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# The mixture assessment or allocation factor: conceptual background, estimation algorithms and a case study example

Thomas Backhaus[1*]

**Abstract**

Current approaches for the prospective regulatory assessment of chemicals do not account sufficiently for elevated mixture risks. The Mixture Assessment Factor (MAF, better labeled a Mixture Allocation Factor) has been suggested for mixtures of industrial chemicals in the EU's Chemicals Strategy for Sustainability, as a pragmatic tool to account for potential mixture risks already during the risk and safety assessment of individual chemicals. The MAF is to be applied in scenarios in which specific mixture risk assessments are not possible, due to a lack of data and/or the complexity of the relevant exposure scenarios. Several approaches and algorithms for calculating a MAF have been suggested in the literature. The $MAF_{exact}$, which is a member of the larger $MAF_{ceiling}$ class, is defined as the maximum fraction of the risk quotient of each chemical that is still acceptable to occur in a mixture, without the sum of risk quotients exceeding 1. This paper provides a comparative overview of the different MAF types discussed in the literature. It argues that the $MAF_{exact}$ is the most promising approach in the context of chemical registration and authorization under regulatory frameworks such as REACH because this approach ensures a protection level that is similar to the protection level used in the current safety assessment of individual chemicals under REACH. Other MAF approaches either disproportionally impact low-risk substances, without leading to any appreciable risk reduction, or hamper risk communication because they lead to fluctuating residual risks after the MAF application. The paper also presents a case study comparing the different MAF approaches and finally discusses the MAF concept in the wider context of chemical regulation.

**Keywords** REACH revision, Chemical risk assessment, Chemical risk management, Chemicals strategy for sustainability, Mixture allocation factor

## Introduction

Hazardous chemicals co-occur. An exposure to a single, pure chemical does not exist in the real world. Instead, chemical pollution is characterized by complex multi-component mixtures that can easily comprise dozens or even hundreds of chemicals, e.g., [1, 2]. The risk of such mixtures to the environment or human health is typically higher than the risks of each of its individual components (at the concentration at which those compounds are present in the mixture). Even if all chemicals are present only at concentrations that do not cause visible toxic effects, i.e., that do not exceed their individual No Observed Effect Concentrations or Levels (NOECs, NOELs), the mixture might still cause a significant toxicity. This phenomenon has been termed the "something from nothing" behavior of mixtures, and has been repeatedly demonstrated to apply for a broad range of complex chemical mixtures, recently for example in [3, 4], see also [5–7] for a summary of older studies.

*Correspondence:
Thomas Backhaus
thomas.backhaus@gu.se
[1] Department for Biological and Environmental Sciences, University of Gothenburg, Carl Skottbergs Gata 22B, 40530 Gothenburg, Sweden

Even if the components are only present at regulatory "safe" concentrations (so-called Environmental Quality Standards, EQS-values), a toxic mixture effect was observed in ecotoxicological assays [8]. Unfortunately, a similar study that uses toxicological (human health relevant) endpoints, and in which all the components of a multi-component mixture are present at concentrations that are deemed "safe" from a public health perspective (based on, for example, Acceptable Daily Intakes or Tolerable Daily Intakes), is still missing, although the aforementioned "something from nothing" phenomenon has been empirically demonstrated also for toxicological assays and endpoints, see [4] and the studies reviewed in [5, 6].

Consequently, controlling the risk of individual chemicals does not necessarily ensure that the overall risk from combined exposures is acceptable, see [5–7] and references therein. Chemical risk assessment and management strategies need to be adapted to the reality of combined exposures [5–7, 9–14].

The question therefore is, in the context of inherently substance-oriented regulatory frameworks such as REACH, the Regulations on Plant Protection Products (PPR) or the Biocidal Products Regulation (BPR): how can the risks that result from the coincidental co-occurrence of different industrial chemicals, biocides, pesticides and/or other chemicals, be accounted for already during the registration or authorization of an individual substance? Specific and targeted mixture evaluations are often not feasible for coincidental mixtures, given that the evaluation of every relevant co-exposure scenario for all uses of a substance is well beyond the capacity of an individual registration/applicant, in particular because the necessary data are rarely available.

For this purpose, the use of a "Mixture Assessment Factor" (MAF) has been suggested in the European Chemicals Strategy for Sustainability (CSS) [14], which recently received specific support in a joint letter by the Environmental Ministers of Austria, Belgium, Denmark, Finland, Luxemburg, Norway, Spain and Sweden to the European Commission [15].

The CSS requests to "*assess how to best introduce in REACH mixture assessment factor(s) for the chemical safety assessment of substances*". However, there are no conceptual reasons why the MAF idea should be restricted to chemicals regulated under REACH. In fact, given that humans and other organisms in the environment are exposed to mixtures comprising chemicals from basically every regulatory realm (biocides, pesticides, pharmaceutical residues, etc.), the MAF idea needs to be extended beyond REACH in the future.

The Swedish Chemicals Agency (KEMI) commissioned a first report on the MAF in 2015 [16], which provided a basis for a report to the Swedish government on instruments for future chemical risk assessment and management [6]. Both documents provide an overview of the fundamental *pros* and *cons* of the MAF as an instrument for the regulatory assessment of mixtures. A follow-up report from 2021 [17] then presented a new algorithm for calculating the MAF, see below.

A consensus seemed to emerge during recent workshops between various stakeholders from academia, research institutes, civil society organizations and representatives of many regulatory authorities that the introduction of a MAF is a pragmatic way forward to account for mixture risks in chemical regulation [18–23]. Concerns are raised especially by toxicologists working in the area of human health assessment (especially the food safety area), arguing that more precise mixture assessment tools are at hand, which should given preference [24]. It is, however, currently unclear how such instruments could be applied to highly complex mixtures of hundreds of co-occurring chemicals, many of which are toxicologically ill characterized. Industry organizations have especially raised concerns about the anticipated economic impacts of introducing a MAF [25].

In the following, I will first analyze the two fundamentally different options for estimating the numerical size of a MAF. Afterwards the different estimation algorithms will be discussed, followed by an assessment of their robustness in view of less-than-perfect input data. All algorithms presented in this paper are made available in an accompanying Github repository, implemented in Excel and R (https://github.com/ThomasBackhausLab/MAF).

These algorithms provide the scientific foundation for estimating the size of a MAF for different mixture scenarios, which in turn is the basis for implementing the MAF in a regulatory context, as outlined above.

## Estimating the MAF

### Operationalizing the zero pollution ambition with respect to chemical mixtures

The increasing realization that humans and the environment are too often exposed to unacceptably high concentrations of various hazardous chemicals and their mixtures led to the establishment of the European zero pollution vision for 2050, which aims to ensure that "*air, water and soil pollution is reduced to levels no longer considered harmful to health and natural ecosystems*" [26].

The estimation of a chemical's maximum concentration that is "not harmful" for the exposed entity results in regulatory threshold values such as the PNEC (Predicted No Effect Concentration) or DNEL (Derived No Effect Level) for industrial chemicals that are regulated under REACH. Safe use is considered to have been demonstrated if the actual concentration of a chemical in the relevant exposure scenarios does not exceed these

regulatory thresholds. That is, the aim of chemical regulation in general is that

$$\frac{\text{Exposure concentration}}{\text{Regulatory threshold}} \leq 1. \quad (1)$$

The maximum acceptable value of 1 for this risk quotient (RQ) is the typical yardstick used during regulatory risk assessment and management.

Under the assumption that Concentration Addition is an adequate approximation of mixture risks and that the summation of RQ values is an adequate approximation of Concentration Addition ([5, 6, 27] and references therein, see also discussion below), it then follows that a mixture poses an acceptable risk if it is ensured that

$$\sum_{i=1}^{n} \frac{\text{Exposure concentration}_i}{\text{Regulatory threshold}_i} = \sum_{i=1}^{n} \text{RQ}_i \leq 1, \quad (2)$$

where $n$ is the number of mixture components.

