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HEALTH INFORMATION

EBOD-FL

Guidelines for mapping the environmental burden of disease in Flanders

ARNO PAUWELS • CLAIRE DEMOURY • EVA DE CLERCQ • BRECHT DEVLEESSCHAUWER

healthy all life long

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Guidelines for mapping the environmental burden of disease in Flanders

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EXECUTIVE SUMMARY

The environment poses a diverse range of health risks. Environmental burden of disease (EBD) studies try to estimate the impact of environmental stressors in terms of mortality or morbidity on a population level. Although environmental risks have been studied in Flanders, an effort to routinely quantify the environmental disease burden completely and coherently has thus far not been established. For this reason, Sciensano and Agentschap Zorg & Gezondheid are partnering up in a project to map the Environmental Burden of Disease in Flanders (EBoD-FL).

The aim of the research is to inventory the burden of disease attributable to all relevant environmental stressors according to a coherent framework. To tackle this objective, the disease burden attributable to environmental stressors is estimated using comparative risk assessment (CRA). As this method determines the attributable burden as a proportion of the total, figures for the recorded disease burden are required to obtain absolute numbers. In EBoD-FL, the EBD is quantified as disability-adjusted life years (DALYs), a summary measure that combines both mortality and morbidity.

Given the extensive list of potential stressor-health outcome pairs, a set of priorities was defined in terms of environmental stressors and health outcomes. The risk factors that will be studied first are those related to air quality, environmental noise and extreme temperature. In terms of outcomes, priority was given to all-cause mortality, respiratory diseases and cardiovascular diseases. This report outlines the CRA methodology in general, and applied to the risk factor-outcome pairs that have been given priority. The basic steps of CRA are:

1. Selection of risk factors: Which risk factors are included in the study and how is exposure quantified as a metric?
2. Exposure assessment: how to measure or model exposure to the risk factors in the population?
3. Identification of stressor-outcome pairs: which health outcomes are caused by the risk factors?
4. Quantification of the stressor-outcome relation: what is the risk of developing the outcome in function of exposure?
5. Calculation of the population attributable fraction: what is the proportion of a disease burden attributed to one or multiple risk factors?

The purpose of this report is to outline the general methodology used to tackle the objective of EBoD-FL and to apply the CRA methodology to the stressors that are prioritized. Additionally, possibilities for the application of the results for evidence-based policy are explored, as well as some challenges and limitations.

CONTENTS

ABBREVIATIONS

AZG	Agentschap Zorg & Gezondheid
BeBOD	Belgian national burden of disease study
BOD	Burden of disease
COD	Cause of death
COPD	Chronic obstructive pulmonary disease
CRA	Comparative risk assessment
CRD	Chronic respiratory disease
CVD	Cardiovascular disease
DALY	Disability-adjusted life year
EBD	Environmental burden of disease
ERF	Exposure response function
GBD	Global Burden of Diseases, Injuries, and Risk Factors Study
HIA	Health impact assessment
IHD	Ischaemic heart disease
PAF	Population attributable fraction
PM	Particulate matter
RR	Relative risk
TMREL	Theoretical minimum risk exposure level
VITO	Vlaamse Instelling voor Technologisch Onderzoek
WHO	World Health Organization
YLD	Year lived with disability
YLL	Year of life lost

INTRODUCTION

1. Background

A growing body of evidence shows that the environment can have adverse effects on health. Our surroundings pose a diverse range of risks, in the form of polluting substances, harmful radiation, disrupting noise and many other factors. Epidemiological studies (typically cohort or case-control studies) are conducted to identify relationships between environmental exposure and increased risk of disease or mortality. An example is ELAPSE (Effects of Low-Level Air Pollution: A Study in Europe; (Stafoggia et al., 2022), a multicentre cohort study assessing the link between low-level air pollution and mortality in seven European countries, including Belgium. Contrary to individual epidemiologic studies, meta-analyses aim to pool the results of multiple studies collected in a systematic review of relevant literature. As such, a meta-analysis synthesizes a large amount of evidence as to overcome the errors of the individual studies and obtain a more accurate relationship.

In contrast to epidemiological studies, that examine the association between exposure and health outcome, **burden of disease** (BOD) studies use these relationships to estimate the contribution of risk factors to mortality or morbidity on a population level. A well-known example is the **Global Burden of Diseases, Injuries, and Risk Factors Study** (GBD), initiated in the early 1990s. The GBD is "a systematic scientific effort to quantify the comparative magnitude of health loss from diseases, injuries, and risks by age, sex, and population over time" (Murray & Lopez, 2017). The GBD study classifies risk factors most broadly as behavioral, environmental/occupational and metabolic risks. The most recent iteration of the study (Murray et al., 2020) examined 87 risk factors in 204 countries and territories. Although the GBD now provides results for all WHO member states, including Belgium, (sub)national studies still have advantages (De Pauw et al., 2022):

- Ownership of the results and the sustainability of the study are guaranteed.
- The research can be tailored to the country- or region-specific context and based on the best available local data, which is often inaccessible to international institutions. The methodology can be adapted to the needs of local researchers, authorities and policymakers.
- Since the research is conducted 'at home', it stimulates the appraisal of local data and expertise, and thereby leads to scientific capacity building.

For these reasons, the **Belgian national burden of disease study** (BeBOD) was initiated, which aims to establish a coherent framework for routinely quantifying the disease burden in Belgium using uniform metrics. A local study provides flexibility in terms of formulating research objectives and priorities. For instance, risks that are not important globally and therefore ignored, can be relevant for specific countries and included in a national study. Conversely, globally important stressors can be ignored if irrelevant in a local context. Additionally, results can be alternatively presented for separate regions or other subnational entities. Particular areas of interest can be isolated and examined in more detail.

In Belgium, there are several national and regional initiatives that assess the burden of disease attributable to environmental risks. In the frame of the EBoDE-project (Environmental Burden of Disease in the European region), Hänninen & Knol (2011) estimated the burden for nine environmental stressors in six countries, including Belgium. For Flanders specifically, Torfs (2003) calculated the BOD and external costs related to various environmental risks. In a similar, more recent exercise, Buekers et al. (2012) assessed the disease burden and external costs of 18 environmental stressors in Flanders.

Aside from comprehensive studies, BOD calculations are also performed for specific environmental risks. In the Flemish Region, the disease burden related to airborne particulate matter is calculated on

a routine basis, with estimates updated on a yearly basis (Statistics Flanders, n.d.). With regard to noise pollution Dekoninck & Botteldooren (2019) generated a time series of the fraction of the Flemish population that are potentially severely annoyed by environmental noise. In the Brussels Capital Region, similar efforts are pursued for air pollution, and the burden of annoyance and sleep disturbance due to environmental noise was estimated in the frame of the noise plan Quiet.Brussels (Leefmilieu Brussel, 2018).

What currently lacks is a coherent and global overview of the contribution of environmental risks to the burden of disease in Flanders. Such an overview would amount to an inventory of all relevant risk factors and the associated mortality and morbidity, which sums up to the total environmental burden of disease. As part of a collaboration agreement with **Agentschap Zorg & Gezondheid** (AZG), Sciensano will develop a mapping of the **Environmental Burden of Disease in Flanders** (EBoD-FL). This research can be situated within the intention of the Flemish government to prevent and detect environmental impact on health. The project is scheduled for the years 2022 to 2026, and will build on expertise developed within BeBOD. This is the first in a series of reports, devoted to a description of the methodology that the project will rely on.

2. Objectives

The overall objective of EBoD-FL is to provide a complete overview of the contribution of environmental risk factors to the total burden of disease in Flanders according to one coherent framework. This means, on the one hand, that the research will ideally consider all of the environmental stressors that are significant within the Flemish context. The aim is thus to quantify the total **environmental burden of disease** (EBD). On the other hand, the resulting estimates are expressed in a single uniform metric, namely a summary measure that combines premature mortality and reduced life quality due to living with disease or injury. This will allow mutual comparison and ranking, an essential property if the results of EBoD-FL are to be used for determining priorities in public health policy.

The methodology of EBoD-FL is **comparative risk assessment** (CRA). CRA estimates the proportion of the disease burden that can be attributed to stressors of interest. This top-down approach ensures that the estimates never exceed the observed BOD figures. This is in contrast to a 'regular' bottom-up risk assessment approach**,** where disease burden is determined in absolute terms by combining population exposure and dose-response relationships. This study will rely solely on CRA, and never on regular risk assessment or a mixtures of methods, as is the case for other BOD studies in Belgium and Flanders (e.g., Buekers et al., 2012; Dekoninck & Botteldooren, 2019; Hänninen & Knol, 2011). As a result, the estimates can always be interpreted as the fraction of the total disease burden that can be explained by environmental stressors.

