


POLICY BRIEF

Open Access



Improved component-based methods for mixture risk assessment are key to characterize complex chemical pollution in surface waters

Leo Posthuma^{1,2}, Rolf Altenburger^{3,4}, Thomas Backhaus⁵, Andreas Kortenkamp⁶, Christin Müller³, Andreas Focks⁷, Dick de Zwart^{8,9} and Werner Brack^{3,4*} 

Abstract

The present monitoring and assessment of water quality problems fails to characterize the likelihood that complex mixtures of chemicals affect water quality. The European collaborative project SOLUTIONS suggests that this likelihood can be estimated, amongst other methods, with improved component-based methods (CBMs). The use of CBMs is a well-established practice in the WFD, as one of the lines of evidence to evaluate chemical pollution on a per-chemical basis. However, this is currently limited to a pre-selection of 45 and approximately 300 monitored substances (priority substances and river basin-specific pollutants, respectively), of which only a few actually co-occur in relevant concentrations in real-world mixtures. Advanced CBM practices are therefore needed that consider a broader, realistic spectrum of chemicals and thereby improve the assessment of mixture impacts, diagnose the causes of observed impacts and provide more useful water management information. Various CBMs are described and illustrated, often representing improvements of well-established methods. Given the goals of the WFD and expanding on current guidance for risk assessment, these improved CBMs can be applied to predicted or monitored concentrations of chemical pollutants to provide information for management planning. As shown in various examples, the outcomes of the improved CBMs allow for the evaluation of the current likelihood of impacts, of alternative abatement scenarios as well as the expected consequences of future pollution scenarios. The outputs of the improved CBMs are useful to underpin programmes of measures to protect and improve water quality. The combination of CBMs with effect-based methods (EBMs) might be especially powerful to identify as yet underinvestigated emerging pollutants and their importance in a mixture toxicity context. The present paper has been designed as one in a series of policy briefs to support decisions on water quality protection, monitoring, assessment and management under the European Water Framework Directive (WFD).

Challenge

Good water quality is vital for human health and ecosystems. Unfortunately, recent reports show that large numbers of European surface water bodies do not achieve a good status (e.g. [1–5]). Especially the concerns about chemical pollution and observations of an insufficient

ecological status of many water bodies trigger the need for better assessments, protective action against chemical pollution and restoration measures.

The current assessment of chemical pollution under the European Water Framework Directive (WFD, [6]) is insufficient, given that only very few (0.2%) of the more than 145,000 commercially relevant and potentially emitted chemicals are considered in water monitoring and management efforts [2, 7, 8]. Of course, chemical-oriented regulations (such as REACH, [9]) provide an

*Correspondence: werner.brack@ufz.de

³ Helmholtz Centre for Environmental Research UFZ, Permoserstr. 15, 04318 Leipzig, Germany

Full list of author information is available at the end of the article

approach to prospectively assess chemical safety, with a fairly comprehensive coverage of the chemicals in trade, but that does not ascertain that water quality is always fully protected everywhere for all those chemicals. These prospective assessments are based on predicted environmental concentrations combined with component-based methods (CBM) for effect assessment. On a European scale, monitoring and management of surface water quality have so far largely focused on per-chemical evaluations of 45 priority substances (PS) of Europe-wide concern, while approximately 300 chemicals are considered as river basin-specific pollutants (RBSP) across the European basins [2, 7]. Such evaluations consist of a comparison of the measured concentration to a critical concentration (the Environmental Quality Standard, EQS), whereby a per-chemical concentration ratio > 1 is interpreted as water quality problem. The per-chemical assessment is combined with an approach known as the “one out, all out” principle for water quality classification, which implies that a water body fails to reach good chemical or ecological status (for PS and RBSP, respectively) if a single chemical has a concentration higher than its EQS [6, 10, 11]. This principle to characterize chemical pollution is used globally since the second half of the twentieth century and has contributed to prioritize measures to improve the surface water quality for the compounds that were identified as water quality threat with this method. However, contemporary chemical monitoring demonstrates the simultaneous presence of hundreds of potentially hazardous anthropogenic chemicals in the water systems of Europe [12], very few of which are PS or RBSP. The risk assessment of these chemicals, required by the WFD due to potential impacts on human health or aquatic ecosystems and their functions, is hampered by the lack of environmental quality standards.

The science of mixture (eco)toxicology is clear: the chemical cocktails encountered in surface waters cause bigger impacts to the environment and human health than each of its components [13]. These observations imply that the use of individual environmental quality standards (EQS) for selected compounds is insufficient to comprehensively judge protection against chemical pollution and that only a holistic, “mixture aware” assessment provides a sufficiently realistic foundation for water quality protection, monitoring, assessment and management [14]. Consequently, the current situation calls for improved mixture risk assessment methodologies, able to make use of the information collected in contemporary chemical monitoring efforts, to identify the likelihood of ecological impacts, identify drivers of mixture risk, and eventually optimize management. In summary, the challenges are to build forth on the strengths of the current system, but also to improve and expand it with regard to (a) comprehensiveness (more

compounds) and (b) mixture risk assessment (given the monitoring findings). For practical use, the further challenge is to (c) fit the improved methods to the regulatory context (in Europe: the WFD) and (d) to the practical needs of water quality assessment and management professionals.

In the present paper, we describe the expansion of the number of chemicals that can be judged by CBMs. We further provide suggestions on how improved CBMs can be productively used for water quality protection, monitoring, assessment and management, alone or in combination with other lines of evidence, such as outcomes of effect-based methods (EBMs). We illustrate that outcomes of CBM-based assessments can be summarized and communicated in various ways. First, CBMs can be applied to characterize mixture risks for selected biological quality elements (species groups considered in the WFD), because these end points are considered separately in the assessment of ecological status [6, 14], or individual species (including human health). Second, mixture risks can be characterized as mixture toxic pressure for a species assemblage [15], which relates closely to the protection end point of hazard to the aquatic ecosystem utilized in chemical policies. Finally, CBMs can be used to quantify the chemical footprint of the mixtures emitted to and present in an area [16], to summarize whether the water volume of that area is sufficient to dilute the chemicals that are present to a level that poses negligible harm to the aquatic ecosystem. The use of chemical footprinting is in line with the holistic principles of the WFD, which considers water system level threats and solutions, and provides a way to communicate complex results on mixture risks in easy-to-understand trends (e.g. implementation of a programme of measures causes a trend of reducing the chemical footprint of an area). The type of CBM output that is chosen for an assessment depends on the specific question at hand.

