Including a Mixture Allocation Factor in the REACH Revision is Crucial for Improving Chemical Risk Management in the EU

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INTRODUCTION

Humans and ecosystems are continuously exposed to complex mixtures of chemicals (1). This issue of "chemical cocktails" has been receiving increasing attention by policy-makers and the public alike. Yet, the potential health and ecological impacts of coincidental mixtures of chemicals that combine in our bodies, and in wildlife, water, sediments, and soil from many sources, receive insufficient attention in chemical risk assessment and management. Instead, regulatory risk assessment primarily evaluates individual substances, and chemical products that might contain intentional mixtures or substances of unknown or variable composition. This gap results in a systematic underestimation of the risks for human health and the environment. As policy makers in the European Union (EU) undertake a revision of the Regulation on the Registration, Evaluation, Authorization and Restriction of chemicals (REACH), they should incorporate a mixture allocation factor to enable more realistic chemical management and create incentives for safe and sustainable innovation without imposing undue administrative burdens.

Coincidental mixtures raise particularly difficult challenges for regulators seeking to ensure safety when approving new chemicals. How can policy-makers and regulators consider the total chemical exposure before allowing a new substance to enter a market where the "safe space" is already partly or fully occupied? Should the manufacturer—who is often unaware of the broader exposure situation—be responsible, or the regulatory authorities, who may lack adequate resources? Must evaluations be handled case by case, or is a generalizable framework possible that accounts for the ubiquitous presence of mixtures when bringing a new chemical to the market?

CONCENTRATION ADDITION FOR PREDICTING AND ASSESSING MIXTURE TOXICITIES

The concept of concentration addition, also termed dose addition, was originally developed to estimate the toxicity or risk of mixtures composed of chemicals with similar modes of action. Perhaps the oldest regulatory implementation of concentration addition is the recalculation of dioxin-like compounds such as dioxin-like polychlorinated biphenyls (dl-PCBs) and

polychlorinated dibenzofurans (PCDFs) into equivalent concentrations of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD). Empirical evidence from the past 30 years has demonstrated. the suitability of the concentration addition concept for modeling not only the toxicity and risks of chemical mixtures composed of similarly acting substances, but of mixtures in general (2). The alternative model, independent action (also called response addition), better describes mixture effects only in rare, exceptional cases (2).

Neither concentration addition nor independent action accounts for synergistic or antagonistic interactions. Although such interactions can in principle occur in any mixture, quantitatively relevant deviations from either model were observed in only about 5% of experimental mixture studies. These cases predominantly involve mixtures of only a few compounds at high concentrations, such as in pesticide formulations or pharmaceutical products, but not in complex mixtures with many components (3).

As a consequence, the World Health Organization (4), as well as the European Food Safety Authority (5) and the US Department of Health and Human Services (6), recommends concentration addition as the default for the initial assessment of mixture risks. The assumption of concentration additivity is discarded only when there is empirical evidence to the contrary.

The toxicity of an individual chemical or a mixture is its inherent capacity to cause adverse biological effects, quantified, for example, as the concentration needed to cause a predefined effect level such as the EC50, the concentration or dose that causes a 50% effect in the exposed organisms. Risk is then the relation between toxicity and the actual or expected exposure. In contrast to a single chemical, the toxicity and risk of a mixture depend on a third factor: the number of components in the mixture. Basically, it is the total concentration of all mixture com-ponents combined that makes the poison, weighted according to each chemical's potency.

Consequently, mixtures can cause harm even when each chemical occurs only at levels that do not cause measurable effects individually, if the number of components in the mixture and their toxic potency are high enough. This has been empirically shown in various ecotoxicological assays and cell-based test systems already in the early 2000s (2). More recent research has shown that mixtures of phthalates and pesticides can cause severe developmental disorders in nonhuman animals, such as undescended testicles or penile malformations, at doses well below each chemical's no-observed-adverse-effect level (7). The components of these mixtures have different mechanisms of action, refuting the argument that mixture effects only have to be taken into

consideration if all mixture components share the same mode of action. Furthermore, studies published as early as 2014 suggest that regulatory compliance with official environmental quality standards does not pre-vent harmful effects from complex heterogeneous mixtures (8).

