Chairman's report of the workshop on a pragmatic approach to address the risk from combined exposure to non-intentional mixtures of chemicals - REACH as an example - Leiden 5-6 March 2020.

This workshop was hosted by the Dutch Ministry of Infrastructure and Water Management (Competent Authority on REACH) and the Swedish Chemicals Agency (KemI) and took place in Leiden, The Netherlands on 5-6 March 2020[1] . The workshop was attended by representatives of Member States authorities, industry, NGO's, ECHA and the European Commission (DG ENV and DG RTD). Discussions focused on a possible regulatory approach under REACH to better protect man and the environment from toxic mixtures by reducing the overall toxic pressure of chemicals from unintentional mixtures. It was generally recognized that exposure to unintentional mixtures may lead to risks, as such is a problem and there is an urgent need to address this issue in a pragmatic manner. Introducing a Mixture Assessment (or Allocation) Factor (MAF) under REACH in Annex I is regarded a possible workable approach that is feasible, fair and fast. Further elaboration on some of the details of the proposal is still needed, as well as an impact assessment and a feasibility study by ECHA to shed further light on some of these details.

Protecting against toxic mixture effects from unintentional mixtures

The EU Commission issued in 2012 that current EU legislation does not provide for a comprehensive and integrated assessment of the cumulative effects of different chemicals taking into account different routes of exposure. The Commission identified the need to do so for the combined exposure to chemicals that have similar modes of action (in the case of protecting human health) or for all types of combined exposures of chemicals that lead to adverse effects to the environment. This need was repeated in 2019 (Council, 2019), and combined exposure was highlighted as one of the priority issues in the Green Deal where the Commission stated in the section on a zero pollution ambition for a toxic-free environment that the regulatory framework will need to rapidly reflect scientific evidence on the risk posed by combination effects of different chemicals (COM, 2019).

Scientific literature clearly shows that risks from exposure to multiple chemicals are much higher than the risks for single substances. As current EU legislation is mainly on single-substance basis, this leads to higher aggregated and combined exposure and therefore to likely unacceptable risks to health and environment[2].

The REACH Regulation provides information on hazard and exposure of over 23,000 single substances brought on the market in quantities over 1 ton/annum to allow for their safe use on their own, in mixtures and in articles. However, the risks caused by combined exposure to unintentional mixtures are not systematically addressed and thus may be underestimated. Detailed risk assessment of all possible combinations of combined exposure under REACH would require a more extensive information requirement, high additional costs for testing and logistical challenges of communicating uses and exposures of substances that could possibly occur in numerous combinations of chemicals. As this is unworkable, a pragmatic approach is proposed as an regulatory measure. It is proposed to adopt an Mixture Assessment (or Allocation) Factor (MAF) under REACH Annex I, either as part of the mandatory DNEL or PNEC derived for all registered single substances to account for the possibility that each substance may eventually contribute to the combined daily exposure of hu-

[1] Agenda to the workshop

[2] Scoping paper
Workshop on a pragmatic approach to regulatory measures addressing the risk from combined exposure to chemicals – *REACH as an example*, 7-2-2020.

mans and the environment, during the risk characterization step of the risk assessment. This proposal was elaborated in a scoping paper, and subsequently discussed during a workshop, which resulted in the following agreements.

It was agreed that:

