

**The dioxin wars and  
the curious world of risk  
assessment**

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**Increasingly risk assessment is based on epidemiology rather than animal data (appropriately so)**

**Typically dose-response relationships are estimated from the whole range of the data - often including some groups with very high exposure - these are then applied to low exposures resulting in low risks - but which are nonetheless important because of the large numbers of people affected. Dioxin is a case in point.**

**NY Times May 17, 1999**

**“In a long awaited report, scientists at EPA say that dioxin is 10 times more likely to cause cancer than previously estimated. Some environmental groups hailed the draft, but some scientists questioned its assertions.”**

**“The report is a revision of 1994 report which EPA submitted to an advisory board.”**

**“Dioxin is formed when chlorine containing chemicals are burned, or when paper is bleached. It settles on plants that are eaten by animals. Once ingested, dioxin accumulates in the fat. When humans eat animals, dioxin is stored in the fat.**

**Since the 1970s, pollution controls have caused dioxin levels in the environment to drop, as a result individuals have less dioxin in their bodies than they once did.”**

**“People with the highest exposures to the chemical may have a 1 in 100 chance of getting cancer from the dioxin in their bodies, the report says.**

**The data came from the agency’s interpretation of studies of Dutch children, of Air Force personnel spraying Agent Orange, and industrial workers.**

**“The EPA said that even though many foods contained dioxin, the food supply itself was safe.”**

**Chlorine council Dr. Francis: “The EPA has a real dilemma. If the food supply is safe, and yet at the same time dioxin is causing cancer, it’s a real contradiction”**

**Greenpeace Rick Hind: “A pesticide would be banned if its cancer risk was one in a million. So why does EPA tolerate dioxin, with a cancer risk of 1 in 100?”**

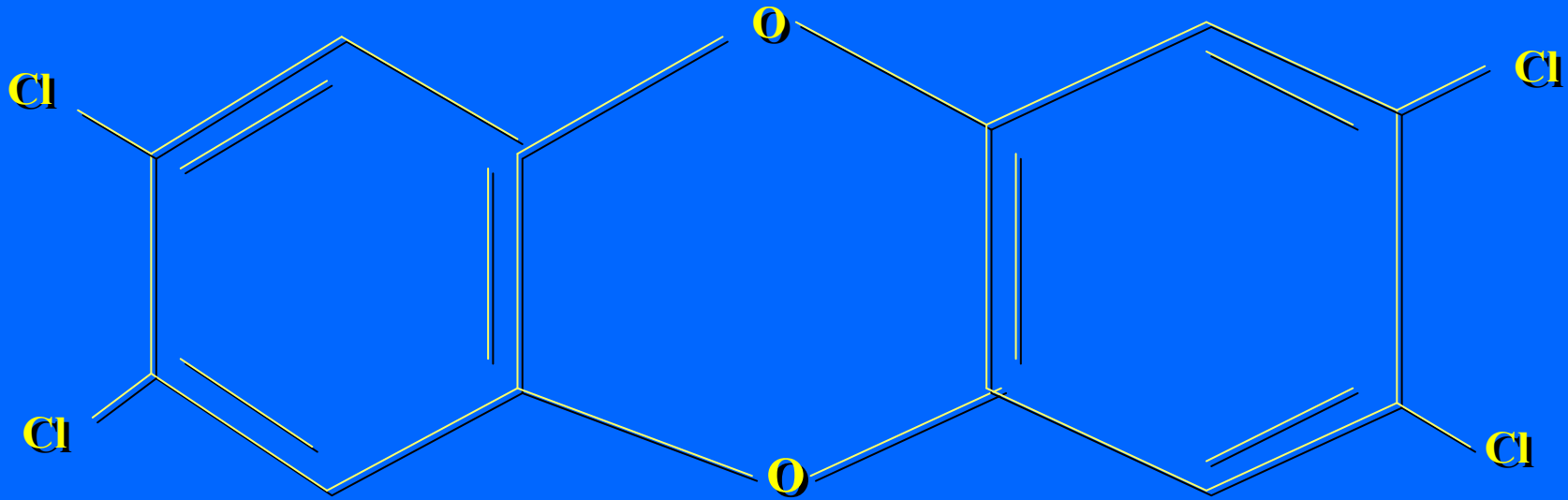
**Some scientists said they doubted the report's conclusions would stand up to scrutiny. A few were scathing in their assessment.”**

