Use of a Margin of Exposure Approach to Characterize Potential Human Cancer Risk from Dioxin Exposure

Larisa Rudenko and Thomas B. Starr, ENVIRON Corporation, Arlington, VA 22203 and Raleigh NC 27615 USA

Introduction

As part of its ongoing reassessment of the potential human health risks from exposure to 2,3,7,8-tetrachlorodibenzo(*p*)dioxin (TCDD or dioxin), the US Environmental Protection Agency (USEPA or the Agency) recently issued a new draft dose-response assessment for dioxin (1). In this draft, the Agency has developed two sets of models to extrapolate from the high exposures encountered in either the human occupational cohorts or the even higher exposures in studies of experimental animals. For modeling the animal tumor data, an attempt was made to link tissue levels of 2,3,7,8-TCDD with tumor incidence data via a two-stage model of carcinogenesis. However, given that there are no direct links between the dose in the Kociba bioassay, measured biochemical markers of exposure (i.e., concentrations of CYP1A2 and activated EGF receptor) and birth or death rates in the two-stage model, both mechanistic data and curve fitting were employed to fit the data in the observable range (1-100 ng/kg/day) and provide an overall estimate of risk at various doses ranging from lower end of the observable response range to TCDD exposures below 1 ng/kg/day.

Exposure estimates for analyses of epidemiologic studies were derived from serum lipid or adipose tissue TCDD levels sampled at various times after exposure ended and were back-extrapolated using first-order elimination kinetics and a biological half-life of 7.1 years. These values were then converted to average daily doses (lADD) for the three cohorts exhibiting increased mortality from all cancers combined and respiratory cancer (i.e., Fingerhut et al. (1991), Zober et al. (1990), and Manz et al. (1991)). Maximum likelihood and 95% lower confidence bounds on incremental cancer risks for these cohorts were developed with additive and multiplicative risk models. Because of the low observed relative risks, ED_{01}, ED_{005}, and ED_{001} exposure levels were estimated.

We have considered the potential use of a Margin-of-Exposure approach as presented in Commission on Risk Assessment and Risk Management (CRARM) (2) report on Risk Assessment and Risk Management in Regulatory Decision Making and the Agency's draft *Proposed Guidelines for Carcinogen Risk Assessment* (3) as an alternative to the mechanism-based modeling and linear extrapolation approaches that USEPA has taken in its current draft chapter. Both the CRARM report and the proposed CRAG stress the need to use the best available science in developing risk assessments, and presentation of those assessments to risk managers in such a way that the best decisions can be made regarding risk reduction. The approaches provided in Chapter 8 provide some complex examples of how mechanistic data and pharmacokinetic adjustments may be incorporated into dose-response assessment. However, they do not take into account the nonlinearity of tumor responses observed in both the human and

animal studies. Nor do they address the empiricisms of receptor-theory, which clearly indicate that the relationship between receptor-binding and biological effect is not likely to be linear (4).

The relationship between exposure and outcome in the Kociba Sprague-Dawley rat bioassay (5) is nonlinear, with the tumor incidence at 1 ng/kg/day actually lower, but not significantly, than that in controls. The epidemiologic data also appear to be nonlinear. Finally, there is no evidence indicating gene mutation as a potential mode of action for dioxin. Given the sufficiency of the mechanistic and toxicologic data indicating nonlinearity, and the lack of mechanistic data indicating the appropriateness of linear extrapolation (e.g., genotoxicity), it would be quite reasonable to follow the default procedure suggested by USEPA's Proposed Cancer Risk Assessment Guidelines and apply the Margin of Exposure (MOE) approach in characterizing potential risk at low exposure levels. We have undertaken such an evaluation with the data sets used by USEPA in their dose-response evaluation.

Results and Discussion

We compared the effective doses at the 1, 5, and 10% levels based on the Kociba et al. (5) and NTP (7) bioassays of 2,3,7,8-TCDD administered via gavage (estimated in Chapter 8) (1) to the geometric mean of the estimated current daily intake (CDI) levels of 2,3,7,8-TCDD by the US population (0.24 pg/kg/day). This estimate is based on dietary intake of between 10 and 20 pg/day and human body weights between 50 and 70 kg [1]. The results of this analysis are summarized in the attached table.

At the ED_{10} level, the MOE for the combined female rat liver tumor data in the Kociba study ranges between approximately 4,200 and 6,300; at the ED_{05} level, the MOE is in excess of 2,700, and at the ED_{01} level, the margin is approximately 60.

