THE RELATIVE SUSCEPTIBILITY OF ANIMALS AND HUMANS TO THE CARCINOGENIC HAZARD POSED BY EXPOSURE TO 2,3,7,8-TCDD: AN ANALYSIS USING STANDARD AND INTERNAL MEASURES OF DOSE

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ABSTRACT

An analysis of the carcinogenic dose-response for 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) in humans and animals was performed based on measured tissue and serum concentrations and using alternatives to administered dose as the dosimetric. The TCDD-related carcinogenic response in rats (female rat liver tumors from Kociba et al. [1], using revised pathology from Goodman and Sauer, [2]) was compared to that in humans (lung cancer rates in Fingerhut et al., [3]). Three dosimetries were used: serum lipid TCDD area-under-the-curve (AUC), peak serum lipid concentration \( C_{\text{peak}} \) and average serum lipid concentration \( C_{\text{avg}} \). Rat serum concentration-time profiles were estimated based on measured adipose lipid TCDD concentrations at the end of the Kociba et al. [1] bioassay, assuming first-order elimination and a half-life of 25 days. Human concentration-time profiles were estimated based on measured serum lipid TCDD concentrations and known dates of first and last exposure, with an assumed 7.5 year half-life and first-order elimination. Comparison of rat and human responses indicated that, using all three of these dosimetries, humans are much less sensitive than rats to the carcinogenic effects of TCDD. Regardless of the dosimetric chosen, the cancer mortality in humans in the NIOSH cohort, if due to TCDD, is relatively insensitive to dose as defined in Fingerhut et al., [3]. Our analysis indicates that human exposure to background levels of TCDD (about 5 ppt serum lipid concentration) is not likely to produce an incremental cancer risk. © 1997 Elsevier Science Ltd. All rights reserved

INTRODUCTION/BACKGROUND

Based on data from laboratory animals, carcinogenesis is one of the primary concerns associated with human exposures to TCDD. A number of scientists have suggested that humans appear to be less sensitive than most animals to the acute and chronic toxic effects of TCDD [4,5,6]. Others believe that
humans respond similarly to rodents, and the EPA's recent reassessment concluded that "average humans can be reasonably assumed to be of average sensitivity [compared to animals] for various effects" [7]. To date, the discussion about relative susceptibility has focused primarily on daily dose (µg/kg-day) rather than on internal biological dosimetry like lifetime AUC, lifetime peak or average body burden, peak or average blood concentration, etc. Data on serum lipid TCDD concentration and incidences of cancer from highly exposed human populations now provide the basis for evaluating the relative sensitivity of humans to TCDD-induced carcinogenesis.

The relationship between tissue dose and carcinogenesis depends upon the postulated mode of action [8]. For example, for DNA reactive chemicals the rate of adduct formation, and, indirectly, carcinogenic mutation, probably is a direct function of the concentration of the chemical in the tissue of interest. The likelihood of tumor development is likely to be a function of the total number of these events over time and thus to the AUC of the blood/tissue concentration of the chemical vs. time. Due to the many factors influencing tumor development, this relationship may not be expected to be a simple linear one.

Tissue dose-response relationships can also be postulated for non-DNA reactive chemicals. For example, for a chemical that produces tumors through repeated cell cytotoxicity, a combination of peak concentration of chemical and time of elevated concentration in blood and tissues, or AUC, is likely to be the relevant dosimetric [8]. The appropriateness of AUC for understanding the effects of chemicals which act through a receptor-mediated mechanism and/or have irreversible effects has been noted in many pharmacology texts [9,10,11,12].

The primary mode of action for TCDD-induced carcinogenesis is generally thought to be due to its capacity to promote tumors rather than initiate them [13]. TCDD is believed to act through binding to the Ah receptor; the ligand-receptor complex then interacts with DNA, probably with the involvement of other proteins. The exact mechanism of promotion is a matter of investigation and debate, but current theories using the two-stage cancer model paradigm postulate that TCDD promotes tumors through increased cell replication, perhaps with selective enhancement of replication in preneoplastic tissue and alteration of protein growth regulatory products [8,13,14]. As for other promotional mechanisms, the eventual development of tumors probably depends upon a sustained tissue dose of sufficient level to continually induce expression of these growth factors. Therefore, AUC dosimetry (perhaps incorporating a threshold [15]) should be most appropriate for predicting the likelihood of a carcinogenic response for TCDD.

