

## Risk Assessment for 2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin (TCDD) based on an Epidemiologic Study

Kyle Steenland, James Deddens, and Laurie Piacitelli

The International Agency for Research on Cancer (Lyon, France) recently concluded that 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) is a human carcinogen. There have been few human studies and risk assessments with quantitative exposure data. The authors previously conducted exposure-response analyses based on estimated external TCDD exposure for 3,538 US male chemical workers and found a positive trend for all cancer with increasing cumulative exposure. In the present study, 1988 data from 170 workers with both estimated external exposure and known serum TCDD levels were used to derive the relation between the two. This derived relation was used to estimate serum TCDD levels over time for all 3,538 workers, and new dose-response analyses were conducted by using cumulative serum level. A positive trend ( $p = 0.003$ ) was found between estimated log cumulative TCDD serum level and cancer mortality. For males, the excess lifetime (75 years) risk of dying of cancer given a TCDD intake of 1.0 pg/kg of body weight per day, twice the background intake, was an estimated 0.05–0.9% above a background lifetime risk of cancer death of 12.4%. Data from this cohort are consistent with another epidemiologic risk assessment from Germany and support recent conclusions by the US Environmental Protection Agency. *Am J Epidemiol* 2001;154:451–8.

carcinogens; dioxins; risk assessment

In 1997, the International Agency for Research on Cancer determined that 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) is a human carcinogen (1), and, in 2001, the US government's National Toxicology Program followed suit (Internet address: [www.niehs.nih.gov](http://www.niehs.nih.gov)). TCDD is a multisite carcinogen in animals; it is not directly genotoxic and operates in animals and humans via an aryl hydrocarbon receptor present in many tissues (1). Epidemiologic evidence points to a generalized excess of all cancers, without any pronounced excess at specific sites.

In 1999, we published an exposure-response analysis of 3,538 male workers exposed to TCDD-contaminated products (trichlorophenol or its derivatives) at eight US chemical plants (2). Exposure scores were assigned to each worker for each job held on the basis of a job-exposure matrix, which was in turn based on 1) an estimated level of contact with TCDD, 2) the degree of TCDD contamination of product at each plant over time, and 3) the fraction of a workday during which a worker was likely to be in contact with TCDD-contaminated products (3). The amount of trichlorophenol

(or derivative) produced at a plant was not used, because it is not directly relevant to exposure level once these three factors are taken into account. The exposure scores were in essence a relative ranking of exposure among all workers, permitting calculation of a cumulative exposure score and analyses of exposure-response trends. In those analyses, we found a significant positive trend for all cancers with increasing exposure.

In the present study, we used data for 170 workers whose serum TCDD levels and exposure scores were available to estimate the relation between exposure scores and serum TCDD level for all 3,538 workers in our cohort. We then conducted a dose-response analysis of all cancer mortality by level of cumulative TCDD in the serum. Finally, we used the estimated relation between serum level and TCDD intake to estimate the risk of cancer mortality by level of TCDD intake, in terms of picograms per kilogram of body weight per day. This is the exposure metric conventionally used in public health recommendations for exposure to TCDD.

### MATERIALS AND METHODS

For one of the eight plants at which our cohort worked, serum levels of TCDD (lipid adjusted) were available for 199 workers as of 1988; for the purposes of back-extrapolation to levels at the time of last exposure, we restricted these workers to the 170 whose 1988 levels were greater than 10 ppt, which was taken as the upper range of a background level (valid back-extrapolation, based on assuming a constant elimination after occupational exposure, is not possible once

Received for publication October 24, 2000, and accepted for publication April 20, 2001.

Abbreviations: TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin; TEQ, toxic equivalent.

From the Robert A. Taft Laboratories, National Institute for Occupational Safety and Health, Centers for Disease Control and Prevention, Cincinnati, OH.