Recommendations

- Implement improved component-based methods (CBMs)—presented below—to assess the likelihood of impacts from pollution with complex chemical mixtures.
- Include all chemicals detected in chemical monitoring programmes [12] and/or predicted by integrated production–emission–fate modelling [17] when assessing mixture risks, and not only those substance for which individual EQS values have already been defined.
- Make an informed choice between established CBM approaches to get insights into the likelihood and magnitude of mixture impacts. CBM approaches described in the literature include (1)

the summation of toxic units (TU), (2) the summation of risk quotients (RQs), (3) mixture toxic pressure assessments based on species sensitivity distributions (multi-substance potentially affected fraction of species, msPAF), (4) the comparative use of concentration addition and independent action and (5) pharmacologically based mixture models. The choice among these methods should be driven by the intended outcome of the study, as well as the available data and the resources available for generating missing data.

- Utilize the wealth of the world's ecotoxicity data resources. Bridge gaps in the ecotoxicity data with QSAR and read across data. Initiate programmes to close data gaps, especially for chemicals with high potential exposure (high production and emission volumes, combined with physico-chemical properties that might result in increased concentrations in European water bodies) and high hazard (exceeding baseline toxicity).
 - Align the use of the CBM methods with the protection and impact end points considered under the WFD in the form of the biological quality elements (BQEs: phytoplankton, macrophytes, phytobenthos, benthic invertebrate fauna and fish).
 - Combine the information obtained from CBM with information from effect-based methods (EBMs), ecological studies and in situ tests to identify water bodies at risk of not reaching good ecological status, to quantify impact levels and to identify drivers of the mixture risks [18, 19]. Further investigation should be implemented if a substantial fraction of the impacts observed in the real world cannot be explained by this approach.
- Use CBM based evaluations to explore abatement strategies and/or the expected impacts of future developments in society. Use chemical footprints (derived from CBM results) to summarize and communicate spatial or temporal trends in chemical pollution levels.
 - Ensure that results from chemical monitoring efforts as well as the (eco)toxicological information that is needed for applying CBMs are stored in publicly available European data repositories in a format directly useful for applying CBMs. These data collections need to be quality assured, traceable and transparent. They also need to be set up and maintained with a long-term perspective in mind.
 - Develop specific regulatory guidance on CBMs for mixture toxicity assessment, to support their consensual EU-wide use in addressing the WFD goals of

protecting water quality and reducing the impacts of chemical pollution.

- Apply the improved CBMs in the context of a water system level assessment, given the holistic basis of the WFD.

Several CBMs are available for mixture assessment, sharing common roots but having different data demands and allowing different conclusions to be drawn. It is therefore crucial to make an informed choice among the different CBMs, in view of the available data and resources as well as the specific study question. Reasons for choosing one of the available CBM methods need be worked out and illustrated in specific guidance.

As the implementation of mixture risk assessments in contemporary policies is frequently called for [20] and therefore subject of studies for multiple policy contexts [21], the above recommendations require an appropriate transfer of mixture approaches into the WFD context. That is, assessors should consider that the approaches to mixture assessment and outcome interpretations differ slightly between assessments of effects to species, sub-groups of species (such as the biological quality elements of the WFD) and whole species assemblages. It is recommended to take these differences into account, as they may result in interpretation biases, whilst they also relate to communicating mixture risks.

Species-level assessments

CBMs applied at the level of species are typically based on the classic concept of concentration addition (CA) [22]. CA is also the recommended approach for estimating EQS values for chemical mixtures within the context of the WFD [11]. According to CA, the toxicity of a mixture for a species can be described as the sum of the so-called toxic units (TUs) of all mixture components. Such TUs are simply the ratio of the concentration of a chemical and a defined common (eco) toxicological parameter such as the species' EC50. The validity of summing up TUs for estimating mixture impacts has been repeatedly demonstrated empirically, in an environmental as well as a human health context and for a broad range of bioassays, (eco)toxicological end points and chemicals alike [22, 23]. Although CA is based on the assumption that all components of a mixture share the same mode or mechanism of action, it has been repeatedly shown that the concept also provides useful, but slightly conservative estimates for the effects of mixtures of non-similarly acting chemicals [13]. This is due to the mathematical relationship between the predictions generated by CA and its conceptual counterpart, independent action (IA) [24]. As a

result, CA has been suggested as a generic first tier in mixture risk assessment by various organizations (e.g. [22, 25]). If sufficient mode-of-action information and data are available, the comparative application of CA and IA can be used to improve the quantification of mixture risks and to improve the identification of mixture risk drivers [26].

TU sums extrapolate from single-substance toxicities to the toxicity of a mixture. They do not, however, extrapolate between bioassays, (eco)toxicological end points and species. However, in a risk assessment context, data from different closely related species are sometimes mixed. If different effect levels are used for different mixture components, say EC50 and NOEC values, a systematic effect-level extrapolation needs to be incorporated into the assessment. CA-based mixture assessment using TU sums yield a risk estimate for one particular (group of) species only. To estimate ecosystem-wide acceptable exposure levels, CA therefore needs to be applied for each relevant species group. The TU sum for the most sensitive group of species, together with an appropriate assessment factor, can then be used to calculate an ecosystem-wide protective level of exposure. The REACH regulation [9] and the methods used to evaluate water quality under the WFD [11] both revolve around the risk quotient (RQ), i.e. the ratio between an expected or measured environmental concentration and the maximum concentration still considered safe for the whole ecosystem in a given scenario. The latter is termed PNEC (predicted no effect concentration) under REACH and EQS (environmental quality standard) under the WFD. The PNEC considers only ecotoxicological impacts, while the EQS also acknowledges impacts on human health, via the consumption of drinking water and fish. PNECs and EQS values are based on a suite of (eco)toxicological data. After deriving a threshold concentration for these end points, the EQS value for a compound under the WFD is based on the most sensitive end point (i.e. having lowest threshold concentration). This value is then divided by an assessment factor (AF) to cover a range of uncertainties. The final step is then to derive the RQ value, using the (predicted or measured) exposure concentration and the EQS. An $RQ < 1$ indicates a policy-acceptable level of chemical pollution, while an $RQ > 1$ indicates reason for concern. The latter situation then triggers follow-up measures, either additional testing or the implementation of risk management measures.