TCDD is present in the environment and in foods at extremely low levels, and has been present in industrial environments only as a contaminant rather than a product. In general, estimates of human intakes of TCDD from the diet have not been precise, and because dermal and inhalation exposure has not been well characterized in the occupational setting, these exposures have not been quantified. However, because TCDD can now be measured in blood at parts per quintillion (ppq) levels, and because of the long half-life of TCDD in humans, exposures which occurred 40 or more years ago can now be estimated with reasonable accuracy. Since the analytical methods have advanced and our understanding of TCDD
pharmacokinetics in humans or animals is reasonably good, one can reconstruct approximate lifetime internal concentrations of TCDD for a given individual or group of animals knowing the internal TCDD concentration at some point in time and periods of TCDD exposures. Given this ability to predict profiles of lifetime internal TCDD concentrations in humans and animals and the controversy over the sensitivity of animals and humans to the carcinogenic effects of TCDD, we attempted to answer one question: "What is the relative susceptibility of humans and rats to the cancer risk due to TCDD?"

**APPROACH**

**Study Selection**

A comparison of the relative susceptibility of laboratory animals and humans requires studies in both humans and animals that have data on both dose and response. In this paper, the cancer endpoint was the response of interest. Two studies (one each in rats and humans) which have data on both biological dose (in this case, some measurement of blood lipid or adipose tissue TCDD levels) and on cancer response were used in our analysis.

**Rats.** The rat bioassay conducted by Kociba et al. [1] is the most widely used and generally accepted animal study of the cancer hazard posed by TCDD. It provides both administered dose (0.001, 0.01 and 0.1 µg/kg-day) and data on liver and adipose tissue concentrations of TCDD at the end of a two year study period; none of the other animal bioassays provide data on tissue levels (Table 1). In this bioassay, tumor incidences of the liver (female only), lung, hard palate/nasal turbinates, and tongue were elevated, while tumors of the mammary gland, uterus, pituitary, pancreas, and adrenal gland were decreased. The liver tissue pathology has been reevaluated twice, first by Squire [EPA,16] and then by Goodman and Sauer [2]. The liver tumor incidences in female rats, using the most recent tumor classification scheme [2], was used in this dose-response comparison between species (Table 1).

**TABLE 1: TCDD Tissue Concentrations, Liver Tumor Counts and Incidence Ratios from Kociba et al. [1]**

<table>
<thead>
<tr>
<th>Dose (µg/kg/day)</th>
<th>Terminal TCDD Tissue Concentrations (ppt)</th>
<th>Total Liver Tumors</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Adipose</td>
<td>Liver</td>
</tr>
<tr>
<td>0</td>
<td>N.D.</td>
<td>N.D.</td>
</tr>
<tr>
<td>0.001</td>
<td>540</td>
<td>540</td>
</tr>
<tr>
<td>0.01</td>
<td>1,700</td>
<td>5,100</td>
</tr>
<tr>
<td>0.1</td>
<td>8,100</td>
<td>24,000</td>
</tr>
</tbody>
</table>
Humans. The potential cancer response to TCDD in humans has been evaluated in studies of several exposed populations [3,17,18,19,20,21,22,23]. Of these, only a few of the more recent studies contain exposure data in the form of measurements of serum lipid concentration of TCDD for some members of the population. The most complete and useful data are available for the Ranch Hand [23] and National Institutes of Occupational Safety and Health (NIOSH; [3]) cohorts (Table 2). Of these two, the NIOSH cohort is larger, and it has greater epidemiologic power to detect any increased incidence of cancer. To date, no increased cancer mortality has been observed in the Ranch Hand cohort [23]. Exposure levels appear to have been greater for a majority of the NIOSH cohort than for the Ranch Hand cohort. Finally, the NIOSH database contains additional information on the dates of first and last exposure, as well as the date of serum measurement. These data, which were obtained from NIOSH, allow one to construct an estimated concentration-time profile for each of the 253 persons for whom serum TCDD measurements were obtained.

