METEOR Cluster WG 4:

Exposure-response functions for health impact assessments

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1. Preamble

METEOR is a cluster of five Horizon Europe projects researching the health impacts of environmental stressors such as air, chemical and noise pollution, and their related socioeconomic costs. Together they lay out a detailed view of how health is impacted by the environment and suggest policy recommendations to protect our health and the planet. More information about the cluster can be found in the METEOR cluster brochure.

The aims of the METEOR cluster are

- To create synergies between projects exploring the health impacts of environmental stressors and create a shared approach.
- To identify key areas of action to reduce the health impacts of environmental pollution and guide the research community in applying the findings further.
- To amplify messages and recommendations to policymakers to address key challenges in environmental pollution.
- To maximize the communication and dissemination of results through our networks.

METEOR's work takes place in 6 working groups bringing together partners from different fields to synergize the outcomes from each project and create joint activities.

WG4 Exposure-response analysis (led by UBDPolicy) explored the exposure-response relationships (ERFs) for health impact assessments that arise from the cluster project focus areas including air pollution, chemical exposures, noise, green spaces and temperature. The **aim** of the working group was to create an inventory of exposure-response functions used in the different projects without striving to reach full consensus or harmonization across projects.

This document provides some background to the inventory including a brief introduction to Health Impact Assessments and considerations for choosing exposure-outcome pairs and ERFs for Health Impact assessments. The inventory is publicly available to researchers, policy makers and others involved or interested in health impact assessments through the METEOR cluster website. The information will also be shared through the websites of the individual projects and cluster and project newsletters.

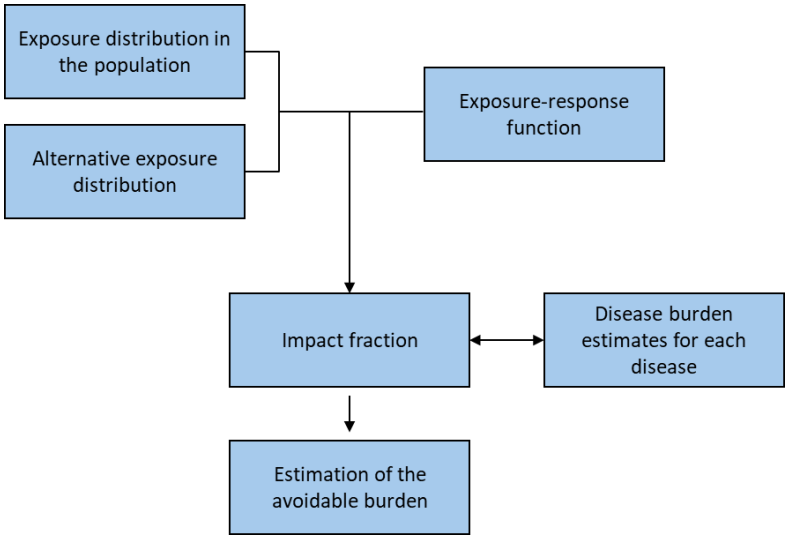
The choices for specific exposure-outcome pairs and quantitative ERFs to be used in the different METEOR projects were made based on the most recent available evidence. As the evidence base continuously grows, these choices may need to be reviewed in the future.

2. Introduction

Public health practitioners and policymakers have a responsibility to ensure good health and wellbeing for the population. To achieve this, they need to be able to evaluate the distribution of diseases and disabilities as well as major risk factors of these diseases in the population to be able to compare different policy options. This supports the best use of limited resources and helps to obtain the best results concerning population health and well-being as well as health equity. Health Impact Assessments (HIAs) and Comparative Risk Assessments (CRAs) can support the creation of new policies or identify the need to refine the ones already implemented based on the most recent evidence. In a CRA, the changes in population health that would result from modifying the population distribution of exposure to a specific (environmental) risk factor or a group of risk factors are evaluated. HIAs are used to estimate the potential effects of a policy or program on future population health.

Quantitative HIAs combine projected changes in (environmental) exposures due to a (proposed) policy with evidence on the relationship between these exposures and health (Figure 1). This involves measuring and mapping exposures, identifying and characterizing the population-at-risk, choosing exposure-response functions (ERF), obtaining background rates for health outcomes of interest from the population at risk, and predicting the health impact.

Figure 1. Calculation of health impacts for exposure scenarios (after (1)).