**Dr. Morton Lippman, NYU. “Scientific evidence since 1994 has been less than definitive”**

**Dr. Michael Gough, retired biologist on 1994 EPA Advisory panel. “There is no reason to think that the cancer risk from dioxin is 10 times higher than had been thought. There has been no epidemiological evidence in the last five years that makes that claim any more credible.”**

**Dr. John Doull, clinical toxicologist Univ Kansas, also a member of 1994 advisory board**

**“The agency seems to have disregarded our advice. Their review of the literature is inadequate and their recommendations appear to me to be unsupported and arrogant. This action appears to be ill-timed, political rather than scientific, and is an embarrassment to science and certainly to toxicology.”**



**2,3,7,8 - tetrachlorodibenzo-p-dioxin**

**TCDD (2,3,7,8-tetrachlorodibenzo-*p*-dioxin) is the most toxic congener of a series of 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**

**TCDD is a potent multi-site animal carcinogen : not directly genotoxic, but appears to be both a promoter and initiator of cancer in animals**

**TCDD acts via an Ah receptor  
in both animals and humans; binding  
somehow alters gene expression**

**Ah receptor present in many tissues  
in animals and humans**

**Carcinogenesis correlated with affinity  
for Ah receptor in animals**

**TCDD is a contaminant in the production of trichlorophenol, used in making herbicides in the 1970s; small amounts also contaminate other processes (eg, paper and pulp)**

**Occupational exposure primarily dermal**

**Environmental exposure via diet**

**Highest exposures have occurred in industrial cohorts, eg 1000-2000 ng/kg blood lipids**

**Background human levels, 5 ng/kg (ppt)**

**Animals in carcinogenesis studies exposed to similar levels as industrial cohorts**

**In 1997 IARC classified TCDD  
as a Group 1 human carcinogen**

**limited human data**

**sufficient animal data**

**mechanistic considerations**

**(Ah receptor)**

**The human evidence was based on 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**

**One of these cohorts, the US NIOSH cohort, is the subject of this presentation.**

## Four industrial cohorts used by IARC in 1997

<b>study</b>	<b>SMR cancer-high exposure subgroup</b>	<b># cancers</b>	<b>Estimated TCDD at end of exposure</b>
<b>Fingerhut et al 1987</b>	<b>1.5 (1.2-1.8)</b>	<b>114</b>	<b>Mean 418 ppt (n=119)</b>
<b>Becher et al. 1996</b>	<b>1.3 (1.0-1.5)</b>	<b>105</b>	<b>Median 141 (n=48)</b>
<b>Hooiveld et al. 1996</b>	<b>1.5 (1.3-1.9)</b>	<b>51</b>	<b>Geo mean 286 ppt (n=48)}</b>
<b>Ott and Zober 1996</b>	<b>1.9 (1.1-3.0)</b>	<b>18</b>	<b>Geo. Mean 400 ppt (n=138)</b>

**US NIOSH (National Institute for Occ Safety and Health) study**

**Mortality study of 12 US chemical plants, updated through 1993**

**5172 workers exposed to TCDD,  
a contaminant of 2,4,5-trichlorophenol (TCP)**

**Exposure-response analyses using  
new job exposure matrix**

**TCDD exposure determined by review  
of plant process, work histories**

**Exposure defined as exposure to  
2,3,7,8 -TCDD.**

## **Phase 1**

**Exposure-response analyses with new job-exposure matrix, for sub-cohort of 3538 workers (69% of cohort) using quantitative exposure scores (Steenland et al. 1999)**

## **Phase 2**

**Convert exposure scores to estimated serum dioxin levels, conduct exposure-response analyses and risk assessment based on serum levels and estimated daily ingestion of dioxin (Steenland et al. 2001)**

## **Job exposure matrix (JEM)**

**Exposure scores (relative rankings)  
based on multiplying 3 factors:**

- 1) TCDD concentration in process materials**
- 2) fraction of day worked on process**
- 3) qualitative 'contact' level (.01-1.5)**

