National Institute for Public Health
and the Environment
Ministry of Health, Welfare and Sport

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RIVM Letter report 2016-0162
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Colophon

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This investigation has been performed by order and for the account of Ministry of Infrastructure and the Environment, within the framework of the REACH Regulation

This is a publication of:
National Institute for Public Health and the Environment
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The Netherlands
www.rivm.nl/en

Synopsis

Addressing combined effects of chemicals in environmental safety assessment under REACH - A thought starter

Within current risk assessment practices of chemicals, safe production and use for humans and the environment is most often evaluated per-chemical. However, in the environment there are always multiple chemicals simultaneously present. It is therefore of importance to assess the combined effects of co-occurring chemicals. The European Commission concluded in 2009 that current risk assessment practices insufficiently consider these combined effects. In this thought starter, the RIVM proposes an approach to account for such effects in the environmental risk assessment of substances under the REACH Regulation.

It is proposed to introduce a data-driven Mixture Assessment Factor (MAF) when assessing the environmental risk of a single substance under REACH. This factor should account for the number of chemicals that may possibly co-occur after emission of the target substance to the environment and that may consequently contribute to the combined effect. In this way is intended to ensure that, after emission to the environment, the substance together with all other chemicals present causes no combined environmental risk. In addition to this generic EU-wide approach, there is the possibility to consider further protective and curative measures on a site-specific basis when needed.

The approach proposed here as a thought starter is not new and has been employed in the Netherlands for quite some time in the derivation of negligible risk levels for the environment. The eventual quantification of the MAF under REACH requires further work with regard to the identification of (the number of) chemicals that contribute most to the overall EU-wide combined effects. An important aspect in this regard is to establish an acceptable protection-level to safeguard the nontoxic environment with regard to combined effects of chemicals. Also important is to determine to what extent combined effects of chemicals should be addressed via a generic approach at EU-level or whether it might be more efficient to address location specific risks at local or national level.

Keywords: mixture, combined effects, environmental risk assessment, biodiversity, chemicals, substances, REACH

Publiekssamenvatting

Combinatie-effecten van chemische stoffen meewegen binnen de milieurisicobeoordeling van stoffen onder REACH - Een mogelijke aanpak

In de huidige beoordeling van stoffen en producten worden de risico's voor mens en milieu veelal per stof bekeken. In het milieu zijn echter altijd meerdere chemische stoffen tegelijk aanwezig. Het is daarom van belang om mee te wegen welke effecten deze stoffen samen kunnen hebben. De Europese Commissie concludeerde in 2009 dat in de huidige risicobeoordelingen van stoffen en producten onvoldoende rekening wordt gehouden met deze combinatie-effecten. Het RIVM reikt in dit discussiestuk een optie aan voor het meewegen van combinatie-effecten in de milieurisicobeoordeling van stoffen onder de REACH regelgeving.

Voorgesteld wordt om bij de beoordeling van de risico's van stoffen een zogenoemde Mixture Assessment Factor (MAF) toe te passen die is afgeleid op basis van veldgegevens. De factor drukt uit hoeveel stoffen bij de risicobeoordeling moeten worden meegewogen om voor een enkele stof te beoordelen of de productie en het gebruik uiteindelijk veilig zijn. Op deze manier wordt beoogd te bereiken dat alle stoffen samen, na emissie naar het milieu, geen milieurisico veroorzaken. Naast deze generieke aanpak onder REACH is er de ruimte om lokale situaties waar nodig individueel aan te pakken.

Het voorstel voor een mogelijke methode om combinatie-effecten van stoffen in het milieu mee te nemen in de risicobeoordeling is niet nieuw. Hij wordt binnen Nederland al geruime tijd gebruikt om risicogrenzen voor stoffen in het milieu te bepalen. De precieze invulling van de MAF moet nog nader worden uitgewerkt. Aandachtspunt hierbij is in welke mate milieueffecten acceptabel worden gevonden, bijvoorbeeld omdat het ecosysteem ervan kan herstellen. Ook is het van belang te bepalen tot op welke hoogte er binnen REACH op generiek Europees niveau rekening gehouden dient te worden met combinatie-effecten. Zo kan het bijvoorbeeld efficiënter zijn om locatie specifieke risico's lokaal, of nationaal aan te pakken.

Kernwoorden: mengsel, combinatie-effecten, milieurisico, biodiversiteit, chemische stof, REACH

Contents

Summary

In 2012, the European Commission concluded that the EU legislation is not fit to address adverse effects for humans and the environment resulting from combined exposure to multiple chemicals. Consequently, combined exposure to these chemicals may be less safe than the chemical safety assessment for the individual chemicals may indicate. This has led to a policy pledge to explore scientifically justified options to take combined effects of chemicals into account in risk assessment and risk management in Europe.

The present thought starter explores a scientifically acceptable option to account for combined effects of chemicals in the environment when registering substances under the REACH Regulation with a focus on the local freshwater risk assessment. Point of departure is that combined effects of chemicals are of environmental concern and that risks of individual chemicals can be aggregated by assuming *concentration addition* as a realistic worst-case approximation in the absence of more detailed insights in the specific (combined) effects of chemicals. The mixture toxic pressure method adopts this approximation to model the potential fraction of species affected by multiple substance exposure as a quantitative measure of the combined toxic pressure of multiple chemicals in the environment, quantified as msPAF[1]. Because recent analyses by Posthuma et al. (2016) has suggested that the msPAF relates to the actual ecosystem integrity observed from field data, the present thought starter identifies the msPAF as a measure to define the protection-level to safeguard a nontoxic environment for combined effects of chemicals. This measure can accordingly be used in further environmental risk assessment and risk management decision making with regard to combined effects of chemicals, e.g. under REACH.

