WP6 Transferability of methodological framework

Task 6.1 Transferability to other stressors and health promoting factors linked to different policy domains

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BEST-COST is funded by the European Union's Horizon Europe programme under Grant Agreement No.101095408.

Deliverable Information	
Deliverable No. & Title	D6.1 Report describing the transferability of the EBD methodology to chemicals and green space accounting for availability of exposure data, population data, exposure-response functions, health data and knowledge gaps
Work Package No.	WP6
Work Package Title	Transferability of methodological framework
Lead Organisation	VITO
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Reviewers	Otto Hänninen (THL)
Nature	*Report*
Dissemination Level	*PU (Public)*
Deliverable Date	31/12/2025
Version Number	Version 1.1

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2 Executive Summary

The BEST-COST WP6 initiative demonstrates the strategic relevance of Environmental Burden of Disease (EBD) frameworks for quantifying health impacts from environmental exposures—extending beyond air pollution and noise to include chemicals and health-promoting factors such as green space.

While EBD methods are well-established for certain domains such as air pollution and environmental noise, their application to chemical exposures remains fragmented, often limited to isolated case studies. This gap undermines the EU's capacity to deliver on its Zero Pollution Ambition and the Chemicals Strategy for Sustainability, both of which call for more coherent, health-protective approaches to chemical risk and burden of disease assessment.

To support the One Substance, One Assessment (OSOA) legislative package—recently adopted by the European Parliament and Council—the WP6 work compared methodological EBD approaches across air, noise, and chemicals. It identified key challenges in exposure assessment, notably the lack of harmonised EU-wide human biomonitoring (HBM) data. Although initiatives like HBM4EU and PARC have advanced the exposure base, national representativeness and integration across domains, such as differences in socio-economic status, remain limited. The OSOA framework, which aims to streamline chemical assessments across EU legislation and to establish a common data platform, offers a timely opportunity to address these gaps. The use of self-administered micro-sampling could open new avenues for gathering high-resolution exposure data.

Chemical exposure assessment is further complicated by the fact that HBM as such cannot distinguish between exposure routes. Complementary environmental measurements such as non-targeted screening and effect-based monitoring are needed for informed regulatory action. Robust exposure-response functions (ERFs) are essential, based on internal or external exposure. While ERFs are available for air and noise, they are largely absent for chemicals, with lead being a rare exception. This lack of causal functions limits the ability to quantify existing health impacts using exposure data and to prioritise regulatory responses.

To illustrate feasibility, WP6 conducted EBD calculations for phthalates—specifically DMP and DBP—linked to diabetes and preterm birth, respectively. These pilot assessments revealed methodological flaws in existing meta-analyses, e.g. the inclusion of inconsistent odds ratios from individual studies and poor exposure reporting. This reinforces the need for transparent, standardised study designs and ERF development, especially for emerging compounds and mixtures of chemicals with similar mode of toxicological action. This very common situation of mixtures exposures with potential mixture effects, will require advanced statistical methods.

Incorporating chemical exposures and their health impacts into EBD frameworks is pivotal for delivering on the EU's Chemicals Strategy for Sustainability, which seeks to reduce the use of harmful substances and promote safer alternatives. By strengthening methodological coherence and data integration, EBD can become a cornerstone of the OSOA approach—enabling consistent, cross-sectoral health impact assessments that inform risk prioritisation and targeted interventions. This will directly support the EU's Zero Pollution commitment to a toxic-free environment under the European Green Deal and ensure that chemicals policy is grounded in health-relevant, science-based evidence.

For green space current HIA methods face notable limitations. The calculation methods developed for air pollution and noise cannot be directly transferred, largely due to the complexity and diversity of green space metrics as well as the multiple mechanisms by which green spaces affect health.

As health effects are the result of the totality of exposures such as noise, air pollution, chemicals, stress (i.e. the exposome) powerful statistical tools are needed to discover and test multi-stressor ERFs.

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3 Introduction

Environmental burden of disease (EBD) assessments are currently more standardised for exposures such as ambient air pollution and environmental noise, whereas methodologies for evaluating chemical exposures remain comparatively underdeveloped (Prüss-Ustün et al., 2003, 2011, 2017). Similarly, quantification of health benefits associated with exposure to green spaces is still in an early stage of methodological evolution.

This deliverable aims to draw conceptual and methodological parallels between well-established EBD frameworks and emerging approaches to assessing the health impacts of modern chemical agents and positive environmental factors, such as urban greenery. To enable this comparison, a methodological framework will be developed to systematically evaluate and contrast current practices across these domains.

Particular emphasis will be placed on the characterising exposure–response relationships, selecting and defining exposure metrics, and integrating them into EBD calculations for both chemical exposures and green space benefits. Illustrative case studies will be provided, focusing on phthalates as a representative chemical compound and green space as a health-promoting environmental factor if possible.

Table 1 gives an overview of the used abbreviations in the report.

Table 1. List of abbreviations

ADHD	Attention Deficit Hyperactivity Disorder
AF	Attributable Fraction
AGD	AnoGenital Distance
AML	Acute Myeloid Leukemia
AOP	Adverse Outcome Pathway
ATSDR	Agency for Toxic Substances and Disease Registry
BBP or BBzP	Benzyl butyl phthalate
BKMR	Bayesian Kernel Machine Regression
BoD	Burden of Disease
CDPC	Common Data Platform on Chemicals
CEP	EFSA Scientific Panel on Food Contact Materials, Enzymes and Processing Aids
CI	Confidence Interval
CRA	Comparative Risk Assessment
DALY	Disability Adjusted Life Year
DBP	Dibutyl phthalate
DCHP	Dicyclohexyl phthalate
DEHP	Di(2-ethylhexyl) phthalate
DEP	Diethyl phthalate
DiBP	Diisobutyl phthalate
DiDP	Diisodecyl phthalate
DiNP	Diisononyl phthalate
DM	Diabetes Mellitus
DnBP	Di-n-butyl phthalate

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DNEL	Derived No Effect Level
DnOP	Di-n-octyl phthalate
EBD	Environmental Burden of Disease
EC	European Commission
ECHA	European Chemicals Agency
EEA	European Environment Agency
EFSA	European Food Safety Authority
EHIS	European Health Interview Survey
ERF	Exposure Response Function
ETC	European Topic Center EEA
EU	European Union
GBD	Global Burden of Disease
GRADE	Grading of Recommendations, Assessment, Development, and Evaluations
HBM	Human Biomonitoring
HBM4EU	Human Biomonitoring for Europe
HBM-GV	Human Biomonitoring Guidance Value
HEAL	Health and Environment Alliance
HIA	Health Impact Assessment
IHME	Institute for Health Metrics and Evaluation
IQR	Inter Quartile Range
MMP	Monomethyl phthalate
NDVI	Normalised Difference Vegetation Index
NOAEL	No observed adverse effect level
OECD	Organization for Economic Co-operation and Development
OR	Odds Ratio
OSOA	One Substance One Assessment
PAF	Population Attributable Fraction
P25	25th percentile
Px	xth percentile
PFAS	Per- and polyfluorinated alkyl substances
$PM_{2.5}$	Particulate Matter with aerodynamic diameter <2.5µm
PoD	Point of Departure
RAC	Risk Assessment Committee ECHA
REACH	Regulation on Registration, Evaluation, Authorisation and Restriction of Chemicals
RoHS	Directive on Restriction of Hazardous Substances
USEPA	U.S. Environmental Protection Agency
YLD	Years Lived with Disability
YLL	Years of Life Lost

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4 Transferability to chemicals

Burden of disease (BoD) calculations are common in air pollution and noise research. However, there is limited experience with other stressors, such as chemicals, e.g., phthalates, bisphenols, flame retardants, etc. (Hänninen et al., 2014). While exposure to air pollution is generally decreasing in the European Union (EU), its health impacts remain large (EEA, 2024). For other stressors, it is expected that exposure and impact will increase in the future, e.g. the global plastic use is projected to triple between 2019 and 2060 (OECD, 2022). Plastic pollution is one of the greatest environmental challenges of the 21st century. It causes damage to ecosystems as well as human health. In parallel with increased use, there is growing recognition of the health implications of micro- and nanoplastics, and plastic-associated chemicals. Therefore, the goal of this deliverable is to explore and define how the methodology for air pollution and noise BoD calculations can be "transferred" to other stressors, such as phthalates, a class of chemicals present in most plastics. This aligns with the Zero Pollution Ambition, which focuses on air and noise pollution but also on plastics (microplastics) (EC, 2024).

In the HBM4EU study, an overview was created of different sources, exposure pathways, and potential health effects related to phthalate exposure (Figure 1). As can be seen, the expected health effects are miscellaneous.

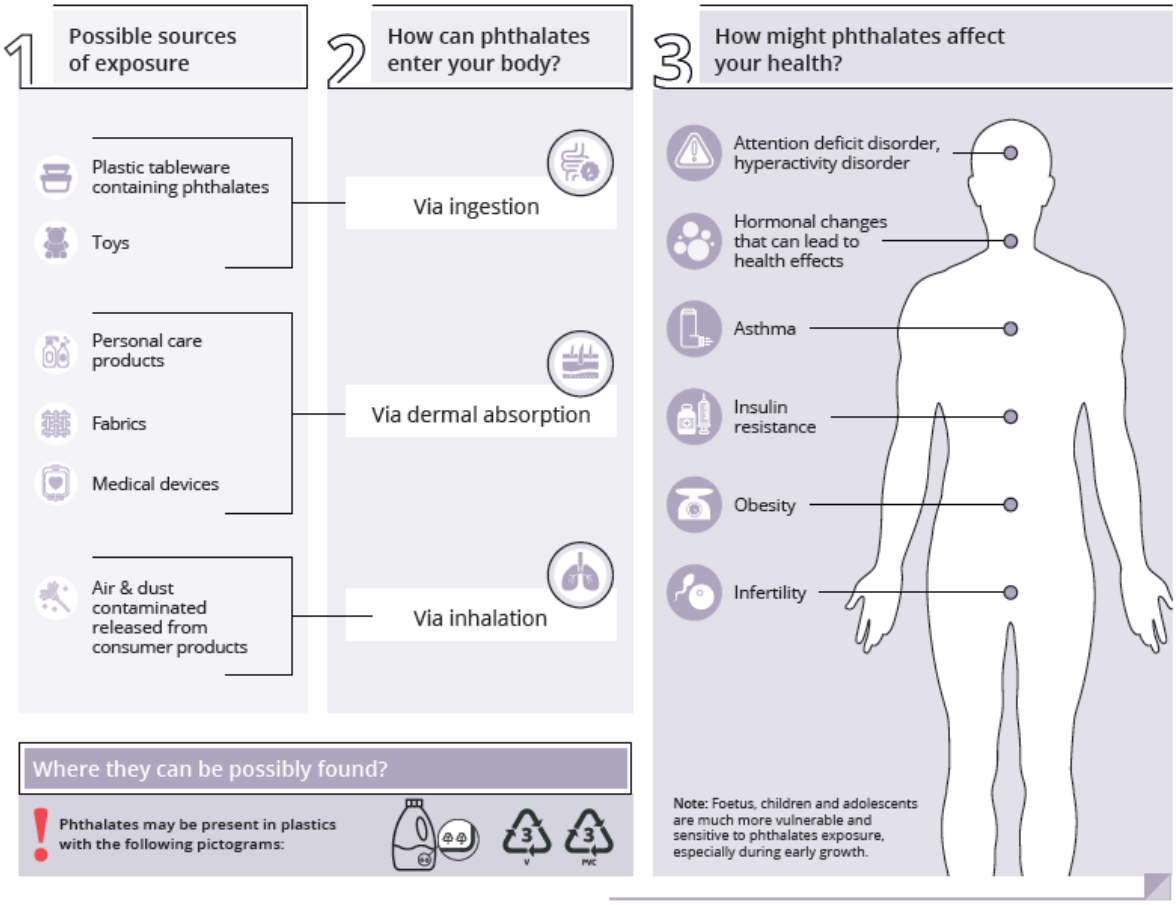

Figure 1 Overview of health effects phthalates (source: (HBM4EU, 2022))

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Phthalates form a family of synthetic chemicals with a wide variety of uses and are found everywhere in the environment. Some phthalates can interfere with our hormone system and are therefore regulated[1]. The "Candidate List" of substances of very high concern (SVHC) 'for authorisation'[2] contains several phthalates that are harmful to reproduction. There are 14 phthalates on the REACH[3] "Authorisation List". Phthalates that are classified as toxic to reproduction (Repr. 1B) are "restricted". Directives tackling phthalates are a.o. the Toy Safety Directive[4], Waste Framework Directive[5], the RoHS Directive[6] and regulations on food contact materials[7].

The aim of this chemical part was twofold.

1. To investigate whether the framework that exists for BoD calculations of air pollution and noise could be easily transferred to chemical substances. Burden of disease calculations for chemicals are still in their early stages of development. For air pollution, a framework from the World Health Organization (WHO) exists, with proposed exposure-response functions to calculate the burden. This is absent concerning chemicals.

2. To apply BoD calculations to phthalates, which are a concern for human health.

4.1 Methods

4.1.1 Methodology transfer framework in BEST-COST

In BEST-COST, a methodological framework will be developed that compares how EBD calculations are performed for air pollution and noise, and how this can be transferred to chemical substances, such as phthalates, for which ad hoc EBD assessments exist.

For air pollution and noise, the methodology is described in the BEST-COST "Methodological report for the quantification of environmental burden of disease" (Task 1.6; Deliverable 1.4).

4.1.2 Proof of concept: phthalates

To obtain an overview of **existing studies** that have performedEBD or cost calculations related to phthalate exposure, a comprehensive literature search was conducted. Searches were performed in the PubMed and Web of Science databases using the following terms: "DALY"

[1] https://echa.europa.eu/nl/hot-topics/phthalates
[2] REACH Authorisation means that a chemical substance can only be used further for very specific uses and for a stricly limited number of years after which 'phase out' is reached.
[3] https://www.echa.europa.eu/regulations/reach/legislation
[4] https://ec.europa.eu/commission/presscorner/detail/en/ip_25_1039
[5] https://environment.ec.europa.eu/topics/waste-and-recycling/waste-framework-directive_en
[6] https://environment.ec.europa.eu/topics/waste-and-recycling/rohs-directive_en
[7] https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32023R1442

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and “phthalate”, or “cost” and “phthalate”. This was further complemented by expert input on relevant studies.

In a second step, the aim was to summarise existing **systematic reviews with meta-analyses** addressing phthalate exposure and associated health effects. A targeted search in PubMed was carried out using the terms “phthalate” and “meta-analysis”, supplemented by umbrella reviews identified in the literature.

Additionally, restriction **reports** submitted to ECHA and evaluated by the SEAC were screened for their use of epidemiological studies in health impact assessments. Recent reports from major international organisations—including ATSDR, EFSA, ECHA, USEPA, and OECD—were reviewed for epidemiological evidence on phthalate-related health effects. Also, studies underpinning the recently established human biomonitoring guidance values for phthalates were analysed for reported health outcomes.

The compiled evidence from these sources was integrated into the **proof-of-concept calculations** for the EBD of phthalates. Two case studies were worked out in which a meta-analysis was conducted, exposure-response curves were derived, and EBD calculations were performed.

