Comparative Dose-Response of the NIOSH and Seveso Populations to the Carcinogenic Hazard of 2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD) Using Alternative Dosimetrics

Sean M. Hays[1], Lesa L. Aylward[2], Paolo Mocarelli[3], Larry L. Needham[4], Paolo Brambilla[3], PierMario Gerthoux[3], Donald G. Patterson[4], Janice Czernec[1], Dennis J. Paustenbach[5], and Nathan J. Karch[2]

[1]ChemRisk — A Division of McLaren/Hart, 29225 Chagrin Boulevard, Cleveland, OH 44122
[2]Karch & Associates, Inc., 1701 K Street N.W., Suite 1000, Washington, D.C. 20006
[3]University Department of Pathology, Hospital of Desio, Desio, Italy
[4]Division of Environ. Health Lab. Sciences, Centers for Disease Control, Atlanta, GA 30333
[5]ChemRisk — A Division of McLaren/Hart, 1135 Atlantic Avenue, Alameda, CA 94501

Abstract

We present an analysis of the comparative cancer dose-response in the NIOSH and Seveso populations using dosimetrics based on lifetime area-under-the-curve (AUC) of the serum lipid TCDD concentration. Serum lipid TCDD concentrations from 246 persons from Seveso were used to estimate serum lipid TCDD concentration-time profiles. Based on this analysis, exposure in the Seveso population is of the same magnitude as in persons in the NIOSH cohort with exposure durations of less than five years. Standard mortality ratios for cancer sites of interest for the NIOSH cohort and the Seveso population were compared. In general, endpoints showing elevations in one cohort were not elevated in the other cohort.

Introduction

We previously presented a comparative analysis of the cancer dose-response for TCDD-induced carcinogenesis in rats and in workers in the occupationally exposed NIOSH cohort using dosimetrics based upon the area-under-the-curve (AUC) of serum lipid TCDD.[1)] In order to add to our understanding of the carcinogenic dose-response for TCDD in humans, we are extending this analysis to data for two additional exposed populations: the United States Air Force "Ranch Hand" population and a subset of the Seveso population. We describe our preliminary analysis of data from the Seveso population in this paper, and present findings for comparison with those of our analysis of the NIOSH cohort.

Methods

Approximate zones of contamination were identified subsequent to the 1976 accident. Zone A represented the highest level of contamination, followed by Zones B and R (total populations of approximately 750, 5,000, and 30,000 inhabitants, respectively). We analyzed the dose-response for cancer mortality in this population using recently presented mortality data[2)] in conjunction with three biologically-based dosimetrics: peak serum lipid TCDD concentration

(C_{peak}), area-under-the-curve (AUC), and lifetime average serum lipid TCDD concentration (C_{avg}). These dosimetrics were calculated using measured serum lipid TCDD levels from blood samples taken within one year of the July 10, 1976, accident for 120 randomly selected individuals from Zone A, 46 individuals in Zone B, and 20 pooled samples (each comprised of blood samples from four individuals) from Zone R. Data for Zone B residents were not randomly selected and probably include data for individuals with higher than typical exposures. The Zone B individuals were chosen in order to follow the most highly exposed persons (that is, persons living in the areas of highest soil levels of TCDD or those living close to persons with chloracne, etc.). The data for Zones R and A are likely to be more representative of general exposures in those areas.

AUC, C_{peak}, and C_{avg} were calculated using the same methods we used previously to analyze the NIOSH cohort of occupationally exposed workers in the United States.[1] Briefly, the measured serum level taken within the year following the accident was back-extrapolated to an estimated peak level at the time of the accident using a 7.5 year half-life for elimination and simple first-order kinetics. We assumed a single, high level exposure with a constant rate of elimination subsequent to the exposure (which may have underestimated exposure for individuals living in Zone B, where persistently elevated levels of TCDD remain in soil). Finally, we assumed that serum levels before exposure were constant at 5 ppt. These assumptions resulted in a two-part concentration versus time curve (time before and after the accident). We calculated three dose measures for each individual. AUC, in ppt-years, corresponds to the integrated area under the concentration versus time curve. C_{avg}, in ppt, is the average concentration from the curve, and C_{peak}, also in ppt, the highest estimated concentration.

