disfunctions, which are omitted in the GDB report, the related unit costs significantly increase. This reveals the importance of further research investigating the connection of chemical emissions to hazardous health impacts. Despite the newer advances, the cost of many pollutants still remains hidden which hampers the possibility to frame economic arguments for the widespread control of chemical emissions. This also marks the need to extend the valuation approaches to support decision making about future regulations. Although the total damage costs from environmental pollutants are decreasing, the higher identified unit costs of various compounds call for global intervention practices. The newer literature suggests that for newer emerging but less characterized chemical such as EDCs, developmental neurotoxicants, and pesticides the actual environmental costs can be immense. The results show that by far the largest costs arise through the emissions of cadmium and mercury. Policy aiming to mitigate toxic emissions should focus primarily on these two substances. For these two compounds we applied a new adjustment due to their accumulation characteristics which influences the unit costs. This new methodology should be considered for further valuation studies and potentially could be improved. Models such as USEtox could be updated with synchronizing them with results from newer epidemiological studies and GBD data.

7 References

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A Cumulative emissions

Reason for different methodology

This section provides an explanation about specific calculations to improve the estimates for cadmium and mercury. The heavy metals cadmium and mercury are known to reside in the body for a long time and exposure can hence lead to accumulation. Environmental prices for cadmium, chromium and mercury emissions need to take these accumulation effects into account. Cadmium is estimated to have a half-life of 10-35 years (WHO, 2019) in the human body, whereas mercury has an estimated half-life of 69 days to 27.4 years. For our calculations we used 11.6 years as a point-estimate for cadmium (based on Amzal et al. (2009)) and 5 years for Mercury (based on a review by Rooney (2014)).

Example

The calculations for the environmental prices of cadmium and mercury can be a little confusing at first glance. This is mainly due to the exponential decay of these substances in the body and the fact that cadmium and mercury emissions have significantly decreased in the EU over the last 50 years. It is therefore instructive to first describe an easy example before explaining the used methodology in more detail.
Suppose for the moment that cadmium that enters the body never leaves the body afterwards (the half-life is infinite). Also suppose that between 1970 and 2020, cadmium emissions in Europe have remained unchanged at 10 tons/year. Finally, suppose that we calculate everything for the median age of the participants reported in the study where the RR was determined: 50 years. To make the explanation more tangible, we invent a character Bob, a man aged 50 in 2020. If we wanted to calculate the lung-cancer related cost of 1 kg of Cd emitted in 2020, we would have to undertake the following procedure:

1. First, we would need to determine the total costs of cadmium through its effect on lung cancer in 2020. This entails determining the relative risk of lung cancer for groups with different cadmium exposure to calculate the fraction of lung cancer costs attributable to cadmium exposure. Assume that the total costs of lung cancer in the EU are 10 billion euros in 2020, and that 20% of these costs can be attributed to cadmium exposure. The total costs of cadmium through its effects on lung cancer then equal 2 billion euros in 2020.
2. To determine the costs from 2020 by the emission of 1 kg cadmium in 2020, it seems that we cannot simply divide the attributable costs (2 billion) by the emissions in 2020 (10 tons). To understand why, notice that Bob has not only been exposed to cadmium in 2020, but also in 2019, 2018, … - all the way to 1970. Furthermore, cadmium that entered Bob's body in 1970 still increases his risk of lung cancer by the same amount in 2020 (under the assumption of an infinite half-life). We should therefore divide the 2 billion euros by the historical emissions during Bob's lifetime:

$$Costs_{2020}\ per\ kg\ of\ Cd_{2020} = \frac{Costs_{2020}}{Total\ emissions\ between\ 1970\ and\ 2020} = \frac{2{,}000{,}000{,}000}{50 * 10{,}000} = 4{,}000\ \frac{€}{kg}$$

3. However, we are still not done with the calculation. Note that until now, we have only calculated the costs made in 2020 by the emission of 1 kg cadmium in 2020. What we

would like to calculate are the total costs of 1 kg of cadmium emitted in 2020: $Costs_{total}$ per kg Cd_{2020}. These costs are much higher since cadmium that is emitted in 2020 can enter someone's body, stay inside for a long time, and only then cause lung cancer. Cadmium emitted in 2020 thus also comes with costs in 2021, 2022, 2023, etc. Since we calculate everything for the median person aged 50, we should calculate the future effects up to 2070. To see why, notice that in 2071, the median-aged person will be born in 2021; too late to have been exposed to the 2020 emissions under our assumptions (remember that the median person is a position in the age distribution and not a physical person named Bob).

4. We should hence add the costs made in 2021, 2022, … , 2069 and 2070 to the previous estimate of 4000 euros/kg. If we do not discount future costs of lung cancer, and assume an infinite half-life, this yields:

$$Costs_{2020}\ per\ kg\ of\ Cd_{2020} = (2070 - 2020) * Costs_{2020}\ per\ kg\ of\ Cd_{2020}$$
$$= 50 * 4000 = 200{,}000\,\frac{€}{kg}$$

Perhaps not surprisingly, this is exactly the same outcome as if we would have naively divided the costs in 2020 (2 billion) by the 2020 emissions (10 tons). However, this equality only holds true because we assumed an infinite half-life and constant cadmium emissions over the period 1970-2020. When we release these assumptions, the intermediary described above do become necessary.

Detailed calculation

In reality, cadmium emissions have steadily declined during the last 50 years. Moreover, cadmium does not have an infinite half-life, but a finite one (we assume 11.6 years in our study). How should we deal with these changes?