Addressing combined effects of chemicals in the environment in the context of registering safe production and use of substances under REACH implies accounting for an *a priori* unknown set of combinations of possible co-occurring chemicals. Challenge is to confine this set to those chemicals, types of chemicals or chemical groups that dominate combined effects in the environment. To date, information is lacking to allow such a chemical specific confinement. Available data do suggest though, that the total number of co-occurring chemicals contributing to combined effects in the freshwater environment depends on the scale at which the effect is assessed (being e.g. a small pond, a river or a catchment area). The available data also suggest that for any given combination of chemicals the overall combined effect seems dominated by only a limited number of all chemicals co-occurring.

In the absence of chemical specific information, combined effects of chemicals may only be taken into account by following a generic approach. For this, the present thought starter proposes to adopt the Mixture Assessment Factor (MAF) concept introduced by Backhaus et al.

[1] multi-substance Potentially Affected Fraction

(2010) and others to account for the possible environmental co-existence of chemicals while assessing safe production and uses of substances under REACH. Under conditions of a level-playing field for chemicals and appreciating the *a priori* uncertainty regarding chemical combinations and relative contributions to the overall toxic pressure, safe production and use is safeguarded when the *n* dominating chemicals equally contribute to the 'toxic space' available within the boundaries of a nontoxic environment. Following this line of thought, the present thought starter proposes that a MAF equal to *n* may be used to account for combined effects of chemicals in the environment when registering safe production and use of substances under REACH. For the environmental risk assessment of a single substance *A* this would imply that the following is motivated by the registrant for every individual local emission scenario *x* of a substance *A*:

$$\frac{PEC(A, local, x)}{PNEC(A)} \leq \frac{1}{MAF}$$

In real life situations though, these *n* chemicals will rarely co-exist at exactly their environmental concentration of 1/*n* of the PNEC. The current proposal of a MAF of *n* is therefore considered a worst-case approach. The apparent uncertainty could be reflected in the MAF provided that a generic distribution profile of relative contributions of the *n* chemicals would be known. Alternatively, statistical distribution models could be used. Current insight in chemical distribution profiles is judged insufficient to support such a more refined distribution in the MAF.

Preliminary data analyses to collect information on the possible magnitude of a MAF suggest that the combined effect of multiple chemicals in the local freshwater environment is most often dominated by 5 to 10 chemicals, irrespective of the type of chemicals involved (Posthuma et al. 2016). This finding is in line with modelling results published previously by Harbers et al. (2006) and Zijp et al. (2014) and is supported by experimental and observational studies by e.g. Backhaus and Karlsson (2014). Though these findings hint that at a local scale and for the freshwater compartment a preliminary MAF may be of the order of 10, these results should be further evaluated for a EU representative data set of monitoring data to draw more firm conclusions as the analyses by Posthuma et al. (2016) is based on a preliminary assessment of direct effects on macrofauna from Dutch monitoring data that not necessarily reflect the EU situation and where not collected with the view to obtain better understanding on the specifics underlying combined effects of chemicals in the environment.

Insight in the number of chemicals, specific chemicals or chemical groups that matter most with regard to combined effects in the environment Europe-wide is needed to further refine and validate the MAF-concept. Several initiatives are currently generating further insight in these areas, like e.g. the EU-project SOLUTIONS and a tailored workshop effort of SETAC. In addition to this, thorough policy discussion is needed to identify the acceptable protection-level related to the European goal of a non-toxic environment for combined effects of chemicals and the resulting need for further regulation. One important element that should be addressed in this context is the appropriate and most effective type of regulation to address the concern at hand, e.g. employing a generic European wide approach through REACH in the phase of substance registration, a more location specific approach via national or regional regulatory instruments, or a combination thereof. Policy discussions should preferably also elaborate on the proportionality and feasibility of implementing optional approaches to take combined effects of chemicals into account in risk assessment and risk management. This should include legal issues related to the potential implementation of a generic approach for combined effects of chemicals in the substances safety assessments under REACH and in other regulatory frameworks. This thought starter identifies that a follow-up discussion is also needed on the applicability of such an approach in other REACH processes such as authorization, restriction and substance evaluation.

1 Introduction

1.1 Setting the scene

In 2012, the European Commission (EC) published a Communication on combination effect of chemicals (EC 2012, COM 2012-252 final), concluding that combined effects of chemicals on humans and the environment are a reason for concern that is insufficiently addressed by the various regulatory frameworks within Europe. These conclusions were e.g. based on an extensive review performed by Kortenkamp et al. (2009) showing clear evidence from realistic exposure situations that combined exposure to chemicals may lead to adverse effects on environmental and human health (see also e.g. Malaj et al. 2015, RIVM 2015, Schäfer et al. 2016, Posthuma et al. 2016 for more recent analyses pointing in that same direction). In the Communication, the Commission highlighted the need to address this issue and stated that scientific options to do so were available. However, it was concluded that current EU legislation does not provide for a comprehensive and integrated assessment of effects from combined exposure to different chemicals and does not have a mechanism for promoting an integrated and coordinated assessment of such kind across the different pieces of EU legislation (see section 5.1 (1) of the Communication). One important limitation identified is that chemical safety is most often evaluated for single chemicals or products and is not taking into account the eventual combined exposure of these chemicals that will arise after emission.

Several (scientific) initiatives are now underway to address combined exposure to multiple chemicals in various domains of risk and safety assessment. Examples hereof are, e.g. the OECD Guidance development on assessing the risks of combined exposure to multiple chemicals, the EFSA Guidance on addressing combined effects of active ingredients of plant protection products[2], the Euromix project[3] addressing food safety, the FP7 project SOLUTIONS[4] addressing surface water toxicity and most recently the EFSA MixTox initiative[5] aiming to harmonize human and ecological risk assessment methods for addressing problems of combined exposure to chemicals.