Species groups and biological quality elements

The WFD considers various species groups to characterize the ecological status of water bodies (biological quality elements, BQE: phytoplankton, macrophytes,

phytobenthos, benthic invertebrate fauna and fish). Those species groups are called biological quality elements (BQE). RQ sums have been suggested for mixture risk assessment for species assemblages, which applies to the BQEs, in analogy to using TU sums. However, RQ sums have different characteristics, because the underlying EQS or PNEC values for the compounds in a mixture might be based on different species and/or end point (e.g. the EQS for compound A is based on fish as the most sensitive end point, and for compound B based on invertebrates). The final RQ sum might therefore be a result from summing up different kinds of toxicity estimates for different species. Additionally, the EQS or PNECs of the mixture components are often derived using different assessment factors (the summed RQs of compounds A and B can be calculated, but have no ecological interpretation due to a 'summing apples and oranges' effect). Depending on the actual data situation, RQ sums are therefore more difficult to interpret quantitatively [14, 27], except for the fact that they are always equal to or higher than the corresponding TU sums. This still allows using RQ sums as a simple first step to screen for potential ecosystem-wide risks, using only existing PNEC or EQS values. That is: no further action is required if the sum of RQs is below 1. If this is the case, there might be scientific difficulties to explain the meaning of the RQ-value, but there is no doubt about that the mixture exposure requires no further regulatory action. Otherwise, more detailed CA-based assessments should be implemented.

Mixture assessment for the species assemblage level

The RQ methods are applied with the implicit assumption that the concentration–effect curves are straight, and that the sum-RQ represent a quantitative indicator of the magnitude of the mixture risk. However, the concentration–effect curves are not straight, and the sum-RQ can in practice yield very high values, whilst the fraction of species that can be affected is maximally 1. For these reasons, the concept of applying species sensitivity distributions (SSD) and mixture models to derive (mixture) toxic pressures for species assemblages has been proposed [28, 29]. Toxic pressures of chemicals and their mixtures are expressed as potentially affected fraction of species (PAF) or multi-substance PAF (msPAF), with values ranging between 0 and 1. These values are directly relevant for the assessment of impacts, as defined in the WFD-Annex II, where the assessor should evaluate the likelihood (a quantitative concept) of impacts of chemical pollution. Note that the SSD model is also applied to derive environmental quality standards from ecotoxicity test data [11], providing a link between protective assessment goals (and their EQSs) and mixture risk assessment.

Summarizing and communicating mixture risks

It is challenging to summarize and communicate the risk information collected for the current set of chemicals considered (a few hundreds), and for the set of monitoring sites with a management area. The assessments yield vast numbers of data points (# chemicals multiplied by # of sampling sites). Methods have been designed to summarize mixture toxic pressure data in the format of the chemical footprint of mixtures in an area [16]. The chemical footprint primarily communicates whether the amount of water in an area is sufficient to dilute the chemicals emitted to that area to a level at which hazards are negligible. By combining this principle with hydrological knowledge, it is possible to not only quantify the size of the chemical footprint for an area, but also to disentangle the relative contributions of upstream and local emissions to the footprint of a water body, and to characterize the net downstream 'export' of mixture toxicity [17].

Requirements

All CBMs use (eco)toxicity and exposure information on the mixture components to assess the risks of chemical mixtures. CBMs are therefore applied after establishing the presence of chemical pollution with chemical screening methods [12], or after prospectively evaluating expected pollution trends [17, 30] and possible exposure scenarios that result from the implementation of different abatement strategies [17, 31].

CBM-based mixture risk assessments are only as accurate as the underlying information on the individual substances. Reliable, publicly available information on the (eco)toxicity of the chemicals potentially occurring in the European environment is therefore crucial. This includes commercially relevant chemicals as well as non-intentionally produced substances such as combustion products and transformation products. Although regulatory repositories, such as the collection of REACH dossiers at ECHA (<https://echa.europa.eu/information-on-chemicals>, visited May 20, 2019), provide important information, various data collections lack traceability, their contents can change without that being tracked and/or include only a subset of the relevant chemicals. Additional efforts are therefore required to establish a long-term EU-wide repository of (eco)toxicological information for potentially relevant chemicals.

Exposure information is equally crucial for reliable CBM-based mixture risk estimates, which is discussed in detail in accompanying policy briefs [12, 17, 32]. Compiling and documenting the data from existing and future chemical monitoring efforts in a European repository would allow to identify pollution trends as well as the typical mixtures to which particular environments or humans are exposed. The IPCHEM data portal that

was recently established by the EU Commission's Joint Research Centre (<https://ipchem.jrc.ec.europa.eu/RDSIdiscovery/ipchem/index.html>) might well develop into such an urgently needed repository on chemical pollution of the European environment.

Pragmatic decisions for data bridging are often needed when applying CBM-based methods, given that consistent data sets are almost never available in a risk assessment context. Given the complexity of the resulting assessments and the number of possible choices for data handling and selecting the various assessment approaches, a thorough and transparent documentation of all input data and the data handling pipeline is crucial. Also, a critical reflection of the overall assessment uncertainty and its explanatory power is needed for each study.

Furthermore, integrating the improved and more comprehensive and mixture impact-oriented CBM assessments into both diagnosis (WFD Annex II) and/or surveillance, operational and investigative monitoring for water quality management requires:

- Recognition that water quality problems caused by the societal use of chemicals in principle encompasses the whole 'universe of chemicals' which can be emitted in a significant quantity to a water body, and are thus of societal and regulatory concern.
- Acceptance that novel approaches are essential for problem-defined and solution-focused approaches to handling the chemical pollution problem, which is to be addressed as a mixture problem.
- Recognition that CBMs can be used for evaluation of both the WFD protection (EQS) and impact assessment needs (ecological status) by utilizing quantitative CBM outputs, which can consist of correctly derived and interpreted risk quotients and/or mixture toxic pressures.
- Recognition that the ecotoxicity data that are needed for a comprehensive mixture risk assessment with CBMs require an extension of the data set that are currently adopted for deriving the EQSs for the regulated compounds.
- Guidance on the use of the CBMs for different purposes and the different formats (for species, for biological quality elements, for whole species assemblages) and on the derivation of management plans on the basis of a correct interpretation of CBM-based results.

