Analysis of Dose Responses for TCDD Health Effects: Implications for Risk Assessment Modeling

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The data analysis of dose responses to establish models of TCDD action is being conducted by the following committee: M. Anderson and J. Mills (Chemical Industry Institute of Toxicology, NC); S. Bayard and P. White (USEPA, Washington, D.C.); K. Cooper, P. Georgopoulos, and L. McGrath (Environmental and Occupational Health Sciences Institute, Piscataway, NJ); E. Silbergeld (University of Maryland, Baltimore, MD); M. DeVito and L. Kedderis (USEPA, NC); and C. Portier (National Institute of Environmental Health Sciences, NC); M. A. Gallo and G. Lucier (Co-Chairs).

The effects of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) on biological systems have been extensively studied at all levels of complexity ranging from sites of action on the gene to whole animal toxicity. The concepts of TCDD action are relatively well understood. However, the discrete details regarding some specific endpoints have not been elucidated. Briefly, the concepts can be presented as response - independent and response - dependent.

The early event(s) which are apparently response - independent are the result of TCDD crossing the plasma membrane by mass action and binding with high avidity to the cytosolic form of the Aryl hydrocarbon (Ah) receptor protein. Beyond this point, the events may be cell and tissue specific. At least two other steps are involved in mediating some responses. One is the release of heart shock protein(s) with addition of nuclear transport protein(s) and subsequent binding to specific sequences on the DNA which are termed xenobiotic response elements (XREs). This pathway of binding is used for many of the models of TCDD action is exemplified by the mass of data that is available regarding TCDD induction of the Cytochrome P450 IA family of proteins. A second, less well studied series of reactions occurs subsequent to initial binding to the cytosolic Ah receptor. These reactions involve tyrosine phosphorylation and effects on membrane bound receptors such as EGF and TGF alpha. Interestingly, this activity may not require nuclear translocation and is associated with changes in immune function and numerous other responses such as cell proliferation.

The committee conducted an extensive review of the literature with the express purpose of identifying those papers whose authors reported dose-response data. In addition, the papers were critically reviewed for consistency with other papers reporting on similar TCDD effects. A special effort was made to identify reports of similar effects in multiple species, both sexes, and at varying ages. Unfortunately, there is a paucity of literature for comparing some critical events.

Hence, the committee selected the following endpoints for initially modelling human health risks: (1) induction of Cytochrome P450 IA1 (or enzyme markers such as AHH and EROD) and IA2 (2-hydroxylation of estradiol); (2) modification of the EGF and Estrogen Receptors; (3) cell proliferation, preneoplastic lesions and tumor incidence; (4) cancer in liver and thyroid; (5) cleft palate and other reproductive toxicity; and (6) immunotoxicity. The committee has also identified key gaps in the database. These gaps prevent understanding of the complete mechanisms of action of TCDD as a carcinogen.

Several simplifications were necessary to pool data for comparisons. For example, oral and intraperitoneal administration were considered equivalent for comparing endpoints measured after extended periods of time. Subchronic exposure of 8 - 13 weeks were also considered to be equivalent if the total administered dose was similar.

The overall results of this research lead to the conclusion that most if not all of the mammalian responses to TCDD are associated with binding to the cytosolic Ah receptor. Furthermore, the majority of the same responses segregate with the Ah Locus. Humans appear to respond to TCDD and its analogs in a manner that is qualitatively and quantitatively similar to experimental animals. However, considerable interindividual variation is evident in the human responses.

Among the most sensitive responses are those biochemical markers which are associated with binding to the Ah Locus: EROD induction, CYPIA1 mRNA induction, changes in concentration of the cytosolic and nuclear Ah receptor. These responses show no evidence of non-linearity. The mathematical relationships for several other endpoints including cancer, cleft palate, and immunotoxicity appear to fit similar functions.

The data suggest several different dose-response relationships for dioxin's effects although all the responses appear to be Ah receptor dependent. This strongly suggests that cell and tissue factors are responsible for the diverse responses known to require activation of the Ah receptor. This type of tissue variability is congruent with the similarity of action of the Ah receptor and the steroid/thyroid hormone family of receptors.

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