The occurrence and effects of combined exposure of chemicals may be addressed by regulating emissions via regulations such as the Industrial Emission Directive (2010/75/EU) or by taking combined exposure into account in the environmental quality assessment under the Water Framework Directive (2000/60/EC). Combined exposure of chemicals could also be addressed prior to market introduction, via substance oriented regulations like the REACH Regulation (2006/1907/EC) or product oriented regulations among which e.g. the Cosmetics Regulation (2009/1223/EC), the Biocidal Product Regulation (2012/528/EU) and the

[2] http://ec.europa.eu/food/plant/pesticides/max_residue_levels/cumulative_risk_en
[3] https://www.euromixproject.eu/
[4] http://www.solutions-project.eu/
[5] https://www.efsa.europa.eu/en/topics/topic/chemicalmixtures

Plant Protection Product Regulation (2009/1107/EC). The current thought starter discusses a possible approach to account for combined effects of chemicals on the environment when registering substances under the REACH Regulation. More specifically, the scope is the consideration of combined effects of multiple chemicals when performing the environmental risk assessment of single-substances in the Chemical Safety Report (CSR) for the local freshwater compartment. It complements the reports by e.g. Backhaus et al. (2010) and Groβ et al. (2011) on addressing combined effects of chemicals in the environment under REACH and by Bunke et al. (2014) who analyzed different approaches to address combined effects of chemicals in technical mixtures under the REACH Regulation. The focus on the local scale freshwater compartment was chosen for practical reasons of data availability and because in practice under REACH local exposure scenarios are often most critical with respect to organizing safe production and use of substances compared to regional or continental exposure scenarios. Though this is not further elaborated here, it is expected that given the similarities between methods a similar approach may also be adopted for the regional and continental scale risk assessment levels.

1.2 Accounting for effects of unknown combinations of chemicals

The possibility to address the safety of combined effects of multiple chemicals on the environment in regulatory risk management depends strongly on the available information. A specific assessment of (expected) combined effects at hand is possible in the presence of knowledge on the exact combination of chemicals. An example of such a system in current regulation is the Biocidal Product Regulation (BPR), which recently introduced a 'sum-PEC/PNEC<1' approach to assess the environmental safety of a known mixture of active ingredients of a biocidal product prior to its market introduction[6]. However, in the absence of specific information on the combination of chemicals present in the environment in the process of registering safe use of a substance under REACH, such a targeted assessment is not possible.

There are several ongoing research efforts that aim to provide more insight into expected combinations of chemicals in the environment in Europe (e.g. the FP7-project SOLUTIONS, and efforts made in the context of a SETAC Pellston Workshop, see also Sections 2.3 and 3). However, to date, there is no specific up-front information available on the relative contributions of individual chemicals within ambient combinations of chemicals to the net risks or effects at the local scale. Substances placed onto the European market end up in spatially highly variable concentrations in the environment all throughout Europe, with a potential 'one-chemical' problem in a local ditch, up to the potentially >100,000-compound combinations of any composition on a large geographical scale (Hendriks et al. 2013). Every environmental sample may therefore harbour a unique combination of substances with unique substance-specific concentrations. Point source emissions result in even more variable concentrations in space and time, e.g. with an expected high concentration gradient around production or waste treatment

[6] Transitional Guidance on mixture toxicity assessment for biocidal products for the environment (May 2014)

facilities, superimposed on the concentration patterns resulting from diffuse emissions. Consequently when registering safe use of a single substance, taking account of possible combined effects of chemicals on the environment would imply considering the potential environmental presence of an endless set of chemical combinations varying with time and space. Insight is needed into this spatio-temporal variability of ambient combinations of chemicals to support the derivation of conceptually sound options for *a priori* (e.g. REACH registration) or *a posteriori* (e.g. Water Framework Directive) approaches for assessing and managing these combined effects.

Backhaus et al. (2010) prepared an overview of different ways to account for combined effects of chemicals under the REACH Regulation. The generic approach, proposed by Backhaus et al. (2010) and others (e.g. Backhaus et al. 2013, JRC 2014, JRC 2015, KEMI 2015) to account for combined effects of chemicals on the environment under REACH, is the application of a Mixture Assessment Factor (MAF) (along similar lines, Price et al. (2014) proposed a Maximum Cumulative Ratio). The Netherlands adopted the MAF concept in the form of a generic factor of 100 more than 15 years ago in the derivation of national Negligible Risk levels for the environment (INS 1999)[7] to account mainly for the potential long-term impact of combined effects of chemicals. The INS-related assessment factor was chosen such that factual emissions of the suite of chemicals known to be produced would not violate the goal of environmental protection.

This thought starter discusses the possible implementation of the MAF concept in the environmental risk assessment of the Chemical Safety Report of a substance registration dossier and proposes some ideas on the possible quantification of this MAF on the basis of available data on combined effects of chemicals on the environment.

1.3 The MAF concept

In short, the MAF concept can be explained as a factor that is applied in a single-chemical risk assessment to account for the possible number of chemicals that contribute to (a large pre-defined fraction, e.g. 90, 95 or 99% of) the net environmental effect of realistic chemical combinations in order to maintain the non-toxic environmental quality standard. An important assumption underlying the MAF concept by Backhaus is that all effects of chemicals on the environment can be aggregated by the model of concentration addition (CA), a model that has been defined on the basis of the pharmacological concept of Simple Similar Action (two or more chemicals affect the same target site of toxic action). It was highlighted by Kortenkamp et al. (2009) and concluded by EC (2012) that this CA approach is most often a realistic worst case for evaluating combined effects of chemicals in the environment in the absence of more specific information on these chemicals, their modes of action and their interplay with species assemblages present in the environment (EC 2012, section 5.1 (5) and (6)).