CRA allows to determine the proportional contribution to disease burden by comparing the actual population exposure to environmental stressors and the associated risks with a theoretical situation of minimal risk. This approach thus disregards whether achieving minimal risk is at all realistic or feasible, which sets CRA apart from **health impact assessment** (HIA). HIA is a tool to examine the potential consequences of proposed policy measures or interventions. The scenarios considered in HIA take into account technological possibilities and as such can be integrated into a cost-benefit analysis.

The domain of this study is Flanders. However, defining Flanders in this context is not straightforward, as it can refer to a geographic area (the Flemish Region) as well as a linguistic population (the Flemish Community). Exposure to environmental risks has a regional territorial character, while health is a competence of the Flemish community, which spans the Flemish Region as well as the Brussels Capital Region. To deal with this ambiguity, the analysis will include both regions and populations, with the option to in- or exclude results depending on the needs. The unit of analysis in this research is the statistical sector, the smallest administrative unit in Belgium. The initial results are generated on this local level, but can easily be aggregated to wider areas.

In the context of EBoD-FL, what is understood as 'the environment' refers to all the physical, chemical and biological determinants of health external to a human being. The social environment is thus excluded from this study. The list of what are typically considered environmental risk factors is extensive and diverse. Relative importance of the various stressors strongly depends on geographic region, degree of economic development and industrialization. As counterpart to the long list of risk factors, a large collection of disease outcomes is potentially associated with environmental exposure, ranging from cancer, respiratory and cardiovascular diseases, to metabolic disorders, neurological effects and sleep disturbance. Aside from cause-specific effects, total all-cause or non-accidental mortality is commonly included as health outcome.

Due to the extensive scope of EBoD-FL – the large number of environmental risks, each linked to one or multiple health outcomes – choices have to be made with regard to which stressor-outcome pairs deserve priority for disease burden investigation in Flanders. Consequently, three proofs-of-concept (POCs) have been proposed:

1. Determine and visualize the contribution of environmental stressors to all-cause mortality and years of life lost
2. Determine and visualize the contribution of environmental stressors to the occurrence/prevalence and disease burden of cardiovascular diseases
3. Determine and visualize the contribution of environmental stressors to the occurrence/prevalence and disease burden of chronic respiratory diseases.

The POCs determine which health outcomes have priority in the research. In making the choice of the environmental stressors that are treated first, results of previous BOD studies in Flanders can be consulted to infer which risks are associated with high impact. In consultation with AZG, it was agreed to start with:

1. Ambient air quality
2. Environmental noise
3. Extreme temperatures

The approach to quantify the EBD depends on whether exposure is examined in the short-term (hours to days) for acute health effects, or in the long-term (season or one to several years) for chronic risks. Initially, the analysis will be limited to long-term exposure and outcomes. For air pollution, chronic exposure is generally considered to have the larger attributable burden as compared to peak exposure values. In term of data availability, what is needed for long-term exposure assessment is generally easier to obtain compared to what is required for acute exposure.

The environmental stressors and health outcomes mentioned so far are those that will be studied in a first phase of the project. As the aim is to provide a complete and coherent overview of the EBD in Flanders, the scope of the research will be gradually expanded to include additional risk factors, mortality and morbidity outcomes and a more complete assessment of long-term and short term effects. This expansion will also occur in time, as the results will be updated when new data becomes available. As such, the content of EBoD-FL will continuously evolve as the project becomes more comprehensive and when the findings are routinely actualized according to new information and scientific insights.

The purpose of this report is to outline the general methodology used to tackle the objective of EBoD-FL and to apply the CRA methodology to the stressors that are prioritized. Additionally, possibilities for the application of the results for evidence-based policy are explored, as well as some challenges and limitations.

METHODS

1. Burden of disease

1.1. DISABILITY-ADJUSTED LIFE YEARS

Given the complex and multifaceted nature of public health, there are a multitude of ways to measure and quantify the BOD. Initially, indicators focused on either morbidity (e.g., disease incidence or prevalence) or mortality (e.g., life expectancy, mortality rates). The previous decades saw an extensive development of **summary measures of population health** (SMPHs), indicators that combine both mortality and morbidity into a single figure. A key advantage is that health impacts of different diseases, injuries or risk factors can each be captured in one figure and mutually compared, which makes evident the use of SMPHs for setting priorities in public health interventions and other policy domains.

The SMPH that is perhaps most widely used is the **disability-adjusted life year** (DALY). The DALY is a gap metric, meaning that it measures the difference between actual population health and a stated norm or goal, usually an ideal situation where the entire population lives to life expectancy in perfect health (Murray et al., 2000).

The method for calculating DALYs applied here, is consistent with the guidelines proposed by BeBOD (De Pauw et al., 2022). DALYs are composed of standard expected years of life lost due to premature mortality (*YLL*) and years lived with disability (*YLD*, eq. 1):

$$DALY = YLL + YLD \qquad (\text{eq. } 1)$$

The YLL component integrates the impact of mortality. For each considered cause of death, YLLs are equal to the age-specific number of deaths M_i multiplied with the standard expected residual life expectancy at age of death RLE_i, summed over all age groups (eq. 2):

$$YLL = \sum_{i=1}^{n} M_i * RLE_i \qquad (\text{eq. } 2)$$

with $i = 1, \ldots, n$ the considered age groups. The YLD component integrates the impact of mortality. A prevalence approach can be applied for estimating YLDs for non-communicable diseases (eq. 3):

$$YLD = p * DW \qquad (\text{eq. } 3)$$

where p is the prevalence of the outcome and DW the associated disability weight. As with the residual life expectancy, the disability weights are sourced from the GBD.

DALY calculation in the GBD originally incorporated age-weighting and time discounting, but these practices were later dropped because of ethical reasons (Murray & Lopez, 2017). Consequently, no age-weighting and time discounting will be applied in this research.

1.2. LOCAL BURDEN OF DISEASE STUDY

The unit of analysis in EBoD-FL is the statistical sector, a subdivision of the municipality. The statistical sector is the smallest geographical unit in Belgium, established in the early 1970s to collect demographic and socio-economic data on a more refined scale than municipalities. As CRA estimates the relative share of the burden related to risk factors, figures for the total burden of disease are required to convert

these fractions into absolute numbers. Given the approach of EBoD-FL to estimate the EBD on the level of the statistical sector, there is a need for BOD figures at this level. According to the POCs, the outcomes to be analyzed in the initial stage are all-cause mortality, **cardiovascular diseases** (CVDs) and **chronic respiratory diseases** (CRDs). The first of these endpoints only has a mortality component, while the latter two are associated with both morbidity and mortality. As POC1 specifies all-cause mortality as outcome, local mortality data is required to calculate YLLs on the level of the statistical sector. For this end, a request was made to Statistics Belgium (Statbel) for the supply of cause of death (COD) microdata. The details of these data are elaborated upon in **Appendix 1**.

Aside from mortality figures and YLLs, data on disease incidence or prevalence is needed to quantify morbidity, or YLDs. For this end, new requests have to submitted in a next phase of the project. Next to Statbel, possible sources for these data are hospital discharge records, patient data compiled by general practitioners (Intego) or information based on the members from mutualities and health insurance companies.

This local EBD strategy contrasts with how attributable burden of disease figures are typically calculated. The BOD figures are usually determined on a country-wide or regional scale, and a single 'flat' estimate of population exposure to risk factors is used to estimate the attributable burden. EBoD-FL on the other hand, determines the BOD numbers and exposure to environmental stressors locally, which allows to calculate the EBD on a fine geographical scale. This approach makes it possible to relate spatial variation of exposure to location-specific mortality figures and disease incidence, which makes the EBD estimates in theory more accurate.

2. Comparative risk assessment

Comparative risk assessment (CRA) is a top-down method for determining the proportion of the burden of disease related to specified risk factors. In CRA, the contribution of risk factors is determined by comparing the existing disease burden to a theoretical ('counterfactual') situation resulting from a different level of population exposure. If the counterfactual exposure level corresponds to minimal risk, referred to as the **theoretical minimum risk exposure level** (TMREL), the result corresponds to a disease burden fraction that is fully attributable to the risk factor in question (Ezzati et al., 2002). When this fraction is multiplied with observed burden figures (e.g., DALYs), it yields an absolute estimate of the BOD. This is opposed to the quantification of the attributable BOD in the risk assessment paradigm, where data on population exposure is combined with dose-response relationships to obtain figures in a bottom-up manner. As a consequence, latter method may result in an attributable burden that is higher than the total observed value.