This constitutes an operationalization of the previously mentioned zero pollution ambition that adequately considers the joint toxicity of chemical mixtures. It should be noted that this operationalization applies to the human health context as well as to the assessment of environmental risks of chemical mixtures.

Equation 2 implies that even if all components in a mixture have an RQ of less than 1, i.e., safe use is demonstrated for each individual chemical in the mixture, the overall RQ sum can still exceed the critical value of 1, and the resulting mixture might therefore still put people or the environment at risk. This gap in the current approach to chemical risk assessment and management has raised concern and is the underlying rational why the issue of mixture toxicities and risks is highlighted as a specific task in the CSS.

### *Two fundamentally different MAF classes: $MAF_{factor}$ and $MAF_{ceiling}$*

Two fundamentally different MAF classes, which will be called $\text{MAF}_{\text{factor}}$ and $\text{MAF}_{\text{ceiling}}$ in the following, are described in the literature and have been discussed at various expert workshops.

#### *$MAF_{factor}$*

This MAF class is based on the reduction of the RQ value of each mixture component by a constant factor, the $\text{MAF}_{\text{factor}}$ [13]:

$$\text{RQ}_{\text{MAF(factor)}} = \text{RQ} \times \frac{1}{\text{MAF}_{\text{factor}}}. \quad (3)$$

An inverse ($1/\text{MAF}_{\text{factor}}$) is used here simply for the purpose of ending up with values for $\text{MAF}_{\text{factor}}$ greater than 1, which are easier to communicate and interpret than values in the range of 0–1. The residual risk (RR) of the mixture after the application of $\text{MAF}_{\text{factor}}$ is then defined as:

$$\begin{aligned} \text{RR} &= \sum_{i=1}^{n} \frac{\text{Exposure concentration}_i}{\text{Regulatory threshold}_i} \times \frac{1}{\text{MAF}_{\text{factor}}} \\ &= \sum_{i=1}^{n} \text{RQ}_i \times \frac{1}{\text{MAF}_{\text{factor}}}. \end{aligned} \quad (4)$$

Achieving the zero pollution ambition as operationalized in Eq. 2 requires to estimate the minimum $\text{MAF}_{\text{factor}}$ that ensures $\text{RR} \leq 1$. It is important to note that applying a $\text{MAF}_{\text{factor}}$ implies that the RQ of every mixture component is lowered by a constant factor, independent of the initial size of its RQ.

In order to differentiate between substances that cause an unacceptably high risks even as a single compound (i.e., substances with an $\text{RQ} > 1$) and the mixture risk, [16] suggests to calculate $\text{MAF}_{\text{factor}}$ only after limiting the initial RQ of every mixture component to a maximum value of 1, i.e., after assuming successful single-substance oriented risk management, implemented during substance registration or via subsequent restrictions.

#### *$MAF_{ceiling}$*

The second MAF class is based on the idea that the MAF defines a new value for the maximum acceptable RQ for each compound, lower than the current value of 1 [17, 28]. The original RQ of a mixture component $i$ is reduced to the new ceiling of $1/\text{MAF}_{\text{ceiling}}$ if it initially exceeds this value. Otherwise, it is left unchanged:

$$\text{RQ}_{\text{MAF(ceiling)},i} = \begin{cases} \text{if RQ}_i > \frac{1}{\text{MAF}_{\text{ceiling}}}, & \text{RQ}_i = \frac{1}{\text{MAF}_{\text{ceiling}}} \\ \text{else RQ}_i \leq \frac{1}{\text{MAF}_{\text{ceiling}}}, & \text{RQ}_i \text{ remains unchanged} \end{cases} \quad (5)$$

Again, the inverse ($1/\text{MAF}_{\text{ceiling}}$) is used in order to end up with numerical $\text{MAF}_{\text{ceiling}}$ values $\geq 1$. As before, the residual mixture risk after the application of the MAF is then calculated as the sum of all MAF-adjusted RQ values:

$$\text{RR} = \sum_{i=1}^{n} \text{RQ}_{\text{MAF(ceiling)},i} \quad (6)$$

Fulfilling the zero pollution ambition, (Eq. 2), requires estimating the smallest possible value for $\text{MAF}_{\text{ceiling}}$ that ensures $\text{RR} \leq 1$. It should be pointed out that the application of a $\text{MAF}_{\text{ceiling}}$ is conceptually similar to the current approach for assessing "safe use" under REACH. The only difference is that $\text{MAF}_{\text{ceiling}}$ is currently set to 1

and, in order to account for the fact that several chemicals share the same emission space, is now adjusted to a value greater than 1 (i.e., $1/MAF_{ceiling} \leq 1$).

#### *Properties of $MAF_{factor}$ and $MAF_{ceiling}$*

Both MAF types share four main assumptions:

1. Multi-component mixtures behave according to Concentration Addition (CA, also called Dose Addition).

This assumption seems justified in view of the empirical data at hand. Synergistic or antagonistic interactions that would lead to a joint risk higher or lower than predicted by CA are rare for relevant multi-component mixtures, see [5, 6] and references therein.

The competing concept of Independent Action (IA, sometimes also called Effect Addition) is not considered for the calculation of the MAF, for three reasons: (1) CA- and IA-based mixture risk predictions of real-world mixtures are often virtually identical [4] and references therein, (2) if they differ, CA provides a slightly (but not excessively) precautionary mixture risk estimate, and (3) the application of IA would require the availability of the full concentration–response curves for all potentially important endpoints for all mixture components—a requirement that is almost impossible to fulfill.

2. The concentration-additive risk of a mixture is adequately estimated as the sum of individual risk quotients (e.g., the sum of PEC/PNEC ratios or Exposure/DNEL ratios) [17].

This implies that PNECs, DNELs and similar regulatory thresholds are adequate and unbiased hazard estimates. However, regulatory thresholds are often, especially for industrial chemicals, derived from few empirical data and the application of conservative assessment factors, and therefore provide hazard estimates that are biased toward precaution. Under these conditions, also RQ sums are conservative mixture risk estimates. This might be less of a problem for data-rich chemicals, such as pesticides.

It should, however, be pointed out that the application of the CA principle does not inflate the overall conservatism. In fact, CA is simply based on the harmonic mean of the component's concentrations [5], and a CA-based mixture risk thus represents an average of the uncertainties (of the exposure as well as the hazard estimates) and assessment factors used for the individual mixture components.

3. The RQ values of the mixture components are independent of each other.

The outlined MAF approaches assume that the RQ values (i.e., hazard profiles and exposure estimates) of the mixture components are independent of each other. If risk mitigation measures lower exposure to a whole range of mixture components simultaneously, for example as a consequence of an STP plant being upgraded with a tertiary treatment, the MAF algorithms would need to be adapted accordingly. However, in the context of REACH and similar frameworks, where chemicals are assessed individually, the assumption of independence between the RQ values is, in all likelihood, fulfilled.

4. The mixture of interest is well defined.

A numerical MAF value can only be calculated for defined mixtures, as it is an application of the family of the so-called component-based mixture assessment approaches [5, 6]. What is more, only those chemicals can be considered during the MAF calculation for which exposure concentrations and adequate thresholds are known. The MAF is therefore not an estimate of the total site-specific risk. It is an estimate of the excess mixture risk, based on the assumption that a given set of exposure data adequately reflect the overall exposure. This implies that (1) the use of obviously incomplete datasets (in which only a subset of relevant chemicals is included) leads to artificially low MAF values and (2) that a MAF value is always based on an underestimation of the actual mixture risk, as there will always be at least some chemicals not included in an exposure estimate. The second point, however, is less relevant for multi-component mixtures, as long as at least the mixture risk drivers are included in the assessment.