The ED_{10} level has been suggested as the point of departure for most long-term rodent studies, as the 10% response rate is at or just below the detection limit of such experiments. A meaningful comparison, then, is between background daily intake and the point of departure or the estimated ED_{10} level (MOE ~5,000). Even if the standard inter-individual and inter-species uncertainty factors of 100-fold were applied to this level, as well as an additional (and possibly unnecessary) 10-fold uncertainty factor to account for sampling variability as suggested by Barnes et al. [7], human daily intake would still be approximately five times below the correspond effective dose (i.e., 0.24 vs.1.5 pg/kg/day).

A similar approach was employed to determine MOEs based on the epidemiologic studies evaluated in Chapter 8. Points of *comparison* (rather than points of *departure*) were selected at the ED_{01}, and ED_{005} levels (i.e., 0.5%, and 1% excess risk levels), as the ED_{10} and ED_{05} would likely have been well above the observable response range. The ratio of average equivalent oral daily dose (IADD) (back-calculated from TCDD measurements in exposed cohort subsets after exposures ceased) to current daily TCDD intake ranges from approximately 60 to 260.

MOEs estimated with multiplicative risk model ED_{01} levels from three occupational cohorts range from approximately 8 (lower bound on the ED_{01} for all cancers from Manz et al. [8] high exposure cohort) to 160 (maximum likelihood estimate for respiratory cancers in the >1 year exposure, > 20 year latency subcohort of the Fingerhut et al. [9] study). For ED_{01}s estimated with an additive risk model, MOEs range from 11 (the lower bound for all cancers in the Fingerhut study) to approximately 90 (maximum likelihood estimate from the respiratory cancer excess in Fingerhut). Given USEPA's policy of using maximum likelihood estimates when data are from human sources, the MOE ranges from 13-160 using the multiplicative model, and 16-89 using the

additive model.

Although it would have been instructive to use similarly the updated Manz et al. cohort data presented by Flesch-Janys et al. [10], but the dose metric employed in that study is based on of peak exposure rather than body burden or area-under-the-curve, so direct comparison of effective doses and daily intake is not possible. We have, however, made a comparison between lipid-adjusted concentrations at the end of exposure in most highly exposed subcohorts of the Flesch-Janys study and current background body burdens of 2,3,7,8-TCDD and total TEQs. For the one exposure decile subcohort that exhibited a significant increase in all cancer mortality (RR = 2.03), the margin of exposure for TCDD ranges over 50-550 times the background body burden.

The utility of these "margins of exposure" for the risk manager is highest when they are presented in the context of safety. For example, a given margin of exposure does not imply any margin of protection, although the larger the MOE, the more likely it is that the lower exposure will be safe. Conversely, a small MOE does not necessarily imply that risk is imminent; in theory, MOEs near 1 are safe for thresholded carcinogens, especially when, as is the case here, the point of comparison below the observable range, and was extrapolated using conservative assumptions. The question of how much protection imparted by an MOE has been partially addressed in the CRAG, CRARM, and in comments previously submitted to the CRARM by ENVIRON. In large part, as stated by USEPA, "to support a risk manager's consideration of the margin of exposure, information is provided about [observations]....as dose (exposure) decreases substantially below the observed data. The goal is to provide as much information as possible about the risk reduction that accompanies lowering of exposure" [3].

MOE estimates are sensitive to the shape of the dose-response curve used in the modeling exercise. Comparison of the ED_{01} and ED_{10} levels for thyroid adenomas in male Osborne Mendel rats from the NTP bioassay indicates that these values differ by approximately an order of magnitude (4 ng/kg/day vs. 42 ng/kg/day); the same tumor type in female rats modeled with a cubic term indicates a very different dose-response (ED_{01} (33 ng/kg/day) vs ED_{10} (72 ng/kg/day)), with corresponding differences in the MOEs (approximately 2-fold), although both sets of tumor data indicate a nonlinearity in dose-response.

Therefore, MOEs calculated for the laboratory animal and occupational cohort studies of dioxin must be considered in the context of qualitative dose-response information. Dioxin exerts its tumorigenic effects in laboratory animals in an apparently nonlinear manner. In addition, for the epidemiologic studies in which small excess cancer risks have been reported, the weak responses appear to occur only at the very highest exposure levels. Given the limited data available on dose-response, nonlinear dose response curves can fit the data at least as well as linear ones. Given the receptor-mediated mode action that appears to underlie dioxin's toxicity, the tumor response observed in animals, and the observations in humans, an overall nonlinear cancer dose-response can be expected, with response falling off more quickly than dose. MOEs calculated from the estimated ED_{01} levels and background daily intake are thus likely to provide a much wider margin of *protection* (or safety) than the simple margin of *exposure* would imply.

