Informing the public about chemical mixtures in the local environment

Currently applied indicators in the Netherlands and ways forward

Hof, M.; de Baat, M.L.; Noorda, J.; Peijnenburg, W.J.G.M.; van Wezel, A.P.; Oomen, A.G.

DOI
10.1016/j.jenvman.2024.122108

Publication date
2024

Document Version
Final published version

Published in
Journal of Environmental Management

Citation for published version (APA):
Hof, M., de Baat, M. L., Noorda, J., Peijnenburg, W. J. G. M., van Wezel, A. P., & Oomen, A. G. (2024). Informing the public about chemical mixtures in the local environment: Currently applied indicators in the Netherlands and ways forward. *Journal of Environmental Management*, *368*, Article 122108. https://doi.org/10.1016/j.jenvman.2024.122108

Journal of Environmental Management 368 (2024) 122108

Contents lists available at ScienceDirect

Journal of Environmental Management

journal homepage: www.elsevier.com/locate/jenvman

Research article

Informing the public about chemical mixtures in the local environment: Currently applied indicators in the Netherlands and ways forward

Matthias Hof [a,b,*], Milo L. de Baat [b], Jantien Noorda [c], Willie J.G.M. Peijnenburg [a,d], Annemarie P. van Wezel [b], Agnes G. Oomen [a,b]

[a] *Centre for Safety of Substances and Products, National Institute of Public Health and the Environment (RIVM), Bilthoven, 3720 BA, the Netherlands*
[b] *Institute for Biodiversity and Ecosystem Dynamics, University of Amsterdam, Science Park 904, 1098 XH, Amsterdam, the Netherlands*
[c] *Centre for Environmental Safety and Security, National Institute of Public Health and the Environment (RIVM), Bilthoven, 3720 BA, the Netherlands*
[d] *Institute of Environmental Sciences (CML), Leiden University, Leiden, 2300, RA, the Netherlands*

ARTICLE INFO

Handling Editor: Lixiao Zhang

Keywords:
Mixtures
Environmental health
Risk assessment
Impact assessment
Prioritization
Effect-based

ABSTRACT

The current use of chemicals puts pressure on human and ecological health. Based on the Aarhus Convention, citizens have the right to have access to information on substances in their local environment. Providing this information is a major challenge, especially considering complex mixtures, as the current substance-by-substance risk assessment may not adequately address the risk of co-exposure to multiple substances. Here, we provide an overview of the currently available indicators in the Netherlands to explore current scientific possibilities to indicate the impacts of complex chemical mixtures in the environment on human health and ecology at the local scale. This is limited to impact estimates on freshwater species for 701 substances, impact estimates of four metals on soil organisms, and impacts on human health for particulate matter (PM_{10}) and nitrogen dioxide (NO_2) in air. The main limiting factors in developing and expanding these indicators to cover more compartments and substances are the availability of emission and concentration data of substances and dose-response relationships at the population (human health) or community (ecology) level. As ways forward, we propose; 1) developing cumulative assessment groups (CAGs) for substances on the European Pollutant Transfer and Release Register and Water Framework Directive substance lists, to enable the development of mixture indicators based on mixture risk assessment and concentration addition principles; 2) to gain insight into local mixtures by also applying these CAGs to emission data, which is available for soil and air for more substances than concentrations data; 3) the application of analytical non-target screening methods as well as effect-based methods for whole-mixture assessment.

1. Introduction

The production and application of chemical substances are an important basis for modern life. However, the widespread use of substances has regrettably also led to contamination of the environment, with risks to human health and ecology. Chemical pollution is listed as one of the nine planetary boundaries, and experts argue that this boundary is, although not quantified, already exceeded as the increasing use and emissions of substances outpace the capacity for risk assessment (Persson et al., 2022). Risk assessment of substances requires detailed information on both the hazard of and the exposure to substances, and this is a major challenge considering the sheer number of produced substances. Current estimates for the number of substances (including intentional mixtures) in use range from 25.000 up to 350.000 (Bond and Garny, 2019; EEA, 2019; Wang et al., 2020). Of these substances, no more than approximately 500 are currently deemed as “extensively characterized” by the European Environment Agency (EEA), with a further 10.000 deemed “fairly characterized” (EEA, 2019). While these statistics become a little less daunting knowing that about 5.000–6.000 substances account for over 99 percent of the total volume of used substances (EEA, 2019), risk assessment is further complicated by the reality that substances do not occur in the environment individually but as complex mixtures (Bond and Garny, 2019; EEA, 2019). Indeed, even with data lacking for most substances, it has been shown that mixtures of

---

* Corresponding author. Centre for Safety of Substances and Products, National Institute of Public Health and the Environment (RIVM), Bilthoven, 3720 BA, the Netherlands.

E-mail address: matthias.hof@rivm.nl (M. Hof).

https://doi.org/10.1016/j.jenvman.2024.122108
Received 7 May 2024; Received in revised form 29 June 2024; Accepted 3 August 2024

known substances in the environment do significantly contribute to the global burden of disease and are a major driving force for biodiversity loss in surface waters (Hänninen et al., 2014; Landrigan et al., 2018; Lemm et al., 2021; Posthuma et al., 2020; Sigmund et al., 2023).

Considering the pressure put on human and ecological health by the use of substances, the European Union has formulated the Green Deal and the related Chemical Strategy for Sustainability, in which it sets the ambitious target of achieving a toxic-free environment (European Commission, 2020). This strategy is to be implemented at both the international and national levels. However, environmental pollution can also be a location-specific problem that may require a location-specific mitigation strategy. It is exactly at that level that local authorities, citizens, and other stakeholders often struggle with acquiring the knowledge, expertise, and capacity required to assess, communicate, and manage the risks arising from substances in their environment. For example, in the EU, 90% of citizens are concerned about the impact of chemicals in everyday products on the environment, and the majority of Europeans does not feel sufficiently informed about the quality of air in their country while considering air-quality related diseases as a serious problem (Kantar, 2020, 2022). As citizens have the right to have access to information on substances in their environment based on the Aarhus Convention (Aarhus Convention, 1998), there is an urgent need for indicators that support local authorities, citizens, and other stakeholders in the assessment of the impacts of substances on human and environmental health in the local environment.

At the EU level, the recently released tool by the EEA called "Check your place" in the European Environment and Health Atlas (EEA, 2023) is a step towards informing citizens about the quality of their local environment. The tool includes multiple indicators such as noise pollution and vicinity to green spaces. However, regarding exposure to chemical substances, the tool is currently limited to air quality factors such as particulate matter, nitrogen dioxide, and ozone concentrations. Information on other environmental compartments, such as soil and surface water, is also limited. In light of the hundreds of thousands of substances potentially present in the environment, the tool does not provide citizens with information on the chemical quality of their environment that covers the extent of substances potentially present.

At the national scale, there are often additional resources available to provide citizens with information on the (chemical) quality of their environment with regard to other substances, environmental compartments, or exposure routes. In this study, we provide an overview of currently available indicators in the Netherlands to explore the current scientific possibilities to indicate the impacts of complex chemical mixtures in the environment on human health and ecology at the local scale. The Netherlands is a developed and densely populated country in which living, heavy traffic, intensive agriculture, and highly industrialized activities often co-occur in close proximity. Furthermore, the Netherlands is relatively data-rich with hundreds of available indicators on the environment which are compiled and made publicly available in the Environmental Data Compendium (EDC, 2023), Environmental Health Atlas (EHA, 2023), Atlas Natural Capital (ANC, 2023), and Emission Registration database (ER, 2024). Examples of similar sources in other countries include the GEOportal Nordrhein-Westfalen (DE), the Environment and Health Atlas of England and Wales (UK), and Leefkwaliteit Vlaanderen for Flanders (BE). The current overview is limited to an analysis of indicators available in the Netherlands, as the information available in other countries is generally less extensive than, or not remarkedly dissimilar to, the information available in the Netherlands.

We assess to what extent current indicators on substances in the local environment address the multitude of substances that can be present, and whether and how the impact of chemical mixtures is currently addressed. This overview provides insight into the current limits and possibilities in quantifying the impacts of chemical mixtures in the environment, which can help prioritize the further development of indicators. The analysis is limited to the possibilities offered by natural sciences to develop such indicators, meaning that possibilities concerning social scientific aspects such as perception, interpretation, or desirability of information are not discussed. This analysis then feeds an outlook on ways forward to develop and expand indicators on the impact of chemical mixtures in the local environment.