$MAF_{factor}$ and $MAF_{ceiling}$ also differ in several important characteristics. For their usefulness in the context of substance registration under REACH one particular difference matters most: $MAF_{factor}$ impacts all substance in a mixture equally, even if a component only contributes marginally to the overall risk. This shortcoming of the $MAF_{factor}$ has been previously criticized [29–31], and, in order to address this criticism, $MAF_{ceiling}$ was developed [17]. In sharp contrast to $MAF_{factor}$, $MAF_{ceiling}$ only affects a small subset of the mixture components, i.e., those chemicals whose original RQ exceeds the critical value of $1/MAF_{ceiling}$; see Fig. 1 and Table 1. The example shown in Table 1 demonstrates that the application of $MAF_{factor}$ implies that even the RQ values of compounds 5–10, with an original RQ of just 0.01, would need to be lowered (by an improved risk assessment or even risk mitigation measures) to a value of 0.006.

This particular characteristic makes the $MAF_{factor}$ largely unsuited for an application within the context of single substance registration or authorization under REACH or similar regulations, as it would impact the plethora of small tonnage chemicals and low-risk substances, without resulting in any conceivable improvement of actual risks. This issue can be minimized by applying $MAF_{factor}$ only to a pre-defined subset of the mixture components (i.e., those with an RQ above a certain critical value), but that would basically be just another approach for approximating a $MAF_{ceiling}$.

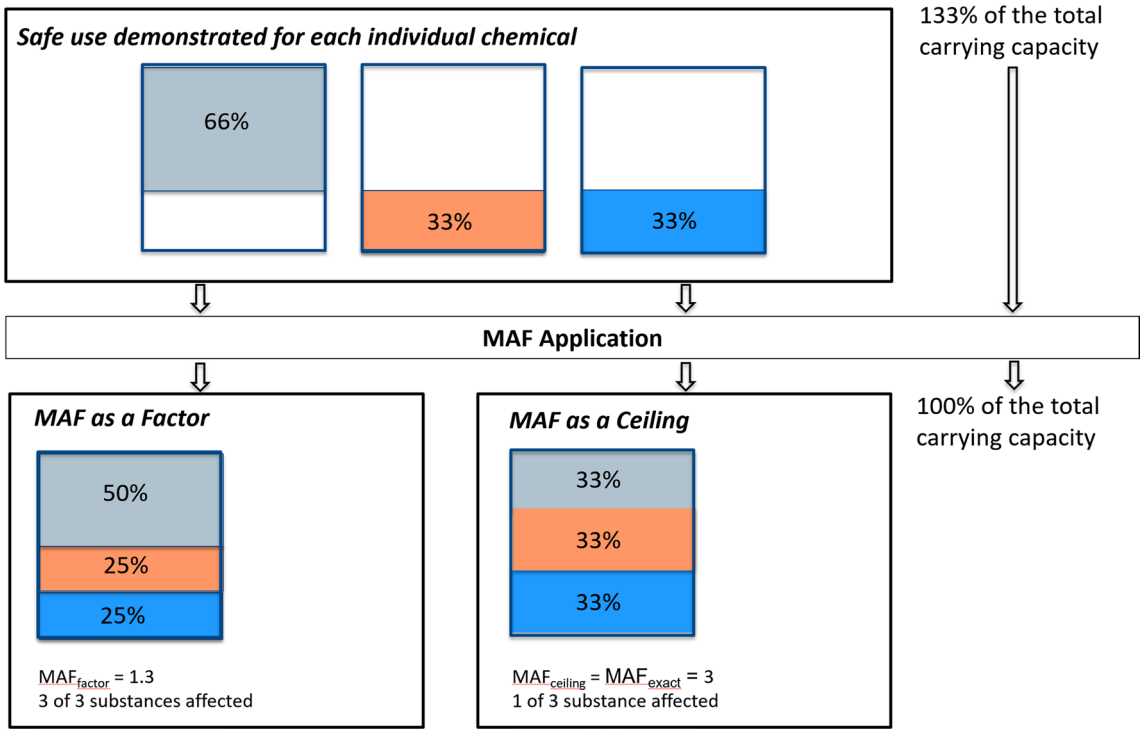


**Fig. 1** The characteristics of the two fundamental MAF classes ($MAF_{factor}$ and $MAF_{ceiling}$). The original (arbitrary) mixture comprises 3 chemicals, being present with a risk quotient (RQ) of 0.66, 0.33 and 0.33, i.e., 66%, 33% and 33% of the carrying capacity of the exposed entity (a human body (DNEL) or an ecosystem (PNEC), symbolized by the open box). For this mixture, "safe use" is demonstrated for each individual chemical. However, the RQ sum is 1.33, i.e., the mixture overburdens the exposed entity with 133% of its carrying capacity. Two different classes of MAF can be applied to estimate by how much the overall exposure needs to be reduced. $MAF_{factor}$ applies an identical factor (1.3. in the example) to *every* substance in the mixture in order to ensure that 100% capacity is not exceeded. In contrast, $MAF_{ceiling}$ establishes a new maximum acceptable single substance RQ of 1/3 = 0.33, which affects only 1 of the 3 mixture components (the first chemical, whose RQ exceed a value of $1/MAF_{ceiling}$). This makes the RQ values of the MAF-adjusted mixture more similar to each other

**Table 1** Numerical comparison of $MAF_{factor}$ and $MAF_{ceiling}$ for a mixture for which safe use is demonstrated for all components

| | Initial mixture | Application of $MAF_{factor} = 1.56$ | Application of $MAF_{ceiling} = 3.57$ |
|---|---|---|---|
| RQ Substance 1 | 0.8 | *0.51* | *0.28* |
| RQ Substance 2 | 0.3 | *0.19* | *0.28* |
| RQ Substance 3 | 0.3 | *0.19* | *0.28* |
| RQ Substance 4 | 0.1 | *0.06* | 0.1 |
| RQ Substances 5–10 | 0.01 | *0.006* | 0.01 |
| Sum (RQ) | 1.56 | 1 | 1 |

Safe use is demonstrated for each individual component of the initial mixture (all RQ values ≤ 1). However, the RQ sum exceeds the critical value of 1. Aim of applying both MAF classes is to reduce the RQ sum from the initial value of 1.56 to a value of 1. The initial mixture used in this example is arbitrary, but follows the typical Pareto-like distribution of RQ values found in relevant mixtures. Values given in italics: RQ values that are lowered (by different amounts) by the application of the MAF

$MAF_{factor}$ reduces the RQ of all mixture components equally by the numerical value of $MAF_{factor}$. $MAF_{ceiling}$, on the other hand, implies different risk reduction requirements for different mixture components. For example, while the RQ of the first compound in Table 1 needs to be reduced by a factor of 0.8/0.28 = 2.86, the RQ values of the second and third compounds only need to be reduced by a factor of 0.3/0.28 = 1.07.

Especially in the context of highly complex multi-component mixtures it should not go unnoticed that the application of $MAF_{ceiling}$ implies that all the chemicals with an RQ below $1/MAF_{ceiling}$ get a "free ride". That is to say that, as long as a concentration-additive behavior of the mixture is assumed, those small-RQ compounds add to the mixture risk—but this contribution is not reduced by the application of the MAF.

A $MAF_{factor}$ that reduces the original RQ sum to a certain pre-defined RR value is always smaller than the corresponding $MAF_{ceiling}$ value, which is a direct consequence of $MAF_{factor}$ affecting all components of the mixture while $MAF_{ceiling}$ only affects the mixture risk drivers. The smaller value of a $MAF_{factor}$ might seem tempting, but care needs to be taken to balance that

against the fact that a $MAF_{factor}$ would impact each and every chemical on the market.