The following components are required to estimate the attributable disease burden with CRA:

- Exposure of the population to the risk factor and a theoretical minimum risk exposure level
- Relationship that gives the risk of a health outcome in function of exposure
- Estimates of disease burden causally linked to the risk factor

Exposure assessment consists of determining the level of exposure in the population, which is then contrasted with the TMREL. If the risk increase in function of exposure is known, this allows to estimate the expected relative increase in disease burden caused by raising the population exposure from the theoretical minimum to the actual level. Such a dose-response relationship can be derived from epidemiologic studies. The calculated relative increase corresponds to the **population attributable fraction** (PAF): the proportion of the disease burden caused by exposure to the stressor. The PAF is multiplied with the total burden, which yields an estimate in absolute numbers, for example expressed in DALYs (Fig. 1).

Generally, CRA consists of five steps (Plass et al., 2022):

1. Selection of risk factors: Which risk factors are included in the study and how is exposure quantified as a metric?
2. Exposure assessment: how to measure or model exposure to the risk factors in the population?
3. Identification of stressor-outcome pairs: which health outcomes are caused by the risk factors?
4. Quantification of the stressor-outcome relation: what is the risk of developing the outcome in function of exposure?
5. Calculation of the PAF: what is the proportion of a disease burden attributed to one or multiple risk factors?

The remainder of this chapter outlines the general CRA methodology. The application to the various stressors is added in appendix 2.

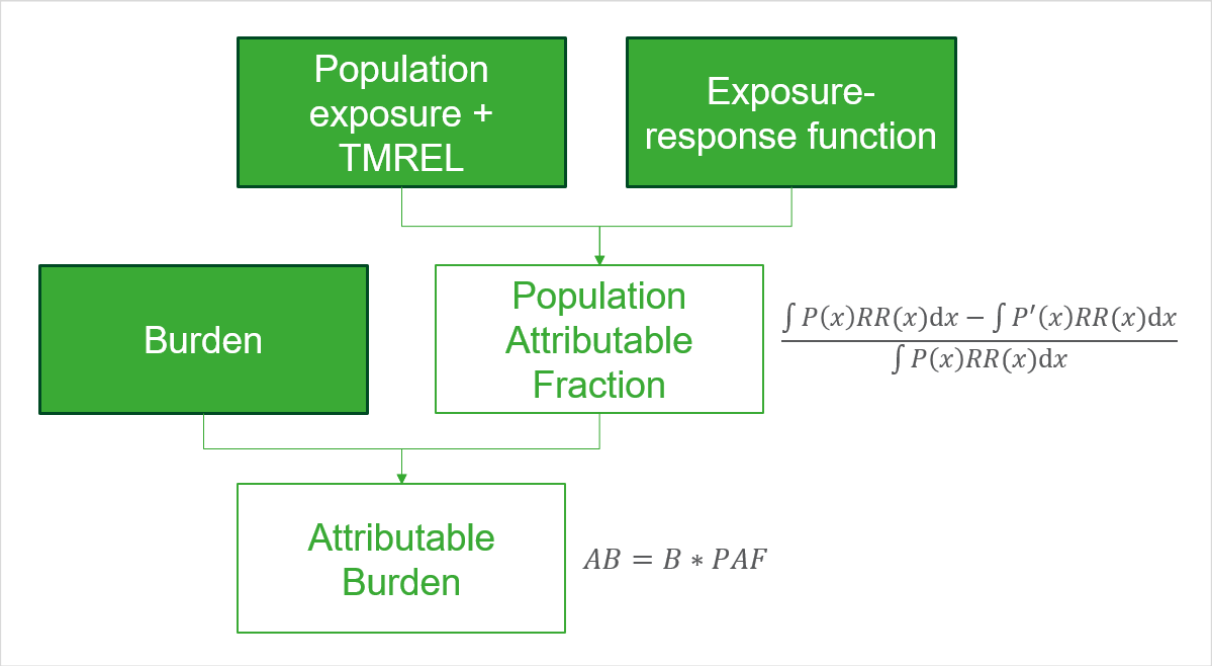

Figure 1 • Flow chart describing the procedure for calculating the attributable burden of disease by means of comparative risk assessment (CRA).

2.1. EXPOSURE ASSESSMENT

When a decision on the inclusion of risk factors is made, the next step is to devise a strategy to estimate the distribution of exposure in the population. As a burden of disease study relies on dose-response relationships that are derived in epidemiologic studies, one can consult the literature on how exposure of the participants is measured. Ideally, the approach to assess population exposure should be as close as possible to the methodology applied to derive the dose-response relationship.

The unit of analysis in this study is the statistical sector. Correspondingly, exposure assessment is carried out on this level. Exposure assessment then amounts to estimating a risk factor exposure level that is representative for the sector's population. This will be pursued by a geo-spatial approach, using a vector file to represent the sector's territory and risk factor data in the form of maps, usually continuous grid data. Aside from deriving a central estimate, the distribution of exposure to risk factors within the territory can be considered to account for the variance and uncertainty of exposure.

For one given stressor, the approach of exposure assessment varies depending on whether chronic or acute health effects are studied. For chronic effects, the risk of developing an outcome is linked to a

long-term mean level of exposure. Correspondingly, the level of exposure is quantified as an annual or seasonal average value. For the short-term approach, the correlation between exposure and outcome in time is important, and as such exposure peaks have to be identified in a time series of e.g., hourly or daily values, that can be linked to acute effects.

As was the case for the selection of a metric to quantify the stressor, the approach to estimate population exposure varies according to the category of the stressor. For air quality, the exposure is usually calculated as a population-weighted average concentration. This means that aside from pollutant concentrations, information on where people reside is taken into account, either through a population grid or address locations. For assessing environmental noise exposure, it is recommended to consider only the most exposed facade of each building. The noise exposure method is thus more elaborate, as not simply the location but also the geometry of buildings is taken into account.

Aside from estimating the existing population exposure, CRA relies on the definition of a theoretical minimum risk exposure level. The TMREL is used as benchmark, which allows to determine the fraction of the BOD associated with the increased risk resulting from a population exposure in excess of this level. Defining the TMREL for risk factors is not always straightforward. For air quality and environmental noise, one could assume that the TMREL is equal to zero pollution and a lack of noise from traffic, respectively. Another possibility is the existence of an exposure threshold, a level under which no adverse effects occur. Whether or not to include a cut-off value affects the burden calculation, as it shifts the benchmark to which population exposure is compared. The inclusion of an exposure threshold is further discussed in the section on the selection of dose-response relationships.

2.2. RISK FACTOR SELECTION

In deciding which risk factors should be included, the first question to address is what exactly constitutes ‘the environment’ in a health context. The WHO defines the environment as “the congregation of all the physical, chemical and biological factors external to a person, and all related behaviours, but excluding those natural environments that cannot reasonably be modified” (Prüss-Üstün et al., 2018). This definition thus excludes socio-economic and cultural factors, genetics and parts of the natural surroundings (e.g., natural breeding grounds for disease vectors, pollen). Although an exhaustive list of what can be classified as environmental risk factors does not exist, some typical examples include (indoor or ambient) air pollution (e.g., particulate matter, ozone), non-optimal temperature, occupational risks, unsafe water and sanitation (Murray et al., 2020); carcinogens (e.g., benzene, dioxins, formaldehyde), environmental noise (e.g., from traffic, industry), heavy metals (e.g., lead), radon, second-hand tobacco smoke (Hänninen & Knol, 2011); dampness and mold, electromagnetic fields and ultraviolet radiation (Buekers et al., 2012).

The relative importance of these factors varies greatly by region and level of industrialization and socio-economic development. According to the GBD, the top environmental risk factors in Belgium are particulate matter, low temperature, occupational carcinogens, lead exposure and occupational ergonomic factors, accounting for 16% of total disease burden and 89% of environmental/occupational burden (IHME, 2022). The GBD list of environmental risks might overlook certain stressors that are negligible on a global scale but important in specific regions or countries. The European perspective EBD study by Hänninen & Knol (2011) showed that second-hand tobacco smoke and traffic noise come in second, respectively fifth of the 9 environmental stressors examined, and are also substantial contributors in the other countries that were studied. Noise and environmental tobacco smoke also rank high in the Flanders EBD study by Buekers et al. (2012) who additionally considered dampness and mold, UV and electromagnetic fields.