**JEM:**

**Data on TCDD contamination of manufactured products available for 8 (of 12) plants from 1960s to 1980s**

**Production of TCDD-contaminated products stopped in 1984**

**Earlier data on TCDD contamination also available at largest plant in cohort**

**JEM: Data on process changes over time also available, allowing estimates of changing TCDD contamination over time**

**Contact level based on job category (eg, production workers higher than engineers)**

**JEM: Exposure scores represent relative rankings, not units of external exposure**

**Dermal exposure is inherently difficult to quantify in standard units of external exposure for inhaled substances**

**Phase 2 of study converts exposures scores to ppt TCDD in serum**

# Median cumulative exposure scores by plant (log scale)



**JEM:**

**In exposure level subcohort,  
343 subjects with chloracne : median  
exposure score 11,546**

**3145 subjects without chloracne:  
median exposure score 77**

**Correlation between exposure  
score and duration:  $r=0.60$**

## Total cohort, cancer SMR results

<b>Death category</b>	<b>Deaths</b>	<b>SMR (95% CI)</b>
<b>All cancers</b>	<b>377</b>	<b>1.13 (0.98-1.08)</b>
<b>Stomach</b>	<b>13</b>	<b>1.04 (0.77-1.78)</b>
<b>Pancreas</b>	<b>16</b>	<b>0.96 (0.55-1.16)</b>
<b>Prostate</b>	<b>28</b>	<b>1.17 (0.78-1.69)</b>
<b>Colon</b>	<b>34</b>	<b>1.16 (0.80-1.61)</b>
<b>Larynx</b>	<b>10</b>	<b>2.22 (1.06-4.08)</b>
<b>Lung</b>	<b>125</b>	<b>1.06 (0.88-1.26)</b>
<b>Kidney</b>	<b>13</b>	<b>1.56 (0.82-2.66)</b>
<b>Bladder</b>	<b>16</b>	<b>1.99 (1.13-3.23)</b>
<b>Leukemia</b>	<b>10</b>	<b>0.81 (0.38-1.48)</b>
<b>Non-Hodgkins lymph</b>	<b>12</b>	<b>1.10 (0.56-1.91)</b>
<b>Myeloma</b>	<b>10</b>	<b>2.07 (0.99-3.80)</b>
<b>Soft-tissue sarcoma</b>	<b>4</b>	<b>2.32 (0.63-5.93)</b>

## SMRs for exposure level subcohort (n=3538)

	Cumulative exposure score							Pvalue linear trend
	0-19	19- 139	139- 581	581- 1650	1650- 5740	5740- 20200	20200+	
Cancer	1.14 (34)	1.15 (39)	0.85 (29)	1.10 (36)	1.15 (40)	1.34 (38)	1.60* (40)	.02
Cancer (lag15)	1.20 (34)	0.90 (27)	1.14 (31)	1.18 (30)	1.33 (34)	1.69* (33)	1.54* (34)	.02

## **Conclusions:**

**Excess all cancers, without any particular site-specificity, restricted to those with highest exposure**

**Data for 2 highest septiles (78 cancers):**

**SMR all cancer 1.46 (1.15-1.82)**

**SMR digestive 1.41 (0.85-2.20)**

**SMR respiratory 1.67 (1.16-2.34)**

## **Confounding by smoking?**

- 1) positive exposure-response trend in nonsmoking related cancers**
- 2) smoking data on limited sample suggest only modest differences between exposed and nonexposed (external)**
- 3) internal comparisons less likely to be affected by confounding**

**Confounding by other chemicals?**

**No significant positive trends with length of total employment**

**Would require that high TCDD exposure be well correlated with high exposure to other carcinogens**

**Our data suggest, based on still relatively small numbers, that TCDD may be the first true all-site human carcinogen....**

**Smoking and asbestos cause cancer at many sites but not all.**

## **Phase 2 of dioxin study**

**\*conversion of exposure scores to estimated TCDD serum levels over time**

**\*analysis of exposure-response in terms of cumulative serum levels**

**\*risk assessment in terms of daily TCDD or TEQ intake (pg/kg BW/day), units used for regulation (1 pg/kg/bw/day=10 ppt TCDD in serum at steady state).  $TEQ=10*TCDD$ .**

