

IS DIOXIN A THRESHOLD CARCINOGEN? A QUANTITATIVE ANALYSIS OF THE EPIDEMIOLOGICAL DATA USING INTERNAL DOSE AND MONTE CARLO METHODS

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Introduction

The shape of the dose-response curve for TCDD carcinogenesis in humans continues to be a subject of debate. Historically, cancer risk assessment for TCDD has been based on the results of traditional rodent studies, under the assumption that tumor-response is linear in the low-dose region. However, a non-linear dose-response curve with a threshold for tumorigenesis is equally plausible and is suggested by the mechanistic and genotox data. In our previous work, we assembled serum sampling data collected for three of the best-studied human cohorts exposed to elevated levels of TCDD: the NIOSH cohort, the Ranch Hand cohort, and the Seveso population. We constructed lifetime serum lipid TCDD concentration-versus-time curves for each person on whom serum sampling was performed and used these curves to estimate mean area-under-the-curve, average concentration, and peak concentration values for the various subcohorts. The combined data set includes several thousand participants, and covers a broad range of exposures.

One of the primary limitations to using the human data in a quantitative assessment is the large degree of uncertainty and variability in the dose and response estimates. To minimize this shortcoming, we employed Monte Carlo techniques to address the variability in the dose estimates (peak, average, area under the curve [AUC]) and response estimates (Standard Mortality Ratio [SMRs] for lung cancer and total cancer) in humans. This analysis supports the conclusion that TCDD is a threshold carcinogen.

Methods and Materials

Population Selection. Data sets reporting both measured serum lipid TCDD levels and cancer mortality response for three exposed populations were included in this analysis (Table 1). Details on the cancer response and dose reconstruction for each of these populations were presented previously^{1,2,3}:

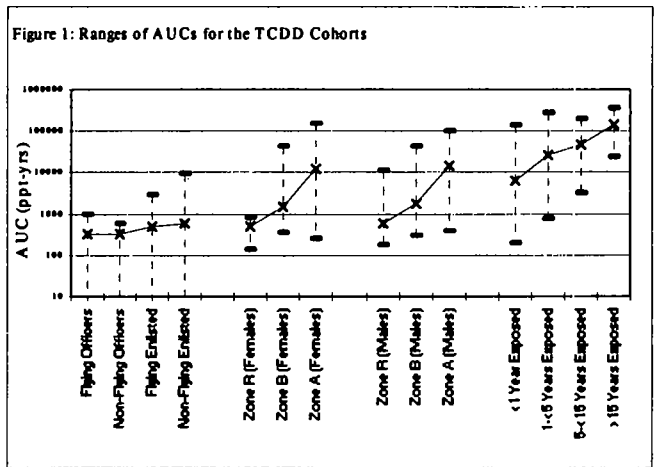
- *NIOSH Cohort* – The NIOSH cohort includes more than 5,000 workers from 12 plants that produced chemicals contaminated with TCDD⁴, including 1,520 workers with more than 20 years latency (as measured from time of first exposure).
- *Seveso Cohort* – Following a chemical accident in Seveso, Italy in 1976, a large residential population was subsequently exposed to TCDD. Sampling data and cancer response have been assembled for Zones A, B, and R (total populations of approximately 750, 5,000, and 30,000 inhabitants, respectively)⁵.

➤ **Ranch Hand Cohort** – Members of the United States Air Force who served in Vietnam in units spraying herbicides (Ranch Hands) were exposed to 2,3,7,8-tetrachlorodibenzo-p-dioxin and carry elevated body burdens of TCDD compared to the general population⁶. The most recent mortality analysis for the Ranch Hand cohort includes follow-up through December 31, 1993⁷. The mortality data in this study are reported for the Ranch Hands as a group, and for subgroups defined by rank (officer, enlisted) and military occupation (flyer, nonflyer).

Table 1. TCDD Dose Metrics and SMRs for Several Human Populations

Exposure Group	Dose Metric			SMR (95%)	
	AUC (ppt-yr)	Cavg (ppt)	Cpeak (ppt)	Total	Lung
<1 Year Exposed	6059	111	597	102 (75-133)	96 (56-147)
>1 Year Exposed	73636	1123	4264	146 (121-176)	139 (99-189)
1-5 Years Exposed	25536	413	2290	165 (119-198)	126 (73-192)
5-15 Years Exposed	47172	738	3213	138 (97-186)	146 (79-232)
>15 Years Exposed	148200	2218	7288	115 (68-175)	156 (71-272)
Ranch Hand					
Zone R (Females)	486	16	38	90 (80-100)	100 (70-160)
Zone B (Females)	1533	62	170	90 (70-120)	60 (10-230)
Zone A (Females)	12340	42	1484	120 (60-220)	..
Zone R (Males)	606	23	54	90 (80-100)	90 (80-110)
Zone B (Males)	1682	51	183	110 (90-130)	120 (90-170)
Zone A (Males)	14416	485	1733	40 (20-100)	100 (40-260)
Full Cohort					
Full Cohort	464	10.0	101	90 (58-125)	12 obs; 13.01 exp.
Flying Officers	331	6.4	28	87 (44-155)	NA
Non-Flying Officers	320	6.8	30	173 (9-850)	NA
Flying Enlisted	493	9.9	108	102 (47-194)	NA
Non-Flying Enlisted	561	13	158	83 (44-155)	NA

Dosimetrics. Concentration-versus-time profiles were calculated as described previously using a three-part curve (time before, during, and after occupational/accidental exposure)^{1,2,3}. Peak serum concentration was back-calculated using the measured serum lipid TCDD concentration, the date of serum measurement (which occurred after the last date of exposure), and an assumed 7.5-year half-life^{8,9}. Figure 1 presents the ranges and means of calculated AUC values for each subcohort.



