MARGIN OF EXPOSURE ESTIMATES FOR TCDD FOR CANCER AND NON-CANCER EFFECTS IN LABORATORY ANIMALS

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Introduction

Margin of exposure (MOE)estimates provide a metric for evaluation of safe or tolerable levels of environmental contaminants. Such estimates provide information on the ratio of the human exposures of interest compared to exposures resulting in effects in experimental animals and humans. Historically, these points of departure for MOE analysis have been intake levels associated with either low or no effect levels (LOELs or NOELs). The MOE approach does not apply uncertainty or safety factors, nor provide any assumptions on the shape of the dose-response curves. In addition, the MOE approach is not a probabilistic estimate of risk. However, the MOE approach can be used to identify exposures which require further investigation into their potential health risks. The present exercise applies the MOE approach to exposures to TCDD and related chemicals resulting in body burden estimates which can be compared directly to body burden estimates in humans resulting from environmental exposures.

Methods

Background human exposure leads to adult body burdens currently estimated at 5 ng TEQ_{DFP}-WHO_{98}/kg body weight[1]. This estimate is based on human serum data from the mid 1990's in the United States in which the median value for serum TEQs from dioxins, dibenzofurans and PCBs was estimated at 20-25 ng TEQ_{DFP}-WHO_{98}/kg lipid. Percent body fat was estimated at 21%. The responses of concern were chosen based on the sensitivity of the responses in experimental animals. Due to the limited space of the abstract, this analysis examines a representative survey of the literature and is meant as an example of the MOE approach as it applies to dioxin and related chemicals. In order to make comparisons between the animal and human data, steady-state body burdens were estimated based on the exposure regimen and the species-specific half-life of TCDD. Half-life estimates for TCDD in rats, mice and rhesus monkeys were 25, 10 and 400 days, respectively. Absorption of TCDD in these studies was assumed to be 100%. The steady-state body burdens for the LOELs and NOELs from studies in which animals received multiple doses of TCDD are presented in Table 1. These are compared on a TEQ basis to background body burdens. A number of important studies examined the effects of TCDD following shortly after a single administration of TCDD. In these studies, body burdens were assumed equal to the administered dose and are presented along with MOEs based on body burden in Table 2.

Results and Discussion

The most sensitive responses are the induction of CYP1A enzymes and alterations in lymphocyte subpopulations in adult mice and marmosets which have LOELs and NOELs less than 1 ng TCDD/kg.. The MOEs for these sensitive responses range from less than 1 to approximately 25. The LOELs for neurobehavioral developmental effects and increases in the incidence of endometriosis in rhesus monkeys are between 41- 69 ng TCDD/kg and that the MOE for these

effects are between 8-14 based on the LOELs. It should be noted that NOELs for these response have not been determined and, therefore, the MOE can be considered less than 8. The NOELs for a multi-generational study and the carcinogenicity study in Sprague-Dawley rats is 18 ng TCDD/kg or less and the MOE is less than 4 for these effects. The MOE for cancer ranges from 4-1600 due to differences in the sensitivity of rats and mice. Rats are more sensitive to the carcinogenic effects of TCDD than are mice, when the dose is expressed as body burdens. The response to sheep red blood cells in mice has NOELs <100 ng TCDD/kg following a single acute exposure to TCDD resulting in MOEs of <20. Reproductive toxicities in adult rodents are relatively insensitive responses with NOELs above 600 ng TCDD/kg and MOE's over 100.

The effects of dioxins and related chemicals are mediated through their interactions with the Ah receptor[2]. This receptor has significant homology between humans and other mammals[3]. In addition a number of *in vitro* studies comparing cells or tissues derived from human and animals indicate that human derived tissues or cells respond similarly to animal tissues or cells at equivalent body burden concentrations[4]. These results indicate that because the MOEs are less than an order of magnitude, some of the subtle biochemical and toxicological effects of TCDD exposures to dioxins may be occurring in humans exposed at or near background concentrations.

This abstract does not reflect USEPA policy.

1. USEPA Exposure and Health Assessment for 2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD) and Related Compounds: PART 3 Integrated Summary and Risk Characterization for 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) and Related Compounds (External Review Draft). Washington DC:U.S. Environmental Protection Agency, 2000.
2. Birnbaum LS. (1994) Environ Health Perspect 102 Suppl 9:157-6.
3. Hahn. ME (1998). Comp Biochem Physiol C Pharmacol Toxicol Endocrinol 121(1-3):23-53
4. DeVito MJ, Birnbaum LS, Farland WH, Gasiewicz TA. (1995) Environ Health Perspect 103(9):820-31.

TABLE 1 COMPARISONS OF THE ESTIMATED LOEL AND NOELS FOR TCDD IN ANIMAL STUDIES USING MULTIPLE DOSE EXPOSURES.

RESPONSE/ SPECIES	STUDY	RANGE OF BODY BURDENS NG/KG		MARGIN OF EXPOSURE
		LOEL	NOEL	
CYP1A rats/mice	Tritscher et al (1992), Sewall et al (1993), Schrenck et al (1994) VanBirgelen (1995), Walker et al (1999) DeVito et al (1994), Vogel et al (1997)	0.15-357	<0.15-125	<1-25
Alterations in Lymphocyte Subpopulations in marmosets, rats and mice	Neubert et al. (1992) Rhile et al (1996); Vogel et al (1997)	0.34-10	0.034 - <10	<1-2
Endometriosis Rhesus Monkey	Rier et al. (1994)	69	<69	<14
Developmental Neurobehavioral effects in Rhesus Monkeys	Schantz et al (1979)	41	<41	< 8
Reproductive toxicity Rhesus monkeys	Schantz et al (1979)	205	41	8-40
Decreased Fucundity of offspring in rats	Murray et al (1976)	18	18	<4
Tumors (all types) Rats and Mice	Kociba et al (1978) NTP (1980)	180-7800	18-780	<4-1000

TABLE 2 COMPARISONS OF THE ESTMATED LOEL AND NOELS FOR TCDD IN ANIMAL STUDIES USING A SINGLE DOSE EXPOSURE.

RESPONSE/ SPECIES	STUDY	RANGE OF BODY BURDENS (NG/KG)		MARGIN OF EXPOSURE
		LOEL	NOEL	
CYP1A Rats and Mice	Kitchin & Woods (1979), Abraham et al (1988), Vanden Heuvel et al (1994), Narasimhan et al (1994), Diliberto et al (1995), VanBirgelen et al (1996)	2-300	0.6-<100	<1-60
PFC response to antigen challenge in mice	Smialowicz et al (1994), Harper et al (1994), Vecchi et al., (1983) Davis and Safe (1988)	100-1200	<100	<20
Ovulation (Ova/rat)	Li et al (1995)	10,000	3,000	600-2,000
Decreased Testosterone in Adult rats	Moore et al, (1985)	12,500	6,000	1,200-2,400
Testes abnormality in adult rats and mice	Moore et al., (1985) McConnell (1978)	12,500-100,000	6,000-50,000	1,200-20,000
Decreased sperm counts in rats (prenatal exposure)	Mably et al (1992) Gray et al (1997)	50-64	<50	<10-13