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Methodological manual for air pollution health risk assessments in Switzerland

Project: Quantification of health impact of air pollution in Switzerland (QHIAS)

Deliverable 5

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ABBREVIATIONS

AP-HRA	Air pollution health risk assessment
ALRI	Acute lower respiratory infections
AQG	Air Quality Guidelines
BC	Black carbon
COLAUS	Cohorte Lausannoise
COMEAP	Committee on the Medical Effects of Air Pollutants
COPD	Chronic obstructive pulmonary disease
CRF	Concentration-response function
DALYs	Disability-adjusted life years
EC	Elemental carbon
EEA	European Environment Agency
ELAPSE	Effects of Low-Level Air Pollution: A Study in Europe
ESCAPE	European Study of Cohorts for Air Pollution Effects
ETC-HE	European Topic Centre on human Health and the Environment
EXPANSE	EXposome Powered tools for healthy living in urbAN SEttings
ERS	European Respiratory Society
FCAH	Swiss Federal Commission for Air Hygiene
FSO	Swiss Federal Statistical Office
GBD	Global Burden of Disease
GeLuft	Quantifizierung des Gesundheitsnutzens der neuen Luftqualitätsleitlinien der Weltgesundheitsorganisation in der Schweiz (Quantification of health benefits of the new WHO Air Quality Guidelines in Switzerland)
HEI	Health Effects Institute
IER	Integrated exposure-response functions
ISA	Integrated Science Assessments
ISEE	International Society for Environmental Epidemiology
LUR	Land use regression
NO_2	Nitrogen dioxide
O_3	Ozone
OECD	Organisation for Economic Co-operation and Development
PM	Particulate matter
ppb	Parts per billion
QHIAS	Quantification of Health Impact of Air Pollution in Switzerland
SAPALDIA	Swiss Study on Air Pollution and Lung Diseases in Adults
Swiss TPH	Swiss Tropical and Public Health Institute

STE	Swiss assessment for transport externalities
UBA	Umweltbundesamt (German Environment Agency)
US EPA	United States Environmental Protection Agency
UFPs	Ultrafine particles
WHO	World Health Organization
YLDs	Years lived with disability
YLLs	Years of life lost

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ABSTRACT

Air pollution health risk assessments (HRAs) are estimations of the health impacts attributable to exposure to air pollution on entire populations. The calculations involved in AP-HRAs are based on the following input data: baseline health data, concentration-response functions (CRF), exposure data, and counterfactual scenario. The most comprehensive AP-HRAs in Switzerland have traditionally been integrated into Swiss assessments for transport externalities (STEs).

The goal of this report is to identify new developments in AP-HRA research and data sets to provide relevant methodological information on how to apply AP-HRAs in Switzerland. For this aim, the most recent international and Swiss literature on this field has been reviewed.

This report concluded that $PM_{2.5}$ or PM_{10} ($PM_{2.5}/PM_{10}$) as well as NO_2 and O_3 are the most suitable air pollution indicators for AP-HRAs in Switzerland due to the availability of concentration model data and evidence for health effect. The health outcomes for the selected pollutants should be selected based on sufficient evidence of association as well as availability of baseline health data and CRF. Selection of pollutant-outcome pairs, CRFs and baseline health data from the WHO project HRAPIE as well as evidence evaluations from the United States Environmental Protection Agency Integrated Science Assessments have been referenced in many AP-HRAs and are still valid, but some of their recommendations are becoming outdated. Therefore, updates of these reports as well as more recent literature reviews should be explored. When selecting the CRFs, European cohort studies such as ELAPSE or ESCAPE are preferred for Switzerland, while meta-analyses from literature reviews can be alternatively used, ideally with a high proportion of European studies. The use of single-pollutant CRFs should still be prioritized over two-pollutant CRFs due to the lack of robustness and effect transfer of the latter. For baseline health data, Swiss statistical data are the preference. If no Swiss routine data is available for some outcomes, data can be derived from the online tool of the Global Burden of Disease or from Swiss epidemiological studies. Regarding the exposure data, data from the Swiss dispersion model PolluMap is recommended, if source specific AP-HRAs are conducted. Otherwise, land use regression models can be alternatively used to calculate the health burden from total air pollution. Concerning the counterfactual scenario, the WHO AQG 2021 should be selected, if the goal of the AP-HRA is to capture the overall health impacts above the minimum air pollution concentration with evidence of health effects.

EXTENSIVE SUMMARY

Air pollution health risk assessments (HRAs) are estimations of the health impacts attributable to exposure to air pollution of entire populations. The calculations involved in AP-HRAs are based on the following input data: baseline health data, concentration-response function (CRF), exposure data, and counterfactual scenario (e.g. Castro et al. 2022b). The most comprehensive AP-HRAs in Switzerland have traditionally been integrated into Swiss assessments for transport externalities (STEs). The STE for 2010 (STE-2010), which was published in 2013, carried out a last major revision of the methodology (ARE 2014). This methodology followed in many aspects the recommendations of the World Health Organization (WHO) "Health risks of air pollution in Europe – HRAPIE" project (WHO 2013a), published in 2013. Since then, the body of research on air pollution and health has grown.

The goal of this report is to identify new developments in AP-HRA research and data sets to provide relevant methodological information on how to apply AP-HRAs in Switzerland. For this aim, the most recent international and Swiss literature on this field has been reviewed. A summary of the main conclusions for various steps in an AP-HRA are presented below.

Select the air pollution indicators

$PM_{2.5}$ or PM_{10} ($PM_{2.5}$/PM_{10}) as well as NO_2 and O_3 are the most suitable air pollution indicators for AP-HRAs in Switzerland based on the evidence for any health effect, the availability of concentration data and the level of concentration. One, a selection or all of them can be chosen for an AP-HRA. PM_{10} and $PM_{2.5}$ are the most common air pollution indicators, which represent a wide range of emission sources. They can be used interchangeable, as they are highly correlated, by applying a conversion factor (around 70% of PM_{10} refers to $PM_{2.5}$ in Switzerland). The use of $PM_{2.5}$ can be prioritized over $PM_{2.5}$ because more epidemiological literature has been published, while PM_{10} can be used as a better indicator of the spatial distribution of traffic in transport-related studies.

Select the health outcomes of the pollutants to be assessed

The health outcomes for the pollutant/s should be selected using the following criteria:

- Sufficient evidence of an association between pollutant and heath outcome
- Available baseline health data for the outcome
- Available CRF for the specific pollutant-outcome pair

The list of health outcomes can be further reduced in a second step by removing overlapping outcome definitions and outcomes from correlated pollutants to avoid double counting of effects as well as by removing outcomes without data or relevance for an eventual monetarization.

Take into account evidence of health effects

It is recommended to primarily consider the evidence published in the WHO project HRAPIE (WHO, 2013a) for $PM_{2.5}$/PM_{10}, NO_2 and O_3 and the United States Environmental Protection Agency Integrated Science Assessments (US EPA ISAs) for $PM_{2.5}$ (US EPA 2019), O_3 (US EPA 2020), NO_2 (US EPA 2016), SO_2 (US EPA 2017) and CO (US EPA 2010). These two sources of information have been used to evaluate evidence of effects in specific pollutant-outcome pairs. However, they are becoming outdated. Therefore, a further evidence assessment or a search of more recent assessments should be carried out. Examples of such relevant, more recent literature are the systematic reviews by the Health Effects Institute (HEI) with association assessments on health effects from traffic-related air pollution (HEI 2022), the causality assessments (Ru et al. 2021) of the Global Burden of Disease (GBD) Study (Murray et al. 2020) as well as studies commissioned by the German Agency for the Environment (UBA) (Breitner et al. 2023; Schneider et al. 2018) and by Health Canada (Health Canada 2016). Two ongoing WHO projects, HRAPIE-

2 (follow-up of HRAPIE) and EMAPEC, will publish updated conclusions soon that may become new international gold standards.

Decide how to address overlapping health outcomes from multiple pollutants

In the selection of pollutant-outcome pairs, the sum of overlapping health outcomes from multiple correlated pollutants (e.g. $PM_{2.5}$ and NO_2 long-term mortality) can lead to double counting of health impacts, if single-pollutant CRFs are used. Single-pollutant CRF should only be used without adding health impacts of different pollutants, i.e. presenting the results in parallel or excluding overlapping health outcomes from pollutants with lower evidence level. Unlike single-pollutant CRFs, two-pollutant CRFs enable to sum up health impacts from two correlated pollutants reducing the risk of double counting. However, challenges remain with the interpretation of paradoxical results due to the lack of robustness of these CRFs and effect transfer. Therefore, single-pollutant CRFs should be prioritized, unlike two-pollutant CRFs are specifically needed.

Collect baseline health data of the selected outcomes and make a choice

The age group of the baseline health data should ideally match as much as possible with the age defined for the pollutant-outcome pair and the CRFs. The sources of baseline health data for AP-HRA in Switzerland can be prioritized as follows:

1. Baseline health data from Swiss databases and registries, e.g. from the Swiss Federal Statistical Office (FSO) or National Agency for Cancer Registration.
2. The online tool “GBD results”, which provides health modelling (not reported) data for specific countries, years and age group categories.
3. Population rates from Swiss epidemiological studies, such as SAPALDIA and COLAUS, do not cover the whole population but are specific for Switzerland.
4. The European rates from European database EUROSTAT using if possible data from similar geographic contexts to Switzerland (e.g. Western Europe), but only if none of the above are available.
5. The recommendations of HRAPIE (or forthcoming HRAPIE-2 and/or EMAPEC) in terms of baseline health data based on international epidemiologic studies. These international estimations can be not specific for Europe.

Compile concentration-response functions in the literature and make a choice

For the CRFs, cohort studies from Europe (such as ESCAPE and more recently ELAPSE) are the preferred source over meta-analyses from systematic literature reviews because of a more coherent analysis approach. Both prospective and administrative cohort studies are adequate. The following further criteria should be considered to choose among available CRFs:

- CRFs obtained ideally from cohort studies with adequate confounding adjustment (otherwise from systematic literature reviews)
- Similar geographical context (Europe, Swiss CRFs may lack statistical precision)
- Single-pollutant model or two-pollutant model depending on the AP-HRA strategy for overlapping outcomes across pollutants
- Large cohort study size or high number of studies (from Europe) in the meta-analysis of systematic reviews
- Recent publication
- Exposure model underlying the CRF well matched to exposure used in the AP-HRA

For long-term all-cause mortality attributed to $PM_{2.5}$ and NO_2 (single-pollutant), the European Respiratory Society and the International Society for Environmental Epidemiology have jointly recommended to use a pooled CRF of the administrative (Stafoggia et al. 2022) and prospective European (Strak et al. 2021) cohorts of the ELAPSE project (Brunekreef et al. 2022; Hoffmann et al. 2022) in European AP-HRAs. Recommendations on the choice of CRFs from the ongoing WHO projects HRAPIE-2 and EMAPEC will be published soon.

Decide on the use of age- and sex specific CRFs

Sex- and age specific CRFs are currently rarely provided in relevant CRF studies. In the absence of such data, it is suggested to use CRFs for broader age groups or all ages as well as for all sex.

Collect air pollution exposure data

Air pollution concentration data from dispersion models or from land use regression models can be used in AP-HRAs. Swiss dispersion model PolluMap are recommmended, if the modelling of different emission sources and compounds is required for source apportionment, as in STEs. For $PM_{2.5}$, PM_{10}, NO_2 and SO_2, air pollution concentration with high spatial resolution (20m x 20m) and exposure data (population-weighted concentration) in Switzerland are available from PolluMap (Heldstab et al. 2020a; Künzle 2022). For O_3, only concentration data (without population weighting) are available and at a lower spatial resolution (200 m x 200 m). The O_3 concentration data require extra steps by the user to derive the population-weighted exposure, and may require metric conversion (to match with the CRF in the epidemiological literature). Land use regression models from the EU project ELAPSE are nowadays available at a similar spatial resolution and for O_3 in metrics that are compatible with CRFs of HRAPIE (de Hoogh et al. 2018b; de Hoogh et al. 2019).

Decide on short-term exposure effects

Short-term effects are included in long-term effects of the same outcome (e.g. long-term mortality includes short-term mortality). This overlap has to be avoided in AP-HRAs. Thus, short-term effects should complement the already selected long-term effects and not overlap with them.

Daily concentration data from short-term concentration models for PM_{10}, NO_2 and O_3 are available for Switzerland from analyses based on PolluMap (Künzle 2021) and also from ELAPSE. To quantify short-term impacts, it is recommended, if possible, to use CRFs that are derived from spatiotemporal resolution to be coherent with the spatial models used for exposure assessment in original CRF studies. Alternatively, the use of spatiotemporal long-term modelling can be used, assuming a (near) linear exposure-response relationship, because they provide similar results as aggregated daily modelling data.

Decide on the use of source-specific exposure effects

$PM_{2.5}$ from traffic is associated with higher risks of mortality than from other sources. On the other hand, relative risks of elemental components of particulate matter decrease when adjusting for total $PM_{2.5}$ mass concentration or NO_2. Therefore, the use $PM_{2.5}/PM_{10}$ as air pollution indicator instead of the sum of single components is still broadly adequate and the total air pollution health impact is most likely captured by a limited set of indicators representing the most relevant air pollution sources. The progress in future research on multi-pollutant approaches might overcome this barrier and help to estimate the weight of sources and specific transport modes in health impacts attributed to total air pollution.

Choose a counterfactual scenario

The choice of the counterfactual scenario for Swiss AP-HRAs partly depends on the aimed health impacts to be captured.

- If the goal of the counterfactual scenario is to reflect the minimum air pollution concentration with evidence of health effects, the WHO AQG 2021 should be selected, i.e. 5 $\mu g/m^3$ $PM_{2.5}$, 10 $\mu g/m^3$ NO_2 and 60 $\mu g/m^3$ O_3 for long-term exposure.
- If the goal is to exclude anthropogenic air pollution, the minimum of the local exposure can be used.
- If the goal of the counterfactual scenario is to capture the whole range of air pollution (including non-anthropogenic), a zero concentration can be considered.

1. INTRODUCTION

1.1 Air pollution health risk assessment (AP-HRA)

Health risk assessments (HRAs) have been defined as “the scientific evaluation of potential adverse health effects resulting from human exposure to a particular hazard” and they provide a methodology to quantify health risks for exposure to risk factors (WHO 2017). For the concept of HRA, alternative terms have been used in the literature, e.g. “health impact assessment” (Martuzzi et al. 2003), “assessment of the health burden” (Lu et al. 2017), “burden of disease assessment” (Evangelopoulos et al. 2020) and “accountability study” (Boogaard et al. 2017), although there can be some conceptual differences among them. For example, a health impact assessment focuses on the health impacts as a result of the implementation of a particular measure and comprise multiple policy steps (WHO 2021).

Ambient (outdoor) air pollution has been considered as one of the main environmental risk factors and therefore included in air pollution HRAs (AP-HRAs) to quantify the attributable health effects (Evangelopoulos et al. 2020). Although there are some methodological differences among HRAs (Castro et al. 2021), AP-HRAs usually use the following main input data to calculate health impacts attributed to air pollution (Figure 1):

- Baseline health data: Incidence or prevalence of a disease or mortality among a certain population group at risk.
- Concentration-response function (CRF): This is the risk of change in prevalence or incidence (effect estimate) for any increment in pollutant concentration. The whole function can be available from epidemiologic literature. However, more often only a single effect estimate (i.e. a relative risk or hazard ratio including a central estimate as well as lower and upper bound of the confidence interval) for a specific increment in concentration (e.g. 5 or 10 µg/m^3) is provided, while the shape of the function is assumed in the AP-HRA (e.g. linear or log-linear). For practical reasons, we use in this document the term CRF to refer to both (the function and the specific effect estimate).
- Counterfactual scenario: Minimum (cut-off) concentration considered in the AP-HRA below which health effects are not quantified or to which they are compared.
- Population exposure: the modelled pollutant concentration, which is weighted for the exposed population.