Reprint requests to Dr. Kyle Steenland, Robert A. Taft Laboratories, National Institute for Occupational Safety and Health, Centers for Disease Control and Prevention, 4676 Columbia Parkway, Cincinnati, OH 45226-1998 (e-mail: [kns1@cdc.gov](mailto:kns1@cdc.gov)).

levels have returned to background). Using 1) the estimated half-life of TCDD (8.7 years (4)), 2) the known work history of each worker, 3) a simple pharmacokinetic model for the storage and excretion of TCDD, and 4) the exposure scores for each job held by each worker over time, we conducted a regression analysis in which the estimated TCDD level at time of last exposure was modeled as a function of exposure scores for these 170 workers.

Considering the group of 170 workers with both exposure scores and 1988 serum levels (>10 ppt), we estimated the serum level at time of last exposure via the following equation:  $y_{\text{last exposure}} = y_{1988} \exp(\lambda \times \Delta t)$ .

Here,  $y$  is the serum level,  $\lambda$  is the first-order elimination rate constant (based on a half-life of 8.7 years (4)), and  $\Delta t$  is the time (in years) between the end of exposure and 1988. For back-extrapolation, an assumed background level of 6.1 (the median level of 79 nonexposed workers from whom blood was also drawn in 1988 (5); range, 2.0–19.7) was subtracted and then added again after the back-extrapolation was complete.

Following the method of Flesch-Janys et al. (6), we then modeled  $y_{\text{last exposure}}$  (minus the background level of 6.1 ppt) for each worker ( $n = 170$ ) as a function of work history and job-specific exposure scores, as follows:

$$E(y_{\text{last exposure}}) = \beta/\lambda \left[ \sum_{i=1}^n \text{exposure score}_i \times (1)\{1 - \exp(-\lambda(t_1 - t_{0i}))\} \times \exp\{-\lambda(t_{\text{last exposure}} - t_1)\} \right],$$

where  $\beta$  is the coefficient to be estimated (i.e., the dose rate per unit of exposure score),  $i$  indexes different jobs 1 to  $n$ ,  $t_{0i}$  refers to the time that the  $i$ th job began, and  $t_1$  refers to the time that the  $i$ th job ended. The key assumptions here are that 1) the serum levels are a function of the level of external exposure, 2) that function can be reasonably represented by first-order kinetics, and 3) the level of external exposure can be estimated by the exposure scores. The coefficient  $\beta$  was estimated via linear regression using a no-intercept model. We chose this model under the assumption that a zero cumulative exposure score should be associated with no serum levels above background.

We used a simple one-compartment, first-order pharmacokinetic model for its simplicity and because it is widely used in the literature, although more complicated pharmacokinetic models might have been used (7). By way of sensitivity analysis, we also analyzed the data by assuming a 7.1-year half-life, an earlier estimate in the literature (8).

Once we had estimated the coefficient relating serum levels and exposure scores, we used this relation to estimate serum TCDD levels over time due to occupational exposure (minus the background level) for all 3,538 workers in our cohort. We used the same Flesch-Janys et al. pharmacokinetic model (6). Next, we integrated these time-specific serum levels over time to derive for each worker a cumulative serum level, or “area under the curve,” due to occupational exposure. We then added an assumed background level of 5 ppt per year (the background level typically assumed in many industrialized countries, and we also used

6.1 ppt in some analyses; results varied little with small changes in assumed background level).

