

Partnership for the Assessment of Risks from Chemicals

Deliverable D6.4

Title: 1st Report on health impact indicators and their policy implications

WP 6 – T6.2.4



Partnership
FOR THE
Assessment
OF
Risks
FROM
Chemicals



Co-funded by
the European Union

This partnership has received funding from the European Union's Horizon Europe research and innovation programme under Grant Agreement No 101057014.

Technical reference	
Work package	WP6 – Innovation in regulatory risk assessment
Task	T6.2 – Integrative exposure and risk assessment
Dissemination level ¹	PU = Public
Lead Beneficiary/ Responsible AE	IRAS/VITO
Contributing Participants	ANSES, AUTH, BPI, DTU, ENSP, FMUL, IISPV, INSA, ISSeP, IVL, KI, MU, NIJZ, OI, NIPH, RIVM, RUMC, Sciensano, STAMI, UBA, USI, UU-IRAS, VITO, and WR-BIOM
Responsible author(s)	Jurgen Buekers (VITO), jurgen.buekers@vito.be Anthony Purece (VITO), anthony.purece@vito.be Ulrike Gehring (UU-IRAS), U.gehring@uu.nl Jelle Vlaanderen (UU-IRAS), J.J.vlaanderen@uu.nl Panagiotis Mallioris (UU-IRAS), p.mallioris@uu.nl Sofie Theresa Thomsen (DTU), sthth@food.dtu.dk Sara Monteiro Pires (DTU), smpi@food.dtu.dk Rafiqa Benchrir (Sciensano), Rafiqa.Benchrih@sciensano.be Eva De Clercq (Sciensano), Eva.DeClercq@sciensano.be Valentine Vermeulen (Sciensano), Valentine.Vermeulen@sciensano.be Claire Demoury (Sciensano), claire.demoury@sciensano.be Carolina Capitão (FMUL), carolinacapitao@medicina.ulisboa.pt Margaux Sanchez (ANSES), margaux.sanchez@anses.fr Philippe Palmont (ANSES), philippe.palmont@anses.fr Vesna Zadnik (OI), VZadnik@onko-i.si Manca Ahačič (NIJZ), manca.ahacic@nijz.si Lucija Perharic (NIJZ), lucija.perharic@nijz.si
Co-authors	See Authors and Acknowledgements
Internal Reviewers ²	Amélie Crépet / ANSES / amelie.crepet@anses.fr Jacob van Klaveren / RIVM / jacob.van.klaveren@rivm.nl Katleen De Brouwere / VITO / katleen.debrouwere@vito.be
External Reviewers ³	Gerardo Sanchez / EEA / Gerardo.sanchez@eea.europa.eu Christophe Rousselle / ANSES / christophe.rousselle@anses.fr
Due date of deliverable	30/04/2025
Actual submission date	19 June 2025

¹ PU = Public

PP = Restricted to other programme participants (including the Commission Services)

RE = Restricted to a group specified by the consortium (including the Commission Services)

CO = Confidential, only for members of the consortium (including the Commission Services)

² WP/task co-leader(s) from the same WP

³ Independent Reviewers that should not be part of the task related to the AD/D or part of projects related to the Task

Document history

Version	Date	Reviewer name/Institutions	Short description of changes
1	18/03/2025	Panagiotis Mallioris (UU-IRAS), Ulrike Gehring (UU-IRAS), Jelle Vlaanderen (UU-IRAS), Jurgen Buekers (VITO), Anthony Purece (VITO)	Preparation of first draft
2	22/04/2025	Katleen De Brouwere (VITO) Amélie Crépet (ANSES)	T6.2 review
3	06/06/2025	Panagiotis Mallioris (UU-IRAS), Ulrike Gehring (UU-IRAS), Jelle Vlaanderen (UU-IRAS), Jurgen Buekers (VITO), Anthony Purece (VITO)	Revisions after reviewers' feedback

“Funded by the European Union. Views and opinions expressed are, however, those of the author(s) only and do not necessarily reflect those of the European Union or the Health and Digital Executive Agency. Neither the European Union nor the granting authority can be held responsible for them.”

Abstract

Environmental burden of disease (EBD) and health impact assessment (HIA) are tools to provide scientists and policy makers with quantitative insights into the impact of environmental exposures (risk factors or stressors) or interventions on public health. More specifically, EBD estimates the disease burden attributable to environmental exposures (e.g. chemicals), while HIA quantifies the health effects of policies and interventions in a population of interest. As such, both frameworks allow for evidence-based actions and resource allocation for combating the burden of disease in a population. Moreover, HIA can be used to assess health impact (in)equities between subpopulations. EBD and HIA combine information on internal/external exposure levels, frequency (prevalence/incidence) of health outcomes, exposure-response functions derived from epidemiological studies and demographic data. More often than not, EBD and HIA analyses require several assumptions or extrapolations due to lack of data. In Y2-3 of PARC (2023-2024) six case studies on EBD or HIA were started to bridge these gaps and to enhance our understanding and inform policy makers on burden of disease related to PARC priority chemicals. These case studies (T6.2.4c) address the three overarching aims of task T6.2.4 for bridging such gaps i.e. data generation (T6.2.4a), methodology (T6.2.4b) and health indicators (T6.2.4d). The current report provides an overview of the methodological challenges, summaries of the case studies with a focus on their contributions to the three aims of Task 6.2.4 (including both findings and challenges) and on what is still pending for their completion. Finally, in addition to the case study summaries, this report (April 2025) provides also an overview of their coordination process by the T6.2.4 leaders and partners, a summary of new case studies initiated in late 2024 and a short description of the adapted procedure for selecting new cases studies for Y5-7 (2026-2028).

Key Words

Environmental Burden of Disease (EBD), Health Impact Assessment (HIA), exposure-response function (ERF), health impact indicators

Table of contents

Abstract	4
Key Words	4
Table of contents	5
Acronyms	7
Glossary	7
1. Introduction	8
1.1. Background	8
1.2. Scientific, societal and regulatory questions	9
1.3. Prioritized chemical families	9
2. Organization of the work	9
3. The Health Impact Assessment Concept	10
4. Methodological challenges	12
4.1 Exposure data	12
4.2 Vulnerable groups/socioeconomic context	14
4.3 Extrapolation from single studies to (inter)national estimates	15
4.4 Defining the counterfactual	16
4.5 Exposure to mixtures	16
4.6 Persistent chemicals in the environment	17
4.7 Probabilistic modelling in EBD	18
4.8 Health data	19
4.9 Exposure-response relationships	20
Causality and weight of the evidence	20
Methodologies to establish exposure-response functions	21
Representativeness of the exposure-response function	22
4.10 Overview of methodological challenges	22
4.11 Development of EBD toolbox in MCRA	23
5. Case studies	24
5.1 Overview of the case studies	24
5.1.1 Pyrethroid-insecticide exposure and ADHD in Europe based on Human Biomonitoring	28
5.1.2 Lead exposure and cardiovascular diseases in European adults	30
5.1.3 Lead (Pb) and methylmercury (MeHg) exposure and IQ loss in children in Europe – single – substance and mixture approach	31
5.1.4 Municipal solid waste incineration emissions and cancer-related mortality	33
5.1.5 Arsenic exposure and lung, bladder, and skin cancer	36

5.1.6	Influence of waste co-incineration in a cement plant on cancer burden and risk assessment for selected chemicals based on HBM data	39
5.2	New case studies started in year 4 (2025)	42
5.2.1	Glyphosate based herbicides and diabetes in EU countries (IRAS (lead), ANSES, SRU, WR-BIOM, Sciensano)	42
5.2.2	Incorporating a time-to-event model to improve the prediction of age of onset or death (RIVM (lead), Sciensano)	43
5.2.3	Exposure to PFAS and infectious diseases (VITO (lead), DTU, FHI, ANSES, NIPH, Sciensano, IISPV)	44
5.2.4	Exposure to cadmium and nephrotoxicity (Sciensano (lead), VITO, RIVM, ANSES, DTU, ENSP)	45
5.2.5	Exposure to a mixture of cadmium and lead and nephrotoxicity (Sciensano (lead), VITO, ANSES, DTU, ENSP)	46
5.2.6	Probability modeling in burden of disease (UBA (lead), Sciensano, VITO, ENSP, ANSES, DTU)	47
5.3	Case studies for Y5 - Y7	48
6.	Summary and Conclusions	50
	References	53

Authors and Acknowledgements

The partner institutions who are involved in this Task 6.2.4 and who have provided input include ANSES, AUTH, BPI, DTU, ENSP, FMUL, IISPV, INSA, ISSeP, IVL, KI, MU, NIJZ, OI, NLZOH, NIPH, RIVM, RUMC, Sciensano, STAMI, UBA, USI, UU-IRAS, VITO, and WR-BIOM.

Acronyms

EBD: Environmental Burden of Disease

HIA: Health Impact Assessment

HBM4EU: Human Biomonitoring for EU

PARC - Partnership for the Assessment of Risks from Chemicals

RA: Risk Assessment

SES: Socio-Economic Status

TLs: Task leaders

WPLs: Work Package Leaders

Glossary

Glossary has been described in Additional Deliverable 6.6.

1. Introduction

1.1. Background

Pollution from anthropogenic activities is widespread, exposing people to numerous chemicals and as such posing a significant threat to public health. Exposure can be measured in various ways and measures of exposure can be categorized either as external or internal exposure. External exposure refers to the amount of a chemical an individual is exposed to. Internal exposure refers to the measurement of biomarkers internally present in the body (e.g. blood, urine) which provides an estimate of the types and amounts of chemicals that an individual has been externally exposed to. Estimation of both types of exposure (external and internal) is applied to characterize exposure, and for internal exposure the recent European HBM4EU project (<https://www.hbm4eu.eu/>) generated substantial new knowledge on chemical exposures. Information is provided on geographical exposure differences, exposure differences by SES (socio-economic status) etc. (<https://hbm.vito.be/eu-hbm-dashboard>).

For air pollution, a large body of evidence on health effects and exposure-response functions is available, summarized e.g. by the WHO in their Air Quality Guidelines (World Health Organization, 2021) that enables health impact assessments, e.g. estimations of the number of premature deaths caused by air pollution (<https://www.eea.europa.eu/en/topics/in-depth/air-pollution>). However, for many chemicals, the impact on health associated with certain exposure is unknown. Moreover, the health impact of exposure to mixtures of chemicals is even more poorly understood. This is even more so the case for vulnerable subpopulations including groups of different ages, socioeconomic status and underlying diseases (Makri and Stilianakis, 2008). Such missing knowledge on the distribution of the burden of disease in a population can be critical for policymakers. For some chemicals, information on exposure-response (effect) associations is available from toxicological or epidemiological studies. The combination of exposure scenarios with exposure-response functions (ERFs) allows the estimation of the health impact, e.g., how many people exhibit a certain health effect or disease related to a certain exposure.

Environmental burden of disease (EBD) analyses are quantitative assessments of health impact (including morbidity and mortality) in a specific population that is attributable to environmental factors such as chemicals. Health impact assessment (HIA) is a tool to estimate the potential effects of a policy or program on a population's health. Both EBD and HIA therefore allows for evidence-based prioritization of resources to reduce the burden of disease. EBD and HIA analyses for current chemical exposure of EU populations can be used to compare the burden of disease attributable to different environmental exposures and to prioritize preventive or mitigatory actions to be taken. Availability of data on external or internal exposure (including geographic variation and variation between sociodemographic groups), health outcomes (disease frequency (incidence or prevalence), life expectancy), exposure-response functions (ERF; based on data from epidemiological as well as toxicological studies and confirmed by mode of action studies), and demographic data are a prerequisite to perform EBDs or analytical HIAs for chemical exposures prioritized in PARC. However, the data required to perform an EBD assessment or HIA are often incomplete. In the first year of PARC (2022-2023), the availability of data for EBD calculations or HIAs was evaluated for PARC priority substances in PARC task T6.2.4.a. Links to other projects in T6.2.4 were made with respect to availability of data for implementation of methodologies to estimate the burden (T6.2.4.b), prioritizing of case studies (T6.2.4.c), and selection health impact indicators to be developed within PARC (T6.2.4.d). Transversal collaborations has been established in with partners from T6.2.3 or mixture RA, partners from T7.2 regarding the FAIRification of data, and partners from T8.3 regarding the development of an EBD/HIA toolbox add-on for the MCRA toolbox.

1.2. Scientific, societal and regulatory questions

Risk assessment (RA), environmental burden of disease (EBD) calculations, health impact assessment (HIA), and (social) cost benefit analyses (SCBA) inform stakeholders and policymakers to help protect and eventually improve human health. SCBA in particular evaluates how the costs and benefits of interventions are distributed among various social and stakeholder groups. The EU Green Deal, in particular the Zero Pollution Ambition (ZPA) policy, in which the Chemical Strategy for Sustainability (CSS) is a cornerstone, aims at reducing the planetary health impact from chemical exposures. EBD and HIA allow to objectify the impact of current chemical exposure on health in EU populations, prioritize preventive or mitigatory actions to be taken, and estimate the EBD and costs avoided as a result of EU policies and regulations. Thus, this project contributes to PARC's specific objective 2 (SO2), namely, European and national RA entities and their scientific networks carry out a joint R&I program to respond to the agreed priorities in chemicals RA.

1.3. Prioritized chemical families

The PARC strategy prioritized chemical families considers pre-existing knowledge on exposure, hazardous properties including epidemiological data for some of the compounds and concerns on cumulative risks. The identification of the first set of priorities for PARC started before the launch of the Partnership with the legacy from HBM4EU and with a survey sent to the interim governing board members. In order to have a clearer view on the prioritization strategy within the different WPs, a survey dedicated to the prioritization of substances and meetings with work package leaders (WPLs) and task leaders (TLs) to discuss the prioritization of methods took place after the beginning of PARC. The approach and results are summarized in PARC deliverable D2.1 Prioritization criteria report WP2. This process led to a list of 9 families prioritized by PARC stakeholders (academia, HBM4EU workshop, European Commission, Ministries of several Member States). The PARC T6.2 task leaders on integrative RA refined these prioritized groups of chemicals with the EFSA and the European Commission to ensure synergies with results reported in EFSA opinions or ongoing discussions within working groups of DG SANTE. Based on these discussions, PFAS, bisphenols, flame retardants, phthalates, pesticides, metals, mycotoxins, endocrine disrupting chemicals, and mixtures were prioritized in T6.2. These PARC 6.2 priority chemicals were taken into account in selection of case studies in T6.2.4 as well as other chemical families in considering other priority criteria.

2. Organization of the work

At first, a data availability matrix has been created based on knowledge of the partners involved in task 6.2.4. This matrix contains information on exposure, exposure-response functions, health data and former estimates of EBD or costs related to chemical exposure (see further results 6.2.4.a and Additional Deliverable 6.6). In 6.2.4.b the methodological challenges of health impact assessments for chemicals that will be faced and addressed in the different case studies are described. In addition, a glossary has been developed under 6.2.4.b with relevant definitions for task 6.2.4 on EBD and HIA of chemicals. In the later stages of the first year of PARC, partners were encouraged to propose potential case studies for collaborative work during the second year. A multi-criteria decision analysis tool was developed by ANSES to prioritize case studies. Partners were then invited to contribute to case studies of their choice based on their expertise, experience, and/or ownership of data relevant to the specific case studies. After these initial tasks, the case studies were placed centrally in Task 6.2.4, providing input to the other three sub-tasks within 6.2.4, namely, data availability, methodological improvements, and indicators. During the second year, partners worked on various case studies focusing on data availability, methodological issues, what the burden

estimate(s) would mean from a policy perspective, and which indicators should be generated in case studies as well as how these will support policy makers.

The projects under 6.2.4 contribute to the aim of T6.2 to develop innovative and practical approaches for human health risk and impact assessment of single, aggregated and combined exposure to chemicals. By doing so, the projects will support the understanding of the contribution of chemicals as upstream determinants of diseases, will contribute to the reduction of human health impact of exposure to hazardous chemicals, and as such to the protection of public health. Additionally, these studies raise awareness among citizens, professionals, and policy makers about the risks of chemical exposures.

Given the great emphasis placed on the case studies, and the fact that each case study generates new data, indicators, and may contribute to methodological developments, it was decided to report in the next section from a central perspective from the case studies.

The six case studies (6.2.4c) developed and carried out within Y2-3 of PARC (i.e. 2023-2024) had three overarching goals. Specifically, these goals were data availability and generation (6.2.4a), improvements in methodology (6.2.4b) and development of new indicators (6.2.4d).

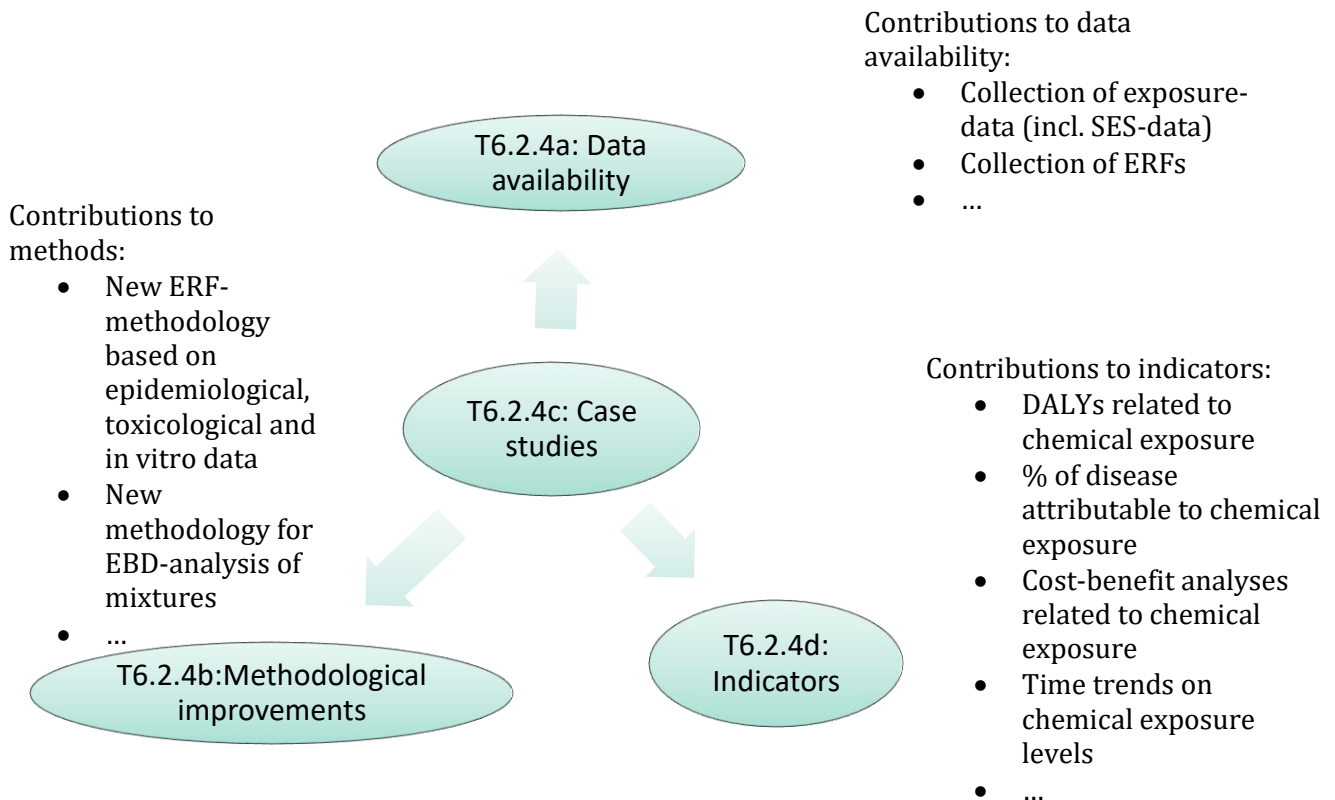


Figure 1. Organization of project in task 6.2.4 with case studies having a central position and other projects linked.

3. The Health Impact Assessment Concept

Public health practitioners and policymakers have a responsibility to ensure good health and wellbeing for the population. To achieve this, they need to be able to evaluate the distribution of diseases and disabilities as well as major risk factors of these diseases in the population to be able to compare different policy options. This supports the best use of limited resources and helps to obtain the best results concerning population health and well-being as well as health equity. Health Impact

Assessments (HIAs) can support the creation of new policies or identify the need to refine the ones already implemented based on most recent evidence.

The aim of a HIA is to predict the effect of an intervention (i.e. proposed policy, program or project) on health and the distribution of these health effects across sub-populations (European Center for Health Policy (ECHP), 1999). Comprehensive HIAs consist of three phases, 1) screening and scoping, 2) appraisal, and 3) reporting and monitoring (World Health Organization (WHO)). In brief, during the screening and scoping phase, an intervention, policy or a project for which a HIA would be beneficial, is selected and potential effects on the determinants of health, health outcomes and population groups are identified. Moreover, the health risks and benefits to be considered are identified, major stakeholders are involved, and the process is clarified. The appraisal is the core of the HIA activity. All relevant data and evidence are gathered and analyzed, affected populations are identified, and health impacts are estimated. In the third phase, results are presented to decision-makers. Also, the process and the effectiveness of the HIA as well as the influence of the HIA on the decision-making process are evaluated. Monitoring the implementation of the planned intervention and the longer-term monitoring of the health of populations can be used to see if the predictions made during the appraisal were accurate, and to see if the health, or health-promoting behaviors of the community, have improved.

Analytical HIAs focus on the collection of information and data for the estimation of health impacts and require the modeling of the impact of the intervention on the distribution of exposure of the population to the environmental factor(s) of interest. HIAs consist of several linked stages that are summarized in **Figure 2**. In brief, an analytical HIA consists of the monitoring or mapping of the exposure of interest in the population; identifying the population at risk; deciding on which pollutant-effect (or impact) pathways are relevant and which of them will be quantified; choosing exposure-response functions; assessing the background disease rates for the health outcomes considered in the population at risk; and predicting the chosen health effects (Amman et al., 2003). HIAs can be supplemented by cost-benefit analyses (CBAs) that quantify the economic costs of the intervention and the (monetized) benefits for public health that result from an intervention. In this document, we will briefly discuss the monetization of health benefits; CBAs, however, are beyond the scope of this document

Once the burden of a disease that is attributable to a specific risk factor or the health impact of an intervention has been assessed in terms of attributable cases or DALYs, it is possible to monetize this impact, i.e. to give it a monetary value, and to estimate the costs that this risk factor represents for society. Unlike market goods and services, there is no market or price associated with pain, disease or death. Thus, monetization can be done through different methodologies, reflecting different points of view.

