

## Dioxin Dilemmas

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Few chemicals have engendered as much public/political controversy as the dioxins, particularly 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD). The scientific base for addressing this complex issue continues to feature differences of opinion among responsible scientists as to the quality and interpretation of data on dioxin epidemiology, animal bioassays, and mechanisms of carcinogenesis. Human studies, conducted over the last 20 years, have raised suspicions about dioxin exposure and risk of cancer, but the epidemiologic dilemmas were numerous. Many of these studies have yielded conflicting results, included few cancer cases, failed to assess confounding, or included inappropriate comparison populations or questionable analytic methods. Perhaps most importantly, for most of these investigations, there was no documentation that the groups studied were indeed exposed to high levels of TCDD.

Although this is not necessarily unusual in the assessment of a body of epidemiologic evidence, the sheer volume of studies on this particular issue allows for some selectivity in those chosen for evaluation. A comprehensive review conducted by a working group at the International Agency for Research on Cancer (IARC) in 1997 chose to focus on the four industrial cohorts with well-established, high-level exposures to TCDD (1). An assessment of the entire cohorts, or the most highly exposed subcohorts within them, yielded a remarkably consistent result of about a 40% overall increase in cancer mortality that was highly statistically significant. This result was not driven by a large excess risk at any one site but by lower level excess risks

for several sites. Up to now, three of these cohorts had developed individual dose estimates that allowed for a dose-response analysis for all cancers combined (2-4). Again, the results were consistent, a significant positive trend in relative risk with increasing exposure.

In this issue of the Journal, the cohort study reported by Steenland et al. (5) was the largest of the four cohorts noted above (6). The current updating of this cohort's experience is important for two reasons. First, the number of deaths available for analysis was increased by more than one third. Second, and most importantly, a job-exposure matrix was developed that allows estimation of a semiquantitative exposure score for each worker, permitting a dose-response analysis for this study. The result was a statistically significant increasing trend in relative risk of all cancers combined with increasing exposure level. The relative risks were 1.3 and 1.6 in the two highest levels. A similar, although less consistent, trend of borderline significance was seen for lung cancer. Thus, the four large industrial cohorts with well established, high-level exposures have similar overall findings and evidence of a positive dose-response relationship for mortality from all cancers combined.

As such, the epidemiologic dilemma has shifted from seeking consistency in meaningful studies to seeking meaning in con-

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sistent studies. As pointed out by the IARC reviewers, "strong evidence of increased risks for all cancers combined, along with less strong evidence of increased risks for cancers of particular sites . . . appears to be unique, compared to established human carcinogens" (1). The classic Bradford Hill criteria for interpreting causality of an association include both "strength of association" and "specificity" (7). There have certainly been discoveries of weak (in relative risk terms) causal associations and of nonspecific causal associations. But the combination of the two is difficult to accept. The standard response would be to call for more research to allow more weight of the evidence to accumulate. However, in the current circumstance, this is unlikely. Virtually all of the heavily exposed individuals who are identifiable have been studied, and fortunately, high-level exposures no longer occur.

My belief, based on the current weight of the evidence, is that TCDD should be considered a human carcinogen. This is not based solely on the updated epidemiology but on the sum of all of the available evidence. Specifically, the consistent impact of high-level exposure to TCDD on total cancer mortality, along with animal testing results and mechanistic considerations that would make such an effect plausible, should lead to acceptance of the association, unless or until proven otherwise.

Much subtler dilemmas arise from attempts to include the epidemiologic information along with bioassay and mechanistic results into risk assessments designed to inform the regulatory process about very low level exposures. Toxicologists have challenged the application of a traditional linear no-threshold model in this instance because the mechanism of TCDD carcinogenesis is likely to be receptor mediated (specifically, activation of the aryl hydrocarbon receptor) and because thresholds for a no-effect dose are a central part of receptor-mediated responses (8,9). This is not simply an academic discussion, since the "allowable daily intake" under a threshold model would be 1500 times greater than under a linear no-threshold model (10).

Recently, the patterns of cancer in those exposed to dioxin as a result of the Seveso accident were said to be more consistent with a nonlinear relationship and thus presumably supportive of a threshold effect (9). In the current report, considerable effort is expended attempting to explain away an apparent lack of linearity in the untransformed dose-response data. The "sublinear response" at the highest dose level is ascribed to the extreme skewness in the dose data and to a greater opportunity for misclassification of the level of exposure at the extremes. Presumably, a counter argument could be made that the risk estimates for the upper exposure levels are actually the more reliable ones, and thus the data are consistent with a supralinear response at lower levels. Could this then be used to argue against a threshold?

What should be clear is that for this exposure, the epidemiologic data simply cannot resolve, or even responsibly address,

mechanistic dilemmas relating to very low-dose risk assessments. This is not the radon and lung cancer risk circumstance where there are multiple high-exposure and high-risk data on underground miners to estimate a dose-response curve and multiple, reliable, low-exposure, and low-risk residential data that can be seen to be consistent with the dose extrapolation (11). The relatively low levels of risk even at the highest TCDD levels evaluated, coupled with imprecision in dose estimation and a lack of consensus about which are the relevant exposure metrics (e.g., cumulative dose versus dose rate and latent period), means that absence of evidence of risk cannot be taken as absence of risk nor can subtle inflections in modeled dose-response curves be construed as reflecting underlying mechanistic principles.

Hopefully, the evidence that human tissue levels of TCDD have fallen by more than 75% over the last 25 years (1) indicates that abatement measures will prevent the remaining scientific dilemmas from becoming public health dilemmas.

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