PERSPECTIVE | CHEMISTRY

Regulate to reduce chemical mixture risk

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Humans and wildlife are continuously exposed to multiple chemicals from different sources and via different routes, both simultaneously and in sequence. Scientific evidence for heightened toxicity from such mixtures is mounting, yet regulation is lagging behind. Ensuring appropriate regulation of chemical mixture risks will require stronger legal stimuli as well as close integration of different parts of the regulatory systems in order to meet the data and testing requirements for mixture risk assessment.

Until about a decade ago, toxicologists, risk [illegible] rs regarded risks from chemical mixtures as negligible, as long as exposures to all single [illegible] il were below the levels judged to be safe for each chemical alone (1, 2). However, an inc [illegible] c evidence has challenged this notion, showing that a neglect of mixture effects can cause [illegible] erestimated (see the figure). International bodies such as the World Health Organization [illegible] ed for considering mixtures in chemical risk assessment and regulation (3). This would ali [illegible] essment with the clinical sciences and their long tradition of investigating drug-drug in [illegible] exceptions, regulatory systems around the world still focus overwhelmingly on single-chemical assessments, and the translation of scientific evidence about mixture effects into better regulation is extremely slow.

The Scientific Basis

The most widely used concept to determine the common toxic effect of combinations of chemicals is dose addition (DA) (3, 4). DA assumes that one chemical can be replaced by an equal fraction of an equally effective dose of another without diminishing the overall combined effect. This may, for example, be the case for combinations of chemicals that exert their toxicity through similar mechanisms, such as by binding to the same receptor.

In one of the earliest predictive mixture studies, DA provided good approximations of the joint effects of mixtures of 50 aquatic toxicants in fish (5). This seminal paper created the conceptual basis for numerous laboratory studies with microbes, mammalian cells, rodents, and isolated human tissues. In these studies, DA proved to be an excellent tool for anticipating experimentally observed combination effects of up to 80 chemicals, including pesticides, industrial chemicals, food contaminants, cosmetics ingredients, and pharmaceuticals (6, 7).

The principles of DA imply that every mixture component contributes to the combination effect in proportion to its dose and individual potency, even when each component is present at levels below its individual effect threshold. This idea has been tested in several experimental studies. The results show that mixture effects occurred when each chemical was present at or below experimental NOAELs (no observed adverse effect levels) for single substances (8). NOAELs are used to derive regulatory limit values through division by an assessment factor, typically 100. Examples are Environmental Quality Standards (EQS) set under the European Water Framework Directive.

The suitability of such EQS for protecting against mixture effects has been tested. Combinations of 14 or 19 pollutants at EQS levels produced substantial toxic effects in microalgae, daphnids, and fish and frog embryos (9), at concentrations 100-fold or more below their individual NOAELs. A mixture of 15 chemicals at the concentrations found in human amniotic fluid altered thyroid hormone signaling and early brain development in *Xenopus* tadpoles (10).

Clearly, single-chemical risk assessments cannot capture such phenomena. Mixture risk assessment is needed for better protection of humans and the environment. Scientifically justifiable tools are available and ready for use in risk-assessment practice.

