Human vs. Animal Sensitivity to the Immunological Effects of TCDD: A Preliminary Comparison

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Introduction

This paper presents a preliminary quantitative comparison of human vs. animal sensitivity to the immunological effects of TCDD as a function of TCDD levels in serum, adipose, and liver. Immunological effects were chosen for this analysis because of recent claims that immune dysfunction in humans may occur at doses far below those required to cause similar effects in animals. In addition, immunological effects are one of the few endpoints where individual body burden data and measures of health effects can be examined in the same human population. A range of lowest adverse effect levels from several studies are identified for immunological effects in animals. These are then compared to a range of no observed adverse effect levels observed in several studies of human populations. `Peak' tissue levels are estimated using a simple one-compartment model based on biologic half-life and the time since last exposure. In addition, total cumulated TCDD tissue concentrations throughout the exposure period were compared and area under the curve was calculated.

Methods

Estimating Peak TCDD Doses and Tissue Levels

Humans: In this analysis, we use a human biological half-life of 7.1 years[1] and a steady-state adipose tissue concentration of 6.9 pg TCDD/g adipose (6.9 ppt). This steady state concentration was derived by assuming 30 years of adult (70 kg) exposure to a "background" uptake rate of 27 pg/day[2]. By incorporating measured levels of tissue TCDD with estimates of time elapsed between exposure cessation and time of tissue TCDD measurement, the peak tissue TCDD concentration is estimated using the following first order equation:

$$Co = Ce^{-kt}$$

Where:

C = peak concentration of TCDD after a time period of elimination, based on:
C_o = the measured concentration
e = natural log
k = the rate constant based on the assumed half-life
t = time since exposure ceased

The area-under-the-curve (AUC) for total integrated concentration for a tissue (or whole body) is estimated by cumulating the TCDD concentration throughout the duration of exposure (T_1) and the time elapsed since cessation of exposure and the assay for adverse health effect (T_2).

Animals: Peak tissue levels and total integrated tissue concentrations in animals can be estimated from the dosing regimen used and estimates of elimination half-life and percent body fat. In this analysis, we use a simple one compartment model to estimate peak serum, liver and adipose levels for a variety of animal studies. For the purposes of this analysis, we assume that the % lipid content of these tissues is the same as that for humans.[3]

Comparing Effect Levels in Animals vs. Humans

Humans: Several epidemiological studies have attempted to measure alterations in the immune system in individuals with elevated TCDD body burdens.[4-12] Many of these studies have focused on general disturbances in the cell-mediated immune system, as measured by reductions in frequency of delayed-type hypersensitivity (DTH), T4/T8 ratios, lymphocyte proliferative responses, and total lymphocyte counts. Of the available data, the studies of Mocarelli et al.[11], Webb et al.[9], and Neubert et al.[12] can be matched with individual body burden data. For the purposes of this preliminary analysis, we examine the results of Mocarelli et al.[11] and Webb et al.[9]

Mocarelli et al.[11] examined serum TCDD levels and immune function in 19 adult Seveso, Italy residents who had been exposed during the 1976 accident. Over half (10/19) of these individuals had developed chloracne and lipid-adjusted serum TCDD levels, which were measured within 1-4 months of the accident, ranged from 828-56,000 ppt. These levels are orders of magnitude higher than background levels of TCDD in human serum, and the 56,000 ppt value is the highest human level ever reported. In 1990, 14 years after the exposure, Mocarelli et al.[11] measured total lymphocyte levels and T4/T8 ratios in these 19 individuals and a control group of 10 individuals whose serum TCDD levels were largely nondetectable (limit of detection of 13-130 ppt). This study showed no significant differences in the immune endpoints in the exposed vs. control groups. Since

these residents were evacuated from the area within months of the accident, it can be assumed that the measured TCDD serum levels represent 'peak' values for each individual. Further, since serum TCDD levels were measured several weeks after exposure, the lipid-adjusted serum levels are equivalent to lipid-adjusted levels in adipose and liver. The mean and range of peak serum, adipose, and liver TCDD levels and the integrated TCDD tissue concentrations for this group are summarized in Table 1.

Webb et al.[9] examined immune function in several Missouri residents in whom adipose TCDD levels had been determined by Patterson et al.[13]. Webb et al.[9] categorized forty "exposed" individuals into the following groups, as defined by adipose tissue level: < 20 ppt (16 subjects), 20-60 ppt (12 subjects), and > 60 ppt (12 subjects). Regression analysis showed no statistically significant correlation between adipose TCDD levels and T4/T8 ratios, total lymphocyte counts, or lymphocyte proliferation. Mean values for these parameters were all within normal ranges for each group. In addition, like Evans et al.[8], none of the individuals were found to be anergic, even those subjects with the highest TCDD body burdens.

For the purpose of this analysis, we evaluated the adipose tissue data from the > 60 ppt group, because their adipose levels are clearly elevated above background, an indication that significant TCDD exposure has occurred. Webb et al.[9] presented individual whole weight adipose TCDD levels for eight of the subjects in the > 60 ppt group; the levels ranged from 131-750 ppt, the mean value was 429 ppt. Adjusting these values to a lipid-based adipose level yields a mean value of 536 ppt and a range of 164-938 ppt.

