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Dioxin: Exposure-Response Analyses and Risk Assessment

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Abstract: Low-levels of dioxin cause cancer in animals. In 1997 dioxin was found to be a human carcinogen by the International Agency for Research on Cancer, based largely on four studies of industrial workers exposed to high levels. Recently there has been interest in estimating human cancer risk at low level environmental exposures. Here we review quantitative exposure-response analyses and risk assessment for low environmental levels based on the largest existing cohort of workers exposed to dioxin (the U.S. NIOSH cohort). We estimate that doubling background levels of exposure, which may occur for example by eating a lot of fish which have accumulated dioxin, will increase lifetime risk of cancer death by 0.1 to 1.0%. In the US the background risk of cancer death by age 75 is 12%, so doubling background levels of dioxin exposure would increase this lifetime risk to somewhere between 12.1 and 13.0%. Our results agree broadly with results from a German cohort, which is the only other cohort for which a quantitative risk assessment has been conducted.

Key words: Cancer, Dioxin, Risk assessment

Introduction

TCDD (2,3,7,8-tetrachlorodibenzo-*p*-dioxin) is the most toxic congener of the dioxins. Dioxins are part of a family of "co-planar" toxins including dibenzofurans and PCBs; the most toxic members all have 2,3,7,8 chlorine substitutions on 2 benzene rings. EPA uses a TEQ (Toxic equivalency) system to rate other dioxins/furans/PCBs in relation to TCDD[1)].

TCDD is a potent multi-site animal carcinogen. It is not directly genotoxic, but appears to be both a promoter and initiator of cancer in animals[1)]. TCDD acts via an Ah receptor in both animals and humans; binding somehow alters gene expression. The Ah receptor is present in many tissues in animals and humans. Animal carcinogenesis is correlated with dioxin's affinity for the Ah receptor.

TCDD is produced in small amounts during combustion of substances containing chlorine and carbon, for example, in waste incinerators. Historically it was also a contaminant in industrial processes, particularly in the production of trichlorophenol, which was used in making herbicides in the 1970s. Trichlorophenol was an ingredient in a common herbicide (2,4,5-T) which was a component of Agent Orange. Small amounts of TCDD also contaminate other processes (eg, paper and pulp processes).

Occupational exposures have been primarily dermal. Environmental exposure occurs via the diet, via consumption of plants and animals which have absorbed environmental TCDD and stored it in their fat tissues. Highest exposures have occurred in industrial cohorts, eg., 1000–2000 ng/kg blood lipids. Animals in carcinogenesis studies have been exposed to similar levels as industrial cohorts. By comparison, background human levels are around 5 ng/kg (ppt).

In 1997 the International Agency for Research on Cancer[1)] classified TCDD as a Group 1 human carcinogen based on limited human data, sufficient animal data, and mechanistic considerations (ie, that the Ah receptor occurred in both humans and animals).

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Table 1. Four industrial cohorts which served as a basis for 1997 IARC dioxin determination

Study	SMR cancer - high exposure subgroup (95% CI)	Number of cancers	Estimated TCDD at end of exposure
Fingerhut *et al*. (1987)	1.5 (1.2–1.8)	114	Mean 418 ppt (n=119)
Becher *et al*. (1996)	1.3 (1.0–1.5)	105	Median 141 ppt (n= 48)
Hooiveld *et al*. (1996)	1.5 (1.3–1.9)	51	Geometric mean 286 ppt (n= 48)
Ott and Zober (1996)	1.9 (1.1–3.0)	18	Geometric mean 400 ppt (n=138)

The human evidence used by IARC came from epidemiologic studies of four heavily exposed industrial cohorts in which an excess of all cancers was observed, without any particular site-specificity, although lung was consistently elevated in all cohorts (Table 1).

One of these cohorts, the US NIOSH cohort, is the subject of this paper. This cohort consists of 5172 workers exposed to TCDD at 12 US chemical plants.

Here we summarize recent exposure-response analyses and risk assessment analyses for the NIOSH dioxin cohort. Demonstration of a positive exposure-response (ie, more exposure, more cancer) is one of the key elements in proving a toxin causes a disease. Besides the NIOSH cohort, there is only one other cohort for which risk assessment has been conducted (the German industrial cohort[2]).