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4.2 Results

4.2.1 Methodological transfer of the EBD framework to other stressors than air and noise pollution

Commonly used metrics to express the BoD attributable to a risk factor are the attributable fraction (AF), the attributable number of cases, YYears of Life Lost (YLL), Years Lived with Disability (YLD) and Disability Adjusted Life Years (DALYs) or costs. Part of the BoD may be related to the exposure to environmental stressors, i.e. the environmental burden of disease (EBD). The commonly used methodology for calculating EBD is the comparative risk assessment (CRA) approach when relative risks are available (see Figure 2). For noise annoyance and cancer effects from e.g. chemicals, a different approach is often used, based on an absolute or unit risk (see Figure 3) (Hänninen et al., 2014). Detailed information on the methodological aspects of these calculations can be found in the BEST-COST Deliverable 1.4. The following data are required in the CRA approach to calculate the EBD: exposure data, population data, exposure-response function (ERF) and total BoD data. The CRA framework is commonly used in ambient air pollution studies (Kienzler et al., 2025) or for indoor air (Asikainen et al., 2016) , but it is unclear what transferability issues arise when it is applied to chemicals. Details on exposure, ERF, population, and health data are described below.

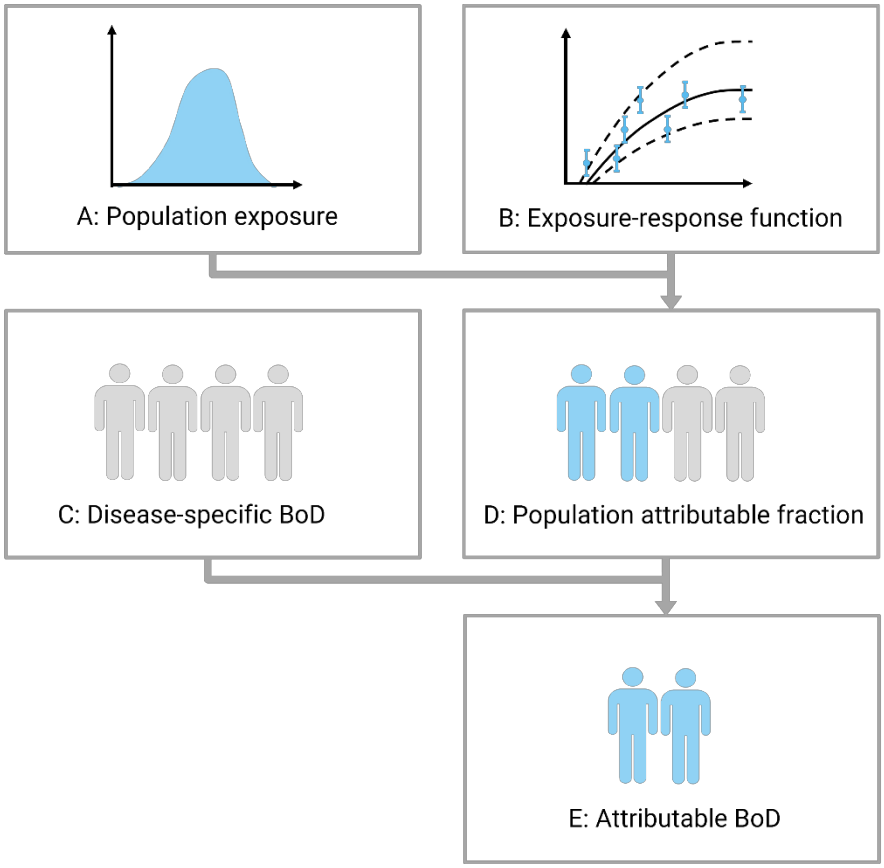

Figure 2. Schematic overview of the steps involved in calculating the attributable burden of disease for one exposure-outcome pair starting from an ERF based on a relative risk. One element of the illustration (person shape) originates from Wikimedia commons.

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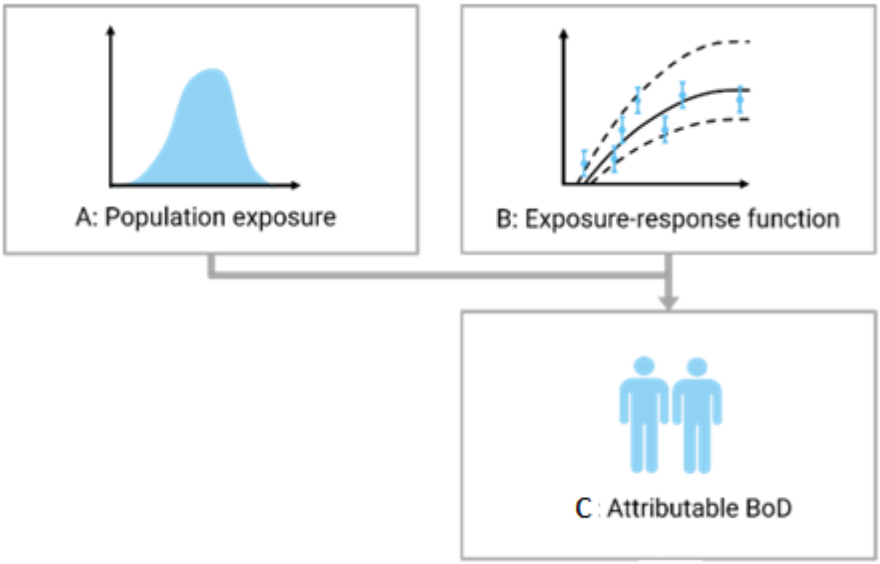

Figure 3. Schematic overview of the steps involved in calculating the environmental burden of disease for one exposure-outcome pair starting from an ERF based on an absolute risk. One element of the illustration (person shape) originates from Wikimedia commons.

1) Exposure

Everyone is exposed to chemicals, but not everyone to the same extent. In air pollution studies, estimates of the burden are often made at the country, regional or city level. Detailed air pollution maps are available for $PM_{2.5}$ for example (e.g. grid 1x1 km or finer). This type of data is not available for chemicals such as phthalates and is also not necessary depending on the exposure route through which people are exposed. If the geographical variation of the exposure is large, then detailed exposure data at a high geographical scale are required e.g. the concentration of NO_2 in air drops significantly when the distance (in meters) to the road increases (WHO, 2013), the exposure to PFAS through local food consumption decreases significantly when the distance (in kilometers) to production facilities or factories applying PFAS increases (Lasters et al., 2022). For other chemicals, the main exposure route may be food. For phthalates specifically, contamination is related to food handling and packaging (HBM4EU, 2022). Given the internationalisation of food markets, the geographic variability in exposure to phthalates will likely be smaller than that to air pollution, for example. For chemicals that are likely to have a large spatial variation in concentration in environmental media, and for which these media are a basis exposure route, the availability of exposure data at a fine geographical scale is a prerequisite.

Exposure to chemicals can be assessed through human biomonitoring (HBM) studies or through assessment of exposure through specific sources, e.g. foods. An advantage of the HBM data is that internal exposure is measured through biomarkers in the body itself, thus providing a clear snapshot of the real exposure. These biomarkers give an idea of the integrated exposure (i.e. through multiple exposure routes). Compared with calculated or modelled external exposure estimates, HBM provides an integrated picture of the exposure. However, HBM data has the disadvantage that exposure cannot be disentangled by exposure routes, i.e., it cannot be traced back to specific sources.

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Another disadvantage of some current HBM data at this stage is that they are not all representative of a particular region or country. This depends on the HBM campaign itself. Therefore, it is important to perform a representative sampling (number of participants, age, sex, region) whenever possible. The recent HBM4EU project (www.hbm4eu.eu), set up to advance HBM in Europe, provides metadata on whether or not monitoring campaigns were representative of a country. The European HBM dashboard (https://hbm.vito.be/eu-hbm-dashboard) provides an overview of HBM exposure data. The database shows that there are many relevant challenges regarding exposure data (HBM data is only available for some countries, selected age groups, etc.). These need to be tackled by more primary data or adequate gap-filling techniques (Plass et al., 2025). For air pollution ($PM_{2.5}$), exposure models applied by the European Environment Agency (EEA) cover the whole EU at high resolution (1x1 km)[8].

Exposure varies among populations. Since exposure (external or internal) percentiles are in most cases given for chemicals (P25, P50, P75…), categorical calculations of the health impact can be assessed rather than continuous calculations. More emphasis should be placed on how exposure distributions differ across persons of different socio-economic status (SES), highlighting the exposure and health inequities among them. The first flagship of the Zero Pollution Ambition and the 10th Sustainable Development Goal call for a reduction in these inequities.

An amendment (Amendment 486) to the One Substance One Assessment (OSOA) regulation concerning the Common Data Platform on Chemicals (CDPC, published in December 2024) mentions the obligation to conduct a regular EU-wide Human Biomonitoring (HBM) study. This would lead to better coverage of information on chemical exposure. Discussions are ongoing between the Council, the Parliament and the EC on how to address this issue.

2) Population data

In air pollution or noise EBD studies, air pollution concentration or noise maps are overlaid with population data (based on home address) to get a kind of population (weighted) exposure. Since people move around in space (e.g., going to work), these maps are rough approximations of reality. For HBM studies, as explained above (see exposure section), this type of exposure assessment is not yet possible. It has to be assumed that the measured exposure in a certain population is representative of the population in which the EBD will be calculated.

3) Exposure-response function (ERF)

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.

For air pollution data, ERFs are proposed by international organisations such as WHO. For example, for morbidity outcomes, there are the REVIHAAP studies, which are being extended (WHO, 2013; Forastiere et al., 2024; EMAPEC, 2024). This process is completely lacking for

[8] https://www.eea.europa.eu/publications/assessing-the-risks-to-health/assessing-the-risks-to-health

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most chemical data. Often, EBD calculations are based on a single epidemiological study (supported by toxicological data and mechanistic information).

Therefore, more effort should be made to improve the application of more robust ERFs. One of the options is to explore the feasibility of systematic reviews (and meta-analysis) for priority chemicals for which health concerns exist. If data is lacking or there are very few studies, this is a data gap. In regulatory toxicology, it may be possible to determine whether exposure to a chemical is toxic or not, but more information is needed to manage the burden in case of toxicity. If a chemical to which we are exposed is toxic, what does it mean for the environmental burden of disease?

In the BEST-COST project, disease models were developed for air pollution and noise. These models are qualitative representations of the health outcomes that are causally related to exposure. The identification of disease models is based on a) biological plausibility (based on epidemiological studies, toxicity studies and human clinical studies) and b) support for causality. For the latter, epidemiological studies should meet specific criteria, such as those of the World Cancer Research Fund, which classify the association as convincing, probable, limited, or unlikely. Another example to assess the quality of epidemiological studies is the GRADE criteria (Grading of Recommendations, Assessment, Development, and Evaluations). This evaluation of the probability of causality is in the domain of air pollution often done by large organisations like WHO or USEPA. However, such a framework is lacking for chemicals. What does exist are reports in which the toxicity of some chemicals is assessed by ATSDR[9], USEPA, EFSA etc. considering evidence mainly from toxicity studies but also evidence from epidemiological studies to some extent, which could serve as a starting point for selecting outcomes for which the burden can be calculated. The results of the evaluation of toxicity may differ between the organisations. Also, in chemical restriction dossiers submitted to ECHA, often evaluations of the possible health impact in the general population due to exposure to chemicals are made (evidence, limited evidence, suggestive); see for example the dossier submitted on a group restriction for PFAS (Figure 4). In some cases, EBD estimates are performed for chemicals starting from opinions from individual research organisations or a group of organisations or scientists based on their interpretation of the scientific literature (Trasande et al., 2015; Ougier et al., 2021).

[9] https://www.atsdr.cdc.gov/

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Health impact category	Type of health effects
Immune outcomes	Reduced vaccine responses in children
	Increased propensity of lower respiratory tract infections
	Increased risk of atopic dermatitis
	Asthma- and allergy-related outcomes (hypersensitivity)
Liver toxicity and metabolic disruption	Increased serum alanine transferase (ALT) which is a marker of liver toxicity and fatty liver diseases
	Increased total and LDL-cholesterol
	Increased risk of cardiovascular diseases
Reproduction and development	Reduced birth weight
	Effects on male and female fertility
	Effects on sex hormones and related outcomes
	Preterm delivery
	Miscarriage and preeclampsia
Carcinogenicity	Increased risk of renal cell carcinoma and kidney cancer
Thyroid functioning	Thyroid disease or changes in thyroid hormones

Table legend

Evidence of an association between exposure and health effect, strengthened by new studies.
Limited evidence of an association between exposure and health effect, supported by new studies.
Suggestive evidence of an association between exposure and health effect, inconclusive new studies.

Figure 4. Current health impact in the general population due to exposure to the most analysed PFAS (BAuA et al., 2023).

There is still a field of tension between toxicologists and epidemiologists, each promoting their own discipline. However, the ECHA chemical safety assessment Chapter R.7a states that biologically relevant findings seen in experimental animals should be considered relevant to humans unless convincing evidence exists to the contrary. The inclusion of epidemiological studies in the derivation of health-based guidance values (values below which exposure is considered as no risk for human health) is increasing; see re-evaluation of BPA and PFAS by EFSA where these values are based on effects on the immune system, based on epidemiological studies (EFSA, 2020; EFSA Panel on Food Contact Materials Enzymes and Processing Aids et al., 2023).

Starting from findings in epidemiological studies, supported by mechanistic evidence (e.g. adverse outcome pathways or AOPs) and toxicity studies, estimates on the burden could be performed leaning on the precautionary principle. The GBD estimated the health burden for certain risk factors (e.g. occupational hazards, ambient air pollution, residential exposure to radon, or childhood lead exposure). According to Grandjean and Bellanger, the GBD project relies upon expert input to select those exposure-outcome relationships that meet the stringiest criteria of causality. As a consequence, some causal connections are favoured. In environmental health, interventions are too complex or long-lasting to provide the necessary documentation of the adverse impacts of environmental risk factors. Therefore, Grandjean and Bellanger conclude that a "realistic and precautionary approach" can be taken to characterise the possible impact of substances (Grandjean and Bellanger, 2017).

Adverse outcome pathways (AOPs) give more insight in biochemical and physiological pathways and help to address causality. Information from observational studies, in vivo studies, in vitro studies, etc. are brought together in AOPs. The OECD defines qAOPS as "*an assembly of key events (KEs) supported by descriptions of how the KEs can be measured and the accuracy and precision with which the measurements are made along with key event relationships (KERs) supported by a quantitative understanding of what magnitude and/or duration of change in the upstream KE is needed to evoke some magnitude of change in the*

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downstream KE"[10]. An AOP starts at the molecular level where a chemical interacts with a biological target which leads to a sequential series of higher-order events to produce an adverse health effect. Modified Bradford Hill criteria have been recently applied for evaluating KERs in quantitative AOP models and can serve as a starting point on the causality ladder (Spînu et al., 2022).

Selection of ERF and ERF modelling can also benefit from integrating data across multiple evidence bases, when data across the exposure range are sparse. For example, integrating available epidemiologic, biomarker, and animal data resulted in more precise estimates of the risk of benzene exposure and acute myeloid leukemia (AML), although the large between-study heterogeneity hampered the interpretation of the results (Scholten et al., 2022).