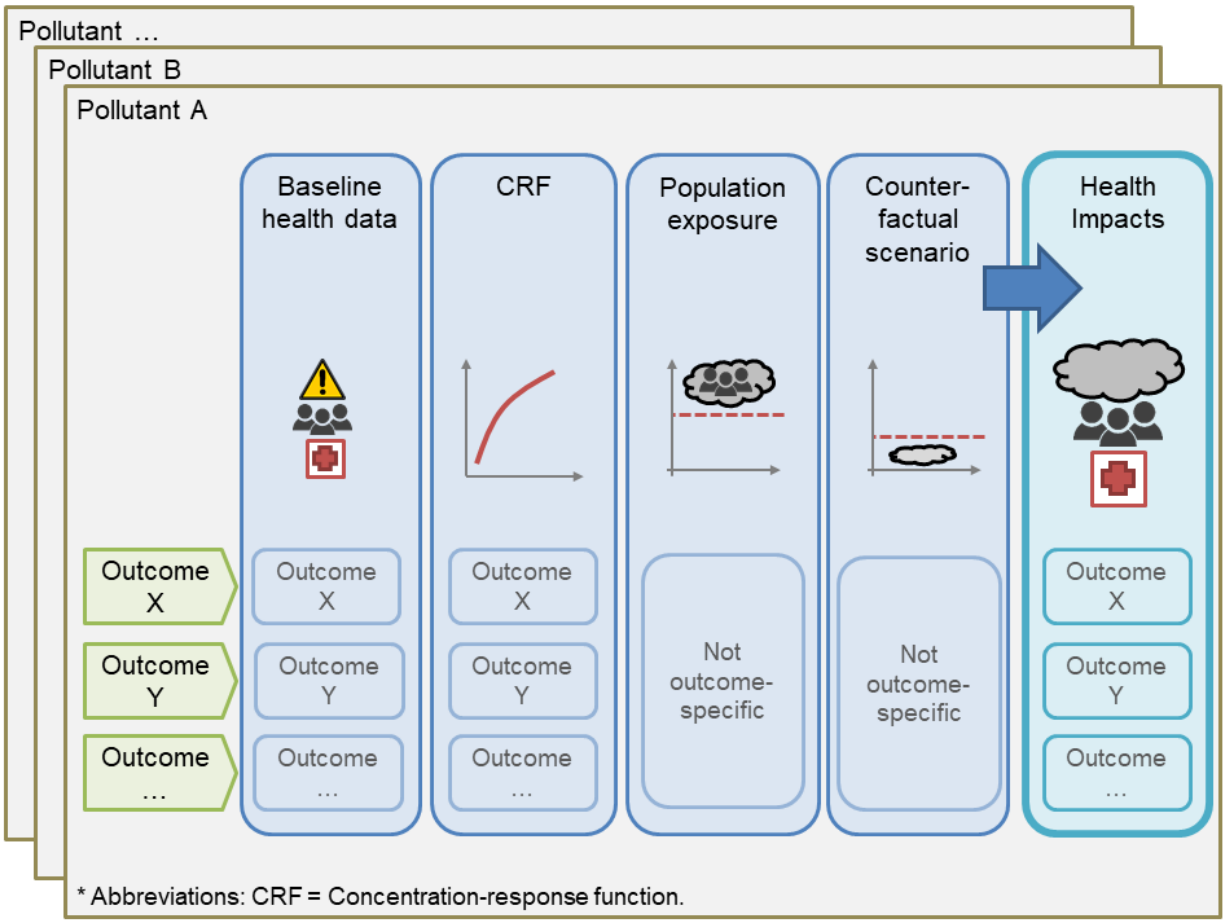

Figure 1: Outline of the main input and output data involved in AP-HRAs

1.2 AP-HRAs for Switzerland

In Switzerland, the most comprehensive air pollution HRAs (AP-HRAs) are integrated in studies on external costs of transport; here abbreviated as STEs (Swiss assessment for Transport Externalities). Swiss public authorities, have commissioned STEs since 1993 (GVF 1996), followed by updates for 1996 (Künzli et al. 2000; Seethaler 1999), 2000 (ARE et al. 2004), 2005 (ARE and FOEN 2008), 2010 (ARE 2014), 2015 (ARE 2019), 2017 (ARE 2020) and 2019 (ARE 2022). The STE for 2010 (STE-2010) contained the last major revisions of the methodology, while later publications were mainly smaller updates of input data of population exposure (ARE 2019).

Most of the key methodological aspects of the AP-HRA in STE-2010 (ARE 2014) were based on the conclusions of two WHO projects published the year before: “Review of Evidence on the Health Aspects of Air Pollution” (REVIHAAP) (WHO 2013b) and the consequent “Health Risks of Air Pollution In Europe” (HRAPIE) (WHO 2013a). REVIHAAP reviewed relevant literature to answer critical questions about the applicability of AP-HRAs to specific pollutants, outcomes and circumstances, while HRAPIE, building on the REVIHAAP results, suggested specific CRFs and counterfactual concentrations for pollutant-outcome pairs

Beyond the STEs, the following national and international studies have carried out AP-HRAs with specific results for Switzerland:

- the Global Burden of Disease (GBD) studies, being the most recent one from 2019 (Murray et al. 2020),
- the WHO burden of disease studies for 2012 and 2016 (WHO 2016a; WHO 2018),

- the yearly EEA air quality reports (EEA 2013; EEA 2014; EEA 2015; EEA 2016; EEA 2017; EEA 2018; EEA 2019; EEA 2020; ETC/ACM 2016; ETC/ATNI 2020; Soares et al. 2022),
- a study of the Swiss Federal Commission for Air Hygiene (FCAH) comparing epidemiological and toxicological approaches for assessing lung cancer mortality (Castro et al. 2020) and
- a AP-HRA for around 1'000 urban areas in Europe (Khomenko et al. 2021b), which covered the ten largest urban areas in Switzerland representing 27% of the Swiss population.

Depending on the AP-HRA and the evaluated year, different input data for Switzerland were used, which led to different results that may become a challenge for communication (Castro et al. 2021).

The WHO Air Quality Guidelines (WHO AQG) were published in 2005 (WHO 2006) and updated in 2021 (WHO 2021). The project GeLuft (Quantifying the health benefits of the new World Health Organization Air Quality Guidelines in Switzerland), which was funded by the Swiss Federal Office for the Environment (FOEN), estimated the health benefits of complying with the WHO AQG 2021in Switzerland deriving an updated list of health outcomes and collecting new CRFs and health data (Castro et al. 2023b). Furthermore, the project GKV21 (Methodology revision of true costs of transport), an updated STE for 2021 including a revision of the STE-2010 methodology, was carrying out at the time that this report was published and will be available in 2024. It should also be noted,that several ambient AP-HRA tools (Anenberg et al. 2016; WHO 2016b), such as the WHO Tool AirQ+, enable the calculation of the health impacts of air pollution for specific geographic areas. These tools could be eventually used for the case study of Switzerland, but with lower flexibility in terms of methodology than ad-hoc AP-HRAs.

Beyond AP-HRAs, some relevant examples of large epidemiological studies that focused on or included the participation of Switzerland are the following: SAPALDIA (Swiss Study on Air Pollution and Lung Diseases in Adults) (Swiss TPH 2021a), ESCAPE (European Study of Cohorts for Air Pollution Effects) (ESCAPE 2019), ELAPSE (Effects of Low-Level Air Pollution: A Study in Europe) (ELAPSE 2021), EXPANSE (Exposome Powered Tools for Healthy Living in Urban Settings) (EXPANSE 2021) and COLAUS (Cohorte Lausannoise) (COLAUS 2021). These studies may provide CRFs and/or baseline health data from a geographic context applicable to Switzerland. New large literature reviews such as the one from the Health Effects Institute (HEI) for traffic-related air pollution (HEI 2022) also provide new CRFs and evidence of health effects. A follow-up project of HRAPIE (HRAPIE-2) is on-going at this moment and will provide updated recommendations within the following years, while the related project EMAPEC (Estimating the Morbidity from Air Pollution and its Economic Costs), with the collaboration of WHO, will provide soon results.

1.3 Goal and structure of this document

Since the publication of STE-2010 (as well as the REVIHAAP and HRAPIE reports), air pollution health research has been considerably refined, which is expected to have consequences for the methods of future AP-HRAs. In the light of these new available resources, the project QHIAS (Quantification of Health Impact of Air Pollution in Switzerland), commissioned by the FOEN, aimed to provide relevant information for future AP-HRAs for outdoor air pollution in Switzerland. This manual is an outcome of the QHIAS project and aims to update AP-HRA methods with the most current scientific knowledge on quantifying the morbidity and mortality attributable to exposure to air pollution.

The manual addresses specific methodological questions related to the main input data involved in AP-HRAs, i.e. pollutant-outcome pairs, baseline health data, concentration-response functions, exposure data and counterfactual scenarios. Firstly, the question is precisely formulated. Secondly, the background of the issue is described focusing on the HRAPIE recommendations

and on the method applied in STE-2010. Thirdly, a state of the art is presented with a review of information from literature and data sources published after HRAPIE and STE-2010. Finally, the conclusions for Switzerland based on the state of the art above are provided.

It should be acknowledged that the availability of data and literature is subject to constant change. Consequently, any conclusions drawn from this study should be re-evaluated in the event of future AP-HRAs.

2. POLLUTANT-OUTCOME PAIRS

2.1 Selection of air pollution indicators

Formulation of the question

Which air pollution indicators can be included in AP-HRAs in Switzerland?

Background

Particulate matter (PM) is a mixture of several solid and liquid air pollutants, but not gases. Therefore, AP-HRAs that only consider PM may not capture the whole health impacts of exposure to air pollution. The most common measure of PM pollution is usually defined by the diameter of the particles in the fraction, i.e. up to 10 micrometer (PM_{10}), up to 2.5 micrometer ($PM_{2.5}$), between 10 and 2.5 micrometer ($PM_{10\text{-}2.5}$, also called coarse) and smaller than 0.1 micrometer ($PM_{0.1}$, also called ultrafine particles or UFPs).

The WHO projects REVIHAAP (WHO 2013b) and HRAPIE (WHO 2013a) recommended the following pollutants (selected as main indicators for air pollution from different sources) for inclusion in AP-HRAs:

- PM, either $PM_{2.5}$ or PM_{10} ($PM_{2.5}$/PM_{10}),
- Ozone (O_3) and
- Nitrogen dioxide (NO_2).

It should be noted, that for coincident health impacts from correlated pollutants (e.g. long-term all-cause mortality for $PM_{2.5}$ and NO_2) cannot be summed because of the risk of double-counting, if the exposures are correlated and the CRFs are not adjusted for the other pollutant (WHO 2013a) (see Section 2.3). The same principle applies to different fractions of PM, whose exposures are highly correlated.

Up to date, all AP-HRAs for Switzerland from STEs have relied exclusively on PM_{10}.This PM fraction has been used as single air criteria pollutant according to a comparative review of this project QHIAS (Castro et al. 2021). PM_{10} was selected instead of $PM_{2.5}$ in STE-2010 because the Swiss Ordinance on Air Pollution Control included air pollution standards for PM_{10}, but not for $PM_{2.5}$ at that time. Moreover, less monitoring stations measured concentrations levels of $PM_{2.5}$ and the quality of exposure model was lower (ARE et al. 2004). Two additional reasons in favor of PM_{10} were argued by STE-2010. Firstly, comparisons across transport modes would be less reliable using $PM_{2.5}$, if some of the transport modes emit a larger proportion of PM_{10}. Secondly, PM_{10} shows a higher spatial correlation with road traffic than $PM_{2.5}$ (ARE 2014).

The authors of STE-2010 also considered (but not applied) the inclusion NO_2 and/or O_3 as additional air pollution indicators. In favor of the inclusion of NO_2, it was argued that it is mainly emitted by motorized traffic and have a high correlation with traffic proximity, but the exposure was highly correlated to PM_{10}, which would lead to double counting of health effects (ARE 2014). Regarding O_3, it was not selected because the health effects were considered to be small compared to those from PM_{10} (ARE 2014).

State of the art

The four international AP-HRAs with specific results for Switzerland used $PM_{2.5}$, while three out of them additionally assessed health impacts attributed to NO_2 and/or O_3. Thus, beyond PM, the GBD study for 2019 (Murray et al. 2020) additionally included O_3, an AP-HRA in around 1,000 European urban areas (10 of them in Switzerland) included NO_2 (Khomenko et al. 2021a) and the yearly AP-HRAs of the EEA (EEA 2013; EEA 2014; EEA 2015; EEA 2016; EEA 2017; EEA 2018; EEA 2019; EEA 2020; ETC/ACM 2016; ETC/ATNI 2020; Soares et al. 2022) included all three, PM2.5, O_3, and NO_2 (Castro et al. 2022b). The WHO burden of disease studies (WHO 2016a; WHO 2018) focused on $PM_{2.5}$ (Castro et al. 2022b). In these studies, the number of health effects and the attributable deaths were higher for $PM_{2.5}$ than for the other two pollutants. The number of premature deaths attributed to O_3 were around 7% to 14% of those attributed to $PM_{2.5}$ and 1% to 70% for NO_2 (Castro et al. 2021). However, the health impacts were never aggregated across pollutants to avoid the above-mentioned double counting (Castro et al. 2022b).

Table 1 summarizes the evidence level and the availability of concentration data for Switzerland of air pollutants. The concentration levels of both, CO and SO_2, in Switzerland are very low, the last decades far below the Swiss air quality limit values (FOEN 2020).

Table 1: Suitability of air pollutants for AP-HRAs in Switzerland.

Pollutant		**Evidence level from US EPA (see Section 2.3)**			**Availability of concentration model data for Switzerland (see Section 5.1)**
Name	**Main emission source**	**Availability of evidence assessment**	**Evidence of effect for any health outcome**	**Long- vs. short-term exposure**	
$PM_{2.5}/PM_{10}$	All	Yes	Sufficient	Long- and short-term	Yes
NO_2	Combustion (transport)	Yes	Sufficient	Long- and short-term	Yes
O_3	Secondary	Yes	Sufficient	Long- and short-term (but mainly short-term)	Yes
SO_2	Combustion (industry)	Yes	Sufficient	Only short-term	Yes
Carbon monoxide (CO)	Combustion	Yes	Sufficient	Only short-term	No
Black carbon (BC)	Combustion	No			Yes
Ammonia (NH_3)	Agriculture	No			Yes
Coarse particles ($PM_{10-2.5}$)	All	Yes	Not sufficient		Yes
Ultrafine particles (UFPs or $PM_{0.1}$)	Combustion	Yes	Not sufficient		No

The choice of the PM fraction (PM_{10} vs. $PM_{2.5}$) is not critical for the calculation in AP-HRAs. Both $PM_{2.5}$ and PM_{10} are fractions of the same pollutant (PM) and their concentrations and CRFs can be re-scaled from one PM fraction to another using a conversion factor based on the proportion specific for the country (Castro et al. 2020). In Switzerland, around 70% of PM_{10} refer to $PM_{2.5}$ (Castro et al. 2020), while the exact value can be ideally derived from the exposure data of the specific year of analysis. Nevertheless, there are some differences related to the concept. PM_{10} covers a wider spectrum of particles sizes than $PM_{2.5}$, while $PM_{2.5}$ penetrates deeper into the lungs than PM_{10} because of the smaller size (Pope and Dockery 2006), which may have implications for the health effects. However, it is assumed, that the larger fraction coarse particles, i.e. particulate matter between 2.5 and 10 micrometer in diameter ($PM_{10\text{-}2.5}$), have independent health effects from $PM_{2.5}$ and PM_{10} effects and they cannot be attributed to $PM_{2.5}$ effects alone see EKL 2013 report (FCAH 2013; Liu et al. 2022).

The policy framework and the availability of concentration data (or exposure data if concentration data are population-weighted) have changed in Switzerland after the publication of the STE-2010. In 2018 the Swiss Government included a long-term air quality standard for $PM_{2.5}$ in the Ordinance on Air Pollution Control (FOEN 2021b). Nowadays, it is technically possible to obtain $PM_{2.5}$ concentration data from the model PolluMap with the same resolution as PM_{10} (see Section 5.1). Furthermore, the study base is currently larger for $PM_{2.5}$ than for PM_{10} and meta-analyses generally show more robust estimates for $PM_{2.5}$ (due to the larger study base) (WHO 2021).

Conclusion

The selection of air pollution indicators mainly depends on the following criteria:

a. The evidence level between the pollutant and any health effect (see Section 2.3).
b. The availability of concentration (or ideally exposure) data for the pollutant (see Section 5.1).
c. The level of concentration (not relevant if very low)

Based on these criteria, we suggest to explore the inclusion of the following air pollutants in AP-HRAs for Switzerland: $PM_{2.5}$/PM_{10}, O_3 and NO_2. It should be noted that the list of proposed air pollutants ($PM_{2.5}$/PM_{10}, O_3 and NO_2) is in line with those included in the WHO AQG 2021 (WHO 2021); which additionally included CO and SO_2. Except in case of special need, we do not recommend to include CO and SO_2 for AP-HRAs in Switzerland because of the following reasons. Their concentration levels are currently far below the Swiss air quality limit values (FOEN 2020). Therefore, these pollutants are not of interest for AP-HRAs in Switzerland. Regarding CO, concentration data were not modelled in Switzerland, epidemiological research is rather scarce and it is not a very specific source indicator that could not be covered with other combustion related indicators. Regarding SO_2, sufficient causality was found only for short-term health effects but no short-term exposure data for this pollutant are available from Swiss models (only long term).

Combustion-related compounds such as black carbon (or elemental carbon) and UFPs could be of interest for AP-HRAs focusing on traffic emissions (or wood burning) and NH_3 for those focusing on agriculture. However, the body of evidence is not sufficient to confirm the causality on health effects and these pollutants are part or precursors of PM. Therefore, their health impacts cannot be added together with PM (risk of double-counting).

Concerning the choice of PM fraction ($PM_{2.5}$ vs. PM_{10}), it should be acknowledged that there are many arguments in favor of the use of $PM_{2.5}$ instead of PM_{10}. There are currently Swiss air quality standards and high-resolution data for both $PM_{2.5}$ and PM_{10} and $PM_{2.5}$ is more frequently used in well-known international AP-HRAs, e.g. GBD and EEA, and in many epidemiological studies providing CRFs. Therefore, the use $PM_{2.5}$ instead of PM_{10} in Swiss AP-HRAs may increase international comparability and take benefit of more robust CRFs. Nevertheless, the use of PM_{10} is also correct and even advisable for specific cases, e.g. if the AP-HRA has a strong focus on

transport (because PM_{10} is better traffic marker) or in case, that the CRF for a specific health outcome is more robust.

2.2 Selection of health outcomes

Formulation of the question

Which health outcomes for the corresponding pollutant(s) (i.e. pollutant-outcome pairs) can be included in AP-HRAs?

Background

HRAPIE suggested a list of pollutant-outcome pairs to be used in AP-HRAs (WHO 2013a) (see an overview in Table A 1 in the Appendix). HRAPIE also provided specific suggestions on how to use these outcomes to add monetized health impacts (WHO 2013a).

STE-2010, which only focused on PM_{10} (ARE 2014), included the same outcomes for PM_{10} as recommended by HRAPIE (WHO 2013a), but distinguishing between premature deaths and years of life lost (YLLs). YLLs show the impact on the reduction of life expectancy and are used for monetarization. Moreover, STE-2010 distinguished between hospitalization admissions and hospital days. Exceptionally, symptom days of asthma for adults (instead of only for children as in HRAPIE) was added to the list of outcomes (see Table A 2 in Appendix).