Left unquantitated in our analysis, as well as the Agency's, is the role that non-TCDD congeners play in contributing to toxicity, and possibly, increased cancer risk. Given that these compounds likely exert their biological effects by binding to the Ah receptor with various affinities, and are present in the environment, the diet, and individuals' body burdens at different stoichiometries, the relative contribution of classes of congeners to risk is yet unknown. For example, it is known that non-dioxin Ah receptor ligands are present in the diet in significant

excess to daily dioxin intake. Even with lower binding affinities, these agonists or partial agonists have the potential to significantly alter predicted biological responses (i.e., efficacy) resulting from low level exposures to dioxin. Thus, effective MOE communications should include explicit discussions of the magnitude of the margin for daily dioxin intake, and common dietary intake of other known AhR agonists (e.g., indole carbinoles in cruciferous vegetables) as part of the overall risk characterization.

Literature Cited

1. USEPA 1997. *Chapter 8: Dose-Response Modeling for 2,3,7,8-TCDD.* Workshop Review Draft. EOA/600/P-92/001C8. January 1997.

2. CRARM. 1996. *Risk Assessment and Risk Management in Regulatory Decision-Making.* Draft report for public review and comment issued by the Commission on Risk Assessment and Risk Management. June 13, 1996.

3. USEPA 1996. *Proposed guidelines for carcinogen risk assessment.* EPA/600/P-92/003C. April 1996.

4. Tallarida, R. 1997. Comments submitted to USEPA as a Workshop Draft Reviewer in response to the January 1997 draft Chapter 8.

5. Kociba, R.; Keyes, D. G.; Beyer, J. E.; Carreon, R. M.; Wade, C.E.; Dittenver, D. A.; Kalnins, R. P.; Frauson, L. E.; Park,C. N.; Barnard, S. D.; Hummel, R. A.; Humiston, C. G.. 1976. *Toxicology and Applied Pharmacology* **46**: 279-303.

6. National Toxicology Program. 1982. Carcinogenicity bioassay of 2,3,7,8-tetrachlodibenzo-*p*-dioxin in Osborne-Mendel rats and B6C3F1-mice (gavage study). *NTP Tech. Rep. Ser. no.* 209. Research Triangle Park, NC.

7. Barnes, D., Daston, G. P.; Evans, J. S.; Jarabek, A. M.; Kavlock, R. J.; Kimmel,C. A.; Park, C. A.; Spitzer, H. L. 1995. *Regul. Toxicol. Pharmacol.* **21**: 296-306.

8. Manz, A., Barger, J.; Dwyer, J. H. 1991. *Lancet* **338**: 959-964.

9. Fingerhut, M. A., Halpern,W. E; Marlow, D. A. 1991. *N. Engl. J. Med.* **324**: 212-217.

10. Flesch-Janys, D., Berger, J.; Gurn, P.; Manz, A.; Nagel, H.; Waltsgott, S.; Dwyer, J. 1995. *Am. J. of Epidemiology* **142**: 1165-1175

Summary of MOE Estimations at Significantly Elevated Tumor Sites

Study/Tumor Site	IADD/ CDI	*Point of Comparison/MOE*											
						Multiplicative Model				Additive Model			
		ED_{10}	MOE	ED_{01}	MOE	ED_{01} ML	MOE	ED_{01} LB	MOE	ED_{01} ML	MOE	ED_{01} LB	MOE
Kociba female rat liver tumor	416,000[1]	~1.25	**~5,000**			0.015 M	**60**	-	-				
NTP male rat thyroid adenoma	295,000[2]	42	**175,000**	4 L	16,000			-	-				
NTP female rat thyroid adenoma	295,000	72	**300,000**	33 C	137,000			-	-				
NTP male mouse liver tumors	295,000	14	**57,000**	1 L	4,000			-	-				
Fingerhut; respiratory	262					39	**160**	21	**87**	21	**89**	12	**48**
Fingerhut; all cancer	262					7	**30**	5	**20**	4	**16**	3	**11**
Zober; all cancer	63					2-6	**8-26**	-	-	-	-	-	-
Manz; all cancer	250					3	**13**	2	**8**	-	-	-	-

IADD= Average equivalent oral daily dose in pg/kg/day, see Table 2 and text; CDI = current daily intake 0.24 pg/kg/day as described in Table 2 and text. IADD/CDI is the MOE for daily intake at the ED_{01}.
Values may differ from Table 2 due to rounding.
ML = maximum likelihood estimate; LB = lower bound on dose

M = 2-stage mechanistic model; L = linear model; C = cubic model

1 100 ng/kg/day ÷ 0.24 pg/kg/day
2 71 ng/kg/day ÷ 0.24 pg/kg/day