[7] INS (1999) did not make reference to the Mixture Assessment Factor (MAF) but did adopt a similar approach as proposed by Backhaus and others to accounting for combined effects of chemicals on the environment.

Chemical safety assessment in the REACH regulation as well as in other regulatory frameworks most often addresses the safety of single substances 'in isolation' using a substance-by-substance approach. For the environment, the safety assessment involves evaluation of the PEC/PNEC[8] ratio, whereby sufficient safety is defined by a PEC/PNEC<1. The PEC is normally derived for the assessment of different spatial scale levels (i.e. for the continental-, the regional- and the local scale) and represents exposure concentrations for realistic emission scenarios. The PNEC is independent of the scale and derived per ecosystem for different ways of exposure to the substance (direct exposure, or indirect exposure via the food chain). Adopting this single-substances approach and assuming the default model of CA for combined effects of chemicals implies the linear summation of individual PEC/PNEC ratios per exposure route in order to get insights in aggregated risks. In case of a 'just safe' situation per chemical this sum can easily exceed the value of 1 when multiple chemicals are present[9].The Biocidal Product Regulation (BPR) utilizes this CA concept to approximate the combined effect of chemicals present in the mixture of a biocidal product as part of the products' environmental risk assessment.

Within the boundaries of the current single-substance oriented chemical safety assessment evaluating PEC/PNEC<1 and applying CA as realistic worst-case approach for aggregated risks, any combination of chemicals would similarly be considered 'safe' when the sum of PEC/PNEC ratios of all *n* chemicals present is below 1. In an *a priori* risk assessment for a single substance in the phase of its REACH registration it is unknown what other chemicals co-occur upon emission in the environment and what their concentrations and relative contributions to the combined effect on the environment are. For this *a priori* assessment this would generally imply that the environmental situation remains 'safe' when each chemical, including the single substance, is at maximum present at $1/n^{th}$ of its PNEC. In this situation, the MAF would be defined by *n* and the above set of concepts would translate into the following generic formula to account for combined effects of multiple chemicals in an *a priori* environmental risk assessment:

$$\sum_{n=1}^{n} \frac{PEC(n)}{PNEC(n)} \frac{1}{MAF} < 1$$

with *n* being the number of chemicals that influence the combined effect on the environment. This approach does not account for the fact that normally in the environment chemicals do not contribute equally to the overall toxic effect (non-equitoxicity of chemicals in the environment is a rule rather than an exception). Assuming that they do contribute in an equitoxic manner can be considered as a worst case assumption. However, in the absence of any more specific information about the combination chemicals present in the environment, there is also no ground to deviate from this assumption because it is *a priori* unknown how the non-equitoxicity is spread over the *n* chemicals that co-occur. Note that for an *a posteriori* evaluation of combined risks of multiple

[8] PEC=Predicted Environmental Concentration; PNEC=Predicted no-Effect Concentration
[9] A risk is defined by a PEC/PNEC > 1.

chemicals, e.g. based on measured water concentrations and an evaluation of non-equitoxicity in that known situation, a MAF would not be needed as a more refined assessment on true locality-based data is possible.

To summarize, a registrant registering the safe use of its substance under REACH uses primarily information about this single substance and currently has no insight in the vast variety of combinations of chemicals that this substance will co-occur with after emission. Based on a level-playing field policy need in the *a priori* evaluation of all substances, the assessment principles boil down to the idea that any potentially emitted chemical should, at maximum, be allowed to occupy a similar share of 'the safe space'. Hence, safe production and use can be motivated by the registrant showing that:

$$\frac{PEC(A)}{PNEC(A)} \leq \frac{1}{MAF}$$

with the *PEC(A)* being the predicted environmental concentration of substance *A* given its substance specific exposure scenario and the *PNEC(A)* being the predicted no-effect concentration of substance *A*. For the sake of the present thought starter, the PEC relates to the local scale level and the PNEC relates to the no-effect concentration for the freshwater compartment.

1.4 The challenge: quantifying the MAF

To account for combined effects of chemicals in the environment, the MAF should preferably not represent the number of chemicals that may potentially be present in the environment (i.e., > 100,000 compounds). The MAF should rather only account for the number of chemicals that dominate the combined effects at the threshold defining the nontoxic environment. Hence, the key question is: how many chemicals do dominate and are there, maybe, other data-driven possibilities to quantify the MAF to account for (a pre-defined large fraction of) the combined toxicity of chemicals in the environment?

Key to an effective concept is that the MAF:

1. Preferably can be applied super-imposed on current approaches, in this case the single-substance environmental risk assessment under the REACH registration process, applying PEC/PNEC ratio's as criterion to establish ecosystem structural and functional integrity.
2. Safeguards that its application on the PEC/PNEC risk assessment maintains ecosystem structural and functional integrity.

Section 2 presents first thoughts on possibilities to quantify the MAF for the freshwater environment at a local scale level. It is stressed that this quantification exercise is primarily based on monitoring data and modelling species sensitivity data on macrofauna species in the Dutch freshwater compartment. The information is obtained from historical chemical and biological monitoring data and it is noted that the set of monitored chemicals does not necessarily represent those chemicals that contribute most to ecotoxicity. Consequently, the eventual quantification of a MAF for use in the context of REACH may benefit from further insight into the spatial distribution of chemical combinations, their combined toxicity and, where possible, in those chemicals or chemical groups that dominate the combined effects of chemicals in the environment throughout Europe. The same holds true for different types of effects (e.g., highly-specific effects, such as endocrine disruption) and for organisms other than the macrofauna addressed here, for which further insight may prove of added value for an eventual MAF derivation.