From the previous paragraphs, it becomes clear that the collection of candidate environmental stressors is extensive and diverse. As a result, there is a need to prioritize a select number of risk factors to be assessed in the first phase. In consultation with AZG, and based on the availability of well documented exposure data with sufficient spatial coverage, a selection of risk factors was made (Table 1). These

risks have been shown to be important contributors to the disease burden in Flanders (Buekers et al., 2012).

Table 1 • Risk factors prioritized in EBoD-FL

Ambient air pollution	Environmental noise	Extreme temperature
Particulate matter (PM)	Road traffic noise (TN_{road})	Heat
Nitrogen dioxide (NO_2)	Railway traffic noise (TN_{rail})	Cold
Ozone (O_3)	Air traffic noise (TN_{air})	

For each stressor, a metric can be selected by consulting epidemiologic studies that examine the link between exposure and health outcomes. As environmental risks can be very different in nature, the chosen metric strongly depends on the type of environmental risk. For example, the approach to quantify the exposure to particulate matter cannot be applied to road traffic noise. Even within one type of risk factor (e.g., air pollution) there are different ways to express exposure (e.g., the ozone metric differs from the other air pollutants; see appendix). The metrics for the selected air pollutants and sources of environmental noise sources are outlined in the dedicated sections in **Appendix 2**. For extreme temperature, further research is needed prior to applying CRA to the related stressors.

2.3. IDENTIFICATION OF STRESSOR-OUTCOME PAIRS

After the selection of stressors and exposure assessment, the next step is to determine which health outcomes are causally linked to the risks. A randomized controlled trial (RCT) is often considered the gold standard for inferring causality, but in practice it might be unfeasible or unethical to conduct such a study (Plass et al., 2022). In case an RCT is not possible, an alternative is to assess the evidence produced by various studies, and conclude on causality based on a set of criteria, such as those proposed by Bradford Hill (1965).

To assess causality between air pollutants and health effects, one can consult the related US Environmental Protection Agency's Integrated Science Assessments (ISAs), which investigate causality based on epidemiologic studies as well as animal toxicology and controlled human exposure. ISAs are available for ozone, particulate matter, carbon monoxide, sulfur oxides, nitrogen dioxide, and lead. The ISAs conclude on whether or not there is sufficient evidence to confirm or refute a causal relationship between the air pollutant and outcome of interest (U.S. Environmental Protection Agency, 2015). Alternatively, one can consult the monographs by the International Agency for Research on Cancer (IARC) for the causal links with cancer outcomes. The IARC classifies air pollution, and more specifically particulate matter, as carcinogenic. The GBD conducts its own causality assessments, based on the World Cancer Research Fund grading system, which is influenced by the Bradford-Hill criteria. They include risk factor-outcome pairs for which there exists convincing or probable evidence (Murray et al., 2020).

According to POCs, the prioritized outcomes are all-cause mortality and respiratory and cardiovascular diseases. The evidence of causality for these outcomes and the stressors selected for this study are discussed in the dedicated sections in **Appendix 2**.

2.4. QUANTIFICATION OF THE STRESSOR-OUTCOME RELATION

Once the causal risk factor-outcome pairs are established, a relationship is needed that relates exposure dose to increased risk for developing an outcome, i.e., a dose-response or **exposure-response function** (ERF). An ERF for a certain stressor-outcome pair returns the relative risk (or other effect measures like the odds ratio or hazard ratio) of developing the outcome at a certain level of exposure. ERFs can be sourced from the epidemiologic literature, where the relationship between exposure and relative risk is derived in longitudinal (cohort, case-control) and ecological studies. Alternatively, the ERF

can be meta-analytic, meaning that it is a pooled estimate from the results of multiple studies collected in a systematic review.

The following order or preference is proposed for the selection of ERFs:

1. WHO guidelines: The first choice to source ERFs are publications of the WHO that formulate recommendations for protecting human health from exposure to certain environmental risks. As these guidelines are based on expected health impacts, they rely on systematic reviews and meta-analyses that combine ERFs from studies collected from all over the world. Examples are the guidelines for air quality (World Health Organization, 2021) and environmental noise (WHO Regional Office for Europe, 2018). Such publications reflect an international consensus and are likely to be adopted by researchers worldwide.
2. Systematic review and meta-analysis: For stressor-outcome pairs not featured in the WHO guidelines, the results from other meta-analyses can be selected. Ideally, these reviews are similar to those that WHO guidelines rely on, meaning that they consider a large amount of studies unrestricted in geographical scope. Preference is given to the most recent qualified meta-analysis, assuming that it incorporates the latest available evidence.
3. Individual study: In case no systematic review and meta-analysis exists for a given risk factor-outcome pair, the ERF can be derived from an individual epidemiological study. Criteria for selecting a study can be based on the precision (e.g. a large sample size), publication date (assuming a more recent study relies on the latest evidence, or a more refined methodology) or the type of study (e.g., preference for cohort over case-control, case-control over ecological study).

Critical components are the shape of the ERF and the possible existence of a threshold below which no risk increase is observed. Some studies find complex ERF shapes, by fitting a polynomial curve to the collected data. These curves can serve directly as ERF, or more commonly, can be discretized so that regular intervals of exposure correspond to a relative risk value (an integrated ERF). On the other hand, other studies approximate the complex ERF curve with a (log-)linear relationship, where the effect measure increases by a factor per increment in exposure.

The inclusion of an exposure threshold relates to the definition of the TMREL. Since the TMREL is a counterfactual exposure distribution that corresponds to no increased risk, i.e., the RR at this level equals 1. The TMREL is used as benchmark, which allows to determine the fraction of the BOD resulting from the increased risk of the actual population exposure in excess of this level. Another possibility is the existence of a threshold exposure level under which no adverse effects occur. Such a threshold is difficult to identify in epidemiologic studies, as samples in the low extreme of the exposure range are scarce. If this is the case, there are two options:

1. A first option would be to refrain from calculating BOD below the bottom exposure value. One could argue that, as the ERF is based on a certain range of observations, the relationship is only valid for exposure values that fall within that range, and it is not justified to extrapolate down to zero exposure. The bottom value could be set to the lowest exposure value observed in the epidemiologic study, or more robustly, to a lower quantile (e.g., the 5th percentile).
2. A second option is to perform BOD calculations for the entire range of exposure values. This practice could be justified in case there is no indication of a threshold. This can be verified by examining the shape of the ERF.

The selection of ERF for the different risk factor-outcome pairs and possible inclusion of an exposure threshold are discussed in the dedicated sections in **Appendix 2**.

2.5. CALCULATION OF THE POPULATION ATTRIBUTABLE FRACTION

The final step in CRA is to combine all of the information outlined in the previous steps to calculate the PAF, the proportion of health outcome Y due to exposure to X in the population. In general, the PAF can be calculated as follows (eq. 4; Plass et al., 2022):

$$PAF = \frac{\int P(x)\, RR(x)\, dx - \int P'(x)\, RR(x)\, dx}{\int P(x)\, RR(x)\, dx} \qquad (\text{eq. } 4)$$

with *P(x)* the distribution of exposure in the population, *P'(x)* the counterfactual exposure distribution, and *RR(x)* the relative risk of the outcome in function of exposure level *x*.

As the counterfactual exposure distribution is the TMREL, *RR(x)* here equals 1 by definition (i.e., no increased risk), and as exposure is assumed to be uniform across the statistical sector, *P(x)* and *P'(x)* both equal 1. As a result, eq. 1 can be reduced to (eq. 5):

$$PAF = \frac{RR(x) - 1}{RR(x)} \qquad (\text{eq. } 5)$$

RR(x) corresponds to the ERF. The way the RR is calculated depends on the nature of the function (continuous vs. categorical, complex vs. linear etc.) and whether an exposure threshold is included. If the ERF is log-linear, and a threshold value is included, the RR is calculated as (eq. 6):

$$RR(x) = \begin{cases} 1, & x < TH \\ RR_0^x, & x \geq TH \end{cases} \qquad (\text{eq. } 6)$$

with *T* the exposure threshold value, and RR_0 the increase in relative risk for a unit exposure increment.