Methods

The US NIOSH cohort was first studied for cancer mortality by Fingerhut et al. 1991, with vital status follow-up through 1987. The cohort consisted of 5,172 workers from 12 chemical plants. Subsequently, follow-up was extended through 1994 adding 37% more deaths. Two sets of analyses were then performed. In Phase 1 we made quantitative estimates of exposure, in terms of 'exposure scores', for 8 of 12 plants in this cohort (3,538 workers, 69% of original cohort, called the "exposure subcohort")[3]. Then exposure-response analyses were conducted for this exposure subcohort using these scores[4]. In Phase 2, these scores were in turn used to estimate individual TCDD serum levels for these 3,538 workers, exposure-response analyses were conducted using estimated serum levels, and a cancer risk assessment was conducted for low environmental levels of dioxin[5].

Exposure in all these studies was defined as exposure to 2,3,7,8 -TCDD. There was simultaneous exposure for many workers to other (less toxic) dioxins. Workers who were also exposed to pentachlorophenol (PCP, a suspect carcinogen) were excluded from the exposure subcohort.

For Phase 1 analyses, we created a job-exposure matrix (JEM) to enable us to estimate exposure scores for the exposure subcohort of 3,538 workers[3]. The exposure scores were relative rankings of exposure, and did not represent any standard units of external exposure. Most TCDD exposure to the workers was dermal. Dermal exposure is inherently difficult to quantify in standard units of external exposure typical for inhaled substances.

The exposure scores were created by multiplying 3 factors: 1) TCDD concentration in process materials, 2) fraction of day worked on process, and 3) qualitative 'contact' level (.01–1.5). Data on TCDD contamination of process materials (manufactured products) were available for the 8 plants in the subcohort from 1960s to 1980s (production of TCDD-contaminated products stopped in 1984). Earlier data on TCDD contamination also available at largest plant in cohort. Data on process changes over time was also available, allowing estimates of changing TCDD contamination over time. Finally, contact level was based on job category, eg., production workers had higher contact level than engineers.

In Phase 2 of dioxin study, we converted exposure scores to estimated TCDD serum levels over time, enabling analysis of exposure-response in terms of cumulative serum levels. This in turn allowed a risk assessment in terms of daily TCDD or TEQ intake (pg/kg body weight/day), the units used for regulation, because one can assume a steady state relationship between a constant intake and a constant serum level (1 pg/kg/bw/day=10 ppt TCDD)[6]. In background populations, TCDD generally accounts for only 10–20% of TEQ. Here we have assumed that 1 TEQ is equivalent for 10*TCDD.

One plant out of the eight plants in the exposure subcohort had data on TCDD in serum for a sample of workers (n=193). We estimated the relation between exposure scores and serum levels for these 193 workers, and then applied this relation to the entire-subcohort with exposure scores (n=3,538).

To develop the relation between exposure scores and serum levels for the 193 workers, we assumed a simple one compartment first-order pharmacokinetic model, such that:

