MECHANISTIC MODELS FOR THE TUMORIGENIC EFFCTS OF TCDD IN ANIMALS AND HUMANS.

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There is a growing controversy regarding "safe" exposure levels for the toxic effects of 2,3,7,8 tetrachlorodibenzo-p-dioxin (TCDD). At the heart of this controversy is the recognition that the toxic effects of TCDD are receptor-mediated. The initial step is considered to be binding to the aryl-hydrocarbon (Ah) receptor which triggers a cascade of events leading to alterations in gene expression.

Several hypothetical models have been proposed for the distribution and toxicity of TCDD. This presentation will adress several issues of importance in the mathematical modelling of carcinogenic risks from exposure to TCDD. Discussed will be the impact of different assumptions concerning cooperativity and endogenous ligands on gene expression for CYP1A1, CYP1A2 and the EGF receptor. A complete pharmacodynamic model for the biochemical effects of TCDD in the liver has been developed[1]. This, combined with a complete physiologically-based pharmacokinetic model[1] is useful in the risk assessment of the effects of TCDD in both rodents and humans. Parameters which define these models have been estimated for both rodents and humans and these will be presented. Predictions and implications of these models will be discussed in detail. Future extensions to include effects in the thyroid will be outlined.

Potential dose surrogates for modifications in cell replication, DNA damage and tumorigenicity will be explored and their implications for low dose risks will be examined[2,3]. Dose surrogates to be discussed will include CYP1A1, CYP1A2 and the EGF receptor. Also included will be a discussion of tertiary effects of TCDD which may have some bearing on low dose risk estimates. Species-to-species differences will be highlighted and the implications of assumptions concerning the rate of exposure and species longevity will be discussed.

Finally, estimates of risk derived from the complete mechanistic model for the carcinogenic effects of TCDD will be presented and discussed. The results support low-dose linear risk estimates for the effects of TCDD as well as low-dose nonlinear effects[3]. The risk estimates from these two types of models differ widely and, in most cases, agree with the carcinogenic findings in humans.

1. Kohn, M., Lucier, G. and Portier, C. A mechanistic model of effects of dioxin on gene expression in the rat liver. (submitted) 1992.

2. Portier, C. J., Tritschler, A., Kohn, M., Sewell, C., Clark, G., Edler, L., Hoel, D. and Lucier, G. Ligand-Receptor Binding for 2,3,7,8-TCDD: Implications for Risk Assessment, *Fundamental and Applied Toxicology* (in press) 1992.

3. Portier, C., Kohn, M., Hoel, D. and Lucier, G. Risks from exposure to 2,3,7,8-TCDD: The effect of using enzyme induction as a dose surrogate. (in preparation) 1992.