2. Methods

To gain an overview of indicators available to local authorities and citizens in the Netherlands, the Dutch Environmental Data Compendium (EDC, 2023), the Environmental Health Atlas (EHA, 2023), the Atlas Natural Capital (ANC, 2023), and the Dutch Emission Registration database (ER, 2024) were screened for indicators related to substances in the environment. The EDC is a website in which environmental indicators from several governmental and research institutes are collated. The website includes information from Statistics Netherlands (CBS), the National Institute for Public Health and the Environment (RIVM), the Netherlands Environmental Assessment Agency (PBL), and Wageningen University and Research (WUR). The two Atlases are a collection of maps with information on the living and natural environment and are managed by the RIVM, the Dutch Department of Waterways and Public Works, and the 12 Dutch provinces (BIJ12). The emission registration database is a centralized database that makes mandatory reported emissions available to the public. The emission database also enables users to easily view emissions through a map-making tool. These sources were chosen because they are publicly available, compile information from multiple sources, and have policymakers and citizens as their target audience. Specific municipalities might possess additional information, which can be difficult to find or access and is not generally available at a national scale. Therefore, this more scattered municipal information is not considered within the scope of the present study.

A list of all indicators in the EDC was acquired upon request. All maps available in the EHA and ANC were added to this list manually. The information included in the EDC and the Atlases relates to information on the environment in general and is not limited to chemical substances only. For example, the websites also provide information on topics such as climate change, biodiversity, average house prices, and the locations of wind turbines. Furthermore, what was considered an indicator was not strictly defined, and ranged from summary statistics at the national level to detailed maps. For this reason, the data entries were filtered based on the following criteria.

- The indicator includes or relates to information on substances in the outdoor environment (e.g. soil, water, air). Particulate matter is also included.
- The indicator provides information at the local scale, at the municipality level, or more refined.
- The indicator has spatial coverage of the entire Netherlands (as opposed to only being available for a specific region or municipality).

Indicators not fulfilling all three criteria were not removed from the database, but filtered out during the analysis so decisions made are transparent and available in the database (SI 1). As the current study focuses on how impacts of mixtures are indicated, the indicators fulfilling the criteria were subsequently categorized according to whether they addressed impacts or provided other types of information on substances. To support this categorization, the indicators were structured according to the Drivers, Pressures, States, Impacts, Responses (DPSIR) framework (Ragas, 2019). The DPSIR framework is a tool that is commonly used in environmental toxicology to help structure environmental issues, or in the case of this study, indicators on environmental issues, according to five categories: Drivers, Pressures, States, Impacts, and Responses. The categories themselves are not strictly defined and may differ per study or user. For this overview, the DPSIR categories were defined as follows:

DRIVERS: Any activity or environmental factor that could influence (i.e. drive) the presence and/or impact of substances in the environment.

Examples are the production or use of substances in a specific area. Lastly, indicators that expressed the capacity of the natural environment to reduce the presence of or exposure to substances were also categorized as drivers.

PRESSURES: Emissions of substances to the environment in a specified area and indicators that describe a mass flow of substances.

STATES: Chemical state of the environment. The occurrence and concentration of substances in specific environmental compartments (water, sediment, soil), including expressions of risk (e.g. concentrations compared to environmental quality standards).

IMPACTS: Quantitative expressions of the degree of (monitored, estimated, or predicted) effects on human or ecosystem health, e.g., disease burden or number of species expected to suffer adverse effects.

RESPONSES: Indicators providing information on activities taken to mitigate current or past impacts of substances in the environment, e.g. remediation efforts.

After categorizing the indicators, we summarized the available information through these indicators per environmental compartment and DPSIR category. The data available through the emission registration database was also included in this overview. Apart from the impact indicators, the indicators were not reviewed in detail. Identified impact indicators were reviewed in detail based on their supporting documents by answering the following questions.

- How is the indicator expressed?
- What are the data requirements?
- How and to what extent are chemical mixtures considered?
- To what extent is aggregation of substances across multiple exposure routes accounted for?
- What are the main knowledge gaps and limitations in determining mixtures of substances?

3. Results

3.1. Summary of available information on substances in the local environment

A brief overview of information currently available in the Netherlands through publicly accessible indicators is presented below according to their DPSIR categories (chapter 3.1.1–3.1.4). Overall, we see that the information currently available to citizens consists majorly of emissions (pressures) and concentrations (states) of substances in the area (Table 1). Concentration data are often reported in relation to some kind of threshold or quality standard. There is a large difference in the amount of concentration data available between environmental compartments, with the most information available for surface water. The impacts of mixtures on the ecosystem in surface water are also well covered, and some limited information is available for impacts on soil organisms. In sharp contrast, insights into impacts on human health are limited to the combined impacts of NO2 and particulate matter in the air. It is not possible to gain insight into the impacts on human health of any other substances and exposure routes through the currently available indicators in the Netherlands. The identified impact indicators and their underlying methods are discussed in detail in chapter 3.2.

3.1.1. Drivers and Pressures

Through the Dutch emission registration database, and the map-making tool that enables users to view the data relatively easily, citizens have access to information on emissions of hundreds of substances in their local environment. In total, the Dutch emission registration database has information on 375 substances. The amount differs per compartment, with information on emissions being available for 121 substances for air, 49 for soil, and 277 for water. This includes substance groups. The emissions included in the emission registration database are

Table 1

Overview of available indicators of substances in the environment and their impacts (NS = non-specific, which means that substances were not identified within the indicator or its description).

Compartment	Driver	Pressure	State	Impact	Response
Non-specific	Locations of use and transport of “hazardous substances” (NS)	Deposition: SO_2, NO_2, NH_3, N			
Air	Mitigating factor of environment: Potential of vegetation to capture PM ($PM_{2.5}$ and PM_{10})	Emission of 121 substances (including some groups), primarily substances on E-PRTR list	Concentration: NO, NO_2, SO_2, NH_3, PM_{10}, $PM_{2.5}$, $PM_{0.1}$, soot, O_3 Human health threshold: NO_2, PM_{10}, $PM_{2.5}$	Human health: Environmental health risk (PM_{10} and NO_2 in air, also includes noise pollution)	
Surface water		Emission of 277 substances (including some groups), primarily substances on E-PRTR list and substances relevant for WFD (45 total + 77 river-basin-specific substances)	Qualitative score according to WFD (WFD substances [45 total] + 77 river-basin-specific substances), Qualitative score on eutrophication (N, P, CHLF-a), Number of pesticides exceeding thresholds and sum of threshold exceedance (NS), Occurrence of substances at drinking water intake sources above 100% or 75% of their threshold (NS)	Ecotoxicological effects on freshwater organisms (quantitative score, based on up to 701 different substances [across all locations], including metals, organic compounds, pesticides, PAHs	Amount and duration of intake stops for drinking water (NS)
Soil	Mitigating factor of environment: Self-cleaning potential of topsoil (NS)	Emission of 49 substances (including some groups), primarily substances on E-PRTR list	Concentration: PFAS	Ecotoxicological effects on soil organisms, based on: Cd, Cu, Zn, Pb	Need for- and status of remediation efforts (NS)
Groundwater	Mitigating factor of environment: Water purification in subsoil (NS)	Change of NO_3 concentration (compared to the previous year)	Occurrence of substances at drinking water intake sources above 100% and 75% of their threshold (NS), Qualitative score according to WFD – (NS)		

based on reporting according to the European Pollutant Release and Transfer Register (E-PRTR, which includes 91 substances), the Kyoto Protocol (greenhouse gasses), and the Water Framework Directive (WFD, 45 substances on the EU priority list). Furthermore, the emission registration database includes some additional substances relevant to national policy, such as an additional 77 river-basin-specific substances being monitored for the WFD.

There are a few additional driver and pressure-related indicators in the other data sources that are informative to a lesser extent. There is an indicator that describes locations containing hazardous substances, like gas pipes or storage facilities. This indicator is focused on hazards associated with incidents (fires, explosions, poisonous clouds), and the substances themselves are not specified, making it less suitable to identify relevant substances. There are also maps of deposition of SO_2, NO_2, NH_3, and total N. Lastly, some maps describe the capacity of the natural environment to reduce the presence of or exposure to substances, which were categorized as drivers for this study; These are maps that describe the presence of vegetation and its capacity to capture particulate matter, the self-cleaning capacity of topsoil, and purification of groundwater in the subsoil.