Only the application of a $MAF_{factor}$ fully preserves the original RQ distribution of the mixture, although the RQ ranking order is not affected by the application of either MAF class.

#### Algorithms to estimate the MAF

At least three different algorithms to establish the numerical value for $MAF_{factor}$ or $MAF_{ceiling}$ have been described in different papers, reports and opinion pieces.

Algorithm 1: represents the simplest and most basic approach: a value for $MAF_{factor}$ or $MAF_{ceiling}$ can simply be set *a priori*, without any consideration of the risk of the original mixture, the underlying RQ distribution or a particular acceptability criterion for the residual risk of the mixture, e.g., [22]. As a consequence, the MAF remains constant across mixture scenarios, but the residual risks fluctuate greatly, in direct relation to the absolute risk and the RQ distribution of the original mixtures.

Algorithm 2: makes use of certain characteristics of the initial mixture in order to establish a MAF. An implementation of this algorithm is presented in [28], where a $MAF_{ceiling}$ is estimated as the number of "risk drivers" in the original mixture. The authors define a mixture risk driver as a chemical that belongs to the sub-group of mixture components that, in their totality, make up a defined percentage of the overall RQ sum, e.g., 90% of the RQ sum (subsequently denoted as $MAF_{90\%}$). Because this approach anchors the MAF to a characteristic of the RQ distribution of the original mixture (i.e., the number of risk driving compounds), different mixtures might result in different MAF values. However, as the approach does not anchor the MAF to the total risk of the mixture and also does not specify an acceptability criterion for the MAF application, the residual risk RR of the mixture after the application of a MAF, calculated according to this approach, varies between different mixtures.

Algorithm 3: establishes the MAF in relation to a predefined acceptability criterion for the MAF-adjusted mixture. An algorithm for calculating the minimum value for $MAF_{factor}$ that ensures an RR of exactly 1 (with a view to the European zero pollution vision, see above) has been presented in [16]. This algorithm calculates the $MAF_{factor}$ as the sum of the individual RQs, after limiting each individual RQ to a maximum of 1 (i.e., the maximum RQ that is still compatible with the current "safe use" idea under REACH). The $MAF_{factor}$ is then numerically identical to the so-called maximum cumulative ratio (MCR) of the mixture after limiting each individual RQ to 1 [16].

An iterative approach to calculate the minimum $MAF_{ceiling}$ that ensures an RR of exactly 1 has been recently published in [17]. This implementation of the $MAF_{ceiling}$ will therefore be abbreviated as $MAF_{exact}$ in the following. Figure 2 provides the details on the logic of the $MAF_{exact}$ calculation. An implementation in Excel and R is available at https://github.com/ThomasBackhausLab/MAF.

Because this algorithm takes the initial RQ distribution into account and is based on achieving a defined numerical acceptability criterion ($RR \leq 1$), the $MAF_{exact}$ values resulting from applying Algorithm 3 are highly specific for each analyzed mixture.

#### Which algorithm to select?

If $MAF_{ceiling}$ is the preferred MAF class, this raises the question on how to select between the different algorithms for estimating numerical MAF values. "Algorithm" 1 (setting an *a priori* MAF value) is the most pragmatic approach, but does not consider any characteristics of environmentally relevant mixtures. In particular, it is basically impossible to define scientific or policy criteria for the a priori selection of a particular numerical value beyond mere convenience and outward appearance. It would be impossible, without accompanying and more detailed analyses, to assess whether, and to what extent, certain policy goals (e.g., the European zero pollution ambition) would be achieved by the MAF implementation via "Algorithm" 1.

Algorithms 2 and 3 differ in one crucial aspect, i.e., the residual risk, which is the RQ sum of the MAF-adjusted mixture. The residual risks after an application of Algorithm 2 might differ considerably even between two mixtures that pose the same initial risk, in dependency of the RQ distribution characteristics of the original mixture. In contrast, the application of Algorithm 3 always results in a residual risk that corresponds exactly to the pre-defined acceptability criterion ($RQ\ sum \leq 1$). This behavior is demonstrated for several arbitrary (but realistic) mixtures in Table 2, contrasting $MAF_{exact}$ and $MAF_{90\%}$ (as an example of a $MAF_{ceiling}$). It can be clearly seen that the application of Algorithm 2 for defining a $MAF_{ceiling}$ leads to risk over- as well as under-estimations, in comparison to the defined acceptability criterion ($RQSum \leq 1$).

In other words: Algorithm 3 ($MAF_{exact}$) captures the entire dynamics of risks across all samples included in the assessment of a certain exposure scenario in the distribution of the resulting MAF values. A certain cut-off value (for example, the upper 95% percentile) of this distribution can then be used to set a sufficiently protective MAF value across tall samples (the definition of "sufficiently protective" would obviously be a policy decision). In contrast, Algorithm 2 captures the dynamics of mixture risks across a range of samples in two interlinked distributions: the distribution of MAF values and the distribution of residual risks. This makes the political discussion about