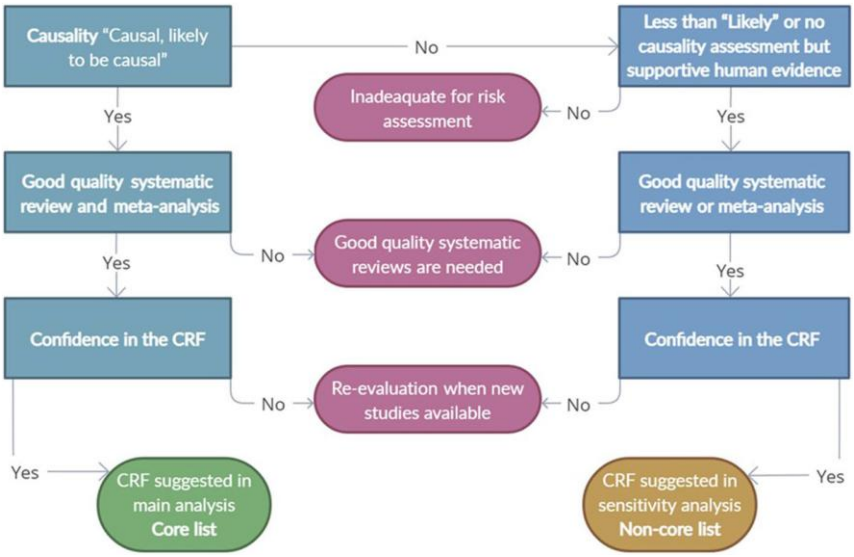
The choice of the exposure-outcome pairs to be included in a HIA and the respective quantitative exposure-response functions is a crucial part of the HIA and requires careful consideration.

3. Selection of exposure-outcome pairs

3.1 Causality assessment

Conducting a HIA requires a causality determination of the health effects associated with the specific exposure and sufficiently robust ERFs (2). Figure 2 shows a schematic overview of steps in choosing the appropriate exposure-response function or concentration-response function. As for the other data used in HIA calculations, the ERFs come with uncertainties that we aim to minimize as much as possible by selecting the most robust ERFs, and at least make them explicit and discuss them.

Figure 2. Schematic overview of steps in choosing concentration-response functions for health impact assessments – schematic overview (Source: Forastiere et al. (2))



We argue that the inclusion of exposure-health outcome pairs in HIAs should be well founded, that decisions about inclusion should preferably rely on the integration of epidemiological, toxicological and clinical studies, and mechanistic explanations, and that only exposure-outcome pairs for which causality assessments suggest associations to be causal or likely causal should be included. However, we also suggest sensitivity analyses including additional exposure-outcome pairs for which causality is not yet established, but for which there is good evidence as limiting the selection to exposure-outcome pairs with established causality generates conservative estimates.

A potential limitation of relying on such fully integrated assessments is that they are not updated and published at a high frequency and as a consequence will not include recent research (e.g. the most recent Integrated Science Assessment (ISA) for NO_2 has been published in 2016 (3)). Moreover, such integrated assessments will be largely limited to air pollution and not be available for other exposures such as noise, green space, temperature, and physical activity. Consequently, choosing causality as a prerequisite may lead to a potential underestimation of the health burden or impact. Therefore, in cases where no (recent) integrated assessments are available, we will rely on confidence in evidence assessments that have been made by exclusively evaluating the epidemiological evidence base. Such confidence assessments using the Grading of Recommendations Assessment, Development and

Evaluation (GRADE) and Office of Health Assessment and Translation (OHAT) approaches have been used for the World Health Organization (WHO) 2018 noise (4) and WHO 2021 air pollution (5) assessments, respectively.

Below we provide an overview of existing causality assessments for the exposures of interest to the METEOR cluster, i.e. air pollution, noise, green space, and temperature.

Air pollution

Causality determinations for the health effects of air pollution on mortality and morbidity have been performed by the US EPA and published in their ISA reports available at https://www.epa.gov/isa. For cancer, causality assessments are performed by the International Agency for Research on Cancer (IARC). These reports provide summaries of the scientific knowledge on the health effects of air pollutants taking into account evidence from controlled human exposure studies, toxicological animal studies and epidemiological studies.

Moreover, the Health Effects Institute (HEI) recently performed evidence assessments for the health effects of traffic-related air pollution of which NO_2 is the most commonly used indicator followed by elemental carbon (EC) and $PM_{2.5}$ (6).

Table 1 provides a summary of the previously mentioned assessments for particulate matter < 2.5 µm ($PM_{2.5}$), nitrogen dioxide (NO_2) and ozone (O_3), including the effects of both short-term and long-term exposure. We did not include other particulate matter (PM) size fractions like PM_{10}, PM_{coarse} and ultrafine particles as scientific evidence was less substantial for these. We also did not include elemental carbon as another indicator of traffic-related air pollution, as including both elemental carbon and NO_2 would result in an overestimation of the health impact of traffic-related air pollution.