1. First, we need to adjust the calculation in step 2 of the example to account for the real, non-constant emissions over time. This is relatively easy: we obtained yearly emission data between 1990 and 2017 from the EEA reports. Subsequently, we calculate the yearly emissions prior to 1990 using a simple backwards linear extrapolation.
2. Nevertheless, this is not enough. We should also take into account the finite half-life: cadmium that entered Bob's body 50 years ago is almost entirely excreted by 2020. We therefore first compute the yearly decay factor, which equals 0.5^(1/11,6). This is the factor by which a fixed amount of cadmium in the body is decreased every year through urinal excretion.
3. Using this yearly decay factor, we calculate the so-called *cumulative excretion-adjusted emissions* between 1970 and 2020. This is the amount of cadmium that would be left in a fictive (and enormous) human body that absorbed *all* the EU emissions between 1970 and 2020. This is an unusual but necessary concept: defined in this way, the cumulative excretion-adjusted emissions give an analogue of the 'total emissions between 1970 and 2020' that was used in step 2 of the example. In short:

$$Costs_{2020}\ per\ kg\ of\ Cd_{2020} = \frac{Costs_{2020}}{Cumulative\ excretion\ adjusted\ emissions\ 1970 - 2020}$$

4. To determine the total costs per kg of cadmium emitted in 2020, we should again account for the future costs made by the 2020 emissions. Assuming an infinite half-life, we could simply multiply the costs in 2020 by the cadmium emitted in 2020 by the specific number of years (which equals the median age, in this case 50 years). However, now that we account for excretion, the calculation becomes slightly more cumbersome.

5. First, we calculate for each of the 50 years remainder of the cadmium emitted in 2020, where this cadmium be absorbed immediately by a human body in 2020. We call this the *excretion-adjusted remainder*. We can then add all these excretion-adjusted remainders together to form the *cumulative excretion-adjusted remainders*. Doing so gives us a measure of the amount of cadmium that remained from the 2020 emissions and will act as a risk-multiplier for lung cancer over the coming 50 years.
6. Subsequently, we multiply the cumulative excretion adjusted remainder by the output of step 3. This gives us the total costs of the cadmium that was emitted in 2020:

$$Costs_{total}\ of\ Cd_{2020} = Costs_{2020}\ per\ kg\ Cd_{2020} * Cumulative\ excretion\ adsjusted\ remainder$$

7. Finally, we calculate the total costs per kg of 2020 emissions. To do so, we simply divide by the 2020 emissions:

$$Costs_{total}\ per\ kg\ of\ Cd_{2020} = Costs_{total}\ of\ \frac{Cd_{2020}}{kg\ of\ cadmium\ emissions\ in\ 2020}$$

This procedure (steps 1 to 7) was then repeated for the other diseases caused by cadmium, and for the diseases caused by mercury. This meant adjusting the emissions data and number of accumulation years to the substance and median age, respectively.

B General framework of economic valuation studies

Most the valuation studies included in our assessment relied on similar methodology as we also applied. The necessary biomonitoring data was mainly collected from the COPHES/DEMOCOPHES survey based on seventeen European countries with recruiting 1,875 child-mother pairs. These subjects aimed to represent the general population thus exposure hot-spots were avoided from the sampling. The data quality and comparability were the utmost importance for the study. The COPHES/DEMOCOPHES studies were carried out for instance for mercury, cadmium, phthalates and BPA which are also included in our report (Schindler et al., 2013). Besides this, data was collected from comparable biomonitoring studies throughout the EU. Depending on the specific substance in focus, slightly different approaches were taken while in principle still following similar methodology. For MeHg related cognitive dysfunction both the CoI (Bartlett & Trasande, 2013) and the expected lifetime earnings (Bellanger et al., 2013) were estimated. The Cost of Illness approach provides an estimate on the economic BoD value which could be gained in terms of direct medical costs and loss of productivity due to illness in case the disease would be prevented. These costs are multiplied with the number of cases to obtain the total economic value (RPA, 2003). In almost all valuation studies the strength of the epidemiological and toxicological literature was evaluated by the criteria of the GRADE Working group and the Danish Environmental Protection Agency, respectively. The probability of causation was assessed based on the criteria formulated by the International Panel on Climate Change (IPCC). As a first step, in all studies the number of exposed people were calculated. In the case of Bellanger et al. (2013) and Bellanger et al. (2015) the number of births in the EU over the exposure limit level were estimated, while other studies estimated the affected population at a specific age (Bellager et al., 2015; Trasande et al., 2015; Legler et al., 2015). Subsequently, based on the biomonitoring studies, the population was distributed into percentile ranges assuming log-normal distribution among them. In most of the studies the lowest exposure group was considered to have zero exposure while other groups were assumed to have the lowest exposure level in each percentile range (except Legler et al., 2015 where all percentile ranges were assigned a median value). The no-effect level was mostly chosen to be the highest exposure group without significant association between exposure and outcome. In the case of IQ losses, the attributable losses were multiplied with the birth numbers in all percentile ranges and were summed up to obtain the total number of IQ point losses. A linear dose-response function (or ERF) was utilized with the assumption that 1µg/L increase of cord blood mercury is associated with IQ loss of 0,093*Std based on an earlier study (Trasande et al., 2006). In the case of Bartlett & Trasande (2013), the estimation was made based on the correlation of 0,18 IQ point loss per part per mln (ppm) of maternal hair mercury content. Concerning obesity from BPA exposure, a linear interpolation was applied from the no-effect value to estimate the weight gain expressed in change in BMI for each category (Legler et al., 2015). Regarding ASD and ADHD connected to phthalate exposure, increments in social responsiveness scores were calculated by multiplying the increments per long-unit increases (identified in a study) by the log (base exp) of RR of each percentile range chemical content.

