Commentary:

Scientific Critique of the Proposed Application of a Mixture Assessment Factor (MAF) to Every Chemical in the EU REACH Chemicals Registration Program

Provided to the EU Public Consultation on the Targeted Revision of the REACH Regulation

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Project Report:
Investigation of the Scientific Basis for the Proposed Application of a Mixture Assessment Factor (MAF) to Every Chemical in the EU REACH Chemicals Registration Program

Introduction

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One of the challenges to ensuring environmental protection is the recognition that chemicals are typically present in the environment in mixtures while environmental risk assessments are conducted on single substances.[1] Ensuring the protection of biota have mostly been conducted retrospectively, such as through effluent or ambient toxicity tests as well as via ecological monitoring studies. However, a new prospective method - Mixture Assessment Factors (MAFs) has been proposed by the European Commission (EC) as part of the Chemicals Strategy for Sustainability (CSS) initiative.[2] The MAF is defined as "the factor by which the regulatory threshold of a given chemical (its PNEC or DNEL, for example) need to be divided in order to ensure a level of protection against unintended mixture effects that is similar to the level of protection aimed for a single substance assessment."[3] A MAF(s) is intended to address uncertainties in environmental risk assessments due to the presence of unintended mixtures of chemicals in the environment.[4] The EC is currently considering "options for addressing the risks of exposure to several substances (combination effects) by introducing one or more MAFs" in the EU REACH chemicals regulation program.

This Project Report focuses on the environmental protection aspects of the CSS initiative and whether a MAF(s) should be applied to every chemical requiring quantitative risk assessment in REACH. Two types of data are considered to address this question:

1. A critical review of relevant data on environmental mixtures, and
2. A case study - the environmental mixture data available on linear alkylbenzene sulfonate (LAS), one of the best studied down-the-drain chemicals in REACH.

1. Review of Key Data on Environmental Mixtures

Research over the past decade has shown that only a relatively few chemicals have been implicated in providing negative causal relationships with ecological effects (Posthuma et al.[5] Vallotton and Price[6]). In a study using the available data on the chemicals in the REACH database, Van de Meent et al.[7] conducted a screening level assessment for mixture toxic pressure in the aquatic environment. The authors noted that "few compounds dominate the predicted impact." As noted by the authors, this pattern has been observed in other fields of science and has been termed the Pareto principle.

The Swedish Chemicals Agency (KEMI) prepared a key report regarding the policy aspects of implementing a MAF(s) in chemical regulation.[3] The report provides a description of a two-step process for calculating a MAF(s) to be applied to environmental mixtures.

The following limitations are apparent when considering the environmental monitoring data used to derive the MAF values:

First, neither environmental monitoring study measured ecological impacts and thus neither could consider whether ecological impacts are driven by mixtures or individual constituents. The later alternative is consistent with the available environmental monitoring data, which that found relatively few chemicals are responsible for most ecological impacts[5,6,7].

Second, effective protection from ecological impacts requires a MAF(s) to cover all substances found in the environment, including biocides, cosmetics, food contact materials, pesticides, and pharmaceuticals, as well as industrial chemicals.[1] Because these substances are covered by different regulatory legislation, the MAF should be considered a mixture allocation factor to allocate the appropriate fraction of the MAF value to each group of regulated chemicals. The MAF value applied to REACH chemicals should be the (as yet unknown) percentage of the full MAF value that applies to REACH chemicals.

Third, the environmental mixtures considered in the KEMI report[3] have limited relevance to the REACH database. This mixture data is taken from two studies. One study[8] focused on pesticides (not included in the REACH database) while the other study[9] detected 55 pesticides, 31 pharmaceuticals and 12 other substances. The size of the other substance group is inadequate to represent the 23,000 chemicals in the REACH registration database.

Fourth, the available monitoring studies almost certainly underestimate the number of chemicals present in the environment. The report suggests for environmental mixtures consisting of more than 30 compounds, the MAF value used should equal n/2. Since the number of detectible compounds in environmental mixtures is likely to number in the hundreds if not thousands, use of n/2 will lead to large MAF values, triggering risk management for a large number of chemicals, contrary to the Pareto principle that relatively few chemicals are responsible for the large majority of environmental impacts.