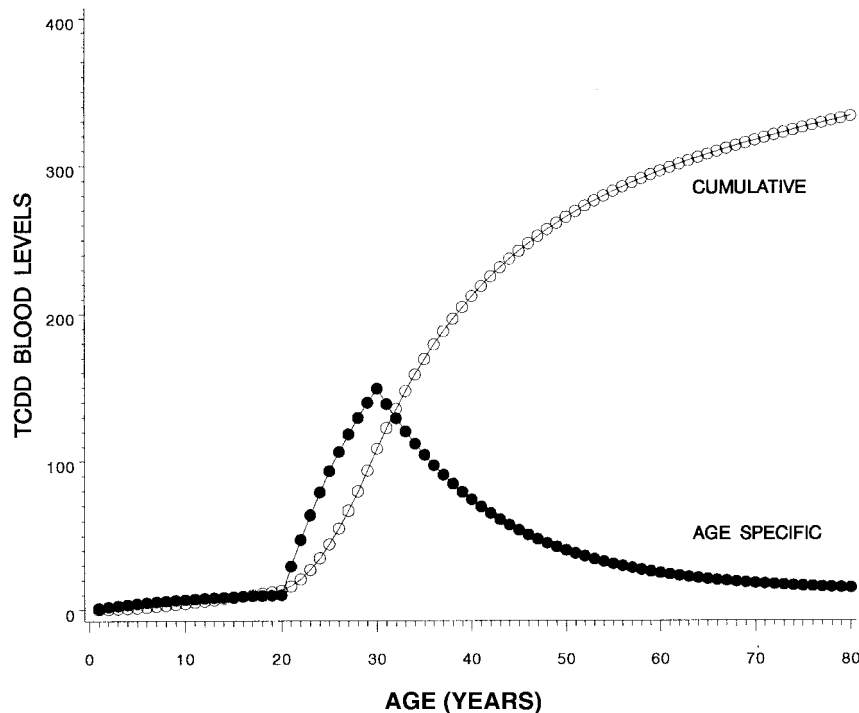
TCDD is built up and simultaneously excreted during exposure, and then serum levels decrease as TCDD is gradually excreted after exposure. Figure 1 illustrates the relation between serum TCDD levels over time and cumulative serum level (the area under the curve). Shown are serum levels (ppt TCDD) for a hypothetical worker exposed to a background-level intake of 1 pg/kg of body weight per day until age 20 years and then occupationally exposed to 20 pg/kg of body weight per day until age 30 years.

Exposure-response analyses were conducted for all cancer mortality (there were 256 cancer deaths), and a background level of 5 ppt TCDD was assumed. Analyses were conducted by using Cox regression (the PHREG procedure in SAS statistical software) in which the time variable was age (9). The model consisted of an exposure variable (time dependent) and categorical variables for date of birth (four categories, fixed). Details can be found in the original publication (2).

We fit models with a variety of exposure metrics, including cumulative serum level and the log of cumulative serum level, with different lags, and average exposure. We also conducted analyses using cumulative serum level and a cubic spline model (10) (five knots; 5, 25, 50, 75, and 95 percent), which provides a relatively unconstrained exposure-response curve. We also fitted several models with cumulative exposure that assumed either no threshold or a piecewise linear model, or a combination of both. The threshold model assumed a flat line (no increasing risk with increasing dose) for low doses; then, at an estimated cutpoint (the threshold), an unconstrained linear dose response began. The piecewise linear model allowed a dose response with two pieces, each linear. The best cutpoints or thresholds for these models were chosen by a process of elimination.

While the focus of our analysis was on TCDD, we also conducted some dose-response analyses by estimated toxic equivalents (TEQs); TEQs enable grouping of all dioxins and furans according to their toxic equivalency factor (1). TCDD was assumed to be the most toxic of all dioxins and furans, with a toxic equivalency factor of 1.0. TCDD represents about 10 percent of all TEQs at environmental levels (11), which means that TCDD is thought to be responsible for about 10 percent of the toxicity of all dioxins and furans. In our data, we assumed that occupational exposure was entirely to TCDD, with no other occupational exposure to dioxins and furans, based on laboratory data indicating that other dioxins and furans did not differ between our own workers and non-exposed controls (5). We assumed that background serum levels were approximately 50 ppt TEQs in our exposure-response analyses, 10 times the background level of 5 ppt TCDD. We then conducted an exposure-response analysis by using TEQs; this was equivalent to adding a background level of 50 ppt rather than 5 ppt in our original analysis.

