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.

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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(incorrect) regression indicates a threshold of about 60 ng/kg, consistent with the results reported by Aylward (Unpublished data), Kirman et al.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

\[ \chi^2(A, B) = \sum_{i=1}^{n} \frac{(\text{SMR}_i - A - B \log E_i)^2}{\sigma_i} \quad [3] \]

where \( A \) and \( B \) are as defined in Equation 1 and \( \sigma_i \) 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 does the result from a least-squares fit that ignores the uncertainties in SMR. Also, as the values of \( \sigma_i \) increase, \( \chi^2 \) decreases. For the unweighted regression (i.e., the regression that is not weighted by population), the value of \( \chi^2 \) defined by Equation 3 is 6.3. This is well below the value from \( \chi^2 \) 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.

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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