Importantly, use of large MAF(s) to account for the knowns and unknowns does not reward decreased uncertainties via higher tier testing – a key attribute to risk assessment.

Our assessment is, while the KEMI report reviews the available data, there is insufficient data to support applying a MAF value(s) to every chemical in the REACH database.

2. Case study - linear alkylbenzene sulfonate (LAS), one of the best studied down-the-drain chemicals in the REACH database.

A case study was considered to further assess the question as to whether a MAF(s) should be applied to every chemical in the REACH database. The case study was created with linear alkylbenzene sulfonate (LAS, REACH Substance Name: Benzenesulfonic acid, C10-13-alkyl derivatives, sodium salts, EC Number: 270-115-0, CAS Number: 68411-30-3), a major ingredient (surfactant) used in laundry

detergents and cleaning products world-wide[10-12]. LAS is a large-production volume chemical (>1000 metric tons per year in Europe) with perhaps the most extensive environmental dossier of any down-the-drain chemical in the world. In addition to the extensive environmental safety data on LAS (see below), relevant data on environmental mixtures containing LAS is available.

LAS Environmental Safety Studies

The available environmental safety data available on LAS consists of: 1) a robust aquatic PNEC value and 2) environmental monitoring data. The data available to derive aquatic PNEC values consists not only of acute and chronic datasets (required for REACH registration) but also high-quality quantitative structure-activity relationships (QSAR), species sensitivity distributions (SSD) and experimental stream study data. The PNEC value in the REACH Registration dossier is based on the NOEC value (0.268 mg/L for C12 LAS) based on experimental stream study data[13].

Several monitoring studies report LAS environmental concentrations in freshwaters in Europe, the US and Japan. The HERA Project report on LAS[10] reviewed monitoring studies conducted in Europe and the US. LAS concentrations in receiving waters in Europe ranged from <0.002 to 0.047 mg/L. In US monitoring studies LAS concentrations in river waters below WWTP mixing zones were generally below 0.05 mg/L. A recent study[14] from Japan reported that none of 4,748 measured LAS concentrations exceeded the experimental stream PNEC (0.268 mg/L). These results indicate negligible risk from LAS in surface waters of Europe, the US and Japan.

LAS Environmental Mixture Studies

Two approaches have been used to assess the real-world safety of environmental mixtures containing LAS: 1) additivity studies and 2) eco-epidemiology studies.

1. Additivity Studies

Additivity studies consider the aquatic toxicity of mixtures of surfactants. These studies are made possible by the finding that anionic surfactants such as LAS exhibit a non- specific mode of action (MoA) – narcosis[15,16]. Aquatic toxicity of mixtures of surfactants can be calculated based on their QSAR properties and MoA. Using this approach, McDonough et al.[17] conducted a probabilistic assessment of US freshwaters by extrapolating monitoring data for LAS, alcohol sulfates (AS), alcohol ethoxysulfates (AES) and methyl ester sulfonates to mixing zone concentrations for 8,800 sites throughout the nation via the iSTREEM® model. Assuming a concentration addition approach (i.e., toxic unit or PEC/PNEC ratios) for all anionic surfactants, the 90th percentile toxic unit value at 7Q10 (critical low flow, seven lowest consecutive flow days over a 10-year period) was 0.0421, indicating that all 4 anionic surfactants together have a large margin of safety, greater than 20-fold.

A more recent monitoring study[18] reported concentrations of anionic, and nonionic surfactants, including LAS, AS, AES and alkyl ethoxylates (AE), their byproducts and degradation products in receiving water mixing zones from 33 WWTPs in Germany. Levels of all monitored substances were below their respective PNEC values. Cumulative risk ratios were less than 1.0 for all WWTPs except for one plant where the calculated cumulative risk ratio was 1.06. However, the study did not use the most updated estimate of the LAS PNEC (reviewed by Dyer and Belanger[19]) which led to an overestimated risk ratio for LAS by a factor of 10. Hence, a reanalysis would conclude that all 33 sites had cumulative risk ratios less than 1.0.