Achievements

The SOLUTIONS project has developed and tested the scientific basis for these recommendations, and provides tools and services to utilize them [33].

Collation and curation of ecotoxicity data to apply CBM

The application of CBMs requires predicted or measured concentrations of chemicals and ecotoxicity data. Exposure data can be obtained from monitoring (e.g. according to WFD-prescribed approaches) or from modelling (e.g. [17]). We produced a curated set of ecotoxicity data (ecotoxicity test data and read-across data) to enable application of CBMs for a wide array of chemicals [15]. The database contains more than 250,000 raw data records—covering a suite of tested compounds and tested species—which can be used for the mixture assessment purposes described below. In daily practice, water quality assessors commonly use ‘digested’ data, derived from such raw data records. At present, it is not feasible to publish this database, due to the fact that it contains a subset of REACH study results that are in part proprietary (see <https://iuclid6.echa.europa.eu/reach-study-results>, accessed August 13, 2019). The combined data could, however, be used for research when, e.g. median effect data are used. Such uses are described below. Note that the European Chemicals Agency and data owners continue to improve accessibility of the REACH study results, which would change the availability of the raw data set.

Utilizing the data for mixture assessments

The curated data set [15] can be used to derive per-chemical risk quotients (RQ), and thereupon to derive indications regarding the WFD objective of protection against chemical pollution effects.¹ As discussed above, RQ results that are simply based on the ratio of the concentration and the EQS may have no meaningful ecological interpretation towards the type and magnitude of risk of the exposure if $\Sigma RQ > 1$. To address the complexities of interpreting RQ and ΣRQ to evaluate the WFD goals of protection and ecological impact magnitudes, we developed and applied innovative methods, by stepwise removal of causes of interpretation bias [34]. According to this tiered system, the assessor starts with available exposure and effect threshold data (either EQSs, or NORMAN-based PNECs), to evaluate whether $\Sigma RQ < 1$. If so, the assessment can stop, because the mixture risk

for the measured compounds implies sufficient protection. If the lowest-tier results in $\Sigma RQ > 1$, the assessor obtains improved mixture risk information by (stepwise) removing unjustified assumptions. Details are explained in [34]. Applied to a series of sites, the approach allows for ranking the expected magnitude of impacts of the mixtures at the sites, so as to help prioritizing measures. Various case studies (see below) were executed with these improved CBM approaches. Note that a Europe-wide study on chemical pollution was made by Malaj et al. [4], whereby these authors derived the exposure-to-effect quotients for ambient concentrations in European waters to the effect end points of three selected species (LC50 or EC50s for an algal, an invertebrate and a fish species). The results of this assessment showed that ambient (measured) concentrations exceeded the impact end points of those species to different degrees. This provides evidence for the conclusion that organic chemicals likely affect those species if they would be exposed to those water bodies, for individual chemicals. In comparison to an EQS-based assessment in which the RQ is directly derived from the exposure/EQS ratio, this interpretation is straightforward, and not potentially biased by the interpretation problems of the EQS-based mixture assessment methods [34].

Assessment of toxic pressures of chemicals and their mixtures for species assemblages

To predict the fraction of species affected by mixtures, SOLUTIONS made expansions and improvements regarding the use of species sensitivity distributions (SSDs) in impact assessment, closely aligned with the WFD-Annex II obligation to assess “the likelihood of impacts”. The collated ecotoxicity database (see above) allowed for deriving SSDs for more than 12,000 compounds. The use of SSDs as the CBM method results in the derivation of toxic pressures (per chemical) or mixture toxic pressures (for mixtures), expressed as (multi-substance) potentially affected fraction of species [29]. The research team utilized an expert user modelling pipeline to apply the SSD-based CBM, as described in a project deliverable [35]. An associated (Dutch) project constructed a software tool for Dutch water boards (accessible via <https://www.stowa.nl/publicaties/ecologische-sleutelfactor-toxiciteit-hoofdrapport-deelrapporten-en-rekentools>, “Tool Chemiespoor”; in Dutch). This CBM approach was used in case studies, for example to derive insights into the spatial variation of the (multi-substance) potentially affected fraction of species (msPAF) resulting from modelled mixture exposure concentrations across European surface waters [15] and from measured concentration in Dutch surface waters

¹ Note that the NORMAN network simultaneously collated and curated ecotoxicity data from various resources, to derive provisional predicted no effect concentrations (PNECs) that can serve the WFD environmental protection goal (<https://www.norman-network.com/nds/ecotox/>). NORMAN derived ‘lowest PNEC’ values for the freshwater compartment for about 40,000 compounds (with a ‘verified status’ as determined via voting by NORMAN experts for over 1000 compounds; website visited: April 29, 2019). The ‘lowest PNEC’, similar to the EQS of the WFD, is derived for the water matrix based on data for various end points (human health, secondary poisoning and direct impacts), and converted to ‘lowest PNEC’ based on expert judgement and data quality-driven application factors.

[36]. In the European case study, the model was used to characterize whether mixture exposures are likely to cause insufficient protection, which is based on re-use of the so-called '95%-protection criterion' (defined as PAF-NOEC < 0.05) for mixtures (as msPAF-NOEC < 0.05). The model was also used to provide a quantitative metric that is empirically associated with species loss (msPAF-EC50). The derivation of the toxic pressure of chemical pollution utilizes the model used for deriving EQSs in its inverse form [9, 11], implying conceptual consistency between deriving EQSs and toxic pressures. The mixture toxic pressure metric PAF-NOEC relates to the WFD environmental objective of protection, whilst the msPAF-EC50 metric empirically relates to impacts on the ecological status [37]. Mixtures matter for ecological status. According to these findings, assessors can use (measured or predicted) concentrations of chemicals in a mixture in combination with the pertinent SSDs and mixture models [15] to derive mixture toxic pressures. Applied to a series of sites allows for ranking the expected magnitude of impacts of the mixtures at the sites, so as to help prioritizing measures.