- Man and the environment are currently exposed to mixtures of chemicals which in various cases lead to unacceptable risks.
- Man and the environment should be protected against these (unintentional) toxic effect of mixtures of chemicals by reducing the overall toxic pressure across the European Union.
- This issue has already been known for decades and has recently been addressed in Council and Commission conclusions (26 June 2019). Many recent scientific studies confirm the toxic effects caused by the combined exposure to chemicals. The 2019 Green Deal and Zero Pollution Ambition form the ultimate call to deal with mixture toxicity.
- There is an urgent need to address this issue in a feasible and pragmatic manner.
- Introducing a Mixture Assessment (or Allocation) Factor (MAF) as a generic/default factor in REACH Annex I is seen as a pragmatic solution to the policy question lying on the table for many years.
- Despite the research that has been conducted it has proven difficult to develop a simple, reliable and workable approach to address risks from combined exposure to unintentional mixtures in a quantitative, mixture-specific manner. For example, REACH registrants cannot assess the risks of the use of other substances from other registrants.
- Now that all single industrial substances have been registered under REACH as of 2018, this presents an opportunity in time to address the issue of assessing combined exposure and effects.
- There is an urgent need to convince Ministries to act; the scientific evidence is available, industry is involved and now policy makers should act.
- Ideally, combined exposure to unintentional mixtures should be addressed across legislations and a consistent and horizontal approach should be considered, for which there is a need for streamlining information from different legislation. To start with a regulatory solution, REACH is the most suitable chemicals regulation .
- Whereas the introduction of the MAF concept in REACH would cover the about 23,000 substances that are currently registered, a consistent and horizontal approach to address combined exposure to unintentional mixtures across legislations should as well be considered.
- Whether the MAF should be introduced in the DNEL/PNEC derivation or in the Risk Characterisation Ratio (RCR) needs to be further discussed as well as the numerical value of the MAF, both of which require a political decision.
- A provisional analysis shows that the impact of the MAF approach on industry may be manageable: some risk assessments in the registrations may need further refinement, without resulting in actual risks. In a limited number of cases further risk management measures are

needed where actual risks are shown and which thus will manage the risks to man or the environment. The impact on SME's needs special attention.

- Communication through the supply chain, to risk assessors and to policy makers about combination toxicity and a MAF is recognized as an important issue. There is a need to reduce exposure for the chemicals that matter.

- The possible consequences and uncertainties of introducing a MAF with a certain magnitude will need to be further investigated and ECHA will try to extend its preliminary assessment of the possible impact of different MAFs on the need to introduce more stringent risk management measures. To improve our understanding on the impact on the different downstream users (e.g. industry, companies, risk assessors, policy makers) and support any follow-up decision making on a possible appropriate approach, Industry and NGOs are as well invited to contribute to this assessment.

- The possible magnitude of the MAF can be determined based on already existing knowledge and the results from the preliminary assessment performed by ECHA of the possible impact of different MAFs on the need to introduce more stringent risk management measures. In principle the same MAF can be used for human health and environment and within environment for soil, sediment, water and sewage treatment plant.

- After the summer of 2020, the Commission intends to publish a strategy paper (a chemicals strategy for sustainability) to which we intend to contribute with our report and contribution to CARACAL. The Commissions' paper will be subject for discussion at the second workshop during autumn 2020.

The workshop:

The workshop was structured along the following questions that were send prior to the workshop to all the participants in the form of a questionnaire:

1. Do you support the proposed approach to adopt a mixture assessment factor (MAF) under the REACH Regulation to account for the fact that any registered substance under REACH may eventually become part of an unintentional mixture to which humans and the environment will be exposed?
2. Do you see alternative approaches?
3. How to adopt and apply the MAF for all substances registered under REACH?
4. Where to include such approach in the REACH legislation?