Currently, estimates of the EBD related to chemical exposure are performed on an *ad hoc* basis. Humans are exposed to a mixture of chemicals, which may have independent health effects or interact with each other. Science is increasingly moving from single-exposure models to multi-pollutant exposure models to assess the link with health effects. Techniques such as Bayesian Kernel Machine Regression (BKMR) and quantile G computation are for example applied in assessing the exposure to a mixture of metals and loss of IQ in children (Fruh et al., 2021; Kim et al., 2023). Another possibility is the application of relative potency factors (Sprong et al., 2023). Also, the correction for overlap to avoid double-counting is sometimes applied (Hauser et al., 2015). With respect to EBD calculations for air pollution, typical scenarios chosen to account for co-pollutant exposure include not summing the impacts of the outcomes, omitting certain exposure-response associations, summing and correcting for overlap, and using multi-pollutant models (BEST-COST deliverable 1.4). Through the use of advanced multipollutant models for mixtures, synergistic or protective effects could be captured but extensive data representing the exposome are needed. The exposome is the comprehensive measure of all environmental exposures an individual experiences throughout their life, from conception to death, including factors like chemicals, diet, lifestyle, infections, stress, and social conditions, and how these collectively influence health and disease, serving as the environmental counterpart to the genome[11].

4) Health data (total burden of disease)

In the comparative risk assessment approach, the population attributable fraction (PAF), i.e., the fraction of the disease related to exposure to the stressor, is estimated. This PAF is applied to the total BoD. BoD estimates are available from international organisations, such as WHO, IHME or national databases.

For chemical exposure, sometimes biomarkers of effect are measured in epidemiological studies, which in some cases may already provide information at an early stage whether exposure to the chemical can be harmful and whether a warning should be issued. These biomarkers of effect are not directly linked to disease outcomes. The understanding of the link between early effect markers and the development of the disease in se is a research area in development.

To conclude, EBD calculations are possible for chemicals, but not in the way they are done for air pollution. In any case, more effort should be put into exposure assessment and the

[10] https://www.oecd.org/en/topics/sub-issues/testing-of-chemicals/adverse-outcome-pathways.html
[11] https://exposomemoonshot.org/globalexposomeforum/

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development and application of robust ERFs considering meta-analysis and the weight of the evidence.

An overview of the methodology applied in the domains of air pollution, noise and chemicals is given in Table 2.

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Table 2. Overview of EBD methodology applied in different research domains of air pollution, noise and chemicals.

EBD framework	Outdoor air pollution	Noise pollution	Chemicals
Exposure	External	External (house façade)	External (e.g. food) and internal (HBM) exposure; External exposure can be aggregated over different exposure routes (oral, inhalation, dermal)
	Maps (resolution e.g. 1x1 km)	Maps	Geospatial relevancy depending on exposure route: e.g. phthalates vs lead. For the general population, main sources of phthalates are food contact materials, consumer products, etc. This means geographic info on concentrations in the environment are less relevant to determine exposure. For lead exposure, exposure can take place via local emissions, leaded water tubes in older houses which means geospatial info is relevant for exposure.
	Spatial static data although dynamic exposure models exist	Spatial static data	HBM: integrated snapshot exposure covering different sources; external exposure via food: food frequency questionnaires account for intake frequency on a daily, weekly, monthly basis
	Country level, city level	Mostly focusing on exposure assessed for END Directive i.e. for transport noise from road traffic focusing on major roads (major roads: >3×106 vehicle passages/year)	HBM: individual HBM data; external exposure via food: individual food frequency data
	Time window calculations: calculations are often performed at a regular basis (for example for EEA yearly)	Calculations are often performed on a regular basis	It can be more frequent for chemicals with short half-life depending on the goal however these exposure estimates are often not performed on a yearly basis
Population data	Exposure overlaid with population data	Exposure overlaid with population data	Measured exposure should be representative for the population in which the EBD is calculated
Exposure-response function	Meta-analysis; meta-regression often using a relative risk (RR)	Meta-analysis resulting in absolute risk. For some outcomes	Often single studies are used; mostly a RR is applied but, in some cases, also a unit risk (cancer risk)

EBD framework	Outdoor air pollution	Noise pollution	Chemicals
		also a relative risk is applied	
	ERF proposed by large international organisations like WHO (e.g. REVIHAAP-HRAPIE 2013 and EMAPEC 2024)	ERF proposed by large international organisations like WHO	ERF proposed by research organisations (excluding lead for which estimates are available from WHO and IHME)
	Causality assessed by USEPA, WHO (World Cancer Research Fund criteria or GRADE)	Causality assessed by WHO (World Cancer Research Fund criteria or GRADE)	Causality assessed by research organisations e.g. PFAS restriction document submitted to ECHA; Realistic and precautionary approach
	Mixture: Not summing, omitting, correction for overlap, multi-pollutant models	Mixture: Not summing, omitting, correction for overlap, multi-pollutant models	Mixture: Not summing, omitting, correction for overlap, multi-pollutant models
Health data	IHME, WHO, (sub)national mortality and morbidity (incidence, prevalence) data registers	IHME, WHO, (sub)national mortality and morbidity (incidence, prevalence) data registers	IHME, WHO, (sub)national mortality and morbidity (incidence, prevalence) data registers

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BEST-COST is funded by the European Union's Horizon Europe programme under Grant Agreement No.101095408

4.2.2 Case study Phthalates

4.2.2.1 Overview of existing studies on burden of disease phthalates

Some preliminary estimates of the attributable burden or costs associated with phthalate exposure in the EU were performed during the last years (ETC HE, 2023; Plass et al., 2025). A search in PubMed on burden and cost studies related to phthalate exposure resulted in 602 hits and the one in Web of Science in 722 hits. After screening the titles, 16 studies were kept from PubMed and 17 from Web of Science. Screening of abstracts, removing of duplicates and combining this with knowledge of reports or studies at the research institutions, resulted finally in 19 studies. A complete overview is given in Table 3.

Table 3. Overview of burden of disease or costs calculations performed for phthalates based on findings in the international scientific literature and grey literature

Nr	Reference	Type	Region	Phthalate	Exposure data	Exposure biomarkers ERF	Outcome	Age group	Information ERF
1	(Legler et al., 2015; Trasande et al., 2015)	Attributable fraction and costs	EU	Sum of phthalates	HBM: DEMOCOPHES	Sum of *MEHP, MEHHP, MEOHP, MCEPP, MBzP, MEP, MBP, MiBP*	Obesity	Adults	Single study; (Song et al., 2014)
	(Legler et al., 2015; Trasande et al., 2015)	Attributable fraction and costs	EU	Sum of phthalates	HBM: DEMOCOPHES	*Sum of MEP, MEHP, MEHHP, MECPP, MEOHP, MBzP, MBP and MiBP*	Diabetes mellitus	Adults	Single study; (Sun et al., 2014)
2	(Bellanger et al., 2015; Trasande et al., 2015)	Attributable fraction and costs	EU	Sum of phthalates	HBM: DEMOCOPHES	Sum of MMP, MEP, MBP and MiBP,	Autism	Children	Single study; (Miodovnik et al., 2011)
3	(Hauser et al., 2015; Trasande et al., 2015)	Attributable fraction and costs	EU	DBP and BBP	HBM: DEMOCOPHES	MBP and MBzP	Male infertility	Adult men	Single study; (Buck Louis et al., 2014)
	(Hauser et al., 2015; Trasande et al., 2015)	Attributable fraction and costs	EU	DEHP and DBP	HBM: DEMOCOPHES	DEHP: Sum of MEHP, MEHHP and MEOHP; DBP: MBP	Low testosterone and increased mortality	Adult men	Single study; (Meeker and Ferguson, 2014)
4	(Attina et al., 2016)	Attributable fraction and costs	US	Sum of phthalates	HBM: NHANES	Sum of *MEHP, MEHHP, MEOHP, MCEPP, MBzP, MEP, MBP, MiBP*	Obesity	Adult women	Single study; (Song et al., 2014)
	(Attina et al., 2016)	Attributable fraction and costs	US	Sum of phthalates	HBM: NHANES	*Sum of MEP, MEHP, MEHHP, MECPP, MEOHP, MBzP, MBP and MiBP*	Diabetes mellitus	Adult women	Single study; (Sun et al., 2014)
	(Attina et al., 2016)	Attributable fraction and costs	US	DBP and BBP	HBM: NHANES	MBP and MBzP	Male infertility	Adult men	Single study; (Buck Louis et al., 2014)
	(Attina et al., 2016)	Attributable fraction and costs	US	DEHP and DBP	HBM: NHANES	DEHP: Sum of MEHP, MEHHP and MEOHP; DBP: MBP	Low testosterone and increased mortality	Adult men	Single study; (Meeker and Ferguson, 2014)
	(Attina et al., 2016)	Attributable fraction and costs	US	DEHP	HBM: NHANES	DEHP metabolites	Endometriosis	Adult women	Single study; (Buck Louis et al., 2013)
5	(Hunt et al., 2016)	Attributable fraction and costs	EU	DEHP	HBM: DEMOCOPHES	DEHP metabolites	Endometriosis	Adult women	Single study; (Buck Louis et al., 2013)
6	(Abtahi et al., 2019)	EBD (DALY)	Iran	DEHP	Drinking water	/	Liver cancer	Adults	(Abtahi et al., 2019)
7	(Cao et al., 2019)	Attributable fraction and costs	China	See Trasande et al. 2015	HBM	See Trasande et al. 2015	See Trasande et al. 2015	See Trasande et al. 2015	Single study; (Trasande et al., 2015)
8	(Zhang et al., 2019)	Attributable fraction	Shaanxi province, China	Sum of phthalates	External to internal	*Phthalate metabolites*	Diabetes mellitus	Adults	Single study; (Sun et al., 2014)

Nr	Reference	Type	Region	Phthalate	Exposure data	Exposure biomarkers ERF	Outcome	Age group	Information ERF
9	(CE Delft, 2021)	Attributable fraction and costs	EU	DBP	HBM	MBP	IQ loss	Children	Single study; (Factor-Litvak et al., 2014)
10	(Trasande et al., 2022)	Attributable fraction and costs	US	DEHP	HBM: NHANES	DEHP metabolites	Mortality (all-cause, cardiovascular, cancer)	Adults	Single study; (Trasande et al., 2022)
11	(Wang and Zhang, 2022)	Attributable fraction and costs	China	See Trasande et al. 2015	HBM	See Trasande et al. 2015	See Trasande et al. 2015	See Trasande et al. 2015	Based on (Trasande et al., 2015)
12	(Malits et al., 2022)	Attributable fraction and costs	Canada	See Trasande et al. 2015	HBM	See Trasande et al. 2015	See Trasande et al. 2015	See Trasande et al. 2015	Singel study; (Trasande et al., 2015)
13	(W. Liu et al., 2022)	EBD (DALY)	China	DEP, DiBP, DnBP, BBzP, DEHP	Indoor air (dust phase)	/	Asthma, eczema, rhinitis	Children and adults	ERF constructed and based on only Chinese studies
14	(Trasande et al., 2024a)	Attributable fraction and costs	US	DBP in plastic	HBM: NHANES	MBP	Male infertility	Adult men	Single study; (Buck Louis et al., 2014)
	(Trasande et al., 2024a)	Attributable fraction and costs	US	Sum of phthalates in plastic	HBM: NHANES	Sum of *MEHP, MEHHP, MEOHP, MCEPP, MBzP, MEP, MBP, MiBP*	Obesity	Adult women	Single study; (Song et al., 2014)
	(Trasande et al., 2024a)	Attributable fraction and costs	US	DEHP in plastic	HBM: NHANES	DEHP metabolites	Endometriosis	Adult women	Single study; (Buck Louis et al., 2013)
	(Trasande et al., 2024a)	Attributable fraction and costs	US	DEHP in plastic	HBM: NHANES	DEHP metabolites	Mortality (all-cause, cardiovascular, cancer)	Adults	Single study; (Trasande et al., 2022)
15	(Tao et al., 2024)	EBD (DALY)	China	DEHP	Inhalation, dust intake and dermal absorption	/	Asthma, dermatitis, (lifetime cancer risk)	Children	Based on study of (W. Liu et al., 2022)
16	(Cropper et al., 2024)	Attributable fraction and costs	38 countries	DEHP	HBM	DEHP metabolites	Mortality (all-cause, cardiovascular, cancer)	Adults	Single study; (Trasande et al., 2022)
17	(Trasande et al., 2024b)	Attributable fraction and costs	US	DEHP, DiNP, DiDP	HBM: ECHO program	DEHP, DiNP, DiDP metabolites	Preterm birth	Babies	Pooled analysis of 13 cohorts (Trasande et al., 2024b)
18	(ETC HE, 2023)	EBD (DALY)	Some EU countries	DEHP	HBM: HBM4EU	Sum of MEHP, MEHHP and MEOHP	Asthma	Children and adolescents	Single study; (Franken et al., 2017)
	(ETC HE, 2023)	EBD (number of cases)	Some EU countries	DiNP	HBM: HBM4EU	MCOP	Obesity	Adults	Single study; (Zhang et al., 2019)
	(ETC HE, 2023)	EBD (DALY)	Some EU countries	DEHP	HBM: HBM4EU	*Sum of MEP, MEHP, MEHHP, MECPP, MEOHP, MBzP, MBP and MiBP*	Diabetes mellitus	Adult women	Single study; (Sun et al., 2014)
	(Plass et al., 2025)	EBD (DALY)	Some EU countries	See (ETC HE, 2023)	See (ETC HE, 2023)	See (ETC HE, 2023)	See (ETC HE, 2023)	See (ETC HE, 2023)	See (ETC HE, 2023)
19	(Hyman et al., 2025)	Attributable fraction	Global	DEHP	HBM: global estimate based on different databases	DEHP metabolites	Mortality (all-cause, cardiovascular, cancer)	Adults	Single study; (Trasande et al., 2022)

A first observation from this overview is that most of the studies on cost come from the US from one research group and are in most cases based on human biomonitoring exposure data.

A second observation is that for a variety of outcomes, EBD calculations exist. The exposure-response functions applied in the EBD or cost studies are based on single studies (cohort and cross-sectional).

The number of studies focusing on EBD is limited compared to studies focusing on costs.

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BEST-COST is funded by the European Union's Horizon Europe programme under Grant Agreement No.101095408

4.2.2.2 Overview of meta-analyses on effects of phthalates in the scientific literature

A search for meta-analyses related to phthalate exposure resulted in 268 hits in PubMed. From these, 74 were selected based on the title and categorized following different outcomes assessed (Table 4). The table was supplemented with a few findings from the umbrella reviews from Symeonides et al. (2024) on the health effects of plastics and additives (search until the year 2020) and from Eales et al. (2022).

Symeonides undertook an umbrella review looking into the health effects of plastics focusing on plastic-associated chemicals (bisphenols, PFAS, phthalates, brominated flame retardants, PCBs). Effects related only to phthalates were spontaneous pregnancy loss, age of puberty, effects on sperm, fine motor/psychomotor development, increased HDL cholesterol and asthma (Symeonides et al., 2024). Formaldehyde was not considered in the review of Symeonides.

The umbrella review performed by Symeonides et al. (2024) was more extended than a review done by Eales et al. (2022), specifically targeting phthalates.

Eales *et al*. reported that robust evidence was found for an association with lower semen quality, neurodevelopment and risk of childhood asthma, and moderate to robust evidence for impact on anogenital distance in boys.