2. Eco-epidemiology Studies

Eco-epidemiology is the retrospective assessment of biological measurements (e.g., macroinvertebrate and fish community status) compared to modeled and/or measured environmental stressors, including chemical mixtures. The relative contribution of these stressors provides an ecological reality check on these stressors, such as mixtures, causing adverse impacts.[20]

Seven eco-epidemiology studies, summarized in Table 1 below, have been conducted in which links have been examined between ecological impacts and either LAS concentrations, or mixture concentrations containing LAS or likely to contain LAS such as municipal effluents. In only one study[22] were observed impacts (3% of total) tied to chemical mixtures consisting of modeled concentrations of LAS, AES, AE and eight other substances. In the six other studies, no link was observed between adverse ecological impacts and LAS concentrations.

Conclusions

1. Research over the past decade has shown that relatively few chemicals have been implicated in providing negative causal relationships with ecological effects. These studies are not supportive of, and indeed contradict proposals to apply a MAF value(s) to all chemicals requiring environmental risk assessment REACH.

2. Proposals to estimate MAF values are hampered by the available environmental monitoring studies. The available studies focus either on pesticides or include numerous compounds such as pesticides and pharmaceuticals that are not representative of the REACH registration database. This is especially relevant when one considers that the REACH registration database consists of over 23,000 unique chemicals while only 12 chemicals representative of the REACH database were considered in the studies.

3. The environmental mixture data available on LAS was examined as a case study on the question of application of a MAF value(s) to every chemical in the REACH database. There is more environmental data on LAS than any other down-the-drain chemical, including the derivation of a robust PNEC value that includes QSARs, SSDs and an experimental stream study as well as environmental monitoring studies in Europe, the US and Japan. Studies are available on the potential ecological impact of environmental mixtures containing LAS. These studies consist of additivity studies of LAS and other surfactants in the US and Germany, and seven eco-epidemiological studies considering environmental mixtures containing LAS.

4. The environmental mixture data available for LAS do not support the application of a MAF value(s) to every chemical in REACH. Rather, the available data indicate that an additional assessment factor to lower the PNEC, such as a MAF, is not needed for LAS despite the fact that it is nearly ubiquitously present in environmental mixtures due to its use as a down-the-drain chemical.

Table 1 Eco-epidemiology studies which specifically considered LAS among the ecological stressors

Study	Sample Sites	Ecological Effects Measure	Conclusion
Dyer and Wang[21]	Urban and rural sites upstream and downstream of 221 WWTPs in Ohio, USA	Impacts observed both upstream and downstream of urban environments, likely related to habitat alterations	Adverse impacts from LAS and other domestic chemicals were not observed
De Zwart et al.[22]	695 sites from Ohio, USA	Modeled concentrations of LAS and other down-the-drain chemicals	3% of observed impacts tied to chemical mixtures
Kapo et al.[23]	1700 sites in Ohio, USA	Chemical mixtures, habitat, watershed characteristics, soils, human population, WWTPs, and landcover.	Surfactant mixtures, including LAS, were not a leading cause for adverse effects
Atkinson et al.[24] and Slye et al.[25]	Effluent dominated Trinity River, Texas, USA	Ammonia, metals and/or other effluent associated stressors like low dissolved oxygen	Surfactants, including LAS, were not found to be potentially causal.
Sanderson et al.[26]	Upstream and downstream of 3 rural WWTPs in Indiana and Ohio, USA	LAS, AES and AE	No negative statistically significant relationships between surfactant mixtures and macroinvertebrate species richness and abundance.
Dyer et al.[27]	Primary sewage discharge to the Balatuin River, The Philippines	LAS, dissolved oxygen, BOD, ammonia nitrogen	LAS concentrations were below protective criteria even in the impact zone produced by primary discharge of wastewater.
Holmes et al.[28,29]	3970 river and stream sites in Federal state of Hessen in Germany	Biological Quality Elements (BQEs) for fish, macroinvertebrates, diatoms and macrophytes	LAS did not drive ecological status

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