

Relative Susceptibility of Animals and Humans to the Cancer Hazard Posed by 2,3,7,8-Tetrachlorodibenzo-p-dioxin Using Internal Measures of Dose

LESA L. AYLWARD,*¹ SEAN M. HAYS,[†]
NATHAN J. KARCH,[†] AND
DENNIS J. PAUSTENBACH[‡]

*Karch & Associates, Inc., 1701 K Street, N.W., Suite 1000,
Washington, D.C. 20006, ChemRisk—A Division of McLaren/
Hart, 29225 Chagrin Boulevard, Cleveland, Ohio 44122, and
ChemRisk—A Division of McLaren/Hart, 1135 Atlantic Avenue,
Alameda, California 94501*

An analysis of the cancer dose-response relationship for **2,3,7,8-tetrachlorodibenzo-p-dioxin** (TCDD) in humans and animals was performed based on measured tissue and serum lipid TCDD concentrations and dosimetrics other than administered dose. Basic pharmacologic principles indicate that measures of internal dose such as AUC should be used **to** describe the dose response relationship in cancer risk assessments of TCDD and other highly persistent compounds. The TCDD-related liver tumor response in female rats (**1, 2**) was compared to that in humans (respiratory tract cancer rates in Fingerhut *et al.*; **4**). Three measures of lifetime dose were used: serum lipid TCDD area-under-the-curve (AUC), peak serum lipid concentration (**C_{pr}**), and average serum lipid concentration (**&**). Serum lipid TCDD concentration vs time profiles for the rat were constructed assuming first-order elimination and a half-life of 25 days. Concentration vs time profiles for humans were estimated based on measured serum lipid TCDD concentrations and known dates of first and last exposure, assuming a 7.5-year half-life and first-order elimination. A comparison of rat and human responses indicated that, using all three of these dosimetrics, humans are much **less** sensitive than rats to the carcinogenic effects of TCDD. For example, at the peak concentration measured in rats exposed to 0.1 pg kg⁻¹ day⁻¹ for **2** years, the human cancer response was more than 9-fold lower than that observed in rats. At comparable average lifetime serum lipid TCDD concentrations, the human cancer response was about **4-fold** lower than observed in rats. When AUC was used as the dosimetric, the highest rat dose group (0.1 pg kg⁻¹ day⁻¹) had a 9-fold greater response at approximately **1/10th** the AUC of the most highly exposed human group; that is, the rat dose-response was more than 90-fold steeper than the human dose response. Interestingly, regardless of the dosimetric chosen, the cancer rate in humans in the **NIOSH** cohort, if due to TCDD, is almost completely insensitive to dose, **Our** analysis indicates that human exposure to background levels of TCDD (about **5 ppt** serum lipid concentration) should not pose an incremental cancer risk.