DISCUSSION PAPER

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Chemicals Strategy for Sustainability

This paper was developed in the context of a stakeholder dialogue that followed our submission to the EU Commission's Roadmap consultation on the future Chemicals Strategy for Sustainability. It is meant to trigger an exchange of policy ideas or suggestions to inform the dialogue but does not constitute the agreed position of Cefic or its Members.

Combined Exposure (unintentional mixtures)

Issue

- To manage the risks chemicals may pose to public and environmental health, their placing on the European market is tightly regulated[1], incorporating a risk assessment that considers the potential impact on environmental and human health. Applied risk assessments typically look at each chemical individually.
- In real life, humans and the environment are simultaneously exposed to low levels of different chemicals (man-made and natural occurring) present in drinking water, food, air, surface water, etc.
- Hazard and risk assessment methodologies are **inherently conservative**: reasonable worst-case exposures are assessed against precautionary safe levels. It is generally assumed that if exposure to each chemical individually is assessed safe, risks resulting from combined exposures become very unlikely. Where needed, risk assessment approaches have been modified to capture potential combined exposures (e.g. structurally similar substances that cause the same toxicity via the same mechanism and the same cellular targets are assessed in a group approach).
- Nevertheless, there are growing concerns related to 'unintentional mixtures' that the Commission has committed to address under the future Chemical Strategy for Sustainability.
- The challenge here is to find a **reasonable and robust approach allowing to 'handle the unknown'** without **uncertainty leading to disproportionate action**. Building upon the findings of the Fitness Check on Chemicals legislation, part of the solution could include a workable methodological framework to manage risks of combined exposure.

Approach proposed

A stepwise approach is needed:

- **Set a clear scope and agree on definitions** based on a specific problem identification.
- **Identify priorities** that reflect the latest scientific understanding. A phased and proportionate approach is needed. The first step is to understand potential for co-exposure, i.e. risk scenarios that capture temporal and spatial flux in exposure, and whether existing measures are shown to be insufficient. Additional regulatory actions are only proportionate and effective for locations,

[1] Via a broad set of regulations like REACH, plant production product legislation, legislation on food contact materials etc.

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processes, uses or chemicals where a potential risk was demonstrated to be driven by combined exposures.

- **Address in a consistent manner across EU legislation.** Combination effects are relevant to different areas of use of chemicals and across different pieces of EU legislation. Priority exposure scenarios need to be agreed upon, **consistently,** considering and going beyond the scientific evaluations already performed among others by SCHEER, the JRC and Horizon 2020/Horizon Europe projects.
- **Rethink current thinking, balance robustness, effectiveness and pragmatism.** Pressure is increasing to implement simple solutions to address the complex issue of combined exposure. Cefic does not believe that the systematic introduction of a generic Mixture Assessment Factor (MAF) under REACH, as proposed by some authorities, is the right approach to solve the issue of unintentional combined exposure. Although it seems straightforward to apply, its simplicity is also its weakness. The rationale behind a generic assessment factor includes many worst-case and theoretical assumptions to cover uncertainties. As a result, the approach covers hypothetical exposures and risks rather than real-life scenarios. It is not based on sound scientific principles, and it would not target the actual co-exposure and use scenarios that are driving the Member States' concerns. Furthermore, the use and exposure scenarios cut across different chemical regulations. Solely addressing it under REACH would result in inconsistent regulation. Finally, the MAF approach is not backed by scientific evidence, but would result in many chemicals potentially ending up with an artificial 'unsafe' status based on hypothetical exposures and risks. This would result in neither effective nor proportionate risk management measures to be taken.

How to do it concretely (which legislation/article, etc)

1. Need to set a clear scope

Terminology is key. Currently, many different concepts are used: some as synonyms, others with different meanings, creating confusion.

Clear definitions of "exposure" building on OECD's set of definitions (2018)[i] :

- **combined exposure**: exposure to multiple substances by a single route (e.g. drinking water) and from multiple substances by multiple routes (e.g. drinking water, food, indoor air), from one or multiple sources of release and/or use(s). Co-exposure is used as synonym.
- **single substance, all routes, i.e. "aggregated exposure"**: exposure to one substance from multiple sources and by multiple routes. Aggregated exposure clearly differs from combined exposure. It can be calculated and this is already well addressed under current legislation, particularly under REACH. There is no need to draw up new/additional requirements[2].

Clear definitions of "mixture":
The word "mixture" has many meanings and interpretations. OECD (2018) defines different types of mixtures. In the context of combined exposure, focus is on:

- **coincidental mixtures:** (a mix of) substances from different sources, occurring in a medium e.g. combination of substances applied dermally from use of two or more product formulations

[i] Considerations for Assessing the Risks of Combined Exposure to Multiple Chemicals, Series on Testing and Assessment No. 296, Environment, Health and Safety Division, Environment Directorate. OECD ENV/JM/HA(2018)10.

[2] E.g. REACH. Chemical safety assessment looks at exposure per type of use. For each use exposure must be below a safe level. The sum of all exposures for all uses must also be below the safe level.

- **environmental mixtures:** substance combinations in one environmental compartment e.g. substances found in soil from various exposure sources (application of product formulation, deposition from air, water run-off, etc.)

The exposure to 'intentional mixtures' (of chemicals)[3] is known and adequately regulated, particularly under CLP as it requires classification of mixtures (most effects are additive and CLP foresees that potential synergistic or antagonistic effects should be taken into account).
The calls for action are mostly for 'unintentional' mixtures, i.e. coincidental and environmental mixtures.