State of the art

All international AP-HRAs for Switzerland included premature deaths and YLLs as mortality outcomes, which was consistent with STE-2010 (Castro et al. 2021). However, only the GBD study 2019 (Murray et al. 2020) covered morbidity outcomes, which were different to those from STE-2010.

The GBD 2019 study summed disease specific YLLs as metric of mortality and disease specific years lived with disability (YLDs) as metric of morbidity (number of cases multiplied by a disability weight and by an average duration) to obtain the so-called disability-adjusted life years (DALYs), which is as mixed concept including both morbidity and mortality. Both YLLs and YLDs were estimated using the same CRFs for each disease. The following diseases were included in the GBD 2019: a) acute lower respiratory infections (ALRI), b) chronic obstructive pulmonary disease (COPD), c) ischemic heart disease, d) tracheal, bronchus, and lung cancer, e) stroke as well as f) diabetes mellitus type 2 (GHDx 2023; Murray et al. 2020). The inclusion of adverse birth outcomes (Ghosh et al. 2021) and dementia (Ru et al. 2021) in forthcoming versions of the GBD has been recently explored. For O_3, GBD 2019 only considered COPD mortality (Murray et al. 2020). The GBD 2019 assessed the scientific evidence of causality for these pollutant outcome pairs and it considered as sufficient.

Using the disease-specific approach as in GBD 2019, may lead to an underestimation of the PM-related mortality compared to using an all-cause approach. At global level, the sum of the mortality attributed to six of this causes of death (the ones used in GBD 2017) has been estimated to be around half of the all-cause non-accidental mortality (Burnett and Cohen 2020). In Germany, the sum of five disease specific mortalities resulted in less than one third of the assessment for all-cause mortality (Tobollik et al. 2022).

It is worth mentioning that the literature providing CRFs for disease specific mortality has been abundant in the last years (Chen and Hoek 2020; Orellano et al. 2020; Stafoggia et al. 2022; Strak et al. 2021). Regarding morbidity, the list of health outcomes and the metric (i.e. incidence or prevalence) can be quite different depending on the AP-HRA, depending on the goal of the AP-HRA and the available CRFs. Recently, the Swiss project GeLuft (Castro et al. 2023b) has made a selection of pollutant-outcome pairs (Table 2), which is different than the one from HRAPIE.

Table 2: Health outcomes selected (and rejected) in the project GeLuft (Castro et al. 2023b)

	Health outcome	Selection
$PM_{2.5}$ long-term exposure	All-cause natural mortality in adults	Selected
	All-cause natural mortality in infants	Selected
	Incidence of acute low respiratory infections (ALRI) in children	Selected
	Incidence of chronic obstructive pulmonary disease (COPD) in adults	Selected
	Incidence of dementia in seniors	Selected
	Incidence of Diabetes Type 2 in adults	Selected
	Incidence of ischemic heart disease	Selected
	Incidence of lung cancer in adults	Selected
	Incidence of low birthweight in term births	Selected
	Incidence of stroke in adults	Selected
	Incidence of asthma in children	Only in appendix (overlap with NO_2)
	Incidence of chronic bronchitis in adults	Only in appendix (overlap with COPD)
	Prevalence of acute bronchitis in children	Only in appendix (overlap with ALRI)
	Incidence of asthma in adults	Not selected (insufficient evidence)
	Incidence of premature births	Not selected (insufficient evidence)
$PM_{2.5}$ short-term exposure	Hospital admissions due to cardio-vascular diseases	Selected
	Hospital admissions due to respiratory diseases	Selected
	Days of restricted activity in adults	Selected
	Work days lost	Selected
	Days of asthma attacks in children	Only in appendix (overlap with incidence of Asthma)
	Days of asthma attacks in adults	Not selected (insufficient evidence)
NO_2 long-term exposure	Incidence of asthma in adults	Selected
	Incidence of asthma in children	Selected
	All-cause natural mortality in adults	Only in appendix (overlap with $PM_{2.5}$)
	Incidence of acute low respiratory infections (ALRI) in children	Only in appendix (overlap with $PM_{2.5}$)
	Hospital admissions due to respiratory diseases	Only in appendix (overlap with $PM_{2.5}$)
	Incidence of leukemia in children	Not selected (insufficient evidence)

Firstly, health outcomes were pre-selected based on STE-2010 (ARE 2014), LUDOK (Kutlar Joss et al. 2020) summarizing the US EPA ISAs, the GBD study (Murray et al. 2020) and including exploration of new GBD outcomes (Ghosh et al. 2021; Ru et al. 2021) and a review of air pollution health effects on children of the European Topic Centre on human Health and the Environment (ETC-HE) (Castro et al. 2022a). In a second step, the outcomes were selected, if sufficient evidence and at least one CRF was available. For the evidence, the report of HRAPIE (WHO 2013a), United States Environmental Protection Agency Integrated Science Assessments (US EPA ISAs) (US EPA 2016; US EPA 2019) and HEI (HEI 2022) were consulted. The health outcomes that overlapped in terms for disease definition or that were available for two pollutants were only shown in the appendix to minimize double counting. Some of the outcomes selected in the project GeLuft were not selected in the project GKV21 because the goal of the latter is to monetize health costs and data on monetary valuation were not available or very low.

Beyond the metric, both mortality and morbidity outcomes are further defined by the age range of the population at risk. In an ideal case, the age range of the outcome is based on the age group of the epidemiological study that provided the CRF and defines the age group of the baseline health data (WHO 2013b). However, some AP-HRAs also pre-defined the age group of the health outcome, if e.g. a sensitivity analysis has to be performed and defining a different age group for each CRF is out of capacity, e.g. as in the project GeLuft (Castro et al. 2023b). A less conservative approach is to use the CRFs to all ages assuming that although the CRF was obtained for a specific age group, other age groups are also affected, but are just less frequent in the population to be considered in epidemiological studies. For instance, the GBD study applies the CRFs for all ages.

Some examples of AP-HRAs without results for Switzerland (Kienzler et al. 2022; Oudin et al. 2022; TRINOMICS 2022a) and guideline reports (Hunt et al. 2016; Narain and Sall 2016) can be found in the literature. Selections of morbidity outcomes differ from one study to another. More details on these studies are provided in the Appendix (see Table A 3).

The WHO is currently collaborating in the following two relevant international projects of high relevance. The project EMAPEC, is carrying out a systematic review and will provide recommendations regarding on the choice of morbidity outcomes for AP-HRAs and their monetary valuation (WHO 2023). This project collaborates with the HRAPIE-2 (follow-up project of HRAPIE), which is also ongoing and both may become soon international standards for the choice of outcomes as HRAPIE. However, they are not yet available.

Conclusion

The health outcomes (mortality and/or morbidity) for the selected pollutant/s can be chosen based on the following criteria:

- Sufficient evidence of an association between pollutant and health outcome (see Section 2.3)
- Available baseline health data for the outcome (see Section 3.1)
- Available CRF for the specific pollutant-outcome pair (see Section 4.1)

In a second step, the list of health outcomes can be further reduced based to avoid the following issues:

- Overlap in terms of disease definition: e.g. COPD is a broader concept than bronchitis, thus if the former is selected, the latter is not needed (otherwise can lead to double counting).
- Overlap of outcome from correlated pollutants: including e.g. long-term mortality for $PM_{2.5}$ and for NO_2 in the same AP-HRA may lead to double counting. One solution is to remove the outcome from one pollutant, but other approaches are available (see Section 2.4)
- Lack of valuation data or relevance for monetazing.

Health outcomes should be clearly defined specifying the metric (incidence vs. prevalence) and the age range. Most AP-HRAs measured mortality impacts using premature deaths and/or YLLs as metrics. YLLs are primarily used to show the impact on the reduction of life expectancy, to monetarize mortality impacts and to estimate of mixed metrics for mortality and morbidity such as DALYs (DALYs = YLLs + YLDs). The GBD study used so far this metric and sum disease specific mortality to calculate the total mortality instead of calculating all-cause natural mortality, as STEs and EEA traditionally did. The attributable mortality calculated using disease specific mortality are much lower than the one using all-cause mortality, which implies that the former underestimate or/and the latter overestimate the results of the AP-HRAs. Given the increasing epidemiologic literature on CRFs for disease specific mortality, the number of diseases that can be included in the assessment of mortality may continue increasing and the attributable mortality may gradually become more robust and closer to mortality impacts calculated based on all-cause natural mortality CRFs. Therefore, assuming some underestimation on the total mortality, the disease specific approach can be used as an alternative to the all-cause approach.

Regarding morbidity, different outcomes can be found depending on the AP-HRA. Divergences on the aimed air pollutants as well as on the selection criteria are behind this differences. The list of outcomes of the Swiss study GeLuft is a recent example of how morbidity outcomes can be selected for $PM_{2.5}$ and NO_2, but it is recommended to adapt it according to the AP-HRAs goals and to review the latest available literature to update the evidence, baseline health and CRF data before carrying out an AP-HRA. Moreover, HRAPIE became for many years an international gold standard for the selection of health outcomes in AP-HRA, follow-up projects such as HRAPIE-2 or EMAPEC will publish new WHO recommendations soon and should be considered.

2.3 Assessment of evidence

Formulation of the question

Which evidence level of association between exposure to air pollution and attributable health effects can be considered?

Background

In 2013, REVIHAAP (WHO 2013b) reviewed the evidence of association between exposure to $PM_{2.5}$/PM_{10}, NO_2 and O_3 with health effects (WHO 2006). Based on the findings of REVIHAAP, HRAPIE rated selected the pollutant-outcome pairs with sufficient evidence and classified them as group A and group B (WHO 2013a) (see Table A 1 in Appendix). The pairs included in Group A referred to those with enough data “to enable reliable quantification of effects”, while pairs in Group B showed “more uncertainty about the precision of the data used for quantification of effects classified” (WHO 2013a).

State of the art

The literature review of US EPA ISAs are one of the most comprehensive causality determinations for air pollution worldwide comprising several pollutants (one pollutant in each report) and using consistent rating scale. The US EPA ISAs have assessed so far the causality of the following air pollutants: PM (US EPA 2019), O_3 (US EPA 2020), NO_2 (US EPA 2016), SO_2 (US EPA 2017), CO (US EPA 2010) and lead (US EPA 2014). The evaluation of PM was split into three PM fractions: $PM_{2.5}$, $PM_{10\text{-}2.5}$ and UFPs (see Table A 4 in Appendix B2).

The US EPA ISAs provided explicit evidence rating in summary tables for broad health concepts, while for some more specific health outcomes only a descriptive evaluation is provided. The Swiss Literature Database and Services on Health Effects of Ambient Air Pollution (LUDOK) (Swiss TPH 2021b) reviewed these descriptive evaluations of US EPA ISAs to derive a summary list of specific health outcomes with a causal and likely causal relationship. These associations were presented

in an interactive infographic (Kutlar Joss et al. 2020). $PM_{2.5}$, NO_2 and O_3 reported the highest number of broad health categories with causal or likely causal relationship, followed by SO_2 and CO. In contrast, $PM_{10-2.5}$ and UFPs do not reach such levels of causal relationship in any of the outcomes (Table 3 and Table 4). This could be mainly due to the fact that literature and research on these two PM fractions is scarce.

Table 3 Long term causal (C) or likely causal (L) relationship of pollutant-outcome pairs from LUDOK (Kutlar Joss et al. 2020), which based on EPA ISAs (US EPA 2010; US EPA 2016; US EPA 2017; US EPA 2019; US EPA 2020).

Long-term outcome			Pollutant		
Mortality vs. morbidity	**Organ system**	**Cause**	**$PM_{2.5}$**	**O_3**	**NO_2**
Mortality	All systems	All-cause (natural) mortality	C		
	Respiratory system	Mortality due to respiratory diseases	C		
		Mortality due to respiratory (tract) infection	L		
		Mortality due to asthma	L		
		Mortality due to COPD	L		
		Mortality due to lung cancer	C		
	Cardiovascular system	Mortality due to cardiovascular diseases	C		
Morbidity	Respiratory system	Asthma	L	L	L
		Respiratory/airway symptoms e.g. wheeze	L		
		Disease exacerbation, increase in symptoms or medication in patients with asthma	L	L	L
		Increase in symptoms for allergy patients		L	
		Chronic bronchitis	L		L
		Impaired lung growth	L		L
		Accelerated decline in lung function	L		
		Lung function decline	L		L
		Airway/respiratory inflammation, inflammatory reaction	L		
		Development of lung cancer	L		
	Cardiovascular system	Atherosclerosis	C		
		Hypertension	C		
		Arrhythmia	C		
		Blood coagulation	C		
	Nervous system	Brain volume (white matter) decline	L		
		Cognitive performance decline (dementia)	L		

Scale: C (dark green) = Causal relationship. L (light green) = Likely causal relationship. (white) = Not available or insufficient data to indicate causality.
Abbreviations: COPD = Chronic obstructive pulmonary disease

Table 4 Short-term causal (C) or likely causal (L) relationship of pollutant-outcome pair from LUDOK (Kutlar Joss et al. 2020), which based on EPA ISAs (US EPA 2010; US EPA 2016; US EPA 2017; US EPA 2019; US EPA 2020).

Short-term outcome			Pollutant				
Mortality vs. morbidity	**Organ system**	**Cause**	**$PM_{2.5}$**	**O_3**	**NO_2**	**SO_2**	**CO**
Mortality	All systems	All-cause (natural) mortality	C				
	Respiratory system	Mortality due to respiratory diseases	L		C	C	
	Cardiovascular system	Mortality due to cardiovascular diseases	C				
Morbidity	Respiratory system	Respiratory/airway symptoms e.g. wheeze		C	C		
		Disease exacerbation, increase in symptoms or medication in patients with asthma	L	C	C	C	
		Disease exacerbation or increase in symptoms in patients with COPD	L				
		Lung function decline in patients with asthma				C	
		Lung function decline	L	C	C	C	
		Airway/respiratory inflammation, inflammatory reaction	L	C			
		Emergency due to respiratory diseases	L	C			
		Emergency due to asthma		C	C	C	
		Emergency due to COPD	L	C			
	Cardiovascular system	Hypertension	C				
		Arrhythmia	C				
		Emergency due to cardiovascular diseases	C				L
	Metabolism / Immune system	Decline in immune defense	L				
		Sugar- and metabolic disorders/diseases (e.g. diabetes)		L			

Scale: C (dark green) = Causal relationship. L (light green) = Likely causal relationship. (white) = Not available or insufficient causality.
Abbreviations: COPD = Chronic obstructive pulmonary disease

Regarding $PM_{2.5}$, the number of outcomes with likely causal or causal relationship in the LUDOK interactive figure is much larger than the number of outcomes suggested by HRAPIE and assessed in STE-2010. It should be noted that the interactive infographic did not specify if the health outcomes refer to a particular age group or to the metric (incidence vs. prevalence). Restricted activity days and work days lost were not mentioned in the US EPA ISA for $PM_{2.5}$ and consequently in the LUDOK interactive figure. Possibly because of their relevance for the

monetarization of health effects, but not strictly diseases (rather consequences of diseases), they were listed in HRAPIE.

More recently, the HEI has carried out a systematic review to assess the association between traffic-related air pollution and many specific health outcomes, 7 for mortality (including both all-cause and cause specific) and 16 for morbidity outcomes (HEI 2022). The morbidity outcomes covered respiratory, cardio-metabolic and birth outcomes and differentiated between adults and children for respiratory outcomes. Two assessments were provided: The first assessment summarized evidence generated from meta-analyses across pollutants where there were three or more exposure-outcome pairs. The second more broad assessment, included the meta-analysis plus a narrative review to incorporate pollutants like UFPs that had too few studies for meta-analysis and important evidence from indirect traffic measures such as traffic density or traffic-related air pollution metrics. Due to rigid inclusion criteria for the selection of studies that represent exposure contrast due to traffic-related air pollution, the number of studies included was limited. Thus, the effect estimates provided might not be as robust as in systematic reviews on ambient air pollution. Moreover, it should be mentioned that the review assessed associations but not was not able to determine causality of the association because mainly epidemiologic evidence was considered and not evidence from experimental and animal studies, as the US-EPA ISAs does.

Focusing exclusively on NO_2, the US EPA (US EPA 2016), the Committee on the Medical Effects of Air Pollutants (COMEAP) (COMEAP 2018) as well as studies commissioned by UBA (Schneider et al. 2018) and Health Canada (Health Canada 2016) have carried out relevant systematic literature reviews to rate the evidence of the association with multiple health effects attributable to this pollutant. Regarding O_3, the US EPA (US EPA 2020) rated evidence based on systematic reviews and the German Federal Office for Environment selected health effects based on evidence reviewing literature in a recent AP-HRA for Germany (Breitner et al. 2023).

Divergences in the evidence rating of specific pollutant-outcome pairs can be found across assessments. These divergences may be caused by the different studies included in the systematic review and the different rating criteria or scales. Table A 5 to Table A 7 (in the Appendix) show the case study of NO_2 as an example, comparing the evidence rating among multiple assessments (Health Canada 2016; Huang et al. 2021; Huangfu and Atkinson 2020; Schneider et al. 2018; Stieb et al. 2021; Stieb et al. 2020; US EPA 2016; WHO 2013a) for long-term and short-term exposure.

Conclusion

It is recommended, as many of AP-HRAs did, to evaluate the existing evidence based on (at least one of) the following two reference sources:

- The WHO project HRAPIE (WHO 2013a) listed recommended outcomes with sufficient evidence for $PM_{2.5}$/PM_{10}, NO_2 and O_3 to be included AP-HRAs
- The US EPA ISAs for $PM_{2.5}$, O_3, NO_2, SO_2 and CO (US EPA 2010; US EPA 2016; US EPA 2017; US EPA 2019; US EPA 2020)

The recommendation of HRAPIE became a gold standard for AP-HRAs and the US EPA ISAs are the most comprehensive, transparent and consistent literature reviews on pollutant-outcome causality worldwide. The LUDOK interactive figure (Kutlar Joss et al. 2020) shows a useful and more detailed overview of the outcomes associated with the exposure to air pollutants derived from the US EPA ISAs.