Dosimetrics Reconstruction

Rats. The concentration-time profile for TCDD in the adipose tissue of the rats in the Kociba et al.[1] bioassay was represented as a simple accumulation whose shape is described by the equation:

\[ C(t) = \frac{D}{VK} (1 - e^{-kt}) \]  

(1)

where \( D \) is the dose (ng/day), \( V \) is the volume of distribution in the body (l or kg), and \( k \) is the first-order elimination rate constant (day\(^{-1}\)). The quotient \( D/vK \) is defined as the steady-state concentration. Using a half-life of TCDD in the Sprague-Dawley rat of approximately 25 days [24] and the measured adipose tissue concentration at the end of the study as an approximation of the steady-state serum lipid concentration [25], the concentration-time profile in the Kociba et al.[1] rats can be described using equation (1) and the resulting dose measures can be calculated (Table 3).

Humans. Scheuplein and Bowers [26] constructed approximate concentration-time profiles in persons from the NIOSH cohort using a three-part curve. For our analysis, we use the same three-part concentration vs. time curve (time before, during, and after occupational exposure: see Figure 1). Construction of the complete curve requires an assumption about half-life and five pieces of information: date of birth, measured serum concentration, date of measurement, date of first exposure, and date of last exposure. Fortunately, these data are available from the NIOSH database for each person with a measured serum concentration.

The curve was constructed in a three-step process. First, peak serum lipid TCDD concentration \( C_{\text{peak}} \) achieved on the day of last exposure is back calculated using the measured serum lipid TCDD
### TABLE 2: Human Cancer Studies -- TCDD Exposure and Cancer Response Data

<table>
<thead>
<tr>
<th>Study/Subcohort</th>
<th># in Group</th>
<th># Sampled</th>
<th>Mean TCDD (ppt)</th>
<th>Median TCDD (ppt)</th>
<th>Range TCDD (ppt)</th>
<th>Stat. Sig. Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>NIOSH'/full cohort</td>
<td>5172</td>
<td>253</td>
<td>233</td>
<td>76</td>
<td>2-3400</td>
<td>All cancers combined: SMR=115 (102-130)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Unspecified sites: SMR=162 (104-241)</td>
</tr>
<tr>
<td>NIOSH/ &lt; 1 yr exposure</td>
<td></td>
<td></td>
<td>69</td>
<td>24</td>
<td></td>
<td>No epidemiologic analysis available.</td>
</tr>
<tr>
<td>NIOSH/ &gt; 1 yr exposure</td>
<td></td>
<td></td>
<td>418</td>
<td>231</td>
<td></td>
<td>No epidemiologic analysis available.</td>
</tr>
<tr>
<td>NIOSH/ &lt; 1 yr exposure and &gt; 20 yrs latency</td>
<td>1516</td>
<td>81</td>
<td>78</td>
<td></td>
<td></td>
<td>None</td>
</tr>
<tr>
<td>NIOSH/ &gt; 1 yr exposure and &gt; 20 yrs latency</td>
<td>1520</td>
<td>95</td>
<td>462</td>
<td></td>
<td></td>
<td>All cancers: SMR=146 (121-176)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Resp. system: SMR = 142 (103-192)</td>
</tr>
<tr>
<td>Ranch Hand*/Full cohort</td>
<td>866</td>
<td></td>
<td>12.8</td>
<td>0-617.8</td>
<td></td>
<td>No elevation in malignant neoplasms of all sites or any site.</td>
</tr>
<tr>
<td>Ranch Hand*/Flying Officers</td>
<td>300</td>
<td></td>
<td>7.9</td>
<td>0-42.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ranch Hand*/Non-flying officers</td>
<td>19</td>
<td></td>
<td>6.7</td>
<td>3.1-24.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ranch Hand*/Flying enlisted</td>
<td>148</td>
<td></td>
<td>18.1</td>
<td>0-195.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ranch Hand*/Non-flying enlisted</td>
<td>399</td>
<td></td>
<td>24.0</td>
<td>0-617.8</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1 Fingerhut et al. [3]
2 Wolfe et al. [23]
TABLE 3: Calculated AUC, $C_{av}$ and $C_{peak}$ Serum Lipid TCDD for Rats in the Kociba et al. [1] Bioassay

