14 August 2020

Comments on CA/MS/47/2020 Synthesis paper for CARACAL provided by KEMI and the Netherlands "*Comments on a pragmatic procedure to regulate the risks of exposure to coincidental combinations of chemicals, in the EU*"

General comments

We would like to thank the Dutch and Swedish Competent Authorities for their initiative and for providing the useful synthesis paper. Evidence from recent EU research projects has demonstrated that the current EU law systematically underestimates the risk from combined exposures. It is high time to move ahead and improve the protection of human health and the environment from mixture effects due to combined exposures.

What is needed now to deliver the promises of the European Green Deal is the political will to react to the clear scientific warnings. It is therefore indispensable to establish a cross-cutting approach to address mixture toxicity, to be integrated in and applied under all relevant EU laws. **We support the proposal to start** the cross-cutting approach **with REACH. We also support the application of a mixture assessment factor as a first step for a simple and pragmatic tool forward in the context of REACH registration. Furthermore, consideration of mixture effects need to be integrated in the REACH risk management processes restriction and authorisation.**

In addition, an EU action plan to reduce exposure to the most common combination of chemicals detected in people should be established by the authorities, as informed by human biomonitoring studies.

Why a mixture assessment factor is key to tackle mixture toxicity better

These are the main reasons supporting a MAF under REACH:

- There is a need to decrease the burden of hazardous substances to reduce adverse impacts on health and the environment and to oblige registrants to ensure safe use - which is currently not the case for combination effects.
- As the option to perform tests for all different unintentional mixture combinations would place an unrealistic burden on registrants, a relevant MAF would help lower costs and save lives of animals to ensure a higher protection from hazardous chemicals.
- Currently uncertainty factors are already used in risk assessments, including for registrations – so the approach proposed is simply an adaptation of already existing tools. This is needed, because the existing factors do not cover mixture effects. This has been clearly shown by Martin et al. [1]

Our proposal therefore is to establish a MAF of 100, which would cover:

a. a factor of 10 addressing the different chemicals contributing to a mixture (several hundred chemicals present are usually present in real life samples, however, it seems that often around 10 chemicals contribute to the majority of toxicity);[2]
b. a factor of 10 addressing different exposures sources of the chemical (ranging from biocides, cosmetics, pesticides, detergents to uses in food contact materials, toys and other consumer products).

This approach would address both the risk of mixture effects due to exposure to other chemicals and the risk of aggregated exposure to both the same chemical and other chemicals from different sources, including uncertainties. Protecting vulnerable groups will also require the appropriate selection of studies and most sensitive endpoints including considerations of critical windows of exposure such as early-life development (as indeed should be the case for every single substance risk assessment).

In a nutshell, we support the introduction of a MAF of 100 in the derivation of the DNEL/PNEC under REACH. However, as much as a MAF is indispensable to adjust chemical regulations to the reality of chemical exposure, it is not sufficient to fully address it. We therefore see the need to develop an overarching approach for addressing unintentional mixtures in the upcoming EU Chemicals Strategy for Sustainability. A focus on minimising exposures to harmful substances/SVHCs (in particular non-threshold SVHCs) will be crucial to develop ways forward for a clean Circular Economy. Here, the increased use of group

[1] https://ehjournal.biomedcentral.com/articles/10.1186/1476-069X-12-53
[2] See scoping paper from Workshop: https://www.chemischestoffengoedgeregeld.nl/content/scoping-paper-workshop-pragmatic-approach-regulatory-measures-addressing-risk-combined

restrictions should play an important role. In addition, it should be explored further, how authorisations can be improved and only be granted with conditions taking mixture toxicity into account.

Specific comments on questions 1-4 raised in paper CA/MS/47/2020

1. **Follow-up Workshop**

We support the idea for a follow-up workshop and propose a focus on:

- Specific ways forward to introduce the MAF in Annex 1 of REACH as well as in other parts of REACH like authorisation and restriction (see also our previous submission).[3]
- Dealing with non-threshold substances
- Addressing real-life mixtures prioritising the known harmful chemicals detected in Human Biomonitoring studies and SVHCs frequently occurring in the environment (see our proposal for an EU action plan under General comments above).
- Making use of grouping of substances in risk management decisions as a crucial tool to reduce harmful mixture effects.

2. **Review of current knowledge**

If a **review of current knowledge** to determine the magnitude of the MAF is carried out**, it should be very focused on clarifying specific unresolved issues.**

- There is no need to repeat another review of the state of the science. The scientific evidence for mixture toxicity is well established and has revealed that chemicals contribute to mixture effects even when they occur at levels below their own individual effect concentrations.
- In addition, experimental outcomes suggest that the assessment of the risk of mixture effects should be based on common health outcomes rather than only similar modes or mechanisms of action.[4]

3. **Ex ante impact evaluation**

- In our view, an ex ante impact evaluation is not needed. Instead ECHA's analysis of impacts on registration dossiers can be used. ECHA`s preliminary survey showed that in most cases the impact would not be significant. [5]
- If an impact evaluation is conducted it should consider the significant limitations of the current proposal: Any change in Annex I (and thus the CSA) is only applicable to substances above 10 tpa. This means the MAF will not apply to the thousands of

[3] https://chemtrust.org/wp-content/uploads/Final-NGO-comments-mixtures-CARACAL-CA_MS_34_2020.pdf
[4] https://www.sciencedirect.com/science/article/pii/S0160412020318250?via%3Dihub
[5] https://www.chemischestoffengoedgeregeld.nl/sites/default/files/ECHA_Jack%20De%20Bruijn.pdf

chemicals produced in lower volumes. Any impact evaluation should include scenarios for how the current proposal could integrate additional measures for registrants of lower volume chemicals and how they can ensure safe use considering combination effects.