To assess the costs of premature death, studies typically use the concepts of the value of a statistical life (VSL) or the value of a statistical life year (VOLY). In the most recent analysis for the revision of the EU ambient air quality directives the European Commission is using a value of 94,660 € for one VOLY allowing the estimation of the cost of one year of life saved - equivalent to the cost of averting one year lost due to premature death (Quinet et al. 2013; European Commission, 2022). This value is unique and does not depend on the age of the person “saved”.

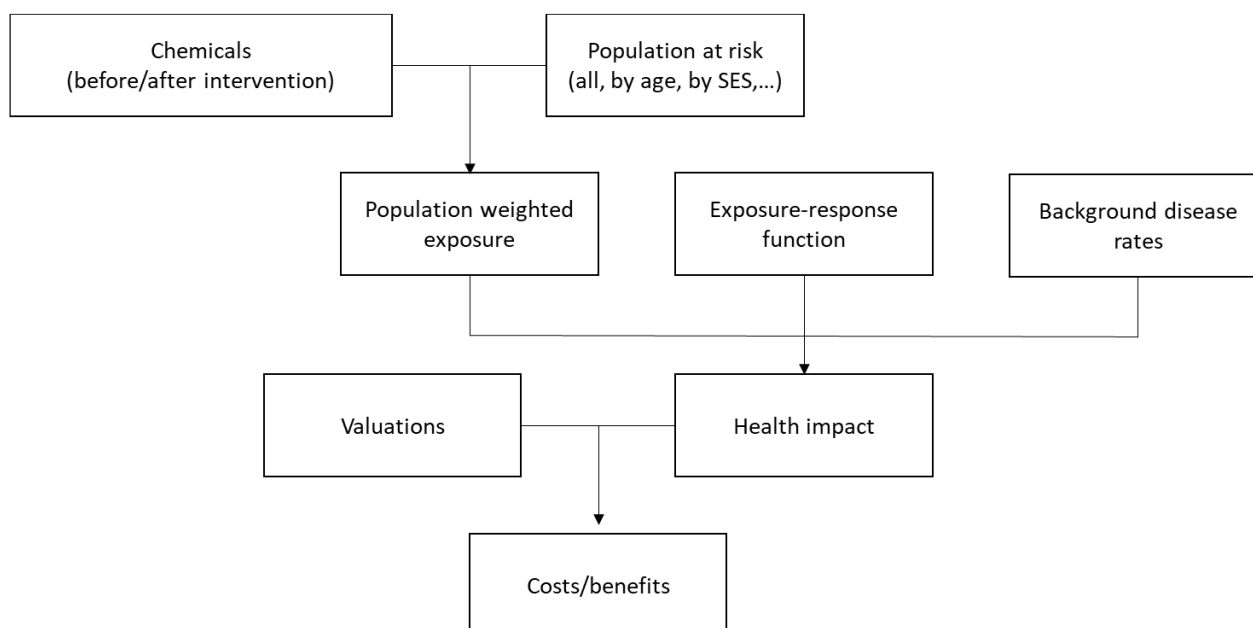


Figure 2. Schematic overview of a quantitative assessment of the health impact of chemicals (analytical HIA).

To evaluate the costs of morbidity, the number of cases can be multiplied by the direct costs of health care (including medication use, doctor visits, etc.), which encompass the part supported by society and, in some cases, the part supported by the patient. Indirect costs including absenteeism and presenteeism (productivity loss) can be added to the direct costs. Apart from the direct and indirect costs, there are also intangible costs related to the loss in quality of life (Ougier et al., 2021).

More detailed information can be found also in Annex A1.

4. Methodological challenges

The availability of data on the distribution of exposure and health outcomes in the population of interest as well as information on the exposure-response functions for the different exposure-response relationships is a key requirement of EBD and HIAs. Other challenges include differences in health impacts between groups with some groups (e.g. low socio-economic status groups) being more susceptible, the extrapolation from a single study to the (inter)national context, the definition of the counterfactual, the assessment of the health impact of mixtures of chemicals and persistent chemicals, probabilistic modeling and causality and weight of evidence of the exposure-health relationships of interest. The challenges with regard to the different types of data are discussed below.

4.1 Exposure data

Exposure to chemicals starts at conception and occurs over the entire lifespan. Chemicals enter the human body through various routes of exposure including inhalation (e.g., via air and dust), ingestion (e.g., via water and foods, pica behavior) and dermal contact (e.g., via direct contact, cosmetics). Other exposure routes such as parenteral exposures are not considered within the scope of this document. Furthermore, fetuses can be exposed through the exposure of their mother. In the context of EBD analyses for the general population, inhalation and oral exposure are typically

considered of highest relevance, although this is certainly not the case for all chemicals (e.g. benzophenones).

Exposure can be divided into external and internal exposure. External exposure refers to the whole dose a human is exposed to while internal exposure refers only to that fraction of the initial chemical dose that is absorbed and distributed throughout the body via systemic circulation (European Commission, 2007) External exposure is often reduced to dietary exposure when ingestion is the main exposure route. Aggregate exposure is the exposure to a chemical via all exposure routes and from different sources.

Exposure assessment is defined by the International Programme on Chemical Safety (IPCS) as “[...] the process of estimating or measuring the magnitude, frequency, and duration of exposure to an agent, along with the number and characteristics of the population exposed. Ideally, it describes the sources, pathways, routes, and the uncertainties in the assessment [...]” (International Programme on Chemical Safety & Organisation for Economic Co-operation and Development, 2004).

Internal exposure can be assessed through human biomonitoring, i.e., the measurement of substances and/or their metabolites in human body fluids or tissues. Both estimates of external exposure, e. g. to particulate matter air pollution (GBD 2019 Risk Factors Collaborators et al., 2020), and internal exposure, e. g. to dioxins (Hänninen et al., 2014) or cadmium (Ougier et al., 2021) have been used in EBD analyses and HIAs.

With the PARC Task 6.2.4. data inventory, we identified the HBM4EU database as an important source of human biomonitoring data for PFAS, bisphenol, flame retardants, phthalates, and pesticides, while data for mycotoxins are more limited. Other sources of exposure data, mainly biomonitoring data, but also some data on concentrations of especially metals in food or drinking water, have been identified (European Food Safety Authority (EFSA), 2024).

Considering that exposure assessment is a key step for further assessments such as risk characterization and EBD assessments, it is fundamental to collect data as representative of the population of interest as possible to decrease the associated uncertainties and to avoid misleading results.

Data referring to external exposure, i.e., exposure through inhalation, food intake or dermal absorption (<https://www.efsa.europa.eu/en/supporting/pub/e201001>) (European Food Safety Authority (EFSA) et al., 2022), are usually collected at the group level by means of air and food sampling/analysis, implying a higher level of uncertainty related with the characteristics of these sampling processes. Exposure through food consumption may be assessed with different levels of representativity (e. g. national, regional, local surveys) and different instruments (e.g. duplicate diet, total diet studies, food frequency questionnaires (FFQs), 24-h dietary recalls) (Scalbert et al., 2019). For each instrument, several sources of uncertainty may be considered (de Nijs et al., 2016), but for a matter of representativity, the use of national food consumption surveys is the best option, especially when performed with harmonized methodologies as recommended by EFSA (Ioannidou et al., 2020). Nevertheless, external exposure assessment presents limitations in the characterization of different levels of exposure within and between different populations, as was previously recognized (Aylward et al., 2014).

Human biomonitoring (HBM) studies may overcome some of these constraints, namely the uncertainty derived from interindividual variability in the uptake since it estimates the exposure at the individual level (Calafat, 2016). However, HBM studies are not exempted from constraints with regard to the representativeness of the sampling that may arise from variation in timing of sample collection in relation to exposure events for chemicals with a short half-life, variation in the physiological characteristics of the biological matrix, and interindividual variation in chemical toxicokinetics (Aylward et al., 2014). Considering these possible sources of uncertainty and designing studies to overcome these aspects, the assessment of internal exposure at the population

level is an important tool and a strong data source for EBD assessments and HIAs (Govarts et al., 2023).

According to the PARC Task 6.2.4 data inventory, for most priority chemicals under scope of this work (see 1.3), HBM data are available for children and adults including pregnant women. For bisphenols, data are largely limited to adults however in the EU DEMOCOPHES HBM project (2010-2012) some countries provided measurements of bisphenols and alternatives in children and pregnant women. Geographical coverage of databases varies between chemicals from single or a few (regions) countries to > 10 EU countries (HBM4EU). Some HBM studies are representative of the exposure of the general population in the whole country whereas others are not.

4.2 Vulnerable groups/socioeconomic context

Fetuses and children (as their organs are still developing), the elderly and people with chronic diseases (because of various vulnerabilities such as compromised immune responses among others), and economically and/or socially disadvantaged individuals (because of higher exposure and/or less favorable health) are considered being particularly susceptible to the effects of exposure to chemicals. However, susceptibility to the same chemical stressors may differ between these groups. For example, neurodevelopmental effects of lead exposure in children (reduced intelligence and cognitive function) have been observed at relatively low levels of lead exposure, with long lasting consequences. In the elderly group, similar internal body burdens of lead would not have such drastic consequences (Agency for Toxic Substances and Disease Registry (ATSDR), 2020). Due to extrinsic factors (e.g. cultural, social, economic or related to lifestyle) some groups may also be more vulnerable than others. Therefore, a group-specific, tailored approach is needed to mitigate the impact of chemical exposures on the health of vulnerable or more susceptible groups. Such an approach requires the identification of the specific chemicals that are most relevant to each group and developing appropriate strategies to protect their health and wellbeing. In this way, it can be ensured that everyone has the opportunity to live a healthier life, irrespective of their age, gender, health status, or socioeconomic status.

Socioeconomic status (SES) is determined by a combination of social and economic factors such as income, level of education, occupation, perceived social standing, place of residence, and potentially also ethnic origin or religious background. The potential differences in exposure to chemicals and pollutants and the health effect thereof between socioeconomic groups have gained increased attention in recent years. Different indicators are being used to capture different aspects of SES, with education, income, and deprivation being the indicators that are included most often. A central theory that is posited in research on environmental chemical exposure and SES is the environmental justice hypothesis. This hypothesis can be interpreted in two ways, namely, that socially disadvantaged individuals experience a larger health impact from the same level of exposure (i.e., outcome inequality), or that socially disadvantaged individuals are more exposed to chemicals and pollutants than their socially more prosperous peers (i.e., exposure inequality). In epidemiological research on chemical exposure, this hypothesis is often interpreted as an unequal distribution in exposure to chemicals. However, recent studies suggest a more nuanced reality, wherein internal exposure to chemicals is heterogeneously distributed across the socioeconomic groups (Tyrrell et al., 2013a)(Den Hond et al., 2015a)(Morrens et al., 2017)(Buekers et al., 2018). More concretely, an association has been found between socioeconomic indicators (proxy for overall socioeconomic status defined differently per study) and exposure to Hg, As, PFAS, polychlorinated biphenyls (PCBs) and chlorinated pesticides (Ramon et al., 2011)(Vrijheid et al., 2012)(Tyrrell et al., 2013b)(Den Hond et al., 2015b)(Morrens et al., 2017)(Buekers et al., 2018)(Montazeri et al., 2021)(Govarts et al., 2023). The other way in which the environmental justice hypothesis can be interpreted is in terms of inequality in the outcome, i.e., the more socially disadvantaged an individual is, the larger the health impact will be for the same level of exposure. This last

interpretation is corroborated by contemporary public health studies. Individuals further down the social ladder have an overall worse health status and are at greater risk of developing several serious illnesses and dying prematurely than those closer to the top (Vrijheid et al., 2012)(Morrens et al., 2017). Moreover, large EU Human Biomonitoring (HBM) campaigns (DEMOCOPES and HBM4EU) showed a significant relationship between socioeconomic standing and chemical biomarker concentrations. An additional concern is that individuals from lower socioeconomic standing are both more susceptible to the health effects of chemicals and more exposed to chemicals, this scenario is more commonly known as “double jeopardy”. Thus, understanding the socioeconomic environment is essential for targeted public health policies and can further help guide resource allocation more effectively to those population groups that are most disadvantaged. This in turn can help address health inequalities, leading to an overall healthier and more equitable society. This furthermore aligns with the objective of the ZPA, which aims at reducing exposure inequalities and related health impacts.

The case studies will consider differences in vulnerability across different subpopulations where data are available. For example, if sex-specific or SES-specific differences are identified in chemical exposure or susceptibility to the associated health effects, a subpopulation-stratified (be it sex- or SES-specific) EBD analysis would be recommended.

4.3 Extrapolation from single studies to (inter)national estimates

For EBD assessments, it is important to select the study population considering the policy relevance (the study will be relevant for the policy needs of a country or region), the data availability (exposure and health outcome data may be available only for a certain subpopulation group or a specific geographic area) and population subgroups (the impact of a risk factor may be limited to a population subgroup and/or data may be only available for these groups) (Prüss-üstün et al., 2003). When data is missing, assumptions can be made, increasing the uncertainty of the estimates. If exposure data are missing for a certain region or subgroup, it can be assumed that exposure follows the same patterns of the data actually reported/available or data gap filling methods based on associations between exposure, demographic and environmental data could be applied. This approach is exemplified by the GBD (2021) study, which estimated lead exposure in data-poor countries based on lead exposure information from data-rich regions, as well as covariates strongly linked to lead exposure—such as the socio-demographic index (SDI), urbanicity, vehicles per capita, the phase-out of leaded gasoline, and the subject’s age (GBD 2021 Risk Factors Collaborators, 2024). In the ETC HE (European Topic Center for Health and Environment) a similar approach is being scrutinized for blood lead concentrations in the EU. Different techniques that can be applied to estimate exposure information include read across, kriging, interpolation, regression analysis etc. If health data are available only at the national level and an estimation at the regional level is needed, then it can be assumed that the distribution of the outcome is similar across all the regions (Prüss-üstün et al., 2003).

If exposure data are available for a specific age group only, for instance adults, extrapolations to other populations i.e., pediatric or geriatric populations, can be performed with modeling tools such as Population Pharmacokinetics (PopPK) analysis to create virtual populations. These tools make use of population characteristics like height, body weight etc. including variability which through probabilistic modeling and Physiological based pharmacokinetic (PBPK) modeling can address variability and uncertainty in EBD assessments by including the variations in the anatomy and physiology of the population for all age groups. These tools provide more suitable estimates for a given population by considering all data points for the calculations. Moreover, probabilistic approaches can consider both the variability and uncertainty in the population through Monte Carlo

simulations and predict mean burden with confidence intervals (Greco et al., 2020). However, the major setback is to have a reliable interval of uncertainty for EBD estimates. Many times, the uncertainty for the major parameters in a single study is not quantified, making it difficult to use Monte Carlo analysis for an EBD uncertainty estimate. For such scenarios, the best approach is to use “low” and “high” estimates which can be obtained from confidence intervals of exposure estimates using empirical techniques and lower and upper confidence intervals of ERFs (e. g. relative risks). Such uncertainty evaluations have little statistical meaning, but they provide an estimate of the range of the health impact of a given environmental risk factor or intervention.

4.4 Defining the counterfactual

When estimating the burden of disease attributable to a certain risk factor, there is a need to define a counterfactual value to which the actual exposure towards that risk factor is compared. There are different options for selecting a counterfactual, depending on how the exposure is classified. In the case of dichotomous exposure (e. g. exposed yes/no), no exposure would be the counterfactual, e. g. no smoking, which carries the lowest risk for health effects. When the exposure is presented in classes, the lowest exposure class can be used as the counterfactual, e. g. the lowest concentration class of particulate matter air pollution. Having a continuous exposure, the lowest observed, the lowest possible or the concentration of a pollutant for which we assume that below that concentration no adverse health effects occur, can be used as the counterfactual. The GBD study has introduced the so-called Theoretical Minimum Risk Exposure Level (TMREL), which defines a theoretical level of exposure associated with the lowest possible risk, a risk defined as an RR close to or equal to one.

The choice of the counterfactual value considerably impacts the quantification of the EBD, making it a sensitive and crucial input parameter. Thus, the selection of the counterfactual value should be evidence-based, transparent and serve the purpose of the assessment. For this reason, results from different studies should be compared with caution. Some outcomes could, at the first glance, lead to erroneous conclusions comparing seemingly similar studies but working with different counterfactual values.

4.5 Exposure to mixtures

A chemical mixture can be defined as any combination of two or more chemicals to which an individual is exposed regardless of the source(s) and spatial or temporal proximity. Mixtures can be intentional or coincidental and several methods are available to assess combined exposure to chemicals (Boobis et al., 2008a)(Organisation for Economic Co-operation and Development (OECD), 2018)(Ottenbros et al., 2021).

Over the past decade, considerable efforts have been made to propose concepts, methods, guidance and applications of the assessment of the risk related to mixtures (Boobis et al., 2008b)(Meek et al., 2011)(Fox et al., 2017)(EFSA Scientific Committee et al., 2019)(World Health Organization (WHO), 2019)(Beronius et al., 2020)(Fischer et al., 2020)(EFSA Scientific Committee et al., 2021). Regarding mixture effects, there is a consensus on the fact that dose addition can be used as the default assumption to perform RA for substances sharing the same common mode of action and (specific) effect(s) or affecting the same target organ (Faust et al., 2001)(Faust et al., 2003)(Jonker et al., 2004)(Junghans et al., 2006)(Kortenkamp et al., 2009)(Backhaus and Faust, 2012)(Altenburger et al., 2013)(European Food Safety Authority (EFSA), 2013)(EFSA PPR Panel (EFSA Panel on Plant Protection Products and their Residues), 2013). Under this assumption the converted dose of each single compound can be summed up to estimate a single exposure dose of the mixture and compared to the toxicological value to perform RA. Another way to perform a RA for

mixtures is to sum up the ratio between the exposure and the toxicological value of each mixture component. Cumulative RAs have been deployed by EFSA for pesticides using food consumption data (European Food Safety Authority (EFSA) et al., 2020b)(European Food Safety Authority (EFSA) et al., 2020a)(European Food Safety Authority (EFSA) et al., 2021). This approach has also been recently applied to biomonitoring data from several European countries (Karrer et al., 2020)(Crépet et al., 2022)(Socianu et al., 2022) for contaminants in breastmilk (Crépet et al., 2022) and for PFAS regarding (National Research Council (US) Committee on Pesticides in the Diets of Infants and Children., 1993)(U.S. Environmental Protection Agency Office of Pesticide Programs, 2001) liver toxicity (Bil et al., 2022) and immunotoxicity (Bil et al., 2023).

In the last decade, several European projects (Acropolis, Euromix, EDCMix, HBM4EU, etc.) have produced data, methods and tools to assess health risks associated with mixtures of chemicals (van Klaveren et al., 2015)(Bopp et al., 2018)(van der Voet et al., 2020)(Vanacker et al., 2020)(Sprong et al., 2023a). Moreover, the European Food Safety Authority presented a roadmap for action on RA of a combined exposure to multiple chemicals with the objective to implement human health RA to mixtures in its regular activities by 2030 (De Jong et al., 2022). Finally, the PARC project 6.2.3 and associated deliverable (D6.2) builds further the method and application of mixture RAs based on human biomonitoring data in a harmonized way. Thus, whereas RA of mixtures is well covered in other projects, the EBD and HIA of exposure to mixtures is a rather unexplored domain.

The assessment of the health impact of mixtures is therefore a major challenge in EBD and HIA (Organisation for Economic Co-operation and Development (OECD), 2018). Biomonitoring data illustrate that humans are exposed simultaneously to several chemicals through different sources (e.g. food, personal care products, environment). Considering co-exposure to chemicals when assessing the disease burden attributable to environmental risk factors will improve HIA. Thus, there is a need to develop a strategy to account for the environmental burden of disease associated with mixtures. One broad hypothesis is to sum up for example the DALYs obtained from individual substance environmental burden of disease estimates; the results would be inconsistent compared to observed number of cases. However, this approach relies on the assumption that exposures and their corresponding effects are independent, which we know is not the case, thus likely leading to an overestimation of the burden/impact. Another way to account for mixtures in HIA that will be developed in Task 6.2.4 of PARC is to use the approach developed in Task 6.2.3 to cumulate the exposure first and then perform HIA. This approach will be developed in the case studies on lead and methylmercury.

4.6 Persistent chemicals in the environment

The degradation rates of the chemical stressors are also of importance. Some chemicals are resistant to degradation in the environment, which allows them to accumulate in the food chain and ecosystems, and to travel from contamination sites to other locations. Such chemicals are referred to as persistent chemicals and include persistent organic pollutants (POPs) or persistent, bio accumulative, and toxic substances (PBTs). In particular, POPs have gained attention with the international legally binding agreement, the Stockholm Convention on Persistent Organic Pollutants, adopted by most countries globally to protect human health and the environment from POPs by reducing or eliminating the release of such substances (United Nations Environment Programme and the World Health Organization, 2013a). Human biomonitoring has been identified as essential when evaluating the trends in human exposures to POPs over time and allows for implementation of actions to reduce and prevent human and environmental exposures to these substances. The Global Monitoring Plan for POPs is an example of a comprehensive human biomonitoring program of POPs (Swackhamer et al., 2009)(United Nations Environment Programme and the World Health Organization, 2013b)(Liu et al., 2022). Although human biomonitoring of internal doses of POPs represents the actual exposure in humans, it neither provides information on the pathways or

sources of exposure nor does it inform about when the exposure happened. The internal dose of POPs, as for other chemicals, can also be estimated via exposure modelling based on information on the source of exposure (e.g. food), concentrations of the POPs in the source, information on exposure frequency and duration, bioavailability from the source, and pharmaco-/toxicokinetics of the given POPs (Swackhamer et al., 2009). Due to the long half-life and bioaccumulation of POPs and other persistent chemicals, physiologically based pharmacokinetic models that take into account the absorption, distribution, metabolism and elimination (ADME) of a given chemical, may be useful to predict the relationship between exposure and tissue concentrations of POPs (Liu et al., 2022). The PARC project 6.2.2 and associated deliverable (D6.2) develops and implements methods to predict internal exposure starting from external exposure, for different routes of exposure and life stages.

In a case study that started in Y4 VITO will lead a case study on studying the association between respiratory effects and exposure to PFAS.