In case a specific health outcome is caused by more than one risk factor, the corresponding PAFs need to be combined prior to multiplication with the observed disease burden figures. This can be achieved by applying the following formula (eq. 7):

$$PAF_{combi} = 1 - \prod_{i=1}^{n} (1 - PAF_i) \qquad (\text{eq. } 7)$$

with *i* = 1, …, *n* the risk factors associated with the outcome of interest.

Uncertainty on the PAF depends on the uncertainty on the ERF and the exposure assessment. Analytical formulas exist to correctly determine the PAF confidence interval, but these tend to be unwieldy. An alternative approach is Monte Carlo simulation, based on the repeated sampling from distributions that approximate the 'true' distribution of the ERF and the exposure value. The basic principle can be explained as follows: If exposure value x and RR_0 are point estimates, the value of PAF corresponds to the central estimate. In the Monte Carlo simulation, the point estimates are replaced with probability distributions, so that repeated sampling and calculation yields a wide range (thousands or millions) of estimates. Based on this set of values, the standard deviation or the confidence interval can be derived. This corresponds to a form of bootstrapping, a statistical method to estimate uncertainty that falls under the broader class of resampling methods (Greenland, 2004).

DISCUSSION

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1. Possibilities

The ultimate objective of EBoD-FL is to obtain an inventory of the environmental burden of disease in Flanders. For each environmental risk factor, the contribution to all relevant health outcomes is quantified according to a uniform methodology, in this case an implementation of CRA. The resulting inventory is coherent, meaning that the attributable disease burden estimates are expressed according to a single metric, the DALY. As a result, the estimates for the different stressors can be mutually compared and ranked in terms of health impact. The EBD inventory should also be complete, meaning that in theory all relevant combinations of risks and health outcomes are covered. In practice however, the inclusion of stressor-outcome pairs is predicated by the availability of reliable data for population exposure assessment. In light of the substantial scope of the project; the proposed research strategy is to start with a set of prioritized stressors and outcomes, after which the list is gradually extended into other domains.

The EBoD-FL inventory will have many dimensions and multiple levels of aggregation. The principal dimensions are the risk factors and the health outcomes. Additionally, the EBD estimate for each risk factor-outcome pair can (potentially) be extended into a mortality (YLL) and morbidity (YLD) component, and a long-term and short-term component. These additional dimensions are not always relevant. For instance, the study of environmental noise as stressor is limited to the long-term approach, while all-cause mortality as outcome is obviously limited to the mortality component. In terms of aggregation, the individual risk factors can be grouped into broader categories, e.g., PM, NO_2 and O_3 into air pollution. This is similar for the health endpoints, e.g., ischaemic heart disease and stroke can both be placed in the cardiovascular category. The local-scale approach to determine the EBD also offers a great deal of freedom in terms of spatial aggregation. The results for the individual sectors can easily be summed to obtain results for wider regions, such as municipalities, provinces, health care regions and Flanders as a whole.

The multidimensionality and layering of the EBD inventory means flexibility in terms of extracting figures. Different subsets of the inventory can be extracted, depending on the information of interest. For instance, instead of comparing the total disease burden, only the contributions to specific outcomes can be considered. The analysis can be limited to a selected category of risk factors, or exclusively to mortality or morbidity. The flexibility in terms of geographical aggregation allows to easily in- or exclude the results for the Brussels Region, depending on whether the interest lies with the Flemish region, or with the Dutch speaking community in Belgium, who also live in the bilingual Brussels region.

The aim is to provide a basis for evidence-based public health interventions. The results can aid the integration of a health perspective into environmental policy, and determine priorities for prevention and further research. Examples of the type of question that the results of EBoD-FL can answer are:

- Which environmental risks have a major health impact in Flanders?
- How does the environmental burden of disease compare to the total burden?
- Which stressors are mostly responsible for premature mortality?
- Which stressors are primarily associated with chronic disease burden?
- In which environmental domains can we expect to realize substantial improvements in public health?
- For which risk factors have exposure and attributable burden declined over the past years?
- For which stressors are exposure and associated burden stable or increasing?
- How do short-term and long-term impacts compare for a single risk factor?
- Which geographical areas are severely impacted by specific environmental stressors?

- Which stressor-based strategies could prove effective at alleviating disease burden at a local level?

The results of EBoD-FL are expressed uniquely in terms of health impacts, or 'human cost'. The attributable disease burden estimates are expressed in the form of DALYs, or in some cases only in terms of YLL or YLD. The related economic costs will not be calculated as part of EBoD-FL. Various methods exist to convert BOD estimates into external costs, such as the 'value of a life year' (Desaigues et al., 2011) and 'value of statistical life' (OECD, 2012) approaches for mortality, and the quantification of the costs of hospital admission, work absenteeism and loss of wealth due to disease suffering for morbidity. As such, the results of EBoD-FL could serve as a starting point for an analysis of economic costs.

Aside from presenting raw figures, various options for the visualization of the results will be proposed and implemented. Depending on the message one wants to convey, different graphs are possible. These could compare risk factors, health outcomes or geographic areas in terms of EBD. As the results are updated when new data becomes available, the time series of results will be extended. This will provide the basis for monitoring, where the evolution in population exposure and EBD can be tracked over time. If the time series is sufficiently extensive, this allows to extract trends, and examine whether the situation is improving, stable or deteriorating. Such monitoring can be part of an assessment of the effectiveness of current measures, to verify which policies prove to be successful and where additional efforts are required. Instead of static graphs, an interactive variant that is altered based on user input is also a possibility. This would especially suit to visualize the multiple dimensions and aggregations of the result matrix. An example is the treemap, such as was developed for BeBOD which allows to visualize the total disease burden expressed in DALYs (Sciensano, 2022). The tool offers various options for (dis)aggregation of results, which could be useful for EBoD-FL as well.

Maps are other means to visualize the results. They offer the opportunity to study spatial patterns in terms of exposure and EBD. As the burden calculation is conducted on the small-scale level of the statistical sector, the choices for spatial aggregation are virtually unlimited. Burden figures of different sectors are simply added up, while exposure values can be aggregated by means of a population-weighted average. Aside from fixed administrative entities, custom regions of interest can be defined and examined in terms of EBD and exposure. As is the case for graphs, options for static as well as dynamic maps can be explored. Interactive maps such as a leaflet allow to zoom in, search and plot different results depending on the user's choice.

What sets apart EBoD-FL from other research projects, is the combination of its objective and wide scope. Other comprehensive EBD studies have been conducted for Flanders (e.g., Buekers et al., 2012) or the wider area (e.g., Hänninen & Knol, 2011). While these studies considered a wide range of environmental stressors, they were to a large extent one-off endeavors. On the contrary, EBoD-FL will continuously expand in scope, and its results routinely actualized. Other routine EBD exercises exist (e.g., the DALY calculations for PM in Flanders), but these are focused on only one or a couple of environmental risks, and thus lack the wide scope of EBoD-FL. Other defining features of EBoD-FL that are (partially) lacking in other initiatives, are its uniformity in methodology (all estimates are derived with top-down CRA) and its spatial dimension (the statistical sector as starting point allowing to zoom in on particular locations).

The project that EBoD-FL perhaps shares most similarities with, is the Environment Health Impact Simulator (E-HIS), developed by VITO by order of AZG (Hooyberghs et al., 2021). The aim of E-HIS is to determine the disease burden and related economic costs of air pollution and environmental noise in Flanders. Their methodology shares some similarities with EBoD-FL, as they estimate the disease burden in a top-down manner, and also work with the statistical sector as unit of analysis. The difference however lies again with the objective and scope of the projects. E-HIS is an implementation of HIA, as it enables to project the health impact and related economic costs of different policy measures and interventions for air quality and environmental noise. In this sense, E-HIS is a prospective tool, that allows to estimate the EBD under different future scenarios.

EBoD-FL, on the other hand, relies on CRA with the objective to create and maintain a complete inventory of the existing EBD. In this sense, EBoD-FL is retrospective, as it estimates current disease burden caused by past exposure to risk factors. Important attributes of EBoD-FL are the aims for completeness and coherence. In contrast to E-HIS, it is not limited to air and noise pollution, but tries to evaluate all environmental risks in order to fully capture the EBD. While E-HIS only considers long-term exposure, EBoD-FL will include short-term analyses where this is relevant. Disease burden in E-HIS is primarily quantified as attributable disease incidence or premature mortality (only considering all-cause mortality). DALYs are not consistently calculated, but only in some cases as an intermediary between disease burden and external costs. This limits the comparability of the estimates, which is one of the pillars of EBoD-FL. All of these differences in terms of methodology and approach point to the distinct aim and applicability of the two projects.