Possible (alternative) regulatory approaches under REACH, questions 1 and 2

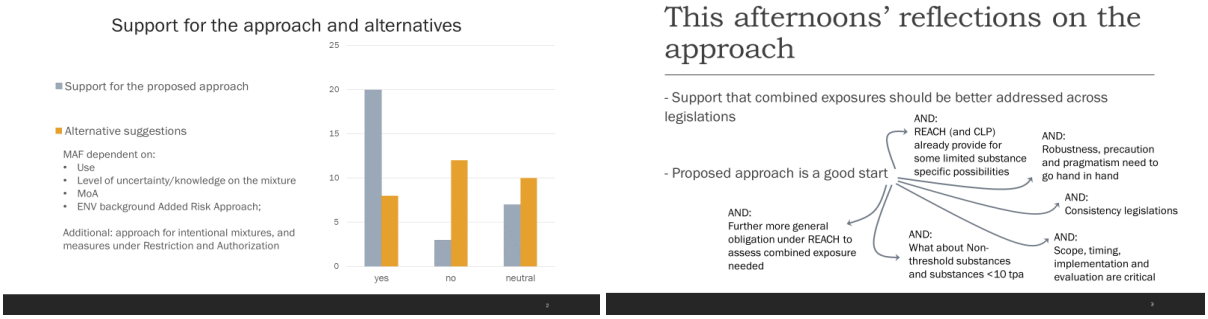

Figure 1 (Left) questionnaire results on question 1 and the alternative suggestions that were brought forward in response to question 2. 30 participants send in their first personal response to the SE/NL proposal. (Right) Reflections brought forward during the workshop by Cefic, ChemTrust and ECHA on the SE/NL proposal.

There was a general agreement among the workshop participants that combined exposure to chemicals should be better addressed across the various chemicals' legislations[3], and that as a first step in the more horizontal process of introducing regulatory measures a possible feasible, fast and fair approach under REACH could be the introduction of a Mixture Assessment Factor (MAF) in Annex I of the REACH Regulation. Views deviated on how to exactly introduce such a factor, either as part of the DNEL or PNEC derivation or as part of the Risk Characterization ratio (RCR) (see later as part of the response to questions 3 and 4 of the questionnaire).

Participants recognised that REACH (and CLP) should already address effects of combined exposure to intentional mixtures, but lacks practical methodology to do so for unintentional mixtures. That this may lead to unacceptable risks for both humans and the environment was clearly demonstrated in the presentations by Thomas Backhaus and Carl-Gustav Bornehag. It was concluded that regulatory action under REACH on intentional mixtures should continue on an ad hoc substance-by-substance basis in parallel to the generic approach for unintentional mixtures that was the topic of the workshop. It was also suggested that once a MAF was introduced in Annex I, the same concept

[3] It was shortly discussed that several legislations include some type of approach to assess and manage risks from mixtures, but that most of these only involve measures on the so-called intentional mixtures or aggregated exposure of a substance via multiple sources and routes of exposure, and that human health and environment are not always equally well protected. It was noted that in addition to per-legislation measures, developing an overarching legislation could be considered to further support consistency in the approach across legislations.

could be taken up to account for effects of combined exposure to unintentional mixtures under the processes of Authorization and Restriction.

Several participants reflected that the approach for addressing effects of unintentional mixtures should be pragmatic, and at the same time robust with regard to the knowledge available on toxicity, specific uses and exposure. As alternatives to the approach proposed by SE and NL, it was suggested that the MAF should reflect (to some extent) the type of use, the level of knowledge (or uncertainty) on the composition of the mixture and/or the mode of action of substances. It was discussed that preferably only those substances that likely occur together in the same mixture should be taken into account together, and that only substances with similar type of effects (or modes of action) or use should be grouped.

However, upon further discussion it was concluded that the REACH Regulation does not provide adequate toxicological and exposure information required for a comprehensive assessment i.e. for the suggested fine tuning[4], and that the REACH registrants neither have the information nor the ability/knowledge and power to act on the composition of unintentional mixtures in order to carry out an assessment that takes into account the potential effects of all unintentional mixtures to which their registered substances(s) might contribute. The participants therefore agreed that a uniform MAF is an appropriate and swiftly implementable approach (see also question 3). It was noted that for certain groups of substances, such as for naturally occurring metals, the environmental abundances may already exceed the no-effect level if a MAF would be introduced; hence, it was recognised that an appropriate approach introducing a uniform MAF requires some further discussion and development on this topic. The so-called added risk approach and the use of exemption/derogation clauses for specific substance groups were two options suggested that could be further explored to resolve this issue. How to deal with combined exposure to non-threshold substances was identified as a second non-resolved topic that requires further elaboration.

Under the assumption that a MAF approach would be included in Annex I, it was discussed that this new measure would enter into force at a certain date, after which all registration dossiers should be updated to be compliant. It was clarified that in order to remain compliant, registrants may have the possibility to further refine their exposure assessments or their DNEL or PNEC derivations. A first tentative impact assessment by ECHA on a group of 24 randomly picked substances suggests that by applying a MAF of 10 only a limited number of substances may require risk management measures that go beyond the further fine-tuning of hazard and exposure assessments at the level of the REACH registrations.