Case studies: prioritization of mixture-impacted sites and of chemicals in mixtures

The case study results provide evidence for the applicability of the improved CBMs and the utility of their outcomes for prevention, ranking of mixture impacts across sites and identification of drivers of mixture risks (including currently not considered chemicals) and management.

European and national scale

Applied to predicted environmental concentrations for more than 22,000 water bodies situated across Europe, these studies suggested that a large fraction of European surface waters are insufficiently protected against adverse effects of chemical emissions, and that the expected impact magnitude of contemporary pollution (expressed as msPAF-NOEC and msPAF-EC50) varies widely across water bodies [35, 38]. These across-site risk ranking results are in line with the aforementioned assessments of Malaj et al. [4] and results of Kortenkamp et al. [14]. These CBM-based results show that chemical pollution is a stress factor that threatens water quality across Europe, with different expected impact magnitudes across water bodies, and suggesting an important role of mixtures of components that are currently not considered. Moreover, the results presented not only a clear ranking of sites regarding mixture risks, but also the relative dominance of some chemicals in causing that (see also the subsequent example). The derivation of mixture toxic pressures (and the ranking of sites and compounds) is

a straightforward assessment which is geared towards large-scale data analyses for water system level analyses. It has therefore not only been applied to predicted exposures, but also to (Dutch) national monitoring data. This yielded national water quality assessment outcomes for mixtures (site and compound ranking), despite differences in sets of monitored chemicals between different water boards [36].

Basin and water body scale

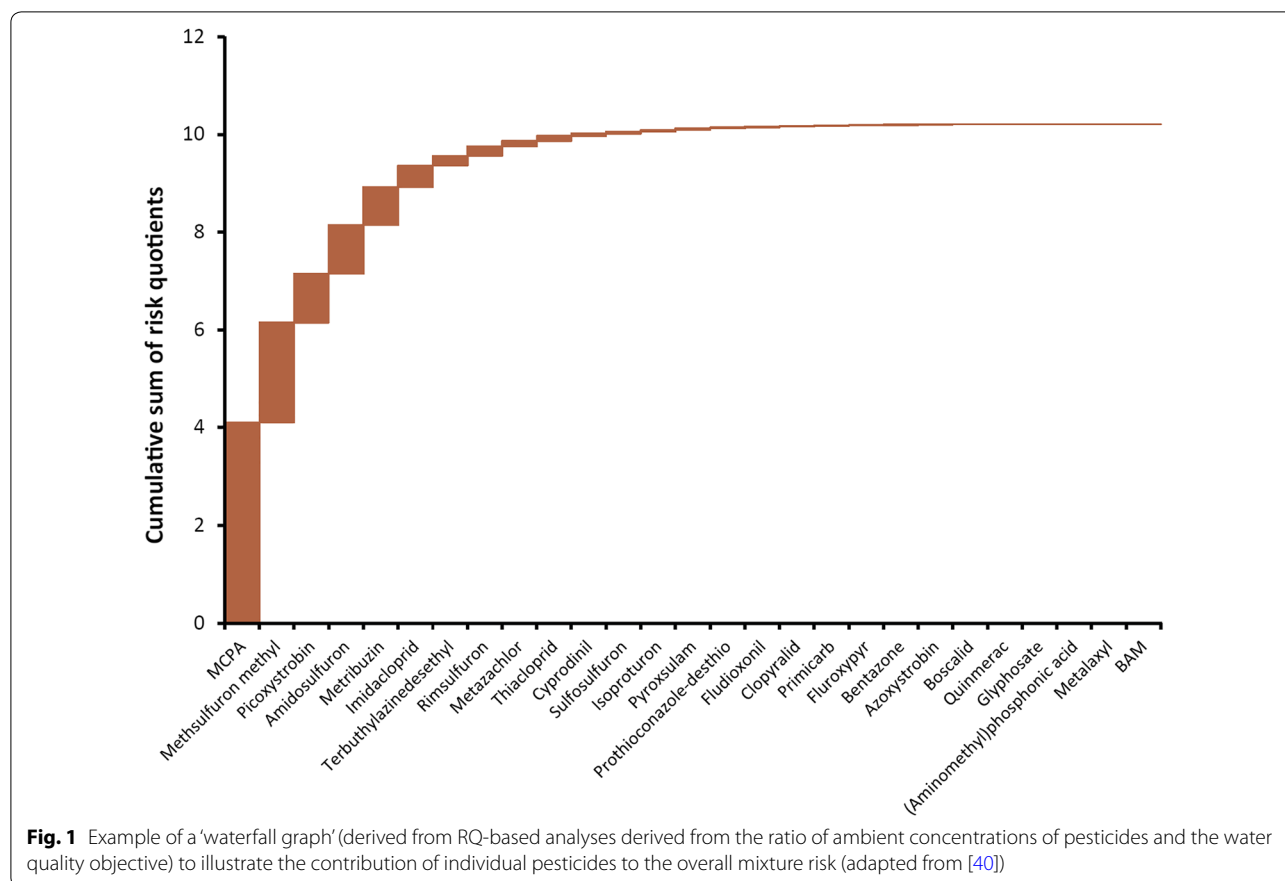
Various studies considered mixture risks for water bodies and basins based on measured concentrations. Munz et al. [39] identified CBM-based mixture toxicity differences between sites up- and downstream of wastewater treatment plants, and were able to identify drivers of mixture toxicity. Gustavsson et al. [40, 41] also showed a relative dominance, now for pesticides in Swedish streams and of monitored substances in coastal waters. These authors communicated those results via so-called 'waterfall graphs', to communicate that some chemical are 'drivers of impacts' (Fig. 1).

Massei et al. [42] identified mixture risks and drivers for mixtures of pesticides and biocides measured in surface waters of seven large European river mouths. Lindim et al. [43] studied pharmaceutical mixtures in Swedish freshwaters, and also identified key drivers of mixture toxicity. Finally, based on reviews of typically emitted compounds from different land uses, Posthuma et al. [44] simulated the mixture risks of those, providing evidence for different land uses being drivers of mixture 'signatures', again with some compounds dominating mixture risks. That is, different land uses cause vastly different packages of emitted chemicals, and vastly different temporal emission and exposure patterns.