3.1.2. States

The number of substances covered by indicators that relate to the occurrence, concentration, and/or threshold exceedances (e.g. environmental quality standard) differs per environmental compartment. For air, the indicators are limited to concentrations of particulate matter (PM_{10}, $PM_{2.5}$, $PM_{0.1}$, soot), nitrogen-based substances (expressed as total nitrogen), sulfur dioxide, and ozone. These indicators include a comparison between concentrations of PM_{10}, $PM_{2.5}$, and NO_2 and human health thresholds. For surface water and groundwater, a qualitative score of chemical quality based on the Water Framework Directive is available. This score is binary (either sufficient or insufficient), with insufficient meaning that at least one priority substance exceeds its environmental quality standard. The scoring system includes 45 priority (groups of) substances that are monitored across Europe and 77 additional river-basin-specific substances. There are also indicators aimed specifically at drinking water intake sites in surface- and groundwater that indicate whether one or more substances were detected above 75% or 100% of their threshold. The indicators for surface- and groundwater do not specify which substances exceed environmental quality standards, nor is it possible to discern how many substances exceed these standards. For pesticides in surface water, there is a specific indicator that sums the individual exceedances of environmental quality standards of multiple pesticides. This enables a more nuanced comparison between locations with at least one substance above its environmental quality standard. Lastly, for soil, only concentrations of PFAS are available.

3.1.3. Impacts

Three indicators focus on the quantitative impacts of substances in the environment. These indicators are the Environmental Health Risk indicator, toxic pressure on freshwater organisms, and toxic pressure on soil organisms. The Environmental Health Risk indicator is focused on impacts on human health (see section 3.2.2 for a detailed overview), while the other two are focused on impacts on organisms in either freshwater or soil. The latter indicators are based on the same

Table 2
Details of impact indicators for chemicals in the Dutch environment, including to which extent mixtures are addressed, and their assumptions and limitations.

Impact indicator	Human or Ecosystem	Expressed as	Compartment	Mixtures	Data requirements	Assumptions and limitations
Environmental health risk	Human	% contribution of local environmental factors to the total average disability adjusted life years (DALY) in the Netherlands	In theory non-specific, but in practice only a few substances in air are included	Yes, individual DALYs for each substance-endpoint combination are summed. Also includes noise as non-chemical stressors. Aggregation across multiple exposure routes is not considered in the method	- Substance data at certain spatial resolution - Dose-response relationships for humans at population level supported by epidemiological and toxicological data - Weighing factors for severity and duration of endpoint for conversion to DALY	- Assumed exposure (duration) - Temporal and spatial interpolation - Assumptions on population characteristics ('average' population) - Stringent requirements for exposure and dose-response relationship data, which are available for only a few substances - Only certain health impacts are included in DALY calculation, sub-clinical effects are disregarded - Expert judgement on what substances and data to use and include
Toxic pressure	Ecosystem	Qualitative score based on chronic and acute predicted multi-substance potentially affected fraction of species (msPAF)	surface water, soil	Yes, based on response addition. Mixture toxicity is calculated by multiplying individual PAFs	- Substance monitoring data at certain spatial resolution - Data of environmental factors affecting bioavailability of substances - Species Sensitivity Distributions	- Assumes that substances have independent action - Effect calculated on the 'average' species assemblage, not the local species - Assumptions on natural occurrence and background concentrations - Expert judgement on which substances and data to use and include - Temporal and spatial interpolation - Limited availability of hazard data - Secondary poisoning and endocrine disruption not addressed

methodology and will be discussed together (see section 3.2.1). An overview of the indicators, how they are expressed, which environmental compartments they apply to, how they address mixtures, and the data requirements, assumptions, and limitations can be found in Table 2.

3.1.4. *Responses*

Two indicators describe responses to the presence of substances in the environment. One indicator describes the number of intake stops per year for drinking water in the rivers Rhine and Meuse. However, it is not reported which substances caused the intake stops. For soil, there is a map that details whether research on soil pollution has been conducted at a location and whether remediation efforts are, or have been, conducted. Again, no details on specific substances are provided.

3.2. *Currently applied methods to determine impacts of mixtures in the environment*

3.2.1. *Toxic pressure indicator (ecological impacts)*

The toxic pressure indicator is an indicator that predicts the impact of a mixture of substances on a community (group of multiple species) and is available for freshwater and soil. Details on the calculation methods are provided in Postma et al. (2021) and Spijker et al. (2011) for freshwater and soil, respectively. The toxic pressure indicator for freshwater systems is based on mixture calculations for 701 substances, including pesticides, metals, polycyclic aromatic hydrocarbons (PAHs), and other organic substances. In contrast, the toxic pressure in soil is based on four metals (Cd, Cu, Zn, and Pb) and does not include other substances.

The indicator is expressed as the predicted potentially affected fraction (PAF) of species that is affected by a mixture, i.e. the multi-substance PAF of species (msPAF). The indicator is calculated by estimating the PAF for each single substance based on the concentration of a substance in the relevant compartment and a species sensitivity distribution (SSD). An SSD is a statistical model that represents the differences in sensitivity to a specific substance between species, i.e. the distribution of species sensitivities to a substance (Posthuma et al., 2019). This enables the estimation of the fraction of species that is expected to be affected (PAF) by a certain concentration of a substance. SSDs for aquatic ecosystems are available for 12.386 substances (Posthuma et al., 2019). The indicator for impacts on soil organisms is based on SSDs for aquatic ecosystems as a proxy for soil ecosystems. In addition to the inclusion of SSDs for each substance, the calculation of PAF requires data on concentrations of substances and on factors influencing the bioavailability of substances. Mixtures are addressed by multiplying the individual impacts, using Equation (1) for an *i* number of substances:

$$msPAF = 1 - \Pi(1 - PAF_i) \tag{1}$$

Where $msPAF$ is the fraction of species affected by the mixture and PAF_i = the fraction of species affected by substance i.

The msPAF is calculated by using SSDs that are based on acute and chronic effects and the results of both are used to score the overall impact of the mixture qualitatively: A $\text{msPAF}_{\text{chronic}} \leq 0.005$ the water quality in regards to toxic pressure is graded as very good, $\text{msPAF}_{\text{chronic}} > 0.005$ and ≤ 0.05 as good, $\text{msPAF}_{\text{actute}} \leq 0.005$ and $\text{msPAF}_{\text{chronic}} > 0.05$ as mediocre, $\text{msPAF}_{\text{actute}} > 0.05$ and ≤ 0.1 as insufficient, and $\text{msPAF}_{\text{acute}} > 0.1$ as bad. The calculation of mixture toxicity for the msPAF indicator is based on the principle of response addition (Bliss, 1939; EFSA et al., 2019). This assumes that the individual substances in the mixture act independently of each other, and only the individual effects of the substances can be summed (in practice “addition” is a misnomer, and multiplication is applied in response addition, see Equation (1)). This contrasts with concentration addition, in which the concentrations (instead of effects) of individual substances with a common mode of action, target organ, or adverse effect are summed to determine mixture effects. By not applying concentration addition in the calculation of msPAF, potential mixture effects of substances that are individually present below their no-effect concentration are not considered. A mixed model was applied in previous iterations of the msPAF indicator, where initially concentration addition was applied to substances with the same mode of action followed by response addition. However, Postma et al. (2021) state that the mixed model is no longer applied for two reasons: the first is the complexity of assigning a single mode of action to a substance as these may differ per organism, and the second reason is that the outcome (i.e., msPAF) is insensitive to applying the mixed model or just response addition.

One of the main limitations of calculating the impact of substances using the msPAF approach is the availability of high-quality SSDs. For the freshwater indicator, 928 out of the 1629 substances with available monitoring data could not be included in the calculation due to a lack of available SSDs of sufficient quality, resulting in an msPAF based on only 43% (701) of the detected substances in Dutch freshwaters. Note that this percentage refers to the overall number of substances included in the indicator across all locations, not the number per location. Statistics on the number of substances per location are not available but are likely lower than 701 due to differences in monitoring efforts between locations.

The availability of concentration data of substances is a second limitation of the method since a substance that is not monitored can also not be included in the calculation of toxic pressure. Furthermore, decisions are required on the desired spatial and temporal resolution, and how to interpolate across time and space. Additionally, only apical effects (effects observable in a whole organism) such as mortality, growth impairment, or reduced reproduction, are included in the SSDs. Indirect effects such as secondary poisoning or effects at a lower level of biological organization (e.g. the cellular level) like endocrine disruption are not included.

These limitations all together exemplify that the method relies on expert judgment, e.g., decisions on which substances to in- or exclude in the calculation, for which substances sufficient data are available to develop SSDs, and which concentrations to use for calculations (e.g., average, median, or maximum concentration during a week, month, or year). Lastly, an important aspect of the interpretation of the indicator is that the impact is estimated for an “average” set of species based on the SSDs and not for the actual species at that location. The sensitivity of the local community to mixture toxicity may differ based on the species present and their level of adaptation to, for example, background concentrations. The toxic pressure indicator must thus be interpreted as a relative expression of the potential toxicity of a mixture between locations or points in time. Nonetheless, it has been shown that an increased mixture toxic pressure, expressed as msPAF, relates to a decrease in species diversity, making it an informative proxy for the potential effects of pollution on ecosystem health when comparing locations or measurements (Posthuma et al., 2020).