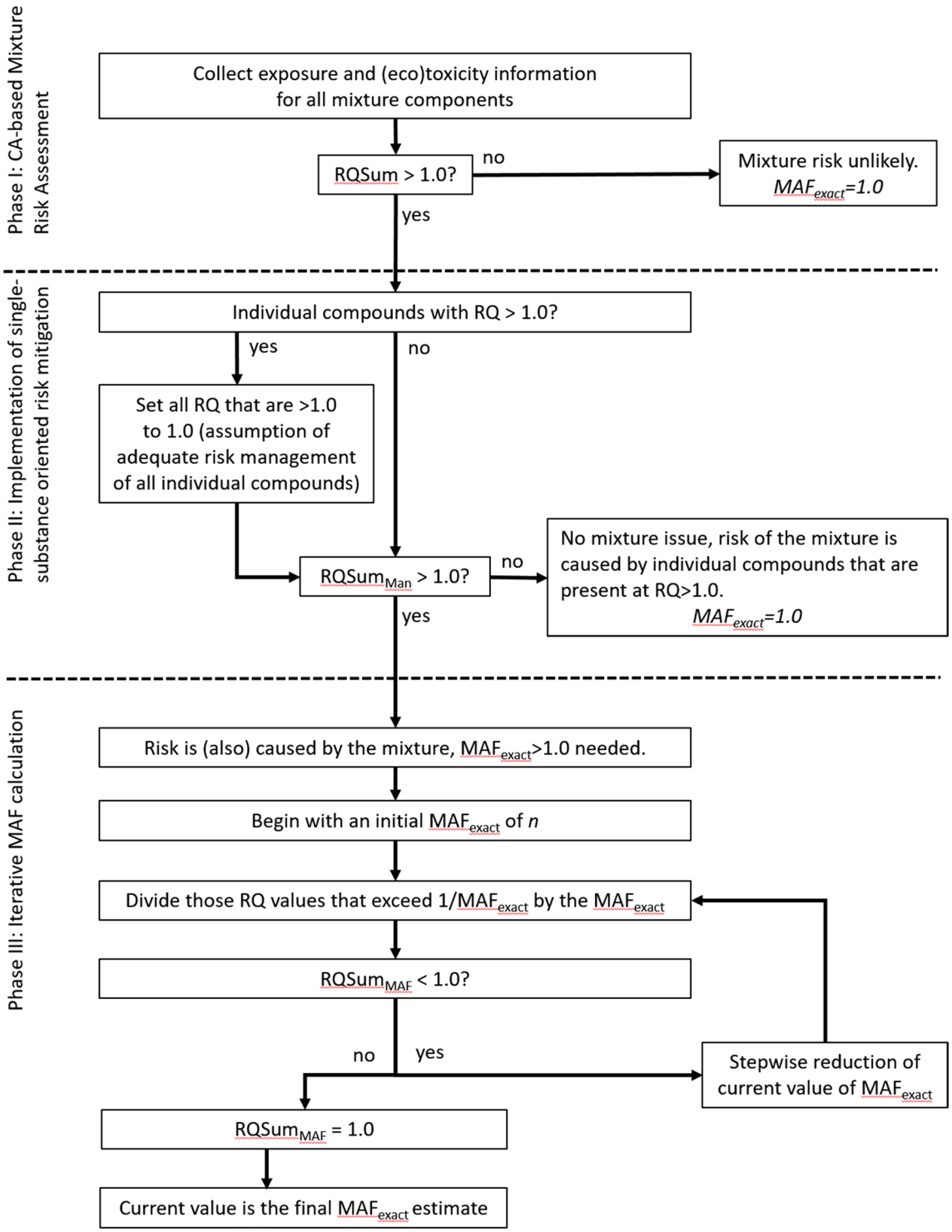


**Fig. 2** Iterative algorithm for estimating $MAF_{exact.}$ RQ: risk quotient such as PNEC or DNEL. RQSum: sum of risk quotients of all mixture components. $RQSum_{Man}$: RQSum after limiting the maximum individual RQ to 1

**Table 2** Numerical comparison of $MAF_{exact}$ and $MAF_{90\%}$

| | Mixture 1 | Mixture 2 | Mixture 3 | Mixture 4 | Mixture 5 |
|---|---|---|---|---|---|
| RQ Substance 1 | 0.8 | 80 | 80 | 80 | 90 |
| RQ Substance 2 | 0.1 | 10 | 10 | 10 | 1 |
| RQ Substance 3 | 0.05 | 5 | 9 | 4 | 4 |
| RQ Substance 4 | 0.05 | 5 | 0.7 | 4 | 3 |
| RQ Substances 5–10 | 0 | 0 | 0.05 | 0.33 | 0.33 |
| Initial RQ sum | 1 | 100 | 100 | 100 | 100 |
| No of compounds for 90% of RQ sum = $MAF_{90\%}$ | 2 | 2 | 2 | 2 | 1 |
| RQ sum after applying $MAF_{90\%}$ | 0.7 | 2 | 2.3 | 4 | 100 |
| $MAF_{exact}$ | 1 | 4 | 5.71 | 10 | 10 |
| RQ sum after applying $MAF_{exact}$ | 1 | 1 | 1 | 1 | 1 |

All mixtures used in this example are arbitrary, but follow the typical Pareto-like distribution of RQ values found in relevant mixtures. In mixtures 1–4, the first 2 components provide 90% of the RQ sum, i.e., $MAF_{90\%}$ is 2 for each mixture. However, the distribution of RQ values in the tail is different between mixtures 1—4, and, as a consequence, the RQ sum after applying $MAF_{90\%}$ is different for the different mixtures, varying between 0.7 and 4. In mixture 5, 90% of the RQ sum is provided by the first compound, and $MAF_{90\%}$ is therefore 1, leading to a massive risk underestimation. In contrast, $MAF_{exact}$ captures the full variability in the RQ distribution in the different $MAF_{exact}$ values, and the resulting RQ sum is always exactly 1 (the pre-defined acceptability criterion)

a sufficiently, but not excessively, protective MAF value more difficult.

In addition, the application of Algorithm 2 also requires to select a "suitable" percentage value *a priori*. Shall the MAF be tied to the number of compounds responsible for 80%, 90% or 95% of the RQ sum? The smaller the percentage value, the smaller the resulting MAF but the higher the residual risk of the mixture. Algorithm 3 does not require taking such a decision.

The fact that the application of Algorithm 3 always results in an exact, pre-defined residual risk of the mixture can be considered highly advantageous, as it facilitates the conversation about suitable numerical MAF estimates and because it allows to tailor the acceptable residual risk (and hence the MAF values) to various policy and feasibility considerations. In the examples outlined in Fig. 1 and Tables 1, 2, the acceptability criterion is set to 1, corresponding to the zero pollution vision for 2050. A less stringent criterion might be set, for example, for environmental samples taken in the vicinity of a sewage treatment effluent stream, or for chemicals found in heavily modified water bodies. It is, however, doubtful whether a less stringent criterion should also be applied in the context of human health assessments.

### Robustness of the MAF estimate

Neither exposure nor hazard estimates are error free. It is therefore important to compare the robustness of Algorithms 2 and 3 against errors in the RQ estimates of the mixture. Both algorithms are quite robust against risk under- and over-estimations that occur in any of the less relevant mixture components (not shown). However, $MAF_{exact}$ and $MAF_{90\%}$ differ in their robustness against over- or under-estimations of the RQ values of the risk drivers. Table 3 shows that $MAF_{exact}$ is incredibly robust against mis-estimations of the RQ of even the most important mixture component.

This is a consequence of the fact that $MAF_{exact}$ introduces a ceiling for the maximum acceptable value for an individual RQ. For the MAF estimation, it is only important whether an RQ value is above or below the critical value of $1/MAF_{exact}$—the exact numerical RQ value is of no relevance (see example in Table 3). This is the reason why the numerical value for $MAF_{exact}$ is identical for all three mixtures shown in Table 3, despite the fact that they pose different risks, with RQ sums between 5.5 and 55.

In contrast, $MAF_{90\%}$ is more sensitive to RQ mis-estimations (Table 3), as the numerical RQ values define the number of components needed to account for 90% of the RQ sum.

Any chemical that is unaccounted for leads to an underestimation of the mixture risk. However, if the MAF is actually applied as an upper ceiling for the maximum acceptable single substance risk contribution, any compound that is not included in the initial assessment contributes with just $1/MAF_{exact}$ at maximum.

### *$MAF_{exact}$ is the preferred approach*

Table 4 provides a summary of the properties of the different MAF classes. In summary, $MAF_{exact}$ has at least seven distinct advantages, compared to other MAF classes:

**Table 3** Consequences for $MAF_{exact}$ and $MAF_{90\%}$ when the "true" risk of the most important mixture component is under- or overestimated by a factor of 10

| | Mixture 1 (actual risk) | Mixture 1 (underestimated risk) | Mixture 1 (overestimated risk) |
|---|---|---|---|
| RQ Substance 1 | 5 | **0.5** | **50** |
| RQ Substance 2 | 4 | 4 | 4 |
| RQ Substance 3 | 0.5 | 0.5 | 0.5 |
| RQ Substance 4 | 0.2 | 0.2 | 0.2 |
| RQ Substance 5–10 | 0.05 | 0.05 | 0.05 |
| RQ sum | 10 | 5.5 | 55 |
| $MAF_{90\%}$ | 2 | 3 | 1 |
| RQ sum after applying $MAF_{90\%}$ | 2 | 1.5 | 55 |
| $MAF_{exact}$ | 5.7 | 5.7 | 5.7 |
| RQ sum after applying $MAF_{exact}$ | 1 | 1 | 1 |

Despite the RQ of the most important compound being under- or over-estimated by a factor of 10 (see boldfaced values), $MAF_{exact}$ remains unchanged, in contrast to $MAF_{90\%}$ (which consistently leads to a residual risk exceeding 1)

