Challenges in risk assessment of chemical mixtures

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Introduction

Chemical mixtures have significant public health relevance. In general, people are exposed to mixtures of chemicals rather than single chemical compounds. Such exposures occur through various environmental media and through multiple routes of exposure. To evaluate the joint toxicity of such complete exposures, it is essential to develop strategies that allow integration of experimental and computational methods for scientifically credible assessments of chemical mixtures.

Methods

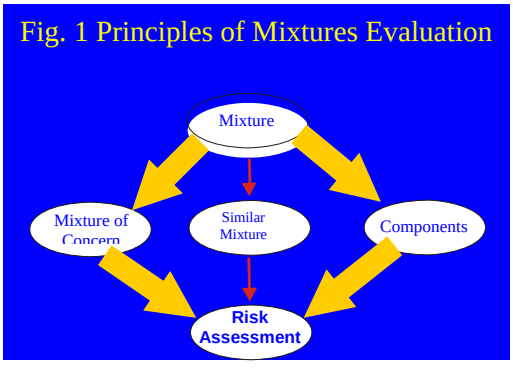
As illustrated in Figure 1, mixtures can be evaluated as a whole entity if data on the particular mixture are available. This is not often the case, but when the data are present, they can be used on a similar mixture. A similar mixture is one that has the same chemicals as the mixture of concern, but in slightly different proportions, or one that has most of the same components in highly similar proportions. If no data are available, approaches to evaluate the toxicity of the components of the mixture are commonly used.

Approaches used to evaluate the toxicity of a mixture based on the toxicity of the components include hazard index (HI) and computation methods such as physiologically-based pharmacokinetic/pharmaco-dynamic (PBPK/PD) and quantitative structure activity relationships (QSAR) modeling (1).

The hazard index approach assumes additivity to assess the health effects of a chemical mixture from the available data on the mixture's components.
HI can be refined by applying:

- weight-of-evidence (WOE) modification to the HI method,
- target-organ toxicity dose (TTD) modification to the HI method,
- toxicity equivalency (TEQ^1) and relative potency, total cancer risk.

For some halogenated aromatic hydrocarbons, ATSDR's guidance values (or minimal risk levels [MRLs]) were derived. MRLs for chlorinated dibenzo-*p*-dioxins (CDDs), polychlorinated biphenyls (PCBs) and polybrominated diphenyl ethers (PBDEs) were based on robust databases summarized in the toxicological profiles for these chemicals (2, 3, 4). The methodology for derivation of ATSDR's guidance values and the use of uncertainty factors in the process has been described in detail in several publications (5, 6).



Results and Discussion

Health guidance values for mixtures containing halogenated aromatic hydrocarbons

ATSDR used three approaches to derivate the health guidance values.

- Selected the most toxic chemical from the mixture and provided the health guidance based on the MRL for this chemical. Then used TEQs to estimate toxicity of the whole mixture.
- Treated the mixture as one entity and developed the health guidance for the whole mixture.
- Treated each chemical from the mixture separately and developed several health guidance values

Risk assessments of CDDs use TEQs[1] to estimate toxicity of the whole mixture. MRLs for acute-, intermediate-, and chronic-duration oral exposures to 2,3,7,8-tetrachloro-dibenzo-*p*-dioxin (TCDD) were based on results from animal studies. TCDD, as the most studied congener, was considered a representative for the whole group and the MRLs derived for this chemical are valid also for total TEQs. In contrast, the chronic MRL for PCBs was based on Aroclor 1254 (a mixture of PCBs with 54% chlorine) exposure. This was given by the study design that exposed animals to a commercial mixture. PBDEs were divided into two groups: lower brominated PBDEs and deca-BDEs: This decision was based on the facts that decaBDE is very poorly absorbed and rapidly eliminated and it is significantly less toxic than lower brominated PBDEs mixtures. Hence, separate MRLs were derived.

Health assessments for mixtures containing halogenated aromatic hydrocarbons and other persistent chemicals

ATSDR completed several assessments for simple mixtures. The following mixtures included halogenated aromatic hydrocarbons:

- CDDs, hexachlorobenzene, dichlorodiphenyl dichloroethane (*p,p'*-DDE), methyl mercury, and PCBs
- cesium, cobalt, PCBs, strontium, and trichloroethylene
- CDDs, PBDEs, and phthalates

The mixtures are important to ATSDR for various reasons. The first mixture is a mixture of persistent chemicals found in fish from contaminated waters of Great Lakes and in human breast milk. The second mixture is often found at the Department of Energy (DOE) hazardous waste sites. The third mixture was chosen based on the chemicals' potential for joint toxic action as endocrine disruptors. Detectable levels of the chemicals are present as the body burden of US human populations (7).

For all three mixtures, assessments were founded on a component-based HI approach qualitatively adjusted by results obtained from the WOE evaluations of binary interactions. Using WOE approach, interaction determinations were based on evaluations of available information on the chemicals regarding metabolism, health effects and other pertinent data available in the literature. First, the direction of interaction is predicted (greater than additive, less than additive, or additive), and then a classification is assigned on the basis of the mechanistic understanding of the interaction and its toxicological significance. Following the WOE determinations, HI were calculated and qualitatively adjusted. For example, if the component-based analyses indicate that several binary combinations will have more than additive joint toxic action, the HI may underestimate the final toxicity of the mixture. Vice versa, if the component-based analyses indicate that several binary combinations will have less than additive joint toxic action, the HI may overestimate the actual hazard presented by the exposure scenario.

Detailed evaluations of the three mixtures were provided elsewhere (8, 9, 10).

[1] TEQ (toxicity equivalent) is defined as the product of the concentration, Ci, of an individual "dioxin-like compound" in a complex environmental mixture and the corresponding TCDD toxicity equivalency factor (TEFi) for that compound. TEFs are based on congener-specific data and compare the relative toxicity of individual dioxin-like compounds to that of TCDD.

Computational methodologies as future directions for mixtures' evaluation

Hazard identification and health risk assessment traditionally rely on results of experimental testing in laboratory animals. It is a long and expensive process, which at the end still involves substantial uncertainty because the sensitivity of animals is unequal to humans. Laboratory testing is also very expensive. Computational methods such as QSAR and PBPK modeling can be applied in the risk assessment of chemical mixtures. QSAR can be used for predictions of toxicity of chemicals for which human/animal data are missing. PBPK modeling can be used to predict interactions for the whole mixture consisting of several components or for binary subcomponents of the original mixture of concern. However, the use of these methods is limited by the availability of suitable PBPK models. A good PBPK model predicts not only the direction of interactions, but also the level at witch the interaction may occur. The latter information is not available if the traditional approaches to mixtures assessment described above are employed. The information may be invaluable to risk assessors in the field who make decisions regarding possible imminent public health threats. ATSDR used the computational techniques for mixtures evaluations in some of the interaction profiles, but not frequently (11). A good example is the evaluation of a mixture of benzene, ethylbenzene, toluene, and xylenes (BTEX) (9). The development of PBPK model for the CDDs, PBDEs, and phthalates mixture is the latest priority of the program.

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