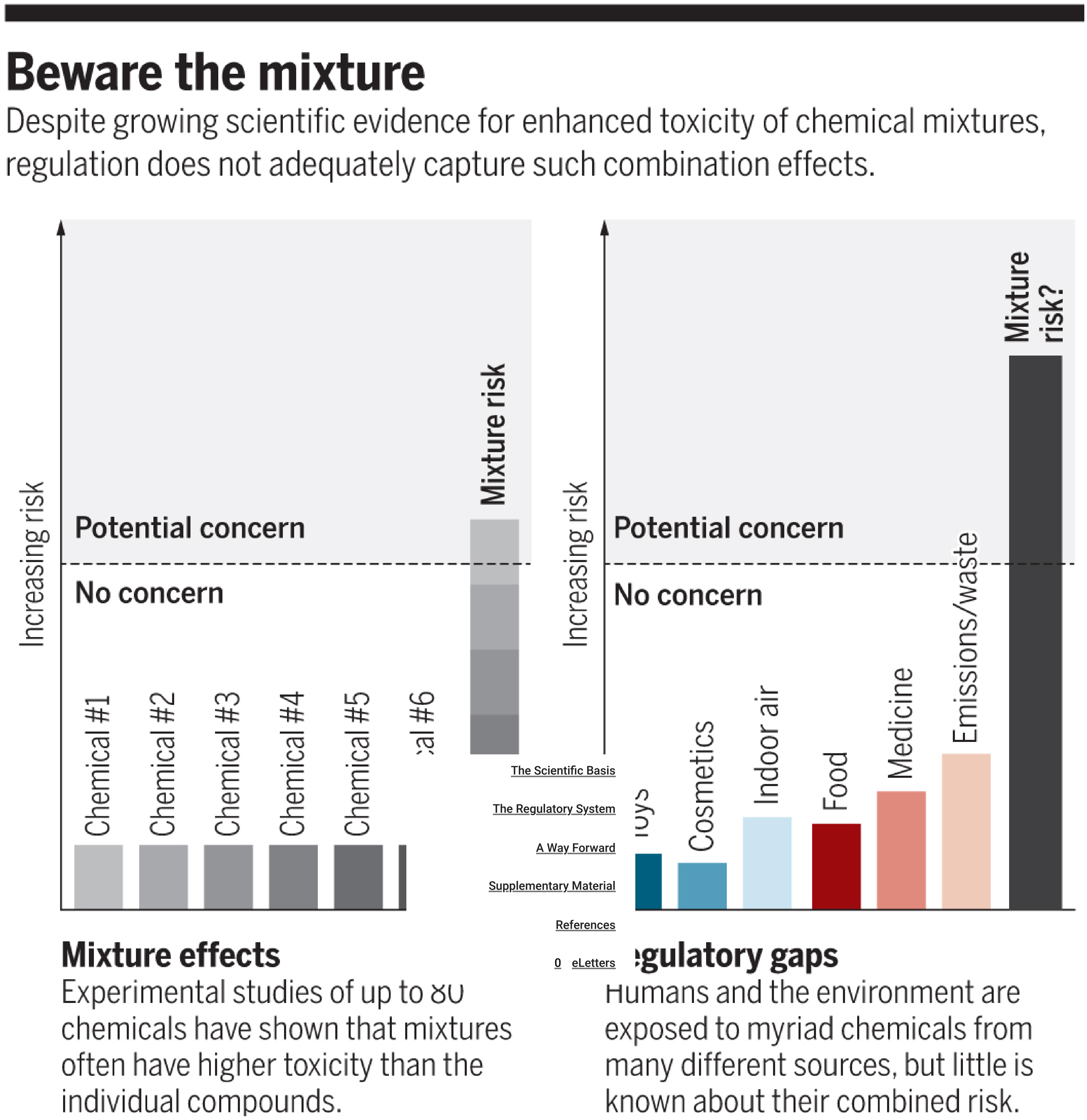
The Regulatory System

In view of the early mixture studies in fish (5), the European Inland Fisheries and Aquaculture Advisory Commission concluded in 1987 that the setting of water-quality criteria for chemicals should focus on mixtures with similar modes of action, rather than on single chemicals. However, Europe-wide water-quality legislation was not enacted at the time, and these insights could therefore not be implemented. Partial implementation was achieved in 2001 with the Water Framework Directive, which includes quality standards for specific groups of chemicals, such as mixtures of different dioxins. However, to this day the possibility of mixture effects between groups of chemicals or with other chemicals is not considered. In response to long-standing concerns about multiple pesticide residues in food, the European regulation on maximum residue levels enacted in 2005 requires the consideration of "cumulative and synergistic effects, when the methods to assess such effects are available" (11). Since then, the European Food Safety Authority has been working to address this obligation.

Compared with Europe, the United States has a longer tradition of dealing with chemical mixtures, although mixture regulation in the United States is confi [illegible] ects, not wildlife. Major stimuli have come from legal provisions for cleaning up sites conta [illegible] waste chemicals and the mandate for assessing risks from multiple pesticides with similar [illegible] ood Quality Protection Act. Mixtures of other chemicals are currently not regulated. Apa [illegible] in combinations, the Japanese regulatory framework does not address mixture risks, [illegible] ed countries (8).