<table>
<thead>
<tr>
<th>Administered Dose ($\mu$g/kg-day)</th>
<th>Terminal Measured Adipose TCDD (ppt)</th>
<th>Calculated Exposures</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>AUC (ppt-years)</td>
</tr>
<tr>
<td>0</td>
<td>N.D.</td>
<td>N.D.</td>
</tr>
<tr>
<td>0.001</td>
<td>540</td>
<td>1,038</td>
</tr>
<tr>
<td>0.01</td>
<td>1,700</td>
<td>3,268</td>
</tr>
<tr>
<td>0.1</td>
<td>8,100</td>
<td>15,572</td>
</tr>
</tbody>
</table>

concentration, the date of serum measurement (which occurred after the last date of occupational exposure), an assumed 7.5 year half-life and the following equation:

$$C_{peak} = \frac{C_{mean}}{e^{-k\Delta t}}$$  \hspace{1cm} (2)

where $C_{mean}$ is the measured serum lipid TCDD concentration and $\Delta t$ is the time in years between last exposure and time of serum measurement. It is assumed that the peak serum lipid TCDD concentration occurred on the last day of employment. This was assumed to keep from overestimating the TCDD exposures, especially for the longer exposed groups of workers. This is exhibited clearly in Figure 1.

Second, the concentration-time curve over the period of occupational exposure is estimated using equation (1) and assuming a constant infusion rate, so that the peak concentration on day of last exposure corresponds to the peak concentration back-calculated in the first step. Finally, a constant 5 ppt serum lipid level was assumed for the years prior to first industrial exposure.

The half-life for TCDD elimination in humans has been determined in several populations [27,28,29,30]. Mean or median values for biologic half-life in humans from these studies range from 5.2 to 9.7 years (a relatively narrow range). Scheuplein and Bowers [26] used a half-life of 7.0 years for their analysis. An intermediate value of 7.5 years was used for this analysis.
Figure 1: Reconstructed concentration-time profile of the serum lipid TCDD concentration for a highly-exposed person from the NIOSH cohort, assuming a first-order elimination half-life of 7.5 years. The time profile shows that steady-state is not reached even after many years of exposure. For this individual, exposure to the TCDD-contaminated process began at the age of 18 and ceased at the age of 36.5. Serum lipid TCDD concentration was measured at age 55. Serum lipid concentration before industrial exposure was assumed to be 5 ppt. This exposure profile yields an estimated peak serum lipid concentration ($C_{\text{peak}}$) of 8,269 ppt, and average serum lipid concentration ($C_{\text{av}}$) of 2,763 ppt, and an integrated serum lipid area-under-the-curve (AUC) of 171,076 ppt-years. The dotted line exhibits the difference in estimated profile when peak exposure is predicted to occur halfway between the first and last day of exposure.

Once the serum lipid TCDD concentration vs. time curve had been developed for each member of the cohort for which serum lipid TCDD levels were known, the AUC and lifetime average serum lipid concentration ($C_{\text{av}}$), through the end of the follow-up period of the Fingerhut et al. [3] study, was calculated (Figures 2a, 2b, and 2c). In order to avoid over-estimating exposure levels among those with low measured serum levels, persons with measured serum lipid levels below 10 ppt at the time of measurement were not assumed to have experienced any excess occupational exposures during their work years; their serum levels were assumed to have been constant at the measured level throughout their employment period.
Figures 2a-c: Calculated dose measures for the four exposure duration groups (1, 2-5, 5-15, and ≥15 years of exposure) defined by Fingerhut et al., [3] in NIOSH cohort. Serum lipid TCDD concentrations were measured in 253 of the 5172 individuals from the NIOSH cohort [3]. The data from the 253 individuals were grouped into corresponding exposure duration groups and the serum lipid TCDD-time profiles were reconstructed. The area-under-the-curve (AUC, ppt-years; Figure a), average ($C_{avg}$, ppt; Figure b) and peak ($C_{peak}$, ppt; Figure c) serum lipid TCDD concentrations were calculated. The log of the average (■) and range (maximum and minimum) of values for each dose measure are plotted for each exposure duration group. There is an obvious trend between exposure duration and calculated dose measure.
Response Measures

We elected to use an "extra risk" formulation for evaluating and comparing response in the rat and human populations:

\[ ER = \frac{P(d) - P(0)}{1 - P(0)} \times 100 \]  

(3)

where \( P(d) \) and \( P(0) \) are the fraction responding at a given dose, \( d \), and zero dose, respectively. This metric is widely used in risk assessment for evaluation of quantal data and allows comparison of responses when the background rates are different (as in this case, for rat liver tumors and human lung and bronchus cancers) [31].