Establishing a data-driven MAF furthermore requires thorough policy discussion. It is suggested that at least the following elements are considered in this context:

- The operationalization of the non-toxic environment goal in relation to combined effects of chemicals;
- The scale at which combined effects of chemicals should be taken into account in order to reach the protection goal;
- The interplay between different regulatory frameworks and how to best address the concern at hand regarding combined effects of chemicals.

These different elements are discussed in Section 3. Suggestions for building blocks to fuel this discussion are provided in Sections 2.1 and 2.2 reflecting on non-toxic environment standards in the possible value of the MAF, and in Sections 2.3 and 2.4 elaborating on the influence of scale on the possible value of the MAF. The thoughts presented in Section 2 on possibilities to quantify the MAF are meant to illustrate the concepts sketched in Section 1.3. The exercise should not be interpreted as a final proposal for a defined MAF.

2 Quantifying the MAF; a thought starter

2.1 Combined toxic pressure in a non-toxic environment

Since the earliest days of designing protective regulations for chemicals the policy protection endpoint for the environment has been defined in terms of maintenance of ecosystems' structural and functional integrity. An early operationalization hereof for use in daily practice is the 95%-protection level, safeguarding that no more than 5% of the species is exposed beyond its No Observed Effect Concentration (NOEC). In other words, the single-chemical chronic toxic pressure is maximized to 5% to maintain the ecosystem's structural and functional integrity (PAF_{NOEC} < 5% [10]). This approach has been used on a per-chemical basis to underpin the derivation of environmental quality standards. The same concept can be applied for the more recently defined nontoxic environment as the policy protection endpoint for the environment (EU Environmental Action Plan 7, Decision No 1386/2013/EU). One possibility to adapt this per-chemical concept to assess the combined toxic pressure from multiple chemicals is to derive the multi-substance Potentially Affected Fraction (msPAF) of species assemblages. The msPAF expresses the probability that the critical effect threshold for a species assemblage in a certain environment is exceeded as a result of combined exposure to multiple chemicals (Traas et al. 2002, De Zwart and Posthuma 2005). The higher the msPAF, the higher is the fraction of potentially affected species. The nontoxic environment could accordingly be defined by the threshold msPAF-level beyond which the toxic pressure on the environment is judged unacceptable. The msPAF combines the statistical approach for deriving environmental concentration limits for single chemicals with the classic combined toxicity models of *concentration addition* and *response addition* for chemicals with similar and dissimilar modes of action on the environment, which is slightly refined compared to the realistic worst-case assuming CA across all chemicals. The msPAF could in principle be derived for any end-point (e.g. NOEC or EC_{50}[11]). In practice though, the msPAF does not cover highly-specific mechanisms of action such as e.g. endocrine disruption, which is primarily due to lack of data. Operationalization of the use of msPAF to define a nontoxic environment requires evaluation of the relation between msPAF and the true fraction of affected species, e.g. based on analysis of monitoring data or impact data collected in tests with (semi-) natural species assemblages.

Posthuma and De Zwart (2012) compared the relationship between predicted msPAF and the field observations on combined effects of chemicals for a large number of samples from a collated set of monitoring data. They showed a clear relationship between the predicted $msPAF_{EC50}$ and the actual loss of aquatic species as derived from analysing the monitoring data. In a follow-up of this work, Posthuma et al. (2016) derived a generic relation between the $msPAF_{EC50}$ and the observed biodiversity of aquatic macrofauna by using

[10] Potentially Affected Fraction (PAF)
[11] EC_{50} is the Effect Concentration for which in 50% of the tested organisms an effect is observed.

Big Data analysis. This analysis of monitoring data using EC_{50} values, suggests that the $msPAF_{EC50}$ relates to taxa loss, which is related to the structural integrity of species assemblages. A higher $msPAF_{EC50}$ is found indicative of a higher taxa loss. Due to a systematic association between the $msPAF_{EC50}$ and the $msPAF_{NOEC}$, it also holds that increased $msPAF_{NOEC}$ relates to higher taxa loss. These findings suggest that the mixture toxic pressure metric may be used to set a protection-level for the combined toxic pressure of chemicals to operationalize the nontoxic environment.

As was pointed out before, it should be noted that these insights are only based on species sensitivity modelling to judge combined effects of multiple chemicals on the species composition of freshwater macrofauna taxa in the Netherlands that were generated for other reasons than to elucidate specific characteristics of combined effects of multiple chemicals. It is likely that a similar relationship pattern will also be valid for other taxa, other endpoints and other environmental compartments like air and soil and for other areas than the Netherlands. However, it is anticipated that the specific (numerical) correlation between the msPAF and the observed loss of taxa will be different for different system parameters (e.g. taxa, endpoint of concern, environmental compartment). Thus, while the presented results suggest that using the msPAF/taxa loss relationship may support operationalizing the protection goal of a nontoxic environment, quantitatively this deserves further study. A logical follow-up of the work by Posthuma et al. (2016) is to assess if a similar generic relationship does hold for other taxa, other endpoints, and other (European) regions. Including other environmental compartments like air and soil would be needed for extrapolating this approach to these compartments also, but this may be challenging because of the limitations in data.