3.3. *Environmental health risk indicator (human health impacts)*

The Environmental Health Risk indicator is expressed as a % of the total disability-adjusted life years (DALYs) caused by environmental factors at a certain location (RIVM, 2023). It is an indicator that combines multiple factors, including non-chemical factors. Currently, the indicator includes impacts from noise pollution, particulate matter (PM_{10}), and nitrogen dioxide in the air. Thus, regarding substances, the indicator only covers the air compartment, although the indicator is theoretically not specific to any compartment. The indicator is calculated by estimating the DALYs for specific endpoints, such as premature death and asthma, of each included factor based on exposure data and dose-response relationships at the population level (Forouzanfar et al., 2015; Prüss-Ustün et al., 2017). The calculation of DALYs also requires endpoint-specific weighting factors based on the severity and duration of the condition. The environmental factor and endpoint-specific DALYs are calculated for the Dutch population, summed, and then divided by the total average DALYs (from any factor, not just environmental) in the Netherlands. Local population characteristics (e.g. presence of vulnerable sub-populations, such as children and the elderly) are thus not considered. Therefore, the indicator should be interpreted as a measure of the environmental quality of the location regarding potential impacts on human health, and not as representative of actual impacts on the local population. Mixtures are addressed indirectly since the DALYs of separate environmental factors are summed. This can be considered a form of response addition, although the calculation method is different than commonly applied for response addition (EFSA et al., 2019). Lastly, aggregation across multiple exposure routes is not considered in the method.

Although PM_{10} can be considered a mixture, the chemical factors explicitly included in the MGR are limited to just PM_{10} and NO_2. The motivation for this practice is the limited availability of exposure data in the Netherlands for other substances. The lack of availability of dose-response relationships is not explicitly mentioned in the handbook of the MGR as a reason for not including more substances in the indicator. However, the indicator is based on the method for the estimation of DALYs, and it is known that this method is limited by strict requirements for causal relationships between environmental factors and clinical effects (Grandjean and Bellanger, 2017; Trasande et al., 2015). Establishing the impacts of substances on human health at ambient exposure levels requires conclusive evidence from both a toxicological and an epidemiological perspective. Consensus among experts is required to determine whether there is sufficient evidence on causality, exposure, and dose-response relationships to include environmental factors in calculations of DALYs. Currently, this is available for only a few substances, and this can be considered a major limitation in the inclusion of more substances in the impact assessment of chemical mixtures on human health. Another limitation is that the DALY method only includes clinical effects and disregards sub-clinical effects (Grandjean and Bellanger, 2017). Lastly, like the indicator for impacts on the ecosystem, the indicator expresses an impact on an ‘average’ population and does not take local population characteristics into account to determine or predict actual impacts.

4. Discussion

4.1. Current possibilities and impossibilities in developing indicators on the impact of mixtures at the local scale

Policy measures toward a toxic-free environment are preferably based on concrete indications of the actual impacts of the whole chemical mixture on human and ecological health. In the current article, we analyzed which indicators of substances in the local environment and their impacts are available in the Netherlands and to what extent they cover the multitude of substances and their mixtures. Currently, indicators of the impacts of mixtures of substances in the environment include the estimated impacts on freshwater organisms that can integrate the combined effects of 701 substances, on soil organisms for a mixture of four metals, and for human health for PM_{10} and NO_2 in air.

Both the ecotoxicological indicators, which are based on the msPAF approach, and the human health indicator, expressed in DALY, require concentration data of substances in an environmental compartment and high-quality dose-response relationships at the community- (ecology) or population (human health) level. Both approaches account for mixtures by multiplying (msPAF) or summing (DALY) the individual estimated impacts of substances in the mixture, and do not account for mixture effects in other ways, such as concentration addition, synergy, or antagonism of substances.

Ideally, to provide citizens with (high spatial resolution) information on exposure to substances in their local environment, indicators that provide information at the local scale and are available nationwide will be developed or expanded to better cover the multitude of substances, compartments, and exposure routes relevant in a local area. For ecology, impacts of mixtures in surface water are already covered relatively well, and the approach could also be applied to soil to account for more substances than the currently included four metals, provided concentration data of additional substances in soil are available (Faber et al., 2023). Air quality is typically not considered as a direct exposure route for organisms in the environment.

In contrast to ecology, high-quality dose-response relationships at the population level are scarcely available for human health. Establishing a clear causal relationship between the presence of substances in the environment and human health requires evidence from both toxicology and epidemiology, which is difficult to establish and not available for most substances (Grandjean and Bellanger, 2017; Trasande et al., 2015). Because of this lack of established dose-response relationships for the human population, it currently seems unfeasible to expand the estimation of impacts on human health for many substances by using the DALY approach or a toxicology-based response addition approach.

Because the current coverage of the chemical universe and relevant exposure routes is small for impacts of mixtures on human health compared to impacts on ecology, and there is also little opportunity to expand these by using currently applied methods, we focus our discussion of ways forward on potential alternative methods for developing indicators for mixtures related to human health.

4.2. Develop mixture indicators for human health based on concentration addition principles and cumulative assessment groups for environmental substances

While quantifying the ***degree of impact*** on human health, i.e. expressing the degree to which a population is (expected to be) affected, is unlikely to be feasible in the foreseeable future for the entire mixture of known and unknown substances in the environment, significant progress has been- and is being made in the assessment of risks of mixtures. Such assessments can express whether a certain effect can be expected or excluded, i.e. the ***likelihood of impact***, but do not necessarily provide information on the degree of that effect (Fig. 1; Marx--Stoelting et al., 2023). Calculating risks does not necessarily require dose-response relationships at the population level but does require some kind of threshold value below which no (unacceptable) effects are expected, which are generally more available (EFSA et al., 2019). Furthermore, the Threshold of Toxicological Concern approach can be used to include substances for which little to no toxicity data is available (Baken et al., 2018). To calculate the risks of mixtures the concentration addition approach is usually applied, which sums the individual risks of specific groups of substances, effectively treating them as dilutions of each other.

Applying concentration addition in mixture risk assessment frameworks strongly relies on decisions on which substances to group. EFSA has developed scientific criteria for grouping substances into cumulative assessment groups (CAGs) for human risk assessment, which applies tiering principles to manage poor data availability (EFSA et al., 2021). The highest tier consists of groups based on mechanistic information of common modes of action or adverse outcome pathways of substances, and lower tiers are based on the grouping of substances with common target organs or adverse outcomes. The underlying principle behind tiering is that lower tiers require less information and are more conservative, i.e. err on the side of overestimating risks, while higher tiers require more detailed information and are more predictive, i.e. higher certainty of risk. However, higher tier grouping may also underestimate risks by excluding substances that do contribute to mixture toxicity (EFSA et al., 2019; Kortenkamp, 2022).

CAGs have previously been established for groups of pesticides based on their effects on the nervous system and thyroid (Crivellente et al., 2019). These are included and expanded upon in the Monte Carlo Risk Assessment (MCRA) platform, which is aimed at the assessment of mixtures and is supported by EFSA (van Klaveren et al., 2023). Outside