Table 4. Overview of studies reporting on meta-analysis by variety of outcomes related to phthalate exposure

Outcome category	Outcome	ICD-10*	Study
Metabolism	Obesity, BMI, adiposity		(Goodman et al., 2014; Ribeiro et al., 2019; Golestanzadeh et al., 2019; Ribeiro et al., 2020; Lee et al., 2022; Wu et al., 2023)
	Metabolic syndrome		(Mérida et al., 2023)
	Cardiometabolic risk factors		(Golestanzadeh et al., 2019)
	Diabetes mellitus	E08-E08.11, E08.3-E08.9, E10-E10.11, E10.3-E11.1, E11.3-E12.1, E12.3-E13.11, E13.3-E14.1, E14.3-E14.9, R73-R73.9	(Song et al., 2016; Yan et al., 2022; Zhang et al., 2022; Yao et al., 2023; Keskesiadou et al., 2024)
	Insuline resistance		(Shoshtari-Yeganeh et al., 2019; Gao et al., 2021)
	Nonalcoholic fatty liver disease	K76.0**	(Pan et al., 2024)
Developmental	Birth size, birth weight, SGA, preterm birth	(P07.2-P07.39, P22-P22.9, P25-P28.9, P61.2, P77-P77.9)***	(Golestanzadeh et al., 2019; Zhong et al., 2021; Wang et al., 2022; Wu et al., 2022; Jin et al., 2023; Yu et al., 2024; Pang et al., 2024; Liu et al., 2024)
	Reproductive disorders, anogenital distance, cryptorchidism, hypospadias		(Bonde et al., 2016; Dorman et al., 2018; Zarean et al., 2019; Yu et al., 2022; Albadawi et al., 2024)
Reproduction	Endometriosis	N80-N80.9	(Cai et al., 2019; Wen et al., 2019; Conforti et al., 2021; Zhang and Ma, 2021; Chitakwa et al., 2024)
	Spontaneous pregnancy loss	N96, O01-O08.9, O36.7-O36.73	(H. Zhang et al., 2020)
	Miscarriage		(Liu et al., 2024)
	Reproductive hormones, sperm quality		(Cai et al., 2015; Wang et al., 2016, 2023; Li et al., 2024; Nowak et al., 2024)
	Uterine leiomyoma		(Fu et al., 2017; Zhang et al., 2024)
	Gestational age		(Zhong et al., 2021)
Neurological effects	Neurodevelopment, cognition		(Lee et al., 2018; Radke et al., 2020; Nilsen and Tulve, 2020; Antoniou and Otter, 2024;

Outcome category	Outcome	ICD-10*	Study
			Liao et al., 2023; Goodman et al., 2023; Yang et al., 2024)
	Autism spectrum disease	F84-F84.9	(Jeddi et al., 2016; Duque-Cartagena et al., 2024)
	ADHD		(Nilsen and Tulve, 2020)
Cardiovascular	Subclinical carotid atherosclerosis		(Mérida et al., 2024)
	Blood pressure, hypertension		(Gao et al., 2023; Golestanzadeh et al., 2019; Hirke et al., 2023; M. Zhang et al., 2023)
	Cardiovascular disease		(Fu et al., 2020)
	Cardiometabolic risk factors		(Golestanzadeh et al., 2019)
Respiratory	Asthma	J45-J46.0	(Jaakkola and Knight, 2008; Smit et al., 2015; Li et al., 2017; Wu et al., 2020; Hatem et al., 2025)
	Allergic rhinitis		(Oh et al., 2024)
	Lung function		(Boissiere-O'Neill et al., 2024)
Skin diseases	Eczema, atopic dermatitis	L20-L20.9****	(Smit et al., 2015; Jung et al., 2021; H. Zhang et al., 2023)
Endocrine effects	Pubertal timing		(Wen et al., 2015; Golestanzadeh et al., 2020; Uldbjerg et al., 2022)
	Thyroid hormone levels		(Kim et al., 2019; Xu et al., 2024)
Cancer	Thyroid cancer	C73	(Yang et al., 2023)
	Breast cancer	C50-C50.629, C50.8-C50.929	(Fu et al., 2017; Liu et al., 2021; H. Liu et al., 2023)
	Cancer risk		(Meng et al., 2024)
Immune effects	Inflammation and immune response		(Hansen et al., 2015; Z. Liu et al., 2022)

*: mapped to non-fatal causes and injuries in the GBD 2021

**: ICD10 Used in Hospital/Claims Analyses

***: ICD10 code for neonatal preterm birth

***: ICD10 code for urogenitial congenital anomalies

****: ICDE10 code for atopic dermatitis

Phthalates are associated with changes in metabolism, effects on reproduction and birth outcomes, neurological effects, cardiovascular effects, respiratory effects, endocrine effects, skin diseases, immune effects and cancer.

4.2.2.3 Overview of exposure-response functions phthalates in reports evaluated by SEAC

In 2016, a dossier for the restriction of four phthalates (DEHP, DBP, BBP, DiBP) was submitted to ECHA and evaluated by the RAC and the SEAC[12]. For the health effects male infertility (due to in utero exposure), cryptorchidism, and hypospadias a fixed etiological fraction was applied in the impact calculation, based on expert knowledge. SEAC did find that the uncertainty of the benefits assessment when reducing exposure was high. The uncertainty related to etiological fractions dominated. More information can be found in Annex 1.

[12] https://echa.europa.eu/nl/registry-of-restriction-intentions/-/dislist/details/0b0236e1806e7a36

4.2.2.4 *Background information on effects phthalates observed in reports from ATSDR, EFSA, ECHA, NIH, USEPA, OECD.*

Documents were screened mainly for effects based on epidemiological studies. Some general conclusions are given here. Detailed information can be found in Annex 1.

In 2017, ECHA evaluated four phthalates (DEHP, BBP, DBP, DiBP) identified as Substance of Very High Concern (SVHC) due to reproductive toxicity (Cat. 1B) in the context of a restriction proposal (ECHA, 2017a, 2017b). The toxicological information used by the ECHA RAC was focused on reproductive toxicity, the effect with the most robust data. Other potential effects on the immune system, the metabolic system and on neurodevelopment, were concisely discussed, even though the RAC recognized that there were (qualitative) indications that they could possibly be equally or more sensitive (e.g. effects on the immune system) than reproductive toxicity. For the reproductive effects, according to the RAC the epidemiological studies have such uncertainties that these do not allow for the conclusion for a causal relationship. For effects on the metabolism, neurodevelopment, the Dossier Submitter reported only weak evidence. Although the RAC considers that such effects cannot be excluded. For effects on the immune system, the RAC noted in its assessment that several studies suggested adverse effects of phthalate exposure on the immune system, in particular leading to allergy, asthma and eczema. The RAC concluded that there is a need for further robust data to perform a risk assessment regarding adverse effects on the immune system (ECHA, 2017a, 2017b).

In 2018 a OECD working paper on the costs of phthalate exposure was published, authored by Mike Holland. The paper mainly builds on conclusions from the Transande papers in which exposure-response functions follow a Delphic approach and are based on single studies. The health impacts linked to exposure to phthalates affect the reproductive system, neurodevelopment, cancer incidence, obesity, diabetes, asthma and allergy. However, the strength of association is variable, and most quantification work is focused on male reproduction (OECD, 2018).

In 2019 EFSA performed a risk assessment of DBP, BBP, DEHP, DiNP and DiDP for use in food contact materials (EFSA, 2019). Overall, the review of the toxicological data focused mainly on reproductive effects. Based on the prospective studies and consideration of animal studies, the CEP Panel (EFSA Panel on Food Contact Materials, Enzymes and Processing Aids) agrees that there are some data that show an association between phthalate exposure (DEHP, DBP, BBP) in utero and reduced AGD in male newborns, although the epidemiological studies reviewed are inconsistent and have some limitations.

ATSDR assessed the toxicological profile of DEHP in 2022 (Agency for Toxic Substances and Disease Registry (ATSDR), 2022). For hepatic, renal, immunological effects, human date were limited and did not show consistent findings. For reproductive effects (decreased serum testosterone and altered sperm parameters in males) and developmental effects (reduced AGD and testicular decent in male infants) epidemiological studies suggest a potential association. Also for metabolic effects (obesity), available epidemiological studies suggest a potential association.

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BEST-COST is funded by the European Union's Horizon Europe programme under Grant Agreement No.101095408

In 2022 the NIH (National Institutes of Health) published a study on the association between phthalate exposure and preterm birth[13] (Welch et al., 2022).

Under the Toxic Substance Control Act (TSCA) information is available on the risk assessment of phthalates based on animal studies (USEPA, 2024). Phthalates considered were DiDP, DINP, BBP, DEHP, DiBP, DBP and DCHP. For BBP, DEHP, DIBP, DBP and DCHP effects on the reproduction system were most sensitive and robust for estimating the risk to human health. For DiDP liver and developmental toxicity were considered and for DiNP cancer and non-cancer hazard endpoints (liver, kidney, neurological and developmental toxicity).

4.2.2.5 Background information on health effects phthalates based on derivation of human biomonitoring health-based guidance values

Phthalates cause diverse health effects. An overview of health effects associated with phthalate exposure was generated in HBM4EU (HBM4EU, 2022). Risk assessment studies do show that health risks in the general population cannot be excluded (Lange et al., 2022; Gerofke et al., 2023).

The HBM guidance values (HBM-GV) to which HBM concentrations in the general population are compared are based on animal studies, and not on epidemiological studies. However, for some chemicals more attention is given to findings in epidemiological studies for derivation of HBM-GV. A HBM guidance value is a guidance value that corresponds to internal exposure levels at which there is no appreciable health risk. An overview of animal studies on which HBM-GV are based is given in Table 5.

Table 5. Overview underlying studies of human biomonitoring guidance values (HBM-GV) derived for phthalates in HBM4EU

Phthalate	HBM-GV based on
DnBP	ECHA DNEL: 0.0067 mg/kg bw/day Based on rat study with LOAEL 2 mg/kg bw/day Effect: loss of germ cells
DiBP	ECHA DNEL: 0.0083 mg/kg bw/day Read across from DnBP (some difference in potency)
BBzP	Based on rat study with LOAEL 100 mg/kg bw/day which results in a TRV like value of 0.111 mg/kg bw/day Effect: change in testosterone, effects on sperm cells
DEHP	Based on 2 generation rat study of BASF with BMDL10 equal to 10 mg/kg bw/day resulting in a TRV of 0.1 mg/kg bw/day Effect: change in thyroid working

HBM-GV were derived by Lange et al. (2021)
BBzP: Benzyl butyl phthalate; DEHP: Di(2-ethylhexyl) phthalate; DiBP: Diisobutyl phthalate; DnBP Di-n-butyl phthalate

The main source of exposure to phthalates and DINCH was found to be consumption of food (via food contact materials). The daily use of personal care and cosmetic products is also an important determinant of exposure. Depending on the properties of the phthalate, other sources such as indoor dust by ingestion or inhalation in the gaseous and particulate phase may also contribute to the overall exposure (HBM4EU: Gerofke et al., 2024).

[13] https://www.nih.gov/news-events/news-releases/preterm-birth-more-likely-exposure-phthalates

4.2.2.6 Calculation of the environmental burden of disease for exposure to dimethyl phthalate and diabetes (example 1)

The goals of the example were to showcase an EBD calculation for phthalates building on the already existing evidence and to highlight strengths and weaknesses in the calculation and gaps for further research. We started extracting data from the overview with existing meta-analysis for phthalates that we created (Table 4). The following data was extracted from each meta-analysis: DOI, author, meta-analysis (yes/no), outcome group (e.g. cardiometabolic), outcome specific (e.g. diabetes mellitus), study population, exposure (phthalate or metabolite), metabolite, exposure window, number of studies in the meta-analysis, effect measure, effect size, upper and lower CI on effect size, significance (yes/no) and additional remarks. The overview included 725 specific lines with information retrieved from meta-analysis on the effects of different phthalates on health. Only effect sizes resulting from a meta-analysis were taken up in the overview and no data from individual studies. The Table is available through Zenodo (DOI:10.5281/zenodo.17910475). Starting from these data, we focused on data for which an odds ratio (OR) or relative risk (RR) was available. Data were ordered according to the largest value of the OR or RR. The top 10 of the largest significant effects retrieved from the meta-analysis are given below (Table 6). Aim was to showcase the EBD calculation for an outcome with a large significant effect.

Table 6. Overview of top 10 of meta-analysis in which the largest effect for phthalates was observed

Study	Outcome	Metabolite	N studies	OR*	95%CI_LL	95%CI_UL
Wen et al. 2015	Precocious puberty	DEHP metabolites	7	4.090	2.300	7.300
Nilsen and Tulve, 2020	ADHD	/	/	3.310	2.590	4.020
Zhang et al. 2022	DM	MMP	3	3.110	1.160	8.370
Li et al. 2017	Asthma	DEHP metabolites	3	2.710	1.390	5.280
Mérida et al. 2024	Carotid intima-media thickness	/	2	2.670	1.890	3.780
Zhang et al. 2022	DM	MiBP	6	2.590	1.100	6.100
Liu et al. 2024	Miscarriage	MEHHP	7	2.560	1.290	5.100
Zhang et al. 2022	DM	MCPP	5	2.390	1.170	4.850
Wu et al. 2023	Obesity risk	MBP	3	2.180	1.070	4.460
Yan et al. 2022	GDM	Combination of several phthalates	2	2.170	1.450	3.260

ADHD: attention deficit hyperactivity disorder; CI_LL : lower limit confidence interval (95%) ; CI_UL : upper limit confidence interval (95%); DM: diabetes mellitus; DEHP: Di(2-ethylhexyl)phthalate; GDM: gestational diabetes mellitus; MBP: (Mono-n-butyl phthalate); MiBP: Mono-isobutyl phthalate; MCPP: Mono(3-carboxypropyl) phthalate; MEHHP: Mono(2-ethyl-5-hydroxyhexyl) phthalate; MMP: Monomethylphthalate *: ordered in decreasing order

The meta-analysis with the largest significant OR was the one from Wen et al. (2015) on precocious puberty with seven studies. Six of these studies were performed in China and one in Puerto Rico. Individual studies were published in Chinese journals and not available in Europe.

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BEST-COST is funded by the European Union's Horizon Europe programme under Grant Agreement No.101095408

The second largest effect was found for ADHD. However, the exposure metric for which the OR was derived was not clearly defined.

Therefore, the study with the third largest health effect was selected to showcase the EBD calculation for phthalate exposure, i.e. diabetes mellitus (DM). We explored deriving an ERF from meta-analysis of Zhang et al (2022). In the meta-analysis, OR (for the highest versus lowest exposure quartile or quintile) were combined regardless of absolute exposure values. The exposure data itself was lacking in the meta-analysis which is a gap. Therefore, we needed to go back to individual studies. The association between diabetes mellitus and phthalate exposure in adult men and women was assessed in three individual studies: (Lind et al., 2012; Dong et al., 2017; Duan et al., 2019). Results were adjusted for sex. Exposure data and OR of the individual studies were retrieved to scrutinize the possibility of deriving an overall OR or RR per a comparable defined change in exposure and to develop an ERF. These data are presented in Figure 5.