**conversion of exposure scores to estimated TCDD serum levels over time based on this one plant**

**\*Use 193 workers to determine relation between exposure scores over time and serum levels over time**

**\*Apply this relation to entire-subcohort with exposure scores (n=3538) at eight plants**

**Assume a simple one compartment first order pharmacokinetic model**

**$y_{t_1} = y_{t_0} \exp(-\lambda \Delta t)$ , where  $\lambda$  can be calculated from half life (8.7 years),  $t_1$  and  $t_0$  are any two points in time,  $y$  is the serum level**

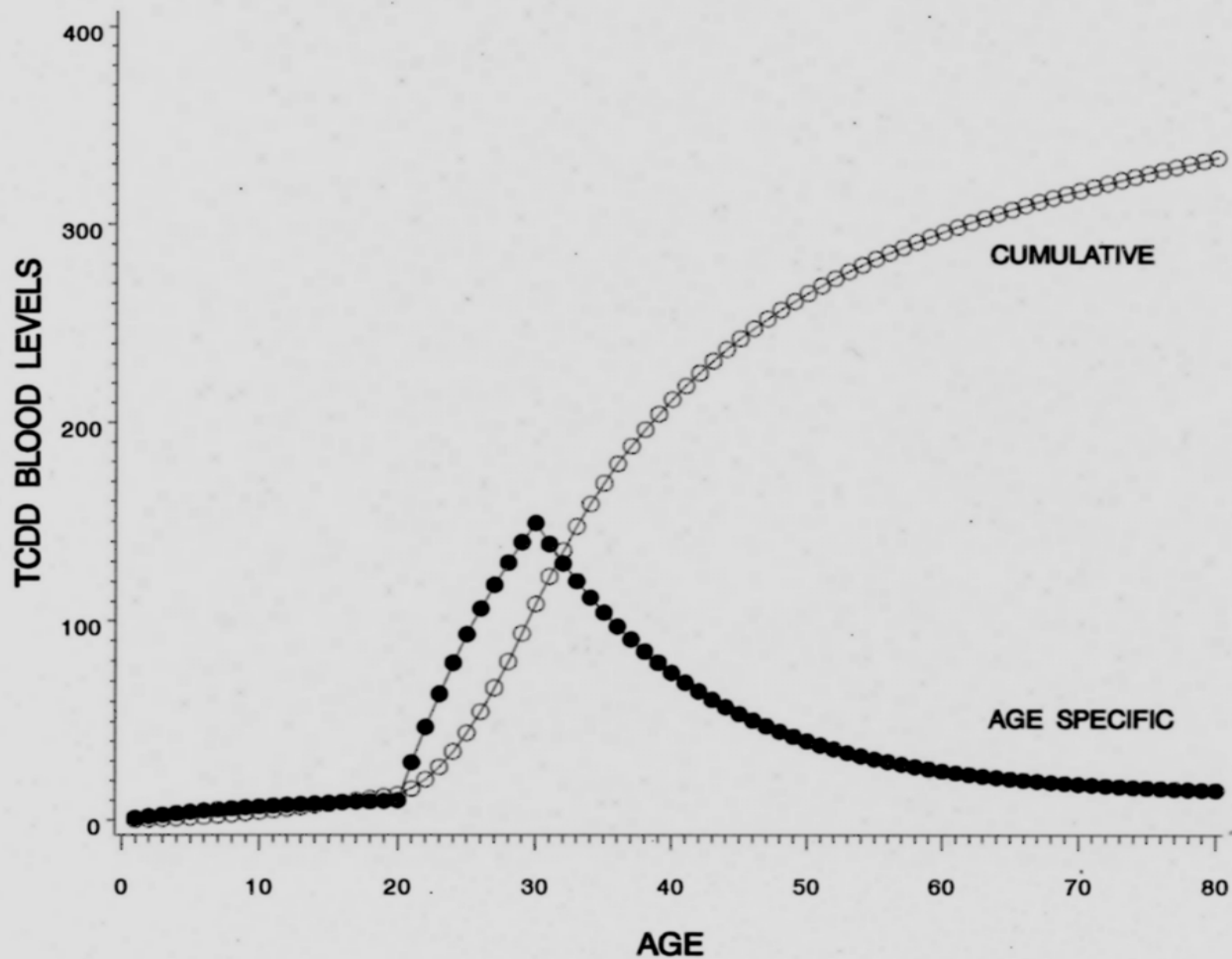
**Serum levels build continually from new exposure and TCDD is continually excreted**