Generally, the NORMDIST exposure function was applied from Microsoft Excel to estimate the increase in incidence of intellectual disabilities and other disorders. The attributable increments were obtained (in case of relevance) with the subtraction of the disease

prevalence in the unexposed group. The increments in incidence or prevalence were then multiplied with the total population to obtain the attributable cases. Overall, the attributable disease burden was calculated based on the equation: disease rate * AF * population size, while the attributable cost was further quantified by disease rate *AF * population size * cost per case. Additionally, (e.g., in the case of Trasande et al., 2016) the Delphi method was used to evaluate the epidemiological and toxicological data, determine low and high ranges and threshold values (if applicable) as well as evaluate potential non-linearity of the exposure relationship. In case of calculating the CoI costs, the guidelines of the Panel on Cost Effectiveness and Medicine were followed. Furthermore, numerous Monte Carlo simulations were performed to estimate probable range of costs (Trasande et al., 2015). The average productivity loss per IQ point was calculated initially for France and was adjusted to the total EU, based on differences in PPP (Pichery et al., 2011; Bellanger et al., 2013). For the costs European data was used or if it was now available it was extrapolated from US data. Most of the costs in the studies are presented in 2010 euros (Hauser et al., 2016).

The US-EPA similarly uses the exposure-response function (ERF) to estimate the human toxicity potential. As linearity is assumed for the exposure response these can be also presented as the slope factor with the dimension of mg intake/kg body mass/day for 70 years. As the approach hypothesises a lifelong exposure the results represent a higher band value for toxicity. For cancers, unit risks can be defined which are usually published in the US-EPA IRIS database. With inhalation a 13 m^3/day inhalation rate is assumed while unit risk for drinking water can be estimated by assuming 2 L/day water consumption. As the ERFs imply yearly exposure the unit risk factors need to be divided by 70 and convert the mg for kg per body mass per day assuming 70 kg weight (Rabl et al., 2014).
The USEtox model calculates the Effect factor (EF) from ED_{50} values using unit risks. The measured or estimated ED_{50} value determines a dose which leads to a 50% increase in disease probability in humans. This data is mainly derived from animal studies and only in a very few cases from epidemiological studies. From this ED_{50} (dose) value the increase in disease cases can be calculated for one kilogram of intake (Fantke et al., 2018). For example, the inhalation unit risk (q*; or slope factor) for cadmium (available from US-EPA IRIS database: https://iris.epa.gov/ChemicalLanding/&substance_nmbr=141) equals to 0.0018 µg/m^3. Based on the relationship provided by USEtox (ED_{50} ~ 0.8/q*) we calculate 0.8/0.0018 =444.444 µg/m^3. USEtox converts to results to kg/person/lifetime to make it fit for the model. In the model 70 years of lifetime is assumed (multiply by 70) and 13 m^3 breathing rate per day (further multiply by 13*365) which equals 14,762,222 µg/person/lifetime or 0.14762 kg/person/lifetime. We use the equation provided by USEtox: EF =f_c/ED_{50} where “fc” is the multiplier for cancer effect which equals to 0,5. According to this equation the results are the following: EF = 0,5/0,14762 =3,39 which yields the EF for cancer cases / kg intake per person/lifetime.

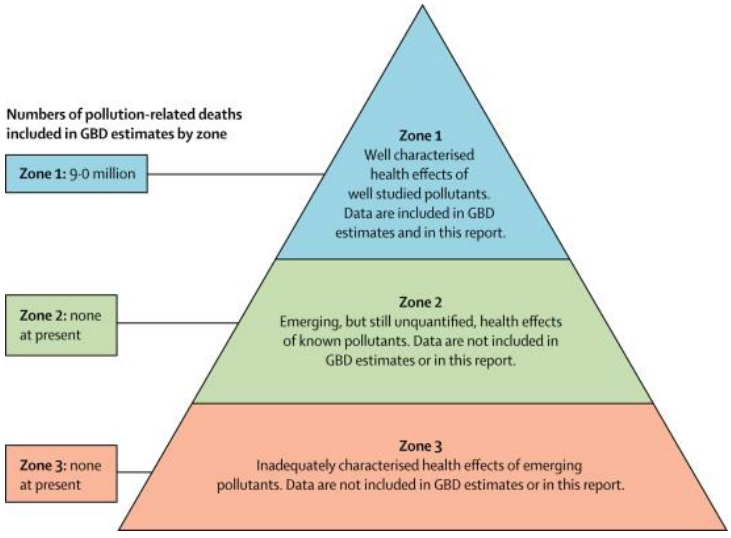
C Classification frameworks for categorizing chemicals

From a regulatory perspective, the toxicity of chemical pollutants has usually been addressed by including them in a so-called list. In this paragraph we will introduce a few classification frameworks and important databases that label chemicals and their relative toxicity.