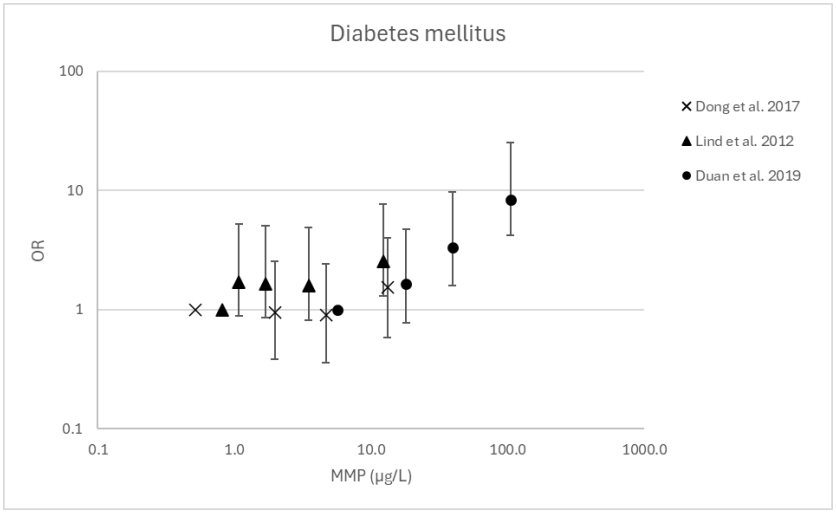

Figure 5. Data from individual studies assessing the effect of phthalate exposure (MMP metabolite) on diabetes.

Additional data was retrieved from the individual studies. These included risk estimates (OR or RR) for each exposure quartile or quintile with 95%CI compared with the lowest reference. The increase in MMP was calculated as associated with the OR by taking the difference between the exposure level of the index category and the reference exposure level. The logarithm of the OR (RR) and the exposure were computed to have a linear scale. The log standard error was calculated from 95% CIs. Results were pooled assuming a linear model. A random-effect meta-regression of log OR with the exposure level as predictor was tested using the *metafor* packages in R (rma function). An important assumption in pooling is that the effects are linear.

The overall OR per unit increase in MMP was equal to 1.021 (95% CI 1.013 to 1.028) per unit increase in µg MMP/L. The TMREL was set at the exposure corresponding to an OR of 1 and was equal to 1.1 µg MMP/L.

The small number of epidemiological studies and study design reduced confidence in the association between phthalates and diabetes mellitus. Additionally, the differences observed in the studies (standardization for creatine, age of the adults, …) makes comparability between studies more difficult.

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Exposure data for the metabolite MMP were retrieved from the European HBM dashboard (https://hbm.vito.be/eu-hbm-dashboard).

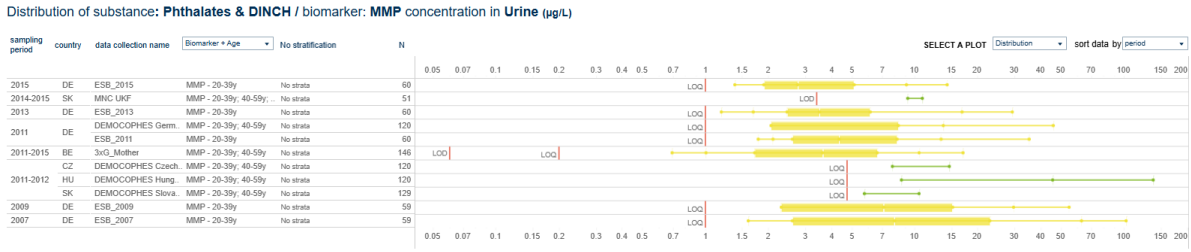

Figure 6. Overview urinary MMP concentrations (µg/L) from the European HBM dashboard

The example is worked out for Belgium. The assumption was made that all adults are exposed to the exposure observed in mothers of the cohort study of 3xG (P05: 0.693 µg MMP/L; P50: 3.625 µg/L; P95: 16.985 µg/L).

Based on information on the exposure distribution in the population and the effect (OR) per unit exposure, the population attributable fraction (PAF) was calculated (Table 8). The OR was taken as a proxy for the relative risk (RR) (Zhang and Yu, 1998) and the Levin equation was used to calculate the PAF (Suzuki and Yamamoto, 2023).

The PAF can be calculated as

$$PAF = \frac{\sum pi \times (RRi - 1)}{\sum Pi \times (RRi - 1) + 1}$$

With **pi** the fraction of the exposed population in a certain exposure stratum and **RRi** the relative risk in the stratum. Demographic data were retrieved from Eurostat.

The focus was on the calculation of YLD or years lived with disability. Mortality indicators (YLL) were not accounted for as the selected effect only applied to diabetes morbidity.

To calculate the YLD , the disease-envelop approach was applied. We selected health data from the European Health Interview Survey (EHIS) (https://ec.europa.eu/eurostat/databrowser/view/hlth_ehis_cd1e__custom_16383207/default/table) which reports on self-reported chronic morbidity. These background prevalence data on diabetes were chosen instead of the background YLD provided by IHME on diabetes mellitus. The reason for this are multiple: (1) results come directly from Eurostat and not from a secondary database, (2) discrepancies were observed between incidence/prevalence data reported by IHME and EU national databases, (3) to get a global estimate on the prevalence, modeling techniques or read-across could be applied. To calculate the YLD associated with phthalate exposure, the prevalence (P) data of EHIS (%), population numbers from Eurostat (n), the PAF and a disability weight (DW) for diabetes mellitus retrieved from IHME were multiplied.

$$YLD = P \times n \times PAF \times DW$$

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A Monte-Carlo simulation was performed (Cristal Ball). Only the uncertainty on the overall OR was considered in the model.

Taking into account several assumptions, it is possible to calculate the EBD related to phthalate exposure. An attempt was made here to calculate the PAF based on an overall OR/ unit increase in exposure derived from several studies. The results of the burden are shown in Table 9. For Belgium, the PAF equals 0.11 (95% CI 0.07 to 0.15). The YLDs are equal to 4407 (95%CI 2890 to 6343). To derive a better estimate of the effect per change in exposure, more studies are needed. Additionally, the study does not consider a mixture approach because it was out of the scope.

Mechanistically phthalates play a role in the development of oxidative stress, impaired inflammatory factors and the expression of peroxisome-proliferator activated receptors (PPARs), which are important for lipid and carbohydrate metabolism. Other mechanisms that can contribute to the development of diabetes type I and II are suggested and are being studied (Zhang et al., 2017; Lin et al., 2017; Mariana Cairrao, 2023; Pérez-Díaz et al., 2024). The metabolite MMP is primarily associated with markers of oxidative stress (Lin et al., 2017). More research is needed here.

Table 7 gives an overview of the strengths and weaknesses of this exercise.

Table 7. Overview strengths, weaknesses, gaps EBD calculation phthalates and diabetes

Strengths	- Derivation of overall change in OR per unit change in exposure in this exercise
Weaknesses	- Small number of studies on the effect - Uncertainty on the TMREL - Mismatch between age, sex population exposure data and population for which OR was derived - Country representativeness of HBM data - Mistakes made in current meta-analysis compared to findings in the individual studies - Starting from meta-analysis and not performing extra search on availability new studies - OR per unit change not available from organisations e.g. WHO for air pollution - No mixture approach considered in this exercise - Health data based on self-reported chronic morbidity, which can induce vies on estimates
Gaps	- Meta-analysis: overall OR not considering the exposure to derive an OR per unit change in exposure - High quality meta-analysis lacking - Missing HBM data for EU countries - Need for more studies addressing long-term health effects at low exposure levels

Overall, more effort should be put into high quality meta-analysis and meta-regression in order not to base the exposure response function on one single study. Meta-analysis should also report more on exposure data so that it is not necessary to go back to the individual studies.

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Table 8. Calculation of population attributable fraction (PAF) for diabetes in the elderly in Belgium based on exposure to phthalates

Exposure Percentile	MMP[a] (µg/L)	N persons in percentile[b]	OR			PAF		
			Mean	95% Lower CI	95% Upper CI	Mean	95% Lower CI	95% Upper CI
P0-P10	0.693	1314341						
P10-P25	1.361	1496402	1.01	1.00	1.01			
P25-P50	2.671	1499171	1.03	1.02	1.04			
P50-P75	5.112	1540920	1.08	1.05	1.11			
P75-P90	8.542	1539118	1.15	1.10	1.21			
P90-P95	13.730	1194318	1.25	1.16	1.35			
>P95	16.985	1035060	1.32	1.21	1.44			
Total		9619330				0.10	0.07	0.13

a: Exposure values based on results 3XG study Belgium
b: Demographic data based on Eurostat: https://ec.europa.eu/eurostat/databrowser/view/DEMO_PJAN/default/table?lang=en

Table 9 Prevalence based Years Lived with Disability (YLD) for diabetes mellitus attributable with phthalate exposure in Belgium for the year 2021

Age group	N persons in percentile[a]	Prevalence (%)[b]	Prevalence (n)	Disability weight IHME[c]	YLD_EBD		
					Mean	95% Lower CI	95% Upper CI
15-24	1314341	1.0	13143	0.05	65	42	87
25-34	1496402	1.3	19453	0.06	116	74	154
35-44	1499171	2.1	31483	0.07	218	140	290
45-54	1540920	3.7	57014	0.08	452	289	600
55-64	1539118	9.3	143138	0.08	1134	725	1508
65-74	1194318	13.4	160039	0.08	1268	811	1686
>75	1035060	14.1	145943	0.08	1156	740	1537
Total	9619330		570213		4407	2820	5861

a: Demographic data based on Eurostat: https://ec.europa.eu/eurostat/databrowser/view/DEMO_PJAN/default/table?lang=en
b: Prevalence data based on data of the European Health Interview Survey (EHIS): https://ec.europa.eu/eurostat/databrowser/view/hlth_ehis_cd1e__custom_16383207/default/table
c: Disability weight retrieved from IHME by dividing YLD/prevalence for diabetes mellitus: https://vizhub.healthdata.org/gbd-results/

4.2.2.7 Calculation environmental burden of disease for exposure to dibutyl phthalate and preterm birth (example 2)

In this second example, an EBD calculation for phthalates and preterm birth was performed, building further on the already existing evidence. Strengths and weaknesses were analyzed. The emphasis in this exercise also lies in the search or derivation of a robust exposure-response function.

We started again from the data retrieved from existing meta-analysis for phthalates that we created and is available at Zenodo (Table 4) (DOI: 10.5281/zenodo.17910475). Starting from these data, we focused on data for which an odds ratio (OR) or relative risk (RR) was available. Data were ordered according to the largest number of studies in the available meta-analyses. The top 10 of meta-analyses based on the largest number of individual studies included is given below (Table 10). Aim was to showcase an example based on a large number of individual studies available in the different meta-analysis.

Table 10. Overview of top 10 of meta-analysis with the largest number of individual studies included

Study_ID	Outcome	Metabolite	N studies*	OR	95%CI_LL	95%CI_UL
Wu et al. 2020	Asthma	MBZP	15	1.170	1.060	1.280
Liu et al. 2024	Preterm birth	MBP	12	1.250	1.040	1.510
Liu et al. 2024	Preterm birth	MEHP	12	1.250	1.020	1.530
Wu et al. 2020	Asthma	MBZP	12	1.170	1.050	1.290
Liu et al. 2024	Preterm birth	DEHP metabolites	10	1.330	1.110	1.590
Wu et al. 2020	Asthma	MBzP	10	1.170	1.030	1.330
Meng et al. 2024	Any cancer	MEHHP	10	1.407	1.201	1.648
Liu et al. 2024	Miscarriage	MEHP	9	1.710	1.280	2.300
Zhang et al. 2024	Uterine leiomyoma	DEHP metabolites	9	1.610	1.180	2.200
Li et al . 2017	Asthma	BBzP	9	1.410	1.150	1.710

*: ordered in decreasing order

For the example worked out, we selected the meta-analysis based on the largest number of individual studies included. The study of Wu et al. 2020 was not selected because it covered the odds for asthma in studies combining findings in children, adolescents and adults. Odds for developing asthma may differ between different age categories. Therefore, the second study (Liu et al. 2024) was selected in this example focusing on “preterm birth”.

Preterm birth (<37 weeks of gestation) may likely be associated with phthalate exposure. The matching results refer to a phthalate that was historically used in personal care products, such as cosmetics, but is still present in plastics and PVC (DBP).

An overview of the individual studies included in the study of Liu et al. (2024) is given below (Table 11). Additional studies included in the meta-analysis of Liu but omitted here were (Chen et al., 2015) and (Ferguson et al., 2019b). These studies were not included here as they were

already accounted for respectively in the studies of Ferguson et al. (2014) and Cathey et al. (2022). Inclusion would result in double counting.

Table 11. Major studies on DBP exposure (metabolite MBP) and preterm birth included in overview of Liu et al. (2024)

Study	Effect size	LL	UL	Measure	N	No. of events	Study design
(Meeker et al., 2009)	4.5	1.2	16.6	OR	60	30	Case control
(Ferguson et al., 2014)	1.16	0.86	1.55	OR	482	130	Case control
(Shoaff et al., 2016)	0.2	0.04	0.96	OR	400	32	Cohort
(Gao et al., 2019)	1.15	0.7	1.91	OR	3400	134	Cohort
(Ferguson et al., 2019a)	1.25	0.9	1.75	OR	854	71	Cohort
(Bloom et al., 2019)	0.59	0.3	1.16	OR	419	28	Cohort
(Zhang et al., 2020)	1.16	0.79	1.7	RR	453	34	Cohort
(Hu et al., 2020)	0.99	0.83	1.17	HR	1972	225	Cohort
(Yland et al., 2022)	0.94	0.6	1.47	RR	417	31	Cohort
(Cathey et al., 2022)	1.78	1.16	2.74	OR	1100	89	Cohort
(Qian et al., 2023)	3.66	1.67	8.03	RR	409	42	Cohort

OR: odds ratio; RR: relative risk; HR: Hazard ratio; LL: 95% lower limit; UL: 95% upper limit; N: number of participants

Studies in Table 11 reported effect sizes in different units of increase in exposure concentration (e.g., per IQR, per ln unit, etc..). First, we standardized all effect sizes (which is not done in meta-analysis study here of Liu et al.) to 'per doubling' of exposure. Then, we conducted a meta-analysis. Reported odds ratios (ORs) or relative risks (RRs) with 95% confidence intervals were transformed to the log scale, and study-specific standard errors were derived from the confidence limits. Random-effects models (ML) were fitted using the 'metafor' package in R to obtain pooled estimates.

The overall pooled effect suggests a statistically significant positive association between MBP (per-doubling) and preterm birth, with a 10% increased risk per doubling of exposure (Figure 7).

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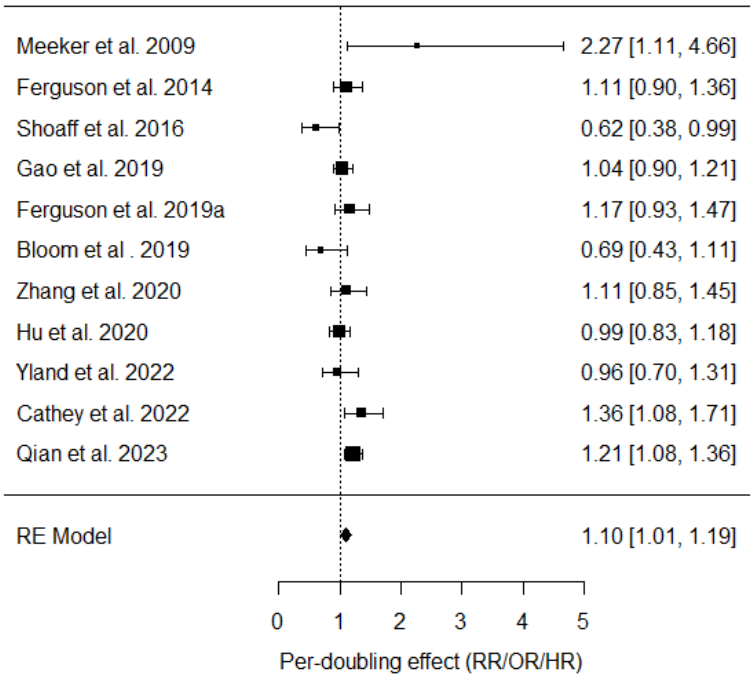

Figure 7. Meta-analysis for exposure to MBP and preterm birth

For exposure–response assessment, we assumed a log-linear model on the doubling scale:

$$\log RR\left(x\ Vs.\ x_{ref}\right) = \beta.log_2(\frac{x}{x_{ref}})$$

where β is the log effect per doubling.