**Derive  $\beta$  via linear regression (no intercept) using the 193 workers with data on serum and exposure score**

**Apply  $\beta$  to all workers in the subcohort with exposure scores**

**Calculate serum level at any point in time and cumulative exposure level - the latter is usually used in studies of occupational carcinogens, sometimes called ‘area under the curve’**

**FIGURE 1**  
**CUMULATIVE AND AGE SPECIFIC TCDD SERUM LEVELS vs AGE**

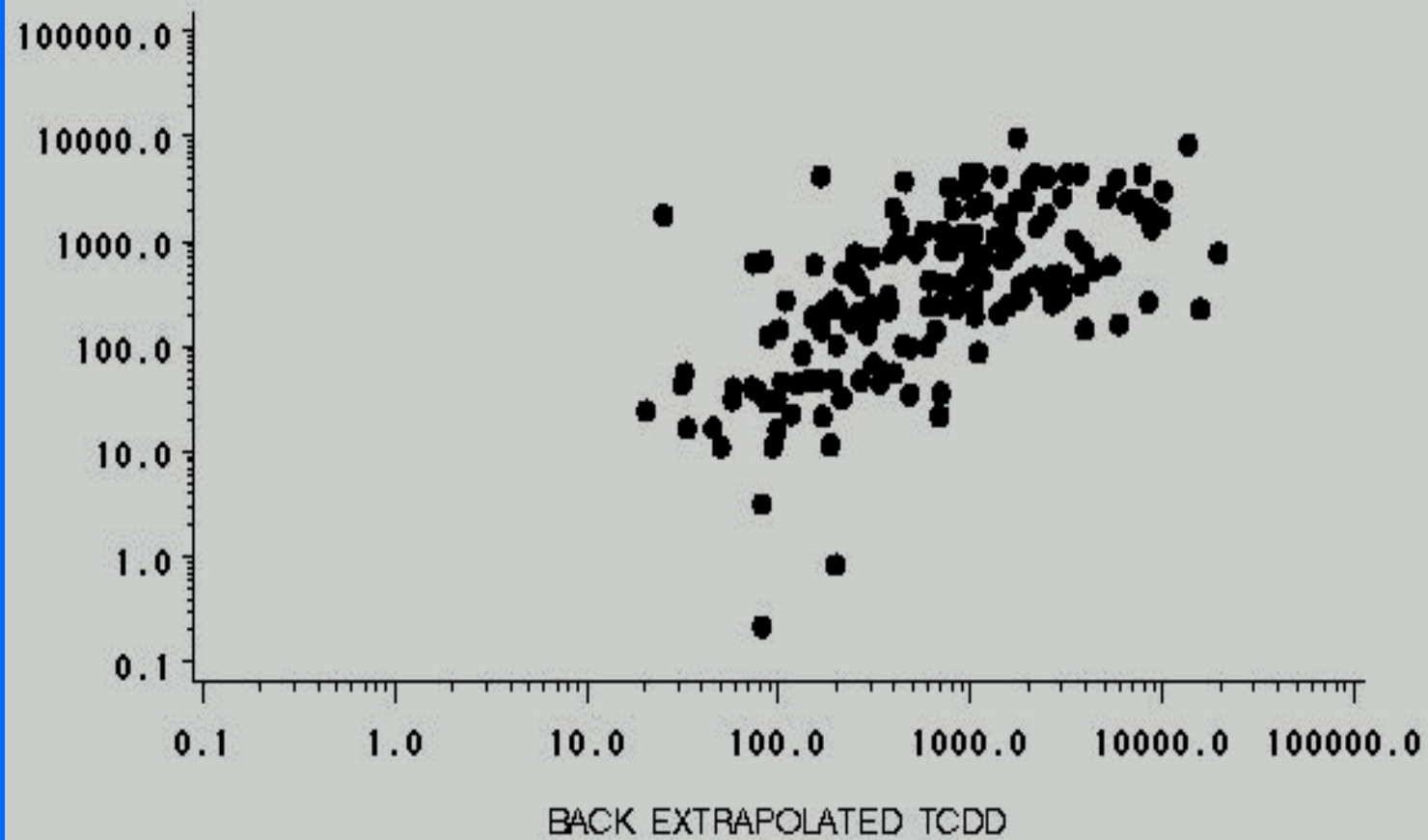


**CUMULATIVE LEVELS HAVE BEEN DIVIDED BY 10**

**The Spearman correlation coefficient between predicted serum level at end of last exposure and observed serum level at that time for 193 workers was 0.65.**