C.1 The Lancet Commission

The Lancet Commission has constructed the *pollutome*, a framework to categorize our existing knowledge about pollution (Landrigan et al., 2018). The framework assorts all forms of potentially harmful pollutants to human health to support research activities concerned with chemical contamination. The model organizes pollution forms into three zones. Zone 1 contains pollutants with well characterized causal relationships to diseases and revealed health burdens. Zone 2 consists of pollutant-disease pairs where causal relationship is being established but not yet well characterized or we have only limited evidence available thus the burden of disease is not yet quantified. The last zone, Zone 3 contains the largest group of chemicals, mostly new substances, where the harmful effects have only started to be discovered recently. This zone includes many already highly dispersed compounds such as pesticides, endocrine disruptors and developmental neurotoxicants which are detectable in almost all human beings. As the effects and the epidemiological role is not fully characterized for compounds in Zone 2 and 3, the contribution of deaths and DALYs of these pollution forms are not known while the real impacts could be immense (Landrigan et al., 2018). The number of deaths related to pollution is only known for Zone 1 with approximately 9 million cases globally each year (Landrigan & Fuller, 2018).

Figure 4 - The pollutome concept



C.2 The Globally Harmonized System of Classification and Labelling of Chemicals (GHS)

The GHS was created to harmonize all existing systems and provide a global consensus system for classification, safety data and labelling of chemicals (as laws and regulation significantly differ by country to country). The overall aim of GHS is to improve the protection of human and environmental health with providing an overarching international system for hazard communication, providing a framework for countries which lack such a system and facilitate evaluation, testing and trade of chemicals. The GHS is designed by the United Nations and the classification system defines categories of the health, physical and environmental hazards of chemicals which classification eases to compare chemicals based on hazard criteria. With the identification and communication of chemical hazards potential exposure can be prevented and accounted for. The primary focus is on the safe use of chemicals for which the identification and communication of hazard potential is essential. The GHS system covers all hazardous chemicals which includes substances, mixtures and other preparations. Classification of chemicals by hazard endpoints (physical, health and environmental) is the essence of good hazard communication. The health endpoints in the GHS system are the following: acute toxicity, skin corrosion/irritation, serious eye damage/eye irritation, respiratory or skin sensitization, germ cell mutagenicity, carcinogenicity, reproductive toxicology, target organ systemic toxicity (single exposure), target organ systemic toxicity (repeated exposure) and aspiration toxicity (UN, 2019). The EU adopted the GHS system in 2008. The GHS was implemented for the classification, labelling and packaging of chemicals (CLP) replacing old rules regarding these matters. During the hazard identification the chemicals are classified into one of the hazard groups. CLP supports users with labelling to communicate and identify chemical hazards.

C.3 IARC classification

The international Agency for Research on Cancer, an autonomous agency of the WHO, classifies chemical compounds based on their carcinogenic potential. Group 1 substances are considered carcinogenic to humans, Group 2A substances are probably carcinogenic, Group 2B substances are possibly carcinogenic and Group 3 substances are not classifiable as carcinogenic to humans but also the potential cannot be ruled out (Samet et al., 2019). The IARC evaluation procedure takes in new chemical agents for review in every new monograph based on the recommendation of an Advisor Group. The group suggests contaminants with potential evidence in case of rapid evaluation needs, current health concerns or based on availability of research studies. The evaluation procedure is carried out by an interdisciplinary Working Group. The Working Group mainly focuses on available published literature taking into consideration all pertinent epidemiological studies, carcinogenicity bioassays, mechanistic evidence and experimental animal data also in the view of current human exposure levels. These studies are evaluated based on their quality and weighted based on their relevance. After this step, the results are reviewed and the strength of evidence is evaluated with considering main findings and limitations. At the end of the process, the working groups describe the rationale behind the decision and classify the compound based on its determined carcinogenic potential (WHO, 2019).

IARC decisions have a powerful impact thus, potential flaws in the classification process can significantly affect human health or industries using the compound. In light of this, the IARC monographs have been targeted by a wide range of criticism. The main arguments have been related to the limitation of the IARC process, the chosen composition of the Working Groups, issues with certain evaluations and that the process relies on epidemiological data which is very limited in most of the cases (Samet, 2015). A diverse group of more than

hundred scientists evaluated the IARC processes to examine potential flaws of the IARC methodology and working procedures. However, these researchers concluded that the IARC provides transparent and appropriate procedure for evaluation of substances without any identified bias in its decision-making processes (Pearce et al., 2015).

C.4 EPA framework and other US-based frameworks

On top of the IARC classification, the US-EPA provides the Integrated Risk Information System (IRIS) program which evaluates carcinogenicity of substances and their quantitative risks (Samet, 2015). It produces systematic reviews about chemical substances and uses the US-EPA CANCER Guidelines to assess the available scientific data. However, this is only one of the roles of the IRIS program. In general, the program focuses on the development of toxicity identification and dose-response analyses of environmental chemical exposures. The IRIS relies on scientific evidence synthesis with a multidisciplinary approach and comprehensive expert peer review processes. It aims to compile scientific information to support decision making and protect public health. The program makes all chemical toxicity data available for the public to provide transparency about its functions (US-EPA, 2020).

The IRIS handbook describes the framework for draft development which starts with scoping and problem formulation to establish the information required for the assessment and identify potential health effects of chemical substances. In the next step, thorough literature screening and searching, the IRIS staff works together with experts from the specific field to ascertain the relevant studies on the chemicals in question. Subsequently, the IRIS staff with required experts evaluates the epidemiological and animal toxicity studies and classifies them based on their scientific confidence and relevance. As a next step, the most relevant studies are selected and evidence is synthesized from human epidemiological studies, animal toxicological studies and mechanistic studies to compile the final results taking strong attention to the variation in the results. Finally, the IRIS staff summarizes the results of the assessment and integrates the new evidence to its system. As soon as there is sufficient evidence, dose-response functions and toxicity values are selected which are used further in toxicity evaluations (US-EPA, 2020).

