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Regulatory and practical considerations on the implementation of a mixture allocation factor in REACH

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Abstract

There is indisputable evidence that the environment, humans and wildlife are continuously exposed not to single but to multiple chemicals from different sources. Exposure to these mixtures can lead to combined risks not yet sufficiently addressed in any of the European chemical legislations. Under the REACH regulation for industrial chemicals, specific environmental mixture assessments are challenged by a lack of data on toxicity, use and exposures and the communication of data along the supply chain. Within the Chemicals Strategy for Sustainability the European Commission proposed to introduce (a) mixture allocation factor(s) (MAF) as regulatory management tool to reduce exposures, effects and potential risks of unintentional mixtures. The MAF is proposed to be applied as default value within the chemical safety assessments undertaken by companies under REACH. Here, we critically review the relevant literature discussing the conceptual background of the MAF and approaches to derive its magnitude. The analysis focuses on the environment and key issues for an implementation in regulatory practise together with remaining uncertainties and needs for possible ways forward. At this stage introducing a MAF in REACH Annex I appears the most pragmatic and immediately implementable measure to address risks from unintentional mixtures in the environment. A so-called $MAF_{ceiling}$ appears as the preferred option of policy makers, since it would only affect relevant substances close to their respective risk threshold. While the magnitude of a MAF will be decided politically, the choice of methods and assumptions to derive its size should be clear and transparent, build on the available scientific evidence and take account for uncertainties. A MAF will be most effective reducing environmental releases and exposure levels if risk mitigation measures are implemented in practise. Its socioeconomic impacts and costs need to be assessed in a balanced way together with the benefits for the environment, society, and for companies—also in comparison to the efforts needed for specific mixture risk assessments. In the future and with the experiences gathered in practise, a discussion is needed on how to assess and regulate unintentional mixtures across different pieces of chemicals legislation to consider the true exposure situation and ensure harmonisation.

Keywords Co-exposure, Mixture risk assessment, Risk management measures, Unintentional mixtures, MAF

Introduction

The increasing rate of production and releases of larger volumes and higher numbers of novel entities with diverse modes of action and complex exposure profiles increase potential risks to the environment and exceed the societies' ability to guarantee, assess and monitor their safe use [1]. In Europe, there are currently more than 23.000 industrial chemicals being produced, used and imported at volumes > 1 ton per year which are

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registered and regulated under Regulation (EC) No. 1907/2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) [2]. These figures do neither include polymers (for which no registration is needed under REACH) nor transformation products. Thus, the actual number of chemicals linked to industrial activities that are potentially emitted to the environment is much larger. For instance, there is an infinite number of possible combinations of the estimated 350.000 anthropogenic chemicals that are registered globally for production and use [3] and abiotic and biotic transformation products co-occurring in the environment. Even more, this figure is expected to continuously increase [4]. According to Persson et al. [1], since the 1950s, the production of chemicals has surged by 50 times, with projections suggesting that it will triple by 2050 in comparison with 2010 levels.

Due to the wide use of chemicals and as proven by numerous scientific monitoring studies, the environment, humans and wildlife are continuously exposed not to single but to multiple chemicals from different sources and via different routes, both simultaneously and in sequence e.g., [5–10]. This extend of co-exposure has profound yet only rudimentarily understood consequences for living organisms, ecosystems and biodiversity [11]. Complex mixtures of chemicals (see Infobox of Fig. 1) can cause joint "combination effects" even if the predicted single substances' effects or risks are below the regulatory accepted "safe" thresholds (i.e., Risk Characterization Ratio below 1 [5, 12–15] (see also next chapter).

Still, European chemicals regulation is largely focused on single substances [14, 16, 17]. Specifically, REACH does neither contain explicit requirements to address combined exposures of intentional chemical mixtures (e.g., [9, 18, 19]), nor addresses the risks of unintentional chemical mixtures [20]. The assessment of unintentional mixtures is so far limited to specific legislative sectors where the mixture under consideration can be well-defined, such as under the regulation (EC) No. 396/2005 on pesticide residues in food [15].

The European Commission in 2020 acknowledged the above-mentioned deficiencies in assessment and management practices to tackle unintentional mixtures, as part of the Chemicals Strategy for Sustainability. Specifically, the European Commission announced (i) to assess how to best introduce in REACH (a) mixture allocation factor(s) (MAF, also called mixture assessment factor) for the chemical safety assessment of substances; and (ii) to introduce or reinforce provisions to take account of the combination effects in other relevant legislation [4].

Several approaches, assumptions and algorithms for calculating a MAF have been suggested in the literature and are scrutinized in the chapter "Review of methods applied to derive the size of a MAF". In principle, the MAF is a predefined fixed factor to adjust the risk characterization ratio. It is currently proposed as introducing a new "ceiling", by reducing the risk characterization ratio of 1 (Infobox 2 of Fig. 2) as regulatory accepted safe use via a MAF to 1/MAF (i.e., RCR < 1/MAF) [21]. In other words, it is the maximum fraction of the risk characterization ratio of each chemical that is still acceptable to occur in a mixture, without the sum of all risk quotients exceeding 1. This would ensure a level of protection that is similar to the level of protection aimed for during the assessment of an individual chemical [22] but considering the co-occurrence and combined effects with other substances. Thus, the MAF approach is a risk management tool, because it aims at lowering the concentrations permitted under an environmental standard to protect against combined toxicities of chemicals [23]. This critical review analyses the central aspects to be considered around the proposal for an introduction of a so-called "mixture allocation/assessment factor" within REACH in the Chemicals Strategy for Sustainability from a regulatory perspective. Due to the complexity of the topic and the expertise of the authors, the present paper has a clear focus on mixtures in the environment and REACH. The needs for particular improvements to account for aggregated environmental exposures of single substances and intentional mixtures under REACH have been discussed in other publications and are not considered here e.g., [19, 24, 25].

Infobox 1 – Intentional and unintentional mixtures

Intentional mixtures occur when chemicals are combined for a specific purpose and use, e.g. in formulations such as paints or varnishes. The composition of intentional mixtures is known at least to the formulating manufacturer.

Unintentional mixtures occur when chemicals are released jointly (e.g. from wastewater treatment plants) and co-occur in environmental media (e.g. rivers) or biota (incl. humans). Their composition is unknown and complex.

[1)] pictogram from https://thenounproject.com

Fig. 1 Information on terminology regarding intentional and unintentional mixtures

Infobox 2 – Regulatory threshold

In the legal framework of REACH, the regulatory threshold for a chemical is presented as risk characterization ratio of an individual chemical "i" (RCR_i). It is the ratio of the predicted environmental concentration (PEC) of a chemical and its predicted no effect concentration (PNEC).

$RCR_i > 1$ indicates an unacceptable risk from a specific use of a chemical for an environmental compartment.

The PEC is estimated for each environmental release category of a chemical during its life cycle via calculations based on defined generic assumptions and information on use and emission patterns (e.g. for its dilution in the receiving water, or its degradation in sewage treatment plant).

The PNEC is derived from ecotoxicological tests of the chemical with surrogate species that represent different environmental compartments (water, air, soil) and trophic levels. Assessment factors (AFs) are applied to the endpoint value of the ecotoxicological test (e.g. EC_{50}) – depending on data availability – to mirror the degree of uncertainty regarding the transfer of results from single species tests to whole ecosystems. Test requirements are dependent on the production volumes, i.e. the amount of a chemical manufactured or imported per year.

Fig. 2 Information on the risk characterisation ratio (RCR) and accepted threshold for the registration of chemicals under REACH in order to demonstrate safe use (derived for each environmental compartment and use category)

First, we shortly provide the conceptual and historical background on the needs and challenges as well as methodologies for the assessment and regulation of unintentional mixtures in the environment under REACH. The subsequent main chapters provide scientific analyses of the aspects which were identified as central around the regulatory implementation of a MAF. In a final outlook future developments and needs are discussed in a broader context.

