

No Evidence of Dioxin Cancer Threshold

David Mackie¹, Junfeng Liu¹, Yeong-Shang Loh², Valerie Thomas^{3*}
Princeton University, Princeton, NJ 08544

¹ *Woodrow Wilson School of Public and International Affairs, Princeton University*

² *Department of Physics, Princeton University*

³ *Princeton Environmental Institute, Princeton University, Princeton New Jersey, USA*

* Corresponding Author: Valerie Thomas, Princeton Environmental Institute, Guyot Hall,
Princeton University, Princeton NJ 08544

No Evidence of Dioxin Cancer Threshold

Key Words: Dioxin, TCDD, Cancer, Threshold

Acknowledgements: This work was carried out as part of a graduate course at the Woodrow Wilson School of Public and International Affairs at Princeton University. Thomas is a Member of the EPA Science Advisory Board (SAB) and was a member of the SAB's 2000 Dioxin Reassessment Review Panel.

Abbreviations

E: Exposure

EPA: Environmental Protection Agency

NIOSH: National Institute of Occupational Safety and Health

SAB: US EPA Science Advisory Board

SMR: Standard Mortality Ratio

T: Threshold

TCDD: 2,3,7,8-tetrachlorodibenzo-p-dioxin

Outline of Headers

Title: No Evidence of Dioxin Cancer Threshold

Headers:

Linear Model as a Threshold Indicator

Log-Linear Regression Results

Monte Carlo Analysis

Conclusion

Abstract

The US EPA has developed an estimate of the human cancer risk from dioxin, using the standard low-dose linear extrapolation approach. This estimate has been controversial, because of concern that it may overestimate the cancer risk. An alternative approach has been published, and was presented to the US EPA Science Advisory Board's Dioxin Review Panel in November 2000. That approach suggests that dioxin is a threshold carcinogen and that the threshold is an order of magnitude above the exposure levels of the general population. We have re-examined the threshold analysis, and find that the data have been incorrectly weighted by cohort size. In our re-analysis, without the incorrect weighting, the threshold effect disappears.

Linear Model as a Threshold Indicator

The US EPA's Dioxin Reassessment, released in draft form in 2000, concluded that dioxin should be classified as a known human carcinogen. It also concluded that the upper limit of human cancer risk for the general population is about one in a thousand, based on current background body burdens in the United States of approximately 5 ng TEQ per kilogram of body weight. This risk assessment was based on the standard low-dose linear extrapolation method (US EPA 2000).

During the EPA Science Advisory Board's (SAB) review of the dioxin reassessment, there was a great deal of discussion of the methods used by EPA to calculate low-dose cancer risk, and it was suggested that other approaches to estimating this risk should be considered (US EPA SAB 2001). During the SAB review, only one alternative calculation of dioxin's cancer risk was presented, and it was discussed at some length. That analysis suggested that dioxin is a threshold carcinogen, and that the threshold is an order of magnitude higher than the exposure levels of the general population (Aylward 2000). This contrasts with the conclusions of Steenland et al. (2001) and Becher et al. (1998), who, using more standard statistical approaches, found no evidence of a threshold. Because the threshold model received considerable attention during the EPA Science Advisory Board review, we have undertaken to review the methods and findings of the threshold analysis.

This threshold analysis was based on a number of related publications (Kirman et al. 2000a; Kirman et al. 2000b; Hays et al. 2001) that examined the possibility of a dioxin threshold using a log-linear regression model. This model can be expressed as:

$$SMR = A + B \log E \quad (1)$$

where SMR is the Standard Mortality Ratio and E is exposure. This model can be interpreted as indicating a threshold if the E-intercept of the best-fit line is greater than zero with SMR is 100 (Figure 1). One sees this more clearly by rewriting the equation (1) as

$$SMR = 100 + B (\log E - \log T) \quad (2)$$

The variable T is the threshold level at which any higher level of exposure will give a *SMR* of more than 100. Of course, since equation (1) is simply a linear model, the *SMR* would be less than 100 at exposure levels below the threshold. This line should not be interpreted as a physical dose-response function; its purpose is to serve as an indicator of threshold behavior. If the simple linear model indicated the presence of a threshold, a more detailed analysis, with a less simple model, would be needed to explore the shape of the dose-response function.