C.5 Control of chemicals in the EU and in the US

In addition to the classification lists, chemicals are also controlled by additional legislation. There are very briefly introduced here.

European Union

Stricter safety measures with pre-market evaluation procedures to target widespread use of toxic chemicals have only been introduced in the last fifteen years (Landrigan et al., 2018). In 2006, the European Union introduced the Registration, Evaluation, Authorization and Restriction of Chemicals (REACH) policy to address the regulatory issues related to chemicals. REACH (EC 1907/2006) aims to improve the protection of human health and the environment through the better and earlier identification of the intrinsic properties of chemical substances. This is done by the four processes of REACH, namely the registration, evaluation, authorisation and restriction of chemicals.

Through REACH, the European Commission places responsibility on industry to manage the risks from chemicals and to provide safety information on the substances. Manufacturers and importers are required to gather information on the properties of their chemical substances, which will allow their safe handling, and to register the information in a central database in the European Chemicals Agency (ECHA) in Helsinki. The Agency is the central

point in the REACH system: it manages the databases necessary to operate the system, co-ordinates the in-depth evaluation of suspicious chemicals and is building up a public database in which consumers and professionals can find hazard information.

The regulation also calls for the progressive substitution of the most dangerous chemicals (referred to as "substances of very high concern") when suitable alternatives have been identified (see also below at the Netherlands). Nevertheless, critiques on the REACH legislation can sometimes be heard as the process still tends to neglect low quantity substances and is unable to reveal diverse supply chain aspects of potentially hazardous chemicals. Moreover, in many instances it is difficult to reveal every negative effect in the initial testing procedures.

Another initiative, the New or Emerging risks of chemicals (NERCs) project aims to prevent chemicals to be highly dispersed before being used and preserve environmental safety and human health. NERCs mainly addresses the discrepancies of REACH and conducts broader assessment of workers, consumers, and the environment (RIVM, 2014).

The Netherlands

The Dutch government takes priority on Substances of Very High Concern (Zeer Zorgwekkende Stoffen, ZZS) that have been formulated in the REACH legislation. ZZS are substances that are dangerous to humans and to the environment, for example because they are carcinogenic, can hinder reproduction or accumulate in the food chain. The policy of the Dutch government is aimed at keeping ZZS out of the living environment. It does this by means of a continuous improvement cycle in which the aim is zero emissions of ZZS; the so-called minimization obligation. Trying to minimize emissions at the source is the central starting point in this respect: avoid using the ZZS and/or taking measures so that ZZS can no longer be released into the living environment. This can be done by replacing (substituting) the ZZS with another less harmful substance, by implementing new production techniques, or by process optimization. If a source approach is not possible, the company should focus on further minimizing the residual emissions, for example by applying downstream reduction techniques.

The selection criterium for ZZS is based on Article 57 of the REACH Regulation (see below):
- CMR substances: carcinogenic (the C for carcinogen), mutagen (the M) and toxic for reproduction (the R for reprotoxic);
- PBT substances: persistent, bio-accumulative and toxic or poisonous;
- vPvB: very persistent and very bio-accumulative;
- substances of similar concern (such as endocrine disrupting substances).

A ZZS can be classified in a substance category and substance class. Most of the substances fall under the category ZZS. The classification of substances follows furthermore three substance classes:
- ERS, extremely risky substances;
- MVP 1, minimization mandatory solids; and
- MVP 2 mandatory gaseous or vaporous substances to be minimized.

This classification is important to determine which emission requirement applies. Appendix 12 of the Activities Regulation contains a list of substances that are ZZS and their substance class.

The United States

The Toxic Substances Control Act (TSCA; 1976) authorises the US-EPA to request reporting and to oversee requirements and restrictions of chemical substances which do not fall under the jurisdiction of FDA (also excluding pesticides). In 2016, the act was modified by the "Frank R. Lautenberg Chemical Safety for the 21st Century Act" to modernize the TSCA which further requires the EPA to assess all existing chemicals and risks while increasing public transparency (US-EPA, 2017a). The US-EPA takes decisions about new chemicals based on the TSCA section 5 which are evaluated by a risk-based approach (US-EPA, 2017b). Under section 8 of TSCA, the Chemical Data Reporting rule requires the collection of information about the types and quantities of manufactured chemicals including import, processing and use information of marketed chemicals. The TSCA chemical substance inventory includes all the manufactured and processed chemicals in the US, by creating exposure related information of all marketed substances. The EPA publishes all the collected information to make it available for the public and to support health, safety and environmental protection in connection to manufacturing processes. With this, aid to provide information about the potential occupational and other exposures to the chemicals in use while supporting easier assessment of human and environmental health effects (US-EPA, 2017a). Another database, the Emergency Response Notification System (ERNS) was created as a cooperation of various governmental agencies and centres. The database stores information about the release of hazardous substances and oil discharges since 1986 which also supports assessment of potential exposures (https://cfpub.epa.gov/si).