Empirical evidence shows that regulatory limit values are too frequently exceeded when considering a concentration-additive behavior of chemical mixtures. For example, a recent mixture risk assessment examining the decline in sperm quality found that cumulative exposures surpassed acceptable total limits by factors ranging from 5 to 100 (9). In some cases, the combined exposures even approached levels known to cause observable harm in animal studies. This means that, despite individual chemical concentrations remaining below their regulatory limit values, the overall mixture would still pose an unacceptable risk.

Taken together, these findings challenge the assumption that current regulatory limit values are sufficiently protective under conditions of combined exposures. Such values include predicted no-effect concentrations, acceptable or tolerable daily intakes, derived no-effect levels, and environmental quality standards, which are all defined as doses or concentrations of a single chemical assumed to cause no harm despite the underlying uncertainties.

NEGLECTING MIXTURE RISKS CONTRADICTS EMPIRICAL EVIDENCE AND TOXICOLOGICAL UNDERSTANDING

Despite the evidence outlined above, it is sometimes argued (10) that mixture risks are negligible as long as all individual components remain below their respective regulatory thresholds. This view assumes that substances without a common mode of action be-have independently, implying that those present at individually noneffective concentrations cannot cause combined effects. Hence, mixture risk assessment is often considered unnecessary, except for strictly similarly acting substances or when the concentration of one or more components exceeds regulatory limits

However, this perspective is based on several problematic and empirically unsubstantiated assumptions. It requires that regulatory thresholds represent absolute no-effect levels without residual risk and that all chemicals in a mixture act on the exposed organism through entirely different and independent mechanisms. Scientifically, one can only conclude negligible risks from mixtures at low doses of its components, if all these conditions are demonstrably fulfilled for a given mixture and exposure scenario. Empirical evidence, however, highlights the rarity of such

scenarios (2). Furthermore, the notion that all relevant chemicals in a complex mixture of dozens or even hundreds of chemicals act strictly in-dependently on a human body or an environmental organism conflicts with the fundamental biological principle that cells, tissues, and organ systems form highly interactive networks.

Some argue that existing standard safety factors, applied to extrapolate experimental data from the laboratory to the real world as part of the regulatory chemical assessment, are too conservative, and would therefore sufficiently account for combination effects. Yet, analyses reveal that these default safety factors barely address uncertainties for individual chemicals. They were never designed to handle mixture hazards and risks (11).

It is important to emphasize that applying concentration addition to the mixture(s) of interest does not imply that every mixed exposure inevitably poses unacceptable risks. However, both empirical evidence and fundamental biological knowledge show that mixture risks cannot be dismissed a priori—even if in-dividual chemicals occur at levels considered "safe" on their own. To ensure effective protection of human health and the environment, the exposure and hazard characterization of coincidental mixtures must become a core element of chemical risk assessment and management.

THE NEED FOR NEW POLICY APPROACHES

Applying concentration addition, independent action, or any other component-based mixture assessment method requires detailed knowledge of the chemical composition and the toxic potency of each mixture component. But real-world mixtures are complex, and toxicological data are often lacking for many chemicals in use. As a result, observed toxic effects in environmental and human samples (e.g., surface waters, blood, tissues) often remain only partially explained by known substances. Indeed, more than 90% of these effects may result from unknown or unidentified chemicals (1).

To pro-actively manage risks and to ascertain chemical safety un-der such limitations, simpler and more pragmatic approaches are needed. In response, the European Commission's Chemicals Strategy for Sustainability proposes to introduce an additional safety factor, the mixture assessment factor or mixture allocation factor (MAF), in the upcoming revision of REACH (12). This proposal has gained explicit support from Sweden, Denmark, Finland, and Luxembourg at

the EU Council meeting in December 2024 (13) and from more than 250 academic scientists working on chemical hazard and risk assessment (14).

Under REACH, risk assessment of an individual chemical revolves around the risk quotient, the dimensionless ratio of the chemical exposure to the corresponding regulatory threshold. A risk quotient of 1 for an individual chemical is the maximum value that is still considered safe under REACH and similar regulations. The MAF approach aims to ensure that the sum of individual risk quotients in a mixture does not exceed 1, adapting the "risk cup" approach originally developed by the US Environmental Protection Agency under the Food Quality Protection Act (15). In this analogy, the total volume of the cup equals an overall mixture risk quotient of 1,

which is filled additively by the individual risk quotients of all mixture components. Originally used to evaluate cumulative pesticide risks, the approach can easily be adapted to industrial chemicals.