Different analyses of the cancer risk from dioxin have been based on different epidemiological studies, using different dose metrics, and different interpretations of the exposures. The US EPA based its analysis of the dioxin cancer risk for humans on three studies, referred to as Hamburg (Flesch-Janys et al. 1998), BASF (Ott and Zober 1996), and NIOSH (Aylward et al. 1996) (US EPA 2000). The US EPA excluded the Seveso study (Bertazzi et al. 1998) and the Ranch Hand study of exposed Vietnam Veterans (Roegerer et al. 1991), arguing that these studies were not sufficiently reliable. In contrast, the dioxin threshold analyses of Aylward, Kirman, Hays et al. include the Ranch Hand and Seveso studies. The analysis by Kirman et al. (2000a) and Hays et al. (2001) included Seveso, NIOSH and Ranch Hand, but excluded BASF and Hamburg. The analysis by Aylward (2000) presented to the US EPA Science Advisory Board included all five studies.

Here we discuss one example of these threshold analyses, following that of Hays et al. (2001), with exposure data expressed as lifetime average serum lipid TCDD concentration, and using the standard mortality data for all cancers combined. These data are shown in Table 1. Analysis for other measures of exposure and other data sets yield results that are quantitatively different, but qualitatively similar to this example. In following this analysis, we are making no judgement about these data or the appropriateness of combining the data into a single analysis. Our approach is to use the same data and the same model as the studies that have concluded that dioxin is a threshold carcinogen, in order to explore the basis of those conclusions.

Log-Linear Regression Results

A key feature of the published threshold analyses is that each point has been weighted by the size of the cohort. This has a significant effect on the results because, as can be seen from Table 1, two of the data points from the Seveso study represent 15,000 people, whereas one of the Ranch Hand data points represents only 19 people. In the population-weighted analysis, the Seveso Zone R female data point was weighted by a factor of 15,000, as was the Seveso Zone R male data point, while the Ranch Hand Nonflying Officer data point was weighted by a factor of only 19. Thus the effect of the population weighting is to drive the best-fit line through the two data points from Seveso Zone R.

There is no justification for weighting the data by cohort size. The statistical power of the larger cohort size is already reflected in the size of the confidence interval for each point.

Figure 1 shows the best-fit point analysis of the data in Table 1. The best fit “threshold” is about 0.5 ng/kg for the unweighted (correct) regression. This is well below the range of background exposures of the general population, which has been reported to be about 3 to 5 ng/kg (Kirman 2000). In contrast, the weighted (incorrect) regression indicates a threshold of about 60 ng/kg, consistent with the results reported by Aylward, Kirman, Hays et al. Note that the weighted regression line passes very close to the two low-dose Seveso data points, as a result of the heavy weighting of those two points.

This point analysis does not provide meaningful measures of the uncertainty in the fit, because the SMR uncertainties are not included in the analysis. However, the scatter and uncertainties in the SRM values are very large, as can be seen from Figure 1. Consequently, the uncertainty in the best-fit threshold value can be expected to be high. This uncertainty will be calculated with Monte Carlo analysis in the next section. Alternatively, an error-weighted chi-square fit can indicate the uncertainties. The best-fit line can be calculated by minimizing the error-weighted chi-square function

$$\chi^2(A, B) = \sum_{i=1}^N \left(\frac{SMR_i - A - B \log E_i}{\sigma_i} \right)^2 \quad (3)$$

where A and B are as defined in equation (1) and σ_i is the uncertainty in the i th SMR value (Press et al. 1987). Because this least-squares fit takes into account the uncertainty associated with each SMR value, it produces a somewhat different best-fit line than the result from a least-squares fit that ignores the uncertainties in SMR. Note also that as the values of σ_i increase, χ^2 decreases. For the unweighted regression (that is, the regression that is not weighted by population), the value of χ^2 defined by equation 3 is 6.3. This is well below the value from χ^2 tables for 12 degrees of freedom and 95% confidence, which is 21, indicating that the log-linear model of equation (1) is statistically consistent with the data set. However, the uncertainty in the threshold value spans several orders of magnitude, ranging from zero to more than 100 ng/kg, and thus could be consistent either with the threshold value calculated with the population-weighted model, or with a zero threshold. Thus, the emphasis should not be on the fact that the best-fit threshold value for the unweighted regression happens to fall below the range of general population exposures, but rather on the very large uncertainty in the estimate of the threshold.