$$y_{t1} = y_{t0} \exp(-\lambda * (t_1 - t_0)),$$

where λ can be calculated from a known half life (8.7 years)[7],

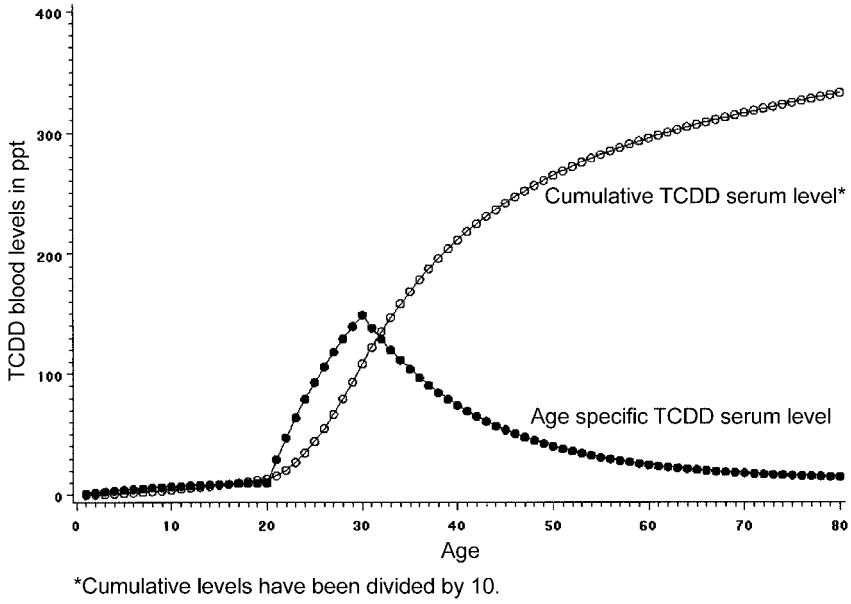

Fig. 1. Illustration of cumulative and age-specific TCDD serum levels versus age, assuming occupational exposure occurs age 20–30.

Table 2. Descriptive statistics for the subcohort with exposure data (n=3538)*

Number in cohort	3538	
Number of deaths	923	
Number of cancer deaths	256	
Mean duration of exposure (yrs)(std dev)	2.7	(4.4)
Estimated median cumulative exposure score (range)	125	(0.002–1,558,400)
Estimated mean cumulative exposure score (std dev)	10,019	(60,311)
Estimated mean (std dev) serum level in ppt at end of followup**	343	(2223)
Estimated median (range) serum level in ppt at end of exposure***	98	(6–210,054)
Estimated mean serum level (std dev) in ppt at end of exposure***	1,589	(8208)

*Estimated serum levels were based on 3,444 workers included in risk sets in exposure-response analyses; 94 workers were not included in any risk set in the exposure-response analyses because their end of follow-up occurred at an age before the age when the first cancer case died. All serum levels in this table include a background of 6.1 ppt TCDD., **Mean year ending followup 1989, 24 years after end of exposure, ***Mean year of last exposure, 1965.

t_1 and t_0 are any two points in time (their difference is assumed to be positive), y is the serum level[8]. With a half-life of 8.7, λ=0.079.

Serum levels build continually from new exposure and TCDD is continually excreted. Figure 1 illustrates this process schematically for a worker exposed between ages 20 and 30.

We assumed the relation (β) between exposure score over time and serum level at time of last exposure (y_{last}) can be modeled as follows:

$$E(y_{last}) = \beta / \lambda [\sum_{i=1}^{n} \text{exposure score}_i * \{1 - \exp(-\lambda (t_i - t_{0i}))\} * \{\exp(-\lambda (t_{last} - t_i))\}]$$

where i indexes jobs 1 to n, t_{0i} refers to the time the ith job began, t_i refers to the time the ith job ended. Then we derived β via linear regression (no intercept) using the 193 workers with data on serum and exposure score. We then applied the estimated β to all workers in the subcohort with exposure scores. We calculated estimated serum level at any point in time as well as cumulative exposure level. Cumulative exposure (sometimes called 'area under the curve') is typically the exposure of interest in studies of occupational cancer, rather than average exposure level.

Results

Table 2 gives some descriptive data for the subcohort of

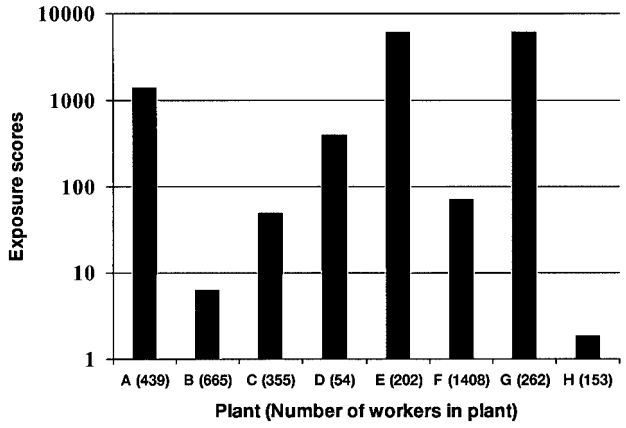

Fig. 2. Median esposure scores by plant for the NIOSH sub-cohort with exposure scores.