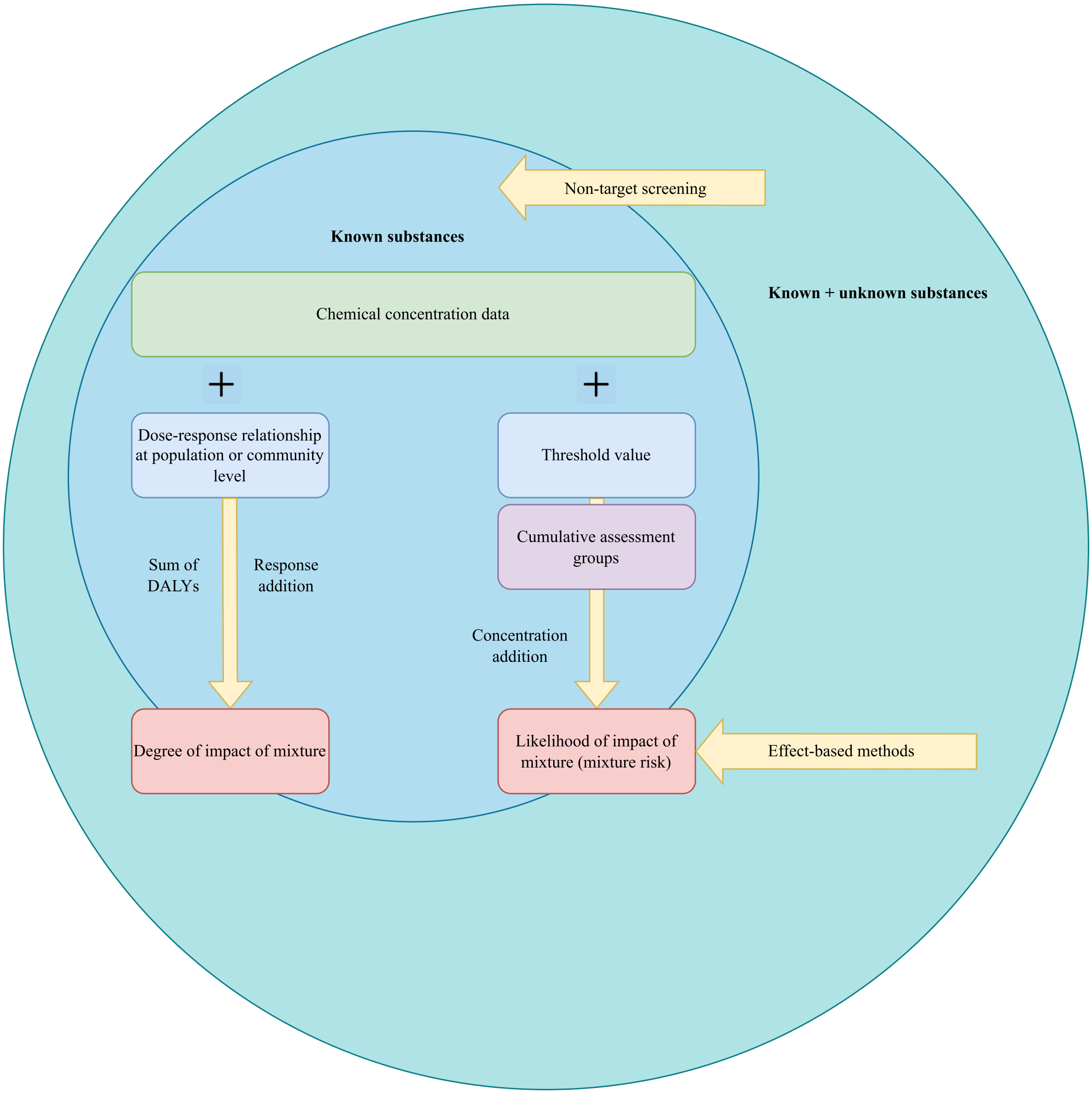

Fig. 1. A schematic overview of ways to develop indicators for mixtures in the environment. Current indicators are based on methods using DALY and response addition, which requires chemical concentration data and dose-response relationships at the population level, to come to an expression of the degree of impact of the mixture. As an alternative, indicators could be developed based on concentration addition and cumulative assessment groups to provide an expression of likelihood of impact (chapter 4.2). These methods only address the impact or risk of the known components in the mixture. Non target-screening and effect-based methods can be applied to include both the known and unknown substances (chapter 4.4).

of MCRA, there are other examples of the CAGs concept being developed, such as for indoor air pollutants by Meek et al. (2022) and in the Chemical Mixture indicator by Boberg et al. (2021) for over 200 substances. The establishment of CAGs for substances on the E-PRTR and WFD priority substances lists, according to EFSA criteria, would be an important first step towards enabling the development of indicators of mixtures in the environment. For example, this could then be applied to develop an indicator of mixture risk for human health when swimming in surface water. The data on surface water substance concentrations are available for this but are currently only translated to impacts on ecology.

4.3. Utilizing available emission data by applying the cumulative assessment group concept

In contrast to surface water, data on concentrations of substances is currently less available for soil and air (Table 1). This could be addressed through additional monitoring, or perhaps through making existing data more findable and accessible. However, there is also an opportunity to better utilize data on local emissions of substances that are available through the emission registration database. For the air and soil compartments, the number of substances with available emission data is larger (121 substances for air, 49 for soil) than publicly available data of concentrations (5 substances, PM and soot for air, PFAS for soil). This emission data could be developed into an indicator that prioritizes substances, substance groups, or locations for which mixture effects seem most relevant to consider by grouping the substances on the list of emitted substances in an area based on CAG principles.

In its simplest form, this emission-based indicator could provide information on the maximum number of emitted substances at a location that affect the same target organ or cause the same adverse effect, with a higher number being of higher priority. A main benefit of a mixture indicator based on local emission data is that it is directly tied to known sources of the emissions, which for example can help the formulation of mitigation measures or argumentation for more stringent emission permits (Bodar et al., 2022; van Wezel et al., 2018). However, an indicator solely based on emissions does not directly reflect risks as it does not adequately account for exposure. Therefore, it should be explored whether an emission-based mixture indicator can be further developed by including estimations of concentrations, e.g. by using chemical fate models (van Wezel et al., 2018), to enable risk assessment. Furthermore, it should also be explored whether results from exposome or biomonitoring studies, such as the European Human Biomonitoring Initiative (HBM4EU), can also be used to prioritize substances or substance groups for which it is known that overall exposure is already high (Luijten et al., 2023; Vermeulen et al., 2020). Lastly, as the emission registration database is currently limited to data on industrial emissions of specific sectors, with a certain volume of activity, it should also be explored to what extent this is representative of the overall emissions in the area.

4.4. *Applying non-target chemical analyses and effect-based methods*

The indicators discussed in sections 4.1-4.3 are all based on methods that calculate mixture impacts or risks based on the individual components of the mixture. By definition, these indicators are limited by the knowledge on the presence and concentration of the substances in the mixture. However, also unknown substances can strongly contribute to mixture toxicity (Fig. 1; Neale et al., 2015). To address this, the application of non-target screening might be useful to detect and identify substances that are otherwise overlooked in monitoring programs. Application of non-target chemical analytical screening methods, such as non-target high-resolution mass spectrometry (HRMS), can vastly increase the number of substances that are monitored, without requiring a priori knowledge of the relevant substances in the area (Vermeulen et al., 2020). Recently, the open-source platform patRoon was released to help with data processing and analysis of HMRS data to identify substances (Helmus et al., 2021). However, to include these substances in mixture risk assessment, their concentrations and hazards should also be determined after identifying their presence. While this remains challenging, there are models available that help estimate concentrations and hazards of substances detected with HRMS (Sepman et al., 2023; Arturi and Hollender, 2023; Peets et al., 2022).

Another approach to mixture hazard and risk assessment is the use of bioassays, in which living cells or organisms are exposed to environmental samples. Bioassays are also known as bioanalytical tools or effect-based methods (EBMs) and integrate the combined biological activity of all substances in a sample. EBMs can overcome the limitations of target analyses by providing a risk-scaled assessment of the mixture toxicity elicited by all known and unknown bioactive substances (Brack et al., 2019; de Baat et al., 2020; Neale et al., 2023a; Gualtieri et al., 2018). The advantage of this approach is that all substances in the sample, known and unknown, and all their interactions are included in the assessment (Fig. 1). Indeed, EBMs often show effects that cannot be explained by mixture-toxicity modeling of substances with known dose-response relationships (Neale et al., 2015). A disadvantage of the method is that, like component-based methods, deducing impacts on populations from the results remains challenging, and the substances driving toxicity are not immediately clear. Currently, distinguishing between acceptable and insufficient environmental quality for such bioanalytical responses is based on effect-based trigger values (Neale et al., 2023b). For surface- and drinking water there are frameworks available for the establishment of effect-based trigger values (Béen et al., 2021; Neale et al., 2023b).

Despite the current challenge of translating bioanalytical responses to toxicological risks, EBMs are very suitable to make a relative comparison between the potency of whole-mixture samples; or to demonstrate the absence of toxicity at a certain location for specific endpoints. The use of EBMs is well established for the chemical quality assessment of surface-, drinking- and wastewater and is also included in the Key Factor Toxicity (STOWA, 2024), which provides guidance for water quality management professionals in the Netherlands (de Baat et al., 2020; Dingemans et al., 2019; Enault et al., 2023; Neale et al., 2022). Until now, effect-based approaches for compartments other than surface-, drinking-, or wastewater are less established, although some examples of their application exist for sediment, soil, and air (de Baat et al., 2019; Pieterse et al., 2015; Gualtieri et al., 2018; Halappanavar et al., 2021; Maciaszek et al., 2023). Incorporating EBM in the chemical risk assessment of other compartments or exposure routes, such as soil, vegetables from vegetable gardens, (indoor) dust, and air would be greatly beneficial for screening the local environment for the toxic potency of mixtures of substances.