Exposure-response analyses in which cumulative serum level was used yielded a regression coefficient, permitting estimation of risk per unit of cumulative serum level (of either TCDD or TEQs). To provide risk estimates for TCDD (or TEQs) intake per day, we used standard assumptions



**FIGURE 1.** Cumulative and age-specific 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) serum levels (ppt) vs. age for male chemical workers, United States. Cumulative levels have been divided by 10.

adopted from the World Health Organization (11), that is, that serum concentrations (lipid adjusted) reflect the concentration in all body fat; that body fat represents approximately 30 percent of body weight; and that, under steady-state conditions, each unit of TCDD (or TEQs) intake in terms of picograms per kilogram of body weight per day results in 10 units of picograms per gram of lipid (equivalently, ppt of lipid), or 2 units of nanograms per kilogram of body weight.

Excess lifetime risk through age 75 years was calculated for males and females. Our cohort consisted only of males, and most cancer mortality data for TCDD are based on males only. We calculated excess lifetime risks for women by assuming that males and females have the same relative risks. However, there is some animal evidence of sex-specific effects for TCDD (1), so extrapolation of risk from males to females for all cancers may be questionable; epidemiologic evidence for females is too scarce to provide a guide. Results from two of the best-fitting models were used. Background exposure was assumed to occur from birth. We adjusted for competing causes (12). Excess risk was estimated for a dose of twice background levels, which we assumed to be an intake of 0.5 pg/kg of body weight per day, which, at steady state, leads to a level of about 5 ppt TCDD in the blood lipids. For risk estimation of TEQs, we assumed a background intake of 10 pg/kg per day, leading to about 50 ppt TEQs in the blood lipids. Background all-cancer and all-cause mortality rates were taken from US vital statistics data for the years 1995–1997 (13).

## RESULTS

Table 1 gives some descriptive statistics for the cohort. Although most workers were exposed to TCDD for only a few years (mean, 2.7), 10 percent were exposed for more than 8 years. This cohort was heavily exposed, as evidenced by their high serum levels at the end of exposure. Estimated serum levels for the entire cohort were in line with the serum levels for the 170 subjects for whom we had actual serum data. The plant in which these 170 subjects worked (plant 1) was in the middle of the distribution of exposure by plant (2).

Figure 2 shows the observed and predicted serum levels of TCDD based on the linear regression of measured serum levels on estimated exposure scores. The Spearman correlation coefficient between the observed back-extrapolated serum level at the time of last exposure and the predicted serum level was 0.65 for these 170 workers ( $p = 0.0001$ ). Application of the regression coefficient relating serum level to exposure score to the entire cohort led to estimated serum levels for each worker over time. For the entire cohort, the Spearman correlation coefficient between cumulative exposure score at the end of exposure and the estimated serum level at the end of exposure was 0.90.

In exposure-response analyses in which cumulative serum level was used as a predictor of all cancer mortality in Cox regression analyses, the best-fitting model used the log of cumulative serum level (the area under the curve) lagged 15 years. The coefficient for this model was 0.097 (standard error, 0.032;  $p = 0.003$ ; model chi-square statistic = 11.3, 4

**TABLE 1. Descriptive statistics for the cohort of male chemical workers exposed to TCDD,\* United States**

Statistic	Value
No. in cohort	3,538†
No. of deaths	923
No. of cancer deaths	256
Mean duration of exposure (years) (SD*)	2.7 (4.4)
Estimated cumulative exposure score	
Median (range)	125 (0.002–1,558,400)
Mean (SD)	10,019 (60,311)
Estimated serum level (ppt) at end of follow-up	
Median (range)	9 (5–52,681)
Mean (SD)‡	343 (2,223)
Estimated serum level (ppt) at end of exposure	
Median (range)§	98 (6–210,054)
Mean (SD)§	1,589 (8,208)

\* TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin; SD, standard deviation.

