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Commentary

No Evidence of Dioxin Cancer Threshold

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Abstract

The U.S. Environmental Protection Agency (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 U.S. 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 reexamined the threshold analysis and found that the data have been incorrectly weighted by cohort size. In our reanalysis, without the incorrect weighting, the threshold effect disappears. *Key words:* cancer, dioxin, TCDD, threshold. *Environ Health Perspect* 111:1145-1147 (2003).

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Introduction

The U.S. Environmental Protection Agency (EPA) released its Dioxin Reassessment in draft form in 2000, which concluded that dioxin should be classified as a known human carcinogen (U.S. EPA 2000). It also concluded that the upper limit of human cancer risk for the general population is about 1 in 1,000, based on current background body burdens in the United States of approximately 5 ng toxic equivalents (TEQ) per kilogram body weight. This risk assessment was based on the standard low-dose linear extrapolation method (U.S. EPA 2000).

During the U.S. EPA Science Advisory Board's (SAB) review of the dioxin reassessment, there was a great deal of discussion of the methods used by the U.S. EPA to calculate low-dose cancer risk, and it was suggested that other approaches to estimating this risk should be considered (U.S. EPA 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 LL. Unpublished data). 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 U.S. EPA SAB review, we have undertaken a review of the methods and findings of the threshold analysis.

Linear Model as a Threshold Indicator

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

$$SMR = A + B \log E, \quad [1]$$

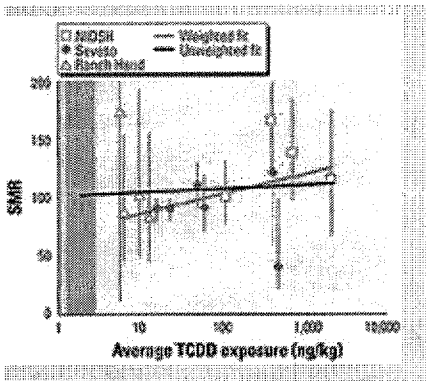


Figure 1. Population-weighted and unweighted linear-log regressions of SMR for all cancers versus TCDD

where SMR is the standard mortality ratio, E is exposure, and A and B are regression parameters. This model can be interpreted as indicating a threshold if the E intercept of the best-fit line is greater than zero with an SMR of 100 (Figure 1). One sees this more clearly by rewriting the Equation 1 as

exposure (data from Table 1). The shaded area shows the range of general population TCDD exposures.

$$SMR = 100 + B\,(\log E - \log T). \quad [2]$$

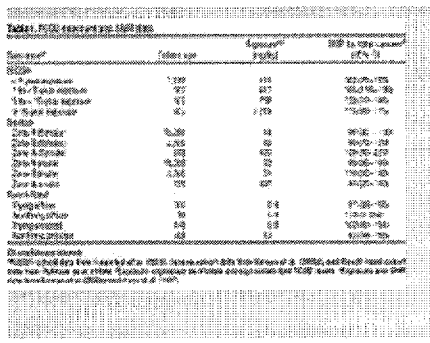
The variable T is the threshold level at which any higher level of exposure will give an SMR of > 100. Of course, because Equation 1 is a simple linear model, the SMR would be < 100 at exposure levels below the threshold. This line should not be interpreted as a physical dose-response function; its purpose 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 more complex 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 epidemiologic studies, using different dose metrics and different interpretations of the exposures. The U.S. EPA based its analysis of the dioxin cancer risk for humans (U.S. EPA 2000) on three studies, referred to as Hamburg (Flesch-Janys et al. 1998), BASF (Ott and Zober 1996), and NIOSH (National Institute of Occupational Safety and Health) (Aylward et al. 1996). The U.S. EPA excluded the Seveso study of a population exposed to dioxin from an industrial accident (Bertazzi et al. 1998) and the Ranch Hand study of exposed Vietnam Veterans (Roegner et al. 1991), arguing that these studies were not sufficiently reliable. In contrast, the dioxin threshold analyses of Aylward (Unpublished data), Kirman et al. (2000a), and Hays et al. (2001) include the Ranch Hand and Seveso studies. The analyses 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 (Unpublished data) presented to the U.S. EPA SAB included all five studies.

In this article we discuss one example of these threshold analyses, following that of Hays et al. (2001)--with exposure data expressed as lifetime average serum lipid 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) concentration--and using the standard mortality data for all cancers combined (Table 1). Analyses for other measures of exposure and other data sets yield results that are quantitatively different but qualitatively similar to this example. In following Hays et al., we are not making judgments 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.

Table 1.

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 shown in 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, whereas 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 3-5 ng/kg (Kirman et al. 2000a). In contrast, the weighted (incorrect) regression indicates a threshold of about 60 ng/kg, consistent with the results reported by Aylward (Unpublished data), Kirman et al. (2000a), and Hays et al. (2001). 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 SMR values are very large, as shown in Figure 1. Consequently, the uncertainty in the best-fit threshold value can be expected to be high. 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

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

where A and B are as defined in Equation 1 and σ_i is the uncertainty in the ith 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 does the result from a least-squares fit that ignores the uncertainties in SMR. Also, as the values of σ_i increase, χ^2 decreases. For the unweighted regression (i.e., 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 > 100 ng/kg, and therefore could be consistent either with the threshold value calculated with the population-weighted model, or with a zero threshold. Therefore, 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 (Unpublished data), Kirman et al. (2000a), and Hays et al. (2001) 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. We chose the SMR distributions 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. Figure 2 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 (Unpublished data), Kirman et al. (2000a), and Hays et al. (2001) However, in the unweighted model, Figure 2 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 epidemiologic data.

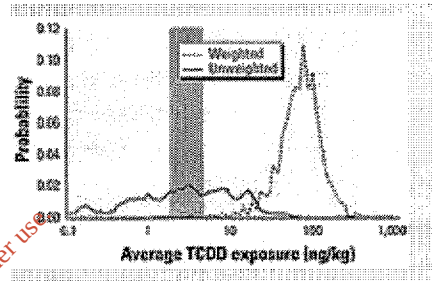


Figure 2. Distribution of possible dioxin cancer "thresholds" from Monte Carlo analysis of unweighted and weighted models. The shaded area shows the range of general population TCDD exposures.

Conclusions

We agree with Aylward (Unpublished data), Kirman et al. (2000a), and Hays et al. (2001) that the log-linear model of Equation 1 is an interesting exploratory approach to analysis of a threshold effect. However, although 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, it completely overlaps the level of general background exposures, and it is consistent with a threshold of zero. Therefore, this analysis provides no evidence for or against the proposition that dioxin is a threshold carcinogen.

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