Humans. In their study of workers, Fingerhut et al. [3] reported standard mortality ratios (SMRs) for individual causes of death. The SMR is the ratio of the observed number of deaths to the expected number of deaths from a given cause based on the age distribution of the population. SMRs were reported for the cohort as a whole, and then for the portion of the cohort that had at least twenty years latency (defined as time since first occupational exposure), and thus, would be more likely to exhibit a cancer response since sufficient time for cancer development would have passed. Fingerhut et al. [3] then divided the 20-year latency cohort into high and low exposure groups (greater than and less than one year exposure, respectively) for epidemiologic analysis (Table 2).

In addition, Fingerhut et al. [3] reported all cancer and lung (trachea, bronchus, and lung) SMRs based on additional divisions of exposure time (less than 1 year, 1 to 5 years, 5 to 15 years, and greater than 15 years) and latency periods (< 10, 10 to < 20 and ≥ 20 years latency). The lung cancer SMRs with the greater than 20 year latency were chosen as representing the best response data for our analyses. Assuming that exposure duration is correlated with total exposure, this breakdown of cancer responses is the most useful for developing a dose-response curve for human cancer (Table 4). For the purposes of our analysis, in order to assign values of AUC, \( C_{\text{peak}} \) and \( C_{\text{avg}} \) to these exposure duration groups, the 253 members of the NIOSH cohort with serum samples were grouped into corresponding exposure duration groups. The concentration-time profiles developed above were used to calculate AUC, \( C_{\text{peak}} \) and \( C_{\text{avg}} \) for each member. These values were then averaged for each exposure duration group (see Figures 2a, 2b, and 2c).

Extra risk for each group was calculated based on an assumption that the observed SMRs will hold for the entire lifetime of the cohort. The background lifetime risk of dying from cancer of the lung and bronchus in the male general population, 7.02%, was used as the background response rate [32]. SMRs were applied to this value to obtain predicted total mortality rates for respiratory tract cancers in each exposure duration group.
TABLE 4: Lung and All Cancer SMRs by Exposure Duration in NIOSH Subcohort With 20 Years Latency

<table>
<thead>
<tr>
<th>Exposure Duration (years)</th>
<th>SMR (20 Year Latency Subcohort)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Lung Cancer</td>
</tr>
<tr>
<td>&lt;1</td>
<td>96</td>
</tr>
<tr>
<td>1 - &lt;5</td>
<td>126</td>
</tr>
<tr>
<td>5 - &lt;15</td>
<td>146</td>
</tr>
<tr>
<td>≥15</td>
<td>156</td>
</tr>
</tbody>
</table>

**Rats:** The extra risk was calculated for each rat group from the Kociba et al., [1] bioassay using equation (3). Ninety-five percent confidence intervals on the rat extra risk values were estimated using a Monte Carlo simulation assuming a binomial distribution on the observed response in each rat dose group (Table 1).

**RESULTS**

The means and ranges of each dosimetric (AUC, C_{avg}, and C_{peak}) for each exposure duration group from Fingerhut et al. [3] are presented in Figures 2a, 2b and 2c, respectively. The values for the different measures of dose for each group showed high inter-individual variation. However, these dosimetrics are clearly related to the exposure duration. If the 253 individuals are representative of the entire cohort, it would be predicted that approximately 5% of the NIOSH cohort would have had peak serum lipid TCDD concentrations in excess of 10,000 ppt.

Figure 3a, 3b and 3c show the rat liver and human lung cancer responses (extra risk) as a function of AUC, C_{avg}, and C_{peak}, respectively. Regardless of which dosimetric is used, the rat cancer response is much more pronounced than that observed in the NIOSH population. For all three measures, the NIOSH workers experienced internal exposures that were comparable to (or higher than) those experienced by the rats. An interesting observation is that, regardless of which of these three internal dose measures are used, these data indicate that the lung cancer response (the most sensitive site in the NIOSH study) in the NIOSH workers is strikingly insensitive to dose.
Figures 3a-c: A comparison of the human and rat cancer dose-response curves. The dosimetrizes used for the comparison are the serum lipid TCDD: a) integrated area-under-the-curve, AUC (ppt-years); b) average concentration, C_{avg} (ppt); and e) peak concentration, C_{peak} (ppt). The human response plotted is the extra risk (■) of developing respiratory tract cancer based on the standard mortality ratios (SMR) observed for the various exposure duration sub-cohorts with 20 years latency in Fingerhut et al. [3]. The rat response plotted is the extra risk (●) observed for the various dose groups from Kociba et al. [1] using the liver tumor incidences determined by Goodman and Sauer [2].
Rats exhibited a greater tumor response at comparable dose levels, regardless of the dosimetric chosen. At comparable peak serum lipid TCDD levels ($C_{peak}$) of approximately 7,000 ppt, the rat response was more than nine-fold greater than the human response. At comparable average concentrations ($C_{avg}$) of about 1,600 ppt, the rat response was more than four-fold greater than the human response. When AUC was used as the dosimetric, the highest rat dose group (0.1 μg/kg-day) exhibited a nine-fold greater response at approximately 1/10th the dose of the most highly-exposed human group. The slope of the rat AUC dose-response curve was more than 90 times greater than the slope of the human AUC dose-response curve.

