Cefic Position Paper on

Combination Effects of Chemicals

Today, EU chemicals policy and risk management schemes predominantly focus on the safety of individual chemical substances. They protect public health and the environment by ensuring that no chemical substance is intentionally present in the environment at levels that might cause harm.

Recent reports have suggested that when chemical substances, both natural and man-made, are combined together they might cause adverse effects to human health and the environment, even if the individual chemical substances (i.e., natural and man-made) are present at levels that are considered harmless. Although there is currently little evidence of such a "combination effect" from typical environmental exposure levels, it is important that we consider the possibility of harm through the risk assessment procedures.

Therefore, the chemical industry is engaged with relevant European and international bodies and agencies to address this concern. The collaborative efforts have revealed that, whilst further research could provide additional insights into such a complex issue, there are already procedures and tools that can be applied to address the potential combination effects of chemical substances. These are described below.

Screening

Research from industry, academic (including the European Commission Scientific Committees) and government sources indicate that in laboratory studies combination effects of chemical substances tend to only occur at relatively high concentrations, where effects from single chemicals are already observed. At the low exposure levels, generally seen in the environment, combination effects are unlikely to occur or are toxicologically insignificant[1].

Current scientific evidence shows that chemicals generally act in an additive way, at worst, rarely interacting in a more than additive way, and when environmental combined chemical exposures pose a risk, the risk is typically driven by one or just a few of the chemicals[2]. This situation usually occurs when one or more chemicals in the mixture approach the no effect or the effect dose/concentration that may have additional uncertainty (safety) factor adjustments added in. As a result, **controlling individual chemicals through the current regulatory schemes will also control the overall risk from environmental combined exposure**.

[1] SCHER, SCCS, SCENIHR. Opinion on the Toxicity and Assessment of Chemical Mixtures, 2012

[2] Boobis A, et al. Critical analysis of literature on low-dose synergy for use in screening chemical mixtures for risk assessment, Critical Reviews in Toxicology 2011, 41:5, 369-383, DOI: 10.3109/10408444.2010.543655

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Despite these findings, the industry continues to research and develop tools to identify and assess any potential risks. Every day, we are exposed to numerous natural and man-made chemicals. For example, our engagement in basic everyday activities such as breathing and eating exposes us to a large number of natural chemicals. It is impossible to predict all the combinations of natural and man-made substances and their concentrations in the environment: let alone to assess them all. Generally, this also tells us that organisms have adapted and are able to manage combined exposures, as combined exposures are the rule and not the exception. The priority is thus to identify the specific combined exposures scenarios where this may not be the case. **Therefore, it is important to have an efficient way of identifying the specific combined exposures that could pose a concern.**

To this end, screening criteria proposed by industry are consistent with those proposed by the EU Commission Scientific Committees. These criteria, and the recently developed **Maximum Cumulative Ratio (MCR)**[3] tool, can be used to identify combinations of chemicals, which are of concern at their actual, realistic exposures, rather than attempting to evaluate many harmless combinations.

Practical tools

As part of our commitment to ensure the safety of our products, the chemical industry is working with academia and Governments to develop and share tools to assist in the risk assessment of both individual substances and combinations of chemicals. In particular, **Cefic has developed a "decision tree, incorporating the MCR tool, for the evaluation of human and ecological effects from exposures to multiple chemicals from a single or multiple sources"**[4]**,** which builds on the risk assessment framework of the WHO and the European Scientific Committees.

The proposed two-stage approach works as follows:

Stage 1: Screening Tool:

In the first stage, a Screening Tool is used to identify those cases where effects from combinations of chemicals might be of potential concern and need further risk management measures:

- Step 1: identify those substances that are present at relevant concentrations in a given environment;
- Step 2: collect all the relevant, available toxicological data in relation to those substances;
- Step 3 : Based on a consideration of levels of exposure and the toxicity data :
  - Where all the substances present are of no, or low concern and there is nothing to suggest a possible combination effect, then the existing individual chemical assessments suffice.
  - Where a combination contains one or more substances at potentially unsafe levels, an additional risk assessment of the individual components is undertaken and, if necessary, additional risk management measures are implemented for the individual substances of concern.

