

ACC Review

»» ISSUE: 23

»» NOVEMBER 2005

»» *A distillation of best practice reflecting ACC's current position*

Dioxin – Part 3 Potential Carcinogenic Health Effects

- »» Dioxin is considered to be carcinogenic and thought to promote rather than initiate cancer.
- »» Four large occupational cohort studies found a statistically significant increase in all-cancer risk from high levels of exposure to 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD).
- »» The International Agency for Research on Cancer has classified TCDD as a Group 1 human carcinogen based on an overall increased risk of cancer but found insufficient evidence to reach conclusions about causality for specific cancer sites.
- »» It is currently not possible to accurately predict the lowest levels at which any given individual is likely to adversely respond to dioxin exposure.

Background

This review is Part 3 of a three part series on dioxin. It briefly summarises the epidemiological evidence for a causal association between 2,3,7,8-TCDD (with or without other dioxin exposure) and carcinogenic adverse health effects. As described in Part 2 in this series, studies that have investigated the causal association of dioxin exposure and specific health effects are limited by a range of methodological issues.

Carcinogenic effects

Data obtained from animal studies^{1,2} indicate a dose-related increase between dioxin exposure and the incidence of tumours at multiple sites.

The strongest evidence of an association in humans comes from four large industrial cohort studies in which dioxin exposures (assessed via blood samples) were high and the prolonged length of follow-up provided sufficient latency for cancer to manifest.¹ The average back-extrapolated blood lipid TCDD levels of the highest exposed sub-groups within these cohorts were 3,600 ng/kg (mean),³ 1,000–2,400 ng/kg⁴, 345–3,890 ng/kg⁵ and 1,842 ng/kg⁷ (mean). These levels are 100 to 1,000 times higher than typical background levels of 2–3 ng/kg¹ and similar to the levels found in rodent studies positive for carcinogenicity. The International Agency for Research on Cancer (IARC) in a meta-analysis of these studies has estimated the overall pooled standardised mortality ratio (SMR) for all-cancers combined to be 1.4 (95% CI: 1.2–1.6), indicating a significant risk for all-cancer mortality at high exposures.¹ This finding, together with evidence of a positive exposure-response relationship, supports a causal relationship.^{3,4,6} The consistency across occupational cohorts of a statistically significant increase of all-cancer mortality rates rather than specific cancer types (as observed with other carcinogens), suggests that dioxin is a cancer promoter rather than initiator.^{1,2} This view is also supported by evidence that suggests that dioxin is not directly genotoxic.¹⁰ The variable results among the studies on specific cancer sites or types may reflect underlying (and subsequently TCDD-promoted) differences in the susceptibilities of the various populations studied due to differences in life histories, exposures, and pre-existing initiating events.⁹ It is for reasons such as these, that while IARC has classified TCDD as a Group 1 human carcinogen (based on the overall increased risk of cancer), it has found insufficient evidence to reach conclusions about causality for specific cancer sites.¹

The Institute of Medicine (IOM)² has studied the data on exposure to dioxin and other chemical compounds contained in the herbicides used in Vietnam using a distinction based on “positive association,” not causality. “Sufficient evidence” of a positive association is considered by the expert committee in situations where, for example, several small studies free from bias and confounding show a positive association consistent in magnitude and direction. On this basis, the IOM review concludes that of the health effects studied there is sufficient evidence of a positive association with the herbicides used in Vietnam with non-Hodgkin’s lymphoma, Hodgkin’s disease, soft tissue sarcoma, and chronic lymphocytic leukaemia.²

Levels of exposure⁹

Due to the often insufficiently detailed and at times conflicting information on the relative risks for various adverse effects as a function of exposure levels (eg serum dioxin), it is currently not possible to accurately predict the lowest levels at which any

given individual is likely to adversely respond. Prediction is further complicated by the limited and controversial understanding of dioxin’s underlying mechanisms of action. This casts uncertainty on whether linear extrapolation models can be used accurately.

Below the exposure levels at which a significant increase in cancer was observed in the industrial cohorts, the shape of the exposure-response curve is unclear, even though various models have been developed for extrapolation. There is some evidence, however, to suggest an increased cancer risk at substantially lower levels than those observed in the industrial cohorts. In 1976 in Seveso (Italy),⁸ an industrial accident released TCDD into the surrounding residential areas. Unlike the industrial cohorts that generally included only men, this cohort also included exposed women and children living in the area. Pooled data in the highest and mid-range exposed residential areas (zones A and B respectively) observed an increase (non-significant) in all-cancer mortality in men, but not women, with a SMR of 1.3 (95% CI: 1.0–1.7). The combined back-extrapolated average serum TCDD level for both zones was 136 ng/kg. This level is around one tenth (or less) of those in the industrial cohorts, and more than 10 times higher than typical background levels.⁸ When considering the findings of this study it is worth noting, however, that it is not considered as robust as the large occupational studies,⁸ and no dose-response relationship was demonstrated.

Issues related to ACC

ACC will consider all claims for work-related dioxin exposure under Section 30 of the Injury Prevention, Rehabilitation, and Compensation Act 2001. ACC will consider each situation carefully, using all available relevant medical evidence to decide whether the person claiming has suffered a personal injury and, if so, whether there is a causal link between that personal injury and the exposure to dioxin in the work environment.

References

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