INTERACTION PROFILES FOR A MIXTURE OF PERSISTENT CHEMICALS

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Introduction

The Agency for Toxic Substances and Disease Registry (ATSDR) is building upon its applied research program to address mixtures of potentially hazardous substances by developing interaction profiles. The primary purpose of the interaction profiles is to evaluate mixtures that are of special interest to environmental public health, based on results reported in the scientific literature, on assessments based on the weight-of-evidence (WOE) methodology, and on other health assessment tools. The interaction profiles are peer and publically reviewed documents to ensure the accuracy of data presented and validity of conclusions. As such, they represent up-to-date views of the U.S. Public Health Service on health assessment issues for mixtures.

Chlorinated dibenzo-*p*-dioxins (CDDs), hexachlorobenzene, *p,p'*-DDE (the predominant metabolite of *p,p'*-DDT), methylmercury, and polychlorinated biphenyls (PCBs) occur with high frequency in water, sediment, and fish from the North American Great Lakes and occur, to varying degrees, in other dietary components including fish from other parts of the world (e.g., the Baltic Sea), human milk, dairy products, and meat. The purposes of the profiles are (a) to evaluate data (if available) on health hazards, and their dose-response relationships, from oral exposure to this five-component mixture, (b) to evaluate data on the joint toxic actions of components of this mixture, and (c) to make recommendations for exposure-based assessments of the potential impact of joint toxic action of the mixture on public health.

ATSDR prepared two documents on this particular mixture. One presented available information on consumption of contaminated fish and potential health effects (1), the other one dealt with developmental impacts of consumption of contaminated breast milk (2).

Methods

Interaction profiles provide environmental health scientists with ATSDR's evaluation concerning whether interactions occur among the chemical components in the mixture, the types of interactions that would be expected, and make recommendations regarding how to incorporate concerns regarding the expected interactions or additivity into the public health assessment of the contaminated site. Interaction profiles provide the results of experimental and theoretical studies available in current literature, an assessment of toxic interactions based mostly on the WOE methodology (3), and generalizable rules that might be used inferentially for other related exposure scenarios.

The WOE scheme consists of two biological categories: mechanistic understanding and toxicological significance. The scoring component for mechanistic data is divided into three

classifications: direct (I), indirect (inferred from the structure-activity relationships) (II), and inadequate or ambiguous (III). The scoring for toxicological significance has components for directly demonstrated (A) and unclear (C) toxicological interactions; the middle rating (B) is applied to either inferred toxicological significance or the demonstration of toxicologically significant interactions in related compounds. A detailed explanation of the WOE method and its use in calculating an adjusted hazard index can be found in the original paper (3).

Results and Discussion

The WOE analysis indicates that only a limited amount of evidence is available to support the possible existence of greater-than-additive or less-than-additive joint actions of a few pairs of the components: (a) hexachlorobenzene potentiation of 2,3,7,8-TCDD reduction of body and thymus weights (4); (b) PCB antagonism of TCDD immunotoxicity and TCDD developmental toxicity (5, 6); and (c) synergism between PCBs and methylmercury in disrupting regulation of brain levels of dopamine that may influence neurological function and development (7, 8). For the remaining pairs, additive joint action at shared targets of toxicity is either supported by data (for a few pairs) or is recommended as a public health protective assumption due to lack of adequate data to assess joint toxic action. In general, overlapping targets of toxicity for these five components provide strong support for the plausibility of joint toxic action, but there is a notable lack of studies to characterize the modes of joint toxic action.

Component-based approaches that assume additive joint toxic action are recommended for exposure-based assessments of possible noncancer or cancer health hazards from oral exposure to mixtures of CDDs, hexachlorobenzene, *p,p'*-DDE, methylmercury, and PCBs, because there are no direct data available to characterize health hazards (and dose-response relationships) from the five-component mixture.

A target-organ toxicity dose (TTDs) modification of the Hazard Index (HI) approach is recommended for conducting exposure-based assessments of noncancer health hazards. Alternatively stated, HIs are computed on an organ specific basis, assuming that target organ toxicities are biologically independent. TTDs for several toxicity targets have been derived for each of the components including TTDs for hepatic, endocrine, immunological, reproductive, developmental, and neurological effects. For assessment of cancer risks from joint toxic action of the mixture, a similar component-based approach is recommended that involves multiplication of intakes of the chemical components by EPA cancer slope factors and summation of the resultant risk estimates.

References

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