The Global Burden of Disease (GBD) study also performs assessments. Since 2021, it uses the Burden of Proof methodology (10) to assess the strength of the epidemiological evidence. The methodology uses a star ranking system to show how strong the link is between exposure and health outcome (5 stars = strong evidence, 1 star = inadequate evidence to determine a link).. To maintain stability in included risk factors and risk–outcome pairs between GBD cycles, risk–outcome pairs previously included in GBD 2019 were retained in GBD 2021 provided that there was convincing or probable evidence (defined as the conventionally calculated 95% UI not crossing the null). A list of exposure-outcome pairs included in GBD 2021 assessments can be found in Table S7 of (11).

Table 1. Causality determinations of short-term and long-term exposure according to US EPA and IARC assessments and the overall confidence assessment by the HEI Traffic panel if this argued for a higher confidence than the US EPA and IARC assessments.

	Pollutant		
Category	**$PM_{2.5}$ (reference)**	**NO_2 (reference)**	**O_3 (reference)**
Short-term exposure			
Respiratory effects	Likely (7)	Causal (3)	Causal (8)
Cardiovascular diseases	Causal (7)	Suggestive (3)	Suggestive (8)
Metabolic effects			Likely (8)
Central nervous system			Suggestive (8)
Mortality	Causal (7)	Suggestive (3)	Suggestive (8)
Long-term exposure			
Reproductive & developmental effects	Suggestive (7)	Suggestive (3) **	Suggestive (8)
Respiratory effects	Likely (7)	Likely (3)	Likely (8)
Cardiovascular diseases	Causal (7)	Suggestive (3)	Suggestive (8)
Metabolic effects	Suggestive (7)	Suggestive (3)	Suggestive (8)
Neurological effects	Likely (7)		Suggestive (8)
Cancer (lung cancer)	Likely (7, 9)	Suggestive (3)	Inadequate (8)
Mortality	Causal (7)	Suggestive (3) High *(6)	Suggestive (8)

*High confidence in evidence for an association, ** EPA is currently working on a new ISA, an upgrade to Likely is expected.

Noise

A causality assessment for noise has been published recently by the Environment Information and Observation Network (12). Based on compiled literature including high-quality reviews and, possibly, original study results published after the review papers, the evidence compiled for each health outcome was evaluated for an association between each source of transportation noise and physical and mental health outcomes. If a systematic evidence rating was applied in the original review, we took the corresponding evidence rating, adapting as needed to fit the terminology of the WHO ENG classification scheme: strong, moderate, low and very low.

Table 2. Evidence rating for road, rail and aircraft traffic noise (From Engelmann et al. (12))

Outcome	**Road**	**Rail**	**Aircraft**
% highly annoyed	High	High	High
% highly sleep disturbed	High	High	High
All-cause mortality	High	Very low	Very low
All cardiovascular diseases*	High	Moderate	Low
Ischemic heart disease	High	Moderate	Low
Hypertension	Very low		Low
Arrythmia	Very low	Very low	Very low
Stroke	High	Very low	Very low
Heart failure	High	Very low	Low
Diabetes	High	Low	Low
Depression	Low	Very low	High
Cognitive impairment adults		Moderate (environmental noise)	
Reading and language in children			Moderate
Executive function			Moderate
Dementia	Moderate	Moderate	Very low

Behavioral problems	Moderate	Very low	Very low
Overweight	Very low to moderate for various markers of overweight		

* Summary rating across all cardiovascular diagnostic groups

Green space

Current evidence indicates protective effects of greenspace for a growing number of long-term health outcomes, in particular all-cause and cause-specific mortality and mental health (13-17), but no formal evidence or causality assessments exist.

Temperature

Likewise, there is strong evidence for increased risk of mortality with hot and cold temperatures (18) , without formal evidence or causality assessments.

Drinking water nitrate

Ingested nitrate has been classified by IARC in 2006 as group 2A carcinogen (probably carcinogenic to humans) under conditions that result in endogenous nitrosation (19). Since then, several high-quality epidemiological studies have been published. In a re-evaluation of the drinking water standard for nitrate commissioned by the Danish Ministry of the Environment, it was concluded that nitrate in drinking water constitutes a health risk, with best evidence for colorectal cancer and suggested lowering the drinking water standard from 50 mg/L to 6 mg/L (20). In light of the recently increasing evidence, a re-evaluation of the cancer risk from ingested nitrate has been placed on the IARC priority list for the period 2025-2029 with “medium priority” (21).

3.2 Considerations for inclusion of exposure-outcome pairs

All-cause vs cause-specific mortality

If causal relationships have been established between an exposure (e.g. $PM_{2.5}$) and both all-cause mortality and cause-specific mortality, we recommend including all-cause mortality in HIAs as including both all-cause and cause-specific mortality would result in an overestimation of health impacts.

All cardiovascular disease vs specific cardiovascular diseases.

Similar to the above, if causal relationships have been established between an exposure (e.g. noise) and both, all circulatory system diseases combined and specific cardiovascular diseases, we advise to include all cardiovascular diseases in our HIAs as including both would result in an overestimation of health impacts.