For human health, the development of effect-based monitoring of air quality is especially relevant as air is a major exposure route to environmental substances for humans (Landrigan et al., 2018). However, we are still far removed from implementing EBM for air quality assessment at a scale that would provide the national coverage needed to reliably make interpretations for such an indicator. First, a standardized method should be defined to allow an equal comparison of air toxicity at locations by effect-based monitoring. This includes the selection of a sampling method and a suite of human health-relevant in vitro assays to cover a sufficient range of chemicals and toxic modes of action. For now, this calls for more studies that apply effect-based methods for the assessment of air quality and that explore and compare different sampling methods (e.g. passive vs active sampling), and the chemical coverage, specificity, and sensitivity of a range of in vitro assays (Érseková et al., 2014; Nováková et al., 2020; Halappanavar et al., 2021). Subsequently, it should be explored to what extent observations with EBM are indicative of actual effects on human health and effect-based trigger values should be derived to distinguish between acceptable and poor air quality. Following this, to bridge the gap between research and practice, air quality management professionals, policymakers, and citizens should be included in the design of an effect-based monitoring program that is informative, practical, and cost-effective (Neale et al., 2023a,b). Finally, EBM could be integrated with- or linked to indicators on the emission or occurrence of substances through the use of CAGs (see chapters 4.2 and 4.3) and adverse outcome pathways.

5. Conclusions

The current use of chemicals leads to pressures on human and ecological health. Yet, quantifying the degree of impact on humans and the environment caused by the resulting complex mixtures of substances is a formidable task. This is especially so at the local scale, where other substances may be relevant in addition to the more ubiquitous factors (e.g. PM_{10} and NO_2 in air) measured at a larger scale. Citizens and other local stakeholders are concerned about the impact of these chemical mixtures and have a right to information on the occurrence in their environment and the potential effects they may exert on human and ecological health. Publicly available information on the impact of mixtures of substances in the Netherlands is currently limited to impact estimations on freshwater species that can incorporate the combined effects of 701 substances, impact estimations of no more than four metals on soil organisms, and impacts on human health for only PM_{10} and NO_2 in air.

The primary limiting factor in incorporating more substances in the mixture assessment is the lack of established dose-response relationships at the population level for most substances. This is especially difficult for human health, as it requires evidence from both toxicology and epidemiology. As a way forward, we propose the development of mixture indicators for human health based on mixture risk assessment and concentration addition principles, as an alternative to approaches using DALY or response addition. To support this, CAGs should be developed for environmentally relevant substances, starting with substances on the E-PRTR and WFD priority substances lists. Furthermore, we note that current data on the use and emissions of substances, for example through E-PRTR, is currently underutilized. By applying the previously mentioned CAGs to available emission data, these data could be used to develop indicators that help prioritize which specific substance(s) (groups), compartments, or emission sources are relevant at a local scale. Lastly, as the previously discussed indicators all depend on knowledge of which substances are present in the environment, non-target screening and effect-based methods should be applied as a complementary approach to gain better insight into the whole mixture of known and unknown substances. Effect-based monitoring is already developed for surface and drinking water, and should also be developed for other relevant compartments, e.g. for the assessment of air quality for human health.

Funding

This research was funded by the Strategic Program of the Dutch National Institute for Public Health and the Environment (RIVM), grant number S/124010.

CRediT authorship contribution statement

Matthias Hof: Writing – review & editing, Writing – original draft, Visualization, Validation, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Milo L. de Baat:** Writing – review & editing, Validation, Supervision, Methodology, Conceptualization. **Jantien Noorda:** Writing – review & editing, Methodology, Conceptualization. **Willie J.G.M. Peijnenburg:** Writing – review & editing, Validation, Supervision, Methodology, Conceptualization. **Annemarie P. van Wezel:** Writing – review & editing, Supervision, Methodology, Conceptualization. **Agnes G. Oomen:** Writing – review & editing, Validation, Supervision, Methodology, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

This research was based on publicly available data. A list of the reviewed indicators is provided in the SI: "SI1_list_of_indicators_09042024.xlsx".

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jenvman.2024.122108.

References

Aarhus Convention, 1998. Convention on access to information, public participation in decision-making and access to justice in environmental matters. https://unece.org/environment-policy/public-participation/aarhus-convention/text.

Arturi, K., Hollender, J., 2023. Machine learning-based hazard-driven prioritization of features in nontarget screening of environmental high-resolution mass spectrometry data. Environ. Sci. Technol. 57 (46), 18067–18079. https://doi.org/10.1021/acs.est.3c00304.

Atlas Natural Capital (ANC), 2023. *Kaarten*. Atlas Natuurlijk Kapitaal. Retrieved November 9,. https://www.atlasnatuurlijkkapitaal.nl.

Baken, K.A., Sjerps, R.M.A., Schriks, M., Van Wezel, A.P., 2018. Toxicological risk assessment and prioritization of drinking water relevant contaminants of emerging concern. Environ. Int. 118, 293–303. https://doi.org/10.1016/j.envint.2018.05.006.

Béen, F., Pronk, T., Louisse, J., Houtman, C., van der Velden-Slootweg, T., van der Oost, R., Dingemans, M.M.L., 2021. Development of a framework to derive effect-based trigger values to interpret CALUX data for drinking water quality. Water Res. 193, 116859 https://doi.org/10.1016/j.watres.2021.116859.

Bliss, C.I., 1939. The toxicity OF POISONS applied jointly. Ann. Appl. Biol. 26 (3), 585–615. https://doi.org/10.1111/j.1744-7348.1939.tb06990.x.

Boberg, J., Bredsdorff, L., Petersen, A., Löbl, N., Jensen, B.H., Vinggaard, A.M., Nielsen, E., 2021. Chemical Mixture Calculator - a novel tool for mixture risk assessment. Food Chem. Toxicol. 152, 112167 https://doi.org/10.1016/j.fct.2021.112167.

Bodar, C.W.M., de Boer, L., ter Burg, W., Janssen, N., Smit, E., 2022. *Cumulatie en vergunningverlening ZZS* [Report]. Dutch National Institute for Public Health and the Environment (RIVM). https://doi.org/10.21945/RIVM-2022-0061.

Bond, G.G., Garny, V., 2019. Inventory and evaluation of publicly available sources of information on hazards and risks of industrial chemicals. Toxicol. Ind. Health 35 (11–12), 738–751. https://doi.org/10.1177/0748233719893198.

Brack, W., Aissa, S.A., Backhaus, T., Dulio, V., Escher, B.I., Faust, M., Hilscherova, K., Hollender, J., Hollert, H., Müller, C., Munthe, J., Posthuma, L., Seiler, T.-B., Slobodnik, J., Teodorovic, I., Tindall, A.J., De Aragão Umbuzeiro, G., Zhang, X., Altenburger, R., 2019. Effect-based methods are key. The European Collaborative Project SOLUTIONS recommends integrating effect-based methods for diagnosis and monitoring of water quality. Environ. Sci. Eur. 31 (1), 10. https://doi.org/10.1186/s12302-019-0192-2.

EFSA, Crivellente, F., Hart, A., Hernandez-Jerez, A.F., Hougaard Bennekou, S., Pedersen, R., Terron, A., Wolterink, G., Mohimont, L., 2019. Establishment of cumulative assessment groups of pesticides for their effects on the nervous system. EFSA J. 17 (9) https://doi.org/10.2903/j.efsa.2019.5800.

de Baat, M.L., Wieringa, N., Droge, S.T.J., Van Hall, B.G., Van Der Meer, F., Kraak, M.H.S., 2019. Smarter sediment screening: effect-based quality assessment, chemical profiling, and risk identification. Environ. Sci. Technol. 53 (24), 14479–14488. https://doi.org/10.1021/acs.est.9b02732.

de Baat, M.L., Van der Oost, R., Van der Lee, G.H., Wieringa, N., Hamers, T., Verdonschot, P.F.M., De Voogt, P., Kraak, M.H.S., 2020. Advancements in effect-based surface water quality assessment. Water Res. 183, 116017 https://doi.org/10.1016/j.watres.2020.116017.

Dingemans, M.M.L., Baken, K.A., van der Oost, R., Schriks, M., van Wezel, A.P., 2019. Risk-based approach in the revised European Union drinking water legislation: opportunities for bioanalytical tools. Integrated Environ. Assess. Manag. 15 (1), 126–134. https://doi.org/10.1002/ieam.4096.

EFSA, Scientific Committee, More, S.J., Bampidis, V., Benford, D., Bennekou, S.H., Bragard, C., Halldorsson, T.I., Hernández-Jerez, A.F., Koutsoumanis, K., Naegeli, H., Schlatter, J.R., Silano, V., Nielsen, S.S., Schrenk, D., Turck, D., Younes, M., Benfenati, E., Castle, L., Cedergreen, N., et al., 2019. Guidance on harmonised methodologies for human health, animal health and ecological risk assessment of combined exposure to multiple chemicals. EFSA J. 17 (3) https://doi.org/10.2903/j.efsa.2019.5634.