FIGURE 2

PREDICTED SERUM TCDD (ppt) AT END OF EXPOSURE  
VERSUS ESTIMATED BACK EXTRAPOLATED TCDD



CUMULATIVE LEVELS HAVE BEEN DIVIDED BY 10

# Descriptive statistics, 3538 men

Mean years of TCDD exposure (std dev)	2.7 years (4.4)
Median (range) serum TCDD (range) at end of exposure	98 ppt (6-210,054)
Mean (std dev) serum TCDD at end of exposure	1,589 ppt (8208)
5 <sup>th</sup> , 10 <sup>th</sup> , 25th percentile at time of last exposure	18 ppt, 21 ppt, 37 ppt

## Rate ratios by septile of cumulative serum level (15 year lag)

Cumulative serum level	Rate ratio (95% CI)
<335 ppt-years	1.00
335-520 ppt-years	1.26 (0.79-2.00)
520-1,212 ppt-years	1.02 (0.62-1.65)
1,212-2,896 ppt-years	1.43 (0.91-2.25)
2,896-7,7569 ppt-years	1.46 (0.93-2.30)
7,568-20,455 ppt-years	1.82 (1.18-2.82)
>20,455 (ppt-years)	1.62 (1.03-2.56)

**Best fitting model: log cumulative exposure  
15 yr lag (model chi sq 11.3, 4df)**

**Cubic spline model (5 knots) did not improve fit**

**A two piece linear model with no lag fit well  
(model chi sq 12.5, 5 d.f.)**

**Models using a threshold did not fit well.**

**Limitation to approach: model with original exposure scores fit better than model ( $p=0.05$ ) with cumulative serum, although a priori the latter model should fit better (biologically relevant dose).**