1. The application of a $MAF_{exact}$ is conceptually identical to the current approach for substance registration and authorization under REACH and similar regulatory frameworks. No new approaches are needed, only the yardstick for defining safe use changes from "safe use is demonstrated if the ratio of expected exposure to hazard threshold is at or below 1" to "safe use is demonstrated if the ratio of expected exposure to hazard threshold is at or below 1/ $MAF_{exact}$".
2. $MAF_{exact}$ focusses implicitly on the mixture risk drivers, where improved risk assessment and/or risk mitigation have a tangible impact. Substances with small risk quotients (chemicals with low emission volumes and chemicals with low hazards) are not affected.
3. Mixtures of no concern always result in a $MAF_{exact}$ of 1. This minimizes the risk of overregulating (groups of) exposure scenarios in which the overall risk is acceptable.
4. The dynamics of the mixture risk across a range of exposure scenarios are captured in the distribution of $MAF_{exact}$ values, and are not scattered across several descriptors (distribution of MAF values, distribution of residual risks after the MAF application, *a priori* decision on a certain percentage of chemicals to be included). This facilitates an informed discussion on suitable protection goals, cost–benefit considerations, etc.
5. Setting the numerical goal of applying $MAF_{exact}$ to "the sum of risk characterization ratios of all individual components shall not exceed 1" is an operationalization of Europe's political goal of a "toxic-free environment" as outlined in the European Action Plan on a "Pathway to a Healthy Planet for All: Towards Zero Pollution for Air, Water and Soil". [26]
6. The $MAF_{exact}$ allows a simple adjustment to different protection goals for different exposure scenarios, simply by setting different numerical values for the acceptable residual risk.
7. The $MAF_{exact}$ is robust against exposure and hazard data of poor quality.

Some of those characteristics are shared with the other MAF classes. However, only $MAF_{exact}$ combines all seven characteristics.

### A case study example

Figure 3 shows the distribution of the RQ values for the mixtures analyzed in Socianu et al. [32]. The underlying exposure data were compiled from aggregated human biomonitoring data that were recorded in the HBM4EU project, https://www.hbm4eu.eu/. 20 chemicals were included in the exposure evaluation of the adult population, 17 chemicals were considered for the infant population, using health-based guidance values for the most critical toxicological endpoint, independent of mode-of-action and grouping considerations.

Figure 3A, C represents the distribution of the median RQ values for the adult and infant population, respectively, while Fig. 3B, D represents the corresponding upper 95% exposure percentiles. No reliable RQ values could be calculated for children for arsenic compounds, pyrethroids and chlorpyrifos. As arsenic compounds actually contribute quite substantially to the overall risk in the adult population, this explains the lower RCR sum for children and emphasizes how critical it is to include all relevant compounds in the mixture assessment.

The resulting MAF values are summarized in Table 5. As expected (see above), the numerical values for

**Table 4** Properties of the different MAF classes

| | Factor | Ceiling | | |
|---|---|---|---|---|
| | $MAF_{factor}$ | $MAF_{exact}$ | $MAF_{80\%}$, $MAF_{90\%}$, $MAF_{95\%}$ | $MAF_{2}$, $MAF_{5}$, $MAF_{10}$, $MAF_{100}$ |
| **Assumptions** | - ***All relevant mixture components identified***<br>- Risk characterization ratios are unbiased estimates for the actual risk contribution of a substance<br>- Summation of risk quotients adequate for estimating mixture risks<br>- Risks of the individual chemicals are independent of each other | - ***All relevant mixture components identified***<br>- Risk characterization ratios are unbiased estimates for the actual risk contribution of a substance<br>- Summation of risk quotients adequate for estimating mixture risks<br>- Risks of the individual chemicals are independent of each other | - ***All relevant mixture components identified***<br>- Risk characterization ratios are unbiased estimates for the actual risk contribution of a substance<br>- Summation of risk quotients adequate for estimating mixture risks<br>- Risks of the individual chemicals are independent of each other<br>- Pareto-distribution of RCR values | - ***All relevant mixture components identified***<br>- Risk characterization ratios are unbiased estimates for the actual risk contribution of a substance<br>- Summation of risk quotients adequate for estimating mixture risks<br>- Risks of the individual chemicals are independent of each other |
| **Regulatory suitability** | - ***Ensures that the mixture risk, after the application of the MAF, is compatible with the European "zero-pollution ambition for 2050"***<br>- ***Similar impact (risk reduction requirements) for all substances, including low-risk compounds and compounds with low emission rates***<br>- Straight forward to implement into the workflow of safety assessment under REACH, after a regulatory MAF value is agreed upon<br>- Concerns over equitable treatment of REACH registrants because registration requires demonstration of safety, not a precise assessment of risks. Registrants with different methodologies to demonstrate safe use would be affected differently by the MAF | - ***Ensures that the mixture risk, after the application of the MAF, is compatible with the European "zero-pollution ambition for 2050"***<br>- ***Impact proportional to (a) the relative contribution of a substance: high-risk substances(high emissions and/or high toxicity) are affected most, low-risk substances are not affected, and (b) the accuracy of the underlying risk estimates: substances with low-quality risk estimates (high assessment factors) are affected more***<br>- Straight forward to implement into the workflow of safety assessment under REACH, after a regulatory MAF value is agreed upon | - ***Residual risk, after the application of the MAF, is systematically higher than what is compatible with the European "zero-pollution ambition for 2050"***<br>- Impact proportional to (a) the relative contribution of a substance: high-risk substances are affected most, low-risk substances are not affected, and (b) the accuracy of the underlying risk estimates: substances with low-quality risk estimates (high assessment factors) are affected most<br>- Simple to implement into the workflow of safety assessment under REACH, after a regulatory MAF value is agreed upon | - ***Unclear, how the residual risk, after the application of the MAF, relate to the European "zero-pollution ambition for 2050"***<br>- Impact proportional to (a) the relative contribution of a substance: high-risk substances are affected most, low-risk substances are not affected, and (b) the accuracy of the underlying risk estimates: substances with low-quality risk estimates (high assessment factors) are affected most<br>- Simple to implement into the workflow of safety assessment under REACH, after a regulatory MAF value is agreed upon |
| **Risk of over-regulation** | - ***None, as long as the basic assumptions are fulfilled*** | - ***None, as long as the basic assumptions are fulfilled*** | - If applied to mixtures with RQsum < 1.0, otherwise no risk of over-regulation | - Depends on the value chosen a priori<br>- If applied to mixtures with RQsum < 1.0<br>- The exact amount of risk over-regulation is unpredictable and scenario-specific |
| **Risk of under-regulation** | - ***None, as long as the basic assumptions are fulfilled*** | - ***None, as long as the basic assumptions are fulfilled*** | - ***Systematic risk of under-regulation for a sizeable fraction of relevant mixtures, even if the basic assumptions are fulfilled***<br>- The exact amount of risk under-regulation is unpredictable and scenario-specific | - Depends on the value chosen a priori<br>- The exact amount of risk under-regulation is unpredictable and scenario-specific |
| **Robustness** | - **MAF estimate depends on the average data quality** (exposure, hazard) of all mixture components | - **Second highest robustness of all MAF alternatives**<br>- The actual numerical RCR value of the mixture components only matters insofar as it determines the proper classification of the substances into "risk drivers" (RCR > 1/MAF) and non-"risk drivers" (RCR < = 1/RCR) | - **MAF estimate depends mainly on the accurate quantitative risk characterization of the "risk drivers",** i.e., those compounds that account for x % of the risk | - **Highest robustness of all MAF alternatives**<br>- MAF value set a priori, which makes it independent of the data quality available for the mixture components |

Under-regulation: a mixture is not specifically regulated although its risk exceeds the safe level. Over-regulation: a mixture is specifically regulated although its risk does not exceed the safe level

$MAF_{exact}$ are highest, but its application affects only between 4 and 8 substances. These are the substances whose initial RQ values exceed the acceptable value of 1/ $MAF_{exact}$.

