Uncertainty analysis of dioxin toxicity - its implication to human risk assessment

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Aim: Complex toxicity profile and wide margin of variation in toxicity among inter- and intra-species are one of the conspicuous features of dioxins toxicity. Available evidences suggest that aryl hydrocarbon (Ah) receptor mediated effects to homeostasis and cellular regulation are involved in divergent toxicities. Most intriguing concern is how toxic dioxins are to humans, and what is the level of variations of toxicity among humans, and if a potential exposure level will pose any significant risk to humans. We examined the source of uncertainties in estimating human risk from dioxins, and propose to present it in an explicit way in risk assessment.

Analysis: Fat content in the body was suggested as a major determinant in distribution and elimination of dioxins. Humans have relatively high fat-content compared to experimental animals and show extremely longer half-life for dioxin elimination of 5.8 years (Poiger & Schlatter, 1986), compared to that of 10-30 days in rodents. Human half-life of elimination is predicted to increase almost linearly from about 4 months in newborn to 5-6 years at the age when the ratio of body fat reaches plateau (Kreuzer et al., 1997). Humans have similar Ah receptor as other animal species, however its binding affinity to TCDD is somewhat lower (dissociation-constant range: 3-15 nM), and show saturation and CYP1A1-induction at one-order higher concentration than rodents with sigmoidal response curves (Okey et al., 1994). Expression of Ah receptor and induction of CYP1A1-dependent enzyme varied widely among individuals (Clark et al., 1992), which may reflect polymorphism in CYP1A1 gene (Kawajiri et al, 1990). Ethnic variation in CYP1A1 polymorphism is also known (Puga et al., 1997). These factors will contribute to variation in toxicity and risk estimation based on dioxin body-burden in humans. The variation in human sensitivity to the chloracnegnic effects ranges two-order of magnitude in body burden (Beck et al., 1979). Body burdens of dioxins appear to be log-normally distributed in humans (Sielken et al., 1977), and there are subgroups, such as fish-eaters who are likely to have much greater body-burdens. Recently, disturbance of signal transduction via tyrosine phosphorylation by TCDD was suggested as another mechanism than gene-transcription level (Enan & Matsumura, 1995).

Proposal: From current knowledge of wide range of variations in toxicity with huge unsolved uncertainty in significance of low-dose exposure of fetus and infant, we propose to select different critical endpoints with different critical-effect doses which may be relevant to each subpopulation. Presentation of pertinent guidance values showing the range of uncertainty in protecting different human subpopulations, such as fetus, infant, pregnant woman and adult, will be desirable.

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References:

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