4.7 Probabilistic modelling in EBD

Parameter uncertainty and variability are major sources of uncertainty in EBD calculations. Uncertainty refers to the fact that all empirically measured quantities such as mean or median values mostly do not represent the true value (e.g. uncertainty of the concentration of lead in contaminated drinking water due to measurement errors). Variability describes the possible values an empirical quantity has due to real world characteristics of the measured quantity of interest (e.g. the range of lead concentration in contaminated drinking water) (Knol et al., 2009). The sources of uncertainty and variability in EBD are diverse and can be dealt with in different ways. Insufficient knowledge about the input parameters, for example, is one source: What is the range and distribution of lead concentration in drinking water in a specific geographic area? And does the sample, which is gathered for determining this, accurately represent the lead concentration of drinking water in that specific area? One way to deal with uncertainty and variability in exposure assessments and also in the EBD calculations is using probabilistic modeling techniques. By following a probabilistic modeling approach, single model parameters are replaced with respective probability distributions. This allows the presentation of the final outcome as an uncertainty distribution, which depicts the probability of possible values for the outcome (Bokkers et al., 2017). This can be applied at several stages of the EBD calculations, in which uncertainty is manifesting, e.g. for common parameters such as relative risks, attributable fractions or disability weights (Knol et al., 2009). An example for a probabilistic method that is commonly used is the Monte Carlo Simulation. Instead of running a model with single point estimates (deterministic), the Monte Carlo simulation runs the model repetitively with random values for each input variable, drawn from respective probability distributions. This results in the generation of a random sample with randomly generated values for each input variable. This is particularly helpful for non-gaussian distributions where using means to represent a population is less representative of the population. After several iterations of this random sampling, a new distribution for the outcome variable is created. Typical statistics like the mean and the standard deviation can be obtained from these distributions. Compared to deterministic approaches, probabilistic modeling techniques using Monte Carlo simulations contain more information about the likelihood and range of e.g. an exposure and thus, can identify parameters with strong impact on the results (Finley and Paustenbach, 1994).

Probabilistic modeling is commonly applied in environmental burden of disease assessments.

4.8 Health data

Health effects from exposure to chemicals can occur from conception onwards, during the entire lifespan. Similar to exposure, health effects can be classified as acute and chronic. Acute health effects vary from unnoticed (subclinical) physiological changes, increased symptoms and medication use, restrictions in daily activities to emergency department visits, hospital admission and in the worst case lead to death (Künzli et al., 2010). Chronic effects include the onset of the disease, which, depending on the type of disease, can result in a reduced life expectancy. Chronic conditions are mostly not curable and result in life-long disabilities, strongly increasing the morbidity-related disease burden.

Incidence and prevalence are commonly used measures of health impact. Incidence is the number of new cases of disease in a given population, i.e. the number of new cases of a disease divided by the total number of persons at risk for the disease over a specified period of time (New York State Department of Health, 1999a). Prevalence is the proportion of a population with a specific disease or condition at a certain time point. It is a measure of the total number of cases in a defined population at a particular time or during a given time period (New York State Department of Health, 1999b). Clinical diagnosis allows identification of a disease, condition, or injury based on a patient's signs and symptoms. Adverse effects observed in experimental animal studies are not directly linkable to human symptoms or pathologies. From a toxicological point of view the critical effect refers to the adverse effect observed at the lowest dose tested on the most sensitive species. Some of these effects are broad outcomes such as decreases of bodyweight or increase of hormones levels, which are not necessarily easily translated into a clinical effect, which is crucial for proper EBD calculations. Thus, knowledge on the association between observed effects and the risk of a given health outcome, for which a disability weight is available, is needed to calculate the health impact. Disability weights, which represent the magnitude of health loss associated with specific health outcomes, are used to calculate years lived with disability (YLD) for these outcomes in a given population. Disability weights can be established from different methodological designs. Depending on the health state description, medical expertise, valuation methods or surveying techniques, the set of obtained disability weight may vary (Charalampous et al., 2022). The GBD study provides disability weights for 440 health states (Global Burden of Disease Collaborative Network, 2020).

With the PARC Task 6.2.4. data inventory, we identified sources of population health data. Data coverage ranges from sub-national to national and global. Important data sources with international coverage include the WHO Global Health Observatory (<https://www.who.int/data/gho>), EUROCAT (https://eu-rd-platform.jrc.ec.europa.eu/eurocat_en, congenital malformations) and the European Cancer Information System (https://knowledge4policy.ec.europa.eu/cancer/topic/cancer-information/ecis_en). Further, e.g. cause of death statistics can be obtained from the European statistical office EUROSTAT which gathers data from European countries and provides free of charge access to stratified data (<https://ec.europa.eu/eurostat/web/main/home>). Lastly, the secondary use of data within the European Health data space provides additional new opportunities https://health.ec.europa.eu/ehealth-digital-health-and-care/reuse-health-data_en

While the standardization of health outcome data from different countries is a strength of the international databases, the amount of detail might be more limited in these databases. However, the larger detail available from the (sub)national databases comes at the cost of heterogeneity of definitions between countries, which may limit the comparability of disease frequencies between countries. For European analyses such as the ones planned for PARC, we would strongly recommend the use of standardized sets when comparisons of the final results are intended.

Health outcomes included in the identified data sources include morbidity and mortality with causes of death. Some registries date back to the 1940ies (e.g. the Norcan database of the Association

of the Nordic Cancer Registries) or 1950ies (e.g. the Belgian Statistical Office), but many databases provide data from the 1990ies onwards.

Like for the exposure data, it is fundamental to collect data that is representative for the (general) population of interest. This helps reduce uncertainty, as relying on single or local estimates may not accurately reflect the situation at a national level or within the study population.

4.9 Exposure-response relationships

The implementation of a HIA or EBD is performed for substances for which information on causality and biological plausibility is available and for which sufficiently robust ERFs exist. Preferably, the ERFs used to calculate the EBD, should be derived from a comprehensive review of the epidemiologic literature and accompanying meta-analysis. They should be supported by experimental findings and mechanistic evidence. As for the other data used in EBD and HIA calculations, the ERFs come with uncertainties that we try to minimize as much as possible and at least make them explicit and discuss them. Sources of uncertainty include the context or formulation (e. g. the selected health outcomes and exposure indicators), the data per se (e. g confidence interval, representativity, robustness, sources), the models (e. g their limits) and the communication of the results (including interpretation).

For air pollution data, ERFs are proposed by an international organisation such as WHO, e.g. for morbidity outcomes there are the REVIHAAP studies which are being extended (WHO, 2013). This process is completely lacking for most chemical data. Therefore, more effort should be made to improve the application of more robust ERFs. In the case studies elaborated on this project, reviews to select adequate ERF were performed.

Causality and weight of the evidence

Causality is an essential element that needs to be scrutinized when performing EBD or HIA. Randomized clinical trials are the gold standard for establishing causality. For environmental exposures, however, randomized trials are mostly not feasible and unethical, and causality needs to be established from the results of observational studies based on a set of criteria e. g. the criteria established by Bradford Hill (Hill, 1965). Different Weight of Evidence (WoE) frameworks have been defined by international agencies or organizations or defined in research projects (EFSA (European Food Safety Authority (EFSA) et al., 2019), ECHA (European Chemicals Agency (ECHA), 2017), ANSES (Bladier et al., 2017). In an EU project Athlete (<https://athleteproject.eu/>), causality and WoE assessment is defined as a stepwise process starting with defining the problem and assembling evidence from different types of sources in lines of evidence like epidemiological studies, in vivo studies, in vitro, in silico studies followed by weighting and integration. Often expert judgement based on some defined criteria is used for weighing and integration of multi-source and heterogeneous evidence. However, combining heterogeneous data often involves pooling or meta-analyzing data from several and different sources (e.g., multiple cohorts and/or datasets with the same characteristics, literature reports or available published studies), which inevitably suffers from problems associated with high variability and uncertainty (Borenstein et al., 2021). New methodologies in which different types of data are integrated are being developed like the development of Bayesian networks (Krewski et al., 2022), Directed Acyclic Graphs (DAGs) (Ferguson et al., 2020), Adverse Outcome Pathways (AOPs) (Perkins et al., 2019). For these networks, modified or evolved Bradford Hill criteria can be applied. According to Hill,

“All scientific work is incomplete - whether it be observational or experimental. All scientific work is liable to be upset or modified by advancing knowledge. That does not confer upon us a freedom to ignore the knowledge we already have, or to postpone the action that it appears to demand at a given time” (Hill, 1965).

Next to this, Bayesian models are being developed in which the ERF is based on multiple data sources (epidemiological, in vivo) (Scholten et al., 2020). For addressing causality in this case, plausible biological hypotheses will still be necessary with consideration of mechanistic data including new approach methodologies (NAMs).

WoE assessments are important in several steps of the EBD or HIA calculation. First, EBD is performed for substances for which information on causality and biological plausibility is available and for which sufficiently robust ERFs exist. The weight of the evidence could thus be used to identify and/or prioritize the substances and effects to be considered. Second, beyond the lines of evidence and their conclusions, the frameworks/approaches of WoE provide us with tools to assess confidence in and uncertainty around the selected data and ERF. This uncertainty can be incorporated into the EBD/HIA calculations, through qualitative or quantitative use. For example, Trasande and colleagues (Trasande et al., 2015) used the results of their WoE approach, so-called probability of causation, in a series of Monte Carlo simulations providing uncertainty ranges in the monetization of their EBD estimates. Such indication of uncertainty comes in addition to the statistical uncertainty traditionally translated with confidence intervals.

According to Grandjean and Bellanger, the Global Burden of Disease project relies upon expert input to select those exposure-outcome relationships that meet stringent criteria of causality. As a consequence, some causal connections are favored: those focusing on infectious diseases and injury and those supported by randomized clinical trials. In the environment and health domain intervention studies are too complex to obtain information on the adverse impact of environmental risk factors. However, Grandjean and Bellanger do find that a “realistic and precautionary approach” can be taken to characterize the possible health impact of chemical substances (Grandjean and Bellanger, 2017).

Methodologies to establish exposure-response functions

The choice of ERF is a crucial step in EBD and HIA and considerably impacts and adds uncertainty around the EBD/HIA estimates. The ERF will mostly be based on association measures such as a relative risk (RR) from epidemiological studies, in terms of an RR function expressing the increase in risk per unit increase in exposure to a given risk factor (Barendregt and Veerman, 2010)(Plass et al., 2022). The evidence is considered to be highest for ERFs that have been derived from a meta-analysis of multiple longitudinal studies as the longitudinal design reflects new cases (incidence) related to exposure, and is indicative of disease development. The degree of certainty is lower for ERFs based on single or small numbers (longitudinal) studies or cross-sectional studies only. Nevertheless, EBD calculations that are based on single high-quality studies can still be meaningful (Hänninen et al., 2014).

For many chemicals, the epidemiological evidence is limited to a relatively small number of (often cross-sectional) studies (Van den Brand et al., 2022). In such situations, where evidence from epidemiological studies is limited, data from in vitro animal studies can also be considered in an integrative approach by combining them with data from epidemiological studies using Bayesian meta-regression models in exposure-response relationship modeling (Scholten et al., 2020). The application of such ERFs in EBD assessments or HIA calculations remains challenging.

In addition to the above, a number of other considerations need to be taken into account when deriving ERFs for use in EBD/HIA. When ERFs are derived from epidemiological studies, assumptions made during the analysis inevitably introduce some uncertainty into the results. The choice of an ERF should consider several aspects such as the matching of range of concentrations, population of interest and the health outcome (Ferguson et al., 2020). The exposure scale of the ERF should be aligned with the exposure data applied in the assessment. Furthermore, the existence of a lower threshold of the effect needs to be considered, in particular in the case of non-genotoxic carcinogens. Finally, the need for use of uncertainty factors should be assessed, such as for extrapolating between individuals (intraspecies extrapolation) and for extrapolating from animals to humans (interspecies extrapolation).

Representativeness of the exposure-response function

The representativeness of the derived ERF for the target population(s) is another important issue that adds to the uncertainty around the EBD/HIA estimates. For example, what is the geographical coverage of the studies on which the ERF is based? Are specific regions or countries over- or underrepresented and can we realistically assume that the ERF can be transferred to underrepresented regions? Other important concerns are the representativeness with regard to demographics (such as age range) and the representation of specific, more susceptible groups. Persons living in deprived areas may be more sensitive or susceptible to the adverse effects of environmental pollution for several reasons including higher exposure levels, co-exposure to other environmental exposures (not limited to chemicals e.g. due to poorer housing conditions or occupational exposures), worse general health status, a poorer lifestyle (e.g. diet, smoking), higher stress levels, and poorer socio-economic status (being associated with lower awareness and more limited financial resources resulting in more limited ability or possibility to choose) (Forastiere et al., 2007)(Morello-Frosch et al., 2011)(Sacks et al., 2011)(Shiue and Bramley, 2015). Greater susceptibility of subjects with a lower SES has been observed for several stressors like air pollution and exposure to lead (Schwartz, 1994)(Jerrett et al., 2004)(Marshall et al., 2020). Ideally, for an EBD assessment or HIA, information should be available on SES-specific exposures and SES-specific ERFs. Estimates of the EBD are sometimes stratified for sex and age but too often SES is considered as a confounder and corrected for in the ERF instead of showing differences by SES.

4.10 Overview of methodological challenges

We described a number of methodological challenges for EBD calculations and HIAs for chemicals in this methodological chapter. These challenges are summarized in **Table 1** below and are/will be addressed within the T6.2.4 case studies. A total of 6 case studies have been performed in 2023/24. A description of the case studies can be found in Chapter 4.1.

Table 1. Checklist of methodological challenges for the case studies

Challenge
Exposure(s) of interest <ul style="list-style-type: none"> - Main exposure routes and exposure routes included in EBD/HIA - Exposure period(s) included (e.g. short-term, long-term, years) - Exposure assessment method - Representativeness of exposure data for population of interest (demographics, geographical coverage, relevant time period)

<ul style="list-style-type: none"> - Extrapolation of exposure data to population of interest? If yes, method used (e.g. PopPK, PBK) - Selection of the counterfactual - Exposure to mixtures addressed? If yes, method used
Health data <ul style="list-style-type: none"> - Health outcomes included/incidence or prevalence - Data source - Disability weights available (e.g. from GBD) - Representativeness for population of interest (demographics, geographical coverage, relevant time period)
Exposure-response function <ul style="list-style-type: none"> - WoE assessment approach - Method to establish ERF (epidemiological studies – longitudinal, cross-sectional, single/multiple studies, experimental data) - Representativeness for population of interest (demographics, geographical coverage, relevant time period)

4.11 Development of EBD toolbox in MCRA

In Y3 of PARC, WR and UBA started with the implementation of modules for EBD analysis in the MCRA software. These modules should allow users of MCRA to perform EBD assessments based on harmonised methodology, as developed in T6.2.4.

The current implementation serves as a proof-of-principle and demonstrator. It enables users to conduct basic bottom-up EBD assessments based on: (i) internal exposure estimates derived from HBM data (further developed in T6.2.3), (ii) internal (aggregate) exposure estimates obtained from external exposure models (further developed in T6.2.1), and (iii) external (dietary) exposure estimates. These modules are integrated within MCRA's generic modular framework, allowing for the propagation of uncertainties from the exposure estimates to the EBD analysis module. Users provide ERFs and BoD indicators as input data using specifically developed data formats. The ERF data format accommodates a wide variety of ERF types (e.g., specified as functions, expressed as effect per doubling of exposure, or expressed for different exposure classes) as well as different effect measures including RR and odds ratios (OR). Similarly, the BoD indicator data format supports multiple indicator types, including DALYs and numbers of cases, enabling specification of disease burden associated with specific effects in defined populations.

The current implementation provides the foundation for a generic framework for EBD analysis in MCRA, designed to accommodate the wide range of EBD analysis types encountered in practice. This framework will be further extended and refined in alignment with the harmonised methodology developed under T6.2.4. Planned short-term extensions include enabling the specification of uncertainty in the ERFs and incorporating this uncertainty into the overall analysis, as well as supporting ERFs that measure effects as shifts in continuous outcomes (e.g., changes in IQ). Additional extensions will be driven by the ongoing development of harmonised methods and the needs identified through case studies in T6.2.4.

5. Case studies

5.1 Overview of the case studies

Within Y2-3 of PARC (2023-2024) six EBD case studies (i.e. T6.2.4c) were carried out. Table 2 provides an overview of their context, their main findings or most updated progress and their completion status. Following Table 1 each case study is summarized individually along with their contributions to the sub tasks of T6.2.4a, T6.2.4b, T6.2.4d.

Table 2. Overview of all case studies

Title	EBD/HIA	Exposure	Outcome (Indicator)	Source population	Main findings	Completed/Published
Preliminary estimate of the environmental burden of disease related to pyrethroid-insecticide exposure and ADHD in Europe based on Human Biomonitoring (VITO)	EBD	Pyrethroids	ADHD (DALYs)	France, Germany, Iceland, Switzerland, and Israel 0-19 years old	<p>Annual DALYs per million inhabitants attributable to pyrethroids</p> <p>Israel: 27 DALYs France: 21 DALYs Switzerland: 12 DALYs Iceland: 12 DALYs Germany: 3 DALYs</p> <p>Direct health economic burden attributable to pyrethroid-induced ADHD (per year, per million of inhabitants)</p> <p>Israel: 2.5 MEUR France: 2.4 MEUR Switzerland: 2.0 MEUR Iceland: 1.7 MEUR Germany: 0.3 MEUR</p>	Yes; https://ehjournal.biomedcentral.com/articles/10.1186/s12940-024-01131-w

					Annual ADHD cases per million inhabitants attributable to pyrethroids Israel: 2189 France: 1710 Iceland: 969 Switzerland: 944 Germany: 209	
Environmental burden of cardiovascular diseases attributable to lead exposure in European adults (Lead: DTU)	EBD	Lead (Pb)	CVD (DALYs)	Adults in Germany, Czech Republic, Spain, Belgium, Slovenia, and Norway	Under development	No
Environmental burden of lead (Pb) and methylmercury (MeHg) exposure on IQ loss in children in Europe – single – substance and mixture approach (ANSES)	EBD	Lead (Pb) and methylmercury (MeHg)	IQ (points loss) and IQ (DALYs), Economic loss indicator proposed	6-11 years and women of childbearing age (18-45y) from seven European countries (Belgium, Czech Republic, Germany, France, Slovenia,	Under development	No

				Sweden, and Spain)		
Environmental burden of municipal solid waste incineration emissions on cancer-related mortality (FMUL)	EBD	Municipal solid waste incinerator (MSWI) emissions	Lung cancer associated mortality (PAF, attributable deaths)	Population living in exposed parishes (based on estimated ground level concentrations), in Portugal	Population attributable fraction 14.53% (2.91, 24.24) Attributable number of deaths per year 17.6 (3.5, 29.5) based on meta-analysis Attributable death rate (per year, per 100,000 habitants) 6.2 (1.2, 10.3) based on meta-analysis	Under preparation for publication
Environmental burden of disease study on arsenic exposure and lung, bladder, and skin cancer (Sciensano)	EBD	Inorganic As through dietary route	Lung, bladder and skin cancer (DALYs stratified by education level)	Belgium, Portugal and Denmark	See Figures 3,4,5	Under preparation for publication
Influence of waste co-incineration in a cement plant on cancer burden (OI and NIJZ)	EBD	Emmissions from waste co-incineration in a cement plant (Goriško region, W Slovenia)	All cancers but non-melanoma skin (geographical vicinity, PM10, PAH, Cr), lung cancer (geographical vicinity, PM10, Cr), non-Hodgkin lymphoma and sarcoma (geographical vicinity, PAH), RA for As, Cd, Hg, Pb, PAH and POPs, using national HBM surveys', and environmental monitoring data to assess exposure. Adult	Portugal and Slovenia	Exposure of adults to tAs, Pb, POPs (sum of dioxins, furans and dioxin – like PCBs) and PAH in the Goriško region does not differ significantly to exposure in other areas of Slovenia indicating that the risk to residents from exposure to selected chemicals is not higher than in the rest of Slovenia. The data from the HBM survey in	1)Assessing the Impact of Waste Co-Incineration at the Anhovo Cement Plant (Slovenia) on the Regional Cancer Burden by Zadnik et al submitted for

			<p>inhabitants of twelve Slovenian regions (three rural, three urban and six polluted areas) were included in the first national HBM survey. Children and adolescents from eight “hot spots” were included in the second national HBM survey. Exposure levels will be compared among the regions to establish whether the residents in Goriško region have higher exposures. Risk will be assessed using the latest HBM-GV values.</p>		<p>children and adolescents is being analyzed.</p>	<p>publication; 2) A report on RA and comparison of risk from exposure to selected chemicals in general population among included Slovenian areas Ahačič et al, under preparation</p>
--	--	--	--	--	--	---

5.1.1 Pyrethroid-insecticide exposure and ADHD in Europe based on Human Biomonitoring

Title	Preliminary estimate of the environmental burden of disease related to pyrethroid-insecticide exposure and ADHD in Europe based on Human Biomonitoring
Institutions involved	VITO (Lead), DTU, UBA, ANSES, BPI, Sciensano, RUMC, IISPV, EEA
Status	Completed
Publications	https://ehjournal.biomedcentral.com/articles/10.1186/s12940-024-01131-w#Abs1
Contribution to task 6.2.4a (Data)	<p>The PARC priority chemical was pyrethroids and already existing data on exposure, disease burden, exposure-response functions (ERF) and direct health costs related to ADHD were collected and used to generate new EBD-data. Those data are publicly available in the European HBM dashboard (exposure), in scientific publications (data on ERF) and in the IHME database (data on disease burden). The main data gaps identified were:</p> <ol style="list-style-type: none"> i. In the HBM4EU studies several countries only measured urinary 3-PBA in children, while others only in adults. This is a problem given that children have higher body burdens of pyrethroids while the EBD-analysis was carried out on adults. Moreover, during HBM4EU it was not mandatory to measure pyrethroid metabolites, making the number of countries with available pyrethroid exposure data limited. Though, this problem will be solved in the PARC HBM studies as pyrethroids will now be a mandatory biomarker to be measured. In this case study, this issue was resolved by only using adult exposure data, as the ERF was based on gestational exposure. ii. The lower SES-groups were systematically underrepresented, therefore it was not possible to perform SES-stratified EBD-analysis iii. There is a lack of epidemiological studies addressing this exposure-effect association which makes it difficult to perform a meta-analysis. On top of this, a meta-analysis is even more complicated seeing differences in exposure window, effect measured (different tools to assess ADHD). At EU level there should be more correspondence or an overview is lacking of which epidemiological studies will be carried out and what (exposure and effect markers) will exactly be measured. iv. The population aggregate exposure values were used as opposed to individual data (though, this would not be a major issue).
Contribution to task 6.2.4b (Methodology)	No new methodological challenges were identified – with the only challenge encountered in Table 1 being to some extent the representativeness of the exposure data, though this was addressed through arguments and justifications – and all the methods used were standard approaches (top-down approach as described in 2.2 of Annex Erreur ! Source du renvoi introuvable.).
Contribution to task 6.2.4d (Indicators)	The indicators used in this case study were population attributable fraction and disability-adjusted life years which are routinely used indicators for these evaluations. Communication of the indicators to the policymakers is not done explicitly. The publishing of the results in the peer reviewed scientific literature is

	for the moment the only communication that is intended (not as in HBM4EU in which indicators are explicitly generated for policy makers).
--	---

Overview summary (i.e. Abstract from the published paper)

“Human biomonitoring (HBM) data indicate that exposure to pyrethroids is widespread in Europe, with significantly higher exposure observed in children compared to adults. Epidemiological, toxicological, and mechanistic studies raise concerns for potential human health effects, particularly, behavioral effects such as attention deficit hyperactivity disorder (ADHD) in children at low levels of exposure. Based on an exposure-response function from a single European study and on available quality-assured and harmonized HBM data collected in France, Germany, Iceland, Switzerland, and Israel, a preliminary estimate of the environmental burden of disease for ADHD associated with pyrethroid exposure was made for individuals aged 0–19 years. The estimated annual number of prevalence based disability-adjusted life years (DALYs) per million inhabitants were 27 DALYs for Israel, 21 DALYs for France, 12 DALYs for both Switzerland and Iceland, and 3 DALYs for Germany; while the annual ADHD cases per million inhabitants attributable to pyrethroids were 2189 for Israel, 1710 for France, 969 for Iceland, 944 for Switzerland, and 209 for Germany. Direct health costs related to ADHD ranged between 0.3 and 2.5 million EUR yearly per million inhabitants for the five countries. Additionally, a substantial number of ADHD cases, on average 18%, were associated with pyrethroid exposure. Yet, these figures should be interpreted with caution given the uncertainty of the estimation. A sensitivity analysis showed that by applying a different exposure-response function from outside the EU, the population attributable fraction decreased from an average of 18 to 7%. To ensure more robust disease burden estimates and adequate follow-up of policy measures, more HBM studies are needed, along with increased efforts to harmonize the design of epidemiological studies upfront to guarantee meta-analysis of exposure response functions. This is particularly important for pyrethroids as evidence of potential adverse health effects is continuously emerging.”