Long-term vs short-term effects of air pollution

There is supportive evidence for effects of long-term and short-term exposure to air pollution on mortality and morbidity. It has been proposed to include only long-term effects in air pollution HIAs as 1) long-term exposure has larger public health impact than short-term exposure, 2) long-term studies on mortality encompass cumulative long- and short-term (exacerbation of pre-existing medical conditions) exposure burdens as associations with mortality represent the effects of long-term exposure to pollutants (incidence and progression of a disease) and short-term exposure to increased concentrations (exacerbation of pre-existing medical conditions) (22). We fully agree with this reasoning for mortality, but argue that inclusion of short-term effects such as exacerbations and hospital admissions should be considered for morbidity.

4. Quantification of exposure-response functions

4.1 Choice of exposure-outcome pairs and exposure-response functions

The choice of ERF is a crucial step in HIA and considerably impacts and adds to uncertainty around the HIA estimates. We suggest to rely as much as possible on ERFs from existing systematic reviews and meta-analyses and to identify the most appropriate and reliable effect estimate for quantitative risk assessment from these meta-analyses.

We recommend including exposure-health pairs for which

- there is persuasive evidence of a **causal relationship** based on causality assessments or confidence in evidence assessments as described in section 3.1,
- **quantitative ERFs** are available from **multiple studies in humans** from different areas of the world,
- the association has been estimated with **minimal risk of chance, bias and confounding**, relying on existing assessments of risk of chance, bias and confounding such as assessments by Forastiere et al. (22), the HEI Traffic Panel (6) and Engelmann et al. (12).

4.2 HIAs for multiple correlated exposures

Policies often affect multiple exposures and thus health impact assessments often require evaluating multiple correlated exposures to provide a comprehensive overview of a policy. Quantifying the joint effects of multiple correlated exposures is challenging as commonly used ERFs rely on single-exposure models that do not account for potential confounding by other environmental exposures because of the insufficient number of studies incorporating multiple exposures. An approach that utilizes ERFs from the more limited number of two-pollutant models to estimate the coefficient difference between single- and two-pollutant models and applies the coefficient difference to single-pollutant model effect estimates from the more extensive evidence base has been proposed by the Committee on the Medical Effects of Air Pollutants (COMEAP) (23). This approach has recently updated for the the NO_2 and $PM_{2.5}$ mixture (24) and expanded to combinations of air pollution (NO_2 and $PM_{2.5}$), noise and greenspace (25), respectively. The use of ERFs from two-pollutant/two-exposure models will mitigate the potential overestimation of health impacts of the exposure mixture. This approach has been adopted by the WHO in the recent Health Risks of Air Pollution in Europe (HRAPIE-2) project (26).

5. Equity considerations in HIAs

Health impacts can be calculated at the full population level, but often the distribution of impacts across the population is important as well. Specifically, the distribution of health impacts across different socio-economic groups is of interest, but differences between ethnic groups and differences in impacts related to age or gender might be of interest as well.

Differences in health impacts across socio-economic, ethnic, age or gender groups can be caused by differences in all elements in the HIA process (Figure 1). Specifically, larger impacts in specific population groups can be caused by:

- higher exposure to environmental stressors,
- smaller impact of an intervention to reduce environmental exposure, related to either the locations affected by the intervention or behavioral responses,
- higher risks for the same exposure (exposure response functions),
- higher background rates of disease or mortality.

5.1 Equity in disease and mortality rates and exposure

For virtually all diseases, background rates of disease and mortality are higher in deprived populations.

In the US, *air pollution* exposure is quite consistently higher in more deprived people and non-white ethnic groups (27). In Europe, these associations are much more diverse, including in direction, e.g. in multiple Italian cities subjects with a higher socio-economic position tend to have higher exposures (28). Associations between socio-economic position and air pollution exposure differ by geographical scale evaluated (28). *Road-traffic noise* has mixed relationships with socio-economic class, similar to traffic-related air pollution (29). *Lack of surrounding green* is mostly associated with lower-socio-economic status. From the economic literature, it is well-known that people are willing to pay higher prices for homes in greener neighborhoods. However, associations between environmental exposures and socio-economic position are not consistent in direction as indicated by the Pereira study in six medium-sized cities (30) and the urban exposome study across Europe (Robinson, 2018).

5.2 Equity and exposure response functions

A large number of environmental epidemiological studies have performed subgroup analyses of associations between environmental exposure and health. Several studies have documented differences in exposure response between men and women, younger and older age groups and individual socio-economic position. However, there are few systematic reviews on this topic and definitions of socio-economic position vary between studies. A recent review from the VALESOR project (31) concluded that the association of all-cause mortality with $PM_{2.5}$ did not differ by education or individual income. However, due to the high heterogeneity observed, further studies are still required to draw firm conclusions.

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