Case study implications

All these case studies show that the systematic application of CBM approaches vastly improves the current practice of evaluating chemical pollution in the context of the WFD, in which a limited number of pre-defined priority compounds are assessed one by one. In fact, all the SOLUTIONS case studies flagged chemicals that are not on the WFD list of priority substances or on the corresponding lists of river basin-specific pollutants as mixture risk drivers in various European aquatic ecosystems. Extension of the consideration of a wider array of chemicals is warranted, as all chemicals may threaten the ecological status because all have the potential to cause that (given the observations collated in the ecotoxicity database).

It was further shown that mixture risks were often driven by only a few compounds, with the dominant compounds showing strong spatiotemporal variations.



Although this, at first sight, could mean that water quality management could focus on a new fixed list of prioritized compounds—those identified as dominant via the CBM analyses—this is not the logical conclusion to be drawn. Every assessment scale (a defined area, with its emissions and hydrological characteristics) will result in its own rank order of sites and chemicals. We are already used to the fact that different scales result in different priority lists, when going from the European scale (the current 45 priority substances) to the river basin scale (currently approximately 300 river basin-specific pollutants, summed over the EU basins). A further step in downscaling would similarly result in different lists of dominant chemicals for different areas. This process can be followed down till the local water body scale. There only one specific chemical might dominate (e.g. one pesticide in a field ditch), whilst it may be far from dominant for the larger surrounding area (if the pesticide is not used there). Hence, there is always dominance of some chemicals in ambient mixtures, but the dominating chemicals vary among water bodies and over time. The latter follows from dominance changes due to, e.g. pesticide use. The WFD environmental goal of good ecological status may not be reached due to any chemical.

Therefore, the WFD text defines pollution as the chemicals (no restriction) that pose a risk to maintaining or reaching the good status (Article 4, and the associated WFD-Common Implementation Strategy (CIS) Document #3, [45]). It appears that the consideration of potentially all chemicals has been lost in practice since the CIS document. Assessors should consider all chemicals and their mixtures, and can apply the improved CBMs to do so. Scale-dependent identification of dominant chemicals provides the chance to identify effective management steps per certain scale of activities.

Anticipating the effects for future emission scenarios and mitigation measures

CBMs can be used to explore foreseeable water quality changes based on future emission scenarios and to predict or retrospectively evaluate abatement success. The former was shown by Van Gils et al. [38]. Exploratory modelling of alternative chemical management scenarios showed a surprising effectivity of a focus on the most hazardous compounds, as identified in chemical safety assessment policies. The latter was also shown by Gustavsson et al. [40]. CBMs can be utilized, therefore, in the context of the solution-focused risk assessment

paradigm, which asks for evaluating alternative management or chemical substitution scenarios. CBMs also fit well into the WFD assessment and management cycle [46], as temporal trends in pollution levels can be evaluated. The application of the approach also demonstrated that the risks and relative importance of various compound groups in relation to land use and waste water treatment plants varied [39]. Application to ‘think tank’ scenarios on future pollution, and evaluation of alternative abatement scenarios, was productive in that it showed which chemical groups and which focus in selecting abatement strategies would reduce predicted impact magnitudes most [30]. These examples also underline how monitoring data (WFD-Annex V) analysed with the CBMs can help to evaluate water quality status and trends. The solution-focused risk assessment approach implies that assessors explore the ‘solution space’ to define optional risk reduction scenarios [31]. Assessors depend on using the CBMs to evaluate mixture risks under the selected management options (as effect-based methods cannot be applied to expected concentrations), provided that there is a method to predict future concentrations. At present, such a method is available for the European scale [17], and work is in progress to develop a similar model for the Netherlands. For local cases, assessors may use available hydrological information to predict expected concentrations of alternative solution scenarios.

Summarizing and communicating results on complex mixtures

SOLUTIONS developed methods to summarize and communicate complex results. For sites, the relative importance of chemicals was suggested to be communicated as ‘waterfall graphs’, Fig. 1 [40, 41]. For the water system level analyses of chemical pollution, SOLUTIONS developed chemical footprints [16]. Aligned with the SOLUTIONS integrated Model Train, the footprinting allows summarizing local mixture toxic pressure, its origins (whether or not sources upstream contribute to local mixture stress) and its downstream impacts (evaluating effects elsewhere, caused by water flows). Regarding abatement, such summaries are key to assess whether abatement should focus on upstream sources of pollution, on local chemical emissions or on effects of downstream (sensitive) protection end points, or on combinations of these approaches. Currently available results have so far been used to illustrate how this approach operates and what type of results can be obtained [17]. The available EU-wide model can be used to derive these footprint results for selected areas and water bodies.

Lessons for improved chemical assessments

The use of CBMs in the case studies clearly emphasized the need for sufficiently sensitive chemical analytical procedures. Ideally, the level of quantification (LoQ) should be around 1/100th of the EQS, or, more realistically, the LoQ should at least approximate the single-substance EQS. SOLUTIONS developed and tested the Kaplan–Meier estimation method to handle compounds with insufficiently high LoQs [47]. Also, the expansion beyond the approximate 300 priority substances and river basin-specific pollutants requires additional hazard data. Repositories on hazard data (such as those of REACH, NORMAN, or the SOLUTIONS curated database of effect data) can be used as a source of such data for the CBM applications, provided that various key aspects are considered. Those are—at minimum—that ecotoxicity data used for a CBM could represent outdoor exposure conditions, and that data used have a transparent and reproducible origin [15, 47]. The consequences of neglecting proper management and choice of (eco) toxicity data are large, as presented in the report of Arle et al. [7]. These authors reported an array of EQS values for RBSP across European basins, whereby the minimum and maximum EQS values for one-third of the listed substances differed up to 10-fold from each other across countries, and more than half (53%) of all the substances differ by more than 10-fold and up to 10⁵-fold from each other. This relates in part to the use of different assessment factors for deriving EQSs.

In general, the practical experiences from the case studies clearly emphasize that the ecotoxicity data repositories that form the basis for all CBM-based methods require substantial improvements in transparency, traceability, consistency and, last but not least, data quality.