For this analysis, a non-systematic and non-exhaustive literature research was conducted to cover recent scientific publications together with available documents and workshop reports to also cover recent proposals and discussions on the topic from the different stakeholders involved (Academia, industry organisations, non-governmental organisations, member state authorities, European agencies and the European Commission). The analyses are further based on considerations and experiences from the regulatory practise in the context of the REACH regulation as well as former research projects on behalf of the German Environment Agency (UBA).

Why a MAF is needed

There is a wealth of monitoring studies that analysed surface waters, wastewater treatment plant effluents, marine and freshwater or biota with targeted chemical screening approaches revealing the co-occurrence of up to 2000 chemicals as mixtures in the environment (e.g., [26, 27]). At the same time, there is clear evidence from laboratory studies that even if all chemicals in a mixture are present at concentrations that do not cause adverse effects, i.e., that do not exceed their individual No Observed Effect Concentrations (NOECs), the mixture might still cause significant toxicity (e.g., [14, 28–31). Additionally, several studies describe mixture risks for the environment from real exposure situations through a combination of measured or modelled concentrations of chemicals with the respective toxicity data (e.g., [7, 9, 32–36]).

For instance, Malaj et al. [34] showed a strong relation of declining ecological status with increasing chemical risks in fish and invertebrates by analysing 223 chemical substances across 4000 European monitoring sites. Similarly, Posthuma et al. [36] demonstrated highly variable mixture risks at European scale and that chemical pollution acted as limiting factor for the ecological status of surface waters. Lemm et al. [18] linked the intensity of seven stressors to recently measured ecological status data for more than 50,000 sub-catchment units covering almost 80% of Europe's surface area. The key conclusion was that chemical mixtures explained 26% of the deviance in ecological status of all European river types. Rorije et al. [9] described cumulative environmental risk assessment results for European fresh water ecosystems, based on chemical surface water monitoring data (1998–2016). Mixture risk characterization ratio's larger than 1 were found for 39% of the place–time combinations across Europe. Furthermore, Finckh et al. [26]

investigated more than 600 chemicals in 445 surface water samples to characterize their chemical footprints (defined as the risk that chemicals or chemical mixtures have adverse effects on a specific group of organisms). This revealed that three quarters of the investigated sites in 22 European river basins exceed established thresholds for chemical footprints in freshwater, leading to expected acute or chronic impacts on aquatic organisms. All the aforementioned studies demonstrate that usually a vast number of chemicals co-occur in the environment as real-life mixtures which cause a significant toxicity. This in turn may negatively affect populations and ecosystems and thus chemical stress may contribute to biodiversity loss next to other drivers, such as climate change and habitat destruction [37, 38].

To predict effects from chemical mixtures, component-based methodologies have been proposed such as Concentration Addition (CA) and Independent Action (IA). These methods assess the overall mixture toxicity on the basis of the known toxicities for the individual components (i.e., substances) at their respective concentrations ([19] and references therein). Both the World Health Organization (WHO) and the European Food Safety Authority (EFSA) accept the principle of CA as the default assumption to predict mixture effects [39, 40]. However, such component-based approaches are only applicable to mixtures with known composition. Yet, mixture compositions in the environment continuously change in time and space, which hinders the reliable prediction of exposure levels even with highly sophisticated models given also the multitude of potential sources and emission pathways. Despite recent ambitions of the European Commission and the responsible European agencies to improve data quality and availability, data on toxicity of individual compounds is currently often lacking or incomplete under REACH and cannot be adequately complemented through modelling approaches. Several studies showed that robust (eco)toxicity and exposure data are still lacking for the majority of REACH registered substances, which impedes to set safe human and environmental exposure limits [2, 41–45]. Furthermore, even when data exist, they are often not fully available or are restricted to specific groups of end users. For example, only a fraction of modelled exposure data under REACH are publicly disseminated, limiting their use among actors and also beyond REACH [41, 46].

Given these challenges, generic approaches such as the introduction of a MAF as a risk management tool can provide a pragmatic and feasible solution. Yet, some concerns have been raised, that a generic approach may be an oversimplification leading to overregulation. For human health assessment more specific mixture assessment tools are proposed e.g., [47, 48]. Indeed, in certain cases specific assessments and regulatory measure could be taken by responsible regulatory authorities for a defined mixture, as also pointed out by Hassold et al. [20] with respect to environmental assessments. However, it seems impossible to apply specific mixture assessments in most cases since highly complex unintentional mixtures of hundreds of chemicals, many of which are toxicologically ill characterized, occur in constantly changing combinations [28]. In addition, under REACH—different to other European chemical regulations—individual companies (i.e., the registrants) are responsible for the prospective safety assessment of the chemicals they intent to bring to the market. Yet, it is unlikely that individual companies will be able to conduct specific mixture risk assessments on a default basis, because they lack knowledge which compounds co-occur as a matter of principle. This is because, they usually process only toxicity, generic use and exposure data on their own substance they register but have no information on other compounds or even specific uses and fate of their chemicals across the entire life cycle. Furthermore, even if data on composition of mixtures, exposure levels and their hazards were known, specific mixture risk assessment approaches would currently not be technically feasible at the level of chemical safety assessment due to the different responsibilities of the various actors involved in the supply chain [19, 20, 24].

The implementation of a MAF with a fixed default value into the chemical safety assessment in REACH would be a pragmatic first step to reduce chemical pressure on the environment through risks from chemical mixtures. The MAF would be implementable in the current logic of REACH registrations and chemical safety assessments. It would recognise that substances (1) unintentionally co-occur, (2) evoke joint effects, and that therefore, (3) environmental risks arising from mixtures need to be tackled and managed by regulation. This would increase the level of protection for the environment against yet underestimated and unrecognised joint effects through combined exposure of chemicals. However, specific assessments (e.g., component based mixture risk assessment) of additional mixture risks for defined scenarios could still be applied in cases where sufficient information (i.e., data on exposure and environmental toxicity) is available as part of the regulatory risk management processes.

Background on the conceptual development of a MAF

Discussions on a MAF with a fixed default value to be set a priori date back to activities in human health assessment in the 70s [49–51], followed by more specific expert reports commissioned by the Dutch National Institute for Public Health and the Environment (RIVM), [52], the Swedish Chemicals Agency (KEMI) and the

Swedish government, respectively [15, 22, 53, 54]. Five major EU research projects (HBM4EU,[1] SOLUTIONS,[2] EDC-MixRisk,[3] EU-ToxRisk[4] and EuroMix[5]), several experts from academia, as well as some nongovernmental organizations (NGOs) further supported the MAF as a tangible step forward [2, 33, 55]. Industry organisations provided positions and analyses conducted on behalf of the European Chemical Industry Council (CEFIC) on the expected impacts of a MAF for companies [56].

In its Chemical Strategy for Sustainability (CSS), the European Commission proposed to introduce (a) MAF(s) specifically into REACH Annex I to address risks of unintentional mixtures during the company's chemical safety assessment of single substance [4]. Accompanying this proposal and in order to substantiate the impact assessment for the CSS, the European Commission contracted a comprehensive study to a consortium (Wood, Ramboll, IOM, University of Gothenburg, European Chemicals Agency (ECHA) and Eurometeaux), including several stakeholder workshops in November 2021 and April 2022 (with participants from the European Commission, ECHA, government representatives, industry and NGOs). The following processes and discussions between stakeholders were summarized, for example, by Spaniol [57] and Backhaus [58]. Generic results of the work on behalf of the European Commission were presented at subsequent REACH meetings of the Competent Authorities for REACH and CLP (e.g., CARACAL 42 in 11/2021 to CARACAL 48 in 03/2023) or became available with a redacted version of an impact assessment.[6] There seems to be a consensus between stakeholders that the implementation of the MAF as $MAF_{ceiling}$ (for details see next chapter) is the preferred and most proportionate approach. A $MAF_{ceiling}$ would target risk driving substances with a risk characterization ratio (RCR) close to 1 most. However, details on the scientific analyses on behalf of the European Commission have not been published so far. The legislative proposal for a MAF was expected as so-called delegated act (including further consultations of member states) but still in the context of the REACH Revision, for which the time plan was postponed in 2023.