For each individual study, exposure distributions (e.g. percentiles p05–p95 where available) were used to define the plausible exposure range.

Study-specific curves were generated across these ranges. A pooled exposure–response curve was constructed using the pooled β and a representative exposure range derived from the median percentiles across studies. Uncertainty bands for the pooled curve were based on the standard error of the pooled β (Figure 8). The threshold at which no effect is assumed, is based on the average of the lowest available percentile in the original studies and equals 5.2 µg/L.

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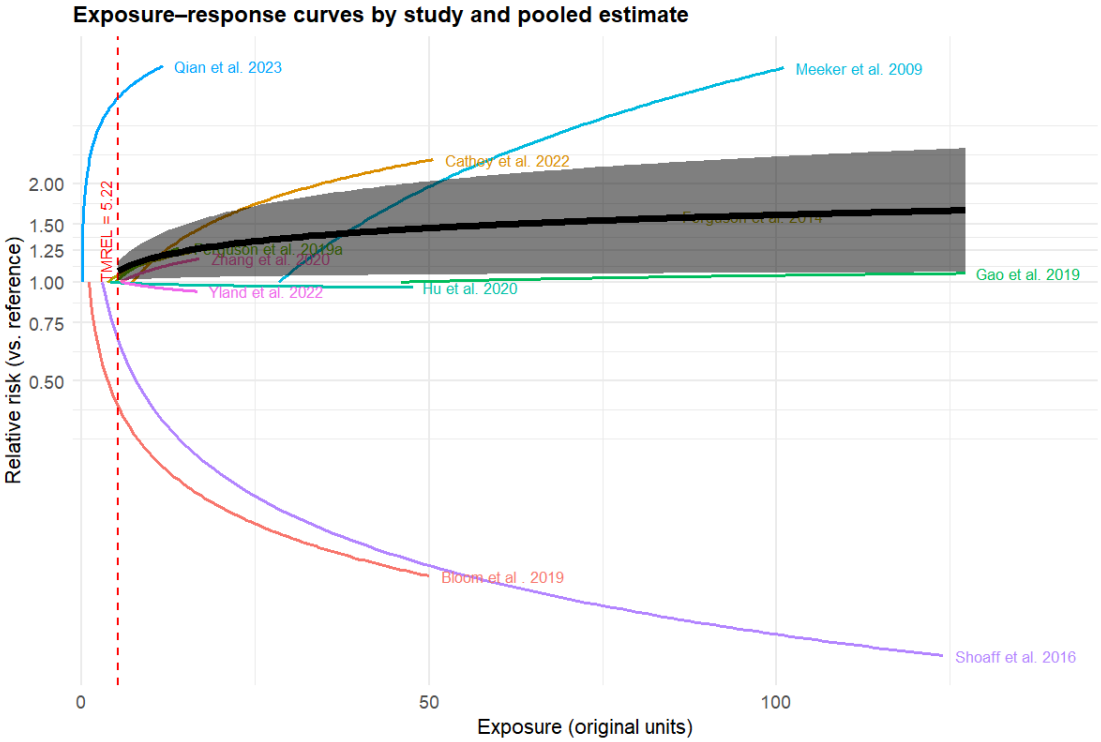

Figure 8. Individual exposure-response curves and pooled estimate for exposure to MBP (µg/L) and relative risk for preterm birth

For the EBD calculation, exposure data for the metabolite MBP were retrieved from the European HBM dashboard (https://hbm.vito.be/eu-hbm-dashboard).

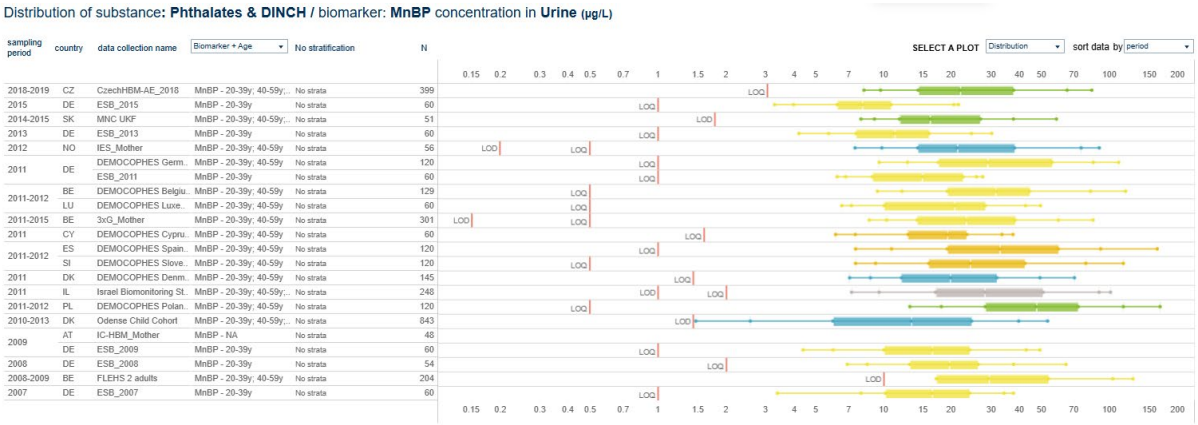

Figure 9. Overview of adult urinary MBP concentrations (µg/L) from the European HBM dashboard

The EBD calculation is worked out for Belgium. The assumption was made that all adults are exposed to the exposure observed in mothers of the cohort study of 3xG (P05: 7.8 µg MBP/L; P50: 27.7 µg/L; P95: 76.4 µg/L).

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Based on information on the exposure distribution in the population and the effect (RR) per doubling of the exposure, the population attributable fraction (PAF) could be calculated (Table 12). The Levin equation was used to calculate the PAF (Suzuki and Yamamoto, 2023).

In a disease envelop approach, the PAF was applied to DALYs for Belgium for preterm birth retrieved from IHME. This means that it is assumed that the rate for being born premature and chances to die is kept identical as observed in the study of IHME. In this way, DALYs for preterm birth related to phthalate exposure were calculated.

$$EBD = BoD\ x\ PAF$$

A Monte-Carlo simulation was performed (Cristal Ball). Uncertainty on the overall RR and on the total burden of disease was taken into account in the model.

For Belgium, the PAF equals 0.19 (95% CI 0.02 to 0.33) (Table 12). The EBD is equal to 1464 DALYs (95%CI 428 to 2576) (Table 13). In 2021 there were 117914 children born in Belgium. According to data from IHME, there were 10460 preterm births accounting for 9% of the total births. This is in agreement with findings from Belgian hospitals[14]. The calculation here shows that a significant number of preterm births (1 in 5) can be associated with phthalate exposure. The study does not consider a mixture approach as other chemicals (PFAS) might as well have an influence on preterm birth. This was out of scope here.

A recent pooled analysis with 16 prospective studies in the US (N=6045) showed an unadjusted OR of 1.17 (1.03-1.312) and an adjusted OR of 1.12 (0.98-1.27) for an IQR increase in MBP (P25= 8.7µg/L and P75=30.1 µg/L). Similar effects were observed for MiBP, MECPP and MCPP (Welch et al., 2022). Unadjusted models accounted for the different studies as a fixed effect. Adjusted models were adjusted for study, maternal age, race and ethnicity, education, and prepregnancy body mass index. The meta-analysis from which we started our analysis (Liu et al., 2024) includes several individual studies of this US pooled analysis.

The studies included in the meta-analysis have found positive associations between prenatal biomarkers phthalate concentrations and preterm birth, a few have shown null or inverse associations. This may be related to several reasons including the lack in power, differences in exposure assessment, variations in baseline risk for preterm birth and phthalate exposure, etc. Overall, there is evidence that exposure to phthalates can result in preterm birth.

Mechanistically, preterm birth may be mediated through oxidative stress and inflammation (Ferguson et al., 2017; Aung et al., 2020; Welch et al., 2022). Additional mechanisms may be dysregulated trophoblast differentiation and endocrine disruption seeing the downregulation of placental genes for these processes (Adibi et al., 2010). These can be affected by phthalate exposure.

The strengths, weaknesses, and gaps identified in the study are somewhat similar to those in the previous exercise. The availability of numerous studies on phthalate exposure and preterm birth is a strength here. As described in this example, it is crucial that more attention goes to high quality meta-analysis which includes also information on the exposure side in order to establish an exposure-response assessment.

[14] FPS Public Health (undated). Minimale Ziekenhuisgegevens (Minimum Hospital Data – MZG).

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Table 12. Calculation of population attributable fraction (PAF) for preterm birth in Belgium based on exposure to phthalates

Exposure Percentile	MBP[a] (µg/L)	Fraction	OR			PAF		
			Mean	95% Lower CI	95% Upper CI	Mean	95% Lower CI	95% Upper CI
P0-P10	8.6	0.10	1.07	1.01	1.13			
P10-P25	10.2	0.15	1.12	1.01	1.24			
P25-P50	14.0	0.25	1.19	1.02	1.38			
P50-P75	23.0	0.25	1.28	1.03	1.56			
P75-P90	38.0	0.15	1.36	1.03	1.75			
P90-P95	59.0	0.05	1.43	1.04	1.93			
>P95	84.0	0.05	1.47	1.04	2.01			
Total		1				0.19	0.02	0.33

a: Exposure values based on results 3XG study Belgium

Table 13. DALYs for preterm birth associated with phthalate exposure in Belgium for the year 2021

	Mean	95% Lower CI	95% Upper CI
Prevalence_ preterm_birth_(<1j)[a]	10460	9984	10821
YLL_preterm_birth_(<1j)[a]	7587	6009	9238
YLD _preterm_birth_(<1j)[a]	118	79	161
DALY_preterm_birth_(<1j)[a]	7704	6143	9358
EBD_DALY_preterm_birth_(<1j)	1464	428	2576

a: DALYs retrieved from IHME (GBD update for year 2021)

4.2.2.8 Applicability of R package Healthiar

As part of our methodological transfer exercise, we evaluated the applicability of the ***healthiar*** R, originally developed in WP4 by Swiss-TPH for estimating the burden of disease attributable to air pollution and noise, to chemical stressor scenarios[15,16]. Specifically, we applied some of the package functions to our two case studies. The objective was to explore whether the functions and computational logic of ***healthiar*** could be adapted to quantify health impacts from chemical stressors.

Our preliminary testing showed that most of the package's functionalities are indeed relevant and can be applied to chemical exposures with "minor conceptual adjustments". This can be tested and discussed in future work in more in detail.

[15] https://best-cost.eu/best-cost-r-package-healthiar-is-now-public/
[16] https://github.com/SwissTPH/healthiar/tree/master

4.3 Conclusions transferability to chemicals

The application of EBD methodologies to chemical exposure is increasingly relevant for public health research. While transferability from established domains such as air and noise pollution is conceptually feasible, the evidence base for many chemicals—particularly modern synthetic compounds—remains fragmented and insufficiently developed.

Causality and evidence gaps

For certain chemicals such as lead, the exposure-response relationship is well established for facilitating robust EBD assessments.

In contrast, newer compounds, such as phthalates pose significant challenges. Despite widespread exposure, epidemiological evidence linking phthalates to specific health outcomes like diabetes is still diverse.

International bodies such as WHO, EFSA, and USEPA have proposed exposure-response functions (ERFs) for air pollutants, enabling standardised burden of disease calculations. However, such curves are limited for chemicals like phthalates, underscoring the need for further research.

Limitations of current epidemiological evidence

Although numerous systematic reviews and meta-analyses exist, the heterogeneity of these studies constrains their utility. Frequently, exposure data is neglected in these analyses. The absence of detailed exposure data in meta-analyses hampers their applicability in EBD frameworks. Also, the large discrepancy in exposure concentrations across these different studies complicates interpretation. Furthermore, methodological flaws are common in some meta-analyses, including duplicate inclusion of studies, inconsistent reporting of odds ratios, and failure to account for units of exposure, which are recurrent issues that compromise data integrity. Additional methodological challenges include the correlated nature of chemicals within and across substance groups and the limited number of studies on this topic. The lack of multipollutant effect studies makes it difficult to account for the attribution of a specific chemical to a certain effect.

For HBM, data availability and harmonisation are increasing under the EU studies HBM4EU and PARC. However, more effort is needed to obtain EU-wide national representative exposure data that allows for EU-wide estimates of EBD.

The integration of evidence from epidemiological studies with in vivo and in vitro data, enabling a weight of evidence approach, was beyond the scope of the current project.

Exposure response derivation

Current practice often relies on a single epidemiological study to derive ERFs for chemical exposures and to be used in EBD assessments. This approach risks oversimplification and may obscure critical nuances such as exposure thresholds and dose-response gradients.

Studies examining phthalate exposure (e.g. diabetes across varying exposure levels) should be systematically reviewed to construct a more representative ERF. This would enhance the accuracy of burden estimates.

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Conclusion

The integration of chemical exposure into EBD frameworks is both necessary and feasible, but it demands rigorous methodological refinement. Strengthening the evidence base—particularly for emerging chemicals like phthalates—requires coordinated efforts to improve study quality, harmonise exposure metrics, and develop “robust ERFs”. Only then can we accurately quantify the health burden and inform effective policy interventions.

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5 Transferability to green space

In this chapter we evaluate whether the methods developed for assessing the burden of diseases due to air pollution and noise can be transferred to green space.

The availability of green spaces, including parks, gardens, and other types of landscaping, plays an important role in creating healthier living environments. Access to greenery can both protect and improve public health by offering places to exercise, relax, and connect with others, as well as by promoting social cohesion. Green areas can also help reduce exposure to heat, air pollution and noise.

Research has shown that having green spaces nearby can have a positive impact on health by helping to reduce a range of diseases (den Hertog et al., 2022). However, the exact mechanisms behind the impacts of green environments on health are still not fully understood, and it remains difficult to isolate and study these mechanisms individually. Because of this, it is challenging to directly link a specific green intervention to a concrete health outcome. For instance, we cannot yet claim that building a city park of a certain size will definitely lead to a measurable decrease in cardiovascular disease in the surrounding neighborhood. This is largely because greenery can influence health in several ways – by reducing harmful exposures, supporting recovery, and encouraging healthier behaviors – and these effects can overlap and interact in complex ways (Figure 10). This makes it difficult for urban planners to give green space the attention it deserves in their decision-making. To address this, it is important to develop quantitative insights that clearly show the health benefits of interventions such as adding more green space.

A large cross-sectional survey from 18 countries illustrated the importance of recent visit frequency to green spaces for physical activity, social contact, and subjective well-being (Pasanen et al., 2023; Eliott, 2023). By simultaneously studying multiple serial pathways, this study has underlined the importance of neighbourhood nature to potentially facilitate a range of health-related and overall health benefits, including well-being. An overview by Chen et al. (2025) shows that while proximity to green space is related to life satisfaction, active engagement with nature or time spent in nature is a stronger predictor of mental health and social well-being than residential proximity.