The need for the use of improved CBMs

The current use of CBMs has two impacts on water quality assessment practices that negatively affect the likelihood of reaching the WFD environmental goals. This is caused by the fact that the indicator system sensitively reacts to extra chemicals becoming monitored and is at the same time highly insensitive to water quality improvements that occur upon abatement investments. These act as ‘hidden triggers’ that counteract reaching the WFD environmental objectives, as the first makes the assessor reluctant to add compounds to a monitoring plan and the second makes the assessor reluctant to invest in abatement as improvements remain hidden. The use of only two classes for chemicals (an exposure concentration is classified as either lower or higher than the EQS) is the root cause of this practical problem. The proposed improved CBM methods [14, 15, 34] provide refined insights into chemical

pollution, required to inform managers on the needs to take protective or restorative management action. The quantitative insights provided by the improved CBMs deliver key insights for management prioritization and planning. The SOLUTIONS case studies showed this and how the use of the improved CBMs substantially—and the resulting ranking of mixture risks among sites and compounds—refines the information for water management prioritization and planning. Examples of the improved efficacy of refined CBM approaches outside SOLUTIONS have started with a landscape-level ‘one pesticide’ assessment for water bodies across the USA in 1996 [48]. Today, such assessments have expanded to mixtures and they are currently in the stage of gaining global appreciation (examples listed in [15]).

Abbreviations

AF: application factor; AS: assessment factor; BQE: biological quality elements; CA: concentration addition; CBM: component-based method; EBM: effect-based method; EC50: effect concentration related to an effect of 50% on a selected end point; ECHA: European Chemicals Agency; EQS: environmental quality standards; LoQ: Level of quantification; msPAF: multi-substance potentially affected fraction of species; NOEC: no observed effect concentration; PNEC: predicted no effect concentration; PS: priority substances; QSAR: quantitative structure activity relationships; RBSP: river basin-specific pollutants; REACH: Registration, Evaluation, and Authorization of Chemicals; RQ: risk quotient; SPR: Strategic Program RIVM; SSD: species sensitivity distributions; TU: toxic unit; WFD: Water Framework Directive.

Acknowledgements

This article has been prepared as an outcome of the projects SOLUTIONS (European Union's Seventh Framework Programme for research, technological development and demonstration under Grant Agreement No. 603437), with further support of the Strategic Program RIVM (SPR) as run under the auspices of the director-general of RIVM and RIVM's scientific advisory board and the University of Gothenburg's FRAM centre for Future Risk Assessment and Management Strategies.

Authors' contributions

LP, TB and WB conceptualized and drafted the manuscript. The other authors helped to further elaborate the manuscript and contributed specific aspects. All authors read and approved the final manuscript.

Funding

Not applicable.

Availability of data and materials

Not applicable; the presented information is based on previously published data only.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Author details

¹ RIVM, National Institute for Public Health and the Environment, P.O. Box 1, 3720 BA Bilthoven, The Netherlands. ² Department of Environmental Science, Radboud University, Nijmegen, The Netherlands. ³ Helmholtz Centre

for Environmental Research UFZ, Permoserstr. 15, 04318 Leipzig, Germany.

⁴ Department of Ecosystem Analysis, Institute for Environmental Research, ABBt-Aachen Biology, Aachen, Germany. ⁵ University of Gothenburg, Carl Skottsbergs Gata 22B, 40530 Gothenburg, Sweden. ⁶ Institute of Environment, Health and Societies, Brunel University, Uxbridge UB8 3PH, UK. ⁷ Wageningen Environmental Research, P.O. Box 47, 6700 AA Wageningen, The Netherlands. ⁸ Mermayde, Groet, The Netherlands. ⁹ DDZ-ecotox, Odijk, The Netherlands.

Received: 7 June 2019 Accepted: 16 August 2019

Published online: 30 September 2019

References

1. EEA (2012) European waters—assessment of status and pressures. EEA Report No 8/2012. EEA, Denmark, Copenhagen
2. EEA (2018) European waters—assessment of status and pressures. EEA Report No 7/2018. EEA, Copenhagen
3. Casado J et al (2019) Screening of pesticides and veterinary drugs in small streams in the European Union by liquid chromatography high resolution mass spectrometry. *Sci Total Environ* 670:1204–1225
4. Malaj E et al (2014) Organic chemicals jeopardize the health of freshwater ecosystems on the continental scale. *Proc Natl Acad Sci* 111(26):9549–9554
5. Schäfer RB et al (2016) Contribution of organic toxicants to multiple stress in river ecosystems. *Freshw Biol* 61:2116–2128
6. EC (2000) Directive 2000/60/EC of the European parliament and of the council of 23 October 2000 establishing a framework for Community action in the field of water policy. *Off J Eur Commun L* 2000(327):1–72
7. Arle J, Mohaupt V, Kirst I (2016) Monitoring of surface waters in Germany under the water framework directive—a review of approaches, methods and results. *Water* 8(6):217
8. ECHA (2019) <https://echa.europa.eu/information-on-chemicals/cl-inventory-database>. Accessed 8 Aug 2019
9. EC Regulation (EC) (2006) No 1907/2006 of the European Parliament and of the Council of 18 December 2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH). European Commission, Brussels
10. EC (2005) Overall approach to the classification of Ecological Status and Ecological Potential. Guidance Document No 13 of the Common Implementation Strategy for the Water Framework Directive. Office for Official Publications of the European Communities, Luxembourg
11. EC (2011) Common implementation strategy for the Water framework Directive (2000/60/EC)—Guidance Document No. 27—Technical guidance for deriving environmental quality standards. Brussel
12. Brack W et al (2019) High-resolution mass spectrometry to complement monitoring and track emerging chemicals and pollution trends in European water resources. *Environ Sci Eur*. <https://doi.org/10.1186/s12302-019-0230-0>
13. Kortenkamp A, Backhaus T, Faust M (2009) State of the art report on mixture toxicity. EC, Directorate General for the Environment
14. Kortenkamp A et al (2019) Mixture risks threaten water quality: The European Collaborative Project SOLUTIONS recommends changes to the WFD and better coordination across all pieces of European chemicals legislation to improve protection from exposure of the aquatic environment to multiple pollutants. *Environ Sci Eur*. <https://doi.org/10.1186/s12302-019-0245-6>
15. Posthuma L et al (2019) Species sensitivity distributions for use in environmental protection, assessment, and management of aquatic ecosystems for 12386 chemicals. *Environ Toxicol Chem*. 38(4):905–917
16. Zijp MC, Posthuma L, Van de Meent D (2014) Definition and applications of a versatile chemical pollution footprint methodology. *Environ Sci Technol* 48:10588–10597
17. Van Gils J et al (2019) The European Collaborative Project SOLUTIONS developed models to provide diagnostic and prognostic capacity and fill data gaps for chemicals of emerging concern. *Environ Sci Eur*. <https://doi.org/10.1186/s12302-019-0248-3>
18. Brack W et al (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* 31:10