† Estimated serum levels were based on 3,444 workers included in risk sets in exposure-response analyses; 94 workers were not included in any risk set in the exposure-response analyses because their follow-up ended at an age before the age at which the first cancer case died. All serum levels given in this table include a background level of 6.1 ppt of TCDD.

‡ The mean year that follow-up ended was 1989, 24 years after exposure ended.

§ The mean year of last exposure was 1965.

df). The model with a 15-year lag for the log of cumulative exposure fit better than the analogous model with no lag (model chi-square statistic = 7.5, 4 df). We also analyzed the data by assuming a half-life of 7.1 years (an earlier estimate in the literature (8)). The resulting exposure-response coefficient for log cumulative serum TCDD level (lagged 15 years) did not change much (it was 4 percent lower).

The cubic spline model, which does not impose a particular form on the dose response, did not provide a better fit than the model in which the log of cumulative serum lagged 15 years (difference in  $-2 \log$  likelihoods, chi-square statistic = 0.9, 3 df;  $p = 0.83$ ) was used, indicating that the model with the log of cumulative serum was a reasonably good one. We also conducted categorical analyses by septile of cumulative serum level. The rate ratios from this analysis are shown in table 2. Figure 3 shows the dose response for the model that used the log of cumulative serum level (lagged 15 years), along with the categorical data analysis.

While the log of cumulative serum (lagged 15 years) provided a reasonable fit to the data, this exposure metric did not fit quite as well as the log of the cumulative exposure score (lagged 15 years), which we used in previous analyses (2). The improvement in log likelihood between the model that used log cumulative serum and the model in which log cumulative exposure score was used was 3.99. A priori the

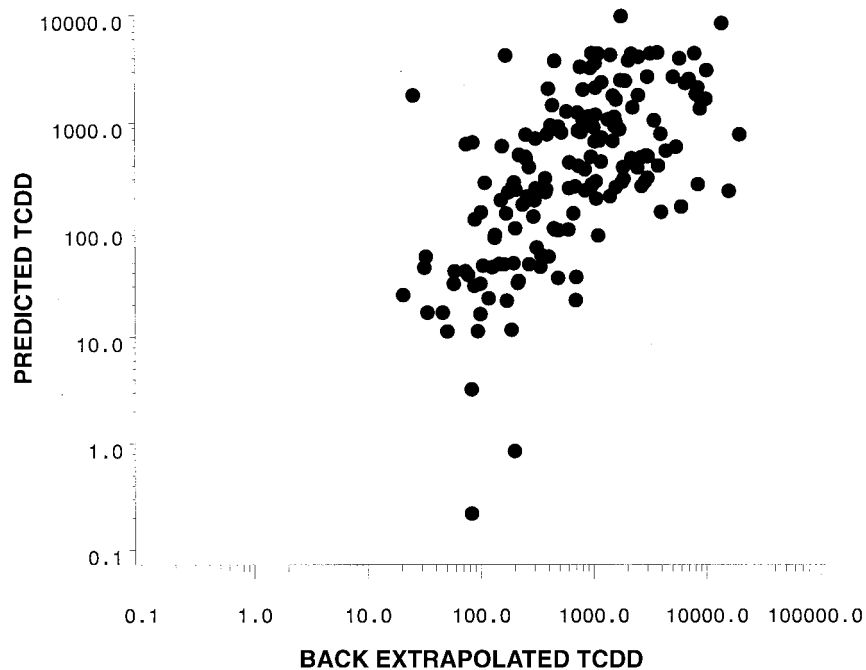
current approach based on serum level, a presumably relevant biologic dose, would be expected to perform better in predicting cancer than our prior approach based on external exposure scores. It is possible that inaccuracies introduced in estimating external exposure score led to a worse fit. However, both metrics provided a good fit to the data, and use of internal dose has the advantage that it permits risks to be assessed in terms of units that can be used for regulation of permissible exposure.