Within the US-EPA, the Office of Resource Conservation and Recovery (ORCR) is delegated with the management of waste (both hazardous and non-hazardous). Under the ORCR the Resource Conservation and Recovery Act regulates hazardous wastes generation, transportation, handling, storage and disposal throughout its life-cycle and provides a hazardous waste management framework. It also focuses on minimizing hazardous waste disposal and stringent waste management (https://www.epa.gov/laws-regulations). As an addition to this role, the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) (with other name Superfund) was created to authorize the president to act on handling, removal and remediation of inactive hazardous waste sites. By this, rapidly respond to chemical releases or potential release threats. As an important part of the CERCLA a fund is created to finance clean-up hazardous waste sites in time of necessity (https://www.epa.gov/enforcement).

D Per capita cost comparison

Table 11 - Total and per capita costs in the EU28

Chemical	Total cost EU28 lower bound (€)	Total cost EU28 upper bound (€)	Per capita cost EU28 lower bound (€/capita)	Per capita cost EU28 upper bound (€/capita)
Mercury	17.5 bln	111.95 bln	34.10	218.23
Cadmium	101.24 bln	127.4 bln	197.35	248.35
Chromium (all)	801 mln	801 mln	1.56	1.56
Arsenic	6.92 bln	10.62 bln	13.50	20.69
Benzo[a]pyrene	1.55 bln	1.55 bln	3.02	3.02
Bisphenol A	393 mln	393 mln	0.77	0.77
Dibutyl phthalate	6.89 bln	6.89 bln	13.44	13.44
Chlorpyrifos	3.23 bln	3.83 bln	9.85	11.68
Glyphosate	0	2.23 bln	0	4.35

Table 11 assesses the total costs in the EU28 and the per capita damage costs of chemicals per year. Cadmium particularly sticks out regarding both lower and higher bound total costs. An important reason behind cadmium's high estimated damage that we accounted for five different disease conditions in the calculation. Nevertheless 101-127 billion is a very high value for damage costs which also leads to high per capita costs. The per capita costs were also estimated for the total EU28, by dividing the total costs with the EU28 population from 2019 (including the UK). In the case of Chlorpyrifos the USA population data was used to gain the per capita costs.

Table 12 - Combined total damage costs in the EU28

Chemical	Combined total cost EU28 Lower bound (€)	Combined Total cost EU28 Upper bound (€)	Combined per capita cost EU lower bound (€/capita)	Combined per capita cost EU upper bound (€/capita)
Mercury	27.79 bln	122.25 bln	54.18	238.31
Cadmium	101.24 bln	127.4 bln	197.35	248.35
Chromium (all)	801 mln	801 mln	1.56	1.56
Arsenic	6.92 bln	10.62 bln	13.50	20.69
Benzo[a]pyrene	1.55 bln	4.47 bln	3.02	8.71
Bisphenol A	1.04 bln	1.04 bln	2.03	2.03
Dibutyl phthalate	6.89 bln	9.53 bln	13.44	18.58
Chlorpyrifos	3.23 bln	121.12 bln	9.85	369.30
Glyphosate	0	2.23 bln	0	4.35

To acquire a broader estimate of damage costs we combined our results with other valuation studies in case the valuation was made for different diseases or disfunctions than what we investigated (Table 12). Upon combination of the results, we added the values from other studies to the lower bound of our results if the total costs were specifically calculated for the EU28 and for the specific compound (mercury, BPA). If we calculated the final values from other studies based on further assumptions (such as the contribution of DBP out of all phthalates, Chlorpyrifos in the US and BaP in the EU28) we only incorporated the damage costs to the upper bound of the combined results. In the case of Chlorpyrifos,

phthalates and BaP, the increase in the combined results is significant. In the case of Chlorpyrifos the increase is almost 40 times compared to our results which can be attributed to the high cost of organophosphate pesticides identified by Bellanger et al. (2015). This also leads to significantly higher per capita cost than any other substances included in this assessment.