19. Backhaus T et al. Assessing the ecological impact of chemical pollution on aquatic ecosystems requires the systematic exploration and evaluation of four lines of evidence. *Environ Sci Eur* (in press)
20. Kortenkamp A, Faust M (2018) Regulate to reduce chemical mixture risk. *Science* 361(6399):224–226
21. Bopp SK et al (2018) Current EU research activities on combined exposure to multiple chemicals. *Environ Int* 120:544–562
22. OECD (2018) Considerations for Assessing the risks of combined exposure to multiple chemicals, series on testing and assessment no. 296, Environment, Health and Safety Division, Environment Directorate
23. Bopp SK et al (2016) Review of case studies on the human and environmental risk assessment of chemical mixtures. EUR 27968 EN. <https://doi.org/10.2788/272583>
24. Drescher K, Bodeker W (1995) Assessment of the combined effects of substances—the relationship between concentration addition and independent action. *Biometrics* 51:716–730
25. EFSA Scientific Committee 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):5634. <https://doi.org/10.2903/j.efsa.2019.5634>
26. Faust M et al (2019) Prioritisation of water pollutants: the EU Project SOLUTIONS proposes a methodological framework for the integration of mixture risks into prioritisation procedures under the European Water Framework Directive. *Environ Sci Eur*. <https://doi.org/10.1186/s12302-019-0239-4>
27. Backhaus T, Faust M (2012) Predictive environmental risk assessment of chemical mixtures: a conceptual framework. *Environ Sci Technol* 46(5):2564–2573
28. Posthuma L, Suter GWI, Traas TP (2002) Species sensitivity distributions in ecotoxicology. CRC-Press, Boca Raton, p 616
29. De Zwart D, Posthuma L (2005) Complex mixture toxicity for single and multiple species: proposed methodologies. *Environ Toxicol Chem* 24(10):2665–2676
30. Bunke D et al (2019) Developments in society and implications for emerging pollutants in the aquatic environment. *Environ Sci Eur* 31:32
31. Posthuma L et al (2019) Exploring the 'solution space' is key. SOLUTIONS recommends an early-stage assessment of options to protect and restore water quality regarding chemical pollution. *Environ Sci Eur*. <https://doi.org/10.1186/s12302-019-0253-6>
32. Slobodnik J et al (2019) Establish data infrastructure to compile and exchange environmental screening data on a European scale. *Environ Sci Eur*. <https://doi.org/10.1186/s12302-019-0237-6>
33. Kramer K et al (2019) The RiBaTox web tool: selecting methods to assess and manage the diverse problem of chemical pollution in surface waters. *Environ Sci Eur*. <https://doi.org/10.1186/s12302-019-0244-7>
34. Kortenkamp A et al (2018) Common assessment framework for HRA and ERA higher tier assessments including fish and drinking water and multi-species ERA via SSD, population-level ERA via IBM and food web vulnerability ERA. SOLUTIONS Deliverable D18.1
35. Van Gils J et al (2018) SOLUTIONS Deliverable D14.1. Modelling framework and model-based assessment for substance screening. Deltares; Leipzig
36. Posthuma L et al (2016) Water System analysis with the ecological key factor "Toxicity". Part 1: The approach, its underpinning and its utility. STOWA; Amersfoort
37. Posthuma L et al (2019) Mixtures of chemicals are important drivers of impacts on ecological status in European surface waters. *Environ Sci Eur*. <https://doi.org/10.1186/s12302-019-0247-4>
38. Van Gils J et al (2018) SOLUTIONS D14.2 Europe wide modelling and simulations of emerging pollutants risk including think tank scenarios. Leipzig
39. Munz NA et al (2017) Pesticides drive risk of micropollutants in wastewater-impacted streams during low flow conditions. *Water Res* 110:366–377
40. Gustavsson M et al (2017) Pesticide mixtures in the Swedish streams: environmental risks, contributions of individual compounds and consequences of single-substance oriented risk mitigation. *Sci Total Environ* 598:973–983
41. Gustavsson MB et al (2017) Chemical monitoring of Swedish coastal waters indicates common exceedances of environmental thresholds, both for individual substances as well as their mixtures. *Peer J Preprints* 5:e2894v1. <https://doi.org/10.7287/peerj.preprints.2894v1>
42. Massei R et al (2018) Screening of pesticide and biocide patterns as risk drivers in sediments of major European river mouths: ubiquitous or river basin-specific contamination? *Environ Sci Technol* 52(4):2251–2260
43. Lindim C et al (2019) Exposure and ecotoxicological risk assessment of mixtures of top prescribed pharmaceuticals in Swedish freshwaters. *Chemosphere* 220:344–352
44. Posthuma L et al (2018) Prospective mixture risk assessment and management prioritizations for river catchments with diverse land uses. *Environ Toxicol Chem* 37(3):715–728
45. EC (2003) Common Implementation Strategy for the Water Framework Directive (2000/60/EC). Guidance Document No. 3. Analysis of Pressures and Impacts. EC, CIS-Working Group 2.1—IMPRESS, Brussels
46. Posthuma L et al (2019) A holistic approach is key to protect water quality and monitor, assess and manage chemical pollution of European surface waters. *Environ Sci Eur*. <https://doi.org/10.1186/s12302-019-0243-8>
47. Gustavsson MB, Hellohf A, Backhaus T (2017) Evaluating the environmental hazard of industrial chemicals from data collected during the REACH registration process. *Sci Total Environ* 586:658–665
48. Solomon KR et al (1996) Ecological risk assessment of atrazine in North American surface waters. *Environ Toxicol Chem* 15:31–76

Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Submit your manuscript to a SpringerOpen® journal and benefit from:

- Convenient online submission
- Rigorous peer review
- Open access: articles freely available online
- High visibility within the field
- Retaining the copyright to your article

Submit your next manuscript at ► [springeropen.com](https://www.springeropen.com)