[1] https://www.hbm4eu.eu/.

[2] https://www.solutions-project.eu/.

[3] https://edcmixrisk.ki.se/.

[4] http://www.eu-toxrisk.eu/.

[5] https://www.euromixproject.eu/.

[6] https://www.corporateeurope.org/en/2023/07/out-reach Date of access: 20.09.2023.

Review of methods applied to derive the size of a MAF

There are two fundamentally different concepts for a MAF (MAF_{factor} or $MAF_{ceiling}$) discussed in the available literature. Backhaus et al. [53] proposed a MAF with its size based on the number (n) of components in a real or assumed mixture that contribute to the same endpoint. The authors suggest to apply the MAF as a constant factor to the risk characterization ration (RCR) in a way that every RCR derived for a use is divided by this factor in order to meet the safe use paradigm of $RCR < 1$. This would imply consequences for the chemical safety assessment and reduce the accepted RCR of every single substance, independently of whether it is close to the accepted threshold of $RCR < 1$ or not.

Broekhuizen et al. [52] described a different approach which moved away from the idea of a MAF dividing the RCR of every substance but instead suggested using the MAF to adapt the accepted safe use paradigm of $RCR < 1$ by generating a new "ceiling" for the $RCR_{MAF} < \frac{1}{MAF}$ under the assumption that substances co-occur and have to share the available risk space—also referred to as risk cup e.g., [15, 22]. This "ceiling" approach has gained more acceptance as a potential risk management tool for unintentional mixtures as it would automatically impact relevant substances that are contributing to risks (i.e., exceeding the RCR_{MAF}), but not those with individual RCR_i far below 1.

Backhaus [28] further elaborated on these different MAF-approaches and suggested the terms MAF_{factor} for the initial approach Backhaus et al. [53] and $MAF_{ceiling}$ for the approach outlined by Broekhuizen et al. [52]. He outlines an iterative procedure to derive a $MAF_{ceiling}$ for a given dataset calculating mixture risks of the known components with CA. The calculation only considers substances risk contributions with a maximum of 1 in order to exclude risks due to single substance exceedances and focuses on the combined exposures and effects below regulatory thresholds. The author, therefore, suggests the term MAF_{exact} for this procedure. More reflections on the conceptual background of a MAF and a brief summary of options to address risks of chemical mixtures can also be found in [58].

Price and Junghans [23] reviewed the approach described in [22, 28] and conclude, that it is "a significant improvement" compared to other MAF approaches, because it is a "risk-based approach" which only addresses the substances contributing most to the mixture risk. However, they criticise the dependence of the calculated MAF_{exact} value on the number of substances in a mixture and the assumption that all chemicals in a mixture are at $RCR_i = 1$ through single substance risk management. Subsequently, the

authors suggest a simplified calculation method and present three slightly different $MAF_{ceiling}$ approaches which yield lower MAF values. The main differences, compared to Backhaus [22] and Backhaus [28] are different assumptions about how single substance risk management lowers the RCR_i of substances to $RCR_i < 1$ in the respective mixture.

In addition to the approaches outlined above, CEFIC proposes to use the maximum cumulative ratio (MCR) as method to derive the size of a MAF [59]. The MCR was originally introduced by Könemann [60] as part of a tool for the determination of the type of joint action of a chemical mixture in fish (i.e., to which degree the toxicity can be described via CA). Price and Han [61] suggested to use the MCR as a measure to quantify the magnitude of the toxicity that is underestimated if no cumulative risk assessment is performed. It allows to evaluate whether the toxicity from exposure to multiple chemicals is relevant for a cumulative mixture risk assessment of several substances contributing (rather equally) in lower concentrations or a single-substance risk assessment of one to few substances that drive the mixture toxicity, so-called risk drivers. More generally speaking, the MCR can be seen as means of prioritisation to assess whether the toxicity of a mixture can be attributed to one or a few chemicals (i.e., the risk drivers) in the mixture (MCR values close to 1) or is equally distributed among all chemicals in the mixture (MCR values close to n, n = number of chemicals in the mixture) and if a mixture risk assessment is required. However, it is not a measure to estimate mixture risks.

In this context it is helpful to consider that exposure to multiple chemicals does not imply a risk per se [61–63]. However, in order to investigate the appropriate size of a MAF, there is a need to be able to identify to which extent the environment is exposed to chemical mixtures and subject to risks from combined effects. Thus, any method capable of identifying the mixture risks, including the MCR, is generally considered applicable to estimate the size of a MAF. Therefore, we conclude that the different methods outlined above are all generally suitable to derive the size of a MAF. The methods could also be used in combination in a weight of evidence approach taking into account the different assumptions and uncertainties behind the methods and building on the available monitoring and modelling data (see section below). Approaching the MAF by different methods could be valuable as regard to increasing scientific confidence in the final result of setting the size of a MAF by expert judgement.

Case studies to estimate mixture risks and a MAF

There are two approaches to characterize the occurrence of chemicals in the environment: prospectively via co-exposure modelling and retrospectively via chemical monitoring of biota or environmental media. Both approaches are data-driven but use different types of data. Prospective co-exposure modelling assesses the probability of co-occurrence of different chemicals at a given site in a given time frame, and estimates the concentrations and concentration ratios of the components of the expected mixture in the environment from data on their use (e.g., tonnages registered under REACH) and data characterizing their fate and distribution in the environment e.g., [6]. Retrospective monitoring studies investigate combined exposures that result from past or ongoing uses or releases of chemicals in the environment by applying various chemical analysis of environmental samples.

The European Commission applied different case studies to estimate environmental mixture risks and derive the potential size of a MAF based on risks resulting from the co-exposure to chemicals (as presented at various stakeholder workshops and documented in Wood E&IS GmbH [21]). While it is considered useful to apply different retrospective and prospective case studies to derive the size of a MAF, it is important to acknowledge the differences between these and their impacts on the resulting MAF size. The main characteristics of the case studies, used by the European Commission, are summarized in Table 1.

The studies differ, e.g., in terms of number of compounds and types of samples analysed or modelled, sources of hazard values for the risk assessment, type of chemical analysis and respective sensitivities, or time scales and regions covered. Both, the quality and type of data the assessment is based upon has large impact on the estimated size of the MAF. For instance, MAF values derived from these different case studies differ by several orders of magnitude (2–500) (see, e.g., [65] as well as discussions held at the online stakeholder workshop in April 2022).