3,538 for whom we were able to estimate exposure scores and serum levels. The average length of exposure was short (2.7 years) but with a wide variation. Both cumulative exposure scores and estimated serum levels show a highly skewed distribution, with a few very high values—making the mean much higher than the median. The gradual clearance of TCDD from the body is evidenced by the difference between the estimated TCDD level at the end of exposure versus the level at the end of follow-up.

Figure 2 shows the median exposure score for each of the eight plants, on a log scale. Note the wide variation between plants, which in fact facilitated exposure-response analyses.

We did not have a gold standard to validate our JEM. However, an indirect validation was available. In the exposure level subcohort (n=3,538), 343 subjects had chloracne, a severe skin rash caused by dioxin. The median cumulative exposure score was 11,546 for these subjects, compared to 3,145 subjects without chloracne, for whom the median cumulative exposure score 77.

Using the JEM, and the exposure scores, we were able to assign cumulative exposure scores to all 3,538 workers and conduct exposure-response analyses for cancer. Table 3 shows the results comparing the cohort to the US population, after dividing the cohort into septiles according to the cumulative exposure score. Analyses were conducted with and without assuming a 15-year lag, a period after first exposure when exposure is not counted. A lag assumption is often used in cancer as a way to take into account a potential latency period, the time between first exposure and any possible cancer effect.

In Table 3 we see that the last septile, or the last two septiles, had a significantly elevated rate of cancer in the exposed cohort vs. the US population (the comparison group). The tests for a linear trend of increasing cancer with increasing cumulative exposure scores were significant whether or not we assumed a lag period.

Further analyses, not shown here, indicated positive significant trends for all smoking-related cancers, and all nonsmoking-related cancers, suggesting that the positive trend for all cancers combined was not due to confounding by smoking (confounding of exposure-response trends by smoking could occur if those with more cumulative exposure were heavier smokers).

We considered the possibility of confounding by other chemicals, given that these workers worked in chemical plants with many exposures. However, there were no significant positive trends with length of total employment, suggesting that other chemical exposures were not confounders.

There was little indication that any particular cancer site was elevated compared to other sites. Instead there appeared to a general increase in all types of cancer for those with highest exposure. For the two 2 highest septiles (78 cancers), the SMR for all cancer was 1.46 (1.15–1.82), for digestive cancer was 1.41 (0.85–2.20), and for respiratory cancer was 1.67 (1.16–2.34). Thus our findings suggest that TCDD might be the first true all-site human carcinogen (smoking and asbestos cause cancer at many sites but not all). The fact that the Ah receptor occurs throughout the body may account for this finding.

Moving to Phase 2, we then conducted internal analyses by cumulative serum level of TCDD (in parts per trillion-years), assuming a 15-year lag. In internal analyses, the lowest exposed group serves as the referent or comparison group for all higher exposed groups. Table 4 gives the results

Table 3. Standardized mortality ratios (SMRs) by cumulative exposure-score septiles, for the sub-cohort with exposure data (n=3,538)

Causes of death	SMR (Cancer deaths)							p-value, test for linear trend
	Septile 1	Septile 2	Septile 3	Septile 4	Septile 5	Septile 6	Septile 7	
All cancers	1.14 (34)	1.15 (39)	0.85 (29)	1.10 (36)	1.15 (40)	1.34 (38)	1.60*(40)	0.02
All cancers, 15-year lag	0.98 (67)	0.90 (27)	1.14 (31)	1.18 (30)	1.33 (34)	1.69*(33)	1.54**(34)	0.02

* p=0.003, ** p=0.01

by septile of cumulative serum level. Table 4 indicates a nearly continual increase in cancer rate with increasing cumulative serum level. There is a slight decrease in cancer risk at the highest septile. This is often seen for occupational carcinogens and might be accounted for by 1) saturation of metabolic pathways at high doses, or 2) greater misclassification at high doses leading toward bias towards null at very high doses, or 3) depletion of a susceptible population at high doses.

We then went on to fit a model for continuous rather than categorical data. The best fitting model used the log of cumulative exposure with a 15-year lag. A piece-wise linear model also fit almost as well, and had a lower slope at low exposure than the model using the log of exposure. Both these models are shown in Fig. 3. A threshold model (not shown) did not fit well, suggesting there was no threshold of exposure below which there was no cancer risk.

