Comment on "Relative Susceptibility of Animals and Humans to the Cancer Hazard Posed by 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin Using Internal Measures of Dose"

SIR: Aylward et al. (*1*) are to be commended for their attempt to use empirical data to address the question of whether the carcinogenicity of TCDD in humans is quantitatively similar to that observed in animals. However, we disagree with the authors' interpretation of their results. The empirical evidence presented by Aylward et al. (*1*) does not lend support to the use of area under the concentration-time curve (AUC) as a dose metric for cross-species extrapolation of toxicity and does not support the authors' conclusion that "humans are much less sensitive than rats to the carcinogenic effects of TCDD". A more appropriate conclusion to draw from their analysis would be that it lends empirical support to the use of lifetime average concentration as a dose metric for cross-species scaling of TCDD carcinogenicity.

Aylward et al. (*1*) considered three measures of dose: average TCDD concentration, peak TCDD concentration, and AUC. However, there are a number of limitations to their analysis. The authors emphasize comparisons of toxicity only at the highest dose levels, such as a peak serum lipid TCDD concentration of 7000 ppt or an average serum lipid TCDD concentration of 1600 ppt. One should note that the confidence intervals surrounding the rat and human risk estimates for these two dose metrics are overlapping at lower (and more environmentally relevant) concentrations, so it is not clear that the risk estimates are significantly different in the low dose range. In fact, Figure 5 in ref 1 suggests that, using the lifetime average concentration dose metric, rats experience lower excess risk than humans for serum TCDD concentrations less than 800 ppt. Since typical background levels of TCDD in the U.S. population are well below the "cross-over" point of Figure 5 in ref 1 [on the order of 2−9 ppt (*2*)], one could reasonably conclude that excess risk estimates based on the rat might actually *underestimate* the human response for exposures of environmental concern. Nevertheless, average serum concentration is clearly the dose metric (of the three considered) which comes closest to normalizing the response seen in rats to the response seen in humans, and in our opinion is therefore the most useful of the three for cross-species scaling.

Aylward et al. (*1*) place their greatest emphasis on the analysis shown in figure 4 in ref 1, which uses AUC as a dose metric for interspecies comparison of carcinogenicity. Inspection of the TCDD concentration-time profiles presented in Aylward et al.'s Figures 1 and 2 (*1*) suggests that AUC was used in the simplest manner, direct comparison of total lifetime AUC, with no adjustment for differences in lifespan. It is not surprising that the greatest difference between rats and humans was found in the analysis using AUC as a dose metric. With units of concentration times time, AUC is the most time sensitive of the three dose metrics that were considered.

There is some precedent for using AUC to extrapolate carcinogenic potency in animals to humans, for several alkylating agents (*3*). However, these materials are chemically reactive, do not act via a receptor, and are rapidly eliminated by chemical decomposition in both animals and humans. These characteristics are not shared by TCDD, which is chemically stable, operates via a well-characterized receptor, and is eliminated slowly and at markedly different rates in rodents and humans. Thus, it would seem unlikely that the precedent of the alkylating agents would apply to TCDD.

Historically, interspecies scaling for quantitative risk assessment has generally been based on either milligrams per kilogram day or milligrams per (kilogram)$^{2/3}$ day ("body weight" or "surface area" scaling, respectively), which are daily dose *rates*, rather than a lifetime cumulative dose.

There are several theoretical analyses (4−6) which suggest that, in general, the most appropriate measure of dose for interspecies scaling of carcinogenesis is milligrams per (kilogram)$^{3/4}$ day, a measure which is intermediate between the body weight and surface area dose metrics. Empirical data on the carcinogenic potencies of 23 chemicals in animals and humans also suggest that a dose metric similar to milligrams per kilogram day is appropriate for extrapolating from animals to humans (*7*). These data virtually rule out the possibility that a dose metric such as cumulative AUC will have general applicability for interspecies scaling of carcinogenicity. Since elimination rates in humans tend to be approximately 4-fold slower than elimination rates in rats (*4*) and humans live approximately 30 times longer than rats (76 vs 2.5 years), rat to human extrapolations based on cumulative AUC are expected to predict approximately 120 times greater risk for humans than extrapolations based on milligrams per kilogram day scaling, and 30 times more risk than milligrams per (kilogram)$^{3/4}$ day. This is not to suggest that allometric scaling relationships should be used in preference to target-tissue specific measures of dose, for TCDD. The point is that, for the general case, if either milligrams per kilogram day or milligrams per (kilogram)$^{3/4}$ day is even approximately correct as a cross-species dose metric, then cumulative AUC must be very far off the mark.

An additional problem with the analysis by Aylward et al. (*1*) is that it fails to take into account the less than lifetime followup of the epidemiologic cohort into account. Methods for making such an adjustment when contrasting toxicologic and epidemiologic data have recently been developed (*8*). Making this adjustment would increase the risk estimates derived from the epidemiologic study somewhat, but would be unlikely to have as large an influence as the decision on whether to use the AUC or the average concentration as the dosimetric for interspecies scaling.

AUC has been used as a chemical-specific dose metric in a number of physiologically based pharmacokinetic (PBPK) models, though not in the same manner in which AUC was used by Aylward et al. (*1*). Careful reading will reveal that the dose metric used for cross-species scaling of carcinogenicity with the PBPK models the authors cited was actually AUC/day, a dose metric more similar to lifetime average concentration than to Aylward et al.'s use of AUC. Gibaldi and Perrier, also cited by Aylward et al., do discuss the use of AUCs for bioequivalency determination, but in the context of an intraspecies comparison, rather than cross-species. Overall, it may be defensible to examine lifetime AUC as one possible dose metric for cross-species scaling, but one should not be surprised when this dose metric fails to normalize the responses seen in animals and humans. This is precisely the conclusion which should be drawn from Aylward et al.'s analysis, not that humans are much less sensitive than rats to the carcinogenic effects of TCDD, but that cumulative AUC is an inappropriate measure of dose for scaling the carcinogenicity of TCDD from rats to humans.

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