Results and Discussion

Table 1 presents the mean, median, and range of the calculated AUC, C_{peak}, and C_{avg} values for individuals from each zone, by sex, and presents similar calculated values from the NIOSH cohort for comparison. Figures 1A, B, and C present box plots of the estimated dosimetrics for the Seveso population by zone and the NIOSH cohort by exposure duration group (<1, 1 to <5, 5 to <15, and ≥15 years exposure). Table 2 lists the relative risks and confidence intervals for selected cancer mortality endpoints for Seveso based on follow-up through 1991.[2] Because the Zone A population is so small, the findings in this group are based on very small numbers of observed cases and are unstable. The Seveso mortality rates encompass 15 years of latency since first exposure for this population, but expected numbers of deaths are still relatively low, so that these rates should still be considered as interim. Table 3 presents selected SMRs from the NIOSH cohort for comparison.[3]

The values of serum lipid TCDD AUC, C_{peak}, and C_{avg} calculated based on sampling data for Zone A indicate that this group has experienced average and peak concentrations comparable to those experienced by the NIOSH subcohorts with exposure durations of up to five years (although individual peak values are among the highest ever measured). AUC values are similar to those in persons with less than 1 year exposure. The exposures in Seveso were acute, whereas the NIOSH cohort were generally exposed chronically. However, given the long half-life and apparent rapid equilibration of TCDD among body lipid stores, the differences in exposure circumstances may not have any practical consequences.

Direct comparison of responses between the Seveso and NIOSH cohorts is possible for a few endpoints. Figures 2A, B, C, and D present cancer mortality SMR values as a function of AUC for all cancers, respiratory cancers, leukemias, and cancer of the rectum, respectively, for both the male Seveso population and the NIOSH cohort. Because the NIOSH cohort is

exclusively male, only male rates from the Seveso population are included in these comparison figures. Qualitatively, endpoints currently showing elevation among male residents of Seveso (rectum, lymphatic and hematopoietic cancers) were not elevated in the NIOSH cohort. Similarly, the elevation in total cancers and in lung cancers observed in the NIOSH cohort have not been observed to date in the Seveso cohort. The lack of consistency in the cancer data between these two populations may be a consequence of the shorter latency period for the Seveso population, of differing exposure circumstances, or may indicate that the observed excesses are not directly due to TCDD exposure.

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Table 1: Estimated serum lipid TCDD AUC, C_{peak}, and C_{avg} for the Seveso and NIOSH cohorts*

Exposure Group	AUC (ppt-years)		C_{peak} (ppt)		C_{avg} (ppt)	
	mean	median (range)	mean	median (range)	mean	median (range)
Seveso						
Zone A, male	14,416	4,076 (370-105,303)	1,733	490 (30-12,754)	485	162 (9-4,050)
female	12,340	3,628 (250-149,682)	1,484	432 (17-18,134)	420	120 (7-6,508)
Zone B, male	1,682	1,291 (293-4,427)	183	134 (25-533)	51	22 (9-211)
female	1,533	1,112 (348-4,538)	170	109 (15-547)	62	39 (6-239)
Zone R, male	606	470 (179-1,145)	54	36 (17-118)	23	16 (8-48)
female	486	413 (137-811)	38	29 (11-77)	16	17 (6-30)
NIOSH						
<1 yr exp.	6,059	2,739 (196-136,823)	597	278 (5-12,977)	111	50 (5-2,176)
all ≥1 yr exp.	41,770	20,260 (736-33,018)	2,960	1,649 (63-24,855)	653	327 (17-5252)
1 - <5 yr	25,536	12,671 (736-276,359)	2,290	1,189 (63-24,855)	413	227 (17-3,572)
5 - <15 yr	47,172	32,135 (3,234-201,843)	3,213	2,250 (243-11,435)	738	477 (62-2,970)
≥15 yr	148,200	130,479 (24,052-353,018)	7,288	6,512 (1,214-17,238)	2,218	2,045 (315-5,252)

* Twenty year latency subcohort.