5.1.2 Lead exposure and cardiovascular diseases in European adults

Title	Environmental burden of cardiovascular diseases attributable to lead exposure in European adults
Institutions involved	DTU (lead), SCIENSANO, VITO, STAMI, RIVM, ANSES
Status	In progress (31/12/2025)
Publications	In progress (2026)
Contribution to task 6.2.4a (data)	Data on lead in blood has been collected for six countries (Germany, Czech Republic, Spain, Belgium, Slovenia, and Norway) via the European HBM dashboard (https://hbm.vito.be/eu-hbm-dashboard). Additionally, data from Sweden and the Netherlands have been compiled via case study partners. The data that will be generated are: <ul style="list-style-type: none"> - Exposure response function of the pair lead-CVD - Burden of CVD associated with lead exposure in European countries (DALYs)
Contribution to task 6.2.4b (methodology)	Systematic review and meta-analysis of longitudinal studies with burden of proof meta-regression for lead in relation to SBD and CVD (in collaboration with IHME)
Contribution to task 6.2.4d (indicators)	Top-down probabilistic approach to calculate attributable Disability-Adjusted Life Years (DALYs) with 2-d Monte Carlo techniques to distinguish between uncertainty (e.g. from ERFs, DALY per case estimates derived from the GBD) and variability (e.g. blood and/or bone lead levels, SBP).

Overview summary

Humans are exposed to lead through inhalation, food and water consumption, and direct contact. At EU level, there is concern about the increased use of lead in energy efficient vehicles¹. The relationship of lead exposure with elevated systolic blood pressure (SBD) and cardiovascular disease (CVD) is well recognized by FAO and WHO. Although exposure to lead has decreased globally since the phase-out of leaded gasoline, recent studies indicate a high global burden of disease associated with human lead exposure ranging from ~ 850,000 cardiovascular deaths (GBD 2019 Risk Factors Collaborators et al., 2020) to > 5.5 million estimated by the World Bank (Larsen and Sánchez-triana, 2023). These discrepancies appear to be due to methodological choices related to the exposure-response function used and in particular, whether the effects on CVD are mediated by SBP or not. The aim of this case study is to estimate the environmental burden of CVD attributable to lead exposure in European adults. As systematic reviews and meta-analyses were lacking, the first step and the foundation of this case study is the development of the ERF for the association between blood and/or bone lead and SBP by conducting a Burden of Proof meta-regression (Zheng et al., 2022) which allows for quantification of known sources of bias. Then, a top-down probabilistic approach will follow to calculate attributable Disability-Adjusted Life Years (DALYs) with 2-d Monte Carlo techniques to distinguish between uncertainty (e.g. from ERFs, DALY per case estimates derived from the GBD) and variability (e.g. between blood and/or bone lead levels, SBP). The case study is still ongoing and findings on the ERF and Pb attributable CVD burden will be available by end of 2025 (see above table).

¹ https://www.hbm4eu.eu/wp-content/uploads/2019/03/HBM4EU_Scoping-Documents_Lead_v1.0.pdf

5.1.3 Lead (Pb) and methylmercury (MeHg) exposure and IQ loss in children in Europe - single - substance and mixture approach

Title	Environmental burden of lead (Pb) and methylmercury (MeHg) exposure on IQ loss in children in Europe - single - substance and mixture approach
Institutions involved	ANSES (lead), DTU, VITO, Sciensano, ENSP
Status	In progress (completion date: September 2025)
Publications	In progress (completion date: end of 2025)
Contribution to task 6.2.4a (Data)	Aggregated human biomonitoring (HBM) data were retrieved/downloaded from the European HBM Dashboard (https://hbm.vito.be/eu-hbm-dashboard) and the Information Platform for Chemical Monitoring (IPCHEM). Additionally, data from Sweden have been compiled via case study partners. Individual HBM data from the French Esteban study were also collected. Data will also be requested from the FLEHS studies. Also, new dose-response relationships were generated through literature reviews and meta-analyses for both lead and methylmercury. From those results, we derived a specific scaling factor to apply in our mixture burden of disease.
Contribution to task 6.2.4b (Methodology)	An epidemiological literature review was performed, followed by meta-analyses to derive the exposure-response functions used in the calculations. All study designs were considered, mainly longitudinal studies for prenatal exposure and transversal studies for postnatal exposure. The main knowledge gap identified is the lack of homogenous matrices and exposure windows in dose-response relationships for lead and methylmercury. This limitation introduces uncertainty into the calculation of the scaling factor. Calculating burden of disease for mixtures will require further methodological advancements in future work.
Contribution to task 6.2.4d (Indicators)	We reported results as IQ points lost (individual and total) and as DALYs associated with intellectual disability. An indicator of economic loss was also proposed.

Overview summary

Lead and methylmercury are neurotoxicants known to impair cognitive development and to cross the placental barrier, affecting fetal development. Early life exposure has been associated with reduced IQ, behavioral problems, and cognitive deficits. Persistent disparities in exposure levels among countries, support the need for further impact studies.

The aim of this case study was to assess the disease burden associated with chronic exposure to lead and methylmercury, individually and as a mixture, on IQ loss in children in Europe (individual and total) and as DALYs associated with intellectual disability. An indicator of economic loss was also proposed.

Data on eExposure levels of children and women of childbearing from across Europe were extracted from publicly-available databases (Table 3). We performed a nonsystematic literature review followed by a meta-analysis to derive dose-response functions. A traditional incidence-based approach was applied to assess the environmental burden of disease associated with lead and methylmercury exposure. For the mixture approach, we derived a scaling factor, allowing us to

express methylmercury exposure levels into lead-equivalent levels. The incidence-based approach was then applied using scaled exposure data.

The case study is still ongoing.

Table 3. Descriptive statistics of exposure for women of childbearing age and children within the Esteban population

Population	Age	Substance	Number of individuals	Median	Mean	IQR	Matrix	Unit
Children	6 – 11 y	Pb	417	10.92	12.01	6.15	Blood	µg/L
Women of childbearing age	18-49 y	Hg	205	640	846	760	Hair	µg/g

5.1.4 Municipal solid waste incineration emissions and cancer-related mortality

Title	Environmental burden of municipal solid waste incineration emissions on cancer-related mortality
Institutions involved	FMUL (lead), VITO
Status	Completed
Publications	In progress (completion date: May 2025)
Contribution to task 6.2.4a (Data)	This case study uses an approach to estimate the population exposed to the mixture emitted by incinerators considering the estimated ground level concentrations. The Graz Lagrangian Model estimates the transport, dilution, and ground-level concentrations based on the heavy metals emissions (arsenic, cadmium, mercury, and lead) measured at the chimney, height, and diameter of the chimney, the topography of the area around the incinerator, the aerodynamic roughness based on occupation and land use, and the intensity and direction of the wind. The focus on heavy metals reflects the pollutants that could be modelled with the available emissions data and software capabilities. Due to limitations in the granularity of the available cancer mortality data, we did not directly model health impacts based on the estimated metal concentrations. Instead, we used the estimated ground-level concentrations to classify parishes into groups of higher and lower exposure to MSWI emissions, which were then used to compare health outcomes between exposed and control (counterfactual data source) groups.
Contribution to task 6.2.4b (Methodology)	A random-effects meta-analysis including observational studies (cohort, case-control, cross-sectional, and ecological) was performed to define the ERF between exposure to municipal solid waste incinerators and specific cancer mortality (i.e. stomach, colorectal, liver, lung, and leukemia) by aggregating the evidence of available studies.
Contribution to task 6.2.4d (Indicators)	Population attributable fraction for cancer mortality and attributable number of deaths by cancer.

Overview summary

Incineration is one of the primary methods for treating urban solid waste. While current legislation establishes emission limits for incineration that are considered safe from a public health perspective, the process still releases various pollutants (in low doses) depending on the waste composition. These include heavy metals, nitrogen oxides, sulfur dioxide, dioxins, and furans. Although low emission levels are deemed safe, strong evidence about the long-term effects of low-dose exposure remains lacking. Notably, waste incineration has been associated with an increased risk of various cancers (Sharma et al., 2013)(Raffetti et al., 2019) and cancer-related mortality (Vinti et al., 2021). Similarly, elevated exposure to heavy metals has been linked to higher risk of cancer (International Agency for Research on Cancer (IARC), 2012)(Barone et al., 2016)(Ancona et al., 2015) and cancer-related mortality (Ancona et al., 2015)(Duan et al., 2020). Estimating the cancer-related mortality burden associated with living in areas exposed to waste incineration activity could provide critical evidence to determine whether stricter mitigation measures are necessary. This case study illustrates an assessment method for estimating the environmental burden of exposure to waste incinerator emissions based on epidemiological studies (and its limitations).

The overall goal of the case study was to estimate the cancer-related mortality attributable to exposure to municipal solid waste incinerator (MSWI) emissions in Portugal. The specific aims were as follows:

- i. To define the population exposed to MSWI emissions in a specific region of Portugal and assess cancer-related mortality by cancer type.
- ii. To define an exposure-response function (ERF) that links exposure to MSWI emissions with cancer mortality, stratified by cancer type.
- iii. To calculate the population attributable fraction (PAF) and estimate the number of attributable deaths.

The exposed population was defined according to the criteria reported in the previous table, section “Contribution to task 6.2.4a (Data)”. To calculate the PAF and number of attributable deaths, the population living in the exposed parishes was used as the whole population of interest (denominator = 289,957 inhabitants, corresponding to 14.1% of the Great Lisbon Area, where the incinerator is located).

The ERF was established based on a meta-analysis of observational studies assessing associations between exposure to municipal solid waste incinerator emissions and cancer mortality outcomes. Due to the limited number of available studies, no differentiation was made between MSWI facilities based on specific technological characteristics (e.g., incineration technology, emission control systems, or waste stream composition), which may influence the environmental and health impacts observed. We opted to calculate pooled effect sizes by combining the different effect measures reported (RR, HR, and SMR). Given the minimum of three studies required for aggregating effect sizes, the estimated effect sizes were calculated for stomach, colorectal, liver, lung, and leukemia cancer mortality. For all cancer types except lung cancer, no statistically significantly increased risk was found. However, a significant positive association was observed for lung cancer mortality (effect size = 1.17, 95% CI: 1.03, 1.32, $I^2 = 21\%$). Based on the results of this meta-analysis, we produced **Table 4**. The calculated PAF was 14.53% (95% CI based on the effect size: 2.91%, 24.24%). Between 2015 and 2019, a total of 608 lung cancer deaths were recorded in the exposed parishes, with an average of 122 deaths per year. Applying the calculated PAF, we estimate that, on average, 18 deaths per year (95% CI: 4, 30) may be potentially attributed to MSWI emission exposure. For this, an RR of 1.26 (95% CI: 1.05, 1.50) was calculated by comparing the sex- and age-standardized lung cancer mortality rates between the exposed and control parishes. Using this RR, the PAF for lung cancer mortality was estimated at 20.63% (95% CI based on the RR: 4.76%, 33.33%). For the same period (2015 to 2019), an average of 25 deaths per year (95% CI: 6, 41) were estimated to be potentially attributable to MSWI emissions exposure.

Table 4. Comparison of Effect Size, Population Attributable Fraction, and Attributable Deaths for Lung Cancer Mortality Using Meta-analysis and Population-Based ERF

	Meta-analysis ERF	Population-based ERF
Effect size estimate	1.17 (1.03, 1.32)	1.26 (1.05, 1.50)
Population attributable fraction	14.53% (2.91, 24.24)	20.63% (4.76, 33.33)
Attributable number of deaths	18 (4, 30)	25 (6, 41)
Attributable death rate (per 100,000 inhabitants)	6.2 (1.2, 10.3)	8.8 (2.0, 14.2)

The comparison of the two approaches reveals some variation in the estimates of lung cancer mortality associated with MSWI emissions. The population-based method estimated a higher PAF (20.63%) and attributable deaths (25 per year) compared to the meta-analysis approach, which yielded a PAF of 14.53% and 18 attributable deaths per year. Given the limitations of both the data

and methods used, these estimates should be interpreted with caution. In this case study, PAF estimates were based on the observed associations identified in the meta-analysis and population-based comparison. Given the limited number of available studies and the predominance of ecological designs, causality could not be formally established through a weight of evidence approach. Nevertheless, considering the consistent positive association with lung cancer mortality, we proceeded with estimating the potential burden of MSWI emissions. The results highlight the complementary nature of the two methods in estimating the impact of environmental exposures on health outcomes, with both approaches suggesting that MSWI emissions could contribute to an increased public health burden. However, due to uncertainties in the exposure data, potential differences in MSWI technologies, and potential confounding factors, the true extent of lung cancer-related deaths attributable to MSWI emissions remains uncertain. High-quality prospective longitudinal studies with individual-level exposure assessment are needed to strengthen the evidence and better quantify this association. Additionally, the potential increased burden of incineration activities should also be balanced with the burden of alternative processes for MSW management.

5.1.5 Arsenic exposure and lung, bladder, and skin cancer

Title	Environmental burden of disease study on arsenic exposure and lung, bladder, and skin cancer
Institutions involved	Sciensano (lead), DTU, VITO, ENSP
Status	Completed
Publications	In progress
Contribution to task 6.2.4a (Data)	This case study developed a comprehensive database for evaluating the health impact of arsenic in Belgium, Portugal and Denmark. At the onset of this case study, only limited biomonitoring data on arsenic were available, and all reviewed literature estimating DALYs focused on dietary exposure. Thus, dietary exposure was chosen for this study's assessment. Occurrence and food frequency data were collected and combined to estimate external (dietary) exposure level for different population groups. Also, DALY computations for different subpopulation groups were performed.
Contribution to task 6.2.4b (Methodology)	Several methodological challenges were identified and overcome. Estimates of dietary exposure were derived by combining occurrence data with consumption data from national food consumption surveys. Arsenic tends to accumulate in the human body, leading to increased concentrations with age (ATSDR, 2007). Therefore, a long-term exposure period is of interest for this study. However, dietary exposure was estimated via 24h recall and food frequency questionnaires. The main strength of this case study is the potential for the application of a harmonized methodology across Belgium, Denmark, and Portugal, providing a consistent framework for comparison and analysis. Additionally, SES stratification of DALY estimates supports addressing the role of socio-economic status in EBD assessment. This is a significant step forward, as it acknowledges the impact of socio-economic factors on the health of populations.
Contribution to task 6.2.4d (Indicators)	DALY stratified by education level

Overview summary

Epidemiological studies demonstrate associations between inorganic arsenic (iAs) from dietary sources and a variety of carcinogenic and non-carcinogenic health effects. There is increasing recognition of the importance of estimating the EBD of chemical contaminants by scientists and policy makers. Yet, comprehensive studies providing a clear picture of the impact of iAs on European populations are lacking, and even fewer are investigating the importance of socio-economic status (SES). This study aimed to estimate the EBD related to dietary exposure to iAs for lung, bladder, and skin cancers across different socio-economic strata for three European countries, Belgium, Denmark, and Portugal. The EBD was estimated using a RA approach following Jakobsen et al. methodology (Jakobsen et al., 2019), with DALY as the main indicator. The exposure-response functions were selected on a non-systematic review of the literature and correspond to those used by Jakobsen et al (2019). Our findings show significant variations in dietary exposure and attributable burden between the three countries. Moreover, iAs exposure levels and attributable burden increase with the education attainment, which serves as a proxy for SES. The Portuguese population experiences

the highest exposure levels and thus the highest EBD for the three education level groups, with particularly elevated rates among the higher SES groups. Belgium and Denmark report significantly lower and more stable rates across education levels, indicating a more evenly distributed cancer burden in these countries. **Figure 3,4,5** provide the DALY estimates for the three types of cancers for Belgium stratified by education level (as a publication is underway no further results are shown here).

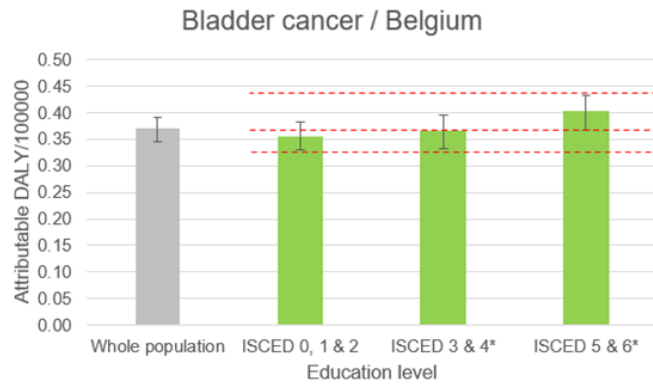


Figure 3. EBD of bladder cancer related to iAs exposure for the Belgian population stratified by education level.

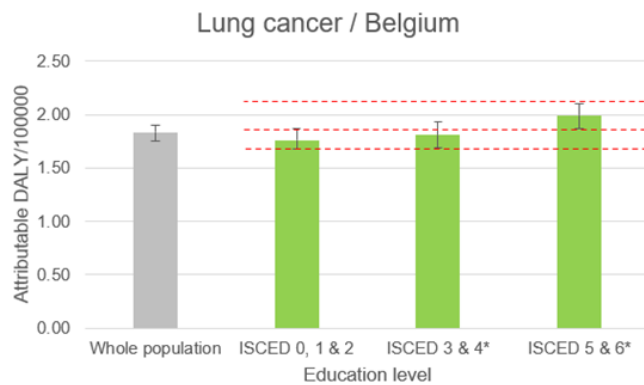


Figure 4. EBD of lung cancer related to iAs exposure for the Belgian population stratified by education level.

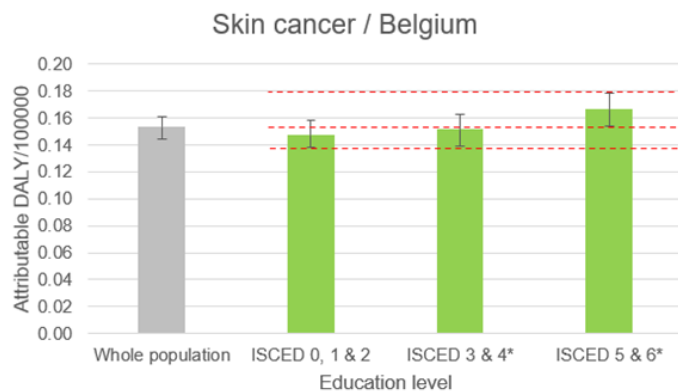


Figure 5. EBD of skin cancer related to iAs exposure for the Belgian population stratified by education level.

This case study provides important estimates of the EBD related to inorganic arsenic exposure for different socio-economic groups, across three European countries, adopting a harmonized

methodology. However, it highlights the necessity for more extensive data collection to improve the accuracy of EBD evaluations. The uncertainty depicted in the figures reflects only that of exposure and YLL estimates. The uncertainty for other input parameters (e.g., ERFs) was not available, resulting in an underestimation in the overall uncertainty.

5.1.6 Influence of waste co-incineration in a cement plant on cancer burden and risk assessment for selected chemicals based on HBM data

Title	Influence of waste co-incineration in a cement plant on cancer burden and RA for selected chemicals based on HBM and environmental monitoring data
Institutions involved	OI (lead) and NIJZ
Status	In progress (The results of geographical analysis [1] will be available in the middle of 2025. Results of RA [2] will be available during the beginning of summer 2025.)
Publications	Yes in progress – expected end of 2025
Contribution to task 6.2.4a (Data)	<p>[1] For the geographical analysis the environmental data are available for our case study from a dedicated national research project in Slovenia (Aris V3-2236). There are available modelled air pollution data (PM10, PAH) and soil sampling data (metals). Further, data on all cancer cases for the entire population in the study area is available in the population-based cancer registry. In addition to individual data, all the cases are geolocated to the coordinate level. Socio-economic status (SES) is applied as a surrogate to exposure to life-style factors. The SES has been captured via deprivation index SI-EDI which is available for individual cancer patients as well as on a small aggregated level for the background population. No individual level exposure data is available in this case study. The possibility of the ecological fallacy is considerable in such case.</p> <p>[2] Exposure data for the RA come from the National HBM survey I (2007-2014) in adult population of Slovenia; i.e. Pb in blood, tAs, Cd and Hg in urine, Me-Hg in hair, metabolites of PAHs in urine, POPs in blood. Further data will be available once the HBM survey II (children and adolescents in hot spots) survey is completed. Pseudonymised HBM survey I data are available for general adult population in 12 regions (three rural, three urban and six polluted by the selected chemicals based on the environmental monitoring), including the Goriško region where the waste co-incinerator is located. Additionally, pseudonymised HBM survey II data on children and adolescents living in eight “hot spots”, including the residents living in the area of the cement plant. will be available in the first half of 2025. Uncertainties may arise from the broad sampling area, particularly in the HBM survey I, resulting in the “dilution” of measured concentrations by mixing data from more and less polluted areas within studied regions. The application of the same exclusion criteria in both polluted and non-polluted areas could further impact exposure estimates. Additionally, pooling certain samples due to limited sample size may dilute concentrations even more and introduce uncertainty in statistical significance.</p>
Contribution to task 6.2.4b (Methodology)	[1] Geographical analysis: Bayesian spatial hierarchical modelling of incidence: risks and PAFs are assessed.

