Downstream Users of Chemicals Co-ordination group

Combined exposures to chemicals
DUCC comments on CARACAL document CA/MS/34/2020

DUCC, representing a broad range of industries that formulate mixtures used by industrial and professional users as well as consumers, thanks the Commission for the opportunity to comment on the above-mentioned document.

The proposal for a generic Mixture Assessment Factor (MAF) is a policy decision rather than a scientific one, based on a belief that current risk assessment methodologies are not sufficiently protective and so proposing additional conservatism not supported by comprehensive evidence. DUCC does not believe that such an arbitrary blanket approach is appropriate and wishes to make the following remarks in support of its position.

- **Methods already exist for cumulative risk assessment**; US EPA has published guidelines for how this can be done[i]. Cumulative risk assessment is based on the understanding that risk is only cumulative if two or more chemicals act by a common mode of action. The best example of the use of cumulative risk assessment is for organophosphate and carbamate pesticides that act by inhibiting cholinesterase. The scoping paper referenced in CA/MS/34/2020 also cites an example for phthalates; this is a good example, but it illustrates the importance of ascertaining that substances act through the same mechanism, as not all phthalates do. Further examples are available in an EFSA opinion on pesticides[ii], the latest opinion of the EU scientific committees on the issue of combined exposures[iii] and a 2012 publication of Cefic's Mixtures Industry Ad-hoc Team on a decision tree for assessing effects from exposures to multiple substances[iv].

- The interaction between substances can be **additive, synergistic, antagonistic or cause potentiation**. It is unclear how a single generic MAF could account for the complex matrix of interactions for all the substances to which potential exposures could occur.
  As more and more toxicity data are generated at a mechanistic level, it will become clearer as to **which chemicals have common toxic effects and should potentially be considered for cumulative risk assessment**. Endocrine disruptor screening for example will provide data on which chemicals interact with specific hormone receptors, as well as their relative potencies. Both pieces of information are essential to establish a common mechanism of action, but this in itself is not sufficient as the basis for Cumulative Assessment Groups should be a common adverse effect. Other modern toxicology technologies like high-throughput screening and toxicogenomics will provide a scientific basis for determining when substances have a common mode of action. See for example Borgert *et al* 2012[v], 2014[vi].

- **It is also necessary to establish a realistic picture of exposures**. There can be no cumulative risk from two substances if they do not occur together. The question of when exposure occurs during the day is important, and exposures for both environment and human health are transient in space and time. As done now, aggregation of exposure is often made on a mg/day basis, which is the same as assuming that all exposures occur simultaneously. This is clearly not true for consumer products; a very simplistic example would be that a person would probably not use make-up and make-up remover at the same time. Similarly in professional applications, a coating, adhesive or sealant would not be applied at the same time as a primer, but only after the latter has fully dried

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and cured. Unless a chemical is eliminated very slowly, the exposure to the chemicals does not occur simultaneously and these should not simply be added. Furthermore risk assessments under REACH often rely on conservative over-estimates of exposure conditions, which also account for cumulative effects of chemicals.

- For professional and industrial uses, combination effects are already taken into account under **occupational safety and health legislation**. In Council Directive 98/24/EC on the protection of the health and safety of workers from the risks related to chemical agents at work, the following obligation is included in Article 4 (Determination and assessment of risk of hazardous chemical agents) (emphasis added):

  "4. In the case of activities involving exposure to several hazardous chemical agents, the risk shall be assessed on the basis of the risk presented by **all such chemical agents in combination**."

- **Assessment factors** of 100 are typically already applied to No Observed Adverse Effect Levels (NOAELs) and No Observed Effect Concentrations (NOECs), providing inherent conservatism in the derivation of DNELs which to some extent covers exposure through multiple routes. For human health an intra-species uncertainty factor of 10 is applied (to allow extrapolation to humans from rats or other mammals), and an inter-species factor of 10 to account for differences in sensitivity in human populations. For the environment, safety factors of 100 or 1000 are applied based on acute testing on three representative aquatic species representing algae, fish (vertebrae) and daphnia (arthropods). Based on non-acute testing a factor of 10 to 100 is applied depending on the number of tests available.

- The recent work by Posthuma *et al.*[vii] on thousands of species sensitivity distribution estimations for chemicals on the European market (then summed) ignores the already established notion that environmental impact can be traced to a **small number of anthropogenic inputs to effluents**, e.g. certain metals, ammonia as a consequence of microbial activity in wastewater, chlorine as a wastewater disinfection process, and occasional spikes from over-applied pesticides. These are also largely controllable by conventional waste treatment technologies. Furthermore many of the chemicals cited in Posthuma *et al* are non-REACH substances, so the objective would not be achieved by applying a MAF in REACH. An **EU-wide holistic approach** to environmental protection could instead be justified based on effluent assessment methods and ecological reality checks; much of this work has already been led by scientists at RIVM.

- Other regulatory options need to be evaluated. For example, under REACH a risk management options analysis could be performed. Regulatory solutions should be tiered and proportionate to address the concerns. Broadly applied a MAF will result in unnecessary compliance activities that will ultimately not achieve the regulatory goals driving the MAF initiative.

In summary, applying an additional assessment factor may appear an easy option based on a limited evaluation of the impact on chemicals, but before taking any such step a fuller evaluation of the impacts and available options should be made based on more diverse scenarios.

DUCC thanks the Commission for taking note of these comments and remains open to further dialogue on this matter.

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[i] https://www.epa.gov/risk/framework-cumulative-risk-assessment
[ii] EFSA Panel on Plant Protection Products and their Residues (PPR Panel) Scientific Opinion on risk assessment for a selected group of pesticides from the triazole group to test possible methodologies to assess cumulative effects from exposure throughout food from these pesticides on human health on request of EFSA. 2009; 7 (9); 1167.
[iii] SCHER, SCCS, SCENIHR, Opinion on the Toxicity and Assessment of Chemical Mixtures, 2012.
[iv] Price *et al*.: A decision tree for assessing effects from exposures to multiple substances. *Environmental Sciences Europe* 2012 **24**:26.
[v] The human relevant potency threshold: Reducing uncertainty by human calibration of cumulative risk assessments. *Regulatory Toxicology and Pharmacology* 62 (2012), 313–328
[vi] Independent Technical Review of Cumulative Risk Approach, Methods, and Recommendations In: July, 2014 Report to the U.S. Consumer Product Safety Commission by the Chronic Hazard Advisory Panel on Phthalates and Phthalate Alternatives
[vii] Species sensitivity distributions for use in environmental protection, assessment, and management of aquatic ecosystems for 12 386 chemicals, *Env. Toxicology and Chemistry*, Vol. 38(4), 905-917.

About DUCC

DUCC is a joint platform of **11 European associations** whose member companies use chemicals to **formulate mixtures** (as finished or intermediary products) for professional and industrial users, as well as for consumers.

DUCC focuses on the downstream users' needs, rights, duties and specificities under **REACH** and **CLP**.

DUCC's membership represents several important industry sectors, ranging from cosmetics and detergents to aerosols, paints, inks, toners, pressroom chemicals, adhesives and sealants, construction chemicals, fragrances, lubricants and chemical distributors industries. Altogether, their membership comprises more than **9.000 companies** across the respective sectors in Europe, the vast majority being SMEs. The calculated turnover of these companies is more than **215 billion euros** in Europe.

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