However, they may become (soon) outdated as new evidence from international studies emerges. Therefore, it is recommended to check the publication of new US EPA ISAs, to consider further systematic literatures with causality/association assessments, e.g the HEI report (HEI 2022) or carrying out such assessments (time consuming) before making a choice of pollutant-outcome

pairs in an AP-HRA. Causality assessments are also performed before including outcomes(Ru et al. 2021) in the GBD Study (Murray et al. 2020). These assessments do not reach the standards of US EPA ISAs, but they can also be used to support decisions on causality given the large impact of the GBD publications.

2.4 Health impacts from multiple air pollutants

Formulation of the question

How can health impacts from different pollutants be computed in AP-HRAs to avoid double counting?

Background

CRFs from single-pollutant models for one pollutant may already contain part of the health effects of correlated pollutants. HRAPIE advised against aggregating health impacts attributable to pollutants with correlated exposure using CRFs from single pollutant models (i.e. without adjustment for other pollutants). Otherwise, AP-HRAs may overestimate health impacts of air pollution due to risk of double counting (WHO 2013a).

To avoid the issue with double counting, REVIHAAP suggested the use of CRFs from two-pollutant models (multi-pollutant model for two pollutants abbreviated here as "two-pollutant CRFs"), i.e. CRFs for one pollutant that are adjusted for the effect of another pollutant (WHO 2013b). HRAPIE pointed out that such two-pollutant CRFs may have some bias, if the correlation across pollutants is high and if there are measurement errors (WHO 2013a). Although the availability of two-pollutant CRFs was limited at that time, HRAPIE found that two-pollutant models lead to 33% lower mortality than single-pollutant models for NO_2. Thus, HRAPIE concluded that the CRF was "better based on the unadjusted meta-analysis, with the acknowledgement that the resulting estimates of the effects of NO_2 may represent an overestimate in the likely range 0–33%" (WHO 2013a).

State of the art

Since the HRAPIE report was published in 2013 (WHO 2013a), several AP-HRAs have included multiple pollutants, frequently $PM_{2.5}$/PM_{10} as well as NO_2 or/and O_3. The exposure to these pollutants are usually correlated (Brunekreef et al. 2021; WHO 2013a). Therefore, the risk of double counting health impacts in overlapping outcomes is high.

Examples of AP-HRAs including O_3 together with $PM_{2.5}$/PM_{10} (summing health impacts or not) are the GBD studies (Brauer et al. 2016; Cohen et al. 2017; Murray et al. 2020; Stanaway et al. 2018), the yearly EEA "Air quality in Europe" reports (EEA 2014; EEA 2015; EEA 2016; EEA 2017; EEA 2018; EEA 2019; EEA 2020; ETC/ATNI 2020) and other AP-HRAs at global, European and French regional (Ile-de-France) level for $PM_{2.5}$ and O_3, (Likhvar et al. 2015), in Finland for $PM_{2.5}$/PM_{10}, NO_2 and O_3 (Lehtomäki et al. 2018). However, the issue is more relevant for NO_2 and $PM_{2.5}$/PM_{10} (than for O_3 and $PM_{2.5}$/PM_{10}) because the evidence show more overlap in health effects (e.g. long-term mortality)

To avoid the issue of double-counting of health impacts, the project GeLuft, commissioned by FOEN, excluded overlapping health outcomes from $PM_{2.5}$/PM_{10} and NO_2 in the selection of pollutant-outcome pairs (see Section 2.2), assigning only one pollutant for each health outcome based on existing evidence (Castro et al. 2023b).

If all health impacts attributable $PM_{2.5}$/PM_{10} and NO_2 are to be presented, without excluding the overlapping outcomes, AP-HRAs have applied the following three main approaches:

1. Using CRFs from single-pollutant models
    a. without any correction

b. with a standard percentage reduction as correction
2. Using CRFs from two-pollutant models, which adjust for another pollutant.

1.a. Single pollutant CRFs without correction

Some AP-HRAs, such as the yearly EEA "Air quality in Europe" reports (EEA 2014; EEA 2015; EEA 2016; EEA 2017; EEA 2018; EEA 2019; EEA 2020; ETC/ATNI 2020), an ETC-HE report estimating the morbidity burden of disease in Europa (Kienzler et al. 2022), a report commissioned by the European-Directorate General for Environment (TRINOMICS 2022b) and an AP-HRA among urban areas in Europe (Khomenko et al. 2021b), covered both $PM_{2.5}$ and NO_2 using single-pollutant CRFs without any correction for the overlap in health outcomes. The attributable health impacts were presented separately across pollutants and without summing them into a single result.

Pros and cons of the decision of using the unreduced CRFs from single-pollutant models were mentioned by the authors of these AP-HRAs. In favor, it was argued e.g. that the "best-available meta-analyses are based on single-pollutant models" because there are more epidemiological studies (Khomenko et al. 2021b). However, it was also acknowledged that the use of these CRFs may lead to an overestimation (double counting), if the results would have been aggregated among pollutants (ETC/ACM 2016; Khomenko et al. 2021b).

1.b. Single pollutant CRFs with correction

A second group of AP-HRAs reduced the CRFs of NO_2 from single-pollutant models to minimize the risk of double counting with $PM_{2.5}$/PM_{10}, as advised by REVIHAAP and HRAPIE. The reduction was only applied to NO_2 (not to $PM_{2.5}$/PM_{10}). AP-HRAs in Finland (Lehtomäki et al. 2018) and in New Zealand (Briggs et al. 2016), applied a standard reduction of 33% (i.e. accounted for only 67% of the EE) in health impacts attributed to NO_2. This percentage referred to the maximal overestimation of the HRAPIE report, as pointed out above, being therefore extrinsic to the CRF used in these AP-HRAs. Other AP-HRA authors, e.g. in UK (Pimpin et al. 2018), used a standard reduction of 60% referring to an average recommendation of the COMEAP: a range from 45 to 75%. It should be noted that from the above-mentioned examples of AP-HRAs, only the one in New Zealand (on transport externalities including further environmental factors beyond air pollution) used the percentage as correction to sum the health impacts attributable to $PM_{2.5}$/PM_{10} and NO_2. The other two AP-HRAs only presented the results separately by pollutant and used the correction just to avoid the overestimation of NO_2 but not for aggregating across pollutants.

2. Two-pollutant CRFs

The number of available CRFs from two-pollutant models has increased in recent years in the literature, while CRFs from multi-pollutant models including more than two pollutants at the same time remain scarce. Some of the two-pollutant CRFs are of special relevance for Europe, particularly those based on European cohorts from the project ESCAPE (Beelen et al. 2014) and more recently ELAPSE (Stafoggia et al. 2022; Strak et al. 2021). However, CRFs from two-pollutant models are still less common than from single-pollutant models. Consequently, there are limited examples of AP-HRAs using two-pollutant CRFs and summing health impacts across pollutants (Castro et al. 2023a; COMEAP 2018; Health Canada 2021).

The health impacts can be aggregated in two general steps: Firstly, the health impact from $PM_{2.5}$ is quantified using a CRF adjusted for NO_2 and the health impact from NO_2 using a two-pollutant CRF adjusted for $PM_{2.5}$. Secondly, the resulting pollutant-specific health impacts can be summed (see practical example for premature mortality in Figure 2).

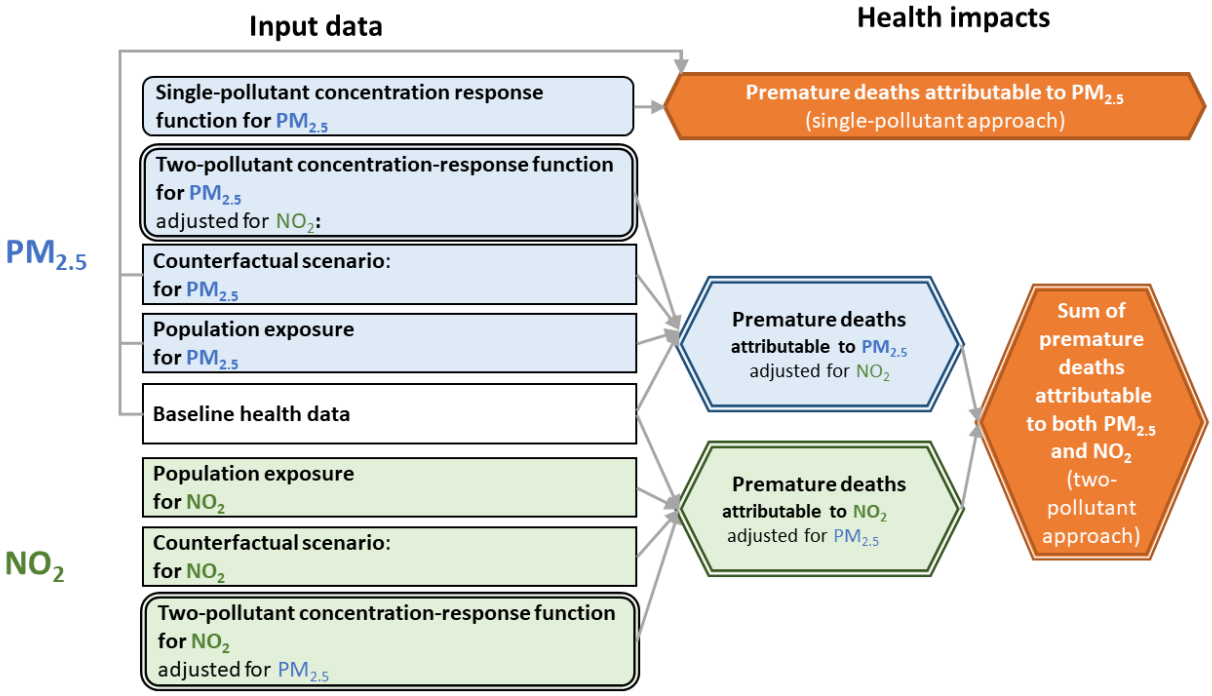

Figure 2: $PM_{2.5}$ single-pollutant vs. $PM_{2.5}$ & NO_2 two-pollutant approach applied to long-term premature deaths. Adapted from Castro et al. (2023a).

A publication of the project QHIAS quantified long-term mortality attributable to $PM_{2.5}$ and NO_2 in Switzerland following the above mentioned two steps and using different CRFs from both single-pollutant and two-pollutant models and compared them (Castro et al. 2023a). The results were seemingly paradoxical when using some of the two-pollutant CRFs: The mortality from one $PM_{2.5}$ single-pollutant CRF was higher than the sum from both $PM_{2.5}$ and NO_2 two-pollutant CRFs from the same study. Moreover, when the two-pollutant approach led to a lower proportion of deaths attributed to $PM_{2.5}$ than to NO_2 (Castro et al. 2023a).

The Committee on the Medical Effects of Air Pollutants (COMEAP) quantified the mortality attributable to $PM_{2.5}$ and NO_2 in UK (COMEAP 2018; Gowers et al. 2020) and also noted that multi-pollutant models can be “complex to interpret”. The COMEAP argued that the so-called effect transfer leads to an underestimation of effects from pollutants with less accurate exposure modelling and an overestimation of effects with more accurate exposure modelling, especially when the pollutants are correlated.

Due to the lower availability of CRFs from two-pollutant models, the COMEAP suggested an approach that enables the derivation of two-pollutant CRFs based on robustly established single-pollutant CRFs. Firstly, a percentage reduction of the CRF from the two-pollutant model as compared to the CRF from the single-pollutant model from the same study with moderate correlation (a conversion factor) was obtained. Secondly, the robustly established single-pollutant CRFs were reduced by applying the above mentioned percentage. This approach was later replicated in the project QHIAS to obtain two-pollutant CRFs based on the single-pollutant CRFs recommended by the European Respiratory Society (ERS) and the International Society for Environmental Epidemiology (ISEE) (Brunekreef et al. 2022; Hoffmann et al. 2022) for the quantification long-term mortality in Europe, which were obtained from ELAPSE cohorts (Stafoggia et al. 2022; Strak et al. 2021). The COMEAP acknowledge the existence of different pathways to quantify long-term mortality attributed to air pollution such as using single-pollutant CRF for $PM_{2.5}$, using single-pollutant CRF for NO_2 or using two-pollutant CRF derived from single-pollutant CRF (one pathway for each study providing two-pollutant CRFs) based on two-pollutant. To reflect the uncertainty behind the pathway, they expressed the result as a range, where the lower and upper bound corresponded to the lowest and highest value of the group comprising the

highest health impact of the single-pollutant pathways and the study specific health impacts from the two-pollutant pathways (COMEAP 2018; Gowers et al. 2020).

Health Canada also aggregated the mortality attributed to $PM_{2.5}$ and NO_2, but it was long-term for the former and short-term for the latter (Health Canada 2021). For $PM_{2.5}$ the authors used a Canadian single-pollutant CRF (Crouse et al. 2012) and for NO_2 a Canadian CRF from a four gas multi-pollutant model, which did not include PM but "best reflected the impact of the overall air pollution mix" (Burnett et al. 2004).

It should be finally mentioned, that new approaches to aggregate health impacts across pollutants have been recently proposed without using multi-pollutant models, e.g. based on a generalized propensity score adjustment approach (Wei et al. 2021; Wei et al. 2020). However, this was out of the scope of this report, which focuses on approaches applied in AP-HRAs at larger geographic scale to prioritize the transferability to country wide AP-HRAS in Switzerland.

Conclusion

The AP-HRA process may involve the selection of pollutant-outcome pairs with overlapping health outcomes from multiple pollutants. If the pollutant exposures are not correlated their attributable health impacts can be summed, while correlated pollutants (e.g. $PM_{2.5}$ and NO_2) can lead to double counting of effects. If only single-pollutant CRFs are used, health impacts from overlapping health outcomes should not be summed to avoid the risk of double counting. The exclusion of overlapping health outcomes arising from pollutants with lower levels of evidence can prevent double counting and facilitate clear communication (Castro et al. 2023b)

Two-pollutant CRFs enable (unlike single-pollutant CRFs) the sum of effects from two correlated pollutants reducing the risk of double counting. However, it should be acknowledged, that this approach may involve some limitations in terms of interpretation of paradoxical results due to lack of robustness of these CRFs and due to undesired effect transfer. The causal effects of two-pollutant CRFs are implicitly disentangled based on the correlation of the pollutants, but this correlation may be determined by several factors (e.g. the accuracy of exposure modelling or correlation with other unmeasured air pollutants and risk factors) not necessary directly representing causation (Castro et al. 2023a). Therefore, we do not recommend using current two-pollutant CRFs in AP-HRAs, unless they are really needed. In that case, their results have to be carefully interpreted.

3. BASELINE HEALTH DATA

3.1 Selection of baseline health data

Formulation of the question

Which are the most suitable baseline health data sources for AP-HRAs in Switzerland?

Background

If national baseline health data were not available, the HRAPIE report provided recommendations on alternative data (WHO 2013a). STE-2010 used, as much as possible, data from the Swiss Federal Statistical Office (FSO). For mortality, the data came from the Statistical Yearbook of Switzerland, while for hospital admissions and days due to respiratory and cardiovascular diseases, the data came from the Medical Statistics of Hospitals (ARE 2014). For those health outcomes without national data, STE-2010 mainly followed the HRAPIE recommendations and used data from the study SAPALDIA (Swiss Study on Air Pollution and Lung Diseases in Adults) (Schindler et al. 2009) for incidence of chronic bronchitis in adults, from the study PATY (Pollution

and the Young) for prevalence of bronchitis in children (Hoek et al. 2012), from the study ISAAC (International Study on Asthma and Allergies in Childhood) for days of asthma symptoms in children (Lai et al. 2009) and from the work of Ostro and Rothschild (1989) for restricted activity days. However, for two health outcomes, STE-2010 used alternative sources, which were not included in the HRAPIE recommendations. Regarding days of asthma symptoms in adults, STE-2010 used unpublished crude data from SAPALDIA and ECRHS (European Community Respiratory Health Survey) (ECRHS 1996), since HRAPIE did not provide any specific recommendation for this outcome. Regarding work days lost, STE-2010 used data from the study HEIMTSA (Health and Environment Integrated Methodology and Toolbox for Scenario Assessment) (HEIMTSA 2008; HEIMTSA 2011) instead of from European Health for All database as suggested by HRAPIE (WHO 2013a).

State of the art

The project GeLuft has recently collected multiple baseline health data for Switzerland to quantify health impacts attributable to $PM_{2.5}$ and NO_2, including more outcomes and more recent health data (Castro et al. 2023b). Currently, as at the time of STE-2010, mortality and hospital data for Switzerland are available from the FSO. Regarding mortality, the FSO collects and provides mortality data by causes, age group and sex since 1990 on a yearly basis (FSO 2021b; FSO 2021c; FSO 2021d). These baseline health data enable the calculation of YLLs (and premature deaths) based on life table data (probability of dying by age and sex) and of cause specific mortality AP-HRAs for Switzerland. Regarding hospitalizations, the Swiss Medical Statistics of Hospitals (FSO 2021a) are compiled every year. The number of hospital admissions and average length of stay in days are available for health outcomes by ICD-10 codes (FSO 2020) and for respiratory and cardiovascular diseases with stratification by age group and sex (FSO 2022). Other Swiss databases used by the project GeLuft were the FSO data on cardiovascular diseases (FSO 2023b), the Vital Statistics BEVNAT for pregnancy and birth outcomes (FSO 2023a) and the cancer registry of the National Agency for Cancer Registration (NKRS 2022).