	[2] RA for the Slovenian adult population will be conducted using exposure data to metals, PAHs and POPs from the first national HBM survey (HBM survey I), interpreted with current HBM-GVs or HBM-TVs. If these are unavailable, German HBM I/II values or BE will be used. If feasible, RA will also be extended to children and adolescents using data from the second national HBM survey (HBM survey II).
Contribution to task 6.2.4d (Indicators)	[1] Two groups of indicators will be provided for different cancer types comparing the polluted and non-polluted areas: Cancer Risk and Population Attributable Fraction (PAF). A gap identified is that as co-incineration has only been in force for a few years, the exposure data and the cancer cases relate to the same period. The latency period between cancer diagnosis and exposure can therefore not be considered. We do not know what the cancer incidence will be in 10 years' time. [2] Risk to the general population arising from exposure to selected chemicals based on the currently available data.

Overview summary

Waste co-incineration in a cement plant generates and releases a mixture of toxic substances, some of which are known carcinogens. The current case study aims at investigating the impact of waste co-incineration at the Salonit Anhovo cement plant (Western Slovenia region) on cancer by assessing the environmental pollutants in the modelled areas and their association with the cancer burden in the population. The case study consists of two parts: i) A geographical analysis with Bayesian spatial hierarchical modelling of incidence: risks and PAFs are assessed ii) A RA for the Slovenian adult population will be conducted using exposure data to metals, PAHs and POPs from the first national HBM survey (HBM survey I), interpreted with current HBM-GVs or HBM-TVs. If these are unavailable, German HBM I/II values or BE will be used. The selection criteria of chemicals in HBM survey I were based on national air and soil monitoring results, toxicological hazard of chemicals, their persistence and bioaccumulation potential, estimated size of exposed populations, analytical capacity, certain public concerns, and trends in other countries. Inclusion of at least 960 participants (40 primiparae and 40 males from twelve areas) was based on the statistician's recommendation to assure reliability of the set goals: to assess exposure of adults to selected chemicals and exposure of babies via maternal milk, to establish the geographical differences in exposure, to identify and evaluate the sources of exposure, to calculate national background reference values, to compare the data internationally, and to generate data for risk assessment. If feasible, RA will also be extended to children and adolescents using data from the second national HBM survey (HBM survey II). Results of the [1] (geographical analysis) will be available during the first half of 2025. The literature review showed that limited evidence exists on association between cancer and exposure to pollutants emitted by I. generation incinerators and I.-II. generation cement plants. There is some low-to-moderate evidence of association between soft tissue sarcoma and non-Hodgkin lymphoma in population exposed to dioxins near I. generation incinerations, but no evidence exists for next generation incinerators. Till now, there is no evidence for co-incinerators. There is moderate evidence for association between incidence of all cancers, lung, prostate, stomach and oropharyngeal cancer and exposure to chromium in occupationally exposed persons working at I.-II. generation cement plants. Using limited evidence available from our umbrella review for our case study the following combination of cancer sites and exposures were selected for geographical analyses: all cancers but non-melanoma skin (geographical vicinity, PM10, PAH, Cr), lung cancer (geographical vicinity, PM10, Cr), non-Hodgkin lymphoma and sarcoma (geographical vicinity, PAH). 2 In RA, the available HBM-GVs, HBM-TVs, German HBM I/II or BE – except potentially for certain

POPs in blood - will be compared to exposure assessed using national HBM I survey data including analyses of uncertainties. These may arise from the broad sampling area resulting in consequent “dilution” of measured concentrations, pooling of samples which further dilutes concentrations and application of the same exclusion criteria in the polluted and non-polluted areas. On the grounds of the existing RAs for tAs and Pb we predict no increased health risk in the region with waste co-incineration in comparison to other regions.

We expect that our bias analysis of HBM studies will highlight the need to propose a new, targeted HBM study in the vicinity of the co-incineration plant. Detailed results will be available in the first half of 2025. Limited evidence exists on association between cancer and exposure to pollutants emitted by incinerators. To fill this gap, it seems reasonable to plan focused European wide epidemiological studies and human biomonitoring studies with various cases. The proposed case study aligns with the European direction on reducing the cancer burden and sustaining a healthy environment. The European Commission’s main priority in health is cancer. Europe's Beating Cancer Plan sets out a new EU approach to cancer prevention, treatment and care with new technologies, research and innovation as the starting point.

5.2 New case studies started in year 4 (2025)

5.2.1 Glyphosate based herbicides and diabetes in EU countries (IRAS (lead), ANSES, SRU, WR-BIOM, Sciensano)

Glyphosate-based herbicides (GBHs) have been used widely worldwide since 1974 (Benbrook, 2016)(Antier et al., 2020)(de Araújo-Ramos et al., 2021), and the EU permission to use GBHs has recently been extended until 2033 (The European Commission, 2023). A growing body of literature has reported on the association of occupational and environmental exposure to GBHs with adverse health outcomes. However, findings are controversial mainly due to some contradictory results, even among meta-analyses (Krimsky, 2022). For example, regarding carcinogenicity there are contrasting conclusions by IARC (IARC, 2017) and ECHA.

Given their extensive use and their potential harmful effects, estimating the burden of disease due to exposure to GBHs is of paramount importance for public health and glyphosate is among the priority chemicals within PARC (Rousselle et al., 2021). As such this case study aims at performing an environmental burden of disease (EBD) of GBHs for the general adult population. Considering data availability which calls for simplicity the initial focus will be only on one chemical (i.e. GHBHs) and if possible/relative its metabolite (i.e. AMPA) (Singh et al., 2020), one health outcome and one country (i.e. the Netherlands). But when data are available, the developed HIA framework will be extended also to other European countries. Based on the availability of exposure data, of interest is the general adult public in rural areas where the main considered routes of exposure are inhalation, food intake and dermal exposure. Currently the outcome with the most detailed exposure response function (ERF) is **type 2 diabetes mellitus (T2DM)** (Li et al., 2023) (using the NHANES dataset), as there the exposure is continuous and measured in urine samples in ng/ml. The inclusion of other outcomes will be considered if there is sufficient information. For example, another health endpoint of interest is non-Hodgkin's lymphoma for which there are four meta-analyses (Zhang et al., 2019)(Schinasi and Leon, 2014)(Chang and Delzell, 2016)(Donato et al., 2020) but there the exposure is categorical based on surveys and thus requires careful considerations. There is also concern on the recent findings on exposure-effect associations in epidemiological studies, including associations between urinary glyphosate and preterm birth (Silver et al., 2021), gestational length (Parvez et al., 2018)(Lesseur et al., 2022) and anogenital distance in children (Lesseur et al., 2021).

Thus, the HIA will need to be conducted in a 'limited data' setting, and we will aim to i) estimate population exposure levels via different ways (e.g. internal and external exposure, PBK models) and compare them with each other and with observed levels available from the literature, ii) explore data-integration such as from experimental animal studies to refine the ERF if needed, iii) investigate which of the various methods for HIA (e.g. comparative RA, Markov Models, system dynamics) is best suited iv) estimate population attributable fraction of T2DM incidence due to GBHs exposure, v) perform uncertainty assessments which is dependent on the HIA method applied, vi) explore plausibility and limitations for inclusion of other potential health outcomes, and vii) after establishing the methodology for one substance expand the framework to a mixture of other pesticides that have been found to co-occur but there methodological developments are needed to obtain conditional associations from the marginal ones reported.

Regarding the criteria mentioned in the document "PARC T6.2.4 selection criteria for methodological case studies" the current HIA case study aims to cover the points 1-5 while it focuses on an exposure which despite its extensive presence around us, HIAs are lacking. In terms of design, the HIA will start by gathering the necessary inputs such as the ERFs and then constructing the methodology suitable for the target population and for informing policy makers as different methods provide different perspectives.

5.2.2 Incorporating a time-to-event model to improve the prediction of age of onset or death (RIVM (lead), Sciensano)

The current method for deriving age of onset or death primarily focuses on the population-based burden, in which average ages of onset or death in a population were derived (Devleeschauwer et al., 2015). However, the use of an average age of onset or death overlooks the fact that they are dose-dependent, i.e., higher exposure is related to an earlier age of onset or death (Bokkers et al., 2012)(Zeilmaker et al., 2010). Furthermore, the average age of onset or death was only related to a particular disease but not to a particular chemical. The average age of onset or death related to a particular disease also incorporates the influence of other risk factors, it can be named as age of onset all risk factors or age of death all risk factors. Therefore, the true age of onset or death attributed to chemical exposure can be understood as the decreased time to event (i.e., disease or death), and are referred to as Δ age of onset or Δ age of death.

This kind of dose-related (and chemical specific) reduction in the time of disease or death onset may directly affect the calculation of incidence at a certain period, thus leading to bias in the estimated burden of disease (EBD) calculation results.

We propose a new approach to estimate the age of onset at individual level with individual risk prediction models and microsimulation. The new approach is described as follows:

1. Conduct a prospective observational study or retrospectively utilize existing data from cohorts or registries where individuals are exposed to the chemical of interest.
2. Data Collection: Collect data on exposure to the chemicals and information on potential confounding variables such as demographic characteristics, lifestyle factors, and other exposures.
3. Data Analysis: Use appropriate statistical models to analyze the data and estimate the relationship between chemical exposure and age of onset, e.g., Cox proportional hazards model or other time-to-event models.
4. Modelling: Develop a model that accounts for potential confounders and covariates to estimate the hazard ratio or relative risk of age of onset associated with exposure to the chemicals of interest. Adjustments for time-varying exposures or covariates may also be necessary.
5. Model validation: Validate the predictive performance of the model by splitting the data into training and testing sets or using more advanced methods such as cross-validation or bootstrap. Assess the model's overall-fitting, discrimination, and calibration.
6. Predict the age of onset: Once the model is fitted, apply it to the whole population to predict the age of onset for all individuals at specific level of exposure to the chemicals. This can involve applying the estimated regression coefficients to the exposure data of interest and calculating the expected age of onset.
7. Using the predicted individual ages of onset, the population-level age of onset can be estimated through simulation.

The new approach will be applied to a case study to estimate the burden of disease (BoD) for dietary exposure to a mixture of cadmium and lead, focusing on their nephrotoxic effects (see 5.2.5 below). Furthermore, we will compare the age of onset or disease derived from this case study with those from other studies that do not use a time-to-event model. We hope this comparison will demonstrate the advantages of our proposed approach and justify its application in other EBD estimations. Ultimately, this integration will enhance the accuracy of estimating the age of onset or death specifically attributable to chemical exposure.

5.2.3 Exposure to PFAS and infectious diseases (VITO (lead), DTU, FHI, ANSES, NIPH, Sciensano, IISPV)

Per- and polyfluoroalkyl substances (PFAS) are a group of synthetic fluorinated compounds widely used in e.g. different consumer products due to their water, oil, and stain resistant properties. Aside from their desirable properties, PFAS are also bio-persistent environmental pollutants that are ubiquitously distributed in both humans and wildlife. The main exposure route to PFAS for humans is through ingestion of contaminated food and beverages, and via inhalation of indoor dust. Moreover, PFAS exposure has also been reported to occur *in utero* via placental transfer, and perinatally during breastfeeding (Impinen et al., 2019).

Exposure to PFAS has been associated with a broad range of toxicological outcomes, with immunotoxicity (increased pneumonia incidence, reduced vaccine antibody titers) being one of the most sensitive health effects. Few studies thus far have focused on estimating what the health impact of PFAS are in the general population. One such study was performed by (Goldenman et al., 2019), who estimated that 785 000 children were at risk of developing/sustaining infections in the EEA due to PFAS exposure (assuming 3% of the population is moderately exposed), corresponding to 1.5 million additional days of fever and a total health-care cost of 52 – 84 billion EUR. However, these risk calculations were conducted before EFSA published the updated tolerable weekly intake (TWI) of 4.4 ng/kg-bw per week (EFSA CONTAM Panel (EFSA Panel on Contaminants in the Food Chain) et al., 2020). It is therefore assumed that far more people are moderately exposed than assumed by (Goldenman et al., 2019), thus possibly posing a more significant public health risk.

In this case study we plan to estimate the environmental burden of disease related to PFAS for the European context based on HBM data from the general population (measured in HBM4EU). The disease burden will be attempted to be estimated from two perspectives:

1. By considering hard clinical immunological endpoints such as respiratory tract infections, infections, additional fever days, additional hospitalization, ...; these endpoints will also be meta-analyzed (if possible) to provide more robust and reliable EBD estimates. An increased propensity of infection based on a meta-analysis would be more clearly anchored in adversity compared to isolated observation on vaccination response. Studies selected on infectious disease and PFAS exposure were based on EFSA reports (EFSA Panel on Contaminants in the Food Chain (CONTAM) et al., 2018)(EFSA CONTAM Panel (EFSA Panel on Contaminants in the Food Chain) et al., 2020), submitted restriction reports (European Chemicals Agency (ECHA), 2022)(BAuA et al., 2023) and a systematic search performed by DTU.
2. Dose response functions will be sought for the relationship between antibody titers and occurrence of hard clinical endpoints (e.g., the diseases against which the respective vaccines provide protection for or other immune effects). This will allow us to estimate the disease burden based on the EFSA TWI for vaccine antibody reduction. However, data on this will probably be limited.

The burden of disease will be estimated for the general European population. The base case analysis will include the “EFSA 4” congeners, namely PFOS, PFOA, PFNA and PFHxS, but can be in additional analysis also be extended to other congeners. As for the burden of disease, the following metrics will be estimated: attributable disease cases, population attributable fraction, disability adjusted life years, and if possible, health economic losses.

5.2.4 Exposure to cadmium and nephrotoxicity (Sciensano (lead), VITO, RIVM, ANSES, DTU, ENSP)

Cadmium (Cd) is a trace metal naturally occurring in the environment, with anthropogenic activities such as agriculture, industry and urbanization highly contributing to its pollution in soil, water and living organisms (Pan et al., 2010). Humans are primarily exposed to Cd through ingestion (food and water) and inhalation (cigarette smoke, occupational fumes, ambient air), resulting in both acute and chronic toxicity (Åkesson et al., 2005)(European Food Safety Authority (EFSA), 2009). For the non-smoking general population, food is the primary source of exposure, particularly staples (especially rice, but also potatoes, and cereals), vegetables, shellfish, and offal products (Åkesson et al., 2005)(Satarug, 2018)(Joint FAO/WHO Expert Committee on Food Additives, 2022) (see also case study on aggregate exposure in PARC Deliverable D6.1). The mean dietary exposure for adults in EU countries ranges from 1.9 to 3.0 µg/kg body weight per week, while high consumers, such as vegetarians or children, have levels between 2.5 and 3.9 µg/kg body weight per week, approaching or exceeding the tolerable weekly intake (TWI) of 2.5 µg/kg body weight per week set by EFSA (2009). Cadmium is regarded as one of the highest priority chemicals by The CTF (Chemical and Toxins Disease Task Force) of the FERG considered (Gibb et al., 2019), and metals are considered one of the priorities within PARC, making a case study on Cd relevant to PARC objectives.

Cadmium accumulates in the body over a lifetime, mainly in the liver and kidneys (Satarug, 2018), and chronic exposure may result in significant health impacts (Pan et al., 2010).

The strongest evidence of health effects is related to kidney dysfunction, potentially leading to chronic kidney disease (CKD) (Zang et al., 2019)(Thomsen et al., 2022)(Redondo et al., 2023)(Huang et al., 2023), and bone demineralization, which may result in conditions like osteoporosis and fractures (Etchie et al., 2013)(Ougier et al., 2021).

Chronic kidney disease (CKD) is defined as a progressive dysfunction in kidney filtration function and its prevalence increases with age. It was estimated to be responsible for 44.5 million DALYs globally in 2021(GBD 2021 Diseases and Injuries Collaborators et al., 2024). In particular, CKD due to dietary cadmium exposure was estimated to account for more than 70,000 DALYs globally, corresponding to 1.0 DALY of CKD due to dietary Cd per 100,000 population in 2015 (Zang et al., 2019).

Cadmium exposure increases with age, exacerbating the risk of developing Cd-related diseases as people age (Satarug et al., 2017)(Genchi et al., 2020). Women are also more vulnerable to Cd exposure due to lower iron stores (Zahra, 2017)(Satarug, 2018), and several studies have already shown a negative association between socioeconomic status (SES) and Cd exposure when SES is considered in terms of educational level (Den Hond et al., 2015a)(Snoj Tratnik et al., 2022).

For these reasons, the relationship between Cd exposure and CKD is likely to be influenced by age, gender, and SES. While several studies have already estimated the burden of CKD due to Cd exposure at the country level in Europe for the adult population, the influence of SES disparities still needs to be taken into account.

In this case study, we aim to estimate the burden of CKD related to Cd exposure in the adult population over 40 years old, considering the influence of socioeconomic status. We will be using dietary cadmium exposure data – estimated via national food consumption surveys (Belgian FCS 2004, INCA2 2006-7, DANSDA 2011-2013, IAN-AF 2015-16) and occurrence data – as such data and SES stratification are available for the target population (in contrast to HBM data) and converting it into urine concentration using a one-compartment toxicokinetic model (Amzal et al., 2009), for which a collaboration with T6.2.2 of PARC will be explored.

5.2.5 Exposure to a mixture of cadmium and lead and nephrotoxicity (Sciensano (lead), VITO, ANSES, DTU, ENSP)

Exposure levels of Cadmium (Cd) and Lead (Pb) are in the same order of magnitude as the reference values set by the EFSA (European Food Safety Authority (EFSA), 2009)(EFSA Panel on Contaminants in the Food Chain (CONTAM), 2010), which raises concerns regarding potential health effects related to these substances. In particular, both chemicals are associated with Chronic Kidney Disease (CKD)(Agency for Toxic Substances and Disease Registry (ATSDR), 2020)(Ginsberg, 2012). Moreover, evidence indicates that co-exposure occurs in the general population since Cd and Pb are foodborne chemicals and are also present in contaminated air and water (Chung et al., 2014). Navas-Acien et al. found a consistent association between individuals in the highest quartiles of blood Cd and Pb levels and reduced glomerular filtration rate (GFR), indicating a strong association between the co-exposure to these metals and CKD (Navas-Acien et al., 2009). The relevance of a mixture approach is underscored by evidence suggesting that co-exposure to Cd and Pb has a more pronounced effect on CKD than exposure to either metal alone (Jain, 2019). Yet, there are still few studies addressing the health impact of mixtures. Therefore, investigating health effects of a combined exposure to Cd and Pb will help refine the methodology of the HIA of mixtures.

In this case study, we will explore multiple exposure data sources for Cd and Pb in the adult European population. Key data sources include the 2009 EFSA report on dietary Cd and the 2010 EFSA report on dietary Pb exposure (European Food Safety Authority (EFSA), 2009)(EFSA Panel on Contaminants in the Food Chain (CONTAM), 2010). Available human biomonitoring data include the DEMOCOPHES study (<https://hbm.vito.be/eu-hbm-dashboard>), as well as HBM data prior to 2008 from (Bierkens et al., 2011). Co-exposure data for Cd and Pb are available from the FLEHS study for Belgium (<https://hbm.vito.be/eu-hbm-dashboard>). Additional external exposure data are provided in (Sprong et al., 2023b) and internal exposure data through T6.2.3 in MCRA.

Both Cd and Pb accumulate in the body over a lifetime, with Cd reaching steady-state levels at approximately age 40 (European Food Safety Authority (EFSA), 2009) (Ginsberg, 2012) and lead accumulating particularly in bone tissue (Agency for Toxic Substances and Disease Registry (ATSDR), 2020). Therefore, this case study will target the general adult population, including the elderly. Chronic exposure scenarios will be modelled to reflect real-life, long-term exposure relevant for health impact assessment (HIA).

The study is currently in its preparatory phase. The start of this case study was delayed pending the availability and learning outcomes from the cadmium-specific case study, which is now sufficiently advanced to support progress. The first coordinators' meeting has already taken place, and deadlines have been set accordingly, with the kick-off meeting scheduled for September. The possibilities for integrating this case study with the methodological case study "Incorporating a time-to-event model to improve the prediction of age of onset or death" (5.2.2, see above) will be explored.

This case study aligns with the PARC T6.2.4 framework by incorporating current evidence on the mixture's health effects and aims to improve the methodology for mixture assessment. Additionally, this case study aligns with and builds further upon the case study on RA of mixtures of metals (Cd, Pb and As) regarding nephrotoxicity in the PARC project on real-life mixtures (see deliverable D.3).

5.2.6 Probability modeling in burden of disease (UBA (lead), Sciensano, VITO, ENSP, ANSES, DTU)

The aim of the proposed case study is to improve the modeling of statistical uncertainties in the assessment of the environmental burden of disease (EBD) by introducing features of probabilistic modeling in the estimation process (see also in section ‘methodological challenges’). Frequently, single model parameters, such as the mean relative risk (RR) and its surrounding confidence interval (CI), are used in EBD assessments. This deterministic approach is advantageous because assessments can be conducted quickly, and the results are relatively straightforward for various stakeholders to interpret. However, the use of such a deterministic approach results in the challenge, that the statistical uncertainties are not adequately or insufficiently represented.

As discussed in the working paper "Challenges in performing Environmental Burden of Disease and Health Impact Assessments for chemicals to be addressed in the PARC case studies" by Plass et al., the use of probability distributions representing EBD input parameters such as RRs or disability weights (DW) can help to overcome this problem. In contrast to the use of single point estimates, the probabilistic approach employs Monte Carlo simulations, which allows the EBD assessment model to be run repetitively with randomly selected values for each input variable, drawn from respective probability distributions.

The estimated burden of disease results for indicators such as disability-adjusted life years (DALYs), can then be presented as probability distributions or as classic parameters, such as the mean and 95% CIs. This probabilistic approach more accurately reflects the uncertainty associated with multiple input variables, providing a more realistic understanding of the uncertainty in EBD results. This is particularly valuable for stakeholders and policymakers, as it supports more informed decision-making.