2. Be proportionate, balancing regulatory pragmatism and scientific complexity

Combined exposure is a complex matter and there are no precedents identifying systematic risks from co-exposures that we could draw upon. Therefore, it is important to gather sufficient evidence and scientifically identify real-life cases to target in a legislative approach.
This should be complemented by reflections upon feasibility, regulatory implementation, proportionality etc.

3. Seek for the most effective regulatory response to address identified risks

Once sufficient understanding of the chemicals driving a combined effect is available, targeted measures to assess and reduce risks can be taken. Double regulation needs to be avoided. For example, combined exposures of workers are already addressed by OSH regulation.

4. Establish key principles of an effective framework after having clarified the risk(s)

- **Target** those (hazardous) chemicals, uses and exposure patterns driving demonstrated risks of combined exposure to 'unintentional mixtures'. While the combination of chemicals one can be exposed to is in theory infinite, the reality is that emissions and use patterns within a given timeframe and spatial scale determine the potential for combined exposure. There is growing evidence from field studies and model predictions indicating 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[4] .
- **Understand and focus on chemicals dominating unacceptable mixture effects.** This will be most effective and is needed to keep the system manageable.
- **Understand and acknowledge the role of local factors** in particular when looking at potential concerns of combined exposure to chemicals via surface water. Local drivers include human and industrial activity, the characteristics of a watershed, as well as urban wastewater management.
- **Data mine existing EU data sources** (REACH database, IPCHEM, research projects like HMB4EU) to generate insights on real-life and potential exposure combinations, typical exposure routes and uses. For example, the research project 'Solutions' developed a modelling train to predict exposures to chemicals via surface water at EU-scale.
- **Further develop non target screening of e.g. surface, ground or drinking water**. Such screening gives a chemical footprint of water sources. Drinking water suppliers do this more and more. This

[3] e.g. paints, biocides, medicines, cosmetics, … Rules to assess their hazards and risks are set in CLP, BPR, PPP directive, cosmetics directive, etc.

[4] Harbers et al., 2006; Zijp et al., 2014; Gustavsson et al., 2017; Backhaus and Karlsson, 2014; Vallotton and Price, 2016; Posthuma et al., 2016

can become good practice in relation to the new risk-assessment requirements of the updated drinking water directive.

- **Consider if and how** whole effluent testing could provide a better understanding of actual exposures and potential impacts that occur in EU receiving waters.
- **Be consistent across legislations and different regulatory agencies, including collaboration across agencies.** The chemicals characterising combined exposure are often regulated under different regimes. For example, fish in surface water can be exposed to a combination of pesticides, pharmaceuticals and industrial chemicals (see monitoring reports submitted by Member States) that would vary depending of the location and season. These can come from different sources and uses. This needs to be addressed via a holistic approach across legislations: water framework directive (receiving environment), pesticides, pharmaceuticals, REACH, industrial emission directive. All agencies involved should work together to ensure consistency of methodology. **No unilateral approach should be taken under REACH.**
- **Build upon lessons learned and good practices from existing methodologies** e.g. typically those applied to pharmaceuticals, EU Research projects like HBM4EU, Solutions, EuroMix and ongoing activities at global level (WHO, OECD). Agencies such as EFSA have been working on practical methods to assess combined exposure, OECD/WHO have worked on conceptual frameworks. Currently, data and methodologies are available but scattered. It is essential to bring them together and start building upon them. The outcome of the latest research would warrant a **comprehensive independent review**, e.g. by a European scientific committee, to support the identification of priority areas and of approaches for effective risk management. **An independent Advisory Board should be constituted to advise the Commission.**
- **Gather monitoring data into a central platform/database.** Monitoring (non-target screening, effect-based monitoring, biomonitoring etc.) can be installed via different legislations (water framework directive, OSH legislation, drinking water directive, etc.). By uploading results to a common platform (like IPCHEM), data can be shared and assessed at EU level.
- High quality, publicly available monitoring data will allow the development of computational models to estimate relevant combined exposures at a local and regional scale with previously demonstrated risks, enabling effective and proportionate risk management.
- -**Consider the conservatism built into existing risk assessments**: The risk assessments conducted as part of the REACH regulation already assume a worst-case approach and have DNEL values that are already orders of magnitude below where any activity was observed in the animal model. Additionally, the exposure calculations for many chemicals overestimates the tonnage and exposures in order to conservatively predict the use in the supply chain. Taken together, there is already a large amount of conservatism built into the current risk assessments. The key question to solve is: where or in which scenarios is this conservatism not sufficient?

Cases/evidence/examples

- Example 1: for chemicals via food posing a demonstrated risk via combined exposure, the necessary measures to assess specific risks can be managed via food regulation.
- Example 2: treated urban wastewater contains different types of substances (pharmaceuticals, pesticides, and all other kinds of chemicals). Downstream, at the outlet of a wastewater treatment plant, combined exposures exist. After a specific unacceptable risk resulting from specific combined exposure, effect-based and targeted (bio)analytical monitoring (imposed via the water framework directive) allows to assess if these exposures are problematic or not. When these are problematic measures can be taken via legislation setting standards for urban wastewater treatment plants.

- Example 3: use of different chemicals at the workplace lead to combined exposure for workers. Substances workers are (potentially) exposed to, are known. Combined exposure assessment is already required under OSH for targeted risk assessment. For substances with a similar health effect, the level and duration of exposure are added to relate to the permissible exposure limit. This procedure can be used for both OELs, company OELs, DNELs or hazard band.