Beyond the FSO Swiss national databases, the online tool “GBD results” has become a rich source of baseline health data worldwide (IHME 2020) and was used for several outcomes in the study GeLuft (Castro et al. 2023b). Deaths, YLLs, YLDs, DALYs, prevalence and incidence data for around 300 diseases, by age (around 60 age group categories), by sex, by year (since 1990) and by country (including Switzerland) can be filtered and exported (IHME 2020). Such data are the result of health modelling (not reported data), but they are appropriate proxies if official statistical data are not available.

Some alternative data sources that could be relevant for AP-HRAs for Switzerland depending on the selected health outcomes (see Section 2.2) are presented below. Two relevant FSO data collections, namely the Swiss Medical Statistics of Hospitals and the Swiss Health Survey are available. The Swiss Health Survey is carried out in a representative sample every five years since 1992 by means of telephone interviews and written questionnaires (FSO 2018b). The results are stratified by sex and age group. The 2017 survey (last update) collected data from people aged 15 or older in more than 22,000 households in Switzerland and it was part of the Swiss population census (FSO 2018b). Thus, the Swiss Health Survey provides health data for multiple diseases, e.g., prevalence of diabetes (FSO 2018a). The Swiss cohort studies SAPALDIA and COLAUS are further potential sources of relevant information to estimate baseline health data. SAPALDIA is a Swiss wide project, initially (1991) with almost 10,000 participants followed since in five waves and provide results in terms of respiratory and cardiovascular diseases as well as diabetes (Swiss TPH 2021a). COLAUS is a Lausanne-based study (around 6,000 participants) focused on cardiovascular diseases (including diabetes) and mental diseases (including dementia) (COLAUS 2021).

Furthermore, EUROSTAT provide European values for prevalence of some diseases such as bronchitis (EUROSTAT 2021a), hypertension (EUROSTAT 2021b) and diabetes (EUROSTAT

2021b). The prevalence rate for Europe could be eventually applied to the population in Switzerland to estimate the prevalence in this country.

It should be mentioned that the ongoing WHO projects HRAPIE-2 and/or EMAPEC might provide recommendations soon that update those from HRAPIE.

Conclusion

After the selection of pollutant-outcome pairs (see Section 2.2), baseline health data have to be collected. It should be noted that the age group of the baseline health data should ideally match the age defined for the pollutant-outcome pair as much as possible, which is based on the age group of the CRFs. In the data search, multiple sources could provide the required data. The following priority order could be applied in AP-HRA in Switzerland.

1. Baseline health data from Swiss databases and registries, e.g. from the FSO or National Agency for Cancer Registration, can be considered as a gold standard in Switzerland due to the regularity and consistent methodology of the data collection. If available, they should be firstly selected.
2. The online tool "GBD results" is an additional data source that provides abundant and very specific health data, which enables the selection by country, year and age group. However, it should be acknowledged that the data are the result of health modelling and not reported data (like the ones from Swiss databases and registries).
3. Population rates from Swiss epidemiological studies such as SAPALDIA and COLAUS as much as they cover the whole population.
4. The use of European rates from international databases (e.g. EUROSTAT) for the population in Switzerland is only recommended, when no Swiss data are available or when comparing with international AP-HRAs in a sensitivity analysis. This needs prioritizing based on similar geographic contexts (e.g. Western Europe over Eastern Europe).
5. The recommendations of HRAPIE in terms of baseline health data based on international epidemiologic studies are still valid and should be considered. However, these estimations may have become outdated. The WHO projects HRAPIE-2 and EMAPEC might update soon such estimations. A disadvantage of these international estimations is that they are not specific for Switzerland. In the best case, they are based on European studies.

4. CONCENTRATION-RESPONSE FUNCTIONS

4.1 Selection of concentration-response functions

Formulation of the question

Which CRFs should be selected for Swiss AP-HRAs when more than one CRF is available?

Background

The WHO project HRAPIE recommended in 2013 the CRFs to be used in Europe for a list of relevant pollutant-outcome pairs, including mortality and morbidity outcomes, attributed to $PM_{2.5}$/PM_{10}, O_3 and NO_2 (WHO 2013a). All CRFs were derived from single-pollutant models (see Section 2.4) and since the focus of HRAPIE was Europe, European studies were given priority over meta-analytical results.

STE-2010 (ARE 2014), which focused on PM_{10}, mostly used the CRFs that were recommended by HRAPIE to carry out the AP-HRA for Switzerland. Only for the incidence of asthma in adults (not included in HRAPIE), STE-2010 used a meta-analysis carried out in STE-2000 (ARE et al. 2004).

State of the art

New epidemiological studies providing CRFs of pollutant-outcome pairs have been published after the HRAPIE recommendations. When undertaking an AP-HRA, the most appropriate CRF(s) for each pollutant-outcome pair of interest have to be identified in the literature. As a result, more than one CRFs can be found for a single pollutant-outcome pair and a choice has to be made. CRFs can be different depending on the study design (cohort vs. literature review or pooled analysis vs. meta-analysis). Moreover, some studies can provide several CRFs depending e.g. on the world region, age group or on the adjustments applied in the model, which makes the choice more challenging. To illustrate this issue in a practical example, Table A 10 and Table A 11 (in Appendix) show a representative (but not exhaustive) sample of relevant CRFs that can be found in the literature for long-term all-cause mortality attributed to $PM_{2.5}$ and NO_2, respectively.

Meta-analyses deriving CRFs from (systematic) literature reviews represent a reliable source of CRFs for global assessments, but require an extra level of scrutiny to determine quality and applicability. They can include studies from very different world regions, which jeopardizes their transferability due to the different geographic and sociodemographic contexts. Despite the adjustment for some local factors, their results can be geographically biased and less informative to the European context. Moreover, it can be challenging to unpick the details in some reviews leading to unknown uncertainty, such as different study design and exposure assessment quality. In contrast, meta-analyses or pooled analyses of European cohort data can have a more coherent analysis approach (Brunekreef et al. 2021). Examples of relevant cohort studies and literature reviews are presented below.

The SAPALDIA study (Swiss TPH 2021a), a Swiss cohort for air pollution and chronic diseases is of specific significance for Switzerland. CRFs derived from larger European study consortia have larger sample size and increase statistical precision. The European projects ESCAPE (Beelen et al. 2014) and more recently ELAPSE (Stafoggia et al. 2022; Strak et al. 2021) and the project EXPANSE (EXPANSE 2021) are of special relevance for the European (and Swiss) context because they are exclusively based on cohorts in Europe.

The ELAPSE project applied harmonized approaches, which ensured the same exposure assessment, outcome treatment and confounder control (Brunekreef et al. 2021); thus without “cherry-picking” model optimization as might happen in some reviews (Rudnicka and Owen 2012). ELAPSE provided two different sets of CRFs from two different analyses:

A. a pooled analysis merging data from eight prospective cohorts with data on the individual level (none of them in Switzerland) (Strak et al. 2021) and
B. a meta-analysis of seven European administrative cohorts, one of them being the Swiss National Cohort (15% of the whole study sample) (Stafoggia et al. 2022).

The prospective cohorts enable a better confounding control due to more detailed data, while the administrative cohorts comprise larger population samples with no selection bias. A in depth discussion comparing of both approaches can be found in a project research report (Brunekreef et al. 2021). For the specific case of long-term all-cause mortality attributed to $PM_{2.5}$ and NO_2 (single-pollutant), the ERS and ISEE have jointly recommended to use a pooled CRF of the administrative (Stafoggia et al. 2022) and prospective European (Strak et al. 2021) cohorts of the ELAPSE project in European AP-HRAs (Brunekreef et al. 2022; Hoffmann et al. 2022).

Beyond these cohort studies, some recent meta-analyses of literature reviews haven been published and can be considered an alternative source of CRFs. The results of the systematic literature reviews and meta-analyses for the WHO AQG 2021 (WHO 2021) were compiled in a special issue of the scientific journal Environment International (Chen and Hoek 2020; Huangfu and Atkinson 2020; Lee et al. 2020; Orellano et al. 2021; Orellano et al. 2020; Zheng et al. 2021). These CRFs included outcomes such as all-cause mortality, cause specific mortality and hospitalizations attributed to long- and short exposure to air pollutants such as $PM_{2.5}$, O_3, NO_2,

SO_2 and CO (see Table A 8 and Table A 9 in Appendix).The HEI has recently published a systematic literature review on health effects of traffic-related air pollution. This review provided evidence of associations between air pollution mainly originating from traffic sources ($PM_{2.5}$ and NO_2 among others) and many specific health outcomes; 7 for mortality (including both all-cause and cause specific mortality) and 16 for morbidity (see Section 2.3) as well as CRFs for these pollutant-outcome pairs based on a meta-analysis of the systematic literature review.

For the choice of CRFs not only the differences between cohort studies and literature reviews, the geographical context and the study size are relevant but also the year of publication. Recent cohort analyses may include more accurate air pollution exposure modelling, while recent meta-analyses of literature reviews can include studies that were not covered by former meta-analyses and (depending on the selection criteria) a higher number of studies.

Furthermore, that the type of exposure data used in the CRF should match with the exposure data used in the AP-HRA, especially for air pollutants with uneven spatial distribution such as NO_2. Thus, AP-HRAs with high-resolution exposure data require CRFs from studies with high-resolution exposure data, while CRFs from monitor-based studies are only suitable if the aim of the AP-HRA is to quantify health effects of background exposure (Schneider et al. 2018).

Recently, the project GeLuft has carried out an AP-HRA searching available CRFs for long-term effects of $PM_{2.5}$ and NO_2 and has shown the selected CRFs in the main part of the report and alternative CRFs in the Appendix, including information on the proportion of European studies in the meta-analyses of literature reviews. Regarding O_3, the German Federal Office for Environment published an AP-HRA focused on this pollutant, including a selection of health outcomes and CRFs reviewing literature (Breitner et al. 2023). WHO projects such as HRAPIE-2 and EMAPEC are working currently to provide new standards for CRFs. The results will be published soon

Conclusion

In order to choose among available CRFs, the following criteria should be considered:

- CRF ideally obtained from cohort studies with adequate confounding adjustment (otherwise from literature reviews from reliable sources or after careful assessment)
- Similar geographical context
- Large study size (cohort studies) or high number of studies (meta-analysis of literature reviews)
- Recent publication
- Exposure model underlying the CRF well matched to exposure used in the AP-HRA

Meta-analyses or pooled analyses of European cohort data, such as those from the project ESCAPE or ELAPSE, especially if the sample size is large and the likely confounding is appropriately adjusted are more applicable to the European context than meta-analyses from literature reviews. Cohort studies are preferred over meta-analyses from literature reviews because of a more coherent analysis approach. Both prospective and administrative cohort studies are informative within ELAPSE, though it should be recognized that while the administrative cohorts provide larger samples, they can suffer higher risk of bias due to residual confounding.

The use of CRFs from a similar geographic context is strongly recommended to carry out AP-HRAs at sub-global levels. In the case of Switzerland, we recommend using CRFs from cohort studies that focus on Europe. European cohorts are preferred over single cohort studies only in Switzerland, e.g. the SAPALDIA cohort in the ESCAPE project (Beelen et al. 2014) and the Swiss National Cohort in the ELAPSE project (Stafoggia et al. 2022). CRFs exclusively derived from Swiss studies are of course suitable for Switzerland, but less precise than the bigger European study consortia due to smaller sample size (lack of statistical precision).

In the case of meta-analyses of literature reviews, if no specific CRF is provided for Europe, it is recommended for Switzerland to prioritize meta-analyses with a high number of studies from Europe.

The new recommendations from the WHO projects HRAPIE-2 and EMAPEC should be considered. They may become soon new standards for the choice of CRFs.

4.2 Use of age- and sex specific concentration-response functions

Formulation of the question

Are there adequate gender- and age specific CRFs in the literature to calculate age and/or sex specific differences in health outcomes?

Background

HRAPIE recommended (and consequently STE-2010 applied) the use of the suggested CRFs for specific age groups. These age groups should ideally match with the age group of the baseline health data. Only for one pollutant-outcome pair, namely all-cause mortality attributable to long-term $PM_{2.5}$/PM_{10} exposure, two different CRFs for specific age ranges were provided: one for adults at the age 30 years and older (Hoek et al. 2013) and one for infants younger than one year old (Woodruff et al. 1997). However, no further age stratification was applied.

Regarding sex, HRAPIE did not make any differentiation among male and female. STE-2010 calculated the long-term mortality separately using the life table approach due to the different mortality data, but the same CRF was applied for both age and sex.

State of the art

The use of age group specific CRFs in the quantification of health impacts of air pollution is still scarce, being the GBD an exceptional case. The GBD 2019 used relative risk models, called “integrated exposure-response functions” (IER). These IERs are complex functions because they can assign a different risk to each age (group), but enable the assessments at global level overcoming the bias of literature on CRFs towards low-polluted or high income countries (Burnett and Cohen 2020; GHDx 2023). For ischemic heart disease and stroke a different risk were assigned to each 5-year age groups starting at the age of 25 years old, while for the rest of outcomes (lower respiratory infections, tracheal, bronchus, and lung cancer, COPD and diabetes mellitus type 2) an CRF was assigned for all age groups. No sex specific CRF was applied (GHDx 2023).

Beyond the IERs produced in the framework of the GBD Study 2019, age and sex specific CRFs in the literature are very limited. A relevant exception of a study providing sex specific CRFs was based on the Swiss National Cohort for air pollution and noise mortality (Vienneau et al. 2023).

Conclusion

Since sex- and age specific CRFs are rarely provided in relevant CRF studies, at least for long-term all-cause mortality. In the absence of such data, we suggest using general CRFs for broader age groups or all ages as well as for all sex and set higher priorities on other selection criteria data for CRFs (see Section 4.1). If necessary, sex and age specific CRFs for all-cause mortality could be derived using data from the Swiss National Cohort.

5. EXPOSURE DATA

5.1 Availability of air pollution exposure data

Formulation of the question

Which models and data sources for long-term and short-term air pollution exposure are available in Switzerland?

Background

The authors of STE-2000 stated that at that time there were air pollution exposure data for the whole of Switzerland for the following five air pollutants: $PM_{2.5}$, PM_{10}, benzene, NO_2 and SO_2 (ARE et al. 2004). STE-2010 did not provide further information on the availability of concentration data.

Regarding the O_3 metric, the authors of STE-2000 and STE-2010 reported a mismatch between available metric from air pollution models and the metric normally used in the epidemiologic literature. Specifically, the number of hours above a limit of 120 µg/m^3 in STE-2000 and the distribution of the 98% percentile of the maximal hourly value in STE-2010 were the only available metrics at that time in Switzerland (ARE 2014; ARE et al. 2004). The CRFs recommended by HRAPIE were expressed as summer months average of daily maximum 8-hours mean over 35 parts per billion for long-term and daily maximum 8-hours mean for short-term.

State of the art

The National Air Pollution Monitoring Network (NABEL) measures the pollution level in 16 monitoring stations in Switzerland, including both urban and rural areas (FOEN 2021e). These monitoring stations collect pollution data of over 25 pollution indicators (see Table A 12 in Appendix). However, air pollution concentration data have to be spatially resolved in models for Switzerland.

For AP-HRAs, population-weighted exposure is required. Thus, concentration and population data need to be combined using spatial analysis. Spatial resolution of the model is not very critical for pollutants with little spatial variation over small distances, like $PM_{2.5}$, since random errors in both directions compensate to a large extent. In contrast, pollutants with higher spatial variation such as NO_2 can be more sensible to spatial resolutions. In particular, for linear CRFs, it is most crucial to derive correct mean population exposure, as estimates are independent of the distribution.

Dispersions models and land use regression (LUR) models are the most frequent methods to derive air pollution exposure from the monitor measurements. Dispersion models, such as PolluMap, use emission data from various sources as an input to model the propagation and chemical transformation. PolluMap is a dispersion model commissioned by the FOEN. It was created in the 1990s by a collaboration between two Swiss companies (INFRAS and METEOTEST).The advantage of dispersion models for AP-HRA is the fact that contributions from different sources (e.g. road traffic, heavy road traffic or railway traffic) and different compounds can be modelled (see Section 5.3). To date, to create daily maps by means of dispersion models requires more efforts because this is typically done with chemical transboundary models. In the last decade, LUR modelling has increasingly become prominent, also for Switzerland (de Hoogh et al. 2018a; de Hoogh et al. 2019; de Hoogh et al. 2013). In these LUR models, the temporal-spatial variability is empirically modelled based on remote sensing data, geographical parameters and meteorological variables. In this way, daily and annual maps can be created. However, LUR models are limited for source attribution.

Long-term exposure

Long-term air pollution concentration data in Switzerland are available for $PM_{2.5}$/PM_{10}, O_3, NO_2, SO_2, BC and NH_3 (Table 5). No air pollution concentration data have been modelled so far at Swiss national level for further potentially relevant pollutants such as Pb, CO or UFPs (i.e. UFPs).

Concentration data with high spatial resolution (20 m x 20 m) are available for four pollutant indicators (PM_{10}, $PM_{2.5}$, NO_2 and BC). These concentration data were estimated using the most recent update of the PolluMap model (FOEN 2021a; Heldstab et al. 2020a; Heldstab et al. 2020b; Heldstab et al. 2021). PolluMap has been improved through successive updates increasing the spatial resolution up to a 20 m grid (Heldstab et al. 2020a). Population-weighted annual mean exposure was obtained for PM_{10}, $PM_{2.5}$, NO_2 and SO_2 in methodological reports on PolluMap (Heldstab et al. 2020a; Künzle 2022).

Concentration data for further pollutants such as O_3, SO_2, BC and NH_3 (in addition to PM_{10} and NO_2) and for multiple years (instead of for a single year) are available only from maps of annual values, commissioned by the FOEN (FOEN 2021c; Künzle 2022). These maps are obtained applying interpolation methods based on PolluMap model results and concentration measurements from the NABEL monitoring stations, except for NH_3, which is based on emissions inventory (Künzle 2022). Therefore, they can be considered as dispersion models (FOEN 2011; FOEN 2013). The spatial resolution of the maps of annual values is lower (100m x 100m for NH_3, 200 m x 200 m for the rest) compared to the PolluMap (20 m x 20 m).