In this case study, we plan to estimate disease burden indicators such as DALYs (and attributable cases / deaths) using probabilistic modeling of the following components: population attributable fraction (PAF) (using uncertainty distribution from the exposure-response function (ERF)), DWs, prevalence of outcome (if published with some measure for uncertainty, e.g. CI). We will also estimate DALYs using the deterministic EBD method in order to compare the two approaches and discuss any potential differences in the results. An R-based script will be developed to facilitate these analyses, which can also be utilized and further developed by other PARC partners.

The risk-outcome pair to test the feasibility of the approach will be lead (Pb) and intelligence quotient (IQ) score loss in Germany, since both data availability and quality of the relevant data is assumed to be good for Germany, especially concerning exposure data from our representative survey German Environmental Survey (GerES). Due to these reasons, Germany will be the study region for our case study.

5.3 Case studies for Y5-Y7

On November 13, 2024 the PARC Governing Board concluded in a validated ranked list of needs for the second half of the PARC project. Within T6.2.4, the emphasis of future activities will be shifting towards specific chemicals and co-exposure to multiple chemicals that cause immune, neurological, developmental or reproductive effect. Therefore, the case studies proposed for Y5 – Y7 will have to be developed accordingly. **Table 5** provides a non-exhaustive list of possible case studies, focusing on specific chemical groups, which adhere to the criteria mentioned above but equally important, that are also feasible to perform. More specifically, this means that the proposed case studies should be on (I) stressors for which HBM data is available from HBM4EU or will soon be available from HBM data collected within PARC, and (II) exposure-outcome pairs for which numeric exposure-response relationships are available in the literature (preferably from meta-analyses of multiple high quality studies for more robust and reliable estimations) or can possibly be derived. Of additional importance is the availability of data on socioeconomic differences in exposure estimates based on HBM data. Case studies assessing chemicals for which HBM data by socio-economic groups exist, will be prioritized.

Primarily, more focus should be on the regulatory relevance of case studies. The eventual selection of case studies will be discussed with all T6.2.4 partners and T6.2 leaders so that both the partners' interests and expertise can be aligned with overall PARC priorities. Case studies focusing more on methodology development in the domain of burden of disease and health impact assessment will also be discussed with T6.2 leads.

Table 5. Overview of prioritized stressors and outcomes for future T6.2.4 activities based on PARC Governing Board suggestions and on available data

Stressor	Outcome	Justification
Organophosphate flame retardants	Developmental, reproductive and neurological effects	- HBM data exists from HBM4EU - Highlighted as a priority in the PARC governing board meeting 13/11/24
Benzophenone UV-filters	Developmental, reproductive, immune and neurological effects	- HBM data exists from HBM4EU - Some countries indicated willingness to measure benzophenone in PARC (though not part of the mandatory set of stressors) - Highlighted as a priority in the PARC governing board meeting 13/11/24
Phthalates, DINCH and other plasticizers	Developmental, reproductive, immune and neurological effects	- Abundant HBM data from HBM4EU available - Multiple compounds part of the mandatory set of stressors and many compounds will be measured additionally by partners in the PARC HBM studies
Co-exposure to multiple pesticides (pyrethroids, organophosphates, neonicotinoids, ...)	Developmental and neurological effects	- HBM data already existing from HBM4EU, especially for organophosphates - Pyrethroids will additionally be a mandatory stressor to be measured in PARC (alongside TCPy (a metabolite of chlorpyrifos and chlorpyrifos-methyl). Moreover, other pesticides will also be measured (albeit on a voluntary basis).
Emergent battery chemicals, metals and metalloids: lithium, nickel and cobalt	Multiple	- Not mandatory to be measured stressors in PARC per se, but many partners have expressed their willingness to measure these via HBM. - Highlighted as a priority in the PARC governing board meeting 13/11/24 for the occupational setting, though given the demand for EVs and other technology, increased exposure in the general population might arise and therefore investigating the associated disease burden might be of interest.

PFAS	Developmental, reproductive, immune and neurological effects	<ul style="list-style-type: none">- Highlighted as a priority in the PARC governing board meeting 13/11/24- Multiple PFAS congeners part of the mandatory set of stressors in HBM4EU and in PARC HBM.
------	--	--

6. Summary and Conclusions

In the 1990's the burden of disease concept was developed by the World Health Organisation in cooperation with the World Bank and Harvard University. A part of the health burden is caused by exposure to environmental pollution i.e. the environmental burden of disease or EBD. EBD and related health impact assessments (HIA) are tools to inform policy making. Burden of disease estimations have been performed for air pollution and noise at a regular basis, but are largely lacking for chemical exposures. For air pollution there is a framework developed by WHO to calculate the burden based on a set of agreed exposure response functions (ERF). For chemical pollution this does not exist, and we are years behind. This is one of the reasons that this task (i.e., T6.2.4) on EBD was included in PARC, namely to advance EBD estimates on chemical exposures.

Within the T6.2.4 of PARC, three overarching aims were set for years 2-4 including improvements in data collection/generation, in methodology and in health impact indicators. To this end, we identified methodological challenges for EBD calculations and HIAs for chemicals in Chapter 3. We aimed at addressing those within the T6.2.4 case studies and for that purpose, we developed a checklist with the challenges to be addressed. We expect the methodological improvements related to these challenges to be an iterative process where methodological approaches will be improved over multiple rounds of case studies. Eventually, we plan a summary paper on the approach to EBD/HIA for chemicals recommended by PARC and the lessons learned from the case studies.

In Y2, several case studies were worked out to test EBD calculations for chemical exposures. The lessons learned from these case studies were:

1. Impact of pyrethroid-insecticide exposure and ADHD in Europe based on HBM data (VITO)
 - Considering the not too extensively available HBM data and epidemiological dose-response functions (between pyrethroids and ADHD), the preliminary estimated burden of disease associated with pyrethroids might be more substantial than initially thought (especially since exposure is omnipresent and since pyrethroids were thought of as a less harmful pesticide, what is not observed in NAMs for developmental neurotoxicity). However, the preliminary estimate has a large uncertainty as described in the published scientific article (Purece et al., 2024). More HBM coverage in Europe regarding pyrethroid metabolite measurements and more robust and harmonized epidemiological evidence for the association between pyrethroids and neurodevelopmental effects are warranted to estimate the burden more accurately.
2. Cardiovascular diseases attributable to lead exposure in European adults (DTU)
 - Multi-disciplinary and cross-country teams are an asset for the collection and interpretation of data needed to conduct an European Burden of disease study.
3. Burden of lead and methylmercury exposure on IQ loss in children in Europe – single – substance and mixture approach (ANSES)
 - Regarding lead and methylmercury environmental burden of disease case study, there is still a need to monitor lead and mercury exposure in Europe, particularly for women of childbearing age and children. In the literature review, we identified a general lack of mercury speciation, which introduces uncertainty related to inorganic or organic mercury exposure. As most health outcomes arise from co-exposure to chemical hazards, future EBD/HIA should work towards developing methodologies to assess mixtures of substances. This will allow identification of each chemical contribution to the disease burden, in order to help risk mitigation.
4. Impact of municipal solid waste incineration emissions on cancer-related mortality (FMUL)

- Both meta-analysis and population-based methods suggest a potential increase in lung cancer mortality attributable to municipal solid waste incineration emissions, but relevant uncertainties remain due to limitations in exposure data assessment and study designs, highlighting the need for robust, individual-level longitudinal studies to quantify this association better. The case-study also demonstrated the need for different and complementary methodological approaches in estimating health impacts of environmental exposures at the community level.
5. Burden of disease study on arsenic (As) exposure and lung, bladder, and skin cancer (Sciensano)
 - The findings of the As case study underscore the importance of addressing socio-economic disparities in environmental health risks, and the challenges arising from the lack of harmonized, SES-stratified data collection across countries, which leads to potentially underestimated burden of disease estimates.
 6. Influence of waste co-incineration in a cement plant on cancer burden (OI and NIJZ) ^[OBJ]
 - NIJZ identified a limited level of confidence concerning the exposure assessment due to uncertainties listed in the text and a need for more targeted studies.
 - OI found no increased cancer risk has been identified in the population living in areas potentially affected by pollution from co-incineration at the Anhovo cement plant.

Six additional case studies were started in Y4:

1. Possible impact of glyphosate-based herbicides and diabetes in EU countries (IRAS)
2. Incorporating a time-to-event model to improve the prediction of age of onset or death (RIVM)
3. Impact of exposure to PFAS and infectious diseases (VITO)
4. Exposure to cadmium and chronic kidney disease (Sciensano)
5. Exposure to a mixture of cadmium and lead and nephrotoxicity (Sciensano)
6. Probability modeling in burden of disease (UBA)

Individual results of the case studies can be found in Chapter 4. Here we discuss some general findings of the case studies of which some are still ongoing.

Exposure data for chemicals are lacking for several EU countries. This is seen for human biomonitoring (HBM) data and is considered as a critical limitation. High quality EU HBM data are a necessary prerequisite. Discussions are ongoing between the Council, the Parliament and the Commission to make HBM more sustainable i.e. by “systematically” collecting data about the levels of chemicals found in humans. Also, data gap filling techniques or exposure modeling techniques could be applied. For external exposures, exposure estimates for dietary exposure have been developed based on e.g. food frequency questionnaires and food measurements. Also here, detailed data are not always easily available or accessible for all EU countries.

Exposure is also not always equally distributed across populations. Differences in exposure exist, for example between age categories. Furthermore, discrepancies between the age categories for which ERFs were derived and the age categories for which exposure data are available, may complicate the issue. Exposure also differs for example by socio-economic status (SES) and one of the flagships of the Zero Pollution Ambition and the Sustainable Development Goals is to reduce exposure and health inequities and to leave no one behind. There is at the moment a big data gap on exposure differences by SES.

Humans are not exposed to one chemical at a time. Through HBM, a snapshot can be created to which mixtures of chemicals persons are exposed. Mixture exposure assessment is relevant for risk and impact assessment. For RA first steps have been made in PARC how these can be addressed.

As discussed above a framework with agreed ERFs to be used to calculate the burden of chemicals is lacking. Heterogeneity across studies and derived ERFs may limit comparability between studies (and meta-analysis). This is something that should be assessed in more detail and has already been done in the different case studies in which several new ERFs have been derived based on (systematic) reviews and meta-analysis (i.e. cardiovascular diseases attributable to lead exposure in European adults (DTU), environmental burden of lead (Pb) and methylmercury (MeHg) exposure on IQ loss in children in Europe – single – substance and mixture approach (ANSES), exposure to PFAS and infectious diseases (VITO)). New case studies focusing on endocrine disruption, immunological effects and related diseases are necessary to derive robust ERFs provided there is sufficient epidemiological evidence in the literature. A global registry framework for epidemiological studies with metadata on information that will be/has been collected could already enhance harmonization of data in the future². Furthermore, science is increasingly moving from single exposure models to multi-pollutant exposure models to assess the link with health effects. Sensitivity analysis remains necessary to address uncertainty.

Epidemiological studies using human biomonitoring measure exposure but also often effect markers (or response markers). These effect markers are often subclinical and cannot directly be linked to health effects. Also in experimental animal studies, adverse effects observed are often not directly linkable to human symptoms or pathologies. This asks for development of more mechanistic knowledge on how subclinical effects and adverse effects in animals can inform EBDs and HIAs. The combination of findings in experimental, mechanistic and epidemiological data will also lead to more transparency in the selection of health outcomes for which the burden can be calculated.

² <https://www.sciencedirect.com/science/article/pii/S1438463921001413?via%3Dihub>

References

- Agency for Toxic Substances and Disease Registry (ATSDR), 2020. Toxicological Profile for Lead. Atlanta (GA).
- Åkesson, A., Lundh, T., Vahter, M., Bjellerup, P., Lidfeldt, J., Nerbrand, C., Samsioe, G., Strömberg, U., Skerfving, S., 2005. Tubular and Glomerular Kidney Effects in Swedish Women with Low Environmental Cadmium Exposure 113, 1627–1631. <https://doi.org/10.1289/ehp.8033>
- Altenburger, R., Backhaus, T., Boedeker, W., Faust, M., Scholze, M., 2013. Simplifying complexity: Mixture toxicity assessment in the last 20 years. *Environ. Toxicol. Chem.* 32, 1685–1687. <https://doi.org/10.1002/etc.2294>
- Amzal, B., Julin, B., Vahter, M., Wolk, A., Johanson, G., 2009. Population Toxicokinetic Modeling of Cadmium for Health Risk Assessment 117, 1293–1301. <https://doi.org/10.1289/ehp.0800317>
- Ancona, C., Badaloni, C., Mataloni, F., Bolignano, A., Bucci, S., Cesaroni, G., Sozzi, R., Davoli, M., Forastiere, F., 2015. Mortality and morbidity in a population exposed to multiple sources of air pollution: A retrospective cohort study using air dispersion models. *Environ. Res.* 137, 467–474. <https://doi.org/10.1016/j.envres.2014.10.036>
- Antier, A.C., Dos Santos, C.S., Cauwer, D.B., Andujar L, G.J., Antier, by C., 2020. A survey on the uses of glyphosate in European countries This report and the related survey were coordinated Quoting this report.
- Aylward, L.L., Hays, S.M., Smolders, R., Koch, H.M., Cocker, J., Jones, K., Warren, N., Levy, L., Bevan, R., 2014. Sources of variability in biomarker concentrations. *J. Toxicol. Environ. Health. B. Crit. Rev.* 17, 45–61. <https://doi.org/10.1080/10937404.2013.864250>
- Backhaus, T., Faust, M., 2012. Predictive Environmental Risk Assessment of Chemical Mixtures: A Conceptual Framework. *Environ. Sci. Technol.* 46, 2564–2573. <https://doi.org/10.1021/es2034125>
- Barendregt, J.J., Veerman, J.L., 2010. Categorical versus continuous risk factors and the calculation of potential impact fractions. *J. Epidemiol. Community Health* 64, 209–212. <https://doi.org/10.1136/jech.2009.090274>
- Barone, E., Corrado, A., Gemignani, F., Landi, S., 2016. Environmental risk factors for pancreatic cancer: an update. *Arch. Toxicol.* 90, 2617–2642. <https://doi.org/10.1007/s00204-016-1821-9>
- BAuA, RIVM, KEMI, NEA, Danish EPA, European Chemicals Agency, 2023. ANNEX XV RESTRICTION REPORT; PROPOSAL FOR A RESTRICTION: Per- and polyfluoroalkyl substances (PFASs).
- Benbrook, C.M., 2016. Trends in glyphosate herbicide use in the United States and globally. *Environ. Sci. Eur.* 28, 1–15. <https://doi.org/10.1186/s12302-016-0070-0>
- Beronius, A., Zilliacus, J., Hanberg, A., Luijten, M., van der Voet, H., van Klaveren, J., 2020. Methodology for health risk assessment of combined exposures to multiple chemicals. *Food Chem. Toxicol.* 143, 111520. <https://doi.org/10.1016/j.fct.2020.111520>
- Bierkens, J., Smolders, R., Van Holderbeke, M., Cornelis, C., 2011. Predicting blood lead levels from current and past environmental data in Europe. *Sci. Total Environ.* 409, 5101–5110. <https://doi.org/10.1016/j.scitotenv.2011.08.034>
- Bil, W., Ehrlich, V., Chen, G., Vandebriel, R., Zeilmaker, M., Luijten, M., Uhl, M., Marx-Stoelting, P., Halldorsson, T.I., Bokkers, B., 2023. Internal relative potency factors based on immunotoxicity for the risk assessment of mixtures of per- and polyfluoroalkyl substances (PFAS) in human biomonitoring. *Environ. Int.* 171, 107727. <https://doi.org/10.1016/j.envint.2022.107727>
- Bil, W., Zeilmaker, M.J., Bokkers, B.G.H., 2022. Internal Relative Potency Factors for the Risk Assessment of Mixtures of Per- and Polyfluoroalkyl Substances (PFAS) in Human Biomonitoring. *Environ. Health Perspect.* 130, 77005. <https://doi.org/10.1289/EHP10009>
- Bladier, C. (ed.), Makowski, D., Albert, I., Bonvallot, N., Boudia, S., Brochot, C., Bruyere, O., Glorennec, P., Martin, P., Meek, B., Saegerman, C., Touvier, M., Watier, L.R.I., 2017. Illustrations et actualisation des recommandations pour l'évaluation du poids des preuves et l'analyse d'incertitude à l'ANSES TA - Expertise; Poids des preuves; Incertitude. ANSES A4 - GT MER - FRA, Bladier, Claire [ANSES (FRA)]; Makowski, David [INRA (FRA)]; Albert, Isabelle [INRA (FRA)]; Bonvallot, Nathalie [EHESP (FRA)]; Boudia, Soraya [Université Paris 5 (FRA)]; Brochot, Céline [INERIS (FRA)]; Bruyere, Olivier [Université de Liège (BEL)]; Glorennec, P.
- Bokkers, B.G.H., Mengelers, M.J., Bakker, M.I., Chiu, W.A., Slob, W., 2017. APROBA-Plus: A probabilistic tool to evaluate and express uncertainty in hazard characterization and exposure assessment of substances. *Food Chem. Toxicol.* 110, 408–417. <https://doi.org/https://doi.org/10.1016/j.fct.2017.10.038>
- Bokkers, B.G.H., Schuur, A.G., Zeilmaker, M.J., 2012. Age of onset in health impact assessment of chemical substances.

- Int. J. Environ. Heal. 6, 37–47. <https://doi.org/10.1504/IJENVH.2012.046853>
- Boobis, A.R., Ossendorp, B.C., Banasiak, U., Hamey, P.Y., Sebestyen, I., Moretto, A., 2008a. Cumulative risk assessment of pesticide residues in food. *Toxicol. Lett.* 180, 137–150. <https://doi.org/https://doi.org/10.1016/j.toxlet.2008.06.004>
- Boobis, A.R., Ossendorp, B.C., Banasiak, U., Hamey, P.Y., Sebestyen, I., Moretto, A., 2008b. Cumulative risk assessment of pesticide residues in food. *Toxicol. Lett.* 180, 137–150. <https://doi.org/https://doi.org/10.1016/j.toxlet.2008.06.004>
- Bopp, S.K., Barouki, R., Brack, W., Dalla Costa, S., Dorne, J.-L.C.M., Drakvik, P.E., Faust, M., Karjalainen, T.K., Kephelopoulos, S., van Klaveren, J., Kolossa-Gehring, M., Kortenkamp, A., Lebret, E., Lettieri, T., Nørager, S., Rüegg, J., Tarazona, J. V, Trier, X., van de Water, B., van Gils, J., Bergman, Å., 2018. Current EU research activities on combined exposure to multiple chemicals. *Environ. Int.* 120, 544–562. <https://doi.org/10.1016/j.envint.2018.07.037>
- Borenstein, M., Hedges, L. V, Higgins, J., Rothstein, H.R., 2021. *Introduction to meta-analysis*, 2nd ed. John Wiley & Sons, Nashville, TN.
- Buekers, J., Colles, A., Cornelis, C., Morrens, B., Govarts, E., 2018. Socio-Economic Status and Health : Evaluation of Human Biomonitoring Chemical Exposure to Per- and Polyfluorinated Substances across Status. <https://doi.org/10.3390/ijerph15122818>
- Calafat, A.M., 2016. Contemporary Issues in Exposure Assessment Using Biomonitoring. *Curr. Epidemiol. reports* 3, 145–153. <https://doi.org/10.1007/s40471-016-0075-7>
- Chang, E.T., Delzell, E., 2016. Systematic review and meta-analysis of glyphosate exposure and risk of lymphohematopoietic cancers. *J. Environ. Sci. Heal. - Part B Pestic. Food Contam. Agric. Wastes* 51, 402–434. <https://doi.org/10.1080/03601234.2016.1142748>
- Charalampous, P., Polinder, S., Wothge, J., von der Lippe, E., Haagsma, J.A., 2022. A systematic literature review of disability weights measurement studies: evolution of methodological choices. *Arch. Public Health* 80, 91. <https://doi.org/10.1186/s13690-022-00860-z>
- Chung, S., Chung, J.H., Kim, S.J., Koh, E.S., Yoon, H.E., Park, C.W., Chang, Y.S., Shin, S.J., 2014. Blood lead and cadmium levels and renal function in Korean adults. *Clin. Exp. Nephrol.* 18, 726–734. <https://doi.org/10.1007/s10157-013-0913-6>
- Crépet, A., Vasseur, P., Jean, J., Badot, P.M., Nesslany, F., Vernoux, J.P., Feidt, C., Mhaouty-Kodja, S., 2022. Integrating Selection and Risk Assessment of Chemical Mixtures: A Novel Approach Applied to a Breast Milk Survey. *Environ. Health Perspect.* 130. <https://doi.org/10.1289/EHP8262>
- de Araújo-Ramos, A.T., Passoni, M.T., Romano, M.A., Romano, R.M., Martino-Andrade, A.J., 2021. Controversies on Endocrine and Reproductive Effects of Glyphosate and Glyphosate-Based Herbicides: A Mini-Review. *Front. Endocrinol. (Lausanne)*. 12, 1–9. <https://doi.org/10.3389/fendo.2021.627210>
- De Jong, E., Voet, H. Van Der, Marx-stoelting, P., Bennekou, S.H., Zwartsen, A., Leys, A., Jeddi, M.Z., Wolterink, G., 2022. Roadmap for action on Risk Assessment of Combined Exposure to Multiple Chemicals (RACEMiC). <https://doi.org/10.2903/sp.efsa.2022.EN-7555>
- de Nijs, M., Mengelers, M.J.B., Boon, P.E., Heyndrickx, E., Hoogenboom, L.A.P., Lopez, P., Mol, H.G.J., 2016. Strategies for estimating human exposure to mycotoxins via food. *World Mycotoxin J.* TA - TT - 9, 831–846. <https://doi.org/10.3920/WMJ2016.2045 LK> - <https://utrechtuniversity.on.worldcat.org/oclc/9962063252>
- Den Hond, E., Govarts, E., Willems, H., Smolders, R., Casteleyn, L., Gehring, M.K., Schwedler, G., Seiwert, M., Fiddicke, U., Castaño, A., Esteban, M., Angerer, J., Koch, H.M., Sepai, O., Exley, K., Bloemen, L., Horvat, M., Le, K., Joas, A., Joas, R., Biot, P., Aerts, D., Koppen, G., Katsonouri, A., Hadjipanayis, A., Krskova, A., Maly, M., Ta, M., Rudnai, P., Kozepesy, S., Mulcahy, M., 2015a. First Steps toward Harmonized Human Biomonitoring in Europe: Demonstration Project to Perform Human Biomonitoring on a European Scale. *Res. | Child. ' s Heal.* 123, 255–263.
- Den Hond, E., Govarts, E., Willems, H., Smolders, R., Casteleyn, L., Gehring, M.K., Schwedler, G., Seiwert, M., Fiddicke, U., Castaño, A., Esteban, M., Angerer, J., Koch, H.M., Sepai, O., Exley, K., Bloemen, L., Horvat, M., Le, K., Joas, A., Joas, R., Biot, P., Aerts, D., Koppen, G., Katsonouri, A., Hadjipanayis, A., Krskova, A., Maly, M., Ta, M., Rudnai, P., Kozepesy, S., Mulcahy, M., 2015b. Research | Children ' s Health First Steps toward Harmonized Human Biomonitoring in Europe : Demonstration Project to Perform Human Biomonitoring on a European Scale 123, 255–263.
- Devleeschauwer, B., Haagsma, J.A., Angulo, F.J., Bellinger, C., Cole, D., Döpfer, D., Fazil, A., Eric, M.F., Mathers, C.D., McDonald, S.A., Pires, S.M., Speybroeck, N., 2015. Methodological Framework for World Health Organization

