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Chemical mixtures: Evaluation of risk for child-specific exposures in a multi-stressor environment ☆

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Abstract

Evaluating the health impact from exposure to chemical mixtures is multifaceted. One component is exposure. Exposure, and consequently risk assessment for mixtures and chemicals in general, are often viewed in terms of a given exposure to a given population at a given location over a given time period. However, environmental exposures are present throughout human lifetime. As a result, an evaluation of risk must include the distinctive characteristics related to chemical exposures which will impact risk depending upon the particular life stage where exposure occurs. Risks to offspring may be associated with unique exposures *in utero*, during infancy, childhood, or adolescent periods. For example, exposure of infants to anthropogenic chemicals via breast milk may be of concern. The Agency for Toxic Substances and Disease Registry's (ATSDR's) approach to evaluating risks associated with exposure to mixtures of chemicals is presented. In addition to the breast milk issues, indoor exposure to combined air pollutants, drinking water contaminants, and soil and dust contaminants are discussed. The difference between a mixture's risk evaluation for children and adults is in the distinct exposure scenarios resulting from variations in behavior, physiology, and/or pharmacokinetics between adults and children rather than in the method for the specific mixtures evaluation per se.
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Introduction

Historically, research on human exposures to chemicals and associated health effects has been mostly conducted on single chemicals. However, environmental chemical exposures are primarily to mixtures of chemicals (DeRosa et al., 2001). The U.S. Agency for Toxic Substances and Disease Registry (ATSDR) developed a program for chemical mixtures of which an integral part is a mixtures health risk assessment. ATSDR has completed evaluations for several simple mixtures of concern that are available to the public in interaction profiles (see www.atsdr.cdc.gov/interactionprofiles/). The risk assessment methodology employed in interaction profiles is widely accepted and endorsed by other scientists. An overview of the methodology was published previously (Wilbur et al., 2004). Similarly, risk assessment evaluations for some of the mixtures are accessible in the open literature (Pohl et al., 2003, 2004; Roney and Colman, 2004).

Most environmental exposures are similar for a given population at a given location and time period; however, human exposures to chemicals also have some distinctive characteristics related to the life stages. Risks may be associated with unique exposures depending upon the period of life, (e.g. *in utero*, infancy, childhood, adolescence, adulthood). This may be especially true between the adult and developing stages. There are many differences between children and adults. The first obvious difference is in size; children consume more food and water per kilogram of body weight, they have higher inhalation rates, and they have larger surface area to volume ratios than adults (Pohl et al., 2005). Physiologically, the young have a greater potential for adverse effects of chemicals on the neurological system. For example, children have a larger brain weight to body weight ratio than adults (the largest difference occurring during the first 2 years of life); neonates through 6-years of age have greater blood flow to the central nervous system (CNS) and a higher blood–brain barrier (BBB) transport which allows greater CNS exposure. This is particularly true for water-soluble chemicals which are normally

☆ The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the Agency for Toxic Substances and Disease Registry.

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impeded by the BBB (Ginsberg et al., 2004). Immaturity of some systems also contributes to children's vulnerability to chemicals. Children may be more sensitive (or sometimes less sensitive) to harmful environmental chemicals because of differences in absorption, excretion, and metabolism. For example, immature liver enzyme function is present from birth to 1 year of age, but the biggest difference is during the first 2 months of life. The decreased enzyme function causes slower metabolic clearance of many drugs and environmental chemicals. Although this decreased enzyme function can also result in decreased metabolic activation to active metabolites, it can also result in a decreased removal of the activated metabolites (Bruckner, 2000; Clewell et al., 2002; Ginsberg et al., 2004).

Whether a risk assessment is based on traditional science methods (e.g., animal toxicology testing) or on some newer methods (e.g., computational toxicology), factors such as uncertainty and variability must be rationalized in some manner. Inherent in the application of scientific judgment is our understanding of the problem associated with not knowing the scientific truth and being required to conduct a risk assessment in light of uncertainty. The scientist must weigh the evidence for and against the potential health outcome of certain exposure scenarios. This paper presents examples of risk assessments that have been conducted by ATSDR on simple mixtures which are associated with various media of unique importance to the young.

Methodologies for the risk assessment of chemical mixtures

Mixture of concern/similar mixture evaluation. As illustrated in Fig. 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. Similar mixtures are expected to have similar fate, transport, and health effects as the mixture of concern. Interactions data on a sufficiently similar mixture are treated as if they were collected using the mixture of concern. The components of both mixtures should have the same fate, transport, and health effects.