The O_3 concentration data from the maps of annual values is expressed using two metrics: maximum monthly 98th percentile and accumulated ozone exposure over a cut-off of 40 parts per billion (ppb). The latter being less relevant for AP-HRAs because it is aimed at estimating ecosystem effects. Therefore, the metric used in Swiss air pollution models is nowadays the same as in STE-2010 and the incompatibility issues of exposure and the metrics of HRAPIE CRFs persist, eventually requiring a metric conversion.

Beyond national Swiss models, continental air pollution models were developed providing air pollution concentrations at the European scale. The ELAPSE project, for example, produced annual average concentrations for Western Europe (including Switzerland) of $PM_{2.5}$, O_3, NO_2 and BC for 2010 at a spatial resolution of 100 m x 100 m (de Hoogh et al. 2018a) and more recently of $PM_{2.5}$, PM_{10}, O_3 and NO_2 for 2000 to 2019 at spatial resolution of 25m x 25 m (Shen et al. 2022). These models based on hybrid LUR modelling combining e.g. satellite data, chemical transport model estimates, road and land use data. O_3 exposure was expressed in annual, warm season and cold season average maximum 8-hour mean for long-term exposure (de Hoogh et al. 2018a; Shen et al. 2022). Therefore, these units are compatible with HRAPIE CRFs (WHO 2013a), unlike those from PolluMap.

Furthermore, the Copernicus Atmosphere Monitoring Service (CAMS) provides user-defined time-series of global concentration analysis and forecasts for about 15 air pollution indicators (plus pollen indicators) at hourly temporal resolution and 0.1° x 0.1° (i.e. 10km x 10km) spatial resolution using nine air quality models (the median ensemble or specific models) (ECMWF 2021). These model outputs are used as input in Hybrid LUR models such as the ones produced in the ELAPSE models. However, the CAMS involves some applicability issues due to limited resolution as well as some uncertainties due to “input parameters, initial and boundary conditions and constitute defects” (Pappa and Kioutsioukis 2021). Therefore, these data are not typically used in health studies.

Table 5 Availability of air pollution concentration data in Switzerland from Swiss dispersion models.

	Pollutant	Source of the concentration data[1]	Type of model	Spatial resolution (grid size)	Metric
Long-term	$PM_{2.5}$/PM_{10}	Swiss map of annual values	Dispersion	200 m	Annual mean (in $\mu g/m^3$)
		PolluMap	Dispersion	20 m	Annual mean (in $\mu g/m^3$)
		ELAPSE	LUR	25 m	Annual mean (in $\mu g/m^3$)
	O_3	Swiss map of annual values	Dispersion	200 m	Maximum monthly 98th percentile
		ELAPSE	LUR	25 m	Daily maximum 8-hour mean
	NO_2	Swiss map of annual values	Dispersion	200 m	Annual mean (in $\mu g/m^3$)
		PolluMap	Dispersion	20 m	Annual mean (in $\mu g/m^3$)
		ELAPSE	LUR	25 m	Annual mean (in $\mu g/m^3$)
	BC	PolluMap	Dispersion	20 m	Annual mean (in $\mu g/m^3$)
	SO_2	Swiss map of annual values	Dispersion	200 m	Annual mean (in $\mu g/m^3$)
	NH_3	Swiss map of annual values	Dispersion	100 m	Annual mean (in $\mu g/m^3$)
Short-term	PM_{10}	Swiss map of annual values	Dispersion	1000 m	Daily mean (in $\mu g/m^3$)
	$PM_{2.5}$	ELAPSE	LUR	100 m	Daily mean (in $\mu g/m^3$)
	O_3	Swiss map of annual values	Dispersion	1000 m	16-hours maximum and 24-hours maximum
	NO_2	Swiss map of annual values	Dispersion	1000 m	Daily mean (in $\mu g/m^3$)
		ELAPSE	LUR	100 m	Daily mean (in $\mu g/m^3$)

Abbreviations: PM_{10} = Particulate matter 10 micrometers or less in diameter. $PM_{2.5}$ = Particulate matter 2.5 micrometers or less in diameter. O_3 = Ozone. NO_2 = Nitrogen dioxide. SO_2 = Sulphur dioxide. CO = Carbon monoxide. BC = Black carbon. NH_3 = Ammonia. LUR = Land use regression.

[1] References of PolluMap: FOEN webpage (FOEN 2021a), report for $PM_{2.5}$, PM_{10} and NO_2 (Heldstab et al. 2020a; Heldstab et al. 2020b) and report for BC (Heldstab et al. 2021). References of Maps of annual values: FOEN webpage (FOEN 2021c) and report (Künzle 2022).

Short-term exposure

Short-term concentration data are only available for PM_{10}, O_3 and NO_2 (Table 5). The company METEOTEST estimated, commissioned by the FOEN, spatially resolved models for short-term exposure data for PM_{10} (daily mean), O_3 (16-hours and 24-hours maximum) and NO_2 (daily mean) according to an e-mail communication with METEOTEST (Künzle 2021). The PM_{10}, and NO_2 daily concentration data are based on the results of the dispersion model PolluMap. They were interpolated with air pollution measurements at monitoring stations operated by the federal government, cantons and municipalities to estimate the hourly values. For O_3 only an interpolation of measurements was used (Ducret 2021; FOEN 2021d). They have a spatial of resolution of 1 km x 1 km (Künzle 2021). Some of these data (PM_{10} daily mean and O_3 daily maximum) are represented in air pollution concentration maps in the website of the FOEN (FOEN 2021d).

Furthermore, researchers of Swiss TPH developed LUR models predicting daily average $PM_{2.5}$ and NO_2 concentrations for Switzerland. Air pollution concentration maps at 100 x 100 meter resolution are available for $PM_{2.5}$ in the period 2003-2013 (de Hoogh et al. 2018b) and 2014-2016 (Saucy et al. 2021b) as well as for NO_2 during the period 2005-2016 (de Hoogh et al. 2019).

Conclusion

AP-HRAs may be conducted with any air pollution concentration data that allow to calculate population-weighted exposure for the pollutant and time scale of interest. To date, long-term concentration data are available for PM_{10}, $PM_{2.5}$, O_3, NO_2, SO_2, BC and NH_3 for long-term exposure and PM_{10}, O_3, NO_2 for short-term. However, one has to bear in mind that for AP-HRAs that go beyond estimating total air pollution impact, but aim at attributing health risk to specific emission sources, dispersion models are more appropriate. Their modular structure allows to model temporal-spatial distribution of all relevant emitters separately. For instance, for the calculation of externalities from transport, as in STE, or any other specific air pollution source, assessment should be based on dispersion models, such as PolluMap.

Short-term exposure data are only available on a much lower spatial resolution than long-term models. This is not critical for AP-HRAs because long-term exposure data can be used for short-term impacts as long as CRFs are linear or close to linear (see Section 5.2).

In case that O_3 is considered in future AP-HRAs, attention should be paid to the metric. The metric O_3 exposure data should match with the metric of the CRF from the epidemiologic study (Breitner et al. 2023). Otherwise, the metric should be converted. Thus, it is recommended to derive transfer functions of the two metrics or to adapt Swiss air pollution models, e.g. PolluMap, to produce the future results in the required metric.

Dispersion modelling for further pollutants, e.g. combustion related compounds (such as black smoke, EC, UFPs), secondary aerosol compounds (such as NH_3) and metals would be of interest to address source-specific AP-HRAs (see Section 5.3), if there is sufficient evidence and CRFs available.

5.2 Use of short-term exposure data

Formulation of the question

Can short-term impacts be quantified based on daily exposure levels of air pollution for Switzerland instead on long-term exposure data as in previous STEs?

Background

HRAPIE suggested CRFs for all-cause mortality attributed to both long- and short-term exposure to $PM_{2.5}$, O_3 and NO_2 (WHO 2013a). However, HRAPIE noted that for $PM_{2.5}$/PM_{10} the “quantification of the effects of short-term exposure should be done for information only” because

they were concerned that the premature deaths attributed to short-term $PM_{2.5}$ exposure were at least to some extend "already accounted for in estimations of the effects of long-term exposure" (WHO 2013a). STE-2010, as previous STE versions and in line with HRAPIE recommendations, did not assess short-term mortality impacts (only long-term). Only the very first STE did this exercise for NO_2 in an annex (GVF 1996).

Beyond mortality, STE-2010 assessed some morbidity impacts that were classified by HRAPIE as short-term, namely asthma symptom days, hospital admissions, restricted activity days and work days lost (see Section 2.1). The annual average air pollution exposure instead of the daily average (as suggested by HRAPIE) was used for these short-term effects, assuming that daily concentrations correspond, on average, to the annual mean (ARE 2014). This approach was based on a framework developed by Künzli et al. (2001).

State of the art

No AP-HRA with specific results for Switzerland, such as those from EEA, GBD or WHO, have ever estimated short-term mortality impacts (Castro et al. 2021). The AP-HRA Tool AirQ+, from the WHO, enables the estimation of short-term mortality. However, AirQ+ refers to HRAPIE to remind that short-term mortality is shown only for information purposes and not as alternative to long-term mortality (Mudu et al. 2018) and that short-term mortality is mostly captured in the long-term mortality (Mudu et al. 2018).

As Section 5.1 has shown, short-term (daily) exposure models for PM_{10}, O_3 and NO_2 are available in Switzerland. The spatial resolution of such models is still lower than for long-term exposure models (depending on the pollutant and the model). In principle, such models could be used for the quantification of short-term health impacts in future AP-HRAs. However, the type of exposure data that was used in studies providing CRFs for short-term effects is a limiting factor. In the past, most studies used a central monitor and thus, as a matter of consistency, the same approach should be taken for AP-HRAs. More recently, also spatiotemporal models have been used, in particular, if a case cross-over design has been applied, e.g. a short-term mortality study for the Zürich area (Saucy et al. 2021a). Most often, little attention is paid to this difference in evidence synthesis, although potentially relevant for the CRF. For example, Orellano et al. (2020) carried out a systematic review and meta-analysis of time-series studies providing CRFs for short-term all-cause and cause specific mortality attributed to PM_{10}, $PM_{2.5}$, NO_2, and O_3 and Orellano et al. (2021) for SO_2. Liu et al. (2019) estimated the CRF for daily mortality in over 600 cities worldwide within the Multi-City Multi-Country (MCC) Collaborative Research Network. However, studies with spatiotemporally resolved time-series (Wu et al. 2022) are still scarce . Spatiotemporally resolved time series in CRFs are required to match with short-term exposure data in AP-HRAs. Otherwise CRFs may have some bias (Butland et al. 2013).

Conclusion

Daily concentration data from short-term exposure models for PM_{10}, NO_2 and O_3 are available for Switzerland (see Section 5). On a first sight, this appears to be the most reliable approach to be applied in AP-HRAs. However, as a matter of consistency, the same exposure model should be used for quantification of short-term effects as in original CRF studies that rely on monitor data in general. The current approach of STE-2010 to use spatiotemporal long-term modelling seems thus not ideal. However, assuming a (closely) linear exposure-response relationship, this provides equivalent results as aggregating daily modelling data of air pollution. Additional uncertainty comes from the fact that current evidence from short-term effect studies is most likely based on a mixture of spatiotemporal modelling and central monitoring. This uncertainty is considered to be relatively small. Nevertheless, if possible, we recommend to use CRFs derived from spatiotemporal resolution to be more coherent with the spatial models used for exposure assessment.

Note that it is expected that long-term effects (both mortality and morbidity) capture both, long-term and short-term effects. For instance, long-term effects on incidence may capture more health implications (and costs if later monetized) than just short-term effects such as hospitalizations. Depending on the economic evaluation, a possible approach could be to monetize the long-term effects of air pollution on all relevant morbidity outcomes alone or in parallel to the previously used short-term effect studies on hospitalizations.

5.3 Use of source specific exposures

Formulation of the question

How can source specific and/or pollutant specific data be considered in the derivation of population-weighted exposure distributions in Switzerland so that health impacts can be estimated not only for traffic but also for other pollutant emission sources (i.e. agriculture, industry and households)?

Background

Transport-related air pollution emissions can be different depending on the transport mode. The FOEN uses since 1999 the air pollution dispersion model PolluMap to obtain concentration data in Switzerland (see Section 5.1). STE-2010 showed the emission data stratified by pollutant (namely PM_{10} and precursors such as NO_x, SO_2, NH_3 and secondary organic aerosols), by sector (namely agriculture and forestry, industry, household and transport) and by transport type (road, rail, air and shipping traffic) as well as transport mode (ARE 2014). The emissions data for PM_{10} were used in STE-2010 to derive the population-weighted mean exposure (not for PM precursors because this report focused on PM_{10}). These exposure data were stratified by sector, transport type and transport mode as well as by age group (<15, >30 and all ages) (ARE 2014). The PM_{10} emission data used in STE-2010 were obtained based on emission inventories and using dispersion modelling for primary particles as well as empirical modelling for secondary aerosols (Heldstab et al. 2013).

STE-2010 noted that there is some evidence of differences between the health risks of PM components from different sources such as tailpipe and abrasion, including both tire and rail brake wear (ARE 2014). However, the authors of STE-2010 assumed the same toxicity for all PM sources (ARE 2014) based on the REVIHAAP report (WHO 2013b). This report cited the work of the US EPA ISA in 2009 suggesting that “there are many components contributing to the health effects of $PM_{2.5}$, but not sufficient evidence to differentiate those constituents (or sources) that are more closely related to specific health outcomes” (US EPA 2009).

State of the art

AP-HRAs aiming source specific health impacts are closely linked to multi-pollutant AP-HRAs discussed in Section 2.3, since specific pollutants (or mixtures of pollutants) can be considered to be a proxy for certain sources. Thus, source specific AP-HRAs depend heavily on the availability of multi-pollutant models to obtain various CRFs in combination with source specific dispersion modelling (see Section 5.1).

After the publication of the REVIHAAP report (WHO 2013b), epidemiological research on specific pollutants and constituents of PM has progressed. The update of US EPA ISA for PM in 2019 (US EPA 2019), confirmed the conclusion of the US EPA ISA in 2009 regarding the lack of evidence to differentiate among PM constituents. Focusing on European studies in the framework of the ESCAPE project, Wang et al. (2014) did not find “significant association between elemental constituents (of particulate matter) representing major sources and cardiovascular mortality”. Some years later, Rodins et al. (2020) found in Germany that there is a higher risk of stroke for PM from transport than for PM from industry. Further sources such as agriculture, forestry or

household were not considered in the study. Furthermore, the authors provided PM component specific hazard ratios by source for PM components. The overall risk of stroke was higher for NH_4, SO_4, than for NO_3, EC and anthropogenic organic compounds (in this order).

The analyses of European cohorts within the framework of the ELAPSE project have investigated source-specific health effects. A pooled analysis of ELAPSE cohorts found that the hazard ratio for long-term all-cause (natural) mortality attributable to $PM_{2.5}$ was higher for traffic than for residual oil combustion, soil, biomass and agriculture, as well as industry (Chen et al. 2022). However, the difference may not be conclusive given the overlapping confidence intervals found in another research work (Lucht et al. 2020). Another pooled analysis of ELAPSE cohort (Chen et al. 2021) investigated (with two different model approaches) the association between all-cause (natural) and cause specific mortality with components of elemental components of $PM_{2.5}$ separately. The authors found that, for all elemental components, relative risks decreased substantially when adjusting for $PM_{2.5}$ or NO_2. Similar conclusions can be derived from an analysis of administrative cohorts of ELAPSE (Rodopoulou et al. 2022). After adjusting for $PM_{2.5}$ and NO_2, only associations of natural mortality with potassium and silicon remained among eight particle components. Therefore, $PM_{2.5}$ is still a valuable proxy of air pollution.

It should be mentioned that, in Switzerland, Castro et al. (2020) carried out a AP-HRAs comparing lung cancer mortality using two different approaches: a) considering PM as a whole with an epidemiologic approach and b) adding up the health impacts attributable to each of the carcinogenic PM components with a toxicological approach (unit risks for each component). They concluded that the health impacts were lower when adding the impacts of the PM components because unit risk and exposure data were available for an insufficient number of components. At global level, the burden of disease contribution of common sources of $PM_{2.5}$ have been estimated (McDuffie et al. 2021).

Conclusion

Emerging research has indicated (without sufficient evidence for final judgment) that $PM_{2.5}$ from traffic may be associated with higher risks of mortality than $PM_{2.5}$ from other sources such as agriculture or industry. However, relative risks of elemental components decrease when adjusting for $PM_{2.5}$ or NO_2. Therefore, $PM_{2.5}$ and NO_2 are suitable indicators to evaluate detrimental health effects of air pollution mixtures. The total air pollution health impact is most likely be captured by a limited set of indicators representing the most relevant air pollution sources, as discussed in Section 2.3.

In specific case, such as AP-HRAs that focus on traffic emissions (or wood burning), one might consider a combustion related compound (black smoke, elemental carbon or UFPs), but there should be sufficient evidence and CRF available. If the health impact of agriculture needs to be assessed, one might consider to include NH_3 as an additional compound but evidence base of causality of health effects is rather weak. Instead, PM from agricultural activities could be alternatively used. Similar considerations could be made for AP-HRA targeted at specific industries with distinct emission profiles (e.g. elemental components).

The application of multi-pollutant approaches (see Section 2.4) might help to estimate the weight of sources and specific transport modes in health impacts attributed to total air pollution. To achieve the most appropriate source apportionment, a limited set of pollutants/components representing the emission spectrum of the relevant sources should be included.

6. COUNTERFACTUAL SCENARIO

6.1 Selection of counterfactual scenario

Formulation of the question

Which is the most suitable counterfactual scenario, i.e. the lowest considered concentration (cut-off value) for Swiss AP-HRAs?