As a part of the Dutch GRIP project, RIVM has reviewed a wide range of scientific studies until 2021 examining the quantitative links between green spaces and health (Lock et al., *In press*). The strength of the scientific evidence was assessed and the areas where more research is needed were identified. To help with the selection of international studies and endpoints, a conceptual model developed for the Netherlands (den Hertog et al., 2022) was used (Figure 10). This model was inspired by an earlier framework of (Hartig et al., 2014), including potential impacts such as increased physical activity, more social contact, reduced stress and better air quality. The impacts described in Figure 10 were based on a literature review and expert consultations.

This review was based on a mixed-method approach. Scientific as well as grey literature between the period 2014-2021 was evaluated (search terms: urban green public green, green area, NDVI, urban parks, health effects of urban green). Ultimately, 19 studies (reviews, meta-analyses and a few Dutch studies) were selected for further evaluation.

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The conclusion of the GRIP project was that establishing a clear, quantitative link between the amount of green space in an area and the effect on specific health conditions remains a challenge. This was partly due to varying definitions of what constituted green space, which could range from trees and parks to recreational areas, and as a result – different measures to quantify green space. The most convincing quantitative relationship in the review was between an increase in the Normalized Difference Vegetation Index (NDVI) and a reduction in all-cause mortality risk, with the risk decreasing with 4% for each 0.1 increase in NDVI (Rojas-Rueda et al., 2019).

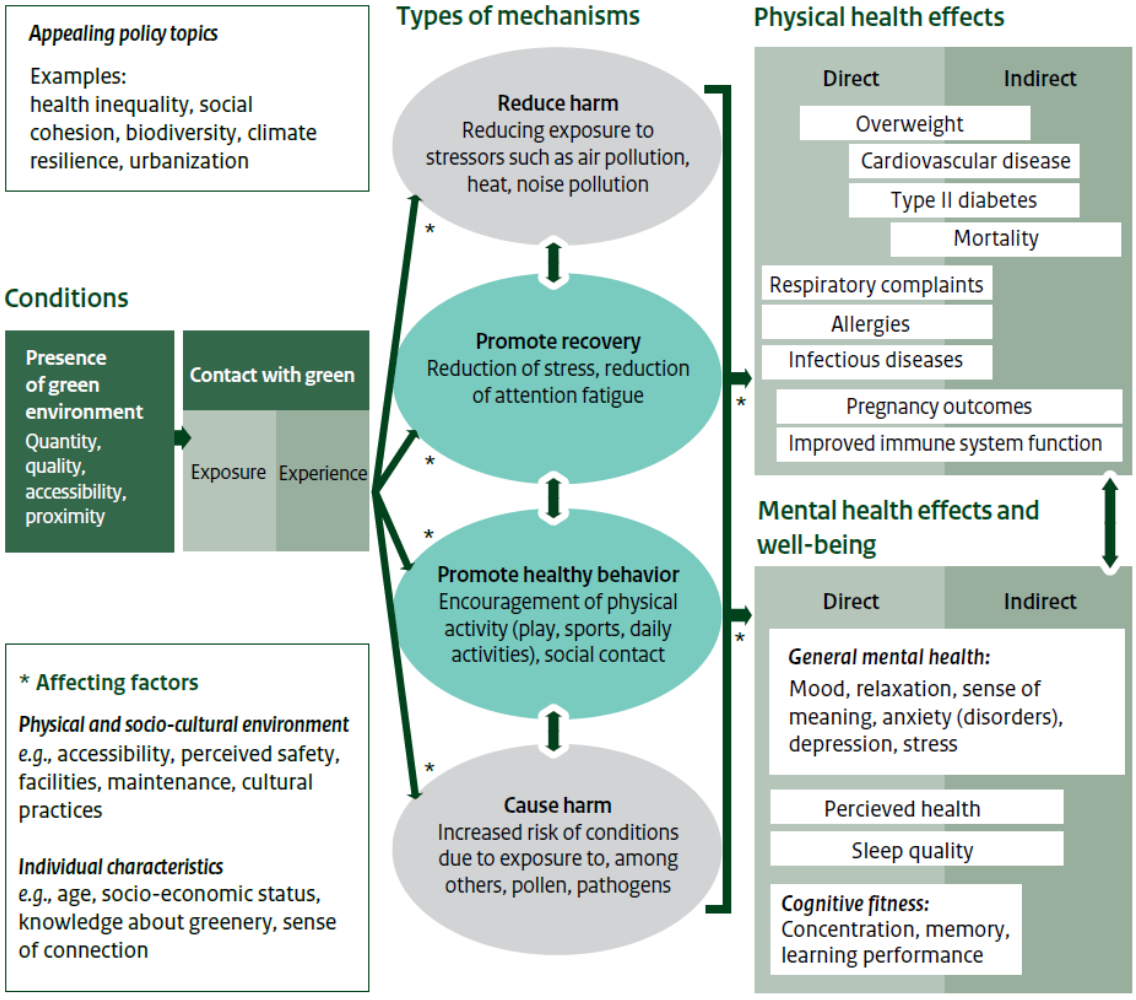

Figure 10. Conceptual model of the effects of green space on health. Translated from den Hertog et al. (2022).

In the quantitative evaluation by Rojas-Rueda and colleagues (2019), nine cohort-studies were included, six of which had a low risk of bias. The results are consistent with previous systematic reviews and meta-analyses that had indicated a marked negative association between the amount of nearby green space and mortality and morbidity. The evaluation focused only on the epidemiological studies with longitudinal study design, providing more robust evidence and quantitative estimates for greenness that can be used for health impact assessment (HIA) and risk assessment.

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In 2024, Xie and colleagues (2024) published a comprehensive overview of meta-analyses evaluating the credibility of the evidence on green space exposure and human health. Using rigorous evaluation protocols, the study showed that only a limited number of the associations can be graded as (highly) credible. The evidence of the association between residential greenness and cardiovascular disease mortality was labelled "convincing" (Table 14). The associations between NDVI and diabetes mellitus prevalence, NDVI and preterm birth, greenspace and small for gestational age, and residential greenness and all-cause mortality were labelled "highly suggestive". Evidence for mental health outcomes such as depression was rated as "suggestive".

Table 14. Evidence from meta-analyses of observational studies linking green spaces and health outcomes supported by convincing, highly suggestive, or suggestive credibility. Adapted from Xie at al. (2024).

Author (year)	Exposure	Exposure contrast	Outcome	Effect estimates (95% CI)	Evidence
Gascon et al. (2016)	Residential greenness[a]	Q1 vs. Q3	Cardiovascular disease mortality	RR 0.96 (0.94, 0.97)	Convincing
			All-cause mortality	RR 0.92 (0.87, 0.97)	Highly suggestive
Meo et al. (2022)	NDVI (multiple buffers)	Per IQR increase	Prevalence of diabetes mellitus	OR 0.88 (0.86, 0.89)	Highly suggestive
			Mortality of diabetes mellitus	OR 0.92 (0.90, 0.93)	Suggestive
Hu et al. (2021)	NDVI (500 m)	Per 0.1 increase	Preterm birth	OR 0.99 (0.97, 1.00)	Highly suggestive
Twohig-Bennett et al. (2018)	Greenspace[b]	Q1 vs. Q3/Q4	Small for gestational age	OR 0.81 (0.76, 0.86)	Highly suggestive
			Preterm birth	OR 0.87 (0.80, 0.94)	Suggestive
			Type II diabetes prevalence	OR 0.72 (0.61, 0.85)	
			Good self-reported health	OR 1.12 (1.05, 1.19)	
Li et al. (2023)	NDVI (multiple buffers)	Per 0.1 increase	Neurodegenerative diseases mortality	RR 0.98 (0.98, 0.99)	Suggestive
Liu et al. (2023)	Percentage greenspace	Per 10% increase	Depression	OR 0.96 (0.95, 0.98)	Suggestive
Qiu et al. (2021)	NDVI (multiple buffers)	Per 0.1 increase	Cardiovascular disease	OR 0.89 (0.86, 0.91)	Suggestive
			Respiratory diseases	OR 0.95 (0.92, 0.98)	
Luo et al. (2020)	NDVI (multiple buffers)	Per 0.1 increase	Overweight/obesity	OR 0.88 (0.84, 0.91)	Suggestive
Lee et al. (2020)	NDVI (multiple buffers)	Per 0.1 increase	Term birth weight	SMD 0.003 (0.002, 0.004)	Suggestive
Zhan et al. (2020)	NDVI (> 300 m)	Per 0.1 increase	Gestational diabetes mellitus	OR 0.62 (0.49, 0.78)	Suggestive
	NDVI (500 m)		Low birth weight	β 22.41 (11.01, 33.82)	

[a] Residential greenness measured as the percentage of green space in an area or as NDVI. [b] Mixed green space metrics including neighbourhood green space, green space-based interventions, proximity to a large green space, or comparing a green environment with an urban or indoor environment. RR: risk/rate ratio; IQR: interquartile range; OR: odds ratio; SMD: standard mean difference.

As documented by the GRIP project (Lock et al., *In press*) and Xie and colleagues (2024), most scientific studies use two general metrics: the NDVI and percentage of green coverage in an area. While these metrics make it easier to compare studies, they are very broad and do not

differentiate between types, qualities, attractiveness, appreciation, safety, or accessibility of green spaces. Because of their broadness, it is difficult to draw robust, health outcome-specific conclusions. Nevertheless, these metrics are currently the standard in research and as such they form the basis for current quantitative insights.

5.1 Workshop on green space

In November 2025, as a part of WP5 of the BEST-COST project, we organized an online workshop "HIA and Green Space", to discuss opportunities and challenges for conducting HIA of green spaces with a panel of experts. For the list of consulted experts see Annex 2. The main findings of the workshop were:

1. **There are still notable challenges when it comes to measuring the health impacts of green space**

Although there is broad consensus on the importance of this issue, current metrics used to assess the health impacts of green space have significant limitations. For HIA, it is crucial to use a metric that is well-established, consolidated, consistently applied over time, and clearly linked to important health outcomes. Establishing such a metric is not straightforward; for example, it took many years for air pollution researchers to agree upon and collect data for metrics like PM2.5.

One of the most commonly used metrics for green space is the Normalized Difference Vegetation Index (NDVI). NDVI is favored because it relies on satellite data that is widely available, standardized, and historically available. Its ease of use and ability to provide a quantifiable assessment of exposure means that NDVI is used in the vast majority of studies investigating the health impacts of green space.

However, NDVI has considerable drawbacks. It fails to capture critical aspects such as the quality, type, accessibility, or actual use of green spaces. Moreover, it does not reflect the mechanisms by which green space can influence health. This creates a disconnect between what is measurable, such as NDVI, and what is truly meaningful for health and policy, like the number of trees planted, time spent in green spaces, or the accessibility and typology of green areas.

As a result, it is challenging to translate research findings based on NDVI into actionable policy recommendations for municipalities or the public, or to clearly link investments in green space to tangible health outcomes. For example, a hypothetical statement such as *"to avoid xxx numbers of hospitalizations for cardiovascular problems you need to increase the NDVI of the city by 0.1"* remains abstract and does not provide practical guidance.

2. **We need better, multiple, exposure metrics**

Relying solely on NDVI as a measure of exposure to green space is insufficient for accurately assessing its health impacts. It is not a single metric or a single mechanism that explains the health benefits of green space. Thus it is important to differentiate between the different kind of mechanisms. This includes: short visual contacts with green, availability of nearby green for daily use and access to larger green areas further away that you visit from time to time for having a longer or really full contact with green space.

There is a strong need to develop and utilize a broader range of additional or alternative exposure metrics that can provide a more comprehensive understanding. For example,

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measuring the **time people actually spend in green spaces**, sometimes referred to as usage, may be a more relevant indicator of health benefits than simply quantifying the amount of green space available. Other metrics, such as the **number and type of trees**, offer tangible data that municipalities can use for cost-benefit analyses and to estimate health benefits per tree planted. However, focusing solely on trees may overlook other important types of greenery, and the choice of tree species can also influence health outcomes, particularly with regard to allergens like pollen. Beyond quantity and type, the **quality and typology of green spaces** are also crucial factors, as is the **proximity and accessibility** of these areas for residents. Metrics like **viewing indices**, which assess how much greenery is visible from a given location, can offer additional insights into exposure. Despite the potential advantages of these alternative metrics, their immediate use in HIAs is limited by the lack of well-established exposure-response functions.

Once a suitable metric has been agreed upon, it is recommended to create a locally relevant green map at a fine resolution to better guide planning and policy decisions. The issue of determining the optimal amount of green space, similar to established guidelines for air pollution or noise, remains an open question that research needs to answer.

3. Health impact assessment methods for green spaces are still limited

Current HIA methods face notable limitations when applied to green space exposure. The calculation methods developed for air pollution and noise cannot be directly transferred, largely due to the complexity and diversity of green space metrics as well as the multiple mechanisms by which green spaces affect health. Most existing exposure-response functions are based on NDVI and tend to focus primarily on mortality or a limited range of physical health outcomes. However, concentrating solely on mortality risks underestimating the full spectrum of benefits provided by green spaces. Moreover, when assessments focus only on mortality, the effect size may appear small and less convincing to policymakers.

This narrow view fails to capture the substantial combined benefits that span multiple health and environmental outcomes. As a result, there is a growing call to expand the range of health outcomes considered in these assessments, particularly Important impacts such as improvements in mental health, stress reduction, increased social contact, enhanced physical activity. These aspects have quite strong supporting scientific evidence, but they are less frequently quantified in current HIAs. The effects on ecosystem services, mitigation of the urban heat island effect, reduction of air pollution, and the role of green spaces as noise barriers are also significant, yet often overlooked. If you consider the impact of green space in isolation, it might seem somewhat negligible for public health, whereas the picture changes substantially if you consider the cumulative and interconnected benefits of green space.

Instead of simply measuring how much greenery is present in an area, research should focus on how people actually interact with green spaces—whether they spend time there, how often they visit, and whether they truly experience the benefits of being in nature (Kruize et al., 2020).

4. Mechanisms and context matter

As visualised in Table 10 the mechanisms through which green spaces benefit health are complex and multifaceted. We still do not know exactly which types of greenery or which specific mechanisms are the most effective in promoting health. Different types of green contact, whether it is visual exposure, proximity for daily use, or access to larger areas for recreation, can provide different and distinct advantages. These diverse pathways cannot be

fully captured by a single metric, making it challenging to assess the overall impact of green spaces on health. Thus, it is important to delve deeper into the underlying mechanisms and explanations for why certain health benefits are expected to occur.

Furthermore, the effects of green space can vary significantly depending on the population group, such as the elderly compared to younger individuals, as well as the specific urban context and local biomes. Taking these diverse mechanisms into account allows for tailored messaging and targeted interventions for different population groups, which is vital for effective health policy.

Overall, to truly understand and capture the complexity of the health impacts of green spaces, and to ensure more accurate and meaningful HIAs, there is a clear need for a more nuanced methodological approach that considers both mechanisms and context when designing green space exposure metrics.