2. Challenges

A first challenge is to develop a methodological protocol for the inclusion risk factor-outcome pairs. As mentioned in the previous chapter on the methodology, one can consult studies that assess the causality between environmental exposures and health outcomes, such as the ISAs. In practice, such assessments are not always conclusive, or even non-existent for some stressor-outcome pairs. In case an assessment on causality is available, there are several scenarios. The two straightforward scenarios are when causality is either proven or disproven, in which case the stressor-outcome pair should be included or excluded respectively. In the remaining scenario, the evidence on causality is inconclusive. In this case, the question is whether a statistically significant association can be found in the epidemiologic literature, and if so, whether the risk factor-outcome pair should then be included or not.

A second challenge relates to integrating short-term (ST) and long-term (LT) exposure into one coherent and comparative framework. When the same stressor is associated with both ST and LT effects, there are two scenarios with respect to the associated outcomes:

- Scenario 1: the ST and LT effects of the stressor concern different outcomes, i.e., the stressor-outcome pairs are unique in terms of ST and LT effects. The solution here is to aggregate the ST and LT burden to the same period, after which the results are comparable and additive.
- Scenario 2: the ST and LT effects of the stressor concern the same outcome, i.e., some stressor-outcome pairs are associated with both ST and LT effects. This situation is more tricky, and multiple solutions are possible:
  - Solution 1: aggregate the ST and LT burden to the same period, equivalent to the solution in the first scenario. However, this might be problematic, as there could be overlap in the disease burden of the ST and LT estimates. As a consequence, the results are possibly not comparable and additive.
  - Solution 2: limit the burden calculation for the stressor-outcome pairs to either the ST or LT approach. The issue here is to establish criteria to decide which approach is best suited. Additionally, if only ST or LT effects are quantified, the question is whether those effects alone account for all of the related EBD, or whether the EBD is underestimated.

A third challenge pertains to the possible burden overlap between stressors that are correlated in space and time. In theory, this could be avoided by using ERFs that are adjusted for risk factors associated with the same outcome. In practice, however, the majority of epidemiologic studies rely on a single-pollutant model, which means this type of confounding is not taken into account. In some cases, a multi-pollutant model is applied, but has difficulty in untangling the health effects of stressors that are highly correlated. In this case, a solution is to estimate the EBD with unadjusted ERFs and afterwards apply a double-counting correction for overlapping stressors. For instance, in the frame of the Review of evidence on health aspects of air pollution (REVIHAAP), it was shown that the all-cause mortality resulting from chronic exposure to $PM_{2.5}$ and NO_2 overlaps for up to 33% (World Health Organization,

2013). For each stressor-outcome pair that has been quantified with unadjusted ERFs, caution thus has to go to correct for overlap before disease burden estimates are added up.

3. Limitations

Generating attributable disease burden estimates inevitably relies on a set of assumptions, and is subject to a degree of uncertainty. Some of these uncertainties have already been referred to, such as those related to exposure assessment and the use of ERFs. These sources of uncertainty can be quantified, for instance by implementing a Monte Carlo simulation. This not the case for other uncertainties. One of such sources are possible errors in the data used to map the stressors. These data consist of model output, and although efforts have been made to validate their results, a degree of bias is still probable. Other examples are the shape of the ERF, which is not always examined, and the possibility of an exposure threshold, for which the data often lacks. Under these circumstances, one is left to assume a linear ERF, and to include or exclude a threshold based on own assessment or expert opinion.

Another limitation is that population exposure is solely addressed based on place of residence. As there is no information on occupation or place of work, occupational exposure to e.g., workplace carcinogens or ergonomic stressors cannot be addressed. Additionally, information on location is usually limited to the current or last-known official place of residence. As a result, exposure changes due to people moving cannot be taken into account. The approach for exposure assessment is thus 'static': the effect of occupational exposure, changing address, commuting, traveling or a second residence is not registered.

A common point of contention relates to what constitutes the most appropriate ERF. One point of view is that the dose-response relationship should be based on a sample that is a large and diverse as possible. Preference is given to meta-analyses that include effect measures from multiple studies, as to cover as much of the world's population as possible. The assumption here is that ERFs are universal, meaning that they reflect an innate biological response that is independent of ethnicity, culture or geographic region. A contrary view is that the ERF should be based on a source population (sampled in the epidemiologic study) that is close as possible to the target population (of interest in the BOD study). The underlying idea is that ERFs are context-dependent, and the results from one population are not transferable to another. In this case, the ERF is ideally sourced from a large cohort study confined to the population of interest. To apply this dilemma to air pollution: should the ERFs for PM, NO_2 and O_3 be sourced from the WHO global air quality guidelines (i.e., a meta-analysis of studies worldwide) or from ELAPSE (Stafoggia et al., 2022), with results limited to the European region or even Belgium specifically? The reason this question is listed as a limitation rather than a challenge, is that a definite answer is not likely to emerge soon, if ever. As a consequence, a choice has to be made to pursue one approach, at the expense of the other.

The previous limitation relates to the portability of the ERF: is the source population (subject of epidemiological studies) representative of the target population (for which the EBD is calculated)? This question is especially relevant with regard to the relatively small populations of the statistical sectors. Given their small size, the distribution of population characteristics might deviate substantially from the larger population sampled in epidemiologic studies. As a consequence, the EBD estimates for individual sectors might be biased. This problem might be alleviated by aggregating to a larger area, or over long periods of time. Alternatively, options could be explored to apply stratified ERFs, as to tailor the dose-response relationship to the specificities of the local populations.

CONCLUSION

The ultimate objective of EBoD-FL, a complete and coherent inventory of the environmental burden of disease in Flanders, is ambitious and extensive in scope. As a starting point, priority was given to stressors related to ambient air quality, environmental noise and extreme temperatures, that will be quantified in terms of their contribution to all-cause mortality, cardiovascular diseases and chronic respiratory diseases as proofs of concept. The scope of the project will be gradually extended to include more risk factors and outcomes. Each estimate is expressed according to a uniform metric, the disability-adjusted life year, which combines the health impact in terms of years of life lost (mortality) and years lived with disability (morbidity).

What differentiates EBoD-FL from other research projects, is the combination of its objective and wide scope. While other comprehensive studies of the EBD in Flanders have been conducted, they were to a large extent one-off endeavors. On the other hand, routine EBD exercises exist, but these are limited to a select number of environmental risks. On the contrary, EBoD-FL will continuously expand in scope, and its results will be routinely updated. In Flanders, other projects similar to EBoD-FL are ongoing, such as the Environment Health Impact Simulator developed by VITO. Although distinct in aim, contact will be maintained with other institutions to ensure a better alignment of the work and to avoid a duplication of efforts.

EBoD-FL could serve as a basis for evidence-based public health interventions, as it allows to answer questions related to environmental impact in a quantitative way. The results can aid the integration of a health perspective into environmental policy, and determine priorities for prevention and further research. In order to achieve this goal, some challenges have to be overcome. One difficulty is to establish clear criteria for selecting risk factor-outcome pairs and to determine the most suitable ERF. Additionally, the EBD related to some stressor-outcome pairs can be quantified by both the short-term and long-term approach, leading to a possible overlap in estimates. Similarly, the ERF for a certain risk factor is not always adjusted for correlation with other stressors, which means the estimates have to be corrected for double-counting before they are added up. Further research is required to deal with these challenges, as well as moments of consultation to devise appropriate and supported solutions.

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CONTENTS

ANNEXES

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Annex 1. Health outcomes

1.1. TOTAL AND CAUSE-SPECIFIC MORTALITY

According to the POCs, the outcomes to be analyzed in the initial stage are all-cause mortality, cardiovascular diseases and chronic respiratory diseases. As each of these endpoints have a mortality component, local mortality data is required to calculate YLLs on the level of the statistical sector. For this end, a request was made to Statistics Belgium (Statbel) for the supply of cause of death (COD) microdata. The word microdata refers to records of individual instances, in this case deaths. These microdata are based on information in death certificates, filled out by the medical doctor that certifies the death. The death certificates are then collected and coded by the regions, and afterwards compiled by Statbel into a single database.

As the COD microdata concern privacy-sensitive information, the request to Statbel had to be well-motivated, involving extensive negotiation, and the signing of a confidentiality contract. An agreement was reached to deliver COD data for the whole of Belgium starting with the year 2000, ending in 2019, the most recent year available. Yearly updates will be delivered until 2026 (i.e., the time range will be extended to reference year 2023), after which a prolongation of the contract can be requested through a simplified procedure. The received microdata is a combination of two datasets:

- MD1A: Deaths of people who were less than one year old ("infant mortality"). These records includes perinatal indicators, which can be used to assess confounding factors.
- PD1A: Deaths of people who were over one year old ("adult mortality").