If no data are available, approaches to evaluate the toxicity of the components of the mixture are commonly used.

Component evaluation. 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/pharmacodynamic (PBPK/PD) and quantitative structure activity relationships (QSAR) modeling (ATSDR, 2004a,b,c).

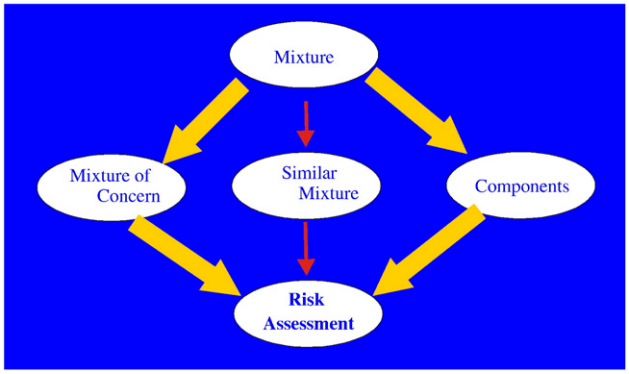

Fig. 1. Principles of mixtures evaluation.

Hazard index evaluation method. For most mixtures, component-based approaches such as the hazard index (HI) are recommended. The hazard index approach assumes dose additivity[1] to assess the health effects of a chemical mixture from the available data on the mixture's components. Exposures or doses for the various components of the mixture are scaled by a defined level of exposure generally regarded as "acceptable" or "safe" (i.e., health-based guidance value) by the agency performing the assessment. This approach is used or recommended by a number of agencies (ACGIH, 2000; EPA, 1986, 1989; National Academy of Sciences [NAS], 1974; National Research Council [NRC], 1989; OSHA, 1993, 2001).

The general equation for the hazard index (HI) calculation is:

$$\mathrm{HI} = \frac{\mathrm{ChemExposure}_1}{\mathrm{DR}_1} + \frac{\mathrm{ChemExposure}_2}{\mathrm{DR}_2} + \frac{\mathrm{ChemExposure}_3}{\mathrm{DR}_n}$$

$\mathrm{ChemExposure}_1$ is defined as the level of exposure to the first chemical in the mixture and DR_2 is some defined level of exposure to the first chemical (i.e., health-based guidance value).

$\mathrm{Exposure}_2$ and DR_2 are the corresponding levels for chemical 2, and the summation can extend to any number of chemicals, signified by the *n*.

When the hazard index for a mixture exceeds unity (1), a concern for the potential hazard of the mixture increases. Separate hazard indexes are estimated for each pathway and exposure duration of concern. For a given duration, hazard indexes are summed across pathways that affect the same receptor population. The obvious advantage of this method is its simplicity. Because it is based on the assumption of dose additivity, the hazard index method is most appropriately applied to components that cause the same effect by the same mechanism of action.

Examples of the health-based guidance values used in the HI calculations are:

- ATSDR minimal risk levels (MRLs),
- EPA reference doses (RfDs) or reference concentrations (RfCs),
- ACGIH threshold limit values (TLVs),
- OSHA permissible exposure limits (PELs).

More information on guidance values was provided by Pohl and Abadin (1995).

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,
- toxic equivalency (TEQ) and relative potency, total cancer risk.

Weight-of-Evidence (WOE) evaluation method. The WOE approach is used as a refinement of HI since additivity cannot be assumed for all the mixtures components. The WOE approach for assessing toxicological interactions in chemical mixtures was developed by Mumtaz and Durkin (1992) and further described by Mumtaz et al. (1994). In this approach, a mixture is broken down into binary pairs and a determination is made based upon the interaction potential of each pair of chemicals. This determination is called a Binary Weight-of-Evidence determination or BINWOE.

[1] "A default assumption commonly used in mixtures risk assessment is that the chemicals in the mixture act independently, such that one does not affect the toxicity of the other. This type of joint action is called *additivity*. If the chemicals in the mixture act independently by similar modes of action to produce similar effects, *dose addition* is expected wherein the mixture components behave as dilutions of one another differing only in their potencies. If, on the other hand, the chemicals in the mixture act by different modes of action (to produce effects that may or may not be similar), *response addition* is the predicted result (whether the response rates are actually added or not depends on how susceptibility to each component correlates with susceptibility to the other components)" (ATSDR, 2004b).