Table 2: Selected mortality rates from Seveso [2)]

Cancer Endpoints	Zone A		Zone B		Zone R	
	Obs.	SMR (95% C.I.)	Obs.	SMR (95% C.I.)	Obs.	SMR (95% C.I.)
Females						
All Cancers	10	120 (60-220)	48	90 (70-120)	401	90 (80-100)
Digestive	5	150 (60-360)	18	80 (50-130)	158	90 (80-110)
Lung (ICD 162)	–		2	60 (10-230)	29	100 (70-160)
Breast	1	60 (10-390)	9	80 (40-150)	67	80 (60-100)
Uterus	–		1	30 (0-240)	27	110 (80-170)
Ovary	1	240 (30-1650)	–		21	100 (60-160)
Brain	–		2	320 (100-1030)	8	110 (50-240)
Lymphoemopoietic	—		7	180 (80-380)	29	90 (60-140)
Hodgkin's	–		2	650 (150-3000)	4	190 (60-580)
Non-Hodgkin's	–		–		8	90 (40-180)
Myeloma	–		4	660 (230-1850)	5	100 (40-250)
Leukemia	–		1	60 (10-400)	12	90 (50-160)
Males						
All Cancers	6	40 (20-100)	104	110 (90-130)	607	90 (80-100)
Digestive	1	20 (0-140)	33	90 (70-130)	226	90 (80-100)
Rectum	–		7	290 (140-620)	19	110 (70-180)
Lung (ICD 162)	4	100 (40-260)	34	120 (90-170)	176	90 (80-110)
Brain	–		1	80 (10-550)	12	130 (70-250)
Lymphoemopoietic	—		12	230 (130-420)	27	80 (50-120)
Hodgkin's	–		2	330 (80-1400)	–	
Non-Hodgkin's	–		2	150 (40-600)	10	110 (50-210)
Myeloma	–		1	110 (20-820)	5	80 (30-200)
Leukemia	–		7	310 (140-670)	12	80 (40-150)

Table 3: Selected mortality rates from the 20 year latency NIOSH subcohort[3)] for comparison

NIOSH Exposure Duration Group	All Cancers		Trachea, Bronchus, and Lung (ICD 162)		Rectum		Lymphatic & Hematopoietic	
	Obs.	SMR (95% C.I.)	Obs.	SMR (95% C.I.)	Obs.	SMR (95% C.I.)	Obs.	SMR (95% C.I.)
<1 year	48	102 (76-136)	17	96 (56-155)	1	100 (3-557)	4	102 (28-260)
All ≥ 1 year	114	146 (121-176)	40	139 (99-189)	2	115 (14-415)	8	125 (54-247)
≥ 1 to < 5	59	165 (119-198)	17	126 (73-192)	NA		NA	
5 to < 15	37	138 (97-186)	14	146 (79-232)	NA		NA	
≥ to 15	18	115 (68-175)	9	156 (71-272)	NA		NA	

NA — Exposure duration subcohort analysis not available; SMRs available only for <1 and ≥1 year exposure groups.

Figure 1: Box plot comparisons of serum lipid TCDD dosimetrics for the Seveso population and the NIOSH cohort, by Seveso zone of residence (A, B, and R) and by NIOSH exposure duration subcohort (<1, 1 to <5, 5 to <15, and ≥15 years exposure, groups 1, 2, 3, and 4, respectively). A: Area-under-the curve, ppt-yrs. B: Average serum lipid TCDD concentration, ppt. C: Peak serum lipid TCDD concentration, ppt.