2.2 Using msPAF for further policy considerations

RIVM (2008) illustrated how the mixture toxic pressure insights may support further policy making by mapping the time and location dependent variability of msPAF hotspots for freshwater locations in the Netherlands evaluated against the established 95%-protection level. A clear spatial variability of regions of higher and lower toxic pressure was shown. Highlighted were those locations where the environment was judged nontoxic (no species loss observable), where the environment may be threatened (emerging small tendencies of species loss, 95%-protection level just not breached) and where impacts on the environment maybe evident (species loss, biodiversity affected, 95%-protection level breached). It is anticipated that the existing EU-wide set of monitoring data does allow generating such a similar overview for Europe. A European hotspot map may feed into the policy discussion and decision making on how to optimally regulate combined effects of chemicals. Logically, the number of hotspots identified depend on the environmental protection level established; the more stringent the protection level, the higher the number of hotspots. The number of hotspots, their spatial distribution, annual variability and relative spread in mixture toxic pressure will affect the choice for the most appropriate set of risk management measures.

2.3 Chemicals that matter most

To date, there is no insight into the specific chemicals, groups of chemicals or chemical classes that dominate combined effects on the environment within Europe. Generation of more specific insight into the number and type of chemicals involved may allow for further targeting the generic approach proposed in the current thought starter. There is information though, that scale matters and that chemicals typically do not contribute equally to the toxic pressure.

2.3.1 Scale matters

The available data on combined effects of chemicals on the environment indicates that the scale (e.g. looking at a small pond, a river delta or a combination of deltas on a continent) is an important factor determining the number of chemicals that may contribute to e.g. 90% or 99% of the effect observed. From a theoretical point of view, this can be understood by comparing an imaginary small pond, in which one chemical is emitted, with the scale of Europe, which includes all European chemical emission sources. The single chemical determines the effect in the pond. All emitted chemicals that (in theory) may co-occur determine the effect in the European environment as a whole. The larger the scale, the larger the number of chemicals potentially contributing to combined effects. This suggests that a generic MAF may depend on the scale at which combined effects of chemicals are to be addressed, i.e. the local scale in the case of the present thought starter, provided that the MAF accounts for the full 100% of the effect.

2.3.2 Little chemicals dominate the combined effect

In addition to the observation that scale matters, there is growing evidence from field studies and model predictions suggesting that for a given type of effect, a large part of the combined effects from multiple chemicals in the environment is caused by a relatively small fraction of the chemicals involved. This suggests it unlikely that combined effects of chemicals in the environment are characterized by a system in which each chemical contributes an equal share to the ecotoxicity.

Most recently, from preliminary analysis of the aforementioned Dutch monitoring data, Posthuma et al. (2016) found that for a given location 5 – 10 individual chemicals can typically be hold responsible for nearly the entire combined toxic pressure ($msPAF_{EC50}$) observed. This finding is in line with modelling results published previously by Harbers et al. (2006) and Zijp et al. (2014) and is supported by experimental and observational studies by e.g. Backhaus and Karlsson (2014), showing that environmental effects of combined exposure to multiple chemical are often dominated by a limited subset of the chemicals present. Their findings hint that at a local scale and for the freshwater compartment, independent of the specifics of the receiving waterbody about 5 – 10 chemicals dominate the combined effects of all chemicals present with each site possibly showing a unique composition of dominant chemicals. However, as noted in Section 2.1 these results should be further evaluated for an EU representative data set of monitoring data to draw more firm conclusions.

A further European-wide analysis of the number of chemicals dominating the combined effects in the local environment may also provide insight into the distributions of the relative contributions of individual chemicals to effects. As was noted in Section 1.3, it can be argued that in real life situations the chemicals dominating the combined effect will rarely co-exist at exactly their environmental concentration of 1/n of the PNEC. These chemicals will most likely exhibit some form of distribution, like the Pareto distribution, known also as the 80-20 rule, saying that 20% of the chemicals are responsible for about 80% of the combined effect in a sample. Another is the root-mean-square distribution in which all dominating chemicals co-exist with an environmental concentration range between 0 – 1/*n* of the PNEC. In the absence of (scientific) information motivating a specific distribution profile of chemical abundances when registering a substance, the present thought starter does not have any ground to deviate from the assumption than that the environmental concentration of the most important chemicals is exactly 1/n of their PNEC. This is a practical 'translation' of the requisite of an *a priori* level playing field in which each compound that may be emitted is allotted (at maximum) an equal share of the available 'safe space' defining the nontoxic environment. Note that neither for single chemicals nor for combinations of multiple chemicals safe use should ever be interpreted as a concept in which the environmental 'space' can be filled; the policy aim remains to reduce and limit exposure – not fill the space.

2.3.3 Outlook on chemicals that matter most

Several on-going initiatives are exploring the spatial diversity of chemicals and their combined effect on the environment with the aim to identify those chemical combinations that matter most in terms of combined toxic pressure on the environment. In line with the observations for the local scale level, preliminary results obtained from these projects seem to suggest that also at spatially larger scales only a fraction of all chemicals present in the environment may significantly contribute to the combined effect.

One of these initiatives is the SOLUTIONS project (Brack et al. 2015, 2017). In 2 to 3 years, this project foresees to deliver a hotspot-map for Europe, visualizing the spatial distribution of combined effects (expressed as msPAF) of REACH registered substances, and an overview of those particular substances that dominate the combined effects in the environment. Potentially, the overview of substances that matter most may support a more targeted approach to taking account of combined effects of chemicals under REACH by possibly only addressing combined effects for that sub-set of registered substances. Preliminary results from this project suggest that approximately 1% of the currently registered substances may dominate 99% of the combined toxic pressure at EU level in 'typical' European freshwaters (Van de Meent et al. *in prep*.). It should be noted though that the results expected from the SOLUTIONS project will depend on the quality of the registration dossiers used as input and should be interpreted with great care. Also, results may change with time as more and more dossiers will be updated and more substances will be registered, e.g. as a result of the 2018 registration deadline for substances registered in the lowest tonnage band.