[3] Paul PS, Xianglu H. Maximum cumulative ratio (MCR) as a tool for assessing the value of performing a cumulative risk assessment. Int. J. Environ. Res. Public Health 2011, 8: 2212-2225; doi:10.3390/ijerph8062212

[4] Price PS et al. A decision tree for assessing effects from exposures to multiple substances. Environmental Sciences Europe 2012, 24(1):26.

- Where cumulative or combination effects are a potential concern, a full cumulative risk assessment is undertaken.

Stage 2: Tiered Risk Management

Where the Screening Tool suggests that there are grounds for concern and that further risk management of combination effects is called for, the decision tree proposes a "Tiered Risk Assessment", combining the most effective approaches (e.g.; the dose/concentration addition approach relating to chemicals with a common mode of action, the independent action approach for those with different modes of action). This approach contains an increasing refinement of hazard and exposure assessment through the different tiers, which provides a structured approach for risk assessment of combination effects.

Proof-of-concept studies[5][6][7][8][9][10][11] (of US[12] and European[13] surface water data and, of residential indoor air monitoring data from European studies) have demonstrated the effectiveness of the decision tree tool.

Concluding remarks

The risk assessment and management approaches, under existing regulatory schemes, protect humans and the environment from exposure to environmentally relevant levels of individual substances. Managing the risks from these substances individually will, in the majority of cases, also ensure that combinations of chemicals do not present a risk to human health or the environment.

Beyond this, our 'combination effects' approach offers a pragmatic and scientific way forward for effective screening of the numerous substances in a given environment, identifying the drivers of risk from combinations of chemicals, and prioritising those cases where there is potential for a cumulative or combination effect that requires a specific risk assessment.

[5] Dourson M et al. Advancing human health risk assessment: Integrating recent advisory committee recommendations. Critical Reviews in Toxicology 2013, 43(6): 467-492.
[6] De Brouwere K et al. Application of the maximum cumulative ratio (MCR) as a screening tool for the evaluation of mixtures in residential indoor air. Sci Total Environ 2014, 479: 267-276.
[7] Vallotton N, Price SP. Use of the Maximum Cumulative Ratio As an Approach for Prioritizing Aquatic Coexposure to Plant Protection Products: A Case Study of a Large Surface Water Monitoring Database. Environ Sci Technol 2016, 17;50(10):5286-93. doi: 10.1021/acs.est.5b06267
[8] Mishra N, Ayoko GA, Salthammer T et al. Evaluating the risk of mixtures in the indoor air of primary school classrooms, Environ Sci Pollut Res (2015) 22: 15080. https://doi.org/10.1007/s11356-015-4619-z
[9] Han X, Price PS. Applying the maximum cumulative ratio methodology to biomonitoring data on dioxin-like compounds in the general public and two occupationally exposed populations. J. Expo. Sci. Environ. Epidemiol 2013, 23, 343e349. http://dx.doi.org/10.1038/jes.2012.74.
[10] Price PS, Zaleski R, Hollnagel H, Ketelslegers H, Han, X. Assessing the safety of co-exposure to food packaging migrants in food and water using the maximum cumulative ratio and an established decision tree. Food Addit. Contam. Part A. Chem. Anal. control. Expo. Risk Assess 2014, 31, 414-421. http://dx.doi.org/10.1080/19440049.2013.865145
[11] Junghans M, Han XL, Kunz P, Watts C, Leverett D, Price PS. Application of the combined decision tree to surface water data from Switzerland, UK, and other EU countries. Toxicology Letters 2013, 221: S25-S25.
[12] Han XL, Price PS. Determining the Maximum Cumulative Ratios for Mixtures Observed in Ground Water Wells Used as Drinking Water Supplies in the United States. Int. J. Environ. Res. Public Health 2011, 8, 4729-4745; doi: 10.3390/ijerph8124729.
[13] Price PS et al. An application of a decision tree for assessing effects from exposures to multiple substances to the assessment of human and ecological effects from combined exposures to chemicals observed in surface waters and waste water effluents." Environmental Sciences Europe 2012, 24(1):34

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About Cefic
Cefic, the European Chemical Industry Council, founded in 1972, is the voice of large, medium and small chemical companies in Europe, which provide 1.2 million jobs and account for 17% of world chemicals production.