

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

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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 data²⁾ in conjunction with three biologically-based dosimetrics: peak serum lipid TCDD concentration

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(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 figures. Qualitatively, end (rectum, lymphatic and hen Similarly, the elevation in t not been observed to date i between these two populat population, of differing exp not directly due to TCDD c

Acknowledgments

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Table 1: Estimated serum li

| Exposure Group | AUC mean |
|----------------------|----------|
| Seveso | |
| Zone A, male | 14,416 |
| female | 12,340 |
| Zone B, male | 1,682 |
| female | 1,533 |
| Zone R, male | 606 |
| female | 486 |
| NIOSH | |
| <1 yr exp. | 6,059 |
| all ≥ 1 yr exp. | 41,770 |
| 1 - <5 yr | 25,536 |
| 5 - <15 yr | 47,172 |
| ≥ 15 yr | 148,200 |

* Twenty year latency subcohort

TCDD concentration (C_{avg}). Levels from blood samples selected individuals from blood samples from randomly selected and s. The Zone B individuals s, persons living in the (with chloracne, etc.). The exposures in those areas. ve used previously to nited States.¹⁾ Briefly, the back-extrapolated to an e for elimination and simple onstant rate of elimination for individuals living in nally, we assumed that ns resulted in a two-part ve calculated three dose tegrated area under the ion from the curve, and

AUC, C_{peak} , and C_{avg} ilated values from the s of the estimated y exposure duration group ve risks and confidence llow-up through 1991.²⁾ e based on very small s encompass 15 years of f deaths are still relatively esents selected SMRs

d based on sampling data ncentrations comparable s of up to five years

AUC values are similar veso were acute, whereas 1 the long half-life and rrences in exposure

I cohorts is possible for a values as a function of ectum, respectively, for 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.

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Table 2: Selected mortality rates from Seveso²⁾

| 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 subcohort³⁾ 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 compares the NIOSH cohort, by Seveso subcohort (<1, 1 to <5, 5 to A: Area-under-the curve, p serum lipid TCDD concentra

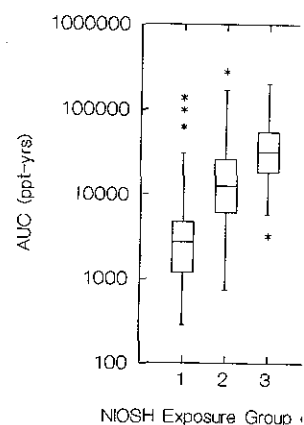


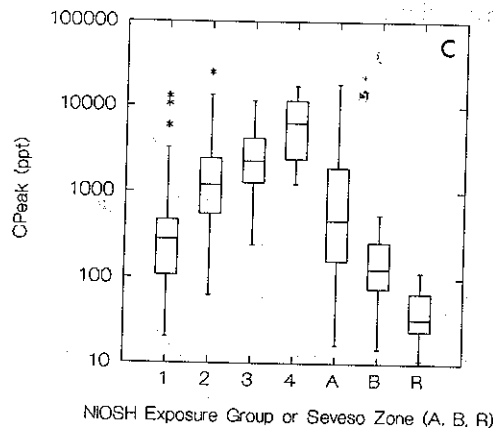
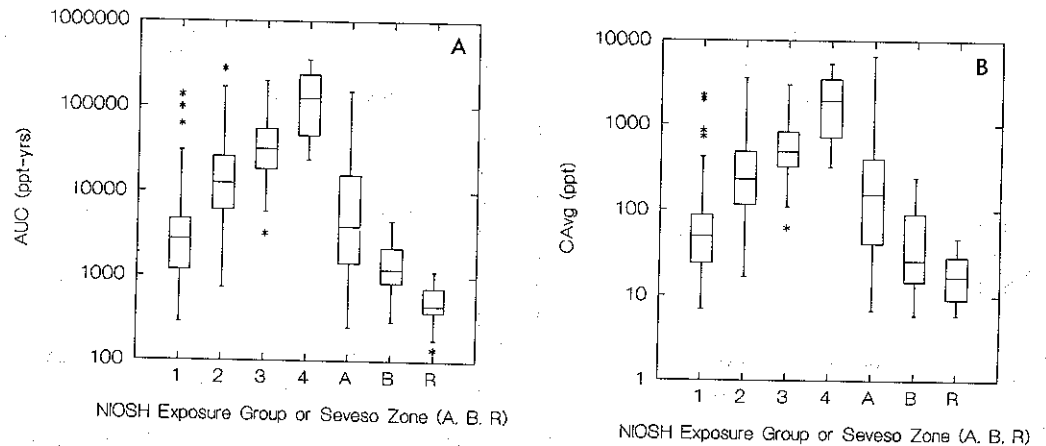
Figure 1: Box plot comparisons of serum lipid TCDD dosimetrics for the Seveso population and the NIOSH cohort, by Seveso zone of residence (A, B, and R) and by NIOSH exposure duration subcohort (<1, 1 to <5, 5 to <15, and ≥15 years exposure, groups 1, 2, 3, and 4, respectively). A: Area-under-the curve,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