- Estimates of the Global Burden of Foodborne Disease 1–20. <https://doi.org/10.1371/journal.pone.0142498>
- Donato, F., Pira, E., Ciocan, C., Boffetta, P., 2020. Exposure to glyphosate and risk of non-hodgkin lymphoma and multiple myeloma: An updated meta-analysis. *Med. del Lav.* 111, 63–73. <https://doi.org/10.23749/mdl.v111i1.8967>
- Duan, W., Xu, C., Liu, Q., Xu, J., Weng, Z., Zhang, X., Basnet, T.B., Dahal, M., Gu, A., 2020. Levels of a mixture of heavy metals in blood and urine and all-cause, cardiovascular disease and cancer mortality: A population-based cohort study. *Environ. Pollut.* 263, 114630. <https://doi.org/10.1016/j.envpol.2020.114630>
- EFSA CONTAM Panel (EFSA Panel on Contaminants in the Food Chain), Schrenk, D., Bignami, M., Bodin, L., Chipman, J.K., del Mazo, J., Grasl-Kraupp, B., Hogstrand, C., Hoogenboom, L. (Ron), Leblanc, J.-C., Nebbia, C.S., Nielsen, E., Ntzani, E., Petersen, A., Sand, S., Vleminckx, C., Wallace, H., Barregård, L., Ceccatelli, S., Cravedi, J.-P., Halldorsson, T.I., Haug, L.S., Johansson, N., Knutsen, H.K., Rose, M., Roudot, A.-C., Van Loveren, H., Vollmer, G., Mackay, K., Riolo, F., Schwerdtle, T., 2020. Risk to human health related to the presence of perfluoroalkyl substances in food. *EFSA J.* 18, e06223. <https://doi.org/https://doi.org/10.2903/j.efsa.2020.6223>
- EFSA Panel on Contaminants in the Food Chain (CONTAM), 2010. Scientific Opinion on Lead in Food. *EFSA J.* 8, 1570. <https://doi.org/https://doi.org/10.2903/j.efsa.2010.1570>
- EFSA Panel on Contaminants in the Food Chain (CONTAM), Knutsen, H.K., Alexander, J., Barregård, L., Bignami, M., Brüschweiler, B., Ceccatelli, S., Cottrill, B., Dinovi, M., Edler, L., Grasl-Kraupp, B., Hogstrand, C., Hoogenboom, L. (Ron), Nebbia, C.S., Oswald, I.P., Petersen, A., Rose, M., Roudot, A.-C., Vleminckx, C., Vollmer, G., Wallace, H., Bodin, L., Cravedi, J.-P., Halldorsson, T.I., Haug, L.S., Johansson, N., van Loveren, H., Gergelova, P., Mackay, K., Levorato, S., van Manen, M., Schwerdtle, T., 2018. Risk to human health related to the presence of perfluorooctane sulfonic acid and perfluorooctanoic acid in food. *EFSA J.* 16, e05194. <https://doi.org/https://doi.org/10.2903/j.efsa.2018.5194>
- EFSA PPR Panel (EFSA Panel on Plant Protection Products and their Residues), 2013. Scientific Opinion on the relevance of dissimilar mode of action and its appropriate application for cumulative risk assessment of pesticides residues in food. *EFSA J.* 11, 3472. <https://doi.org/https://doi.org/10.2903/j.efsa.2013.3472>
- EFSA Scientific Committee, John, S., Bampidis, V., Benford, D., Bragard, C., Hernandez-jerez, A., Bennekou, S.H., Halldorsson, T.I., Machera, K., Naegeli, H., Koutsoumanis, K.P., Lambr, C., Nielsen, S.S., Schlatter, J.R., Schrenk, D., Silano, V., Dirk, J., Biesebeek, T., Turck, D., Younes, M., Benfenati, E., Testai, E., Dujardin, B., Lou, J., Dorne, C.M., Hogstrand, C., 2021. Guidance Document on Scientific criteria for grouping chemicals into assessment groups for human risk assessment of combined exposure to multiple chemicals. *EFSA J.* 19, e05194. <https://doi.org/https://doi.org/10.2903/j.efsa.2021.7033>
- EFSA Scientific Committee, More, S.J., Bampidis, V., Benford, D., Bennekou, S.H., Bragard, C., Halldorsson, T.I., Hern, A.F., Koutsoumanis, K., Naegeli, H., Schlatter, J.R., Silano, V., Nielsen, S.S., Schrenk, D., Turck, D., Younes, M., Benfenati, E., Castle, L., Cedergreen, N., Hardy, A., Laskowski, R., Leblanc, J.C., Kortenkamp, A., Ragas, A., Posthuma, L., Svendsen, C., Solecki, R., Testai, E., Dujardin, B., Kass, G.E.N., Manini, P., Jeddi, M.Z., 2019. Guidance on harmonised methodologies for human health, animal health and ecological risk assessment of combined exposure to multiple chemicals. *EFSA J.* 17, e05194. <https://doi.org/https://doi.org/10.2903/j.efsa.2019.5634>
- Etchie, A.T., Etchie, T.O., Adewuyi, G.O., Krishnamurthi, K., Saravanadevi, S., Wate, S.R., 2013. Prioritizing hazardous pollutants in two Nigerian water supply schemes: a risk-based approach. *Bull. World Health Organ.* 91, 553–561. <https://doi.org/10.2471/BLT.12.115774>
- European Chemicals Agency (ECHA), 2022. ANNEX XV RESTRICTION REPORT PROPOSAL FOR A RESTRICTION SUBSTANCE NAME (S): Per- and polyfluoroalkyl substances (PFAS) in firefighting foams CONTACT DETAILS OF THE DOSSIER SUBMITTER: European Chemicals Agency (ECHA).
- European Chemicals Agency (ECHA), 2017. WEIGHT OF EVIDENCE/UNCERTAINTY IN HAZARD ASSESSMENT. Background Document & Examples.
- European Commission, 2007. Scientific Committees Toolbox - Exposure [WWW Document]. URL https://ec.europa.eu/health/scientific_committees/opinions_layman/glossary/def/exposure-exposed-expose.htm#:~:text=Exposure can be divided into,the body via systemic circulation
- European Food Safety Authority (EFSA), 2024. Data collection [WWW Document]. URL <https://www.efsa.europa.eu/en/resources/data-collection>
- European Food Safety Authority (EFSA), 2013. International Frameworks Dealing with Human Risk Assessment of Combined Exposure to Multiple Chemicals. *EFSA J.* 11, 3313. <https://doi.org/https://doi.org/10.2903/j.efsa.2013.3313>
- European Food Safety Authority (EFSA), 2009. Cadmium in food - Scientific opinion of the Panel on Contaminants in the

- Food Chain. EFSA J. 7, 980. <https://doi.org/https://doi.org/10.2903/j.efsa.2009.980>
- European Food Safety Authority (EFSA), Anastassiadou, M., Choi, J., Coja, T., Dujardin, B., Hart, A., Hernandez-Jerez, A.F., Jarrah, S., Lostia, A., Machera, K., Mangas, I., Mienne, A., Schepens, M., Widenfalk, A., Mohimont, L., 2021. Cumulative dietary risk assessment of chronic acetylcholinesterase inhibition by residues of pesticides. EFSA journal. Eur. Food Saf. Auth. 19, e06392. <https://doi.org/10.2903/j.efsa.2021.6392>
- European Food Safety Authority (EFSA), Cascio, C., Dorne, J. Lou, Kass, G., Arcella, D., Binaglia, M., Dujardin, B., Fabrega, J., Heppner, C., Liem, D., 2022. Theme (concept) paper - Advancing Aggregate Exposure to Chemicals in EU (ExpoAdvance). EFSA Support. Publ. 19. <https://doi.org/10.2903/sp.efsa.2022.e201001>
- European Food Safety Authority (EFSA), Craig, P.S., Dujardin, B., Hart, A., Hernandez-Jerez, A.F., Hougaard Bennekou, S., Kneuer, C., Ossendorp, B., Pedersen, R., Wolterink, G., Mohimont, L., 2020a. Cumulative dietary risk characterisation of pesticides that have chronic effects on the thyroid. EFSA journal. Eur. Food Saf. Auth. 18, e06088. <https://doi.org/10.2903/j.efsa.2020.6088>
- European Food Safety Authority (EFSA), Craig, P.S., Dujardin, B., Hart, A., Hernández-Jerez, A.F., Hougaard Bennekou, S., Kneuer, C., Ossendorp, B., Pedersen, R., Wolterink, G., Mohimont, L., 2020b. Cumulative dietary risk characterisation of pesticides that have acute effects on the nervous system. EFSA journal. Eur. Food Saf. Auth. 18, e06087. <https://doi.org/10.2903/j.efsa.2020.6087>
- European Food Safety Authority (EFSA), Hart, A., Maxim, L., Siegrist, M., Cruz, C., Merten, C., Lahaniatis, M., Smith, A., 2019. Outcome of the Public Consultation on the draft Guidance on Communication of Uncertainty in Scientific Assessments. EFSA supporting publication 16, EN-1540. <https://doi.org/10.2903/sp.efsa.2019.EN-1540>
- Faust, M., Altenburger, R., Backhaus, T., Blanck, H., Boedeker, W., Gramatica, P., Hamer, V., Scholze, M., Vighi, M., Grimme, L.H., 2003. Joint algal toxicity of 16 dissimilarly acting chemicals is predictable by the concept of independent action. Aquat. Toxicol. 63, 43–63. [https://doi.org/10.1016/s0166-445x\(02\)00133-9](https://doi.org/10.1016/s0166-445x(02)00133-9)
- Faust, M., Altenburger, R., Backhaus, T., Blanck, H., Boedeker, W., Gramatica, P., Hamer, V., Scholze, M., Vighi, M., Grimme, L.H., 2001. Predicting the joint algal toxicity of multi-component s-triazine mixtures at low-effect concentrations of individual toxicants. Aquat. Toxicol. 56, 13–32. [https://doi.org/10.1016/s0166-445x\(01\)00187-4](https://doi.org/10.1016/s0166-445x(01)00187-4)
- Ferguson, K.D., Mccann, M., Katikireddi, S.V., Thomson, H., Green, M.J., Smith, D.J., Lewsey, J.D., 2020. Evidence synthesis for constructing directed acyclic graphs (ESC-DAGs): a novel and systematic method for building directed acyclic graphs 322–329. <https://doi.org/10.1093/ije/dyz150>
- Finley, B., Paustenbach, D., 1994. The benefits of probabilistic exposure assessment: three case studies involving contaminated air, water, and soil. Risk Anal. 14, 53–73. <https://doi.org/10.1111/j.1539-6924.1994.tb00028.x>
- Fischer, B.C., Rotter, S., Schubert, J., Marx-Stoelting, P., Solecki, R., 2020. Recommendations for international harmonisation, implementation and further development of suitable scientific approaches regarding the assessment of mixture effects. Food Chem. Toxicol. an Int. J. Publ. Br. Ind. Biol. Res. Assoc. 141, 111388. <https://doi.org/10.1016/j.fct.2020.111388>
- Forastiere, F., Stafoggia, M., Tasco, C., Picciotto, S., Agabiti, N., Cesaroni, G., Perucci, C.A., 2007. Socioeconomic status, particulate air pollution, and daily mortality: differential exposure or differential susceptibility. Am. J. Ind. Med. 50, 208–216. <https://doi.org/10.1002/ajim.20368>
- Fox, M.A., Brewer, L.E., Martin, L., 2017. An Overview of Literature Topics Related to Current Concepts, Methods, Tools, and Applications for Cumulative Risk Assessment (2007-2016). Int. J. Environ. Res. Public Health 14. <https://doi.org/10.3390/ijerph14040389>
- GBD 2019 Risk Factors Collaborators, 2020. Global burden of 87 risk factors in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. Lancet 396, 1223–1249. [https://doi.org/10.1016/S0140-6736\(20\)30752-2](https://doi.org/10.1016/S0140-6736(20)30752-2)
- GBD 2021 Diseases and Injuries Collaborators, 2024. Global incidence, prevalence, years lived with disability (YLDs), disability-adjusted life-years (DALYs), and healthy life expectancy (HALE) for 371 diseases and injuries in 204 countries and territories and 811 subnational locations, 1990–2021: A systema. Lancet 403, 2133–2161. [https://doi.org/10.1016/S0140-6736\(24\)00757-8](https://doi.org/10.1016/S0140-6736(24)00757-8)
- GBD 2021 Risk Factors Collaborators, 2024. Lead exposure (Appendix) https://www.healthdata.org/sites/default/files/methods_appendices/2021/zhao_lead_writeup_gbd2020_jw_up_dated_08072023.pdf.
- Genchi, G., Sinicropi, M.S., Lauria, G., Carocci, A., 2020. The Effects of Cadmium Toxicity. Int. J. Environ. Res. Public Heal. Rev. 17, 1–24.

- Gibb, H.J., Barchowsky, A., Bellinger, D., Bolger, P.M., Carrington, C., Havelaar, A.H., Oberoi, S., Zang, Y., O'Leary, K., Devleeschauwer, B., 2019. Estimates of the 2015 global and regional disease burden from four foodborne metals – arsenic, cadmium, lead and methylmercury. *Environ. Res.* 174, 188–194. <https://doi.org/https://doi.org/10.1016/j.envres.2018.12.062>
- Ginsberg, G.L., 2012. Cadmium risk assessment in relation to background risk of chronic kidney disease. *J. Toxicol. Environ. Health. A* 75, 374–390. <https://doi.org/10.1080/15287394.2012.670895>
- Global Burden of Disease Collaborative Network, 2020. Global Burden of Disease Collaborative Network. Global Burden of Disease Study 2019 (GBD 2019) Disability Weights. Institute for Health Metrics and Evaluation (IHME), Seattle, United States of America. <https://doi.org/https://doi.org/10.6069/1W19-VX76>
- Goldenman, G., Fernandes, M., Holland, M., Turgan, T., Nordin, A., Schoumacher, C., McNeill, A., 2019. THE COST OF INACTION; A socioeconomic analysis of environmental and health impacts linked to exposure to PFAS. The Nordic Council of Ministers, Copenhagen.
- Govarts, E., Gilles, L., Rodriguez, L., Santonen, T., Apel, P., Alvito, P., Anastasi, E., Raun, H., Andersson, A., Andryskova, L., Antignac, J., Appenzeller, B., Barbone, F., Barnett-itzhaki, Z., Barouki, R., Berman, T., Bil, W., Borges, T., Covaci, A., Csako, Z., Hond, E. Den, Buekers, J., Ca, A., Dvorakova, D., Fabelova, L., Fletcher, T., Frederiksen, H., Halldorsson, T.I., Gabriel, C., Ganzleben, C., Thomas, G., Haug, L.S., Horvat, M., Huuskonen, P., Imboden, M., Jagodic, M., Janasik, B., Janev, N., Karakitsios, S., Katsonouri, A., Klanova, J., Kokaraki, V., Kold, T., Koponen, J., Laeremans, M., Laguzzi, F., Lange, R., Lemke, N., Lignell, S., Karin, A., Lobo, J., Luijten, M., Makris, K.C., Mazej, D., Melymuk, L., Meslin, M., Mol, H., Niemann, L., Montazeri, P., Murawski, A., Nübler, S., Nunes, B., Olafsdottir, K., Palkovicova, L., Papaioannou, N., Pedraza-diaz, S., Piler, P., Plichta, V., Poteser, M., Probst-hensch, N., Rambaud, L., Rauscher-gabernig, E., Rausova, K., Remy, S., Riou, M., Rosolen, V., Rousselle, C., Rütther, M., Sarigiannis, D., Silva, M.J., Thomsen, C., Tkalec, Z., Tolonen, H., Trnovec, T., Uhl, M., Nieuwenhuysse, A. Van, Vasco, E., Verheyen, V.J., Viegas, S., Marie, A., Vogel, N., Vorkamp, K., Wasowicz, W., Weber, T., Stewart, L., Sepai, O., Schoeters, G., 2023. Harmonized human biomonitoring in European children, teenagers and adults: EU-wide exposure data of 11 chemical substance groups from the HBM4EU Aligned Studies (2014–2021). *Int. J. Hyg. Environ. Health* 249. <https://doi.org/10.1016/j.ijheh.2023.114119>
- Grandjean, P., Bellanger, M., 2017. Calculation of the disease burden associated with environmental chemical exposures: application of toxicological information in health economic estimation. *Environ. Health* 16, 123. <https://doi.org/10.1186/s12940-017-0340-3>
- Greco, S.L., MacIntyre, E., Young, S., Warden, H., Drudge, C., Kim, J., Candido, E., Demers, P., Copes, R., 2020. An approach to estimating the environmental burden of cancer from known and probable carcinogens: application to Ontario, Canada. *BMC Public Health* 20, 1017. <https://doi.org/10.1186/s12889-020-08771-w>
- Hänninen, O., Knol, A.B., Jantunen, M., Lim, T.A., Conrad, A., Rappolder, M., Carrer, P., Fanetti, A.C., Kim, R., Buekers, J., Torfs, R., Iavarone, I., Classen, T., Hornberg, C., Mekel, O.C.L., 2014. Environmental burden of disease in Europe: Assessing nine risk factors in six countries. *Environ. Health Perspect.* 122, 439–446. <https://doi.org/10.1289/ehp.1206154>
- Hill, A.B., 1965. THE ENVIRONMENT AND DISEASE: ASSOCIATION OR CAUSATION? *Proc. R. Soc. Med.* 58, 295–300. <https://doi.org/10.1177/003591576505800503>
- Huang, J., Luo, L., Wang, Yongbo, Yan, S., Li, X., Li, B., Huang, Q., Wang, Yunyun, Zhang, Y., Wei, S., Wang, Yibaina, Zeng, X., 2023. The burden of chronic kidney disease associated with dietary exposure to cadmium in China, 2020. *Environ. Pollut.* 336, 122434. <https://doi.org/https://doi.org/10.1016/j.envpol.2023.122434>
- IARC, 2017. International Agency for Research on Cancer. Monographs on the evaluation of carcinogenic risks to humans. Some organophosphate insecticides and herbicides volume 112.
- Impinen, A., Longnecker, M.P., Nygaard, U.C., London, S.J., Ferguson, K.K., Haug, L.S., Granum, B., 2019. Maternal levels of perfluoroalkyl substances (PFASs) during pregnancy and childhood allergy and asthma related outcomes and infections in the Norwegian Mother and Child (MoBa) cohort. *Environ. Int.* 124, 462–472. <https://doi.org/10.1016/j.envint.2018.12.041>
- International Agency for Research on Cancer (IARC), 2012. Arsenic, metals, fibres, and dusts | IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Lyon.
- International Programme on Chemical Safety & Organisation for Economic Co-operation and Development, 2004. IPCS risk assessment terminology, IPCS harmonization project document ; no. 1. World Health Organization.
- Ioannidou, S., Horváth, Z., Arcella, D., 2020. Harmonised collection of national food consumption data in Europe. *Food Policy* 96, 101908. <https://doi.org/10.1016/j.foodpol.2020.101908>

