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A Novel Application of a Competitive Binding Model in Dioxin Risk Assessment

VENKATESWARA R. RAO AND ALAN UNGER

Quantitative Analysis Division, Science Applications International Corporation, 7600-A Leesburg Pike, Falls Church, Virginia 22043

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The EPA-recommended toxicity equivalence factor (TEF) approach to estimating the lifetime incremental cancer risks for dioxins does not address (a) differences in the severity of toxicity according to the composition of chemical mixture and (b) potentials for modification of tissue-level doses of congeners in mixtures and consequently the cancer risk estimates. Our earlier efforts to model the binding of congeners to the Ah receptor in the low-dose range and to develop quantitative estimates for the formation of fractions of Ah receptor–congener complexes resulted in the definition of a unique parameter, defined as competitive binding ratio (CBR), to adjust tissue-level doses for mixture exposure. We made an effort to incorporate CBR values in the dose–response analysis and risk characterization of congeners in two distinct exposure scenarios. The modified approach to estimating tissue-level doses of congeners in mixtures by the use of a competitive binding model indicated that (a) the Ah receptor affinity is an important criterion in the determination of tissue-level dose of congeners, (b) the TEF doses calculated by using the model algorithms modified the tissue-level doses for congeners in mixture exposures, and (c) the combined lifetime incremental cancer risks for all congeners were generally lower when model algorithms were used in the dose–response analysis. However, the percentage contribution of toxic congeners was significantly higher when model algorithms were used. The percentage contribution of higher congeners with low toxicity was considerably reduced when model algorithms were used. Our preliminary results indicate that the standard approaches tend to overestimate the combined total risks of higher congeners with low toxicity, but underestimate the risks of more toxic congeners. © 1995 Academic Press, Inc.

INTRODUCTION

The arylhydrocarbon (Ah) receptor-mediated molecular mechanism as the basis for most of the known toxic effects involving exposures to low levels of dioxins does not address the effects of higher congeners of dioxins on the severity of the health hazard of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) in chemical mixtures. Chemical analysis of environmental media and biotic receptors indicates that TCDD is a minor component representing 0.8%, whereas the higher isomers account for over 99.2% of the total dioxin mass (Czuczwa and Hites, 1985; Rappe *et al.*, 1986, 1987). Experimental data from *in vivo* and *in vitro* studies indicate that (a) several higher congeners with substitutions at 2,3,7- and 8-positions and polychlorinated biphenyls (PCBs) with both *para* and at least two substitutions at the *meta* positions effectively compete and bind to Ah receptors in the presence of TCDD (Haakee *et al.*, 1987; Biegel *et al.*, 1989a,b) and (b) higher congeners of dioxin and some PCBs produce biochemical and toxicological effects similar to those of TCDD, albeit at higher concentrations (Gierthy and Crane, 1985; Kannan *et al.*, 1987; Couture *et al.*, 1988; Pluess *et al.*, 1988).

The hazard of TCDD in a mixture of other congeners with similar mechanisms of action and different toxic potentials is not clear. The EPA-recommended approach uses toxicity equivalence factors (TEF) for the more abundant octa-, hexa-, hepta-, and pentaisomers (EPA, 1987). According to the TEF method, the combined dose of a mixture of congeners is calculated as the sum of the product of the concentration and their TEF values. Although the available biochemical and toxicological data for the congeners have been critically analyzed for deriving their TEF values, their application in the dose–response analysis does not account for (a) the simultaneous presence of congeners with similar biochemical mechanisms and differing toxic potentials on the tissue-level doses, (b) differences in the severity of toxicity according to the composition of chemical mixture, and (c) congeners modifying the tissue-level doses and consequently the cancer risk estimates depending upon the environmental source and composition of congeners in a mixture.

As a part of our continuing studies on chemical interactions in carcinogenesis, we are interested in characterizing the cellular-level doses of TCDD and other

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