[4] Including such information would lead to a serious increase of toxicity test requirements and an increase in communication through the supply chain

Ideas and motivations behind possible approaches, question 3

How to apply the MAF

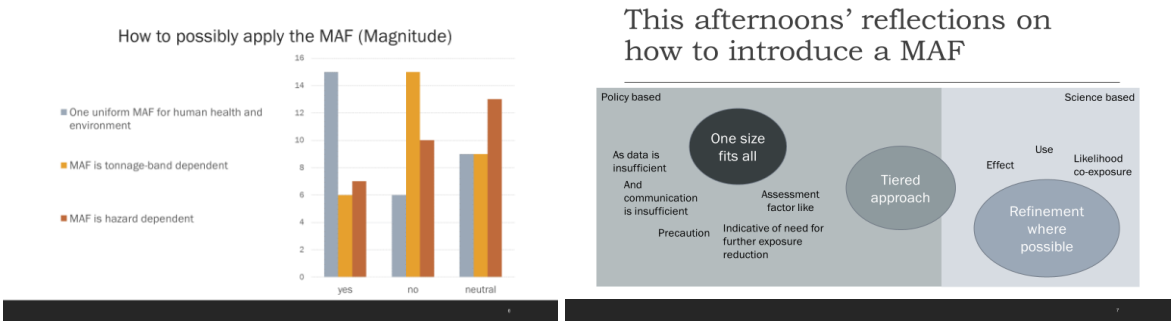

Figure 2 (Left) questionnaire results on question 3 on how to possibly adopt (design) and apply a possible MAF. 30 participants send in their first personal response to the SE/NL proposal. (Right) Reflections brought forward during the workshop by Cefic, ChemTrust and ECHA on the SE/NL proposal.

The workshop participants supported that a MAF might be best introduced as a one-size fits all approach. This was reflected also by the results from the questionnaire i.e. question 3 (see Fig. 2), that showed clear support for the one-size fits all MAF, whereas there was little support for a MAF depending on either the registered tonnage-band of a substance or its hazard. Other options were discussed, e.g. one for environment and one for human health, one for consumers and one for workers[5], and/or a tiered approach that would allow reducing the MAF-value as a function of the information available on the mixture composition and combined effects[6]. However, it was concluded that for each of these more targeted approaches, information was normally lacking to the registrants to be able to apply these approaches. The one-size fits all approach on the other hand, is the low data-demanding approach that would make sense under REACH, given its regulatory scope and the concern at hand (i.e. risks to humans and the environment from combined exposure to substances from unintentional mixtures), and is feasible with the current level of information required on toxicity and exposure characteristics of substances, and the communication thereof through the supply chain. It was furthermore noted that proposals of a similar kind as the present SE/NL proposal were already developed over 10 years ago, which strengthened the support to not wait any longer for a possibly more sophisticated approach to appear as presented by ECHA and Thomas Backhaus. This conclusion was drawn while acknowledging that:

- For the environment, no-effect-levels are established based on the most sensitive species and consequently these effects are not directly comparable;
- On average, effect addition is identified as a realistic approach to approximate the overall environmental toxic pressure;
- As for the environment and human health, additivity of effects is complex;

[5] It was discussed to what extent a MAF should be specified for environment (with the possible differentiation between water, soil, sediment, air, STP) and for human health (with the possible differentiation between workers and consumers). Motivation for this further specification is the notion that these different "compartments" have different protection levels afforded by current legislation (with humans at individual level and the environment at ecosystem level) and that the combined exposure may be of a quire different nature. The differences were recognized by all participants and at the same time, there were no clear arguments as to how these differences would materialize into a different MAF. Discussion on the magnitude of the MAF was not a topic of the current workshop and will be addressed in the future.

[6] Upon further investigation though, it remained unclear what such an approach would be like in reality, as the concern is about unintentional mixtures on which Registrants under REACH at this moment in time have no prior knowledge, few?/no? information requirements that typically allow toxicological assessment to identify mode of actions for mixtures, and no legal possibility to control what is included in a nonintentional mixture.