The factor by which the initial RQ values need to be reduced differs substantially between those compounds that are affected by the application of $MAF_{exact}$. For example, the maximum risk reduction is required for PFOS in the upper 95% percentile scenario. Even from a single substance perspective, its risk is too high, by a factor of 2.84 (Fig. 3B). Taking MAF considerations into account, the risk contribution needs to be lowered by an additional factor of 10.1 (= $MAF_{exact}$). On the other hand, the risk contribution of DEHP in the same exposure scenario (Fig. 3B) is acceptable from a single substance perspective (RQ = 0.17), but would need to be lowered by a factor of 1.7 to reach the critical value of 1/ $MAF_{exact}$ = 0.1, i.e., the maximum risk contribution that is acceptable also from a mixture perspective.

The application of $MAF_{90\%}$ leads to largely similar results as $MAF_{exact}$, but with a residual risk constantly exceeding 1 (Table 4). This shows, again, that the application of $MAF_{90\%}$ (or similar types of MAF values estimated using algorithms from group 2) does not ensure that the application of the MAF would achieve the goal of the European zero pollution ambition (RCR sum of not more than 1). As discussed earlier, this might be acceptable in certain situations (e.g., mixtures in heavily modified bodies of water). But this should be an intentional regulatory decision, not a semi-random result of insufficiently accurate numerical MAF estimations.

#### Mixture assessment factor or mixture allocation factor?

The MAF is conceptually different from the "classical" assessment factors used in regulatory chemical risk assessment and management, e.g., under REACH. Such assessment factors conservatively account for data gaps. It is the responsibility of the registrant to adjust them according to the amount and quality of the (eco)toxicological data at hand. As a consequence, a registrant can reduce assessment factors along the guidelines provided by regulatory authorities, by providing more and better (eco)toxicological data.

In sharp contrast, a MAF is the result of a combined hazard and exposure assessment. Given that an individual registrant rarely has the possibility to impact broader co-exposure patterns, the MAF-size cannot be adjusted in the context of a typical tiered risk assessment approach.

The MAF is actually an allocation factor, similar to the allocation factors used for example by the WHO to distinguish the contributions of different exposure pathways to an overall chemical exposure during drinking water quality assessment [33]. Allocation factors reflect the notion that the exposed entity (human or environmental organisms) has a given tolerance for toxic stress and that the different exposure pathways all occupy a certain fraction of the available exposure space, i.e., they all contribute to filling up a "risk cup", in proportion to the corresponding individual risk quotients. The risk cup / allocation factor concept is applied in the context of evaluating coincidental mixtures already for certain pesticide mixtures under the Food Quality Protection Act of the United States [34]. Taken together with the generally accepted notion that Concentration Addition is a suitable first tier of mixture risk evaluations in general [5, 6] and references therein), the risk cup concept lends itself naturally to a broader application for mixture risk assessments.

#### The MAF in a regulatory context

The MAF has been suggested as an instrument to account for the fact that real-world mixtures typically cause a risk that is higher than the risk of each of the individual component (at the concentration at which it is present in the mixture), without requesting a whole range of in-depth and scenario-specific mixture risk assessments from each company that registers a substance or applies for its authorization. The MAF is therefore a regulatory instrument for improving the risk assessment and risk management of chemicals, to be applied mainly in the prospective assessment during substance registration or authorization.

$MAF_{exact}$, as described in detail above, is the scientific approach to estimate the maximum acceptable risk contribution of each component in a given mixture, so that the RQ sum of a given mixture reaches exactly 1. $MAF_{exact}$ is therefore an estimate that is specific for each analyzed mixture. There are two options on how to translate such a scientific specific MAF into a regulatory MAF, i.e., a numerical estimate that can be included in a regulatory framework. Deriving a regulatory MAF requires to decide on one numerical estimate that is representative for a broader exposure scenario, e.g., all the mixtures occurring in a given geographical area or in a defined human (sub-)population. A basic prerequisite for setting a regulatory MAF is that the understanding of co-exposure patterns in the scenario of interest and of the (eco) toxicological properties of the involved chemicals is sufficient to derive reliable estimates on maximum acceptable concentrations.

The first option for estimating a regulatory MAF is to average the exposure data from all mixtures included in a given scenario, in order to describe the typical exposure situation and then calculate a MAF value on this basis

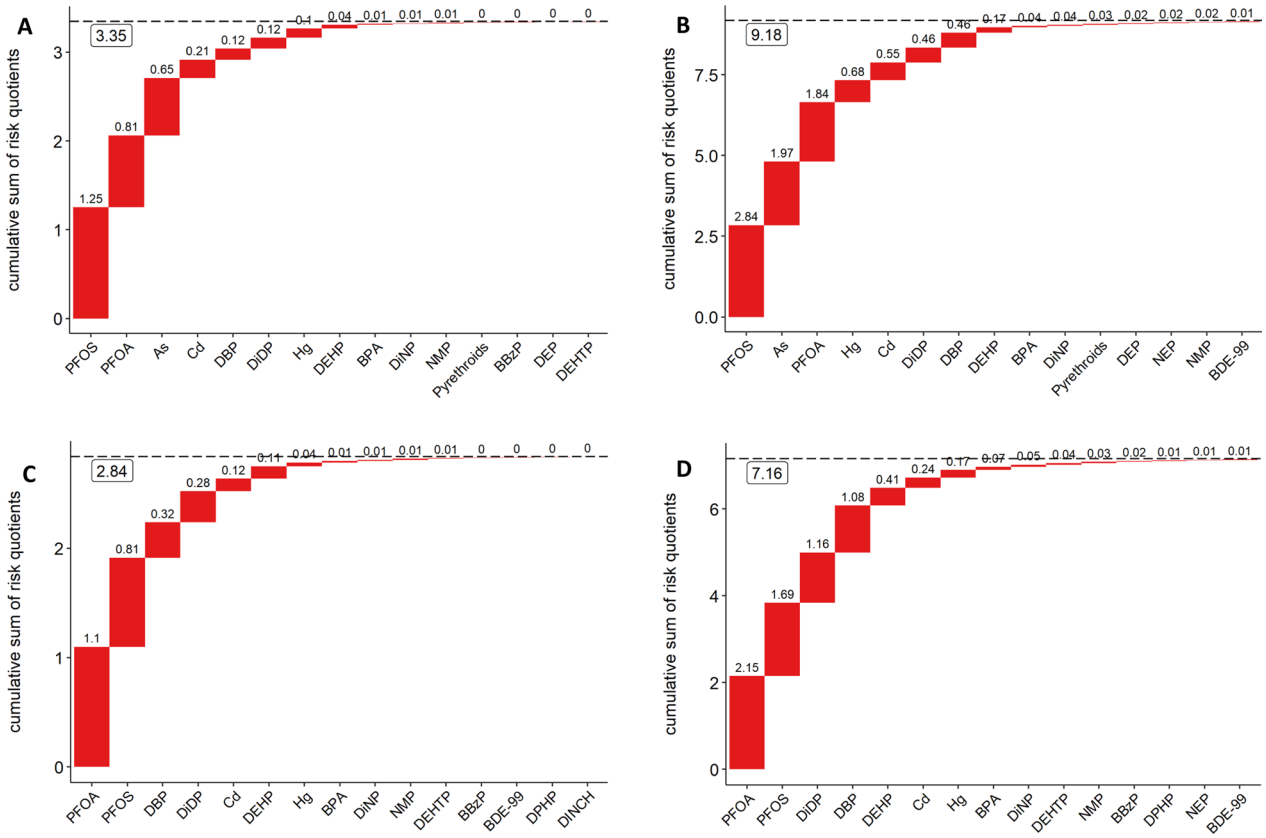


**Fig. 3** Distribution of RQ values in the study by Socianu et al. [29]. **A** RQ values based on median exposure (50% percentile) of adults. **B** RQ values based on maximum exposures (95% percentile) of adults. **C** RQ values based on median exposure (50% percentile) of children. **D** RQ values based on maximum exposure (95% percentile) of children. Only the 15 compounds with the highest RQ values are plotted. *DEP* diethyl phthalate, *BBzP* butylbenzyl phthalate, *DEHP* di(2-ethylhexyl)phthalate, *DiBP* di-iso-butyl phthalate, *DiDP* di-isodecyl phthalate, *DiNP* di-isononyl phthalate, *DEHTP* di-2-ethylhexyl terephthalate, *DPHP* di(2-propylheptyl) phthalate, DINCH: di-isononyl cyclohexane-1,2-dicarboxylate, *PFOS* perfluorooctane sulfonic acid, *PFOA* perfluorooctanoic acid, *BPA* bisphenol A, *BDE-99* polybrominated diphenylether 99, Cd: cadmium, As: arsenic compounds, Hg: mercury. RQ values taken from Socianu et al. [32]. Please note the different scales of the y-axis in the four sub-plots