Background

The counterfactual scenario is the minimum considered concentration, which is to be compared with the population exposure. This concept can also be referred as “reference”, “threshold”, “cut-off” concentration or “theoretical minimum risk exposure level” (eventually with slight differences in terms of meaning).

The REVIHAAP report stated regarding $PM_{2.5}$ that “the data clearly suggest the absence of a threshold below which no one would be affected” (WHO 2013b). HRAPIE confirmed this conclusion by explicitly pointing out that the all-cause (natural) mortality “impacts should be calculated at all levels” (WHO 2013a). STE-2010 (and previous) chose for PM_{10} a more conservative counterfactual scenario for long-term exposure: 7.5 µg/m^3 PM_{10} (Castro et al. 2021). The authors of STE-2010 argued that this value corresponded to the average of the lowest values where epidemiologic studies provided data (mean of 5 and 10 µg/m^3 PM_{10}) (ARE 2014) at that time.

Regarding NO_2, HRAPIE recommended assessing only those all-cause natural mortality attributed to long-term exposure above an annual population-weighted mean counterfactual scenario of 20 µg/m^3 and zero concentration for the rest of the outcomes (WHO 2013a).

Regarding O_3, REVIHAAP did not find a clear cut-off for the effect of both long- and short-term exposure on mortality. For short-term exposure, REVIHAAP pointed out that although the evidence of threshold is inconsistent, “where a threshold is observed, it is likely to lie below 90 µg/m^3 (45 ppb, maximum 1 hour)” (WHO 2013b). However, HRAPIE set the threshold for these health effects at 70 µg/m^3 (35 ppb) for long- and short-term exposure, alternatively at 20 µg/m^3 (10 ppb) for short-term exposure, (WHO 2013a).

State of the art

As a previous QHIAS publication has shown (Castro et al. 2022b), the value of the counterfactual scenario can be different depending on the aim of the AP-HRA. Comparative risk assessments can use counterfactuals to compare the health impacts in two different policy scenarios, e.g. current exposure vs. national air quality standards or before and after a particular policy measure. To quantify the health impacts of the overall air pollution exposure, AP-HRAs have applied so far the following three different approaches for setting the counterfactual scenarios .

A. Zero counterfactual concentration, i.e. no cut-off, to capture the health impact of the whole air pollution assuming no threshold of health effect (Briggs et al. 2016; COMEAP 2018; ETC/ACM 2016; Lehtomäki et al. 2018).
B. The minimum exposure with evidence of health effects, different to zero, based on CRF studies to capture only impacts attributed to air pollution above a certain threshold of health effect (Achakulwisut et al. 2019; Castro et al. 2020; COMEAP 2018; de Hoogh et al. 2018b; ETC/ACM 2016; Lehtomäki et al. 2018; Murray et al. 2020; Schneider et al. 2018; WHO 2016a). This minimum exposure for CRF studies has been used with some variations based on:
    1. the recommendation of HRAPIE,
    2. the WHO Air Quality Guidelines 2021 (or 2005 in older publications),
    3. a project specific estimation of the minimum,

4. the uniform distribution of the minimum and 5th percentile of the exposure,
5. the 5th percentile of the minimum exposure.

C. The minimum local exposure from air pollution monitoring stations far from human activity to capture only impacts attributed to anthropogenic air pollution, excluding air pollution from natural sources (Briggs et al. 2016; Health Canada 2021; Khomenko et al. 2021b; Schneider et al. 2018). This minimum local exposure has been obtained using the lowest reported value among exposure monitoring stations or average of low-traffic areas.

Specific values for counterfactual scenarios from some AP-HRAs are available in the Appendix (Table A 13). Regarding the AP-HRAs with specific results for Switzerland, it should be mentioned that the EEA "Air quality in Europe" reports have been a remarkable example for many years of AP-HRAs strictly following the HRAPIE recommendations for counterfactual scenarios. Thus, the EEA used 0 µg/m^3 for $PM_{2.5}$ (counterfactual option A in the list above), 20 µg/m^3 for NO_2 and 70 µg/m^3 for O_3 (ETC/ACM 2016).

The new WHO Air Quality Guidelines 2021 (WHO AQG 2021) are a special case (counterfactual option B2 in the list above). They are air quality standards, but they are based on the lowest reliably observed values with sufficient epidemiologic evidence for adverse effects (Table 6). Therefore, using the WHO AQG 2021 as counterfactual enables the quantification of health impacts of the overall air pollution exposure. It should be noted that the WHO AQG 2021 for PM_{10}, i.e. 15 µg/m^3 $PM_{10,}$ is much higher than the $PM_{2.5}$ value, i.e. 5 µg/m^3 $PM_{2.5}$ (in Switzerland equivalent to around 7 µg/m^3 PM_{10}; assuming that around 70% of PM_{10} refer to $PM_{2.5}$) (Castro et al. 2020). The $PM_{2.5}$ value it is based on a higher number and more recent studies (WHO 2021),

Table 6 WHO Air Quality Guidelines 2021, adapted from WHO (2021).

Pollutant	Averaging time	Recommended level
$PM_{2.5}$	Annual	5 µg/m^3
	24-hour[2]	15 µg/m^3
PM_{10}	Annual	15 µg/m^3
	24-hour[2]	45 µg/m^3
O_3	Peak season[3]	60 µg/m^3
	8-hour[2]	100 µg/m^3
NO_2	Annual	10 µg/m^3
	24-hour[2]	25 µg/m^3
SO_2	24-hour[2]	40 µg/m^3
CO	24-hour[2]	4 mg/m^3

The WHO AQG 2021 have being used in AP-HRAs for long-term exposure to $PM_{2.5}$ and NO_2, e.g. for European cities (Khomenko et al. 2021a), for Switzerland (Castro et al. 2023a) and European countries (including Switzerland) commissioned by the EEA (EEA 2021; Soares et al. 2022). The change in the traditional choice of the counterfactual scenario in EEA publications is of international relevance. Thus, 5 µg/m^3 $PM_{2.5}$ (instead of 0 µg/m^3 $PM_{2.5}$), 10 µg/m^3 NO_2 (instead of 20 µg/m^3 NO_2) were selected as counterfactual scenarios following the recommendations of WHO

[2] 99th percentile (i.e. 3–4 exceedance days per year).

[3] 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.

AQG 2021. The authors of the EEA report acknowledged that the data of the WHO AQG 2021 "do not provide evidence of the risk function assuming a linear shape below 5 µg/m^3" (Soares et al. 2022). For long-term exposure to O_3, 60 µg/m^3 was used as counterfactual, following the recommendations of HRAPIE, instead of the 70 µg/m^3 as in the WHO AQG 2021 (Soares et al. 2022). This EEA report also included a sensitivity analysis using the following alternative scenarios: 0 µg/m^3 and 2.5 µg/m^3 $PM_{2.5}$ (lowest average background concentration in Europe) and 0 µg/m^3 and 20 µg/m^3 for NO_2 (ETC/ACM 2016) and SOMO10 (20 µg/m^3) for O_3 as the alternative metric recommended by HRAPIE (Raaschou-Nielsen et al. 2012).

The GBD 2019 used a uniform distribution between the minimum concentration (lower bound) and fifth percentile concentration (upper bound) of the cohort studies used for determining the CRFs (counterfactual option B4). Applying this approach, the counterfactual scenario was 2.4 to 5.9 µg/m^3 $PM_{2.5}$ and 29.1 to 35.7 ppb (around 58.2 to 71.4 µg/m^3) for O_3 (Murray et al. 2020). Castro et al. (2020), used 2.4 µg/m^3 $PM_{2.5}$ (3.3 µg/m^3 PM_{10}) as counterfactual concentration in an AP-HRA of lung cancer mortality in Switzerland committed by the FCAH. The value of the counterfactual value refers to the lowest concentration of the studies that determine the CRF used in global assessment of $PM_{2.5}$-related long-term mortality (Burnett et al. 2018), which was the same as the lower bound of the counterfactual scenario used in the GBD 2015.

An AP-HRA for European urban areas (Khomenko et al. 2021b) chose two counterfactual has found no $PM_{2.5}$ concentration "below which no health effects were observed", at least until the lowest concentration of the study, which was 2.5 µg/m^3 $PM_{2.5}$ (see statement figure in the source). This is in line with the absence of threshold for $PM_{2.5}$ suggested by HRAPIE (WHO 2013b).

Conclusion

The choice of the counterfactual scenario can highly influence the estimated health impacts (Castro et al. 2021). The choice of the counterfactual scenario for Swiss AP-HRAs partly depends on the aimed health impacts to be captured.

- If the goal of the counterfactual scenario is to reflect the minimum air pollution concentration with evidence of health effects, as it was the case for STEs, the new WHO Air Quality Guidelines should be considered as point of reference due to the international relevance. For the case of long-term exposure to $PM_{2.5}$, a counterfactual based on the WHO AQG 2021, 5 µg/m^3 $PM_{2.5}$, is in the range of the uniform distribution used for GBD 2019, i.e. 2.4 to 5.9 µg/m^3 $PM_{2.5}$. Concerning AP-HRAs using PM_{10} instead of $PM_{2.5}$ as main air pollution indicator, the WHO AQG 2021 value for $PM_{2.5}$ seems to be more reliable than the one for PM_{10}, given that it is based on a higher number and more recent studies (WHO 2021), therefore more adequate to be used in AP-HRAs.
- If the goal of the counterfactual scenario is to capture the whole range of air pollution, a zero concentration can be assumed. It should be acknowledged that, HRAPIE (WHO 2013a) and REVIHAAP (WHO 2013b) agreed already in 2013 that there is probably no threshold for health effects of $PM_{2.5}$/PM_{10}. Recent literature, such as Brauer et al. (2022), supports this assertion. (Brauer et al. 2022).
- If the goal is to focus on anthropogenic air pollution, the minimum of the local exposure data measured in monitoring stations located far from human activity can be used as counterfactual scenario.

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Appendix A: Pollutant-outcome pairs

Table A 1: Health outcomes with sufficient evidence for causality according to HRAPIE (WHO 2013a).

Pollutant	Long- vs. short-term	Health outcome	Group[1]
$PM_{2.5}/PM_{10}$	Long-term	Mortality, all-cause (natural), age 30+ years	A
		Postneonatal (age 1–12 months) infant mortality, all-cause	B
		Prevalence of bronchitis in children, age 6–12 (or 6–18) years	B
		Incidence of chronic bronchitis in adults (age 18+ years)	B
	Short-term	Mortality, all-cause, all ages	A
		Hospital admissions, CVDs (includes stroke), all ages	A
		Hospital admissions, RDs, all ages	A
		RADs, all ages	B
		Work days lost, working-age population (age 20–65 years)	B
		Incidence of asthma symptoms in asthmatic children aged 5–19 years	B
O_3	Long-term	Mortality, respiratory diseases, age 30+ years	B
	Short-term	Mortality, all (natural) causes, all ages	A
		Mortality, RDs, all ages	A
		Mortality, CVDs, all ages	A
		Hospital admissions, CVDs (excluding stroke), age 65+ years	A
		Hospital admissions, RDs, age 65+ years	A
		Minor RADs, all ages	B
NO_2	Long-term	Mortality, all (natural) causes, age 30+ years	B
		Prevalence of bronchitic symptoms in asthmatic children aged 5–14 years	B
	Short-term	Mortality, all (natural) causes, all ages	A
		Hospital admissions, respiratory diseases, all ages	A

Abbreviations: CVDs = Cardio-vascular diseases. RADs = Restricted activity days. RDs = Respiratory diseases.

[1] Group A = Pollutant–outcome pairs for which enough data are available to enable reliable quantification of effects. Group B = pollutant–outcome pairs for which there is more uncertainty about the precision of the data used for quantification of effects.

Table A 2: Health outcomes included in the AP-HRA of STE-2010 for PM_{10} exposure (ARE 2014).

Pollutant	Long-term vs. short-term exposure	Health outcome				
		Mortality vs. Morbidity	Organ system	Cause	Metric	Population group
PM_{10}	Long-term	Mortality	All systems	All (natural) causes	Premature deaths	Adults
						Infants
					Working YLLs	Workers
					YLLs	Adults
						Infants
		Morbidity	Respiratory system	Chronic bronchitis	Cases (incidence)	Adults
				Acute bronchitis	Cases (prevalence)	Children
	Short-term	Morbidity	All causes	All (natural) causes	RADs	Adults
					Work days lost	Workers
			Respiratory system	Asthma	Symptom days	Adults
						Children
				Respiratory diseases	Hospital admissions	All
					Hospital days	All
			Cardiovascular system	Cardio-vascular diseases	Hospital admissions	All
					Hospital days	All

Abbreviations: YLLs = Years of life lost. RADs = Restricted activity days.

Table A 3: Further examples of reports including a selection of morbidity outcomes.

Source	Description of the study
(TRINOMICS 2022a).	Study to support the impact assessment for a revision of the EU Ambient Air Quality Directive, commissioned by the European Commission, estimated the health impacts attributable to exposure to $PM_{2.5}$ using the same morbidity outcomes as HRAPIE, but adding incidence of lung cancer and stroke. In the appendix additionally considered myocardial infraction, diabetes mellitus type 2 and COPD (TRINOMICS 2022b).
(Kienzler et al. 2022)	An IONET report of the ETC-HE estimating European burden of disease in DALYs attributable to air pollution (including $PM_{2.5}$, NO_2 and O_3) selected the following pollutant outcome pairs: Asthma in children, COPD, ischemic heart disease, lung cancer, stroke, and diabetes mellitus for $PM_{2.5}$, asthma in adults, stroke and diabetes mellitus for NO_2 and hospital admissions for respiratory diseases for O_3. The authors prioritized prevalence in this outcomes over incidence and they based the selection on the evidence reported in HRAPIE (WHO 2013a) and GBD (Murray et al. 2020) as well a report from the German Environment Agency (UBA) (Schneider et al. 2018).
(Oudin et al. 2022)	A study funded by the Swedish Environmental Protection Agency (Oudin et al. 2022) found enough evidence for the following health outcomes mainly based on based on HRAPIE (WHO 2013a) and GBD (Murray et al. 2020): Lung cancer, autism, dementia, myocardial infraction, stroke, COPD, diabetes type 2, preeclampsia/gestational hypertension, low birth, weight and preterm birth for PM2.5, as well as low birth weight, preterm birth, lung cancer, asthma and bronchitis for NO_2.
(Hunt et al. 2016; Narain and Sall 2016)	A World Bank report (Narain and Sall 2016) and a report commissioned by the Organisation for Economic Co-operation and Development (OECD) (Hunt et al. 2016) provided recommendations for the selection of morbidity outcomes and their valuation. The World Bank report showed concern about the inclusion of numerous morbidity outcomes in AP-HRAs because it “raises the possibility of double counting or inconsistency in cost estimation methods for different outcomes” (Narain and Sall 2016). Therefore, it refers to a short core set of health outcomes (and the associated pollutants) proposed by the OECD report (Hunt et al. 2016). All $PM_{2.5}$/PM_{10} outcomes from of HRAPIE (WHO 2013a) were select, except asthma, minor restricted activity days was the only outcome proposed for O_3. Exceptionally, acute lower respiratory infections (ALRI) from $PM_{2.5}$/PM_{10} was added to the list because GBD used it and because of the international relevance of the disease. NO_2 was not considered as pollutant because of lack of exposure data (Hunt et al. 2016).

Table A 4: Causal determination of air pollutants according to US EPA ISAs (US EPA 2010; US EPA 2016; US EPA 2017; US EPA 2019; US EPA 2020).

Long- vs. short-term	Health effects (eventually including both morbidity and mortality)	Pollutant						
		$PM_{2.5}$	$PM_{10-2.5}$	$PM_{0.1}$	O_3	NO_2	SO_2	CO
Long-term	Total mortality	C	S	I	S	S	I	N
	Respiratory[1]	L	I	I	L	L	S	I
	Cardiovascular[1]	C	S	I	S	S	I	I
	Metabolic	S	S	I	S			
	Nervous system	L	S	S	S			S
	Reproduction and fertility [2,3]	S	I	I	S	I	I	
	Pregnancy and birth outcomes[2, 4]	S	I	I	S	S		S
	Postnatal development [3,4]					I	I	S
	Cancer	L	S	I	I	S	I	
Short-term	Total mortality	C	S	I	S	S	S	S
	Respiratory[1]	L	S	S	C	C	C	S
	Cardiovascular[1]	C	S	S	S	S	I	L
	Metabolic	S	I	I	L			
	Nervous system	S	I	S	S			S
	Reproduction and fertility	S	I	I				
	Pregnancy and birth outcomes	S	I	I				

Scale (and color legend):

- C (dark green) = Causal relationship.
- L (light green) = Likely causal relationship.
- S (yellow) = Suggestive of, but not sufficient to infer, a causal relationship.
- I (dark red) = Inadequate to infer a causal relationship.
- N (brown) = Not likely to be a causal relationship.
- (white) = Not available.

[1] For CO, respiratory and cardiovascular effects exclude morbidity, which is not the case for other pollutants.

[2] For NO_2, pregnancy was included in the reproduction and fertility category instead of in the birth outcomes category.

[3] For SO_2, "Reproductive and Development" effects was presented as a single category.

[4] For CO, "Birth outcomes and Developmental" effects was presented as a single category.