The variables of the microdata include:

- COD ID: a pseudonym that serves as a unique identifier
- Basic demographics: age, sex, country of birth
- Cause of death: specified according to the International Statistical Classification of Diseases and Related Health Problems (ICD), 10th revision. In the ICD, CODs are coded hierarchically, where the first digit (a roman numeral) refers a broad category of diseases or injuries, and the subsequent digits progressively specify the cause. At the insistence of Statbel, the number of digits was limited for causes that are considered to be extra sensitive. There are several ways to specify the COD:
  - Underlying cause: the cause that is ultimately responsible for the death. The underlying cause if of prime interest, and also the one that is reported in COD statistics.
  - Immediate cause: this refers to the final event before death. Additionally, up to two intermediate causes can be specified, but these are not necessarily filled out.
  - Associated causes: up to three associated causes can be specified, but these are not necessarily filled out
  - External cause: a separate field is reserved in case the underlying COD is external. Additionally, the type of death is specified, meaning natural or a type of external cause (accident, suicide, homicide)
- Statistical sector: the place of residence of the deceased person is given in the form of the statistical sector code.

These microdata allow to compute total mortality figures, such as number of deaths, mortality rates, and years of life lost, the mortality component of the DALY. As the underlying cause of death is specified,

cause-specific mortality can be addressed. The ICD codes specify the COD with varying detail, depending on how many digits are given. For CVDs and CRDs, the following ICD codes are considered:

- Cardiovascular diseases: IX
  - Ischemic heart disease: I25
  - Stroke: I60-I64
- Chronic respiratory diseases: X
  - Chronic obstructive pulmonary disease: J40-J44
  - Lower respiratory infections: J09-J18

The assess the EBD of long-term exposure, the mortality figures can summed over one of multiple years. As the full date of death is given, short-term effects can be examined as well. For acute outcomes, correlation in time is important, as exposure and mortality follow each other in a time span of a days to weeks. The attributable cases can then be summed over one or multiple years to compare them to the chronic burden. The COD microdata only allow to address the mortality component (YLL) of the EBD. A request for local incidence data to account for morbidity (YLD) is planned for next year.

Annex 2. Risk factors

1.2. AIR QUALITY

1.2.1. Risk factor selection

For air quality, the selected risk factors are particulate matter (PM) with a diameter smaller than 10 micrometers (PM_{10}) and with a diameter smaller than 2.5 micrometers ($PM_{2.5}$), nitrogen dioxide (NO_2) and ozone (O_3). PM refers to all of the fine microscopic particles suspended in the air. As $PM_{2.5}$ only contains the smaller particles of PM, its composition and health effects are different compared to PM_{10}. NO_2 is a gas formed by combustion, as occurring in car engines and power plants. O_3 is not emitted directly but formed in the atmosphere by photochemical reactions. Each of these stressors is counted among the 'classical air pollutants' by the WHO (World Health Organization, 2021). The GBD only considers $PM_{2.5}$ and O_3, but the EBD study by Buekers et al. (2012) considers all four.

The metric used to assess long-term exposure is the annual mean concentration, expressed in the form of a mass concentration as micrograms per cubic meter (µg m^{-3}). Ozone forms an exception, for which a simple yearly average concentration is inadequate because of its strong seasonal and diurnal variation. A more complex metric is used, labelled 'peak season ozone' and is defined as the average of daily maximum 8-hour mean O_3 concentration in the six consecutive months with the highest six-month running-average O_3 concentration. For Belgium, the ozone peak season corresponds to the months April to September. Black/elemental carbon will not be studied because of a strong overlap with NO_2 in terms of exposure, and with $PM_{2.5}$ in terms of mortality. The short-term approach is essential for some stressors, such as ozone and heat, and has to be addressed in a future phase.

1.2.2. Exposure assessment

Air pollution exposure is based on high-resolution concentration maps for Belgium provided by IRCEL-CELINE. These pollution maps are the result of state-of-the-art models, calibrated against actual measurements but still subject to a degree of uncertainty. The output used for assessing PM10, $PM_{2.5}$ and NO_2 exposure is from ATMO-Street, which is the interpolation-dispersion model RIO-IFDM (used for O_3) expanded with a street canyon module. Both models have a 10 m grid spacing. For the domain of Flanders plus the Brussels Region, ATMO-Street is available for the years 2016-2020 (2017-2020 also include the Walloon Region). Prior years (2009-2015) are modeled with RIO-IFDM, which means results for these years are not comparable with 2016-2020 output.

While exploring the air pollution grids (both RIO-IFDM and ATMO-Street) overlaid with statistical sector vector file, it became apparent that the raster maps do not fully cover the territory of Flanders. The result is that certain sectors (N = 550) near the national border do not fully overlap with the pollution grids. The 'missing value problem' is limited for most of these sectors, but in the most extreme cases more than half of the sector's territory is not covered. As was personally communicated by an IRCEL collaborator, the problem occurred when the original model output was clipped to the extent of the Belgian territory. To omit this issue, IRCEL provided us with the unclipped grids. These maps are split into the Flemish and Brussels region on the one hand, and the Walloon regions on the other, as these domains are modelled separately. These maps differ slightly from the results for Belgium as a whole that are available as open data. The raster maps for O_3 expressed in the peak season metric had to be requested as well, as the maps publicly available rely on another unit.

Based on the air quality maps, one area-level mean concentration is extracted for each statistical sector. For each air pollutant, the exposure level for statistical sector *s* is calculated as the mean concentration *C* (eq. 8):

$$\bar{C_s} = \frac{1}{n}\sum_{i=1}^{n} C_i \qquad \text{(eq. 8)}$$

with *i* = 1, …, *n* all of the concentration values of the pollution raster that overlap with the sector's territory.

The exposure value is thus calculated straightforwardly as a spatial average, and not as a population-weighted average that takes into account residential addresses. In the supplementary materials of Chen & Hoek (2020) and Huangfu & Atkinson (2020), the meta-analyses referenced in the WHO air quality guidelines, the exposure assessment method of each of the reviewed studies is briefly outlined. In the majority of the cases, exposure of the subjects is quantified by linking the participant's address to a pollution raster, most of which have a relatively low resolution of a few hundred meters or even more than a kilometer. Alternatively, the address location is linked to the nearest monitoring station, or if the exact address is unknown, an average concentration value for the district or municipality is used as exposure value. In each of these cases, exposure is estimated with a considerable deal of uncertainty. Therefore, we argue that calculating population-weighted average in this case offers no advantage over a spatial average, and propose to use the latter as the approach to assess population exposure to the air pollutants.

1.2.3. Identification of stressor-outcome pairs

The EPA's Integrated Science Assessments were consulted to assess the causality between long-term exposure to air pollution and the outcomes specified in the POCs. ISAs are available for the four air pollutants considered ($PM_{2.5}$, PM_{10}, NO_2 and O_3). These assessments study the relationships with various health outcomes, including total non-accidental (all-cause) mortality, respiratory effects and cardiovascular effects. Depending on the available evidence, the relationship is rated as causal, likely to be causal, suggestive of causality, inadequate to infer causality, and not likely to be causal (U.S. Environmental Protection Agency, 2015). The conclusions of the ISAs for the risk factor-outcome pairs for long-term exposure that are relevant at this stage of the research are summarized in Table 2 (U.S. Environmental Protection Agency, 2016, 2019, 2020).

Table 2 • Conclusions on the causality between long-term exposure to selected air pollutants and health outcomes, based on the U.S. EPA's ISAs.

Outcome	$PM_{2.5}$	PM_{10}	NO2	O_3
All-cause mortality	Causal	Suggestive	Suggestive	Suggestive
Respiratory effects	Likely	Inadequate	Likely	Likely
Cardiovascular effects	Causal	Suggestive	Suggestive	Suggestive

Of course, a causal relationship between air pollutants and respiratory and cardiovascular effects does not indicate a causal link between these risks and more specific CRDs and CVDs. In case the evidence points (suggestive) causality for these effects, the epidemiologic literature can be searched for ERFs that link exposure and more specific outcomes such as COPD, ALRI, IHD and stroke. If such studies find a statistically significant association and are sufficiently corrected for confounding, including these risk factor-outcome pairs would be justified.