The concept of land-use type related fingerprinting of combinations of chemicals is another activity that received attention at an international SETAC Pellston Workshop in 2015. This workshop aimed to simplify the diversity of environmental chemical combinations and is currently followed up on. The hypothesis that was presented there follows the idea that a chemical fingerprint (i.e. a typical combination of chemicals with a typical distribution of relative shares to toxicity) of a city-runoff is different from the fingerprint of an industrial area, an agricultural area or a household-chemicals emission scenario. From this land-use specific fingerprinting, generic area-specific combination profiles of chemicals may be defined to support a more targeted approach for taking combined effects of chemicals into account in emission and risk profiling for risk management purposes. Possibly, such fingerprinting could support the derivation of area-specific MAFs when needed.

2.4 A preliminary MAF; order of magnitude

In summary, the scientific information collated so far in various case studies suggests that scale is of influence on the total number of chemicals influencing the combined effect in the environment and that this effect is dominated by only a few chemicals. For the local scale level, Section 2.3 suggested that about 5 – 10 chemicals dominate the direct combined effect on biodiversity. Assuming a worst case of co-existence at equal toxic shares of 1/*n* of their individual PNEC, would lead to the derivation of a preliminary MAF in the range of 5 – 10, provided the reservations made earlier that further work is required to become conclusive of the number and type of chemicals that matter most EU-wide. A conceptual example on the evaluation of safe use under the REACH Registration process is shown in the box below, assuming a MAF of 10.

Motivating safe use of substance *A* in the CSR: a conceptual example
Say that the information available would motivate a MAF = 10 to account for combined effects of chemicals on the fresh water compartment at a local scale level. Then the registrant can motivate safe production and use of a substance *A* when for all *x* individual local emission scenario's identified in the CSR the following is true:

$$\frac{PEC(A, local, x)}{PNEC(A)} \leq \frac{1}{10}$$

It should be noted that eventually the value of the MAF will also depend on a policy decision with regard to the required coverage of the combined effect. The MAF of 5 – 10 in Section 2.3 reflects the number of chemicals typically found in literature to account for >95% of the combined effect, i.e. a coverage of >95%. A choice for 100% coverage would require taking all chemicals into account and would result in a MAF of *n* being equal to all chemicals typically present. However, if it is decided that REACH should cover only 80% of the combined effect of chemicals in the environment, less than 5 – 10 chemicals are expected to dominate this part of the effect and consequently a MAF lower than the 5 – 10 may result. Note that this number is derived for direct effects on aquatic organisms, with taxa loss as response endpoint.

3 Addressing concerns under the REACH Regulation

The aim of the current thought starter is to discuss a possible approach to account for combined effects of chemicals when registering safe production and use of single substances under the REACH Regulation in the Chemical Safety Report. An approach to account for these effects in the environmental risk assessment is proposed here for local freshwater compartments. It is noted that accounting for combined effects of chemicals deserves equal attention under other REACH processes like Authorization, Restriction and Substance Evaluation and should be topic of further discussion. Other topics that are not addressed here but do deserve further attention are the possible extrapolation of the approach to other environmental compartments (marine water, sediment, soil and air) [12] and the development of a possible approach to account for combined effects of multiple chemicals on human health.

3.1.1 Addressing concerns in the registration phase of REACH

For the registration phase of REACH, it is concluded in Section1.3 that taking account of combined effects of chemicals in the environmental risk assessment of a single substance calls for a generic approach because the combination of chemicals present at any location in the EU is *a priori* unknown. One such approach is to introduce a mixture assessment factor (MAF) as was proposed previously by Backhaus and others. The available information suggests that a preliminary MAF of the order of 10 can be derived for the freshwater local environment and that the MAF can be implemented as a generic approach superimposed on the established environmental risk assessment in the REACH registration phase. This MAF would apply for all substances registered under REACH and for all local emission scenarios. Preferably though, a less generic and more targeted approach should be followed, potentially addressing only those substances that are found to dominate combined effects of chemicals in EU fresh waters. On-going research, e.g. with regard to land-use specific chemical fingerprints and the on-going modelling of EU-wide emission profiles of substances based on REACH registration data by SOLUTIONS, may eventually support a more targeted approach (see Section 2.3.3).

Establishing the eventual value of the MAF also requires further policy discussion with regard to the maximum acceptable effect of chemicals in a nontoxic environment in terms of mixture toxic pressure (see Section 2.2) and the coverage of the effect to be addressed in a generic approach within the REACH registration process (see Section 2.4). This discussion requires insight into the spatial distribution of combined toxic pressure in the environment in the EU, preferably linked to the numbers and types of chemicals involved, as well as a consideration of effects other than direct effects on growth and reproduction (considered here with the $msPAF_{EC50}$). As indicated in Section 2.3, it is anticipated that the

[12] It is noted that in the Netherlands, various methods for environmental assessment of sediment and soil encompass assessments of combinations of chemicals, see RIZA (2008) and SenterNovem (2007) respectively.

existing EU-wide set of monitoring data does allow for generating such EU-wide insights.