Table 4. All cancer rate ratios by septile of cumulative serum level (lagged 15 years)*

Cumulative serum level (ppt-years)	Rate ratio (95% CI)
<335	1.00
335–520	1.26 (0.79–2.00)
520–1,212	1.02 (0.62–1.65)
1,212–2,896	1.43 (0.91–2.25)
2,896–7,568	1.46 (0.93–2.30)
7,568–20,455	1.82 (1.18–2.82)
>20,455	1.62 (1.03–2.56)

*Septiles chosen based on occupational cumulative serum levels (lagged 15 years) of all decedents with values greater than 0 (some decedents had 0 because they were lagged out). Lagged out subjects included in lowest category. All subjects have a background level of 7 ppt per year added to their occupational exposure, up to 15 years before end of follow-up (15 year lag). Number of cancer deaths by septiles were 64 (includes lagged out), 29, 22, 30 31, 32, and 48.

The relevant exposures for the general population are in the very low dose region of the curves in Fig. 3. A typical background of 5 ppt gives cumulative serum level of 300 ppt-years by age 60, while doubling background levels results in 600 ppt-years. For purposes of risk assessment for the environment, we calculated lifetime risk of cancer at twice background levels, in the low dose area of the curves. We used a standard formula to convert rates to individual risks of cancer death by age 75, adjusting for competing causes of death[9].

Table 5 gives the results using either the model with log cumulative exposure or the piecewise linear model. We assumed females had the same risk as men from TCDD, although there were no females in our study population. The lifetime risk of cancer death (by age 75) in the US is about 12% for men and 11% for women. Doubling background rates of TCDD, which might occur by eating a lot of fish in which TCDD had accumulated, for example, would be expected to increase lifetime risk of cancer death by about 1% for men using the model with log cumulative dose, and by about 0.1% using the piece-wise linear model.

Conclusions

We found a lifetime excess risk of cancer death in range of 1 in 1000 to 1 in 100, after a doubling of background intake of TCDD. Our data also agree with the only other quantitative risk assessment based on human epidemiology (German cohort[2]).

Our results are sensitive to the shape of the curve in the low dose range, typical of all extrapolation of risk from high

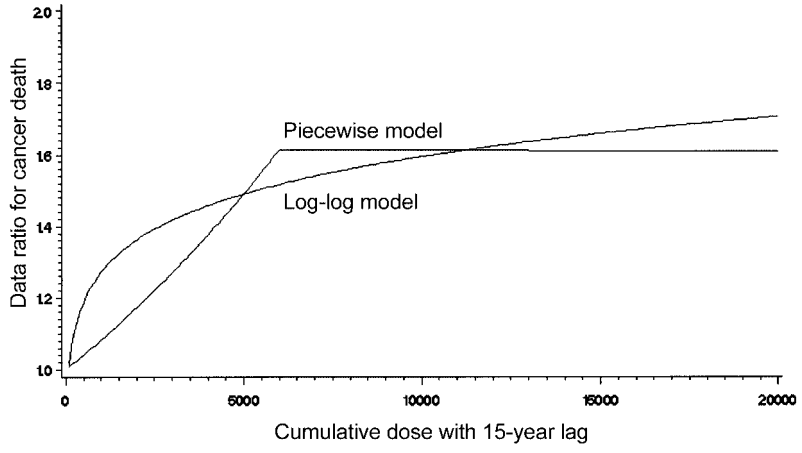

Fig. 3. Dioxin and cancer risk in the NIOSH cohort, using two different models.

Table 5. Estimates of lifetime (through age 75) excess risk of dying from any cancer due to exposure to TCDD or to TEQs, above background risk

Model*	Exposure level	Sex	Lifetime excess risk above background (95% CI)	Background risk**	Model chi-square (degree of freedom)
Log cumulative serum levels, (ppt-years),15-year lag	1.0 pg/kg body weight/day, TCDD	Male	0.0094 (0.0032–0.0157)	0.124	11.3 (4)
		Female	0.0080 (0.0027–0.0135)	0.108	11.3 (4)
	10.0 pg/kg body weight/day, TEQs	Male	0.0132 (0.0028–0.0192)	0.124	9.2 (4)
		Female	0.0113 (0.0024–0.0164)	0.108	9.2 (4)
Piece-wise linear, No lag	1.0 pg/kg body weight/day, TCDD	Male	0.0005 (0.0002–0.0008)	0.124	12.5 (5)
		Female	0.0004 (0.0002–0.0007)	0.108	12.5 (5)
	10.0 pg/kg body weight/day, TEQs	Male	0.0071 (0.0029–0.0014)	0.124	12.4 (5)
		Female	0.0060 (0.0024–0.0097)	0.108	12.4 (5)