**But use of serum levels as exposure provides results needed by risk assessors.**

FIGURE 3  
RATE RATIOS VERSUS CUMULATIVE SERUM LEVELS

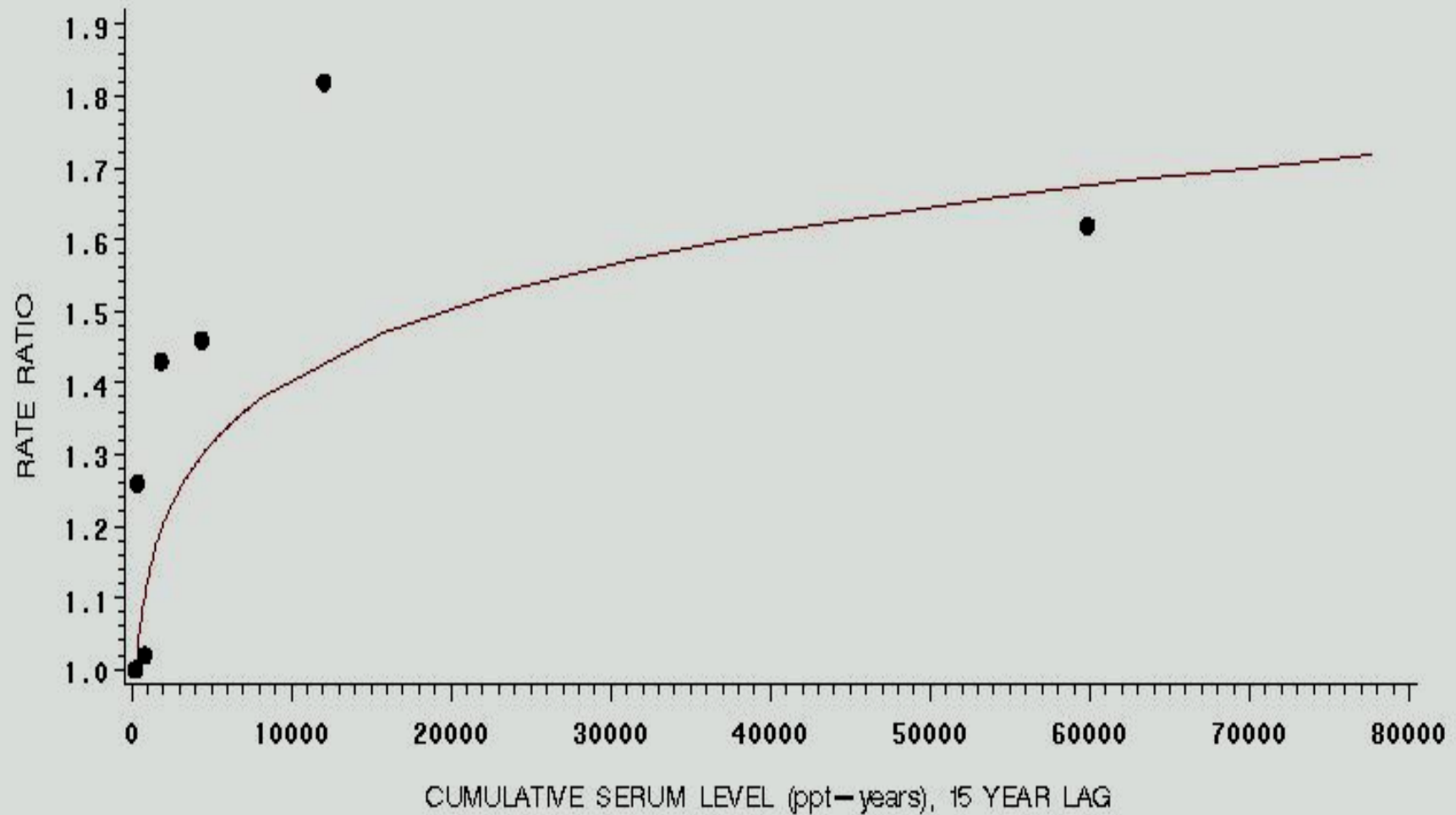
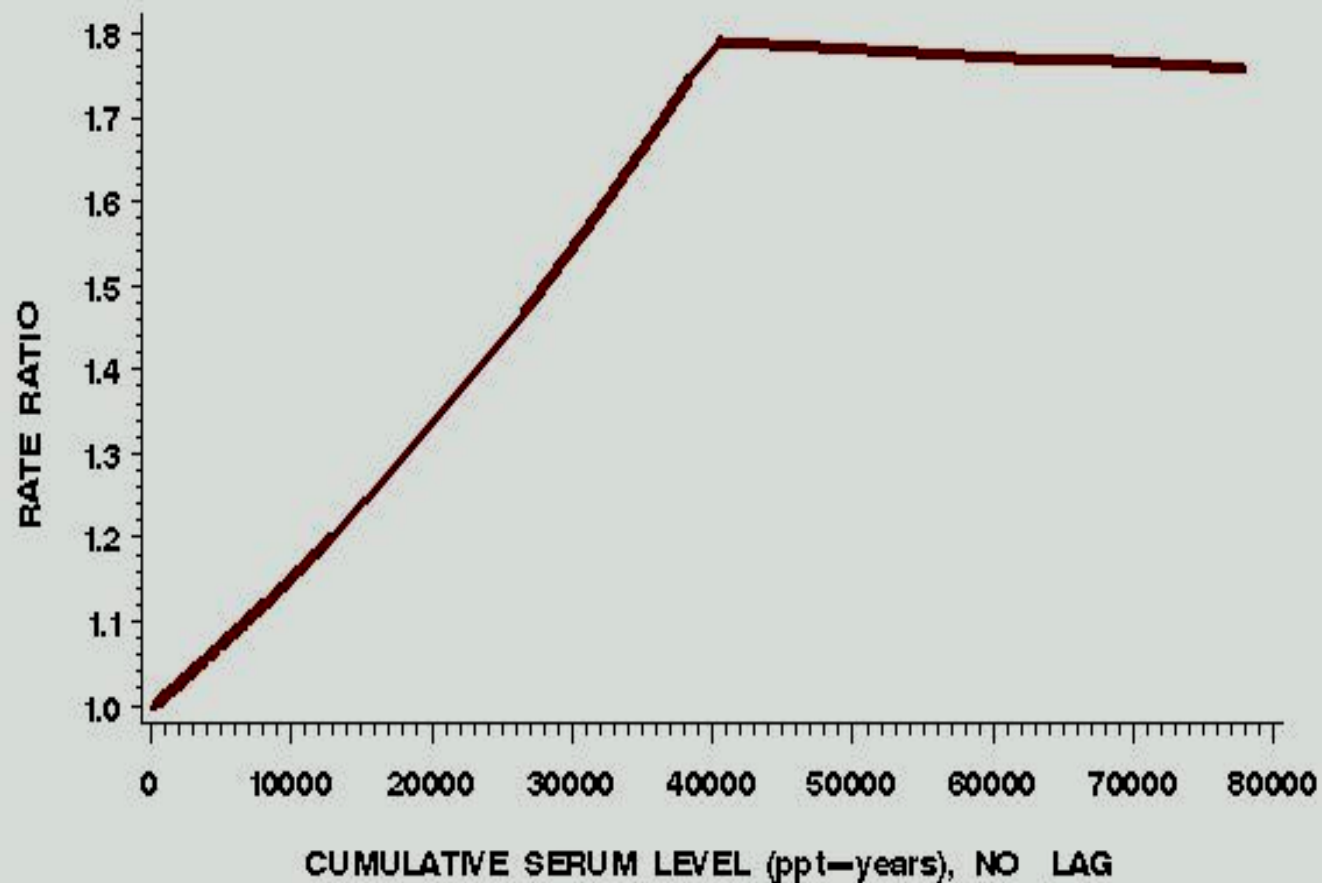