EFSA, Scientific Committee, More, S.J., Bampidis, V., Benford, D., Bragard, C., Hernandez-Jerez, A., Bennekou, S.H., Halldorsson, T.I., Koutsoumanis, K.P., Lambré, C., Machera, K., Naegeli, H., Nielsen, S.S., Schlatter, J.R., Schrenk, D., Silano, V., Turck, D., Younes, M., Benfenati, E., et al., 2021. Guidance Document on Scientific criteria for grouping chemicals into assessment groups for human risk assessment of combined exposure to multiple chemicals. EFSA J. 19 (12) https://doi.org/10.2903/j.efsa.2021.7033.

Emission Registration database (ER), 2024. Emissieregistratie. Retrieved February 2. https://www.emissieregistratie.nl/.

Enault, J., Loret, J.-F., Neale, P.A., De Baat, M.L., Escher, B.I., Belhadj, F., Kools, S.A.E., Pronk, G.J., Leusch, F.D.L., 2023. How effective are water treatment processes in removing toxic effects of micropollutants? A literature review of effect-based monitoring data. J. Water Health 21 (2), 235–250. https://doi.org/10.2166/wh.2023.235.

Environmental Data Compendium (EDC), 2023. Compendium Voor de Leefomgeving (CLO). Retrieved November 9. https://www.clo.nl.

Environmental Health Atlas (EHA), 2023. Atlas leefomgeving. Retrieved November 9. https://www.atlasleefomgeving.nl.

Érseková, A., Hilscherová, K., Klánová, J., Giesy, J.P., Novák, J., 2014. Effect-based assessment of passive air samples from four countries in Eastern Europe. Environ. Monit. Assess. 186 (6), 3905–3916. https://doi.org/10.1007/s10661-014-3667-z.

European Commission (EC), 2020. COMMUNICATION from the COMMISSION to the EUROPEAN PARLIAMENT, the COUNCIL, the EUROPEAN ECONOMIC and SOCIAL COMMITTEE and the COMMITTEE of the REGIONS Chemicals Strategy for Sustainability towards a Toxic-free Environment. https://eur-lex.europa.eu/legal-content/EN/ALL/?uri=COM:2020:667:FIN.

European Environment Agency (EEA), 2023. Check your place. European Environment and Health Atlas. Retrieved October 26. https://discomap.eea.europa.eu/atlas/?page=Check-your-place.

European Environmental Agency (EEA), 2019. The European Environment: State and Outlook 2020 : Knowledge for Transition to a Sustainable Europe. European Environmental Agency. https://data.europa.eu/doi/10.2800/96749.

Faber, M., Hof, M., Lahr, J., Swart, E., Posthuma, L., 2023. Characterisation of Toxic Pressure of Chemical Pollutants in Vulnerable Areas. Methods and Guidance for Operational Characterisation. [Report]. Dutch National Institute for Public Health and the Environment. RIVM). https://doi.org/10.21945/RIVM-2023-0379.

Forouzanfar, M.H., Alexander, L., Anderson, H.R., Bachman, V.F., Biryukov, S., Brauer, M., Burnett, R., Casey, D., Coates, M.M., Cohen, A., Delwiche, K., Estep, K., Frostad, J.J., Kc, A., Kyu, H.H., Moradi-Lakeh, M., Ng, M., Slepak, E.L., Thomas, B. A., et al., 2015. Global, regional, and national comparative risk assessment of 79 behavioural, environmental and occupational, and metabolic risks or clusters of risks in 188 countries, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet 386 (10010), 2287–2323. https://doi.org/10.1016/S0140-6736(15)00128-2.

Grandjean, P., Bellanger, M., 2017. Calculation of the disease burden associated with environmental chemical exposures: application of toxicological information in health economic estimation. Environ. Health 16 (1), 123. https://doi.org/10.1186/s12940-017-0340-3.

Gualtieri, M., Grollino, M.G., Consales, C., Costabile, F., Manigrasso, M., Avino, P., Aufderheide, M., Cordelli, E., Di Liberto, L., Petralia, E., Raschellà, G., Stracquadanio, M., Wiedensohler, A., Pacchierotti, F., Zanini, G., 2018. Is it the time to study air pollution effects under environmental conditions? A case study to support the shift of in vitro toxicology from the bench to the field. Chemosphere 207, 552–564. https://doi.org/10.1016/j.chemosphere.2018.05.130.

Halappanavar, S., Wu, D., Boyadzhiev, A., Solorio-Rodriguez, A., Williams, A., Jariyasopit, N., Saini, A., Harner, T., 2021. Toxicity screening of air extracts representing different source sectors in the Greater Toronto and Hamilton areas: in vitro oxidative stress, pro-inflammatory response, and toxicogenomic analysis. Mutat. Res. Genet. Toxicol. Environ. Mutagen 872, 503415. https://doi.org/10.1016/j.mrgentox.2021.503415.

Hänninen, O., Knol, A.B., Jantunen, M., Lim, T.-A., Conrad, A., Rappolder, M., Carrer, P., Fanetti, A.-C., Kim, R., Buekers, J., Torfs, R., Iavarone, I., Classen, T., Hornberg, C., Mekel, O.C.L., EBoDE Working Group, 2014. Environmental burden of disease in Europe: assessing nine risk factors in six countries. Environ. Health Perspect. 122 (5), 439–446. https://doi.org/10.1289/ehp.1206154.

Helmus, R., Ter Laak, T.L., Van Wezel, A.P., De Voogt, P., Schymanski, E.L., 2021. patRoon: open source software platform for environmental mass spectrometry based non-target screening. J. Cheminf. 13 (1), 1. https://doi.org/10.1186/s13321-020-00477-w.

Kantar, 2020. Attitudes of Europeans towards the Environment. European Commission. Special Eurobarometer 501, 43–44. https://data.europa.eu/doi/10.2779/902489.

Kantar, 2022. Attitudes of Europeans towards air quality. European Commission. Special Eurobarometer 524, 8. https://data.europa.eu/doi/10.2779/91313.

Kortenkamp, A., 2022. Invited perspective: how relevant are mode-of-action considerations for the assessment and prediction of mixture effects? Environ. Health Perspect. 130 (4), 041302 https://doi.org/10.1289/EHP11051.

Landrigan, P.J., Fuller, R., Acosta, N.J.R., Adeyi, O., Arnold, R., Basu, N., Baldé, A.B., Bertollini, R., Bose-O'Reilly, S., Boufford, J.I., Breysse, P.N., Chiles, T., Mahidol, C., Coll-Seck, A.M., Cropper, M.L., Fobil, J., Fuster, V., Greenstone, M., Haines, A., et al., 2018. The Lancet Commission on pollution and health. Lancet 391 (10119), 462–512. https://doi.org/10.1016/S0140-6736(17)32345-0.

Lemm, J.U., Venohr, M., Globevnik, L., Stefanidis, K., Panagopoulos, Y., Van Gils, J., Posthuma, L., Kristensen, P., Feld, C.K., Mahnkopf, J., Hering, D., Birk, S., 2021. Multiple stressors determine river ecological status at the European scale: towards an integrated understanding of river status deterioration. Global Change Biol. 27 (9), 1962–1975. https://doi.org/10.1111/gcb.15504.

Luijten, M., Vlaanderen, J., Kortenkamp, A., Antignac, J.-P., Barouki, R., Bil, W., Van Den Brand, A., Den Braver-Sewradj, S., Van Klaveren, J., Mengelers, M., Ottenbros, I., Rantakokko, P., Kolossa-Gehring, M., Lebret, E., 2023. Mixture risk assessment and human biomonitoring: lessons learnt from HBM4EU. Int. J. Hyg Environ. Health 249, 114135. https://doi.org/10.1016/j.ijheh.2023.114135.

Maciaszek, K., Gillies, S., Kawichai, S., Prapamontol, T., Santijitpakdee, T., Kliengchuay, W., Sahanavin, N., Mueller, W., Vardoulakis, S., Samutrtai, P., Cherrie, J.W., Brown, D.M., Tantrakarnapa, K., Johnston, H.J., 2023. In vitro assessment of the pulmonary toxicity of particulate matter emitted during haze events in Chiang Mai, Thailand via investigation of macrophage responses. Environ. Res.: Health 1 (2), 025002. https://doi.org/10.1088/2752-5309/ac9748.

Marx-Stoelting, P., Rivière, G., Luijten, M., Aiello-Holden, K., Bandow, N., Baken, K., Cañas, A., Castano, A., Denys, S., Fillol, C., Herzler, M., Iavicoli, I., Karakitsios, S., Klanova, J., Kolossa-Gehring, M., Koutsodimou, A., Vicente, J.L., Lynch, I., Namorado, S., et al., 2023. A walk in the PARC: developing and implementing 21st century chemical risk assessment in Europe. Arch. Toxicol. 97 (3), 893–908. https://doi.org/10.1007/s00204-022-03435-7.