In addition, more recent state-of-the-art methods such as non-target screening (NTS), which have been developed to detect thousands of different chemicals in a sample by their exact molecular mass, cannot capture all chemicals present in one sample since the definite assignment of molecular structures to chemical identities remains a difficult task [15]. Thus, even the best available chemical monitoring techniques cover only a relatively small fraction of the tens of thousands of man-made chemicals in daily use, not to mention the unknown number of associated transformation products in the environment. Consequently, it is neither possible nor economically feasible to adequately

Table 1 Main characteristics of environmental monitoring and modelling studies applied by the Europen Commission as a basis to assess the size of a MAF

	Type of data	No. of compounds	Region	Matrix	Sources of hazard values	Reference
Deltares exposure modelling study	Exposure modelling	1785	All major EU river basins	Surface water	Chronic species sensitivity distribution (SSD) HC_{50} from Posthuma et al. [64]	van Gils et al. [7],van Gils et al. [6]
UK environment agency compilation of monitoring data	Chemical monitoring data	1144	UK	Surface water, groundwater, precipitation, marine water	Water Framework Directive EQSs, NORMAN Network PNECs and chronic SSD HC_{50} from Posthuma et al. [64]	Spurgeon et al. [27]
River Erft sampling campaign	Chemical monitoring data	153	Western part of Germany	Surface water	UBA ETOX, US EPA ECOTOX, ECHA information on chemicals, Pesticides Properties Database	Markert et al. [35]

characterize the entire chemical burden in the environment and risks arising thereof. At present using a combination of modelling and chemical monitoring studies (as done, for example, by [7]) seems, therefore, the most pragmatic and suitable way forward.

Range of proposed MAF values

Several studies and reports analysed environmental and human monitoring data in order to estimate mixture risks or a suitable MAF size or at least the minimum values required to meet the current safe use paradigm of RCR < 1 with different mathematical approaches e.g., [22, 27, 52, 54, 66]. For the environment, the proposed magnitude of a MAF ranges from 3 [65] over 10 [9, 52] to 100 [55] and even 700 [22]. Broekhuizen et al. [52] concluded on the basis of a Dutch freshwater-monitoring data set that a MAF of 10 might be sufficiently protective and reported that typically only 5 to 10 chemicals dominate the overall mixture risk. Similarly, Spurgeon et al. [27] and Rodea-Palomares et al. [66] showed, that environmental "real-world" mixtures were indeed dominated by only a few mixture risk drivers. Rorije et al. [9] indicated that a relatively low fractional reduction of environmental concentrations by an effective MAF of 10 could increase the percentage of sites that are sufficiently protected against risks from unintentional mixtures. This was also supported by earlier analyses by Backhaus and Ericson [54]. However, limitations in the data sets which were not designed specifically for mixture risk assessments did not allow to derive the magnitude of a MAF with high confidence and mixture risks may be underestimated. Again, the challenge of the large spatial temporal variability of "real-life" exposures indicates that the MAF cannot reflect every single scenario and is—as a generic risk management tool—subject to generalisation.

In another approach data from an exposure modelling study Posthuma et al. [67] who derived toxicity thresholds for 12,386 chemicals based on hazard concentrations (HC_{05}) values from species sensitivity distributions (SSDs). HC_{05} values describe the maximum concentration that is not hazardous for more than 5% of the potentially exposed species. Van Gils et al. [7] used the data in order to characterise the "real life" mixture exposure situation of surface waters at European scale. The results of this exercise were subsequently used as a case study to estimate MAF sizes as presented by Backhaus at a stakeholder workshop in April 2022. Based on this case study, MAF_{exact} values between 175 and 573 would be needed to lower the RCR_{MAF} to exactly 1 for the median of all samples from this case study ($MAF_{exact} = 175$), or the 95th percentile of all samples, respectively ($MAF_{exact} = 573$) [21].

Compared to MAF values based on monitoring studies, the estimation of MAF values derived from modelling usually yields higher values. This can be attributed to the fact that the exposure modelling study by Posthuma et al. [67] considers a larger number of substances per mixture (median: 1785 substances) and aims at addressing a European wide scale in comparison with the more local monitoring studies (median: 2–104) (as presented at the above mentioned workshop). Another, probably less relevant, aspect for the estimation of higher MAF values is the accuracy of the exposure modelling. While validation of the models applied by van Gils et al. [7] showed that they "were accurate on average" (error within one and two

orders of magnitude for 65% and 95% of the substance/basin combinations, respectively) the authors also stated that "concentrations of […] REACH registered chemicals were generally overpredicted".

Accounting for uncertainties

It is clear that at this stage, that the size of the MAF also needs to account for uncertainties not covered in standard environmental risk assessment. These uncertainties are namely (1) the variability of the derived MAF values related to different methods and assumptions behind, and (2) the extrapolation from modelling or monitoring based assessments to "real-world" conditions which can never reflect reality in all its dimensions (e.g., due to spatial and temporal changes of exposure patterns, see previous section) [7].

In single substance assessments the regulatory reference values (PNECs or environmental quality standards (EQS)) for terrestrial and aquatic organisms are derived by means of NOEC or similar toxicity indicators (EC_X) and an assessment factor to account for multiple sources of uncertainties and for limited data sets. These assessment factors should account for inter- and intraspecies, acute-to-chronic, lowest- to no-observed-effect concentration, and laboratory-to-field extrapolation [68], OECD [69], ECHA [70], ECHA [71], ECHA [72]. Depending on the set of data available, the assessment factors to be applied can range from 1000 (when only one short-term toxicity study in algae, daphnia and fish is available) to 1 (if species sensitivity distribution method to derive the PNEC is applied). As a counter-argument against the implementation of a MAF, it is often claimed these established assessment factors used in single substance assessment are overly protective ([15] and references therein). In contrast to the widespread assumption, however, such factors do not account for simultaneous exposures to many chemicals and joint toxicities [51]. Accordingly, it was already suggested in the early 1970s to consider possible mixture effects in humans with an overall default assessment factor of 100, dividing it into two sub-factors of 10, each accounting for either intra- or interspecies variability [49, 50]. Thus, the idea of protecting against effects of mixtures in chemical risk assessment is not new but was not further developed by academia or regulators for several decades. Not the purported intrinsic conservativeness of assessment factors but the complexity of the mixture risk assessment issue and a lack of data were chosen as justifications for discounting mixture effects [51]. One should bear in mind that the selection of the magnitude and type of assessment factor to use (i.e., how large a margin of safety is needed) is primarily a policy and not only a science-based decision, because definitive data frequently are insufficient for making accurate extrapolations from known to unknown circumstances (e.g., extrapolating toxicity thresholds among various species or different exposure durations [51, 68].

The size of the MAF to be applied in REACH will finally be decided politically. To account for the above-mentioned uncertainties either the magnitude of the MAF could be increased or an extra assessment factor could be added (as suggested by the European Commission). The latter appears inconsistent with the initial idea that the MAF per se constitutes a risk management tool and not an assessment factor and the assumption that the magnitude should be derived on the basis of multiple lines of evidences (calculation methodology, data sets used, effectivity in light of adjustment options and reflection of uncertainties).

Adjustment options during chemical safety assessment

Applying a MAF by default both during the chemical safety assessment within each new registration process but also during dossier updates for all chemicals already registered could generally have three risk management implications [28]:

(1) No further action is needed by the registrant if the RCR of the chemical is < 1/MAF.
(2) If RCR > 1/MAF further exposure and/or hazard data can be provided by the registrants to refine the environmental risk assessment which may lead, e.g., to a reduction of the assessment factors during hazard assessment or refinement of the PEC with further information or assumptions and thereby a reduction of the RCR of the respective chemical. For instance, if chronic toxicity data are provided for three trophic levels instead of acute data of only one trophic level, the assessment factor can be lowered from 1000 to 10 [70]. Introducing a MAF would consequently lead to improved quality and better compliance of the environmental risk assessment in the REACH dossiers, which could be regarded as a "co-benefit", but which would not reduce actual emissions and exposure levels of chemicals.
(3) If RCR > 1/MAF is based on a large set of exposure and toxicity information that cannot be further refined, specific risk management measures need to be implemented to ensure that the risks are actually reduced. For the downstream user using chemicals during a particular stage of their life cycle (e.g., in the production of mixtures, materials or articles), there are adequate measures that can be taken to effectively reduce emissions. Such additional measures are, e.g., adoption of risk mitigation measures at manufacturing or processing sites, lowering allowed

production volumes, or withdrawal of certain uses or registrations. These measures intend to result in reduced emissions of substances and thereby their exposure and related effects on the various environmental organisms. Consequently, such measures should reduce the likelihood of these substances contributing to unintentional mixture risks, which is clearly in line with the safe use paradigm of REACH. However, it is important to bear in mind that such risk mitigation measures have to be applied along the supply chain and thus communication among actors is crucial in order to make such measures effective.