4. **Partner expert group**
   A partner expert group may become a useful platform to continue with some of the detailed discussion. However, it is important to start the necessary procedures as quickly as possible: The MAF can be introduced through a change in Annex I of REACH via an implementing act. In the authorisation processes, it can be implemented by authorisation applicants, in application of an updated guidance. In the restriction processes, it can already be used by dossier submitters and by RAC when assessing restrictions.[6]

Reflection on comments from other stakeholders

We disagree with some of the concerns that have been brought forward during the discussions at the CARACAL meeting or raised in written comments.

Regarding scientific uncertainties:

Claims about unclear science with regard to the existence of additive effects as a result of combined exposures must be denounced as ill-founded attempts to divert attention away from the urgent need for political action on chemicals mixtures. It should be emphasised that already back in 2009 the scientific evidence of combination effects of chemicals was acknowledged and addressed by EU Council Conclusions on Combination effects of chemicals. In 2019, a conference organised by the EU research projects EDCMixRisk and EuroMix highlighted again the urgent need to integrate these findings into policy and law by adopting regulatory approaches as well as employ better assessment tools for tackling mixture effects.[7] The overarching conclusion from these projects was that current regulation of man-made chemicals systematically underestimates the health risks associated with combined exposures to EDCs or potential EDCs.[8] Also, a 2019 joint statement from JRC and researchers from EDCMixRisk, EuroMix, EUToxRisk, HBM4EU and SOLUTIONS recommended

[6] RAC already used a MAF to take into account mixture effects of reprotoxicants used in tatoo mixtures. Committee for Risk Assessment (RAC)Committee for Socio-economic Analysis (SEAC), see Opinion on on Annex XV dossier proposing restrictions on substances used in tattoo inks and permanent make-up ECHA/RAC/RES-O-0000001412-86-240/FECHA/SEAC/ ECHA/SEAC/RES-O-0000001412-86-265/F. https://echa.europa.eu/documents/10162/dc3d6ea4-df3f-f53d-eff0-540ff3a5b1a0

[7] https://chemtrust.org/chemical-cocktail-mixture-effects/

[8] https://edcmixrisk.ki.se/wp-content/uploads/sites/34/2019/03/Policy-Brief-EDC-MixRisk-PRINTED-190322.pdf

an application of a MAF as a way to decrease the total burden of exposure to chemical mixtures.[9] Not to act now means ignore important research findings.

Regarding animal testing:

The proposal on the table suggests the application of a MAF which would systematically take into account combination effects as a default in the registrants´ risk assessments. To our understanding, the proposal does therefore not trigger the need to do more animal testing, nor additional test requirements. On the contrary, the proposal would allow moving away from the current practice of conducting countless animal studies for the sake of arguing back and forth about an agreed ´safe level´ for a single substance, and instead truly making progress to minimising exposures and thus protecting human health and wildlife.

Regarding the compatibility with other assessment approaches

The use of a MAF as a generic and major tool to assessing mixture toxicity will not prevent the use of specific mixture risk assessment (tools/approaches), where desirable or needed in other situations or legal contexts. An important aspect of the proposal to insert a MAF in REACH is the fact that it will be up to registrants to apply it as part of their chemical safety assessments. The alternative to using a MAF would be a detailed risk assessment approach on a case-by-case basis. This would require high quality data on hazards and exposures and a specific knowledge of all potential mixture exposure scenarios- which is not realistic. Even if the current data gaps on single substances in REACH registration dossiers will be partly closed over time, (e.g. triggered by ECHA`s increased compliance checks), it is impossible to expect assessments for all unintended mixture situations of a given chemical across its whole life-cycle. The only way forward for mixture risk assessment is the proposed generic approach.

This still leaves the possibility for conducting specific mixture risk assessments in other legal contexts, e.g. in EFSA`s approach on evaluating pesticide residue levels or in cases where a detailed risk assessment is needed to evaluate a contaminated site. However, it should be noted that such specific mixture risk assessments are often sector specific and do not include exposure to the same or similar substances from other sources. Therefore, such specific mixtures assessments could be aligned with the MAF concept by adding an additional factor of 10 to reflect the second part of the proposed MAF of 100 that covers exposure from different sources (see page 2, point b).

[9] https://www.sciencedirect.com/science/article/pii/S0160412019331538