Applying a MAF reduces the maximum acceptable risk quotient of an individual mixture component from 1 to a lower value, so that that the sum of all risk quotients does not exceed the critical value of 1. The MAF simply quantifies the size of the fraction of the risk cup that an individual chemical is allowed to occupy at maximum. In its simplest form, the MAF equals n, the number of chemicals in the mixture. For example, in a five-component mixture, if each chemical's risk quotient does not exceed 1/5, the total mixture RQ will remain ≤ 1, assuming additivity, and the MAF would therefore be 5. In real-world coincidental mixtures, however, many components occupy far less than 1/n-th of the risk cup. This free portion can be taken up by other mixture components, resulting in an overall MAF value lower than the theoretical maximum MAF of n (see the figure).

Not all chemicals with a risk quotient below 1/MAF would be affected by the introduction of the MAF (chemicals 3 and 4 in the figure). This ensures that producers of low-risk chemicals (i.e., chemicals with negligible risk quotients) are not unduly burdened with risk mitigation measures that provide only limited benefits for human health or the environment. By contrast, chemicals with risk quotients above 1/MAF (chemicals 1 and 2 in the figure) would require risk management actions, such as emission reductions, to bring their contributions below the maximal acceptable level.

The MAF concept is straightforward to implement into the current risk evaluation of chemicals under REACH. It has the major advantage that it does not require a series of detailed and specific mixture risk evaluations for each of the tens of thousands of chemicals on the market. However, such a pragmatic approach, though enabling faster, more flexible, and resource-efficient decision-making, comes with additional uncertainty.

The critical regulatory challenge is to determine MAF values that ensure sufficient protection of human health and ecosystem integrity, while avoiding unnecessary alterations of the risk assessment and management of chemicals that do not materially contribute to mix-ture risks. Currently, MAF sizes ranging from 5 to 100 are discussed by different stakeholders, on the basis of either pragmatic considerations and/or the evaluations of existing data on typical exposure situations involving chemical mixtures.

The upcoming revision of REACH offers an opportunity to policy-makers and regulators to integrate the MAF into the upcoming REACH revision as a fundamental instrument to make chemical risk management "mixture aware," potentially starting with a modest value of 5 (i.e., at the lower end of the currently discussed values). Policy-makers and regulators should then commit to a regular review and refinement of the MAF, as new data emerge. This would also allow adjustment of the numerical value of the MAF, in view of changing numbers, emission patterns, and toxicological characteristics of the industrial chemicals on the European market. Such work could also entail detailed analyses whether a "one size fits all" MAF value (sufficiently, but not excessively conservative) can be applied across all industrial chemicals, or whether different MAF values are needed to account for different exposure scenarios. The European Chemical Agency's datasets on production valuable foundation for these efforts.

Initially focusing the MAF on industrial chemicals is a logical first step, given that REACH regulates the majority of chemicals on the European market. However, its scope should be broadened in the future to also address co-exposures involving other chemical groups such as pesticides, biocides, and pharmaceuticals.

Current regulation requires producers, importers, and users to ensure safe chemical use, regardless of the presence of other chemicals. Recognizing that the tolerable chemical burden is collectively used up by multiple substances challenges this core principle. In this respect, the safety regulation of industrial chemicals and other substances should learn from the impact assessment of chemical emissions on global warming, where the warming potentials of different greenhouse gases are

recalculated so that they are all expressed in a common measure as CO2 equivalents before assessing their contribution to global warming. This is a large-scale application of the concentration addition principle. Establishing and implementing the REACH regulation has already spurred innovations, such as the replacement of several sub-stances of very high concern with less problematic alternatives, or the development of animal-free testing methods. Incorporating the MAF into the forthcoming REACH revision would not only enable a more realistic chemical management but would also create incentives for safe and sustainable innovation, all without imposing undue administrative burdens.

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FIGURE - The principle of the mixture allocation factor (MAF)

The "risk cup" represents the maximum available safe emission space. Although safe use may be demonstrated for each individual component of a mixture (top line), the sum of the risk contributions exceeds the risk cup (bottom left). Applying the MAF, which affects only the two largest risk drivers, ensures that the mixture remains within the safe emission space (bottom right).