Improving access to and quality of data for better mixture assessment

To improve mixture risk assessment, to better quantifying the real chemical pressure from mixtures on the environment in Europe, to perform specific mixture risk assessments for defined scenarios, and to size the MAF in a scientifically sound manner in the near future, better monitoring data as well as data on exposure and hazards are needed. An improved access to data could be first achieved by a centralized European data infrastructure, which allows compilation, open-access and exchange of chemical monitoring data of substances across different regulatory areas as well as related regulatory information such as regulatory status, tonnages produced/marketed and uses [73]. Second, the data basis on (eco) toxicity and other hazardous properties need to be improved and transparently available to different actors while respecting confidential business information (CBI) via central data platforms such as the ECHA database.[7] The CSS also highlights this need and the European Commission considers a similar approach as outlined above with the ongoing work on the "one substance, one assessment" approach [4, 74]. It is planned to establish a common data platform and introduce a one-stop shop' access to data on chemicals held by the EU agencies and the European Commission. This includes data on hazards, physico-chemical properties, presence in the environment, emissions, uses, environmental sustainability of chemical substances and information on ongoing regulatory processes [74]. It is also planned to populate this data base with systematic collection of human biomonitoring and environmental monitoring data generated. In this context it would be also helpful to store raw target and non-target screening data converted into a common (open) format to allow for 'on demand' access to retrospective data analysis [73, 75]. Furthermore, such a data base should be designed in a way that results of novel methodologies relevant for mixture risk assessment can be stored. These include effected based in vitro tests and effect directed analysis [76], as well as new approach methodologies for chemical hazard characterization [77, 78]. Concluding, such an European data platform could substantially improve access to and amount and quality of data relevant for mixture risk assessment. Finally, clear terminology and revision of methodologies as regard to mixture risk assessment practices in ECHA guidance would help companies to generate more reliable data according to quality criteria to be set.

Limitation of a MAF to certain tonnages

Data requirements for the registration of substances under REACH differ depending on the annual tonnage that is to be registered. In order to omit publishing their actual production volumes and thus to protect CBI, registrants register their substances in different tonnage bands (1–10 t/a, 10–100 t/a, 100–1000 t/a and > 1000 t/a). The data requirements for the tonnage bands are laid down in REACH Annexes VII–X. Generally speaking, the data that has to be provided for the registration increases with increasing tonnage, i.e., more comprehensive tests have to be performed for substances registered with higher tonnages. The general assumption is, that the likelihood of environmental or human exposure increases with the chemicals amount used, thus more information on the hazard is needed to adequately estimate the risk of the respective chemical. In the process of developing proposals for the introduction of a MAF it was discussed at different stages to adhere to this concept and apply the MAF only to substances registered above a certain tonnage band, because these are assumed to contribute mostly to mixture risks due to their higher exposure potential.

However, it needs to be considered that environmental risks due to co-occurrences and combined effects may occur for all substances and are rather dependant on their potential of being released to the environment, on hazardous properties, and on risk management measures in place. Assuming lower mixture risks for lower tonnage substances is an oversimplification that fails to fully recognise these aspects from a scientific point of view. As has been shown by numerous studies, co-occurrence of chemicals even at low concentrations can lead to increased risks for adverse effects in the environment (see chapter "Why a MAF is needed" for details).

A simple analysis of the REACH registered substances database[8] shows, that limiting the MAF, for example, to substances registered > 1000 t/a would exclude a large fraction of potentially relevant substances. Around 66% (4974) of all substances with a chemical safety assessment and a full & active registration under REACH (7526) are

[7] https://echa.europa.eu/information-on-chemicals.

[8] https://echa.europa.eu/web/guest/information-on-chemicals/registered-substances (date of access 24.05.2023).

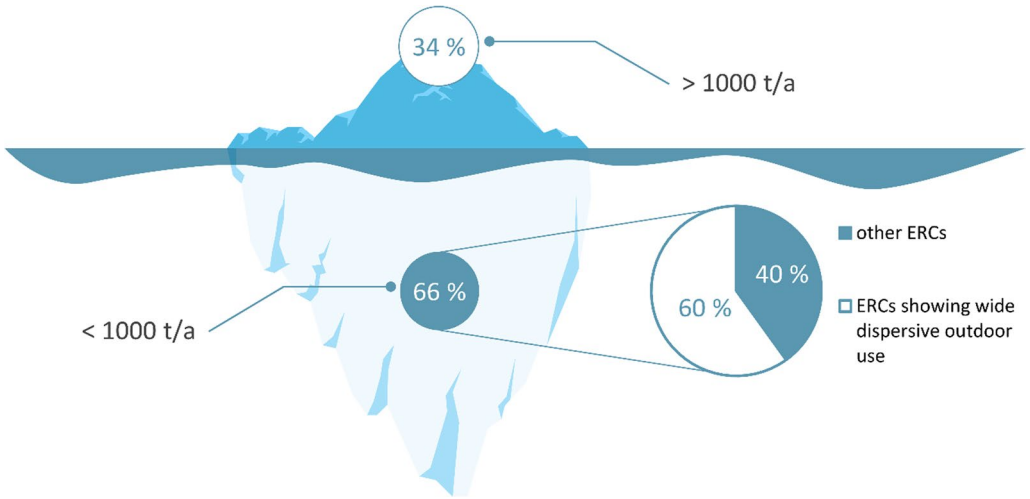

Fig. 3 Numerical fraction of all chemicals with full and active registration under REACH that are registered with > 1000 t/a (34%) and < 1000 t/a (66%) and the fraction of chemicals thereof that are registered with environmental release categories (ERCs) that indicate a high potential of emissions to the environment due to indicated wide dispersive outdoor uses (ERCs 8d, 8e, 8f, 9b, 10a, 10b). 66% (4974) of all substances with a chemical safety assessment (7526) are registered in tonnage bands < 1000 t/a. Among these 60% (2981) are registered with environmentally relevant ERCs. We considered only the substances with chemical safety assessment and a full & active registration in the analysis

registered in the < 1000 t/a tonnage bands. Sixty per cent (2981) of these substances (or 40% of all substances with chemical safety assessment and a full & active registration) are registered with environmental release categories (ERCs) that contain wide dispersive outdoor uses and thus have a high potential of being released to the environment (ERCs 8d, 8e, 8f, 9b, 10a, 10b, see Fig. 3). One could also argue that all substances registered with any of the ERCs (4907 or 99% of all substances registered in the < 1000 t/a tonnage band) are relevant to the environment since also emissions from point sources to the environment (e.g., from manufacture) contribute to the overall chemical burden of the environment (Fig. 3).

Considering the above, it could be argued from a perspective strictly looking at an improved level of protection for the environment not to limit the application of a MAF to substances registered above a certain tonnage band, because it could potentially mitigate positive effects of the MAF. If the MAF is implemented in Annex I as part of the risk characterisation procedure, it could by default apply to all substances for which an RCR is provided (usually this covers all substances with chemical safety assessment, i.e., those registered at ≥ 10 t/a with documentation of safe use for hazardous substances). As a $MAF_{ceiling}$—which seems to be the preferred option of policy makers and stakeholders—would only affect substances close to an RCR of 1, it would "automatically" affect the relevant substances and uses.