3.1.2 *Judging most appropriate risk management measures*

Management of ecological risks of chemical combinations can be applied prior to production and use of chemicals (with the additional option of the Product Environmental Footprint approach for products, to select the safest product option), or after production and use addressing the emission and use of individual chemicals, groups of chemicals or all chemicals. REACH is an example of a source-oriented regulation at the level of chemicals, the product footprint an approach at the level of products, and the Water Framework Directive an example of an environmental compartment oriented regulation. Generic policies like the REACH Regulation, local policies that intervene at individual point sources (e.g. via emission permits) and catchment-oriented policies such as the Water Framework Directive logically need to be employed in combination to manage the environmental effects of potentially vastly differing toxic emissions and -pressures across regions, sites and water bodies (see e.g. Brack et al. 2017). The number of hotspots of toxic pressure (msPAF) exceeding the environmental protection level, their spatial distribution, annual variability and relative spread, will affect the choice for the most appropriate set of risk management measures. Furthermore, initiatives like that from SETAC of developing area specific chemical emission profiles may add insight in area-specific (land-use) combined effect concerns, which may allow further differentiation of how to best address these combined effects of concern (e.g. locally, at a generic EU level, or possibly via more specific design oriented measures addressing product development).

Insight in the spatial distribution of chemical hotspots in Europe may not only impact the set of regulatory risk management measures to be employed to address combined effects of chemicals most efficiently and effectively, it may also impact on the most preferable approach to address these effects in the REACH registration phase. One variation on this theme is described by Bunke et al. (2014) proposing an approach to address the combined effect of a technical mixture registered under REACH (not taking into account other environmentally abundant chemicals). Another variation could be developed in which each individual registrant only addresses the combined effects in the environment for the chemicals emitted at their industrial production or use sites. Addressing combined effects of technical mixtures by Bunke et al. (2014) could possibly be discussed in addition to the generic MAF approach proposed in the present thought starter. Addressing combined effects only for industrial emissions could be a preferable approach over a EU-wide generic one when monitoring or modelling data suggest that the hotspots of combined effects of chemicals concentrate in industrial areas only. In that case, the question may be raised if the Industrial Emission Directive wouldn’t be the more appropriate regulatory tool to manage the observed effects. The option of co-regulating co-emitted chemicals by a single company (e.g., by evaluating net emissions of a company with emission permits for a given number of chemicals) is consequently not elaborated here in detail. It is expected that for such an option, the available methods for chemical risk assessment can be applied in a relatively straightforward manner and that for the development of such an approach key would be to implement a structure to support a 'known combined chemicals emissions' policy at company level. In the Netherlands, an assessment of combined exposure to multiple chemicals is included in the evaluation of necessary emission reduction measures in the context of granting emission permits (RWS 2016).

3.1.3 *Possible implications of the current proposal under REACH*

The proposal to address combined effects under REACH via the implementation of a MAF concept as expressed in the current thought starter does have implications on the current role and responsibility of REACH registrants. No longer will they be responsible for the safe production and use of their substance only, now they will carry a mutual responsibility of this safety against the background of all other chemicals that co-exist in the environment. When such a concept is introduced in REACH, a similar responsibility may hold for companies, municipalities or countries producing, bringing on the market or emitting chemicals that are outside the scope of REACH. Though this discussion is beyond the scope of the current paper, this element deserves careful policy considerations as it may affect safety assessments under e.g. the BPR, PPP, Veterinary medicine directive. Such discussions are to be expected under the overarching concepts voiced in the European Charter of Fundamental Rights (Title IV, Article 37) and the 7th Environmental Action Plan for reaching a nontoxic environment in 2020.

4 Conclusions for further discussion

This thought starter brings forward that:

1. Natural environmental exposures are always to combinations of chemicals, some generally adopted modelling tools and data sets are available to assess their combined effects and there is a policy objective to address combined effects of chemicals in the phase of safety assessment of chemicals (EC 2012, section 5.1 (1), (3), (4), (5) and (6)).
2. Mixture toxic pressure assessment (msPAF) is a suitable method to assess the toxic pressure in the environment from combined exposure to multiple chemicals. A generic relation can be derived between mixture toxic pressure and ecosystem integrity (or taxa loss), which may be adopted as a method to discern a nontoxic environment.
3. The available data on combined effects of chemicals in the fresh water environment and the current insights with regard to underlying mechanisms suggests it is possible to propose a generic Mixture Assessment Factor (MAF) to account for combined local effects of chemicals at the phase of registration of substances under REACH.
4. Combined effects of chemicals in the environment can be taken into account in the single-substance environmental risk assessment under REACH by safeguarding that the following is true for every individual local emission scenario *x* of a substance *A*:

$$\frac{PEC(A, local, x)}{PNEC(A)} \leq \frac{1}{MAF}$$

5. Further spatial mapping of impacts of combinations of chemicals in Europe, their number and type is needed to feed into a more detailed discussion on the magnitude of the MAF, possibly tailor made for e.g. area-specific circumstances. Several initiatives are on-going that may provide further insight in these issues.
6. Insight up to now suggests that irrespective of the type of chemicals involved, the combined impact in the local environment is most often dominated by 5 to 10 chemicals, but keeping in mind the following uncertainties:
   a. This range is based on preliminary assessment of taxa loss data for macrofauna.
   b. Among the chemicals, the subset may not represent the true set of toxic influences.
   c. The information is obtained from Dutch monitoring data and does not necessarily reflect the EU situation.
7. Hence, the available information in the freshwater environment at local scale suggests a preliminary MAF may be of the order of 10.
8. Thorough policy discussion is needed to operationalize the environmental protection level for combined effects of chemicals (here suggested in terms of mixture toxic pressure) and as a consequence, the need to regulate combined exposure to chemicals in a more generic approach under REACH, more

location specific by national or regional regulatory instruments, or a combination thereof.
9. This policy discussion should preferably also elaborate on the proportionality and feasibility of accounting for combined effects under REACH, including legal issues and including a discussion on possible consequences for other regulatory frameworks.
10. A follow-up discussion is needed on the applicability of the approach proposed here in other REACH processes such as Authorization, Restriction and Substance Evaluation, and for other environmental compartments.

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