Cancer Response. Specific elevated cancer responses varied among the exposed populations. The most complete data are available for the total cancers and lung cancer endpoints. Thus, these endpoints were chosen for further analysis in conjunction with the dosimetry data described above. A Poisson distribution was used for observed cancer deaths to recalculate simulated SMRs.

Monte Carlo Simulations. Monte Carlo simulations (5000 trials) were performed using bootstrapping from the distributions for internal dose for all exposure groups and cohorts (Figure 1) and from Poisson distributions for observed total and lung cancer deaths (Table 1).

Dose Response Modeling. A log-linear model was used to fit individual simulations from the combined data set of dose (AUC) and observed response (SMR) for lung and total cancer. The data were weighted based on the size of the cohort. The dose-response model was unrestricted, allowing for positive and negative values for both slope (potency) and x-intercept (threshold dose).

Results and Discussion

The point estimates for total cancer dose-

response for these three populations are presented in Table 1 and Figure 2 (total cancers only). Distributions are presented for the slope (SMR/AUC) and intercept (AUC) for the log-linear fits from the Monte Carlo analyses for human total cancers (Figure 3, Table 2; lung cancer data not plotted due to space limitations). The data are overwhelmingly consistent with a positive x-

Figure 3: Distributions of Slope and Intercept for Log-Linear Fits to Dose-Response Data

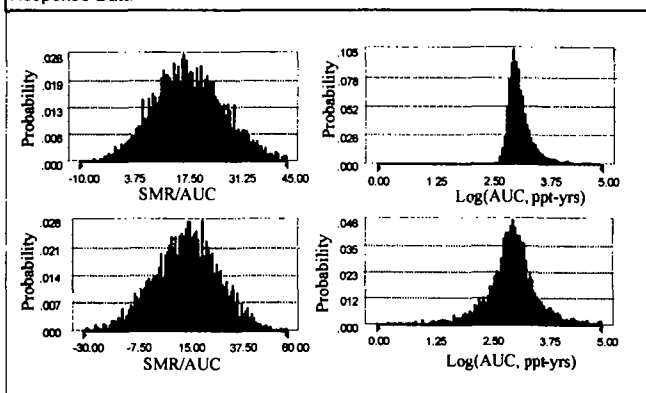
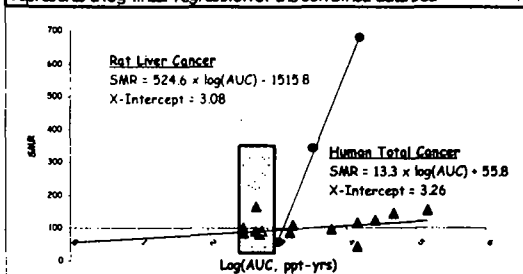


Figure 2: Dose-response trends for total cancer mortality for several subcohorts exposed to TCDD and the rat liver tumor data from Kociba et al. (1978). Shaded region is the level corresponding to current background exposures to TCDD in the environment. Solid gray line represents a log-linear regression of the combined data set.



intercept, or threshold, for excess cancer response. More than 95 percent of the lung cancer simulations, and more than 99 percent of the total cancer simulations, exhibited a positive threshold. The data are also highly consistent with a positive slope for the dose-response relation for total cancers, with more than 98 percent of simulations exhibiting a positive slope. The dose-response data for lung cancer show more variability, with a much wider range of slopes, and approximately 14 percent of the simulations demonstrating a non-positive slope.

Typical mean background levels of serum lipid TCDD are about 3 to 5 ppt, with upper 95th levels of 10 ppt or less^{10, 11}. This corresponds to typical lifetime AUCs of 210 to 700 ppt-yrs (3 to 10 ppt for 70 years). Based on this Monte Carlo analysis of the epidemiological data, the most probable values for an x-intercept for both the human lung cancer and total cancer data are above the background exposure level, at approximately 1300 and 1800 ppt-yrs, respectively. The slopes for lung cancer and total cancer generated during this analysis varied widely among the simulations. Both simulations were consistent with an increase in SMR of approximately 12 to 13 percent for each order-of-magnitude increase in TCDD AUC. The results of this analysis support the theory that TCDD is a threshold carcinogen, and the threshold is likely to be above current background exposure levels in the United States.

Table 2: Distribution of slope and intercept values from Monte Carlo runs

Dose-Response	Slope	X-Intercept	% of Monte Carlo Runs	
			Lung	Total
Threshold carcinogen	+	+	83.40%	98.30%
Nonthreshold carcinogen	+	-	2.60%	0.00%
Threshold noncarcinogen	-	+	12.60%	1.10%
Nonthreshold noncarcinogen	-	-	1.40%	0.60%

Acknowledgments

We gratefully acknowledge Paolo Mocarelli, Larry L. Needham, Paolo Brambilla, PierMario Gerthoux, and Donald G. Patterson for providing serum TCDD sampling data for the Seveso population.

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