The **key takeaways** from the workshop were that there is no single perfect indicator for assessing the health impacts of green space, and that the future work should focus on developing and validating multiple complementary metrics to better capture the complexity of green space exposure and its mechanisms. This would ensure that the findings are both scientifically robust and relevant for policy and urban planning. The experts involved in the workshop also provided the following recommendations and next steps:

- Move away from the ambition of relying on a single indicator to assess the health impacts of green space. Instead, multiple exposure metrics should be used to provide a more complete and accurate picture.
- Development of a more nuanced set of indicators is essential, as this will help to better reflect the various mechanisms through which green space can influence health.
- The focus of future research should be on key health determinants, such as physical activity, social contact, and stress reduction, and examine how these factors are related to green space. This approach could lead to the development of more meaningful metrics that capture the broader associations between green space and health outcomes.
- Recognize that current HIAs for green space are incomplete and should not be over-interpreted. Researchers and policymakers should be transparent about the limitations of the existing metrics and the underestimation of impacts.
- Encourage greater collaboration. This includes developing and sharing methodologies, such as conversion models between NDVI and different metrics, or viewing indices, to help standardize and improve HIAs. Additionally, there is a need for further research to establish exposure-response functions for alternative metrics and to expand the range of health determinants and outcomes considered.

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6 Conclusion

The Environmental Burden of Disease (EBD) approach provides a critical tool for informing policymakers about the extent of the health impact from different risk factors. This BEST-COST work package (WP6) explored the transferability of EBD methodologies—well-established for air pollution and noise—towards chemical exposures and health-promoting factors such as green space. Currently, EBD applications for chemicals and green space remain fragmented and underdeveloped, often limited to ad hoc case studies.

As a first step, methodological approaches were compared across air pollution, noise, and chemicals, highlighting both commonalities and gaps that must be addressed to enable EU-wide burden estimates for chemicals. Chemical exposure assessment can rely on human biomonitoring (HBM) data for internal exposures or modelling approaches mainly for external exposure based on environmental concentrations, depending on the substance. However, harmonised EU-wide HBM data is lacking. Initiatives like HBM4EU and PARC enabled making important progress regarding internal exposure information, but significant data gaps persist, especially regarding national representativeness. The use of self-administered micro-sampling would open new avenues for gathering high-resolution (internal) exposure data at large scale.

Unfortunately, HBM data solely (without any external information) faces limitations for direct exposure mitigation, notably the inability to distinguish exposure routes. Complementary measurements in consumer products, food, drinking water, air etc. are necessary ("Where is the internal exposure coming from?"). New monitoring approaches—such as non-targeted screening and effect-based monitoring—may complement the knowledge base with information on hitherto unknown chemicals that may add up to the disease burden. Exposure entails a wide range of different chemicals with possible overlapping health effects. To address mixture effects, emerging statistical approaches like BKMR (Bayesian Kernel Machine Regression) offer promising avenues. Robust exposure-response functions (ERFs) with clear causal stressor-outcome links are essential. While such functions are introduced for air pollution and noise (e.g. WHO-defined RR), they are largely absent for chemicals, with lead being a notable exception.

As a proof of concept, we focused on phthalates, given their relevance to plastic pollution and the large database available for exposure as well as for health effects. A new database of EBD assessments and meta-analyses per phthalate and health outcome was compiled and made available via Zenodo (DOI: 10.5281/zenodo.17910475). Two EBD calculations were performed—one estimating the impact of DMP exposure on diabetes, and another estimating the impact of DBP exposure on preterm birth—based on the individual studies underlying the meta-analyses. Going back to the individual studies was necessary due to poor reporting and a lack of exposure data in existing meta-analyses, which sometimes suffer from methodological flaws such as duplicate inclusion, inconsistent odds ratios, and do not always cover differences in exposure.

Incorporating chemical exposures into Environmental Burden of Disease (EBD) frameworks is both essential and achievable, provided that methodological approaches are significantly strengthened. Advancing the evidence base—particularly for compounds of concern such as phthalates—calls for coordinated action to enhance study design, to standardise exposure

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assessment, and to establish reliable exposure-response functions (ERFs). These improvements are critical to accurately estimate health impacts and guide informed, effective policy decisions.

For green space, access to greenery can both protect and improve public health by offering places to exercise, relax, and connect with others, as well as by promoting social cohesion. Green areas can also help reduce exposure to heat, air pollution and noise. The calculation methods developed for air pollution and noise cannot be directly transferred to green space though. This is largely due to the complexity and diversity of green space metrics as well as the multiple mechanisms by which green spaces affect health. Most existing exposure-response functions for which robust evidence is available are based on NDVI (normalized difference vegetation index) and tend to focus primarily on mortality or a limited range of physical health outcomes. However, concentrating solely on mortality risks may underestimate the full spectrum of benefits provided by green spaces. Moreover, when assessments focus only on mortality, the effect size may appear small and less convincing to policymakers. Instead, development of a more nuanced set of indicators is essential, as this will help to better reflect the various mechanisms through which green space can influence health. The focus of future research should be on key health determinants, such as physical activity, social contact, and stress reduction, and examine how these factors are related to green space.

Still, much more data on various sorts of exposure (noise, air pollution, chemicals, stress etcetera) and throughout the whole life cycle are necessary within the exposome concept. This will provide an integrated picture of the totality of exposures that may cause health effects, each as such or in various combinations. With sophisticated statistical approaches, new ERFs should emerge.

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7 Annex 1

7.1 Overview of exposure-response functions phthalates in reports evaluated by SEAC

Reproductive effects after phthalate exposure have been observed in male rats. Similar effects have been observed in humans known as “testicular dysgenesis syndrome” or TDS.

The human health and environmental benefits associated with reduced exposure to the four phthalates in articles are discussed qualitatively in the dossier. To illustrate the magnitude of these impacts and the proportionality of the proposed restriction the Dossier Submitter quantified and monetized the impacts with the strongest strength of evidence between exposure and observed effect: male infertility (due to in utero exposure), cryptorchidism, and hypospadias.

The number of attributable cases and associated costs related to exposure to the four phthalates was calculated (Table 15). The derived etiological fraction given in the dossier was based on the report by the Nordic Council of Ministers (Olson, 2014). The Nordic Council used a fixed estimate for the etiological fraction (top-down approach) based on expert knowledge so no exposure-response curve was applied.

Table 15. Quantification and monetisation of human health benefits in restriction report for 4 phthalates to ECHA

	Infertility	**Cryptorchidism**	**Hypospadias**
Incidence rate in EU-population	15%[21]	2.4%[22]	3%[23]
Derived aetiological fraction associated with exposure to the four phthalates in articles (as % of all new born males)*	0.08%	0.018%	0.021%
Annual cases attributable to four phthalates in articles	**2 110**	**480**	**540**

*: The specific fraction used for the main case benefit estimation scenario was established on the basis of an expert opinion by Norden (2014), specifically for the health outcomes related to TDS, presented in the dossier.

SEAC did find that the uncertainty of the benefits assessment was high. The uncertainty related to aetiological fractions dominates and is of unknown direction.

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7.2 Background information on effects phthalates observed in reports from ATSDR, EFSA, ECHA, USEPA, OECD.

7.2.1 ATSDR

The toxicological profile for DEHP was assessed in 2022 (Agency for Toxic Substances and Disease Registry (ATSDR), 2022). According to the ATSDR, human epidemiological studies evaluating potential adverse effects from phthalates are insufficient to draw firm conclusions regarding the exposure-response relationships for individual phthalate esters. Therefore, ATSDR is for the risk assessment in favour of a chemical group approach. The table below lists the health effects for which potential associations are suggested based on animal data and limited human data.

Table 16. Overview health outcomes for which selected animal studies, along with limited human data, suggest potential associations with DEHP exposure (Agency for Toxic Substances and Disease Registry (ATSDR), 2022).

Outcome category	Information
Hepatic	Human data regarding hepatotoxicity are limited and do not show consistent findings. In rodents, high DEHP doses resulted in degenerative and necrotic hepatic changes. At lower DEHP doses, there is evidence of liver enlargement (increased liver weight, hepatocellular hypertrophy) associated with peroxisomal proliferation in rodents; however, these responses are considered adaptive and human relevance is unclear due to association with the nuclear receptors, particularly PPARα. Thus, doses associated with hepatomegaly were not considered adverse effect levels unless hepatocellular degenerative or necrotic changes or evidence of biliary or other liver cell damage were also present. The lowest doses associated with the liver weight increases and hepatocellular hypertrophy are noted even though the dose levels are considered NOAELs.
Renal	Human data regarding renal effects following DEHP exposure are extremely limited, and do not report consistent findings. In animals, there is some evidence that the kidney is a sensitive target of DEHP toxicity following oral exposure. However, most of the available studies observed kidney damage only at high doses.
Immunological	Human data regarding immunological effects following DEHP exposure are extremely limited. Results from studies evaluating potential associations between prenatal exposure and childhood risk of wheezing or increased IgE were inconsistent. However, some animal studies provide evidence that DEHP is an immune adjuvant in sensitized animals at low exposure levels. The human health relevance of findings from sensitized animals is uncertain in the absence of clear evidence that the immune system is a target of DEHP toxicity in humans or unsensitized animals.
Reproductive	Epidemiological studies suggest a potential association between DEHP exposure and decreased serum testosterone and altered sperm parameters in males. Available studies on fertility effects in humans do not indicate an association between DEHP exposure and infertility. In animals, the available oral and inhalation studies provide evidence that the male reproductive system, particularly the testes, is susceptible to DEHP toxicity. Evidence from animal studies indicates decreased male and female fertility at high oral doses.
Developmental	Epidemiological studies suggest a potential association between reduced AGD and testicular decent in male infants and prenatal DEHP exposure. In addition,

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Outcome category	Information
	human epidemiological studies provide mixed results for potential relationships between exposure to DEHP and preterm birth, early puberty, and delayed mental and psychomotor development in children. Studies in animals indicate that altered glucose homeostasis and the development of the reproductive system following early life exposure is a particularly sensitive target of DEHP toxicity.

For metabolic effects, available human epidemiological studies suggest a potential association between DEHP exposure and obesity in adults. Most of these studies have numerous limitations arising from cross-sectional design and lack of consistent control for potential confounders. Most animal studies evaluating body weight focus on body weight decreases following exposure to high levels of DEHP. Only a limited number of rodent studies reported elevated body weight following oral exposure (Agency for Toxic Substances and Disease Registry (ATSDR), 2022).

Toxicological profiles were also available for DnBP (ATSDR, 2001), DnOP (ATSDR, 1997) and DEP (ATSDR, 1995) but were older than the year 2001.

7.2.2 EFSA

The EC asked EFSA to carry out preparatory work to re-evaluate the health risks from plasticizers such as phthalates (EFSA, 2022).

In 2019 EFSA performed a risk assessment of DBP, BBP, DEHP, DINP and DiDP for use in food contact materials (EFSA, 2019). Overall, the review of the toxicological data focused mainly on reproductive effects. The CEP Panel (EFSA Panel on Food Contact Materials, Enzymes and Processing Aids) is aware of this limitation and considers that all the potential toxicological endpoints should be examined with the same degree of rigor.

Most of the epidemiological studies on reproductive outcomes, excluding prospective studies on phthalates and AGD (anogenital distance), have various methodological shortcomings (e.g. small sample sizes, cross-sectional design).

Based on the prospective studies and consideration of animal studies, the CEP Panel agrees that there are some data that show an association between phthalate exposure (DEHP, DBP, BBP) in utero and reduced AGD in male newborns, although the epidemiological studies reviewed are inconsistent and have some limitations.

Epidemiological studies with larger sample sizes and with better exposure characterization (e.g. multiple samples of urine to measure exposure) plus controlling of confounders are needed. In epidemiological studies that investigated other reproductive outcomes, data available is not sufficient to draw conclusions (EFSA, 2019).

7.2.3 USEPA

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Under the Toxic Substance Control Act (TSCA) information is available on the risk assessment of phthalates based on animal studies (USEPA, 2024). Phthalates considered were DiDP, DiNP, BBP, DEHP, DiBP, DBP and DCHP. For BBP, DEHP, DiBP, DBP and DCHP effects on the reproduction system were most sensitive and robust for estimating the risk to human health. For DiDP liver and developmental toxicity were considered and for DiNP cancer and non-cancer hazard endpoints (liver, kidney, neurological and developmental toxicity) were considered.

7.2.4 ECHA

In 2017, ECHA evaluated four phthalates (DEHP, BBP, DBP, DiBP) identified as Substance of Very High Concern (SVHC) due to reproductive toxicity (Cat. 1B) in the context of a restriction proposal (ECHA, 2017a, 2017b).

The toxicological information used by the ECHA RAC was focused on reproductive toxicity, the effect with the most robust data. Other potential effects on the immune system, the metabolic system and neurodevelopment, were concisely discussed, even though the RAC recognized that there were (qualitative) indications that they could possibly be equally or more sensitive (e.g. effects on the immune system) than reproductive toxicity.

For the reproductive effects (congenital malformation of the male genitalia, semen quality, pubertal timing and testicular cancer), according to ECHA the epidemiological studies have such uncertainties that these do not allow for the conclusion for a causal relationship.

For effects on the metabolism, the Dossier Submitter of the ECHA opinion reported only weak evidence. Although the RAC considers that such effects cannot be excluded. It's acknowledged that these data are insufficient for PoD and DNEL derivation, however the RAC supports the Dossier Submitter to include the possibility of these effects in the uncertainty analysis and in the socio-economic analysis (SEA). In the uncertainty analysis it was stated that '*a number of experimental and epidemiological studies suggested possible effects on the metabolic system and neurological development. It is not clear from the data whether the selected DNELs based on reproductive toxicity are sufficiently protective against these other effects*.'

For neurodevelopmental effects, ECHA concluded that effects have not yet been elucidated. The Dossier Submitter considered the available data as weak. However, the RAC denotes that available epidemiological and experimental data do indicate that such effects cannot be excluded.

For effects on the immune system, the ECHA noted in its assessment that several studies suggested adverse effects of phthalate exposure on the immune system, in particular leading to allergy, asthma and eczema. ECHA concluded that there is a need for further robust data to perform a risk assessment regarding adverse effects on the immune system (ECHA, 2017a, 2017b).

7.2.5 OECD/ OECD working papers on the costs of phthalate exposure

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The OECD working paper authored by Mike Holland mainly builds on conclusions from the Transande papers in which exposure-response functions follow a Delphic approach and are based on single studies. The health impacts linked to exposure to phthalates affect the reproductive system, neurodevelopment, cancer incidence, obesity, diabetes, asthma and allergy. However, the strength of association is variable, and most quantification work is focused on male reproduction (OECD, 2018). The studies performed by (Olson, 2014) and (HEAL, 2014) are also discussed, which assume a fixed percentage of specific diseases attributed to endocrine disruption.

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8 Annex 2

Alphabetical list of the participants of an *Online workshop HIA Green Space* (November 3 2026):

1. Jurgen Buekers (VITO, Belgium)
2. Xuan Chen (IRAS, The Netherlands)
3. Payam Dadvand (ISGlobal, Spain)
4. Leo De Nocker (VITO, Belgium)
5. Tamara Iungman (ISGlobal, Spain)
6. Sasha Khomenko (ISGlobal, Spain)
7. Hanneke Kruize (RIVM, The Netherlands)
8. Pierpaolo Mudu (WHO)
9. Sinaia Netanyahu (WHO)
10. Arno Pauwels (Sciensano, Belgium)
11. Carmen Peuters (ISGlobal, Spain)
12. Brigit Staatsen (RIVM, The Netherlands)
13. Maciek Strak (RIVM, The Netherlands)
14. Karen Van de Vel (VITO, Belgium)

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BEST-COST is funded by the European Union's Horizon Europe programme under Grant Agreement No.101095408

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