Meek, M.E., Bette, De Brouwere, K., Szigeti, T., Zastenskaya, I., 2022. A user-friendly tool to assess combined exposures to indoor air pollutants in public spaces of children. Food Chem. Toxicol. 165, 113141 https://doi.org/10.1016/j.fct.2022.113141.

Neale, P.A., Ait-Aissa, S., Brack, W., Creusot, N., Denison, M.S., Deutschmann, B., Hilscherová, K., Hollert, H., Krauss, M., Novák, J., Schulze, T., Seiler, T.-B., Serra, H., Shao, Y., Escher, B.I., 2015. Linking in vitro effects and detected organic micropollutants in surface water using mixture-toxicity modeling. Environ. Sci. Technol. 49 (24), 14614–14624. https://doi.org/10.1021/acs.est.5b04083.

Neale, P.A., Escher, B.I., De Baat, M.L., Dechesne, M., Deere, D.A., Enault, J., Kools, S.A. E., Loret, J.-F., Smeets, P.W.M.H., Leusch, F.D.L., 2022. Effect-based monitoring to integrate the mixture hazards of chemicals into water safety plans. J. Water Health 20 (12), 1721–1732. https://doi.org/10.2166/wh.2022.165.

Neale, P.A., Escher, B.I., De Baat, M.L., Dechesne, M., Dingemans, M.M.L., Enault, J., Pronk, G.J., Smeets, P.W.M.H., Leusch, F.D.L., 2023. Application of effect-based methods to water quality monitoring: answering frequently asked questions by water quality managers, regulators, and policy makers. Environ. Sci. Technol. 57 (15), 6023–6032. https://doi.org/10.1021/acs.est.2c06365.

Neale, P.A., Escher, B.I., De Baat, M.L., Enault, J., Leusch, F.D.L., 2023. Effect-based trigger values are essential for the uptake of effect-based methods in water safety planning. Environ. Toxicol. Chem. 42 (3), 714–726. https://doi.org/10.1002/etc.5544.

Nováková, Z., Novák, J., Kitanovski, Z., Kukučka, P., Smutná, M., Wietzoreck, M., Lammel, G., Hilscherová, K., 2020. Toxic potentials of particulate and gaseous air pollutant mixtures and the role of PAHs and their derivatives. Environ. Int. 139, 105634 https://doi.org/10.1016/j.envint.2020.105634.

Peets, P., Wang, W.-C., MacLeod, M., Breitholtz, M., Martin, J.W., Kruve, A., 2022. MS2Tox machine learning tool for predicting the ecotoxicity of unidentified chemicals in water by nontarget LC-HRMS. Environ. Sci. Technol. 56 (22), 15508–15517. https://doi.org/10.1021/acs.est.2c02536.

Persson, L., Carney Almroth, B.M., Collins, C.D., Cornell, S., De Wit, C.A., Diamond, M.L., Fantke, P., Hassellöv, M., MacLeod, M., Ryberg, M.W., Søgaard Jørgensen, P., Villarrubia-Gómez, P., Wang, Z., Hauschild, M.Z., 2022. Outside the safe operating space of the planetary boundary for novel entities. Environ. Sci. Technol. 56 (3), 1510–1521. https://doi.org/10.1021/acs.est.1c04158.

Pieterse, B., Rijk, I.J.C., Simon, E., van Vugt-Lussenburg, B.M.A., Fokke, B.F.H., van der Wijk, M., Besselink, H., Weber, R., van der Burg, B., 2015. Effect-based assessment of persistent organic pollutant and pesticide dumpsite using mammalian CALUX reporter cell lines. Environ. Sci. Pollut. Control Ser. 22 (19), 14442–14454. https://doi.org/10.1007/s11356-015-4739-5.

Posthuma, L., Van Gils, J., Zijp, M.C., Van De Meent, D., De Zwart, D., 2019. Species sensitivity distributions for use in environmental protection, assessment, and management of aquatic ecosystems for 12 386 chemicals. Environ. Toxicol. Chem. 38 (4), 905–917. https://doi.org/10.1002/etc.4373.

Posthuma, L., Zijp, M.C., De Zwart, D., Van De Meent, D., Globevnik, L., Koprivsek, M., Focks, A., Van Gils, J., Birk, S., 2020. Chemical pollution imposes limitations to the ecological status of European surface waters. Sci. Rep. 10 (1), 14825 https://doi.org/10.1038/s41598-020-71537-2.

Postma, J., Keijzers, R., Slootweg, J., Posthuma, L., 2021. *Toxiciteit van nederlands oppervlaktewater in de jaren 2013-2018* (STOWA-nummer: 2021-43). STOWA.

Prüss-Ustün, A., Wolf, J., Corvalán, C., Neville, T., Bos, R., Neira, M., 2017. Diseases due to unhealthy environments: an updated estimate of the global burden of disease attributable to environmental determinants of health. J. Publ. Health 39 (3), 464–475. https://doi.org/10.1093/pubmed/fdw085.

Ragas, A.M.J., 2019. 1.2. DPSIR. In: Environmental Toxicology, an Open Online Textbook. Vrije Universiteit, Amsterdam. https://maken.wikiwijs.nl/147644/Environmental_Toxicology__an_open_online_textbook#!page-5414986.

RIVM, 2023. *Milieu gezondheids risico indicator (MGR)*. Gezonde leefomgeving. User guide available upon request from. https://www.gezondeleefomgeving.nl/instrumenten/MGR.

Sepman, H., Malm, L., Peets, P., MacLeod, M., Martin, J., Breitholtz, M., Kruve, A., 2023. Bypassing the identification: MS2Quant for concentration estimations of chemicals detected with nontarget LC-HRMS from MS ^{2} data. Anal. Chem. 95 (33), 12329–12338. https://doi.org/10.1021/acs.analchem.3c01744.

Sigmund, G., Ågerstrand, M., Antonelli, A., Backhaus, T., Brodin, T., Diamond, M.L., Erdelen, W.R., Evers, D.C., Hofmann, T., Hueffer, T., Lai, A., Torres, J.P.M., Mueller, L., Perrigo, A.L., Rillig, M.C., Schaeffer, A., Scheringer, M., Schirmer, K., Tlili, A., et al., 2023. Addressing chemical pollution in biodiversity research. Global Change Biol. 29 (12), 3240–3255. https://doi.org/10.1111/gcb.16689.

Spijker, J., Mol, G., Posthuma, L., 2011. Regional ecotoxicological hazards associated with anthropogenic enrichment of heavy metals. Environ. Geochem. Health 33 (4), 409–426. https://doi.org/10.1007/s10653-011-9385-3.

STOWA, 2024. Key Factor Toxicity. Retrieved April 8, from https://www.sleutelfactortoxiciteit.nl/key-factor-toxicity-introduction.

Trasande, L., Zoeller, R.T., Hass, U., Kortenkamp, A., Grandjean, P., Myers, J.P., DiGangi, J., Bellanger, M., Hauser, R., Legler, J., Skakkebaek, N.E., Heindel, J.J., 2015. Estimating burden and disease costs of exposure to endocrine-disrupting chemicals in the European union. J. Clin. Endocrinol. Metabol. 100 (4), 1245–1255. https://doi.org/10.1210/jc.2014-4324.

van Klaveren, J.D., Kruisselbrink, J.W., van der Voet, H., Engel, J., van Voorthuijsen, T., van Lenthe, M.S., de Boer, W.J., Chen, G., van Donkersgoed, G., de Jong, E., 2023. The MCRA platform for EU regulatory actions: governance, user guidance and FAIRification. EFSA Supporting Publications 20 (10). https://doi.org/10.2903/sp.efsa.2023.EN-8251.

van Wezel, A.P., van den Hurk, F., Sjerps, R.M.A., Meijers, E.M., Roex, E.W.M., ter Laak, T.L., 2018. Impact of industrial waste water treatment plants on Dutch surface waters and drinking water sources. Sci. Total Environ. 640–641, 1489–1499. https://doi.org/10.1016/j.scitotenv.2018.05.325.

Vermeulen, R., Schymanski, E.L., Barabási, A.-L., Miller, G.W., 2020. The exposome and health: where chemistry meets biology. Science 367 (6476), 392–396. https://doi.org/10.1126/science.aay3164.

Wang, Z., Walker, G.W., Muir, D.C.G., Nagatani-Yoshida, K., 2020. Toward a global understanding of chemical pollution: a first comprehensive analysis of national and regional chemical inventories. Environ. Sci. Technol. 54 (5), 2575–2584. https://doi.org/10.1021/acs.est.9b06379.