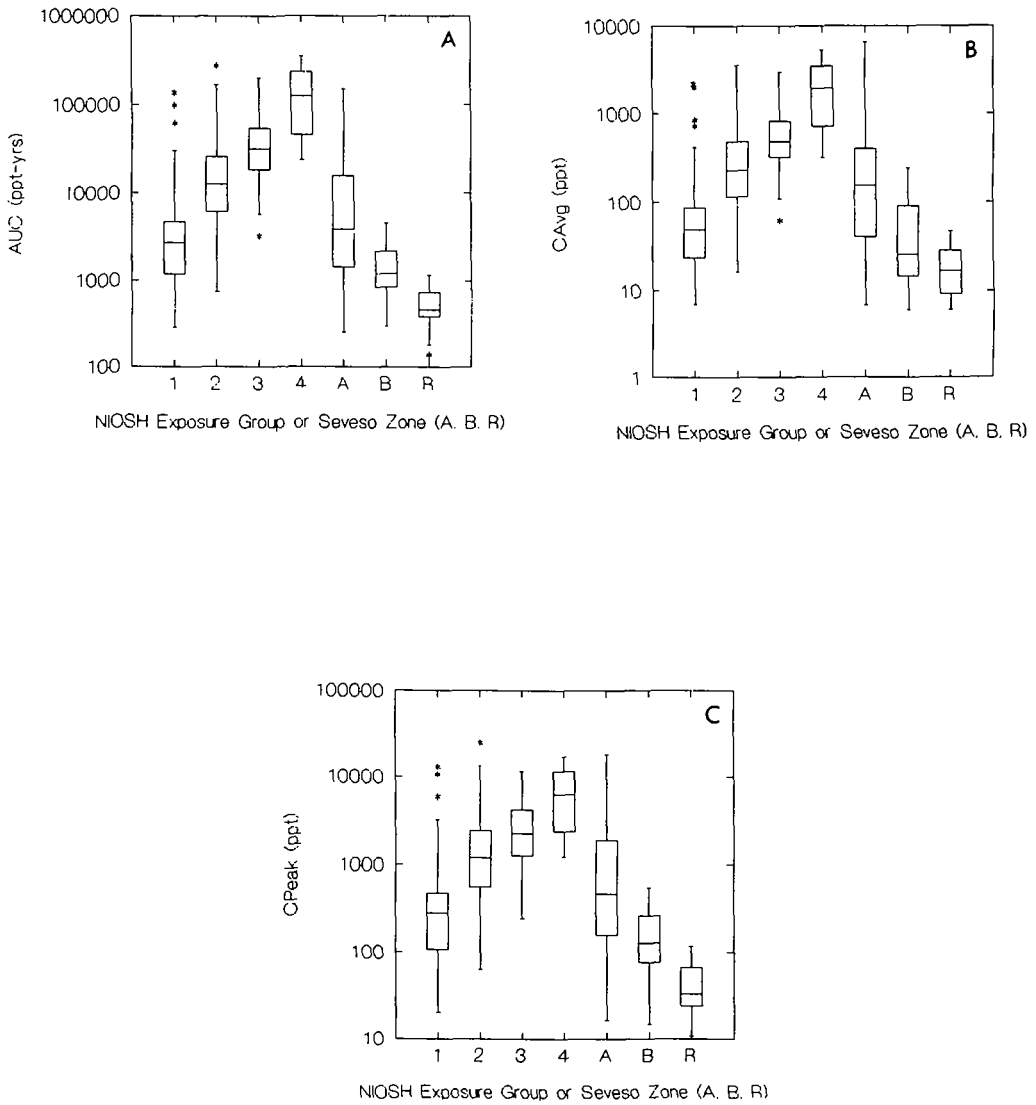

Figure 2: Cancer mortality SMRs versus serum lipid TCDD AUC for the NIOSH[3] and male Seveso[2] populations. A: All cancer mortality. B: Lung cancer mortality. C: Rectal cancer mortality. D: Lymphatic and hematopoietic cancer mortality. For rectal and lymphatic/hematopoietic mortality, cancer rates were available only for the <1 year and ≥1 year exposure duration groups from the NIOSH cohort. No cases of these two cancers were observed in the Zone A Seveso subcohort, but less than 1 of each was expected.