Arguments in favour of limiting the application of a MAF to a subset of substances could be to minimize the additional workload and related costs to registrants as well as overall costs for society (e.g., due to substances and their functions not being available any more). Indeed, implementing a MAF under REACH, that applies to all registered substances for which an RCR is provided, would mean that the environmental risk assessment in every REACH registration dossier where an RCR was calculated would need to be re-evaluated. Reducing workload and related costs to registrants could also be achieved with a stepwise implementation of a MAF according to tonnage bands, as was done for registration deadlines when REACH was first introduced. This could also give affected registrants the time needed to adjust to the MAF and thus reduce their overall costs as well as those for society.

Overall, it seems important to quickly implement the MAF into REACH in order to close the current gap and finally address unintentional mixtures and an appropriate level of protection for the environment. Further adjustments are possible when experiences in regulatory practice are gained and more analyses become available.

Applicability of a MAF to non-threshold substances

Non-threshold substances are chemicals for which it is not possible to derive thresholds for a safe use or exposure. This is because the magnitude of adverse effects can hardly be predicted for various reasons: (i) a clear dose–response relationship cannot be estimated, (ii) effects occur at very low concentrations, (iii) effects only occur in the long term, (iv) are severe, or (v) irreversible. This can be the case, e.g., for (very) persistent, (very) bioaccumulative and toxic (PBT/vPvB) substances, persistent,

mobile and toxic (PMT) or very persistent and very mobile (vPvM) substances, endocrine disruptors (EDs) or certain carcinogenic substances. Under REACH, such substances may have an obligation for a specific assessment and exposure minimisation by registrants. They can be identified and then managed as substances of very high concern (SVHC) by regulatory authorities in order to minimise their production and release to the environment, trigger information obligations and promote substitution. However, risk characterization ratios are usually derived by registrants and available in the chemical safety reports.

Whether a MAF, if implemented under REACH, can and should be applicable also to non-threshold substances repeatedly featured in the different discussions around the implementation of a MAF. Different options have been proposed, e.g., at the online stakeholder workshop in April 2022 [21]:

- Non-threshold substances should be excluded from the MAF
- MAF could be applied to non-threshold substances where dose–response relationships exist or can be derived
- a qualitative assessment can be applied to address risks from unintentional mixtures where no threshold for effects is available
- MAF should only apply to non-threshold substances.

Current regulatory frameworks do not consider combined toxicity to be relevant for substances which are carcinogenic, mutagenic or toxic to reproduction (CMR) due to the fact that these substances exert their effects through specific modes of action. However, scientific evidence suggests, that CMR substances, as well as other substances with properties of concern contribute to the combined toxicity of chemical mixtures for the environment irrespective of having similar or dissimilar modes of action e.g., [14, 22, 79–82]. Thus, it would be logical to also consider non-threshold substances when implementing a MAF into REACH. These substances also co-occur in the environment and contribute to mixture risks. Focusing on the level of protection of the environment, it could be argued that the well-documented background contamination with non-threshold substances leaves only a limited acceptable proportion of risks for other substances. Thus, non-threshold substances could be equally addressed by the MAF where an risk characterization ratio is documented in the chemical safety report, following the logic that the environment can only tolerate a certain level of contamination before the "risk cup" flows over.

On the other hand, non-threshold substances are already addressed under REACH. Applying a MAF to these substances could also be perceived as unnecessary overregulation. However, practical experience from the regulation shows that minimization of the exposure to non-threshold substances via authorisation or restriction procedures can only be achieved in the long run even if group-based regulations are stepped up. Hence in light of the aim to improve the current regulatory practice, it might be considered inconsistent to address co-exposures and combined effects of hazardous substances via a MAF, while not considering non-threshold substances. This was also recognized by CEFIC, who propose to focus on SVHCs via a decision tree for prioritising relevant substances for which a MAF should be applied to.[9]

Impacts of a MAF: expected costs and benefits

When defining a regulatory measure like the implementation of a MAF in REACH it is important to reflect on the expected benefits and impacts for the protection goals as well as for the risk assessment and management processes and involved actors.

Costs and benefits for the environment

As described in the beginning, the chemical quality of surface waters is still deemed insufficient for a large range of substances [18]. In particular the co-occurrences and combination effects of chemicals elicit joint effects even below or at their individual accepted safe thresholds, e.g., [32, 34, 83]. This is what a MAF aims to address. If it is applied effectively a MAF is expected to support in improving the quality of environmental media by reducing emissions of harmful chemicals and contribute to protecting and preserving biodiversity and the livelihood of organisms including wildlife and humans.

As the MAF is to be applied during the chemical safety assessment of companies and reduces the anticipated safe operating space of a risk characterization ratio below 1 to 1/MAF (if implemented as $MAF_{ceiling}$) it will directly impact the calculation of safe use amounts for each compartment and use of a chemical in the registration dossiers. In order to scrutinize the possible impact of a MAF, ECHA analyzed chemical safety reports of selected substances and modelled risk characterization ratios for certain use categories. The question was whether a MAF in different magnitudes (2, 5, 20, 50) would be "adsorbed" without any changes (no revision) and/or lead to refinements of the respective chemical safety assessments (i.e., PEC estimation, use of monitoring data, refinement of PNEC) and/or risk reduction measures (additional risk management measures, withdraw use). Indicative results were presented during stakeholder workshops and in an associated background document [21]. It was estimated

[9] https://cefic.org/policy-matters/mixture-assessment-factor/ Date of access 12.03.2024.

that around 20% of the registered substances (with mandatory chemical safety report, exposure scenario and risk assessment) could be affected by a MAF in general and irrespective of its size. With a MAF of 10, around 70% could encounter moderate refinements, around 10–15% risk mitigation measures and around 5–10% withdrawal of uses or further testing. Potential environmental benefits in terms of reduced emissions might be expected if risk reduction measures and withdrawal of uses at risk are the consequence. Keeping in mind that a "$MAF_{ceiling}$" would only affect substances with a risk characterization ratio close to 1, a MAF indeed could support minimizing emissions of certain uses even in a targeted way focusing on substances with a high risk—the extent is however depending on its magnitude. Unfortunately, the cited assessments by ECHA focused on substances with high risk characterization ratios due to their properties and uses (e.g., wide dispersive) and is not representative of the full range of registered substances. To gain better insights on the impact of a MAF, further analyses are warranted.

Besides the direct effects a MAF may have, indirect effects of its implementation may be beneficial in terms of environmental risk assessment and management. The MAF is expected to enhance data quality due to refinements during the chemical safety assessments, such as, e.g., hazard data (increased use of available studies, new approach methodologies (NAMs), or if needed also new experimental tests) as well as more realistic exposure estimates (see chapter "Adjustment options during chemical safety assessment"). This will make environmental risks assessments more realistic and reliable. In addition, better data would also support specific assessments of defined mixtures as an additional risk management option in justified cases. Moreover, the implementation of a MAF will bring potential benefits through incentivizing the development of new, safer chemicals or technical alternatives to chemicals in case of that certain uses are withdrawn. Hence, a MAF might also indirectly foster the production and use of less hazardous chemicals.

Unfortunately, at the time being we have to rely on assumptions as detailed analyses of potential impacts are lacking. In addition, after an introduction of a MAF, the impact of a MAF in terms of reduced emissions needs to be monitored. Such analyses will be usually part of the regular REACH Review process and documented in the so-called REACH baseline studies. This could either be done on the basis of expected refinements and/or risk reduction measures of registrants and downstream users, or also supported by a monitoring of environmental compartments or biota. Indeed, it is fully unknown whether a MAF would only lead to a refinement of exposure scenarios on paper or will in reality have an effect on environmental emissions. The European Environmental Agency (EEA) together with ECHA and Joint Research Centre (JRC) are currently developing a system of indicators in order to follow the implementation and impacts of the actions outlined in the Chemical Strategy for Sustainability also for unintentional mixtures. For this purpose, defined sites and scenarios are needed as a baseline of concentrations, to which future analyses can be compared in a consistent way. Systematically collected samples from the German[10] and other environmental specimen banks could support co-exposure assessments in time and space as well.