It was supported that, until there is convincing information motivating the derivation of a more case-specific MAF, a one-size fits all MAF is the most feasible and fair approach for the time being. How to deal with non-threshold substances is a topic for further elaboration in the future.

Where to apply the MAF, question 4

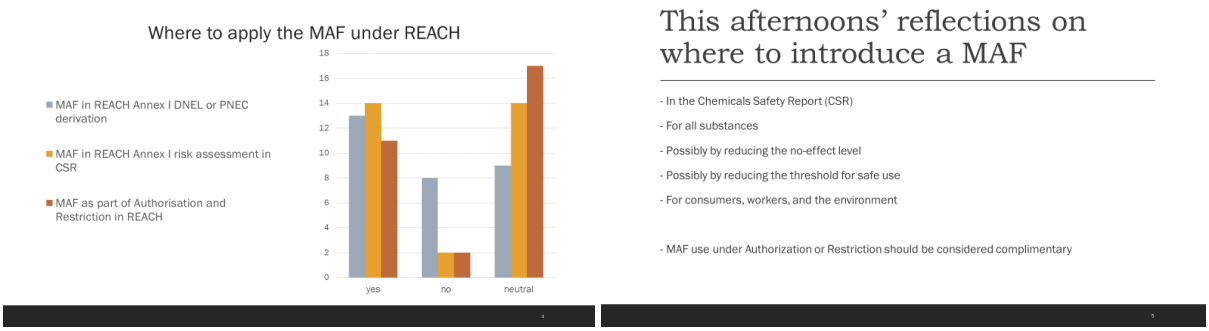

Figure 3 (Left) questionnaire results on question 4 on where in Annex I to introduce a MAF. 30 participants send in their first personal response to the SE/NL proposal. (Right) Reflections brought forward during the workshop by Cefic, ChemTrust and ECHA on the SE/NL proposal.

The proposal is to introduce the MAF at the level of the DNEL and PNEC derivations. Alternatively was discussed to introduce a MAF under the risk characterisation step of the risk assessment, i.e. reducing the acceptable risk characterisation ratio (RCR). The questionnaire results showed no clear preference for including the MAF in the DNEL/PNEC derivation or in the RCR. In the discussion pros and cons for both scenarios (DNEL/PNEC or RCR) have been discussed. In the boxes below, the motivations brought forward for both scenarios are summarized. It is stressed that both scenario's lead to the "mathematically" same outcome for safe use exposure scenarios at the level of the REACH registration dossiers, but may have different downstream implications. As a follow-up action, further study of possible impacts of the two scenario's on the supply chain, including down-stream legislations, was concluded.

Authorization and Restriction were recognized by the participants as two additional places under the REACH Regulation where effects from combined exposure to unintentional mixtures should be addressed. It was suggested that once a MAF was introduced in Annex I, the same concept should be taken up to account for effects of exposure to unintentional mixtures when assessing safe use of substances and mixtures under these processes.

<u>Scenario-1:</u> MAF at DNEL/PNEC level
Annex I: *suggestions for adoption*
As an additional assessment factor in the DNEL and PNEC derivations.

Motivation:
DNELs and PNECs are used at registrants/formulators level to derive RCRs and set exposure scenarios, and at formulator/end user level to decide on their own safe use. DNELs and PNECs furthermore are used to help deriving exposure scenarios of mixtures. The underlying toxicological information that is used to derive the DNEL or the PNEC is also used for classification and labelling of intentional mixtures and for setting OELs, EQSs (or other environmental quality standards), emission limits (e.g. in FCMs, toys, construction materials, industrial emissions, etc.), and as a basis for deciding in acceptability of specific uses (e.g. cosmetics). In general, in those latter cases no MAF or similar approach to deal with mixtures, is currently in place.

