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Dioxin and cancer: a critical review

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Abstract

2,3,7,8-tetrachlordibenzo-*p*-doxin (TCDD) would not have been designated as a Group 1 carcinogen by IARC had there not been a change in the criteria used for inclusion in this

category. Furthermore, there is no precedent for indicating, as did IARC, that a single chemical acts as a pluripotential carcinogen by modestly increasing human risk for all cancer while not increasing the risk for any single cancer at least moderately. IARC moved TCDD to Group 1 based on mechanistic considerations focusing on the *Ah* receptor. However, while occupancy of the *Ah* receptor by TCDD may be necessary for its toxicity, it is not sufficient for toxicity or for potential carcinogenicity. Animal evidence relating TCDD exposure to cancer is much stronger than that for humans. However, the large inter-species variation in the relevant dose–response slopes severely limits generalizations from animals to humans. The epidemiologic studies of occupational exposures, pesticide applicators, and community exposures following industrial accidents, notably Seveso, have generated overall relative risks of all cancer of about 1.0. Only case-control studies of soft-tissue sarcoma and non-Hodgkin's lymphoma, all by the same investigator, reported elevated risk from TCDD exposure. However, these results have not been replicated. The representation that a chemical compound (TCDD) would be a late-stage carcinogen for all types of cancer has no precedent and lacks biological foundation. Virtually all late-stage or promoting carcinogens (e.g., hepatitis-C virus, asbestos, and estrogens) cause a very limited number of forms of cancer. The exposure–response meta-analysis of TCDD and cancer developed by the United States Environmental Protection Agency (USEPA) is seriously compromised by its failure to adequately fit the data. The studies used by the USEPA also likely underestimate TCDD body burdens and may be confounded by smoking and other occupational exposures. Furthermore, the use of a linear dose–response model by the USEPA is scientifically unjustified since the underlying model of TCDD as a human carcinogen is based primarily on its supposed receptor-mediated, non-genotoxic (or promotional) mode of action. There are few examples of an agent being suspected as a human carcinogen for decades and then eventually moving into the category of "known" human carcinogens. In contrast, there are hundreds of compounds that remain for decades on lists of "suspected" human carcinogens despite the lack of confirming evidence. The long-term accumulation of negative, weak, and inconsistent findings suggests that TCDD eventually will be recognized as not carcinogenic for humans.

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Article Outline


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