Monte Carlo Analysis

The studies by Aylward, Kirman, Hays et al. use Monte Carlo analysis to calculate the uncertainty. We have undertaken a similar analysis, for both the unweighted and the population-weighted models, and these results are shown in Figure 2. The SMR distributions are chosen so that the confidence intervals match those specified in Table 1. We tried several distributions, including Poisson distributions, and found that the results are largely independent of the details of the SMR distributions.

The figure shows that in the population weighted model, the threshold distribution is above the background exposure, and is approximately one order of magnitude wide, consistent with the results reported by Aylward, Kirman, Hays et al. However, in the unweighted model, the figure shows that the distribution is very broad, covering more than three orders of magnitude, and overlaps the range of the general population background exposure. This broad distribution of potential thresholds is consistent with the high degree of scatter and uncertainty of the epidemiological data.

Conclusion

We agree with Aylward, Kirman, Hays, and their collaborators that the log-linear model of equation (1) is an interesting exploratory approach to analysis of a threshold effect. But while this general approach can be useful, the reported high threshold is incorrect, because of the incorrect weighting of the data.

Without the population weighting, the range of potential thresholds is very wide and completely overlaps the level of general background exposures, and is consistent with a threshold of zero. Thus, this analysis provides no evidence for or against the proposition that dioxin is a threshold carcinogen.

References

Aylward LL, Hays SM, Karch NJ, Paustenbach DJ. 1996. Relative susceptibility of animals and humans to the cancer hazard caused by 2,3,7,8-Tetrachlorodibenzo-p-dioxin using internal measures of dose. *Environ Sci Technol* 30(12):3534-3543.

Aylward LL. 2000. Public Comment to the Dioxin Reassessment Review Committee of the Science Advisory Board (SAB). November 1.

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.

Bertazzi PA, Bernucci I, Brambilla G, Consonni D, Pesatori AC. 1998. The Seveso studies on early and long-term effects of dioxin exposure: A review. *Environ Health Perspect* 106(Suppl 2):625-631.

Fingerhut MA, Halperin WE, Marlow D.A, Piacitelli LA, Honchar PA, Sweeney MH, Greife AL, Dill PA, Steenland K, Suruda AJ, 1991. Cancer mortality in workers exposed to 2,3,7,8-Tetrachlorodibenzo-p-dioxin. *New Engl J Med* 324(4):212-218.

Flesch-Janys D, Steindorf K, Gurn P, Becher H. 1998. Estimation of the cumulated exposure to polychlorinated dibenzo-p-dioxins/furans and standardized mortality ratio analysis of cancer mortality by dose in an occupationally exposed cohort. *Environ Health Perspect* 106(Suppl 2):655-662.

Hays SM, Aylward LL, Finley B, Paustenbach DJ. 2001. Implementing a cancer risk assessment for dioxin using a margin of exposure approach and an internal measure of dose. *Organohal Comp* 53:225-228.

Hays SM, Aylward LL, Mocarelli P, Needham LL, Brambilla P, Gertoux PM, Patterson DG, Czernek J, Paustenbach DJ, Karch NJ. 1997. 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. *Organohal Comp* 34:305-310.

Kirman CR, Aylward LL, Karch NJ, Paustenbach DJ, Finley BL, Hays SM. 2000a. Is dioxin a threshold carcinogen? A quantitative analysis of the epidemiological data using internal dose and Monte Carlo methods. *Organohal Comp* 48:219-222.

Kirman C, Hays S, Aylward LL. 2000b. Carcinogenic Risks at background exposures: analysis of human epidemiologic data. Available: <http://www.isrtp.org/nonmembers/Aylward.htm>. [accessed 4 November 2002]

Ott MG, Zober A. 1996. Morbidity study of extruder personnel with potential exposure to brominated dioxins and furans. 2. Results of clinical laboratory studies. *Occup Environ Med* 53:844-846.

Press WH, Flannery BP, Teukolsky SA, Vetterling WT. 1987. Numerical Recipes: The Art of Scientific Computing. Cambridge, UK:Cambridge University Press.