Table 13 - Total and per capita damage costs in the Netherlands

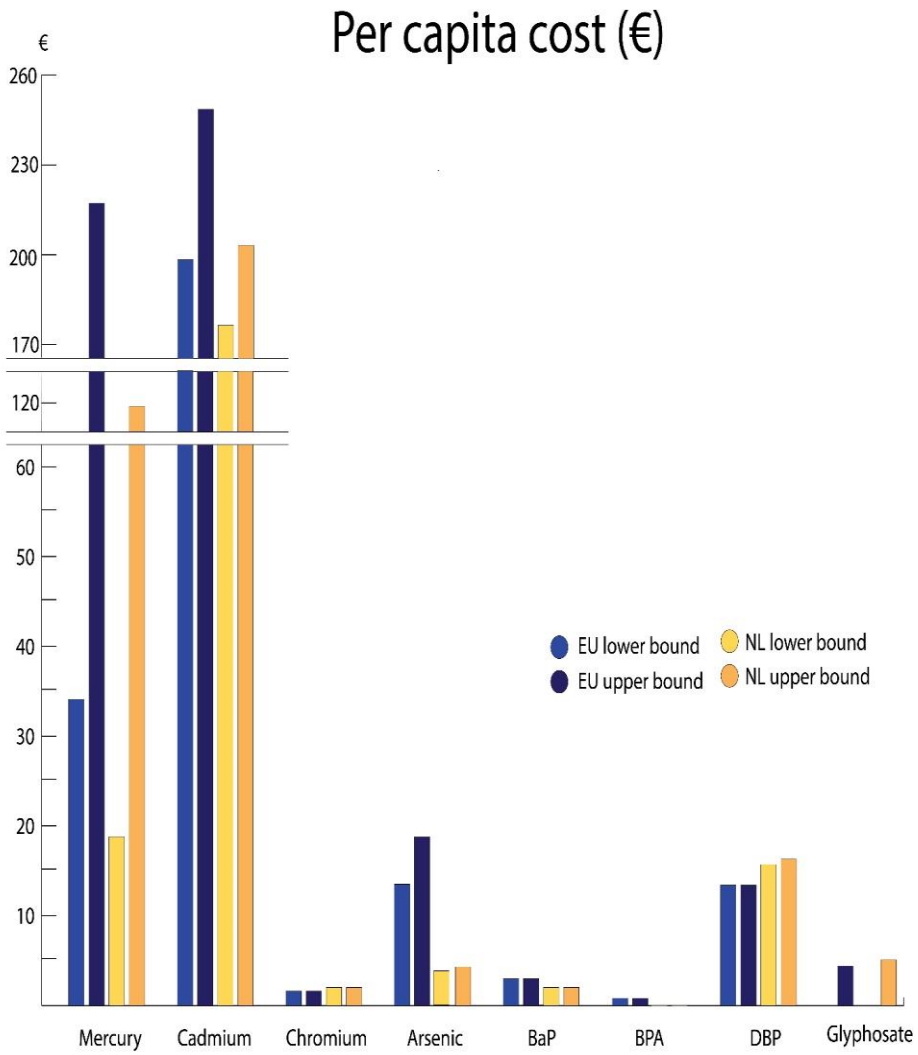
Chemical	Total cost NL lower bound (€)	Total cost NL upper bound (€)	Per capita cost NL lower bound (€/capita)	Per capita cost NL upper bound (€/capita)
Mercury	331.37 mln	2.09 bln	19.04	119.82
Cadmium	3.05 bln	3.58 bln	175.21	205.82
Chromium (all)	34.93 mln	34.93 mln	2.01	2.01
Arsenic	73.65 mln	79.64 mln	4.23	4.58
Benzo[a]pyrene	34.11 mln	34.11 mln	1.96	1.96
Bisphenol A	1.03 mln	1.03 mln	0.06	0.06
Dibutyl phthalate	272.5 mln	282.9 mln	15.66	16.25
Chlorpyrifos	3.23 bln*	3.83 bln*	9.85	11.68
Glyphosate	0	88.97 mln	0	5.11

The total costs in the Netherlands are mainly influenced by the different incidence rates of various diseases compared to the EU28 average (Table 13). Generally, the total costs for the Netherlands remain in similar order (highest costs remain the highest) while significant differences are also present which is further revealed in the per capita costs (Table 14).

Table 14 - Per capita damage cost in the EU28 and in the Netherlands

Chemical	Average per capita cost EU (€/capita)	Average per capita cost NL (€/capita)
Mercury	126.17	69.43
Cadmium	222.85	190.52
Chromium (all)	1.56	2.01
Arsenic	17.09	4.40
Benzo[a]pyrene	3.02	1.96
Bisphenol A	0.77	0.06
Dibutyl phthalate	13.44	15.96
Glyphosate	4.32	5.08

