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Dear Dr. Armitage

I would like to provide the following comments to the Science Advisory Board Dioxin Review Panel:

It has come to my attention that the PBPK/PD model used by EPA in their proposed risk assessment for dioxin uses a Hill constant of n = 0.6 for cyp1a2 induction, taken from the PBPK/PD models of Wang et al. (1997) and Santostefano et al. (1998). This parameter is important in that it determines dose-dependent liver uptake due to binding of TCDD by cyp1a2 and it also governs the low-dose risk extrapolations in US EPA default approaches that assume low-dose linearity.

During the 1980's, I was a key contributor to development of PBPK/PD models for TCDD (Leung et al., 1990) and published refined model structures for TCDD (Andersen et al., 1993; 1997) and TBDD (Kedderis et al., 1993). The late Michael Kohn and colleagues at NIEHS also developed PBPK/PD models for TCDD in the early 1990's (Kohn et al., 1993). All these other efforts by competent modeling teams, treating the liver as a homogenous compartment, successfully described data sets on liver concentration and level of CYP1A2 induction in liver with an n-value for cyp1A2 induction of 1.0. It seems only natural to ask why the Wang et al. model required a lower value for this parameter before using their n = 0.6 value to support the default linear risk assessment.

Working with the 2000 dioxin risk assessment writing team, I was closely involved with evaluating PBPK/PD models for dioxin and remain knowledgeable about the Kohn et al. paper and those papers on which I was a co-author. However, in 2000 the team did not evaluate the Wang et al (1997) paper in any detail. Because of the discrepancy in n-vales, I have taken a look at the parameter tables from the various TCDD models to see if there are any striking differences that would provide some understanding of the different n-values between Wang et al. and all the other papers. Based on this evaluation, it appears to me that the difference arises because of questionable model parameter selection in the Wang et al. paper for one key parameter.

The largest difference in the Wang et al (1997) model versus other models for dioxin is the maximum induction of cyp1a2 in liver. Wang et al. (1997) use 600; the Kohn et al. (1993), Andersen et al. (1993)

and Kedderis et al. (1993) models used values between 10 and 20. These lower values are more consistent with the measured increases in CYP1A2 in various studies.

It is my opinion that the value of 0.6 for the Hill constant is required to keep the induced cyp1a2 low as dose increases to avoid getting near the unrealistic value of 600 fold for maximum induction of cyp1a2. The fits would likely be more consistent with an n = 1.0 if a more realistic value were used for the maximum induction. I don't know of any data consistent with a 600 fold increase for cyp1a2.
In summary, the Hill constant of n= 0.6 for cyp1a2 induction used in the Wang et al. PBPK/PD model is likely an artifact of the unrealistically high value for maximum induction and should not be used in the US EPA dioxin risk assessment without more careful consideration of the alternatives, i.e., n=1.0 and lower maximum induction. The latter values are more consistent with the experimental data themselves and with the broader experience in modeling the kinetics and enzyme induction by TCDD and related compounds.

It bears emphasis here that I did not receive any funding support in reviewing these models and preparing these comments.

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