Roegner RH, Grubbs WD, Lustik MB, Brockman AS, Henderson SC, Williams DE, Wolfe WH, Michalek JE, Miner JC. 1991. Air Force Health Study: An Epidemiologic Investigation of Health Effects in Air Force personnel Following Exposure to Herbicides. Serum Dioxin Analysis of 1987 Examination Results. Washington DC, National Technical Information Service.

Steenland K, Deddens J, Piacitelli L. 2001. Risk assessment for 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) based on an epidemiologic study. *Am J Epidemiol* 154(5):451-458.

US EPA SAB. 2001. Dioxin Reassessment – An SAB Review of the Office of Research and Development’s Reassessment of Dioxin. US EPA Science Advisory Board. EPA-SAB-EC-01-006. Washington DC: U.S. Environmental Protection Agency.

US EPA. 2000. Dioxin Reassessment: Draft Exposure and Human Health Reassessment of 2,3,7,8-Tetrachlorodibenzo-p-Dioxin (TCDD) and Related Compounds. Part II: Health Assessment of 2,3,7,8-Tetrachlorodibenzo-p-Dioxin (TCDD) and Related Compounds. NCEA-I-0835. Washington DC: U.S. Environmental Protection Agency.

Table

Table 1. TCDD Exposure and Standard Mortality Ratio (SMR) Data.

| Sub-cohort | Cohort Size (a) | Exposure (b) (ng/kg) | SMR for Total Cancers (b) (95% C. I.) |
|--------------------|-----------------|-------------------------|--|
| NIOSH | | | |
| <1 yr. exp. | 1,516 | 111 | 102 (75-133) |
| 1 to <5 yr. exp. | 507 | 413 | 165 (119-198) |
| 5 to <15 yr. exp. | 507 | 738 | 138 (97-186) |
| ≥ 15 yr. exp. | 507 | 2218 | 115 (68-175) |
| SEVESO | | | |
| Zone R (female) | 15,000 | 16 | 90 (80 – 100) |
| Zone B (female) | 2,500 | 62 | 90 (70-120) |
| Zone A (female) | 375 | 420 | 120 (60-220) |
| Zone R (male) | 15,000 | 23 | 90 (80-100) |
| Zone B (male) | 2,500 | 51 | 110 (90-130) |
| Zone A (male) | 375 | 485 | 40 (20-100) |
| RANCH HAND | | | |
| Flying Officer | 300 | 6.4 | 87 (44-155) |
| Nonflying Officer | 19 | 5.8 | 173 (9-850) |
| Flying Enlisted | 148 | 9.9 | 102 (47-194) |
| Nonflying Enlisted | 399 | 13 | 83 (44-155) |

(a) Seveso cohort data from Kirman et al. 2000a. NIOSH cohort data from Fingerhut et al. 1991. Ranch Hand Cohort data from Aylward et al. 1996

(b) Exposure expressed as lifetime average serum lipid TCDD levels. Exposure and SMR data from Kirman et al. 2000a and Hays et al. 1997.

Figure Legends

Figure 1. Population-weighted and un-weighted linear-log regressions of SMR for all cancers vs. TCDD exposure. Data from Table 1. The gray shaded area shows the range of general population TCDD exposures.

Figure 2. Distribution of Possible Dioxin Cancer “Thresholds” from Monte Carlo analysis of unweighted and weighted models. The gray shaded area shows the range of general population TCDD exposures.