- Jain, R.B., 2019. Co-exposures to toxic metals cadmium, lead, and mercury and their impact on unhealthy kidney function. *Environ. Sci. Pollut. Res. Int.* 26, 30112–30118. <https://doi.org/10.1007/s11356-019-06182-y>
- Jakobsen, L.S., Fabricius, F.A., Nissen, J., Christensen, T., Andersen, R., Poulsen, M., 2019. The Disease Burden of Dietary Exposure to Inorganic Arsenic in Denmark, 2018. *Expo. Heal.* <https://doi.org/10.1007/s12403-019-00334-8>
- Jerrett, M., Burnett, R.T., Brook, J., Kanaroglou, P., Giovis, C., Finkelstein, N., Hutchison, B., 2004. Do socioeconomic characteristics modify the short term association between air pollution and mortality? Evidence from a zonal time series in Hamilton, Canada. *J. Epidemiol. Community Health* 58, 31–40. <https://doi.org/10.1136/jech.58.1.31>
- Joint FAO/WHO Expert Committee on Food Additives, 2022. Evaluation of certain food additives and contaminants; Ninety-first report of the Joint FAO/WHO Expert Committee on Food Additives. Geneva.
- Jonker, D., Freidig, A.P., Groten, J.P., de Hollander, A.E.M., Stierum, R.H., Woutersen, R.A., Feron, V.J., 2004. Safety evaluation of chemical mixtures and combinations of chemical and non-chemical stressors. *Rev. Environ. Health* 19, 83–139. <https://doi.org/10.1515/reveh.2004.19.2.83>
- Junghans, M., Backhaus, T., Faust, M., Scholze, M., Grimme, L.H., 2006. Application and validation of approaches for the predictive hazard assessment of realistic pesticide mixtures. *Aquat. Toxicol.* 76, 93–110. <https://doi.org/10.1016/j.aquatox.2005.10.001>
- Karrer, C., Andreassen, M., von Goetz, N., Sonnet, F., Sakhi, A.K., Hungerbühler, K., Dirven, H., Husøy, T., 2020. The EuroMix human biomonitoring study: Source-to-dose modeling of cumulative and aggregate exposure for the bisphenols BPA, BPS, and BPF and comparison with measured urinary levels. *Environ. Int.* 136, 105397. <https://doi.org/10.1016/j.envint.2019.105397>
- Knol, A.B., Petersen, A.C., Sluijs, J.P. Van Der, Lebre, E., 2009. Dealing with uncertainties in environmental burden of disease assessment. *Environ. Heal.* 8. <https://doi.org/10.1186/1476-069X-8-21>
- Kortenkamp, A., Backhaus, T., Faust, M., 2009. State of the art report on mixture toxicity - Final report, Executive summary. Brussels, Belgium.
- Krewski, D., Saunders-Hastings, P., Baan, R.A., Barton-Maclaren, T.S., Browne, P., Chiu, W.A., Gwinn, M., Hartung, T., Kraft, A.D., Lam, J., Lewis, R.J., Sanaa, M., Morgan, R.L., Paoli, G., Rhomberg, L., Rooney, A., Sand, S., Schünemann, H.J., Straif, K., Thayer, K.A., Tsaoun, K., 2022. Development of an Evidence-Based Risk Assessment Framework. *ALTEX* 39, 667–693. <https://doi.org/10.14573/altex.2004041>
- Krimsky, S., 2022. Glyphosate-Based Herbicides and Public Health: Making Sense of the Science. *J. Agric. Environ. Ethics* 35, 1–10. <https://doi.org/10.1007/s10806-021-09874-z>
- Künzli, I., Perez, L., Rapp, R., 2010. Air Quality and Health .
- Larsen, B., Sánchez-triana, E., 2023. Global health burden and cost of lead exposure in children and adults : a health impact and economic modelling analysis 7, 831–840. [https://doi.org/10.1016/S2542-5196\(23\)00166-3](https://doi.org/10.1016/S2542-5196(23)00166-3)
- Lesueur, C., Pathak, K. V., Pirrotte, P., Martinez, M.N., Ferguson, K.K., Barrett, E.S., Nguyen, R.H.N., Sathyanarayana, S., Mandrioli, D., Swan, S.H., Chen, J., 2022. Urinary glyphosate concentration in pregnant women in relation to length of gestation. *Environ. Res.* 203, 1–18. <https://doi.org/10.1016/j.envres.2021.111811>
- Lesueur, C., Pirrotte, P., Pathak, K. V., Manservigi, F., Mandrioli, D., Belpoggi, F., Panzacchi, S., Li, Q., Barrett, E.S., Nguyen, R.H.N., Sathyanarayana, S., Swan, S.H., Chen, J., 2021. Maternal urinary levels of glyphosate during pregnancy and anogenital distance in newborns in a US multicenter pregnancy cohort. *Environ. Pollut.* 280, 117002. <https://doi.org/10.1016/j.envpol.2021.117002>
- Liu, R., Zacharewski, T.R., Conolly, R.B., Zhang, Q., 2022. A Physiologically Based Pharmacokinetic (PBPK) Modeling Framework for Mixtures of Dioxin-like Compounds. *Toxics* 10. <https://doi.org/10.3390/toxics10110700>
- Makri, A., Stilianakis, N.I., 2008. Vulnerability to air pollution health effects. *Int. J. Hyg. Environ. Health* 211, 326–336. <https://doi.org/10.1016/j.ijheh.2007.06.005>
- Marshall, A.T., Betts, S., Kan, E.C., Mcconnell, R., Lanphear, B.P., Sowell, E.R., 2020. income with childhood brain outcomes. *Nat. Med.* 26. <https://doi.org/10.1038/s41591-019-0713-y>
- Meek, M.E.B., Boobis, A.R., Crofton, K.M., Heinemeyer, G., Raaij, M. Van, Vickers, C., 2011. Risk assessment of combined exposure to multiple chemicals: A WHO/IPCS framework. *Regul. Toxicol. Pharmacol.* <https://doi.org/10.1016/j.yrtph.2011.03.010>
- Montazeri, P., Thomsen, C., Casas, M., Bont, J. De, Haug, L.S., Maitre, L., Papadopoulou, E., Sakhi, A.K., Slama, R., Saulnier, P.J., Urquiza, J., Grazuleviciene, R., Andrusaityte, S., Mceachan, R., Wright, J., Chatzi, L., Basagaña, X., Vrijheid, M., 2021. Socioeconomic position and exposure to multiple environmental chemical contaminants in six European

- mother-child cohorts 222, 864–872. <https://doi.org/10.1016/j.ijheh.2019.04.002>. Socioeconomic
- Morello-Frosch, R., Zuk, M., Jerrett, M., Shamasunder, B., Kyle, A.D., 2011. Understanding the cumulative impacts of inequalities in environmental health: implications for policy. *Health Aff. (Millwood)*. 30, 879–887. <https://doi.org/10.1377/hlthaff.2011.0153>
- Morrens, B., Hond, E. Den, Schoeters, G., Coertjens, D., Colles, A., Nawrot, T.S., Baeyens, W., Henauw, S. De, Nelen, V., Loots, I., 2017. Human biomonitoring from an environmental justice perspective : supporting study participation of women of Turkish and Moroccan descent 1–9. <https://doi.org/10.1186/s12940-017-0260-2>
- National Research Council (US) Committee on Pesticides in the Diets of Infants and Children., 1993. Pesticides in the Diets of Infants and Children. Washington (DC): National Academies Press (US);, US. <https://doi.org/10.17226/2126>
- Navas-Acien, A., Tellez-Plaza, M., Guallar, E., Muntner, P., Silbergeld, E., Jaar, B., Weaver, V., 2009. Blood cadmium and lead and chronic kidney disease in US adults: a joint analysis. *Am. J. Epidemiol.* 170, 1156–1164. <https://doi.org/10.1093/aje/kwp248>
- New York State Department of Health, 1999a. Basic Statistics: About Incidence, Prevalence, Morbidity, and Mortality - Statistics Teaching Tools. [WWW Document]. URL <https://www.health.ny.gov/diseases/chronic/basicstat.htm>
- New York State Department of Health, 1999b. Basic Statistics: About Incidence, Prevalence, Morbidity, and Mortality - Statistics Teaching Tools. [WWW Document].
- Organisation for Economic Co-operation and Development (OECD), 2018. Considerations for assessing the risks of combined exposure to multiple chemicals; Series on Testing and Assessment No. 296.
- Ottensmeyer, I., Govarts, E., Lebret, E., Vermeulen, R., Schoeters, G., Vlaanderen, J., 2021. Network Analysis to Identify Communities Among Multiple Exposure Biomarkers Measured at Birth in Three Flemish General Population Samples. *Front. Public Heal.* 9, 1–10. <https://doi.org/10.3389/fpubh.2021.590038>
- Ougier, E., Fiore, K., Rousselle, C., Assunção, R., Martins, C., Buekers, J., 2021. Burden of osteoporosis and costs associated with human biomonitored cadmium exposure in three European countries: France, Spain and Belgium. *Int. J. Hyg. Environ. Health* 234. <https://doi.org/10.1016/j.ijheh.2021.113747>
- Pan, J., Plant, J.A., Voulvoulis, N., Oates, C.J., Ihlenfeld, C., 2010. Cadmium levels in Europe: implications for human health. *Environ. Geochem. Health* 32, 1–12. <https://doi.org/10.1007/s10653-009-9273-2>
- Parvez, S., Geron, R.R., Proctor, C., Friesen, M., Ashby, J.L., Reiter, J.L., Lui, Z., Winchester, P.D., 2018. Glyphosate exposure in pregnancy and shortened gestational length: A prospective Indiana birth cohort study. *Environ. Heal. A Glob. Access Sci. Source* 17, 1–12. <https://doi.org/10.1186/s12940-018-0367-0>
- Perkins, E.J., Gayen, K., Shoemaker, J.E., Antczak, P., Burgoon, L., Falciani, F., Gutsell, S., Hodges, G., Kienzler, A., Knapen, D., McBride, M., Willett, C., Doyle, F.J., Garcia-Reyero, N., 2019. Chemical hazard prediction and hypothesis testing using quantitative adverse outcome pathways. *ALTEX* 36, 91–102. <https://doi.org/10.14573/altex.1808241>
- Plass, D., Hilderink, H., Lehtomäki, H., Øverland, S., Eikemo, T.A., Lai, T., Gorasso, V., Devleeschauwer, B., 2022. Estimating risk factor attributable burden – challenges and potential solutions when using the comparative risk assessment methodology. *Arch. Public Heal.* 80, 1–12. <https://doi.org/10.1186/s13690-022-00900-8>
- Prüss-Üstün, A., Prüss-Üstün, A., Campbell-Lendrum, D., Corvalán, C., Woodward, A., 2003. Introduction and methods Assessing the environmental burden of disease at national and local levels.
- Purece, A., Thomsen, S.T., Plass, D., Spyropoulou, A., Machera, K., Palmont, P., Crépet, A., Benchrih, R., Devleeschauwer, B., Wieland, N., Scheepers, P., Deepika, D., Kumar, V., Sanchez, G., Bessems, J., Piselli, D., Buekers, J., 2024. A preliminary estimate of the environmental burden of disease associated with exposure to pyrethroid insecticides and ADHD in Europe based on human biomonitoring. *Environ. Heal. A Glob. Access Sci. Source* 23. <https://doi.org/10.1186/s12940-024-01131-w>
- Raffetti, E., Treccani, M., Donato, F., 2019. Cement plant emissions and health effects in the general population: a systematic review. *Chemosphere* 218, 211–222. <https://doi.org/10.1016/j.chemosphere.2018.11.088>
- Ramon, R., Murcia, M., Aguinagalde, X., Amurrio, A., Llop, S., Ibarluzea, J., Lertxundi, A., 2011. Prenatal mercury exposure in a multicenter cohort study in Spain. *Environ. Int.* 37, 597–604. <https://doi.org/10.1016/j.envint.2010.12.004>
- Redondo, H.G., Guillier, L., Bemrah, N., Jakobsen, L.S., Thomsen, S.T., Pires, S.M., 2023. Harmonized approach to estimate the burden of disease of dietary exposure to four chemical contaminants - A French study. *Sci. Total Environ.* 894, 164804. <https://doi.org/https://doi.org/10.1016/j.scitotenv.2023.164804>
- Rousselle, C., Tannous, M., PARC Task 2.1 partners, 2021. Partnership for the Assessment of Risks from Chemicals

Deliverable D2.1 Prioritisation criteria report WP 2 A common science-policy-agenda.

- Sacks, J.D., Stanek, L.W., Luben, T.J., Johns, D.O., Buckley, B.J., Brown, J.S., Ross, M., 2011. Review Particulate Matter – Induced Health Effects : Who Is Susceptible ? 446–454. <https://doi.org/10.1289/ehp.1002255>
- Satarug, S., 2018. Dietary Cadmium Intake and Its Effects on Kidneys 6, 1–23. <https://doi.org/10.3390/toxics6010015>
- Satarug, S., Vesey, D.A., Gobe, G.C., 2017. Health Risk Assessment of Dietary Cadmium Intake : Do Current Guidelines Indicate How Much is Safe ? 284, 284–288.
- Scalbert, A., Huybrechts, I., Gunter, M.J., 2019. The Food Exposome BT - Unraveling the Exposome: A Practical View, in: Dagnino, S., Macherone, A. (Eds.), . Springer International Publishing, Cham, pp. 217–245. https://doi.org/10.1007/978-3-319-89321-1_8
- Schinasi, L., Leon, M.E., 2014. Non-hodgkin lymphoma and occupational exposure to agricultural pesticide chemical groups and active ingredients: A systematic review and meta-analysis. *Int. J. Environ. Res. Public Health* 11, 4449–4527. <https://doi.org/10.3390/ijerph110404449>
- Scholten, B., Vlaanderen, J., Stierum, R., Portengen, L., Rothman, N., Lan, Q., 2020. A Quantitative Meta-Analysis of the Relation between Occupational Benzene Exposure and Biomarkers of Cytogenetic Damage 128, 1–7.
- Schwartz, J., 1994. Low-Level Lead Exposure and Children's IQ: A Meta-analysis and Search for a Threshold. *Environmental Res.* 42–55.
- Sharma, Raman, Sharma, M., Sharma, Ratika, Sharma, V., 2013. The impact of incinerators on human health and environment. *Rev. Environ. Health* 28, 67–72. <https://doi.org/10.1515/reveh-2012-0035>
- Shiue, I., Bramley, G., 2015. Environmental chemicals mediated the effect of old housing on adult health problems: US NHANES, 2009–2010. *Environ. Sci. Pollut. Res.* 22, 1299–1308. <https://doi.org/10.1007/s11356-014-3468-5>
- Silver, M.K., Fernandez, J., Tang, J., McDade, A., Sabino, J., Rosario, Z., Vélez Vega, C., Alshawabkeh, A., Cordero, J.F., Meeker, J.D., 2021. Prenatal Exposure to Glyphosate and Its Environmental Degradate, Aminomethylphosphonic Acid (AMPA), and Preterm Birth: A Nested Case-Control Study in the PROTECT Cohort (Puerto Rico). *Environ. Health Perspect.* 129, 57011. <https://doi.org/10.1289/EHP7295>
- Snoj Tratnik, J., Kocman, D., Horvat, M., Andersson, A.-M., Juul, A., Jacobsen, E., Ólafsdóttir, K., Klanova, J., Andryskova, L., Janasik, B., Wasowicz, W., Janev Holcer, N., Namorado, S., Coelho, I., Rambaud, L., Riou, M., Van Nieuwenhuysse, A., Appenzeller, B., Kolossa-Gehring, M., Weber, T., Esteban-López, M., Castaño, A., Gilles, L., Rodriguez Marti, L., Schoeters, G., Sepai, O., Govarts, E., 2022. Cadmium exposure in adults across Europe: Results from the HBM4EU Aligned Studies survey 2014–2020. *Int. J. Hyg. Environ. Health* 246, 114050. <https://doi.org/https://doi.org/10.1016/j.ijheh.2022.114050>
- Socianu, S., Bopp, S.K., Govarts, E., Gilles, L., Buekers, J., Kolossa-Gehring, M., Backhaus, T., Franco, A., 2022. Chemical Mixtures in the EU Population: Composition and Potential Risks. *Int. J. Environ. Res. Public Health* 19. <https://doi.org/10.3390/ijerph19106121>
- Sprong, R.C., Te Biesebeek, J.D., Chatterjee, M., Wolterink, G., van den Brand, A., Blaznik, U., Christodoulou, D., Crépet, A., Hamborg Jensen, B., Sokolić, D., Rauscher-Gabernig, E., Ruprich, J., Kortenkamp, A., van Klaveren, J., 2023a. A case study of neurodevelopmental risks from combined exposures to lead, methyl-mercury, inorganic arsenic, polychlorinated biphenyls, polybrominated diphenyl ethers and fluoride. *Int. J. Hyg. Environ. Health* 251, 114167. <https://doi.org/10.1016/j.ijheh.2023.114167>
- Sprong, R.C., van den Brand, A.D., van Donkersgoed, G., Blaznik, U., Christodoulou, D., Crépet, A., da Graça Dias, M., Hamborg Jensen, B., Morretto, A., Rauscher-Gabernig, E., Ruprich, J., Sokolić, D., van Klaveren, J.D., Luijten, M., Mengelers, M.J.B., 2023b. Combined chronic dietary exposure to four nephrotoxic metals exceeds tolerable intake levels in the adult population of 10 European countries. *Food Addit. Contam. - Part A* 40, 1568–1588. <https://doi.org/10.1080/19440049.2023.2272716>
- Swackhamer, D.L., Needham, L.L., Powell, D.E., Muir, D.C.G., 2009. Use of measurement data in evaluating exposure of humans and wildlife to POPs/PBTs. *Integr. Environ. Assess. Manag.* 5, 638–661. https://doi.org/10.1897/IEAM_2008-094.1
- The European Commission, 2023. COMMISSION IMPLEMENTING REGULATION (EU) 2023/2660 of 28 November 2023 renewing the approval of the active substance glyphosate in accordance with Regulation (EC) No 1107/2009 of the European Parliament and of the Council and amending Commission Implementi.
- Thomsen, S.T., Jakobsen, L.S., Redondo, H.G., Outzen, M., Fagt, S., Devleesschauwer, B., Hansen, M., Fabricius, F.A., Pires, S.M., 2022. Burden of Disease of Dietary Exposure to Four Chemical Contaminants in Denmark, 2019. *Expo. Heal.* 14, 871–883. <https://doi.org/10.1007/s12403-022-00461-9>

- Trasande, L., Zoeller, R.T., Hass, U., Kortenkamp, A., Grandjean, P., Myers, J.P., DiGangi, J., Bellanger, M., Hauser, R., Legler, J., Skakkebaek, N.E., Heindel, J.J., 2015. Estimating burden and disease costs of exposure to endocrine-disrupting chemicals in the European union. *J. Clin. Endocrinol. Metab.* 100, 1245–1255. <https://doi.org/10.1210/jc.2014-4324>
- Tyrrell, J., Melzer, D., Henley, W., Galloway, T.S., Osborne, N.J., 2013a. Associations between socioeconomic status and environmental toxicant concentrations in adults in the USA : NHANES 2001 – 2010 ☆. *Environ. Int.* 59, 328–335. <https://doi.org/10.1016/j.envint.2013.06.017>
- Tyrrell, J., Melzer, D., Henley, W., Galloway, T.S., Osborne, N.J., 2013b. Associations between socioeconomic status and environmental toxicant concentrations in adults in the USA : NHANES 2001 – 2010 ☆. *Environ. Int.* 59, 328–335. <https://doi.org/10.1016/j.envint.2013.06.017>
- U.S. Environmental Protection Agency Office of Pesticide Programs, 2001. Preliminary Cumulative Hazard and Dose-Response Assessment for Organophosphorus Pesticides: Determination of Relative Potency and Points of Departure for Cholinesterase Inhibition. Washington, D.C. 20460.
- United Nations Environment Programme and the World Health Organization, 2013a. Human exposure to POPs across the globe: POPs levels and human health implications. Results of the WHO/UNEP milk survey.
- United Nations Environment Programme and the World Health Organization, 2013b. Human exposure to POPs across the globe: POPs levels and human health implications. Results of the WHO/UNEP milk survey.
- Van den Brand, A.D., Bajard, L., Steffensen, I., Brantsæter, A.L., Dirven, H.A.A.M., Louisse, J., Peijnenburg, A., Ndaw, S., Mantovani, A., Santis, B. De, Mengelers, M.J.B., 2022. Providing Biological Plausibility for Exposure–Health Relationships for the Mycotoxins Deoxynivalenol (DON) and Fumonisin B1 (FB1) in Humans Using the AOP Framework 1, 1–21.
- van der Voet, H., Kruisselbrink, J.W., de Boer, W.J., van Lenthe, M.S., van den Heuvel, J.J.B.H., Crépet, A., Kennedy, M.C., Zilliacus, J., Beronius, A., Tebby, C., Brochot, C., Luckert, C., Lampen, A., Rorije, E., Sprong, C., van Klaveren, J.D., 2020. The MCRA toolbox of models and data to support chemical mixture risk assessment. *Food Chem. Toxicol. an Int. J. Publ. Br. Ind. Biol. Res. Assoc.* 138, 111185. <https://doi.org/10.1016/j.fct.2020.111185>
- van Klaveren, J.D., Kennedy, M.C., Moretto, A., Verbeke, W., van der Voet, H., Boon, P.E., 2015. The ACROPOLIS project: Its aims, achievements, and way forward. *Food Chem. Toxicol. an Int. J. Publ. Br. Ind. Biol. Res. Assoc.* <https://doi.org/10.1016/j.fct.2015.03.006>
- Vanacker, M., Quindroit, P., Angeli, K., Mandin, C., Glorennec, P., Brochot, C., Crépet, A., 2020. Aggregate and cumulative chronic risk assessment for pyrethroids in the French adult population. *Food Chem. Toxicol. an Int. J. Publ. Br. Ind. Biol. Res. Assoc.* 143, 111519. <https://doi.org/10.1016/j.fct.2020.111519>
- Vinti, G., Bauza, V., Clasen, T., Medlicott, K., Tudor, T., Zurbrügg, C., Vaccari, M., 2021. Municipal Solid Waste Management and Adverse Health Outcomes: A Systematic Review. *Int. J. Environ. Res. Public Health* 18. <https://doi.org/10.3390/ijerph18084331>
- Vrijheid, M., Martinez, D., Aguilera, I., Ballester, F., Basterrechea, M., Esplugues, A., Guxens, M., Larran, M., Lertxundi, A., Mendez, M., Murcia, M., Marina, L.S., Villanueva, C.M., Sunyer, J., 2012. Socioeconomic status and exposure to multiple environmental pollutants during pregnancy : evidence for environmental inequity ? <https://doi.org/10.1136/jech.2010.117408>
- World Health Organization, 2021. WHO global air quality guidelines, WHO global air quality guidelines. Particulate matter (PM2.5 and PM10), ozone, nitrogen dioxide, sulfur dioxide and carbon monoxide.
- World Health Organization (WHO), 2019. FAO/WHO Expert Consultation on Dietary risk assessment of chemical mixtures (Risk assessment of combined exposure to multiple chemicals). Geneva.
- Zahra, N., 2017. Perilous effects of heavy metals contamination on human health. *Pakistan J. Anal. Environ. Chem.* 18, 1–17. <https://doi.org/10.21743/pjaec/2017.06.01>
- Zang, Y., Devleeschauwer, B., Bolger, P.M., Goodman, E., Gibb, H.J., 2019. Global burden of late-stage chronic kidney disease resulting from dietary exposure to cadmium, 2015. *Environ. Res.* 169, 72–78. <https://doi.org/https://doi.org/10.1016/j.envres.2018.10.005>
- Zeilmaker, M.J., Bakker, M.I., Schothorst, R., Slob, W., 2010. Risk assessment of N-nitrosodimethylamine formed endogenously after fish-with-vegetable meals. *Toxicol. Sci.* 116, 323–335. <https://doi.org/10.1093/toxsci/kfq093>
- Zhang, L., Rana, I., Shaffer, R.M., Taioli, E., Sheppard, L., 2019. Exposure to glyphosate-based herbicides and risk for non-Hodgkin lymphoma: A meta-analysis and supporting evidence. *Mutat. Res. - Rev. Mutat. Res.* 781, 186–206.

<https://doi.org/10.1016/j.mrrev.2019.02.001>

Zheng, P., Afshin, A., Biryukov, S., Bisignano, C., Brauer, M., Bryazka, D., Burkart, K., Cercy, K.M., Cornaby, L., Dai, X., Dirac, M.A., Estep, K., Fay, K.A., Feldman, R., Ferrari, A.J., Gakidou, E., Gil, G.F., Griswold, M., Hay, S.I., He, J., Irvine, C.M.S., Kassebaum, N.J., Legrand, K.E., Lescinsky, H., Lim, S.S., Lo, J., Mullany, E.C., Ong, K.L., Rao, P.C., Razo, C., Reitsma, M.B., Roth, G.A., Santomauro, D.F., Sorensen, R.J.D., Srinivasan, V., Stanaway, J.D., Vollset, S.E., Vos, T., Wang, N., Welgan, C.A., Wozniak, S.S., Aravkin, A.Y., Murray, C.J.L., 2022. The Burden of Proof studies: assessing the evidence of risk 28. <https://doi.org/10.1038/s41591-022-01973-2>