Figure 5 - Per capita costs in the EU and in the Netherlands

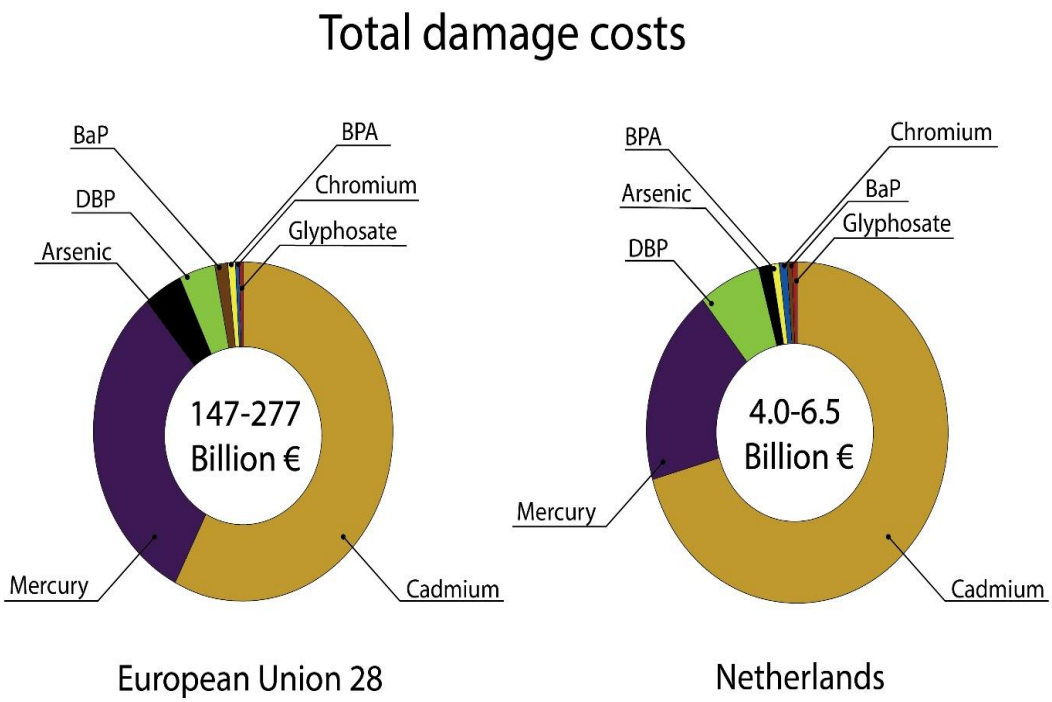


In Table 14 and Figure 5 it is shown that the per capita costs are similar for the EU and for the Netherlands. However, there are significant differences between the per capita costs of mercury, arsenic and BPA. The main reason for the lower per capita mercury costs can be explained with the lower incidence rate of ischaemic heart disease in the Dutch population compared to the average EU28 population (GBD, 2019). The results are lower despite the fact that for the EU we only calculated with myocardial infarction in our results while for the Netherlands IQ loss was also included. Most of the arsenic related health issues come from contaminated drinking water consumption (Tolins et al., 2014). Arsenic exposure in the Netherlands is also much lower than in many other countries in the EU28 due to the low arsenic content of the drinking water (Ahmad et al., 2020). Thus, the lower per capita cost are the consequences of low environmental exposure of the Dutch population. In the case of BPA, the costs are also considerably lower which is due to the much lower incidence of childhood obesity in the Dutch population than the EU28 average (GBD, 2019). These results also indicate that the results should be extrapolated carefully between countries as high intercountry differences can be present concerning exposure data and various disease

incidences. This also implies that our results are open for scrutiny and the availability of more specific exposure data could highly increase the precision.

All in all, Dutch values are thus lower than the EU averages in the calculations of this research as the Dutch population is relatively healthier.

Figure 6 - Average combined damage costs of all pollutants in Europe and in the Netherlands



Source: Own calculations.

Figure 6 shows the combined total costs of 8 compounds for the EU28 and for the Netherlands (Chlorpyrifos was left out). The figure shows that mercury and cadmium is responsible for the most damage cost, approximately 85% of the costs calculated from the adverse health effect due to high human exposure. These eight compounds represent about 0.89 to 1.67% of the EU28 GDP and 0.47-0.76% of the Dutch GDP (https://data.worldbank.org, 2019).

E Intake fractions from Usetox

To acquire the intake fraction values (amount of human intake in kg/amount of emission in kg) for various substances, the USEtox model and database was used. In USEtox, the intake fraction is derived from the multiplication of fate and exposure matrices (FF * XF) and expresses the fraction of emitted chemical pollutants which reaches and enters the human body via different pathways. From the USEtox documentation the 'USEtox_results_organics' and 'USEtox_results_inorganics' sheets (inorganics for metals and organics for every other compound available for download on: https://usetox.org) were adopted to calculate the percentage of intake compared to emissions in kg in the EU. Within these main excel sheets the necessary information was collected from the 'Intake fractions iF' sheet. The total intake fraction for each compartment was calculated for three different intake routes: inhalation, ingestion by drinking water and ingestion by food. For this purpose, the intake fraction for all different food sources were summed up including above ground produce, below ground produce, dairy, fish and meat intake, while for drinking water and inhalation the single given values were used for the different compartment and scales. The intake fractions were identified separately for each emission to various compartments (Emission to industrial indoor air, Emission to urban air, Emission to continental rural air, Emission to continental freshwater, Emission to continental sea water, Emission to continental natural soil, Emission to continental agricultural soil).
In addition, for pesticides the application for wheat was included in the calculations which was determined by USEtox as an additional value. In the final version, the household indoor air compartment was not included as the study is concerned with environmental emissions. The population densities were determined based on the USEtox model where urban (and indoor) density of 8,333 person/km^2 and for rural setting 111 people/km^2 were applied. To arrive at total intake fractions for each compartment, the following calculations were done on the data described:

- Emissions to air: for each uptake route, the average of the intake fractions for urban and continental rural was calculated. These averages are added together to derive the total intake fraction for emissions to air.
- Emissions to water: the intake fractions for continental freshwater only are taken. The intake routes are added together to derive the total intake fraction for emissions to water.
- Emissions to soil: intake fractions for emissions to soil are divided into continental natural, and continental agricultural. For each uptake route, an average intake fractions was calculated, where continental agricultural is weighted 65%, and continental natural is weighted 35%. The intake fractions for each uptake route are added together to arrive at the total intake fraction for emissions to soil. The weighting factors (65-35) are based on land cover data for the Netherlands. In the Netherlands, approximately 65% of the country is considered agricultural land

A table was created to present the intake fraction values for the nine chemical compounds involved in this report. Intake fractions lower than 10-7 were not included in the assessment due to their marginal contribution to the intake. To gain the percentage wise share of chemical emission reaching the human population the fractions (derived from USEtox) were multiplied by a factor of 100 (Table 15).

Table 15 - Intake fractions derived and modified base on USEtox

	Intake fractions (%)		
Chemical	**Emission to Air**	**Emission to Water**	**Emission to Soil**
Mercury	2.97	0.04	3.23
Cadmium	1.22	0.08	1.31
Chromium (all)	0.01	0.04	0.01
Arsenic	0.05	0.07	0.04
Benzo[a]pyrene	0.006	0.004	0.0001
Bisphenol A	0.003	0.011	0.001
Dibutyl phthalate	0.009	0.006	0.002
Chlorpyrifos	0.002	0.03	0.0002
Glyphosate	0.002	0.004	0.003

In the end the intake fractions were not being used in our research.

E.1 Characterization factors

The characterization factors at midpoint and endpoint levels were also derived from USEtox, using the same two data sheets as we used to derive the intake fractions (USEtox_results_organics and USEtox_results_inorganics). From these sheets we took data from the 'Human tox CF' sheet which demonstrates the human toxicity both at midpoint and endpoint levels for different compartments for cancer and non-cancer cases. These characterization factors were used as a reference for our compounds as it provides comparative units in CTUh.