Costs and benefits for industry

A direct consequence of an implementation of a MAF would be a temporarily increase of the workload for registrants checking and updating their registration dossiers and safety data sheets in order to comply with the REACH requirements [REACH Art. 22 and Art. 31 (9)]. This is dependent on the concrete implementation, e.g., whether updates are required immediately or in the course of regularly foreseen updates. Costs and administrative burdens will be needed for the refinement of the risk assessments, the generation of additional tests or modelling data, or costs for the development of safer chemicals, technical alternatives and substitution.

Currently, it is difficult to predict to what extent efforts will be needed for detailed refinements as this will depend on the magnitude of the MAF as well as on implementation details. In order to investigate the possible economic impact of a MAF, CEFIC commissioned a study by Ricardo [84]. This interview-based study assessed the impact of a higher MAF of 10 on 6 chemical safety reports (CSRs) for four different substances (three with respect to the environment) with expected high, medium and low economic impact and tonnages > 1000 tons per year. The focus was on adjustment measures such as, e.g., dossier updates, generation of new data, risk mitigation measures, emission monitoring and withdrawal from the market. According to the study, the magnitude of the economic impact would depend on the environmental compartment. The consequences for industrial, consumer or professional users were not quantified and details behind the assumption that certain uses will be withdrawn are not provided. Overall, the study claims the monetary loss of > € 3.05 billion by 2040, the reduction of the European gross domestic product of € 5–20 million for one case study and € 0.2–1.4 billion for the second case study, and the loss of thousands of jobs, loss of competitiveness and the disruption of all supply chains. Unfortunately, the study did not include any statistical analysis, is based on a very limited sample size

[10] https://www.umweltprobenbank.de/en.

and the number and type of substances evaluated are not representative. Hence more detailed impact analyses are warranted. It has been claimed by the NGO ChemSEC that with respect to REACH industrial costs are often not balanced against financial and societal benefits and were historically overestimated [85]. Also the cited study by Ricardo [84] does not consider beneficial aspects for companies nor society. For example, the withdrawal of a specific use may promote the development of alternative substances or technologies, prevent job losses and spur innovation and competitiveness among companies, a cornerstone of REACH. However, such impact analyses are lacking.

Moreover, future concepts and methods for impact analyses need to consider the benefits for ecosystems and be better balanced, i.e., taking economic impacts and financial benefits into account together with societal benefits as reduced health costs and environmental benefits such as reduced ecological impacts maintaining ecosystem services and reducing remediation costs or costs for purification of raw or surface water to drinking water.

In conclusion, a successful implementation of a MAF under REACH could also be perceived as "best-practice" example and competitive advantage. In particular it has to be kept in mind that the MAF as a generic approach prevents from doing laborious and cost-intensive-specific assessments with component-based approaches on a regular basis, which was, for example, also proposed by CEFIC.[11] Such assessments require prioritisation processes, definitions of exposure scenarios, additional sampling or testing and the definition of additional individual risk management measures. Component-based specific assessments might be an option for specific cases when appropriate data on exposures, effects and uses are available and would rather fall under the responsibility of authorities as concluded by Hassold et al. [20].

Costs and benefits for authorities and risk management

A clear advantage of a MAF approach is that no separate cumulative assessment of risks is required nor is there any need to directly manage the risks of combined exposures [23]. While the MAF is proposed to be applied during the chemical safety assessments of companies, it may also affect the workload of ECHA and authorities. Additional efforts may be required for this issue during compliance checks and testing proposal evaluations in case of updated registration dossiers. It certainly needs some reflections whether and to which extent ECHA's role and work needs to be extended in order to check MAF based refinements on a random basis. It might also be the task of member state authorities to evaluate the effectivity and sufficiency of a MAF and the need for further regulatory measures for a certain substance during substance evaluations. Furthermore authorities could initiate specific mixture assessments to identify remaining mixture risks and propose additional regulatory measures for defined groups and/or mixtures of substances. Still, in conclusion, also for authorities a MAF seems to be a more efficient solution than fully relying on time and effort-consuming-specific mixture assessments.

[11] https://cefic.org/policy-matters/mixture-assessment-factor/.

Outlook

The current risk assessment and management of chemicals in the context of REACH focuses on single substances, while unintentional mixtures are not addressed. Although most recent monitoring data e.g., [7, 9, 18, 66], do not represent the full spectrum of ambient mixture exposures in Europe, they substantiate a clear need for adapting policies, notably REACH, to achieve the EU goals for a toxic-free environment and underpin the need for a MAF.

Evidences for the co-occurrence of various chemicals and their combined "cocktail effects" in the environment have been known for a long time. Already before REACH was introduced, discussions took place on how to address intentional and unintentional mixtures in the legislative text. However, unintentional mixtures were left unaddressed. Currently, the REACH regulation only refers to formulated intentional mixtures ("technical mixtures") and aggregated exposures of one substance from various uses ("combined exposures") with obligations during the chemical safety assessment of companies. The implementation of a MAF with a defined default value in REACH Annex I, currently seems to be the most pragmatic and practicable measure to manage the complex exposure situation and risks of chemical mixtures for > 23.000 chemicals within Europe. The MAF would address unintentional mixtures and aim at an appropriate level of protection for the environment taking account of yet unrecognised joint effects through combined exposure of the various chemicals that are regulated under REACH. This can only be effective if the MAF is applied and respective risk mitigation measures are implemented by companies which truly reduce chemical exposure levels. For a successful implementation of the MAF, the aims and scope of the measure should be transparently described and communicated to all stakeholders along the supply chain. This could be achieved, e.g., by adding a brief section into Title 1 of REACH and in relevant guidance documents together with definitions and general provisions. At a later stage, detailed adjustments (e.g., MAF size, limitation to certain tonnage bands, applicability to non-threshold substances,

interplay with specific assessments and measures), could be introduced during future revisions after more scientific evidence and experiences from the implementation become available. Still, an assessment of the socio-economic and environmental costs and benefits of the MAF approach as well as possible impacts are needed.

In addition to this, more reflection is needed in future on how to deal with environmental mixtures across the different substance-oriented legislations. From a scientific point of view, a MAF should cover risks from unintentional mixtures in the environment regardless of the regulatory framework the individual mixture components are subject to. Indeed, when it comes to analysing monitoring data in practise it is difficult to allocate a substance to a specific single framework as many substances have different uses (e.g., additives or active ingredients in plant protection or biocidal products). The use and emissions of the multitude of various chemicals regulated under different legislative frameworks, respectively, contributes to the overall chemical pressure on the environment. Monitoring data clearly demonstrate, that REACH chemicals only constitute a certain part of the environmental co-exposures. An example of this situation is provided, e.g., by the LIFE APEX project[12] [75, 86] which screened top predators and fish Europewide for > 65.000 chemicals by wide scope target and suspect screening techniques detecting up to 2.500 chemicals (including transformation products and natural compounds) in single samples [87, 88, unpublished data]. A logical consequence would be that a MAF should cover risks from all co-occurring substances and not only those falling under REACH. This would need to be reflected by an appropriate size of the factor as well as a comprehensive data basis for the derivation of its size. There are no conceptual reasons why the MAF should be restricted to chemicals regulated under REACH only. In this context a stepwise-specific mixtures assessment as proposed for plant protection products [89], could be applied alternatively to a MAF for chemicals across different regulations in cases where sufficient data on exposure and hazards are available.

