IS DIOXIN A THRESHOLD CARCINOGEN? A QUANTITATIVE ANALYSIS OF THE EPIDEMIOLOGICAL DATA USING INTERNAL DOSE AND MONTE CARLO METHODS

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Introduction

The shape of the dose-response curve for TCDD carcinogenesis in humans continues to be a subject of debate. Historically, cancer risk assessment for TCDD has been based on the results of traditional rodent studies, under the assumption that tumor-response is linear in the low-dose region. However, a non-linear dose-response curve with a threshold for tumorigenesis is equally plausible and is suggested by the mechanistic and genetox data. In our previous work, we assembled serum sampling data collected for three of the best-studied human cohorts exposed to elevated levels of TCDD: the NIOSH cohort, the Ranch Hand cohort, and the Seveso population. We constructed lifetime serum lipid TCDD concentration-versus-time curves for each person on whom serum sampling was performed and used these curves to estimate mean area-under-the-curve, average concentration, and peak concentration values for the various subcohorts. The combined data set includes several thousand participants, and covers a broad range of exposures.

One of the primary limitations to using the human data in a quantitative assessment is the large degree of uncertainty and variability in the dose and response estimates. To minimize this shortcoming, we employed Monte Carlo techniques to address the variability in the dose estimates (peak, average, area under the curve [AUC]) and response estimates (Standard Mortality Ratio [SMRs] for lung cancer and total cancer) in humans. This analysis supports the conclusion that TCDD is a threshold carcinogen.

Methods and Materials

Population Selection. Data sets reporting both measured serum lipid TCDD levels and cancer mortality response for three exposed populations were included in this analysis (Table 1). Details on the cancer response and dose reconstruction for each of these populations were presented previously[1,2,3]:

- *NIOSH Cohort* – The NIOSH cohort includes more than 5,000 workers from 12 plants that produced chemicals contaminated with TCDD[4], including 1,520 workers with more than 20 years latency (as measured from time of first exposure).
- *Seveso Cohort* – Following a chemical accident in Seveso, Italy in 1976, a large residential population was subsequently exposed to TCDD. Sampling data and cancer response have been assembled for Zones A, B, and R (total populations of approximately 750, 5,000, and 30,000 inhabitants, respectively)[5].