For Webb et al.[9], we have estimated that the exposure duration (T_1) was approximately 3 years (1971-1973).[13] The time between peak tissue levels and immunoassay (T_2) is approximately 17 years (1973-1990). As shown in Table 1, the mean peak adipose TCDD level was 1,656 ppt (range = 491 - 2,910 ppt), the mean integrated adipose TCDD concentration was 6.8×10^4 (ng TCDD/kg-adipose • day) (range of 2.0×10^4 - 8.4×10^6).

Animals: TCDD induces thymic atrophy in almost all experimental animals, followed by a depressed function of cell-mediated immune response.[4] Table 2 summarizes the animal studies in which such changes have been measured following TCDD administration; these studies form the basis for comparison to human responses.

Summary and Conclusions

As noted in Table 1, peak tissue levels and integrated doses for blood, adipose, liver, and whole body are roughly similar for all three laboratory animal species. This suggests that, at least in the monkey, mouse, and guinea pig, the tissue TCDD levels required to initiate

immune dysfunction are comparable. Conversely, the human tissue TCDD levels associated with no immune effects can range up to several orders of magnitude higher than those observed in animals. As noted in Table 1, even the lowest peak body burdens and tissue levels associated with the humans in the Webb et al.[9] and Mocarelli et al.[11] studies are much greater than those required to elicit effects in animals. The same is true of integrated tissue concentrations.

These findings suggest that humans may be far less sensitive to TCDD immunological effects than laboratory animals. Nonetheless, the USEPA and others have implied that animals and humans are likely to be equally sensitive to all adverse noncancer effects (reproductive, immunological, developmental, etc.) and that, for some effects (*e.g.*, immunological), humans may be even more sensitive than animals. This seems inconsistent with the findings presented in the preliminary analysis since human subpopulations with extraordinary exposures to dioxin fail to demonstrate immunological effects at exposures much higher than those required to elicit effects in laboratory animals. In short, pending a thorough quantitative comparison of TCDD effect levels in humans vs. animals for a number of toxic endpoints, it is far too premature to suggest that humans are as sensitive or more sensitive than laboratory animals to many, or most, TCDD-induced health effects.

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Table 1. TCDD Doses and Tissue Levels Associated with Human No-Effect-Levels and Animal Low-Effect-Levels for Immunological Endpoints[1]

	Body Burden (ng TCDD/kg-b.w.)		Peak Tissue Level $\left(\frac{ng\ TCDD}{kg\ tissue}\right)$			Integrated Tissue Concentration $\left(\frac{ng\ TCDD}{kg\ tissue} \times day\right)$		
	Average	Peak	Blood	Adipose	Liver	Adipose	Liver	Body
Humans								
Webb et al.[9]	2.23 (0.66 - 273)	332 (98 - 589)	23.7 (4.0 - 53.5)	1,656 (491 - 2,910)	14.3 (4.2 - 25.1)	6.8×10^4 (2.0×10^4 - 8.4×10^6)	5.9×10^2 (1.8×10^2 - 7.2×10^4)	1.7×10^4 (5.0×10^3 - 2.1×10^6)
Mocarelli et al.[11]	19.4 (1.3 - 86)	2,020 (132 - 8,990)	81.9 (5.3 - 364)	10,080 (660 - 44,800)	86.9 (5.7 - 386)	4.0×10^5 (2.6×10^4 - 1.8×10^6)	3.4×10^3 (2.2×10^2 - 1.5×10^4)	9.9×10^4 (6.5×10^3 - 4.4×10^5)
Animals								
Marmoset[12]	5.9	9.6	0.40	49.7	0.43	3.3×10^3	29	834
Mouse[15]	3	9.3	0.62	76.8	0.66	1.3×10^3	11	332
Guinea Pig[18]	22.4	38.3	1.70	205	1.8	6.7×10^3	58	1,680

1 For human data, values presented are arithmetic means; ranges are given in parentheses.

Table 2. Studies Reporting Significant Alterations in Cell-Mediated Immune Endpoints in Animals Exposed to 2,3,7,8-Tetrachlorodibenzo-p-dioxin

Species	Exposure Duration	Route	LOEL[1] Dose	Response	Reference
Mouse	once a week for 4 weeks	intra- peritoneal	4 μg TCDD/kg b.w.	· decreased DTH	Clark et al.[16]
Guinea Pigs	once a week for 8 weeks	gavage	0.008 μg TCDD/kg b.w.	· decreased lymphocyte count	Vos et al.[18]
Marmosets	once a week for 30 weeks	subcutaneous	0.3 ng TCDD/kg b.w. for 24 weeks, followed by 1.5 ng TCDD/kg b.w. for 6 weeks	· decreased T4/T8 ratios	Neubert et al.[14]

1 Lowest observed effect level.