The implementation of the MAF into REACH is central to achieve a regulation of unintentional environmental mixtures. A successful implementation of a MAF under REACH could be regarded as best-practice example and serve as blueprint for the implementation of similar measures in other legislations. Clear and consistent requirements in relevant European chemical regulations, in particular the other substance-oriented legislations, would help to manage risks from unintentional mixtures in the future. This would also support the achievement of the European Zero Pollution Ambition laid down in the European Green Deal.

[12] https://lifeapex.eu/.

Conclusions

Here we provide a brief overview over the main conclusions from our analysis which draws from the aspects discussed in all previous chapters. The main aspects from each conclusion are summarized in Fig. 4.

Why a MAF is needed: Considering the currently available approaches for mixture risk assessments and responsibilities as well as data availability and communication between actors under REACH, a MAF implemented into REACH as risk management tool appears as the most pragmatic measure to reduce the risks from unintentional mixtures in the environment.

Background on the conceptual development of a MAF: Discussions around a MAF date back several decades. There is a wealth of scientific reports which analyse and support this approach. a $MAF_{ceiling}$ seems the most proportionate approach since it targets substances close to individual risks and hence relevant for potential mixture risks.

Review of methods applied to estimate the size of a MAF: Different methods and evidences using monitoring and modelling data are suitable to derive MAF values. These could be combined in a weight of evidence approach considering the different underlying assumptions and uncertainties when deciding on the appropriate magnitude of a MAF what also became clear in subsequent chapters.

Case studies to estimate mixture risks and a MAF: Case studies used to derive mixture risks and an appropriate size of a MAF can only give indications for the environmental risks from co-exposures that the MAF has to address. This is due to a lack of reliable prospective and retrospective data and analytical methods describing the (co-)occurrence of chemicals in the environment and their (eco)toxicity. These aspects need to be transparently addressed when defining the final size of a MAF or when re-evaluating it in the future.

Range of proposed MAF values: Current proposals on the magnitude of a MAF for the environment cover a range of several orders of magnitude and are strongly dependant on the data basis used and assumptions made.

Accounting for uncertainties: Uncertainties related to different calculation methods, underlying assumptions and data basis (i.e., monitoring versus modelling) would need to be considered when sizing the MAF in order to ensure an adequate protection level under "real-world" conditions.

Adjustment options during chemical safety assessment: The MAF aims at reducing the overall emission

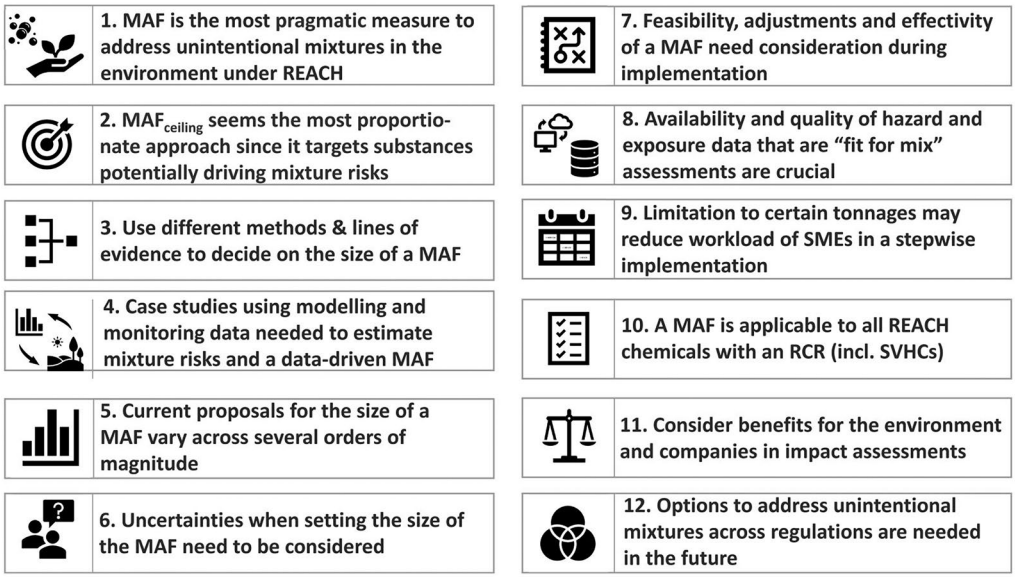

Fig. 4 Conclusions on the practical considerations and recommendations for action when implementing a mixture allocation factor (MAF) in REACH

of chemicals and thus will be most effective if respective risk mitigation measures are implemented that are actually reducing chemical exposure levels. In this context communication of information to relevant downstream users through the supply chain is crucial.

Improving access to and quality of data for better mixture assessment: To improve mixture risk assessment and underpin the magnitude of a MAF, a centralised data base as envisaged by the European Commission should be populated with Europe-wide, quality assured data on chemical hazards (including results from new approach methodologies) and exposure as well as results from well-designed surveys which are representative for co-exposures scenarios. The quality of data of substances could be improved by revision of ECHA guidances.

Limitation of a MAF to certain tonnages: Limiting the implementation of a MAF to a subset of substances could potentially weaken positive effects on the protection goal environment. A stepwise implementation of the MAF for the different tonnage bands could be applied to mitigate potential impacts on registrants' costs for society.

Applicability of a MAF to non-threshold substances: A MAF can apply to all substances for which a risk characterization ratio was derived and documented in the chemical safety report and thus could also apply to SVHCs where technically possible.

Impacts of a MAF: expected costs and benefits: Benefits for the environment would be reduced emissions of relevant substances with potential risks while companies may encounter increased costs and workload but also gain from innovation. Balanced impact analyses considering not only the costs but also ecological as well as economic benefits are needed.

Outlook: Options to address mixture risks across the different European substance-oriented but also media and emission-oriented legislations, need to be developed and discussed at policy level in the future. It is important to reflect the "real-world" situation, that the environment is exposed to mixtures composed of substances with various origin and regulated via different legislative frameworks.

Abbreviations

CA	Concentration addition
CARACAL	Competent authorities for REACH and CLP
CCH	Compliance check
DEV	Dossier evaluation
EC_X	Effect concentration causing X% effect
ECHA	European Chemicals Agency
EEA	European Environment Agency
EDs	Endocrine disruptors
EGD	European green deal
ENV	Environment
EFSA	European Food Safety Agency
ERCs	Environmental release categories
EU	European Union
HC_{05}	The maximum concentration that is not hazardous for more than 5% of the potentially exposed species; derived from species sensitivity distributions
HH	Human health
HI	Hazard Index
IA	Independent action
JRC	Joint research centre
KEMI	The Swedish Chemical Agency
MAF	Mixture allocation factor or mixture assessment factor
MCR	Maximum cumulative ratio
NAMs	New approach methodologies

NGOs	Nongovernmental organisations
NOEC	No observed effect concentration
NTS	Non-target screening
PBT/vPvB	(Very) persistent, (very) bioaccumulative and toxic compounds
PMT/vPvM	(Very) persistent, (very) mobile and toxic compounds
REACH	Regulation EC 1907/2006 on registration, evaluation, authorisation and restriction of chemicals
RIVM	The dutch national institute for public health and the environment
RCR	Risk characterization ratio
SSD	Species sensitivity distribution
SVHC	Substance of very high concern
TU	Toxic units
UN	United Nations
UBA	German environment agency
WHO	World health organisation

Author information
The statements in this paper represent solely the views of the authors and the German Environment Agency not necessarily the views or official policies of other German competent authorities or ministries or people that kindly provided information.

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Competing interests
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