Table A 5: Rating scale of weight of evidence of health effects in the QHIAS project summarizing scales in literature on NO_2

Hypothetical equivalence of weight of evidence across studies	Subscale	WHO (2013a)	US EPA (2016); Health Canada (2016), Stieb et al. (2021); Stieb et al. (2020)	Schneider et al. (2018)	Huangfu and Atkinson (2020)
High		Group A (enough data are available to enable reliable quantification of effects)	Causal relationship	Strong evidence	High certainty
Medium		Group B (more uncertainty about the precision of the data used for quantification of effects)	Likely to be a causal relationship	Moderate evidence	Moderate certainty
Low	A		Suggestive of, but not sufficient to infer, a causal relationship	Weak or insufficient evidence	
	B		Inadequate to infer a causal relationship		
	C		Not likely to be a causal relationship		

Table A 6: Evidence of attributed to short-term exposure to NO_2 by health outcome and systematic review

Health outcome			Evidence of health effects for short-term exposure				
Group	Outcome details (if needed)	Mortality vs. Morbidity	WHO (2013a)[1]	US EPA (2016)[2]	Health Canada (2016)	Schneider et al. (2018)	Stieb et al. (2020)
All-cause	Total all-cause	Mortality	High	Low - A	Medium	High	
Respiratory	Total respiratory	Mortality				High	
	Total morbidity	Morbidity			High		
	Total mortality & morbidity	Mortality & morbidity		High			
	Hospital admissions	Morbidity	High				
Cardio-vascular	Total	Mortality				Medium	
	Total mortality & morbidity	Mortality & morbidity		Low - A	Medium		
	Ischemic heart disease	Morbidity					Medium

Note: See conversion between original scale and the QHIAS scales in Table A 5.

[1] The WHO (HRAPIE) evidence for total mortality refer to daily maximum 1-hour mean concentration, and for hospital admissions to both daily maximum and 1-hour mean concentration or 24-hour mean.

[2] The assessment for respiratory effects is mainly based on asthma. There is more uncertainties for other outcomes such as allergy, COPD, respiratory infection, respiratory effects in healthy populations, and respiratory mortality

Table A 7: Evidence of attributed to long-term exposure to NO_2 by health outcome and systematic review

Health outcome			Evidence of health effects for long-term exposure						
Group	Outcome details (if needed)	Mortality vs. morbidity	WHO (2013a)	US EPA (2016)	Health Canada (2016)	Schneider et al. (2018)	Huangfu and Atkinson (2020)	Huang et al. (2021)	Stieb et al. (2021)
All-cause	Total all-cause	Mortality	Medium	Low - A	Low - A	Low	Medium	Low	Low - A
Respiratory	Total respiratory	Mortality				Low	Medium	Low	Low - A
		Mortality & Morbidity		Medium	Medium				
	ALRI	Mortality					High		
	Asthma for adults	Morbidity				Medium			
	Asthma for children	Morbidity				Low			
	Bronchitic symptoms in asthmatic children	Morbidity	Medium						
	Chronic bronchitis	Morbidity				Low			
	COPD	Mortality				High	Medium		
		Morbidity				Low			
Cardiovascular & diabetes	Total cardio-vascular	Mortality				High		Low	Low - A
		Mortality & Morbidity			Low - A				
	Total cardio-vascular & diabetes	Mortality & Morbidity		Low - A					
	Diabetes	Mortality & Morbidity				Medium			
	Hypertension	Mortality				Low			
	Hypertension for adults	Morbidity				High			
	Hypertension for children	Morbidity				Low			
	Ischemic heart disease	Mortality				High			Low - A
		Morbidity				Low			
	Myocardial infarction	Mortality				Medium			
		Morbidity				Low			
	Heart failure	Mortality & Morbidity				Medium			
	Stroke	Mortality & Morbidity				Medium			
	Cerebro-vascular	Mortality							Low - B
Cancer	Total cancer	Mortality & Morbidity		Low - A	Low - A				
	Lung cancer	Mortality & Morbidity				Low			Low - A
Pre- & post-birth	Premature birth	Morbidity				Low			
	Low birth weight	Morbidity				Low			
	Reproductive & developmental effects	Morbidity			Low - A				
	Fertility, reproduction & pregnancy	Morbidity		Low - B					
	Birth outcomes	Morbidity		Low - A					
	Postnatal development	Morbidity		Low - B					

Appendix B: Concentration-response functions

Table A 8: Sources of CRFs in the special issue "update of the WHO Global Air Quality Guidelines" for PM

Air pollution exposure	Health outcome	Publication providing CRFs in the special issue "update of the WHO Global Air Quality Guidelines"
PM long-term exposure	All-cause (natural) mortality in adults	Chen and Hoek (2020)
	Mortality due to respiratory diseases	Chen and Hoek (2020)
	Mortality due to ALRI	Chen and Hoek (2020)
	Mortality due to COPD	Chen and Hoek (2020)
	Mortality due to lung cancer	Chen and Hoek (2020)
	Mortality due to cardiovascular diseases	Chen and Hoek (2020)
	Mortality due to stroke	Chen and Hoek (2020)
	Mortality due to IHD	Chen and Hoek (2020)
PM short-term exposure	All-cause (natural) mortality	Orellano et al. (2020)
	Mortality due to respiratory diseases	Orellano et al. (2020)
	Mortality due to cardiovascular diseases	Orellano et al. (2020)
	Mortality due to cerebrovascular diseases	Orellano et al. (2020)

Abbreviations: COPD = Chronic obstructive pulmonary disease. IHD = ischemic heart diseases. ALRI = acute lower respiratory infection.

Table A 9: Sources of CRF in the special issue "update of the WHO Global Air Quality Guidelines" for O_3, NO_2, SO_2 and CO

Air pollution exposure	Health outcome	Publication providing CRFs in the special issue "update of the WHO Global Air Quality Guidelines"
O_3 long-term exposure	All-cause mortality	Huangfu and Atkinson (2020)
	Mortality due to respiratory diseases in adults	Huangfu and Atkinson (2020)
O_3 short-term exposure	All-cause mortality	Orellano et al. (2020)
	Hospital admissions due to asthma	Zheng et al. (2021)
NO_2 long-term exposure	All-cause (natural) mortality in adults in adults	Huangfu and Atkinson (2020) [3]
	Mortality due to respiratory diseases	Huangfu and Atkinson (2020)
	Mortality due to COPD	Huangfu and Atkinson (2020)
	Mortality due to ALRI	Huangfu and Atkinson (2020)
NO_2 short-term exposure	All-cause (natural) mortality	Orellano et al. (2020)
	Hospital admissions due to asthma	Zheng et al. (2021)
SO_2 short-term exposure	All-cause (natural) mortality	Orellano et al. (2021)
	Mortality due to respiratory diseases	Orellano et al. (2021)
	Hospital admissions due to asthma	Zheng et al. (2021)
CO short-term exposure	Hospital admissions due to myocardial infarction	Lee et al. (2020)

Abbreviations: COPD = Chronic obstructive pulmonary disease. ALRI = Acute lower respiratory infection.

Table A 10: Potentially relevant CRFs for $PM_{2.5}$ long-term all-cause mortality in Europe.

Type of study	Authors	Geo-graphic context	Pollutant adjustment	# of studies	Effect estimate (95% confidence interval)
Suggested by HRAPIE	Hoek et al. (2013)	Global	No information	11	1.062 (1.040, 1.083) per 10 µg/m³
Meta-analysis of systematic review	HEI review on traffic-related effects (HEI 2022)	Global	Single-pollutant	12	1.03 [1.01;1.05] per 5 µg/m³
	Chen and Hoek (2020)	Global	Mixing multi-& single-pollutant	25	1.08 (1.06, 1.09) per 10 µg/m³
		Europe	Mixing multi-& single-pollutant	5	1.07 (1.03, 1.11) per 10 µg/m³
	Pope et al. (2020)	Global	No information	33	1.09 (1.07, 1.11) per 10 µg/m³
		Europe	No information	10	1.12 (1.06,1.19) per 10 µg/m³
	ERS-ISEE statement (Brunekreef et al. 2022) based on ELAPSE cohorts	Europe	Single-pollutant	8 (7+1)	1.118 (1.060, 1.179) per 10 µg/m³
Meta-analysis or pooled analysis of cohorts in Europe	Stafoggia et al. (2022) Administrative cohorts of the ELAPSE project	Europe	Single-pollutant	7 cohorts	1.053 (1.021, 1.085) per 5 µg/m³
			Multi-pollutant adjusted for NO_2		1.003 (0.982, 1.025) per 5 µg/m³
	Strak et al. (2021) Prospective cohorts (pooled) of the ELAPSE project	Europe	Single-pollutant	1 pooled cohort (from 8 cohorts)	1.130 (1.106, 1.155) per 5 µg/m³
			Multi-pollutant adjusted for NO_2		1.083 (1.054, 1.113) per 5 µg/m³
	Beelen et al. (2014) ESCAPE project	Europe	Single-pollutant	19 cohorts	1.04 (1.00, 1.09) per 5 µg/m³
			Multi-pollutant adjusted for NO_2		1.06 (0.98, 1.15) per 5 µg/m³
Single cohort in Switzerland	Stafoggia et al. (2022) ELAPSE project	Switzerland (Swiss National Cohort)	Single-pollutant	1 cohort	1.026 (1.015, 1.038) per 5 µg/m³
	Beelen et al. (2014) ESCAPE project	Switzerland (SAPALDIA cohort)	Single-pollutant	1 cohort	Not available (but represented in the forest plot)

Table A 11: Potentially relevant CRFs for NO_2 long-term all-cause mortality in Europe.

Type of study	Authors	Geo-graphic context	Pollutant adjustment	# of studies	Effect estimate (95% confidence interval)
Suggested by HRAPIE	WHO (2013a)[1]	Global	Single-pollutant	11	1.055 (1.031, 1.080) per 10 µg/m^3
Meta-analysis of systematic review	HEI review on traffic-related effects (HEI 2022)	Global	Single-pollutant	11	1.04 (1.01,1.06) per 10 µg/m^3
	Huangfu and Atkinson (2020)	Global	Mixing multi-& single-pollutant	24	1.02 (1.01, 1.04) per 10 µg/m^3
	Stieb et al. (2021)	Global	Two-pollutant	9	1.006 (0.976, 1.036) per 10 ppb
		Europe	Single-pollutant	5	1.060 (1.004, 1.119) per 10 ppb
	Huang et al. (2021)	Global	Two-pollutant	9	1.05 (1.02, 1.08) per 10 ppb
		Europe	No information	13	1.03 (1.02,1.05) per 10 ppb
Meta-analysis or pooled analysis of cohorts in Europe	ERS-ISEE statement (Brunekreef et al. 2022) based on ELAPSE cohorts	Europe	Single-pollutant	8 (7+1)	1.045 (1.026, 1.065) per 10 µg/m^3
	Stafoggia et al. (2022) ELAPSE project	Europe	Single-pollutant	7 cohorts	1.044 (1.019, 1.069) per 10 µg/m^3
			Two-pollutant adjusted for $PM_{2.5}$		1.042 (1.020, 1.065) per 10 µg/m^3
	Strak et al. (2021) ELAPSE project	Europe	Single-pollutant	1 pooled cohort (from 8 cohorts)	1.086 (1.070, 1.102) per 10 µg/m^3
			Two-pollutant adjusted for $PM_{2.5}$		1.050 (1.031, 1.070) per 10 µg/m^3
	Beelen et al. (2014) ESCAPE project	Europe	Single-pollutant	8 cohorts	1.01 (0.99, 1.03) per 10 µg/m^3
			Two-pollutant adjusted for $PM_{2.5}$		1.01 (0.97, 1.05) per 10 µg/m^3
Single cohort in Switzerland	Stafoggia et al. (2022) ELAPSE project	Switzerland (Swiss National Cohort)	Single-pollutant	1 cohort	1.050 (1.041, 1.059) per 10 µg/m^3
	Beelen et al. (2014) ESCAPE project	Switzerland (SAPALDIA cohort)	Single-pollutant	1 cohort	Not available (but represented in the forest plot)

Abbreviation: ppb = Parts per billion.

[1] Meta-analysis carried out in the framework of HRAPIE based on studies collected by Hoek et al. (2013).

Appendix C: Air pollution concentration data

Table A 12: Air pollution indicators and their availability of concentration data from monitoring stations as well as exposure data from model estimations at Swiss national level.

	Air pollution indicator (as in NABEL)	NABEL monitoring stations		Availability of exposure data from models
		Number of stations (percentage out of the total, 16)	Mean frequency of measurements	
Particles	Particulate matter PM_{10}, HiVol	15 (94%)	Daily	No
	Particulate matter PM_{10}, cont.	16 (100%)	10-Minutes	Yes (LT&ST)
	Particulate matter $PM_{2.5}$, HiVol	12 (75%)	Daily	No
	Particulate matter $PM_{2.5}$, cont.	16 (100%)	10-Minutes	Yes (LT)
	Particle number concentration[1]	5 (31%)	10-Minutes	No
	Aerosol size distribution	1 (6%)	10-Minutes	No
	EBC in $PM_{2.5}$	9 (56%)	10-Minutes	Yes (LT)
	TC in $PM_{2.5}$, cont.	1 (6%)	Hourly	No
	EC/OC in $PM_{2.5}$	9 (56%)	Daily	No
	PAH in PM_{10}	12 (75%)	3-Months	No
	Pb, Cd, As, Ni, Cu in PM_{10}	15 (94%)	Annual	No
	Cl^-, NO_3^-, SO_4^{2-} in PM_{10}	4 (25%)	Monthly/Daily	No
	Na^+, K^+, Ca^{2+}, Mg^{2+} in TSP	2 (13%)	Daily	No
Gases	Sulphur dioxide (SO_2)	9 (56%)	10-Minutes	Yes (LT)
	Nitrogen oxides (NO_x, NO_2, NO)	16 (100%)	10-Minutes	Yes (LT&ST)
	NO_2 selective methods	4 (25%)	10-Minutes	No
	Nitrous oxide (N_2O)	2 (13%)	10-Minutes	No
	Ozone (O_3)	16 (100%)	10-Minutes	Yes (LT)
	Carbon monoxide (CO)	10 (63%)	10-Minutes	No
	Carbon dioxide (CO_2)	5 (31%)	10-Minutes	No
	Methane (CH_4)	6 (38%)	10-Minutes	No
	Non-methane hydrocarbons	3 (19%)	10-Minutes	No
	BTX (Benzene, Toluene, Xylene)	3 (19%)	Daily	No
	Volatile Organic Compounds (VOC)	2 (13%)	Daily	No
	Halogenated compounds	1 (6%)	Daily	No
	Sulphur hexafluoride (SF_6)	1 (6%)	Daily	No
	Ammonia (NH_3)	3 (19%)	10-Minutes	Yes (LT)

Abbreviations: HiVol = High volume. PAH = Polycyclic aromatic hydrocarbons. EC/OC = Elemental carbon / Organic carbon. TC = Total carbon. EBC = Equivalent black carbon. LT = Long-term exposure model. ST = Short-term exposure model

Legend of availability of exposure data: Green = Yes. Red = No.

[1] Particle number concentration is a proxy for ultrafine particles ($PM_{0.1}$).

Appendix D: Counterfactual scenario

Table A 13: Examples of counterfactual scenarios used in AP-HRAs since 2013.

Type of counterfactual scenario		Value of the counterfactual scenario (and examples of AP-HRAs applying it)
Category	**Definition**	
Zero counterfactual concentration	No threshold	$PM_{2.5}$ 0 µg/m^3 (Briggs et al. 2016; ETC/ACM 2016; Lehtomäki et al. 2018) (also as recommended by HRAPIE) NO_2 0 µg/m^3 (COMEAP 2018; Lehtomäki et al. 2018)
Minimum exposure with evidence of health effects in CRF studies	According to HRAPIE (with some threshold)	NO_2 20 µg/m^3 (ETC/ACM 2016) O_3 70 µg/m^3 (D8M over 35 ppb, i.e. SOMO35) (ETC/ACM 2016; Lehtomäki et al. 2018)[1]
	According to the WHO Air Quality Guidelines of 2021	$PM_{2.5}$ 5 µg/m^3 (Castro et al. 2023a; EEA 2021; Khomenko et al. 2021a; Soares et al. 2022) $PM_{2.5}$ 10 µg/m^3(Castro et al. 2023a; EEA 2021; Khomenko et al. 2021a; Soares et al. 2022)
	According to the WHO Air Quality Guidelines of 2005	$PM_{2.5}$ 10 µg/m^3 (Khomenko et al. 2021b) $PM_{2.5}$ 40 µg/m^3 (Khomenko et al. 2021b)
	Project specific estimation of the minimum	$PM_{2.5}$ 2.4 µg/m^3 (Castro et al. 2020) following Burnett et al. (2018), which based on GBD 2015 NO_2 10 µg/m^3 (Schneider et al. 2018) 5 µg/m^3 (COMEAP 2018)
	Uniform distribution of the minimum and 5th percentile of the exposure	$PM_{2.5}$ 2.4 to 5.9 µg/m^3 (Murray et al. 2020 App1; WHO 2016a) O_3 58.2 to 71.4 (29.1 to 35.7 ppb, D8M) (Murray et al. 2020 App1)[1]
	5th percentile of the minimum exposure	NO_2 3.76 µg/m^3 (2 ppb) for asthma incidence (Achakulwisut et al. 2019)[1]
Minimum local exposure from air pollution monitoring stations far from human activity	Lowest reported value among exposure monitoring stations	$PM_{2.5}$ 5 µg/m^3 for European cities (Khomenko et al. 2021b) 2.5 µg/m^3 for Canada (Health Canada 2021) O_3 52 µg/m^3 (26 ppb, D1M; 28 ppb in summer) (Health Canada 2021) NO_2 3.5 µg/m^3 for European cities (Khomenko et al. 2021b). 0.3 µg/m^3 (0.15 pbb) for Canada (Health Canada 2021)[1]
	Average of low-traffic areas	NO_2 10 µg/m^3 for Germany (Schneider et al. 2018) 14 µg/m^3 for New Zealand (Briggs et al. 2016)

Abbreviation: ppb = parts per billion. D8M = Average of the daily 8-hours maximum. D1M = Average of the daily 1-hour maximum.

[1] Assuming that 1 ppb O_3 is equivalent to 2 µg/m^3 and 1 ppb NO_2 is equivalent to 1.91 µg/m^3.