FIGURE 4  
RATE RATIOS VERSUS CUMULATIVE SERUM LEVELS  
PIECEWISE LINEAR



**The relevant exposures for the general population are very low; background of 5 ppt gives cumulative serum level of 300 ppt-years by age 60, doubling background gives 600 ppt-years**

**For purposes of risk assessment for the environment, calculate lifetime risk at twice background, in the very low dose area of the curves. Use standard formula to convert rates to individual risks, by age 75.**

## Lifetime excess risk by age 75

Exposure level, sex	Model	Lifetime excess risk (%) by age 75	Background risk (%)
1 pg TCDD/kg/bw, males	Log cumexp (ppt-years), lag 15y	0.9 (0.3-1.6)	12.4
1 pg TCDD/kg/bw, females	Log cumexp (ppt-years), lag 15y	0.8 (0.3-1.4)	10.8
1 pg TCDD/kg/bw, males	Piece wise linear, no lag	0.05 (0.02-0.08)	12.4
1 pg TCDD/kg/bw, females	Piece wise linear, no lag	0.04 (0.02-0.07)	10.8

\*0.05/kg/bw=steady state 5 ppm in serum=background

## **Conclusions:**

**Our data agree with the EPA, which has since updated (Dec 2003, <http://www.epa.gov/ncea/pdfs/dioxin/nas-review/>) their 1999 work but has essentially reached the same conclusions, based largely on human data from this cohort and 2 German cohorts.**

**Lifetime excess risk in range of 1 in 1000 to 1 in 100, with doubling of background exposure**

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

**This accounts for the order of magnitude difference between the model using  $\log(\text{cumexp})$  (fast increase at low doses) and the two-piece linear model (lower increase at low doses)**

**There is no truly nonexposed group in industrialized societies. Low background levels of dioxin may be increasing cancer rate - no way to know. We can only estimate the effect of an increase (eg., a doubling) over background, not the effect of completely eliminating dioxin from the environment.**

**Note that excess lifetime risk of 1% occurs due a rate ratio of only about 1.07, due to doubling of background exposure.**

**This occurs because ‘all cancers’ is responsible for a high background risk of death (10-12% risk of death from all cancers by age 75). Hence a small rate ratio can still increase absolute risk appreciably**

**Roughly,  $1.07 * 12\% = 12.8\%$ , a 0.8% excess risk**

**This means that almost any epidemiologic data which shows an increasing risk with increasing dose, absent a threshold, can easily result in an appreciable lifetime excess risk, unless the estimated dose-response slope is so low as to be nearly zero.**

**“Appreciable” means on the order of 1 per 1000. EPA considers excess risks for death above 1 per 100,000 to be a trigger for regulation of environmental toxins.**

**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 which may indeed appreciably increase risk. It may be difficult to decrease exposure levels in the general population.**