(see the case study described above). The second option is to calculate a specific MAF for each individual mixture, i.e., for each sample. From the resulting distribution of all the sample-specific MAF values, a sufficiently protective regulatory MAF can then be estimated, for example by selecting the upper 95% percentile of the distribution of sample-specific MAF values.

The second approach allows a more detailed analysis and provides a better understanding of exposure and risk dynamics. However, implementing this approach might not always be possible. For example, the individual exposure profiles of the participants in a human monitoring study are often not available for re-analysis due to privacy considerations.

It will be a major challenge to decide which samples should be grouped together for sizing a regulatory MAF. How broad or how specific are the criteria used for grouping samples to define a regulatory MAF? Are the grouping criteria defined in relation to, for example, chemical class, geographic area or exposed (sub)population)?

If the scenario definition is too broad, the resulting regulatory MAF risks being either over- or under-protective for many of the situations that were grouped together. If the scenario definition is too specific, there will be a whole collection of MAF values to be considered for a given substance, making the MAF less useful as a regulatory instrument. Finding the right balance here depends on the differences of the MAF values in scenarios of different specificity. Collecting and analyzing case studies in detail, in order to provide a better understanding of necessary MAF sizes in relation to mixture risks, will be a in important task for the future, for example in the context of the European Partnership for the Assessment of Risks from Chemicals (PARC).

The MAF reflects the acceptable contribution of an emitted chemical to the overall toxic burden of an ecosystem or a human population. It is based on a broad

**Table 5 MAF values determined in the study by Socianu et al.** [29]

| | RQ sum | $MAF_{factor}$ | | | $MAF_{exact}$ | | | $MAF_{90\%}$ | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Value | Res. risk | NAS | Value | Res. Risk | NAS | Value | Res. Risk | NAS |
| R50 (adults) | 3.35 | 3.1 | 1 | 20 | 7.03 | 1 | 4 | 5 | 1.2 | 4 |
| R95 (adults) | 9.18 | 5.53 | 1 | 20 | 10.1 | 1 | 8 | 6 | 1.54 | 8 |
| R50 (children) | 2.84 | 2.74 | 1 | 17 | 5.85 | 1 | 4 | 5 | 1.12 | 4 |
| R95 (children) | 7.16 | 5.08 | 1 | 17 | 9.46 | 1 | 7 | 5 | 1.63 | 6 |

RQSum: sum of the individual risk quotients of the initial mixture. $MAF_{factor}$, $MAF_{exact}$, $MAF_{90\%}$: MAF values calculated according to the different algorithms (see text). Value: numerical value of the MAF, Res. Risk: residual risk, i.e., the sum of the risk quotients after applying the MAF. NAS: number of affected substances, i.e., number of substances for which the initial risk quotient needs to be reduced

The investigated mixtures comprised 20 substances (adults) and 17 substances (children), respectively. For details, see Socianu [29]

overview of chemical exposures, amended, if necessary and feasible, by specific considerations (e.g., presence of PBT/vPvB substances or endocrine disrupters) as well as political/socio-economic considerations such as risk–benefit evaluations. Only regulatory authorities can be expected to accrue the necessary knowledge on chemical use and emissions across different actors and use patterns, necessary to initially size and then adjust the MAF in view of evolving scientific knowledge and ever-changing exposure patterns. However, even authorities might need to develop improved exposure evaluations that go beyond current generic estimates and better take co-exposure patterns into account. Finally, only regulatory authorities can be provided with a political mandate to balance the different economic and societal demands, in order to ensure a fair sharing of the available emission space.

The size of the MAF is a result of integrating the co-exposure patterns in a given large-scale scenario with the hazard profiles of the involved compounds. Especially the former will change continuously, as chemical use and production change. Also regulatory decisions, such as use restrictions, will impact the emissions of the affected chemicals. It will therefore be important to design future chemical monitoring and modeling campaigns with a view on describing co-exposure patterns, and to systematically feed the results of these activities back into the review process of chemical regulations.

The current analysis focusses on chemicals that are toxic to the exposed entities and that have no natural background concentration. Incorporating such substances, e.g., phosphate, nitrate or metals, will require further fine-tuning and adjustment of the MAF concept.

Our current understanding of co-exposure patterns and of the (eco)toxicological potency of many of the involved chemicals is still limited, but is continuously increasing across the board. While it is clear that a MAF is urgently needed now, given that current approaches for chemical risk and safety assessment insufficiently protect against elevated mixture risks [5, 6, 13, 35], the first-generation of MAF values might need to be (partly) driven by pragmatic considerations, which should be refined in regular intervals, in view of new empirical data (and changes in chemical use and emission). As usual, the challenge will be to derive a sufficiently, but not excessively protective value, while avoiding paralysis by analysis.

Chemicals on the European market will be affected differently by the application of a MAF:

1) Chemicals with low emission rates and/or low hazards. Chemicals with an RQ value of less than 1/MAF will not be affected by the implementation of a MAF. However, the underlying documents that support chemical safety assessment would need to be checked accordingly, which requires a limited effort from all companies producing or importing chemicals for the European market.
2) Chemicals with an RQ value exceeding 1/MAF for which the RQ value can be lowered by providing better/additional data on their exposure and/or hazard. This group includes chemicals whose safety assessment is based on only few empirical data and cautious default hazard and exposure assessments. Implementing a MAF for those chemicals will require investing additional resources to improve the precision of the underlying exposure and/or hazard assessments, but does not have any direct consequences for the marketing of the chemical.
3) Chemicals with an RQ value exceeding 1/MAF for which the RQ value can only be lowered by implementing additional risk mitigation measures, i.e., exposure reductions.

In particular, the implementation of exposure reduction measures for the third group of chemicals will support achieving the European zero pollution ambition, as outlined in the Chemicals Strategy for Sustainability [14] and European zero pollution action plan [26].

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**Author contributions**
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**Availability of data and materials**
All data are provided within the text. The underlying algorithms are made publically available at https://github.com/ThomasBackhausLab/MAF, implemented in Excel and in the statistical software R.

## Declarations

**Ethics approval and consent to participate**
Not applicable.

**Consent for publication**
Consent for publication is provided by the EU Commission as well as the Swedish Chemicals Agency.

**Competing interests**
Parts of the presented work were performed as contract research for the Swedish Chemicals Agency and the European Commission. Neither organization had any impact on the scientific content of the work. T.B. is an unpaid member of the EU Commission's Committee on Health, Environmental and Emerging Risks (SCHEER). T.B. is also an unpaid member of the board of the International Panel on Chemical Pollution (IPCP), a Swiss foundation working on global issues related to chemical pollution. T.B. is also an unpaid member of the board of the Food Packaging Forum (FPF), a Swiss foundation working on chemicals in food contact materials.

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