**DISCUSSION**

These results indicate that the NIOSH population was exposed to a range of tissue doses of TCDD that are comparable to ($C_{avg}$, $C_{peak}$), or, if one assumes that AUC is the proper dosimetric, much higher than those of the rats. The similarity of internal doses to which the humans and rodents were exposed indicates that use of a low-dose extrapolation model such as the linearized multistage model is unnecessary to estimate cancer for the NIOSH human population based on the rats from the Kociba et al. [1] study. Of course, some extrapolation model is necessary to predict risk due to exposures lower than those of the NIOSH cohort.

Our analysis has implications with respect to estimating the risk of human exposure to background concentrations of TCDD. For example, the average AUC in the 1 to 5 year exposure group in the NIOSH cohort (in which the SMR for all cancers and for lung cancers was slightly elevated, but not significantly) was nearly 1,000 times greater than average "background" AUC in the general human population. The workers exposed for less than 1 year, which represent an apparent "no-effect level" group in the NIOSH cohort (lung cancer SMR less than 100), had average AUCs of approximately 17 times background. Similarly, the members of the Ranch Hand cohort, which has a latency period of at least 20 years, and whose exposures were elevated above background, also have exhibited no increase in cancer risk [23]. Our results indicate that there may be little or no excess cancer risk associated with background exposure to TCDD. This is not surprising since several experiments in rodents provide evidence that there may be a true threshold for carcinogenesis from TCDD exposure; this is consistent with current hypotheses that suggest that TCDD acts as a late-stage carcinogen, or promoter [1,33,34,35].

The AUC approach has been considered the dosimetric of choice for nearly 30 years for chemicals which act through a biological mechanism which depends on maintaining a specific blood or tissue concentration for a specific period of time in order to produce a specific response [10,11,12]. It is probably the most appropriate dosimetric for chemicals with a long biologic half-life since daily dose does not capture the fact that a single exposure can produce, at least in the case of TCDD, 40 years of systemic circulation of the chemical. Since the heavily halogenated chemicals like DDT, PCBs, PBBs and chlordane
all share a number of similar properties, e.g., high lipid solubility, poorly metabolized, long half-life, and lack of genotoxicity, it would appear that the AUC dosimetric would be a more appropriate predictor of chronic adverse effects than daily dose.

Like other assessments, this analysis includes some uncertainties and limitations:

**Lifetime scaling issues.** Estimates of AUC for humans will appear much larger than those for animals because, all else being equal, humans live much longer (70 years vs. 2 years for rats). On a mechanistic basis, AUC may still be an appropriate dosimetric for a response such as cancer. Scaling on the basis of cell turnover rate in the tissues of interest (rat liver and human respiratory tract) might improve the comparison; however, we were unable to locate appropriate, comparable cell turnover rates for the two tissues. Instead, we included a calculation in which we scaled for the difference in lifetimes by dividing the estimated AUC values by the time period of exposure (2 years for rats, birth to end of follow-up for humans), resulting in an average concentration. We have presented results in this analysis both on the basis of an unadjusted AUC and on the basis of the average concentration. The results are qualitatively similar, although the degree of difference in sensitivity is not as great when evaluated on the basis of $C_{\text{avg}}$ rather than AUC.

It is important to note that the half-life for TCDD in humans is much longer as a fraction of lifetime than the half-life in rats (7.5 years/70 years vs. 25 days/730 days, or 10.7% vs. 3.4% of lifetime). This indicates that, for a given administered dose, humans experience higher tissue concentrations for a longer period of time, even when adjusted for lifetime. These species differences are accounted for in our analysis through the evaluation of relative sensitivity using both AUC and $C_{\text{avg}}$ as dosimetries.