1.2.4. Quantification of the stressor-outcome relation

The first choice for ERFs are those integrated in the most recent Air Quality Guidelines (AQGs) published the WHO (World Health Organization, 2021). These ERFs are comprised of a meta-analytic effect derived from multiple epidemiologic studies identified in systematic reviews. These reviews consider the health effects of the 'classical air pollutants' in terms of total and cause-specific mortality outcomes. The health effects of both PM types are similar, although more pronounced for $PM_{2.5}$ compared to PM_{10}. This finding fits the results of the causality assessment by the U.S. EPA. For chronic NO_2 exposure, only all-cause and respiratory mortality outcomes are examined, although the ISA for this stressor finds the evidence suggestive of causality for the link with cardiovascular effects. This indicates that it might be necessary to consult other reviews that do study this stressor-factor outcome pair. For long-term O_3, the dose-response relationships are even weaker. The AQGs do include the ERF for O_3 and all-cause mortality, where the bottom of the 95 % CI coincides with a RR of 1.00. Consequently, a choice must be made to include all-cause mortality of chronic O_3, or to limit the study to acute mortality.

Regarding the shape, the (all-cause and cause specific) mortality ERFs for $PM_{2.5}$, PM_{10}, NO_2 and O_3 are generally either linear or supra-linear (i.e., a steeper curve at lower concentration). In the systematic reviews performed in the context of the AQGs, the meta-analytic effect is calculated using the inverse variance method assuming linear dose-response relationships (World Health Organization, 2021). For PM, some individual studies reported non-linear functions Chen & Hoek (2020), while Huangfu & Atkinson (2020) did not find strong evidence to reject the linearity assumption for NO_2 and O_3. In light of this, we propose to apply a linear ERF to calculate the PAF. This approach differs from the GBD, which uses integrated ERFs, based on non-linear functions.

With regard to an exposure threshold, most studies for PM do not find indication of a cut-off value (Chen & Hoek, 2020). In Huangfu & Atkinson (2020), it is not mentioned whether the individual studies find evidence for a threshold. As a consequence, we suggest that an exposure threshold should not be applied to long-term EBD calculation for the air pollutants. This is congruent with a joint statement released by medical, public health, scientific societies and patient representative organizations, stating that "harmful health effects [of air pollution] can be observed all the way down to very low concentration levels, with no observable thresholds below which exposure can be considered safe" (Hoffmann et al., 2021).

1.2.5. Calculation of the population attributable fraction

The PAFs for exposure to the air pollutants can be calculated with the simplified formula (eq. 5), where the relative risk is calculated linearly without the inclusion of an exposure threshold (eq. 6).

1.3. ENVIRONMENTAL NOISE

1.3.1. Risk factor selection

Environmental noise can result from different sources, such as transportation (road traffic, railway and aircraft), wind turbines noise and leisure activities (e.g., concerts, nightclubs). The Environmental noise guidelines for European Region provide recommendations for protecting human health from exposure to environmental noise (WHO Regional Office for Europe, 2018). Based on the evidence quality and the

expected efficacy of reducing exposure, the recommendations are strong or conditional. As the recommendations formulated are strong are for traffic noise and mostly conditional for the other sources, we propose to start with noise from road, railway and air traffic, and to optionally extend this list with wind turbine and leisure noise at a later stage.

The health effects of environmental noise are addressed by relying a long-term approach. As such, the indicator used is usually a yearly average sound pressure level, calculated for specific hours of the day (daytime, evening or night) or for the day as a whole. A common metric is the noise level taken over the day, evening and night (L_{den}), expressed in decibels (dB). In the calculation of L_{den}, the evening value gets a penalty of 5 dB and the night value of 10 dB, as noise during these hours are considered to have a larger impact (European Environment Agency, 2010).

1.3.2. Exposure assessment

The exposure assessment is based on the strategic environmental noise maps provided by the regions. These maps consist of output from extensive acoustic models, that take into account the distribution of noise sources with differing properties and the geometry of the surroundings. The results are updated every 5 years, currently available for the reference years 2011 and 2016. The maps for 2021 are planned to be published next year in 2023. The sources accounted for in the strategic noise maps are:

- Road traffic, for routes with more than 3 million vehicles per year;
- Rail traffic, for railways with more than 30,000 passages per year;
- Aircraft traffic, for airports with more than 50,000 aircraft movements per year, excluding training flights with light aircraft.

These maps are thus limited to major highways and busy railways. The requirement for airports only applies to Brussels Airport in Zaventem. Agglomerations with populations exceeding 100,000 need to be covered by separate noise maps. These maps are more comprehensive, as they are not limited to only major roads, railways and airports and include other sources, such as trams and industry (including ports). For Flanders, the agglomerations that qualify for separate modelling are Antwerp, Ghent and Bruges, while Leuven will be included in the next update. The Brussels Region is modelled as agglomeration, and as such has detailed noise data available.

Epidemiological studies that examine the health effects of noise usually consider the noise level at the most exposed facade of the subject's dwellings (WHO Regional Office for Europe, 2018). Assessing population exposure to environmental noise should pursue the same strategy, which makes for a complex procedure that takes into account noise levels, the location of residences and the geometry of dwellings. Alternatively, one could start with a sensitivity analysis, where the complex approach for noise exposure assessment is implemented for a selected noise source and number of sectors, and the results compared to a simpler method, equivalent to the approach for air pollution. If the difference is limited, the simpler variant can be pursued, which would limit the computational resources and the data required.

An important difference between the noise maps compared to the air quality maps, is that the latter cover all emission sources, while the former don't. Exposure in the population could therefore be underestimated. A 'full-coverage' noise map for Flanders does exist, but is limited road traffic noise (Dekoninck & Botteldooren, 2019).

1.3.3. Identification of stressor-outcome pairs

The assessment of causality between noise exposure and health outcomes is not as well established as for air pollution. With regard to cardiovascular effects, a plausible pathway is that exposure to environmental noise induces a stress reaction, which in turn can impact the circulatory system. Another possibility is that nighttime noise leads to sleep deprivation, which can also be linked to cardiovascular

outcomes (Hahad et al., 2019). As certain cardiovascular conditions can lead to death, exposure to environmental noise can in theory be linked to all-cause mortality as well.

1.3.4. Quantification of the stressor-outcome relation

The most recent Environmental Noise Guidelines for the European Region (WHO Regional Office for Europe, 2018) do not consider all-cause mortality as health outcome when deriving advised noise levels for traffic noise. When consulting the epidemiologic literature, it appears that a consensus regarding traffic noise and all-cause mortality has not been reached. A positive correlation for road traffic exposure was identified in one meta-analysis by Hao et al. (2022) (who pooled the results of their cohort study with other effect estimates collected in a systematic review), in a large cohort study from two Danish cities (Thacher et al., 2020), and a weak correlation in a London cohort study (Halonen et al., 2015). The study by Hao et al. (2022) suffers from some limitations, as the ERF identified by their 'main model' does not adjust for all confounding factors, and their meta-analysis includes studies that overlap in population. On the other hand, no significant association was found in another meta-analysis by (Cai et al., 2021), and in a 'mega-cohort' study from Barcelona (Nieuwenhuijsen et al., 2018). According to Cai et al. (2021), there are few studies for railway and aircraft noise, and those that do exist find no relationship.

With regard to cardiovascular effects, the WHO environmental noise guidelines consider the incidence of IHD as outcome. Based on the commissioned systematic review and meta-analysis (van Kempen et al., 2018), they report a significant ERF for IHD incidence and traffic noise from roads and aircraft. For railway noise, the study found no evidence to support a link with IHD. The review by van Kempen et al. (2018) also examines stroke as health outcome, but found no significant correlation with any of the traffic noise sources.

Given the evidence currently available, it appears that in terms of exposure to traffic noise and the prioritized health outcomes, only the association of noise from road and aircraft traffic with IHD is sufficiently supported. On the other hand, some studies find a significant link between traffic noise exposure and mortality outcomes as well, and given the link with IHD, it seems plausible that a relationship exists but is too weak to be identified in the current data. Therefore, we propose to limit the burden calculation of traffic noise to IHD morbidity, with the option to extend the calculation to mortality outcomes if future evidence supports this.

1.3.5. Calculation of the population attributable fraction

The PAF can be calculated with the simplified formula (eq. 5). The possibility of an exposure threshold for the calculation of the relative risk (eq. 6) has to be further researched.

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MORE INFORMATION

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