*Based on a Cox regression exposure-response model in which the exposure is either 1) the log of cumulative serum level (in ppt-years of TCDD or TEQs), with a 15 year lag, 2) cumulative serum level with no lag and the model is piece-wise regression, in which two separate linear slopes are estimated. The former model fits better than the latter. Excess risk is defined as risk above background risk. Background exposure is here assumed to be either 0.5 pg/kg/day TCDD, leading to a constant serum level of 5 ppt TCDD, or 5.0 pg/kg/day of TEQs, leading to a constant serum level of 50 ppt TEQs. TEQs are toxic equivalencies which represent combined toxicity of all dioxins and furans based on toxic equivalency factors; TCDD is the most toxic dioxin/furans and has a toxic equivalency factor of 1.0. TCDD is presumed to represent 10% of all TEQs.
**Background risk of cancer death by age 75.

occupational exposures to low environmental exposures.

This accounts for the order of magnitude difference between the model using the log of cumulative dose (fast increase at low doses) and the two-piece linear model (lower increase a low doses).

There is no truly non-exposed group in industrialized societies. Low background levels of dioxin may be increasing our overall cancer rates, but it is difficult to know with certainty because there is no population in industrialized societies without low-level dioxin exposure. We can only estimate the effect of an increase (eg., a doubling) over background, not the effect of completely eliminating dioxin from the environment.

Dioxin poses a challenge to regulators, similar to other recent environmental exposures (air pollution/mortality, arsenic in drinking water/cancer, and diesel fumes/lung cancer). Large numbers of people are exposed to levels not much above background, but such levels may indeed appreciably increase cancer risk.

References

1) International Agency for Research on Cancer (IARC) (1997) Monographs on the evaluation of carcinogenic risks to humans, Vol. 69, Polychlorinated dibenzo-para-dioxins and polychlorinated dibenzofurans. IARC, Lyon.
2) Becher H, Steindorf K, Flesch-Janys D (1998) Quantitative cancer risk assessment for dioxins using an occupational cohort. Environ Health Perspect **106** (suppl 2), 663–70.
3) Piacitelli L, Marlow D, Fingerhut M, Steenland K, Sweeney M (2000) A retrospective job exposure matrix for estimating exposure to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin. Am J Ind Med **38**, 28–39.
4) Steenland K, Piacitelli L, Deddens J, Fingerhut M, Chang L (1999) Cancer, heart disease, and diabetes in workers exposed to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD): an update and exposure-response analysis of the NIOSH TCDD cohort. J Natl Cancer Inst **91**, 779–86.
5) Steenland K, Deddens J, Piacitelli L (2001) Risk assessment for 2,3,7,8-*p*-dioxin (TCDD) based on an epidemiologic study. Am J Epidemiol **154**, 451–8.
6) WHO (World Health Organization) (1998) Assessment of health risk of dioxins: re-evaluations of tolerable daily intake (TDI), WHO report Mar 25–26, WHO, Geneva (http://www.who.int/pcs/docs/dioxin-exec-sum/exe-sum-final.html).
7) Pirkle J, Wolfe W, Patterson D, Needham L, Michalek J, Miner J, Peterson M, Phillips D (1989) Estimates of the half-life of 2,3,7,8-TCDD in Vietnam veterans of Operation Ranch Hand. J Toxicol Environ Health **27**, 165–71.
8) Flesch-Janys D, Steindorf K, Gurn P, Becher H (1998) Estimation of the cumulated exposure to polychlorinated dibenzo-*p*-dioxins/furans and SMR analyses of cancer mortality by dose in an occupationally exposed cohort. Environ Health Perspect **106** (suppl 2), 655–62.
9) Gail M (1978) Measuring the benefits of reduced exposure to environmental carcinogens. J Chronic Dis **28**, 135–47.