**Data limitations.** Serum sampling for TCDD was performed on only 253 persons out of a cohort of almost 5,200. These 253 were from two of ten plants involved in the study and did not constitute a random, representative sample. If the exposures of the 253 differed substantially in degree or kind from those of the remaining 4,900 workers, estimates of their concentration-time profiles will not be representative of the whole cohort. Another limitation is inherent in the classification of exposure duration using years exposed by Fingerhut *et al.*, [3] for the calculation of group SMRs. Our calculations indicate that while there is a definite trend in internal dosimetries with exposure duration, there is substantial misclassification as well. This could obscure the true dose-response relationship.

**Assumption that NIOSH cancers are due to TCDD.** The cause or causes of the observed cancer response in the NIOSH cohort are still a matter of debate. The dose-response pattern seen here, in which cancer mortality rates were strikingly insensitive to large differences in total
exposure, suggests that some other factor might be responsible for the excess cancer seen in this cohort. For example, smoking data were gathered for only about 5 percent of the cohort, and the 5 percent was not randomly selected from the cohort. In addition, two cases of mesothelioma were observed, which strongly indicate asbestos exposure. Since respiratory tract cancers (particularly lung) were the only specific cancer site elevated in the study, the possibility of confounding by smoking and asbestos exposure cannot be ignored. Finally, workers in the chemical plants included in the NIOSH study had exposure to numerous other industrial chemicals. None of these other exposures were analyzed or included in a formal way in the Fingerhut et al. analysis, although the authors have presented their views about this and other relevant issues [3]. Thus, the attribution of the observed respiratory tract cancers response to TCDD exposure is a conservative assumption, that is, is not likely to underestimate (but may have overestimated) any actual effect due to TCDD exposure.

Response metric. We compared rat liver tumors observed in a bioassay to human respiratory tract cancers observed in a cross-sectional cohort study. Use of these responses raises several questions. The rat response includes tumors found at a defined time point, terminal sacrifice, while the human SMR includes only those tumors that produced fatalities. However, the mortality rate from lung cancer is very high, and thus, the SMR is a reasonable estimate of the incidence of respiratory tract cancers. Further, the majority of liver tumors in the bioassay were found in rats dying before terminal sacrifice. These two responses were the most sensitive responses observed in the two populations.

The analysis presented here is based on follow-up of 20 years since first exposure. As this cohort is followed over additional years, it is plausible that the degree of elevation in respiratory tract cancers compared to expected levels may increase or decrease, or that other sites may show cancer elevations. Rates of diagnosis of lung cancer in the general population peak around age 60, then decline, so the background rate of lung cancer is likely to fall in this population over time [32].

Hormonal influences. Liver tumors occur in female, but not male rats. Liver tumor development is prevented in female rats by removal of the ovaries [34]. Thus, use of liver tumors in female rats to predict the cancer incidence rates in a largely male human population (workers studied in NIOSH) may not be appropriate. However, the current EPA slope factor is also based largely upon the female rat liver response, and is thus the basis for the current regulatory approach to cancer risk assessment for TCDD.

Sensitive subpopulations. This analysis is limited because the NIOSH cohort consists of male workers exposed during adulthood to TCDD. We cannot evaluate the potential response of
potentially sensitive subpopulations such as persons exposed \textit{in utero} or during childhood. Nor can we evaluate the response of subpopulations that may be sensitive due to genetic factors in this genetically heterogeneous population.

None of the possible limitations in this analysis change the conclusion that humans appear to be less sensitive than rats over a wide range of doses to the cancer hazard posed by TCDD, or that background exposure levels of TCDD are not likely to pose a significant cancer hazard to humans. To develop a more complete understanding of the relative susceptibility of humans to the cancer hazard posed by TCDD compared to rats, including identification of a possible threshold for carcinogenesis, additional representative serum TCDD data for members of the NIOSH cohort are needed. In addition, it would be useful to conduct a similar analysis of the Seveso residents and the Ranch Hand population. These are among the best groups for improving our understanding of the potential human health risks from TCDD at moderate to high doses and to identify an accurate method for estimating any low dose risks.

\section*{LITERATURE}