Except for the above specific requirements [illegible], regulatory systems, including in the EU and United States, still overwhelmingly focus on single chemicals and ignore possible mixture effects from combined exposure. This limitation is systemic because regulatory frameworks have evolved into numerous silos that define differing rules and data requirements for different uses of chemicals—such as for plant protection products, biocidal products, pharmaceuticals, cosmetics, food and feed additives, household chemicals, or industrial chemicals—and for the protection of environmental compartments, such as indoor and outdoor air; marine, fresh, and groundwater; soils; and sediments.

Integration across the boundaries of these silos is difficult, and currently there are no strong initiatives to achieve such integrations. As a result, no regulatory system can currently safeguard against risks from exposure to coincidental multicomponent mixtures of substances from multiple sources via multiple exposure routes. Even relatively straightforward ideas, such as jointly considering mixture risks from pesticide residues and food contaminants, are not implemented.



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Beware the mixture Despite growing scientific evidence for enhanced toxicity of chemical mixtures, regulation does not adequately capture such combination effects.GRAPHIC: A. KITTERMAN/*SCIENCE*

A Way Forward

To improve the capabilities of chemical regulatory systems in dealing adequately with mixture risks, several interdependent strands of policy initiatives are needed.

Necessity of legal mandates

Without explicit legal mandates for considering mixture effects, nothing will move forward. A first step toward this goal will be to enshrine the obligation for mixture risk assessment into all relevant sectorial regulations, such as those for air, soil, water, and food. The next big challenge will be to enact mandates that require the authorities to consider chemicals from multiple regulatory domains, and not just, for example, pesticides. This step would bring regulatory practice in line with the realities of a multichemical world, in which all kinds of chemicals arrive together in our bodies and the environment, transcending the artificial boundaries of established regulatory silos.

Enabling mixture risk assessment

Even if the appropriate legal requirements are enacted, the task of translating scientific knowledge of mixture toxicology into appropriate regulatory approaches is complex. The data for single chemicals needed to conduct mixture risk assessments are often unavailable. This lack of data applies to both exposures and toxicity and is even the case for pesticides, arguably one of the most rigorously tested group of chemicals. A recent stepwise mixture risk assessment of pesticides stalled for lack of suitable single-chemical data needed to refine the analysis in terms of specific toxicities. The exercise ended in a risk assessors' no-man's-land in which no assurance of an absence of risks could be given, but neither could possible risks be further substantiated (12).

Thus, any legal mandate for conducting mixture risk assessments must be complemented by harmonized single-chemical testing requirements across all regulatory silos in order to ensure the availability of comparable toxicity data for all components of coincidental mixtures. Currently, each regulatory silo has its own data requirements, but these must be aligned better to facilitate the integration needed for mixture risk assessment.

Implementing intermediate measures

Until appropriate mixture risk-assessment methods are worked out and implemented, a pragmatic, intermediate measure could be to lower all safety limits for single chemicals by a certain factor. The application of such an additional mixture assessment factor (MAF) has been frequently suggested, most recently by Dutch authorities (13). In that publication, the authors chose a MAF of 10 on the basis of the observation that often only a limited number of chemicals contribute to a mixture effect, despite the fact that exposure is to many more chemicals. Most chemicals are present at levels that are too low to have a substantial impact on the overall combined effect. However, more information about typical coexposure scenarios is needed to substantiate the choice of a MAF.

Research for better regulation

To achieve a better understanding of typica … humans and wildlife, extensive research is ur-
gently required, including both modeling a … approaches (14). Another long-standing con-
cern is how to anticipate synergisms and ar … micals; synergistic effects exceed and antago-
nistic effects fall short of the calculated ad … ng of when these effects arise is limited (4), and
research is needed to support the predictio … ssessment practice. Scientists must also ad-
vance concepts for dealing with sequential … te concepts of mixture toxicology into epidemi-
ology, which has tended to focus on single-

Fortunately, there is growing awareness of the importance and the urgency of the matter, expressed in a recent policy brief released by the European Commission's Joint Research Centre (15). This provides hope that we may see substantial progress toward tackling the issue through research and policy initiatives.

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Supplementary Material

File (aat9219-kortenkamp-sm.pdf)

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