| Zone R | |
|--------|----------------|
| Obs. | SMR (95% C.I.) |
| 401 | 90 (80-100) |
| 158 | 90 (80-110) |
| 29 | 100 (70-160) |
| 67 | 80 (60-100) |
| 27 | 110 (80-170) |
| 21 | 100 (60-160) |
| 8 | 110 (50-240) |
| 29 | 90 (60-140) |
| 4 | 190 (60-580) |
| 8 | 90 (40-180) |
| 5 | 100 (40-250) |
| 12 | 90 (50-160) |
| | |
| 607 | 90 (80-100) |
| 226 | 90 (80-100) |
| 19 | 110 (70-180) |
| 176 | 90 (80-110) |
| 12 | 130 (70-250) |
| 27 | 80 (50-120) |
| - | - |
| 10 | 110 (50-210) |
| 5 | 80 (30-200) |
| 12 | 80 (40-150) |

hort³) for comparison

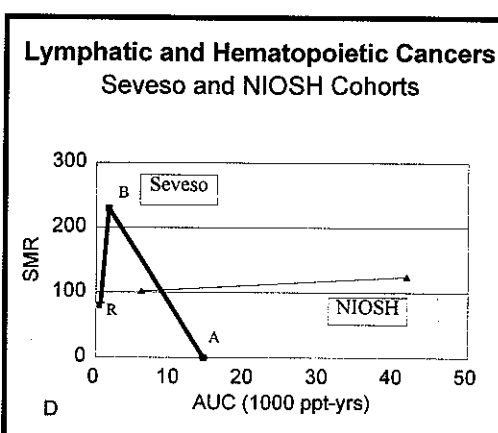
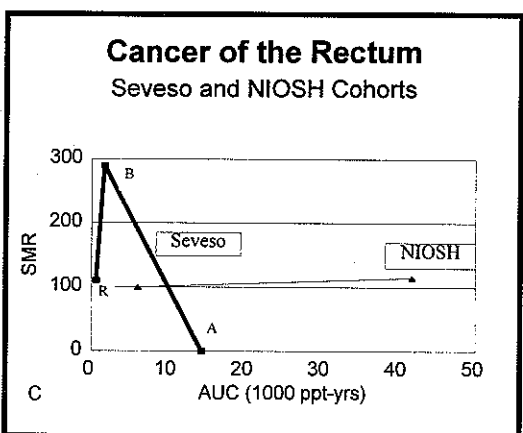
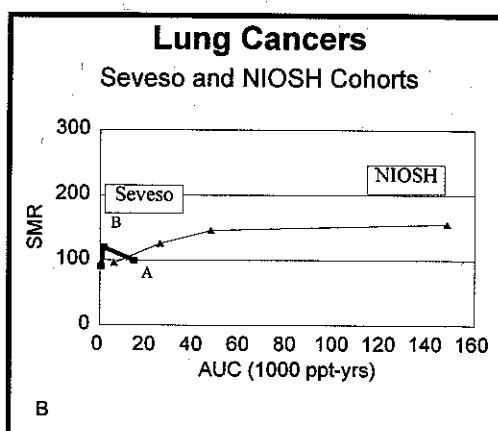
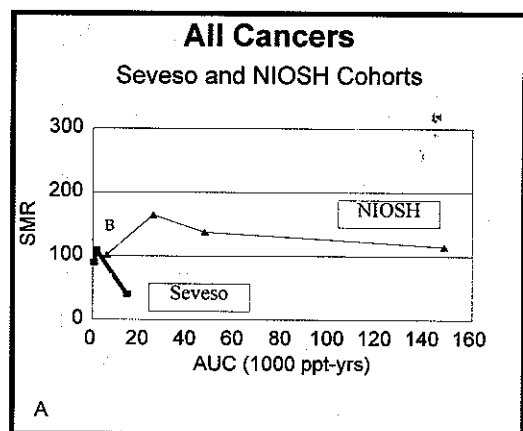
| Obs. | SMR (95% C.I.) | Lymphatic & Hematopoietic |
|------|----------------|---------------------------|
| 4 | 102 (28-260) | -557 |
| 8 | 125 (54-247) | -415 |
| NA | | |
| NA | | |
| NA | | |

1 year exposure groups.



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Figure 2: Cancer mortality SMRs versus serum lipid TCDD AUC for the NIOSH³⁾ and male Seveso²⁾ 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.



Estimating Minimally Rats and Humans U

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Abstract: TCDD causes effects vary significantly. effects. We have applied related protein induction al daily TCDD intake require in humans. The calculation 25% body fat. ED01s und for rat and human, respect the human PB-PK/protein i starting point for margin of

Introduction: TCDD an (CYP450) family isozymes CYP1A2 is not uniform th centrilobular and there is a areas of the liver where th induced cells in the liver centrilobular toward the p induced cells is indicative TCDD.³ Recently, quant both total induction in liver

Cancer risk assessments w standard defaults for in extrapolation. The upper calculated from this appro largely ignored information increases in information a significance of regional dis estimates of the expected publication of the proposed