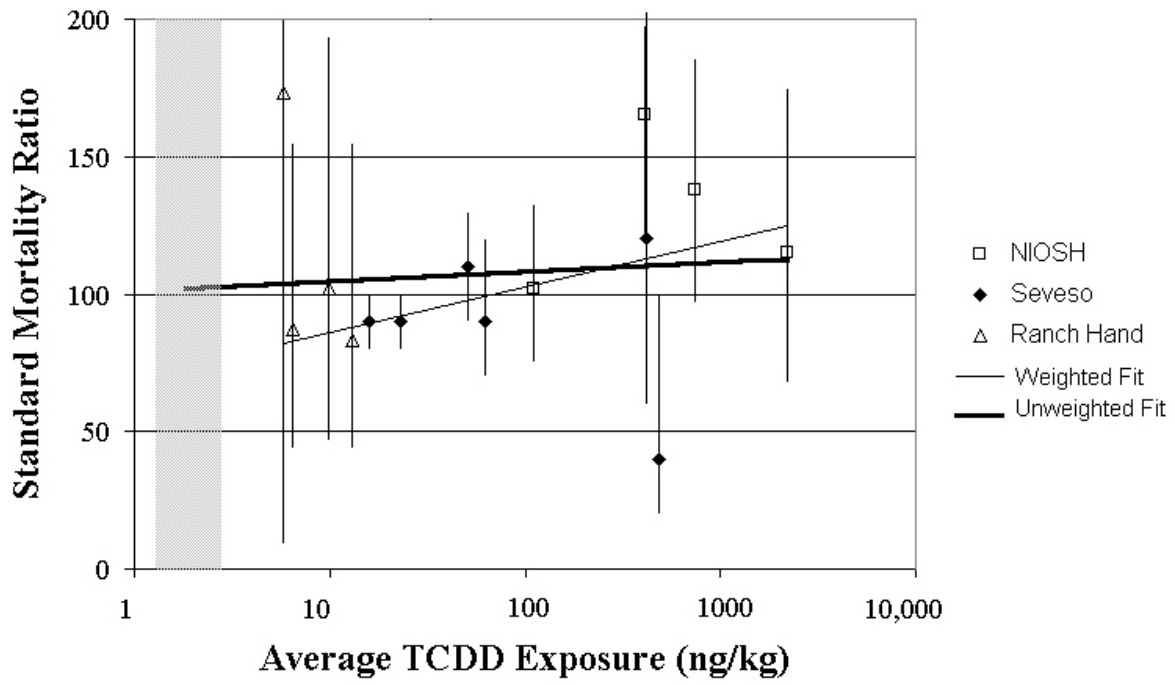


Figure1.

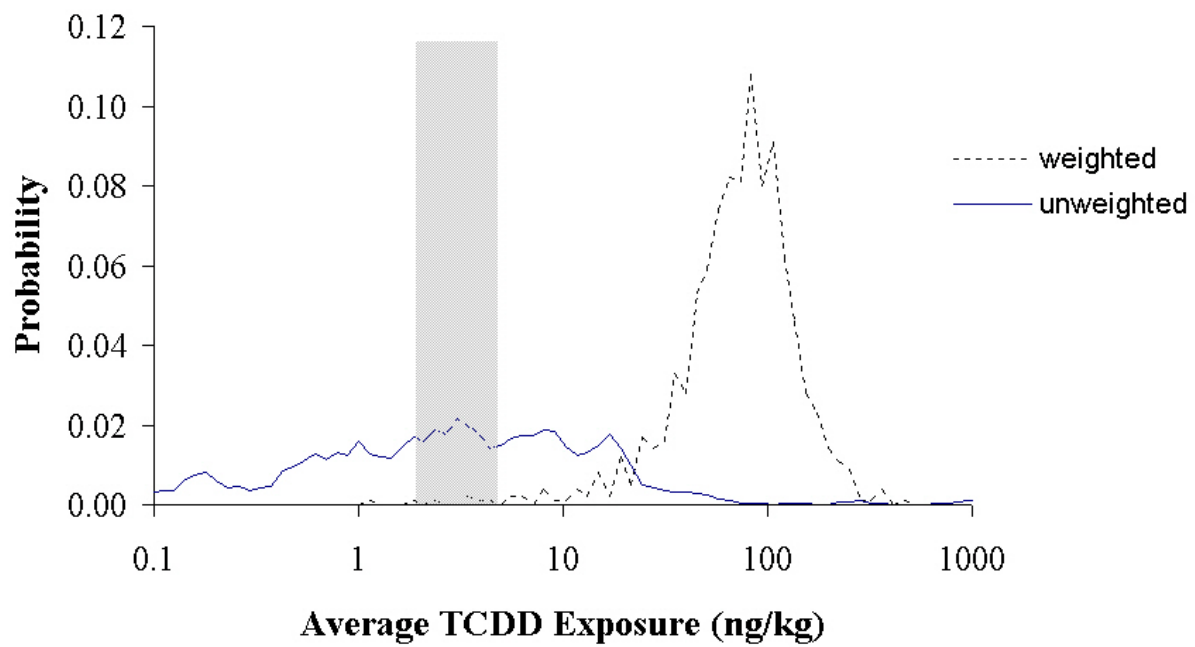


Figure 2.