Introducing the MAF in the derivation of the DNEL or PNEC will have the effect that the MAF will be consistently applied across all substances and regulatory context and provides all downstream users with a consistent starting point for their hazard and risk assessment[7]. This in itself will bring transparency of action. As the MAF is only introduced once, namely by the substance lead registrant in the substance hazard assessment, independent of all use-specific and/or local considerations, this approach is relatively labour efficient (e.g. "downstream" users can simply work with the DNEL and PNEC and do not have to consider effects of combined exposure actively by themselves). It is thereby also relatively "fail-proof" and minimizes the chance of non-compliance down the supply chain and across legislations. This also removes the necessity of conducting complex mixture toxicity assessments at various stages in the supply chain (including life-chain, multi-constituents, CLP mixtures, multi-chemical exposure at the workplace, multi-chemical exposure at home and via food, multi-chemical body burden from all sources, multi-chemical environmental load, etc)..

One could furthermore argue that introducing the MAF in the DNEL or PNEC most accurately reflects the evidence that the extrapolation from substance specific lab-toxicity test to effect in humans or the eco-system needs to take into account the presence of other (yet unknown) chemicals that are always there by default[8].

A counter argument, advocating against introducing the MAF in the derivation of the DNELs and PNECs is that these are Europe's best estimates of a safe exposure level per substance, and this intrinsic value should be preserved[9]. When the MAF is introduced here, a paradigm change of the definition of PNEC and DNEL may be needed, i.e. these no-effect levels then will be derived taking into account a certain toxic pressure from a mixture of chemicals. Another counter argument is that DNELs and PNECs are communicated and used across legislations to feed the hazard and risk assessment for a high variety of different purposes of which some may become confused when there is a MAF 'hidden' within their value[10]. This could be perceived as a lack of transparency because the MAF is not explicitly communicated. This could result in a rather rigid system in which there is no inherent flexibility to fine-tune acceptable exposure levels. Exceptions should in that case be actively introduced in the regulatory text. The option of deriving a DNEL/PNEC for mixtures in addition to the DNEL/PNEC for the substance was discussed; this option might take care of the counter argument of transparency and use of the DNEL/PNEC across legislations, but may introduce the confusion on which DNEL/PNEC to use and when.

<u>Scenario-2:</u> MAF applied in Risk Characterisation Ratio (RCR)
Annex I, 6.4: *suggestions for adoption*
For any exposure scenario, the risk [..] is adequately controlled [..] if:
the exposure levels [..] do not exceed [x] percent of the appropriate DNEL or PNEC for any exposure scenarios

[7] One substance, one (hazard) assessment.
[8] Exposure is never to a single substance but always to a cocktail of substances.
[9] E.g. if the DNEL/PNEC wasn't correct before, why should it be correct now? Changing the DNELs and PNECs for all substances for which these have been derived may lead to serious opposition in the community of toxicologists.
[10] I.e. upon using a certain substance as reference toxic value for deriving quality standards for other substances. The question than may arise: Does the MAF still have to be applied on top of the quality standard derivation or is it already included? As a possible way to resolve this, it was suggested to introduce two sets of DNELs and PNECs: a single-substance DNEL and PNEC (the traditional one) and mixture corrected DNEL and PNEC (including the MAF correction).

Motivation:
The introduction of a MAF should be interpreted as a risk management option. It was argued that this would be the most transparent and least scientifically confusing way of introducing the paradigm shift that co-exposure to non-intentional mixtures should always be taken into account in the risk assessment for a single substance[11]. From this point of view, the MAF should rather be introduced to reduce the risk quotient that we in Europe accept as sufficiently safe.
Introducing the MAF by lowering the RCR requires that the different sector legislations each have to take their own legislative decisions. This introduces some degree of flexibility for each legislation to decide on how to address effects through combined exposure but might as well result in further delays or introduce non-harmonised approaches. It also introduces more work to the user and requires more knowledge to execute the MAF and organize safe use, which again may reduce compliance. Furthermore, different protection levels may apply for different uses and different sectors, which may introduce inequality (some sectors have to 'pay' more), challenges consistency and could cause confusion ("which protection level do I have to apply this time….?").

[11] Hazard and risk assessors could otherwise develop the idea that "for years, they have been doing the wrong thing".