Exposure-response analyses also were conducted for estimated TEQs; we used the log of cumulative TEQs with a 15-year lag and assumed a background steady-state level of 50 ppt. These analyses again resulted in a significant positive trend. The fit was not quite as good as the model in which TCDD was used (exposure-response coefficient = 0.134; standard error, 0.051;  $p = 0.008$ ; model chi-square statistic = 9.2, 4 df).

A piecewise linear model with a single cutpoint at 40,000 TCDD ppt-years fit nearly as well as the model in which the log of cumulative serum level was used (model chi-square statistics = 12.5, 5 df and 11.3, 4 df, respectively). The piecewise linear model showed an increasing slope up to 40,000 serum TCDD ppt-years, after which there was a virtually flat linear dose response (reflecting the tailing off of the dose response at the highest doses (table 2)). About 10 percent of the cohort had cumulative serum TCDD levels of more than 40,000 ppt-years. Adding a component for a threshold model did not improve the fit of the no-lag piecewise linear model (model likelihood = 12.4, 6 df).

We explored whether the observed positive dose response was consistent between the eight plants under study. An interaction model with separate interaction terms for seven plants increased the model likelihood over the model that used log cumulative serum to a degree approaching conventional statistical significance (chi-square statistic = 13.6, 7 df;  $p = 0.06$ ), indicating some, but not extreme, heterogeneity between plants. The coefficients (standard errors) for log cumulative serum across the eight plants were 0.03 (0.12), 0.08 (0.04), 0.09 (0.06), 0.09 (0.04), 0.10 (0.04), 0.11 (0.06), 0.14 (0.04), and 0.21 (0.07).

Regarding the tendency of the dose-response curve to tail off at very high doses, which we observed in both categorical and continuous analyses, we have argued previously (2) that exposures may have been poorly estimated for those workers exposed to the very highest levels of TCDD. A number of these workers had very short, high exposures during cleanup of a spill. This mismeasurement may be one reason for the tailing off of the dose-response curve at very high doses. Other possibilities include a saturation effect, in which very high exposures do not have any increased effect on outcome, or a depletion of a hypothetical susceptible population as relative risks increase, especially for a disease (all cancers) with a high background rate. Such tailing off of the curve at very high exposures has been seen in other exposure-response curves for occupational carcinogens, including cadmium (14), radon (15), diesel (16), and arsenic (17). (Lubin et al. (18) have argued that measurement error may account for this phenomenon in the arsenic data.)



**FIGURE 2.** Predicted serum level of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) (ppt) in male chemical workers at the end of exposure vs. the estimated back-extrapolated TCDD level, United States.

**TABLE 2.** Rate ratios, by septile of cumulative serum level (lagged 15 years),\* from the categorical analyses of male chemical workers exposed to TCDD,† United States

Cumulative serum level (ppt-years)	Rate ratio	95% confidence interval
<335	1.00	
335–<520	1.26	0.79, 2.00
520–<1,212	1.02	0.62, 1.65
1,212–<2,896	1.43	0.91, 2.25
2,896–<7,568	1.46	0.93, 2.30
7,568–<20,455	1.82	1.18, 2.82
>20,455	1.62	1.03, 2.56

\* Septiles were chosen on the basis of the occupational cumulative serum levels (lagged 15 years) of all decedents for whom values were greater than 0 (some decedents had 0 values because they were lagged out). Lagged-out subjects were included in the lowest category. All subjects had a background level of 6.1 ppt per year added to their occupational exposure, up to 15 years before the end of follow-up (15-year lag). Numbers of cancer deaths by septile were 64 (includes lagged out), 29, 22, 30, 31, 32, and 48, respectively.

† TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin.

Lifetime risk was estimated by assuming a constant intake of 1 pg/kg per day of TCDD, above a background of 0.5 pg/kg per day (or 10 pg/kg per day of TEQs, above a background of 5 pg/kg per day of TEQs). This intake would

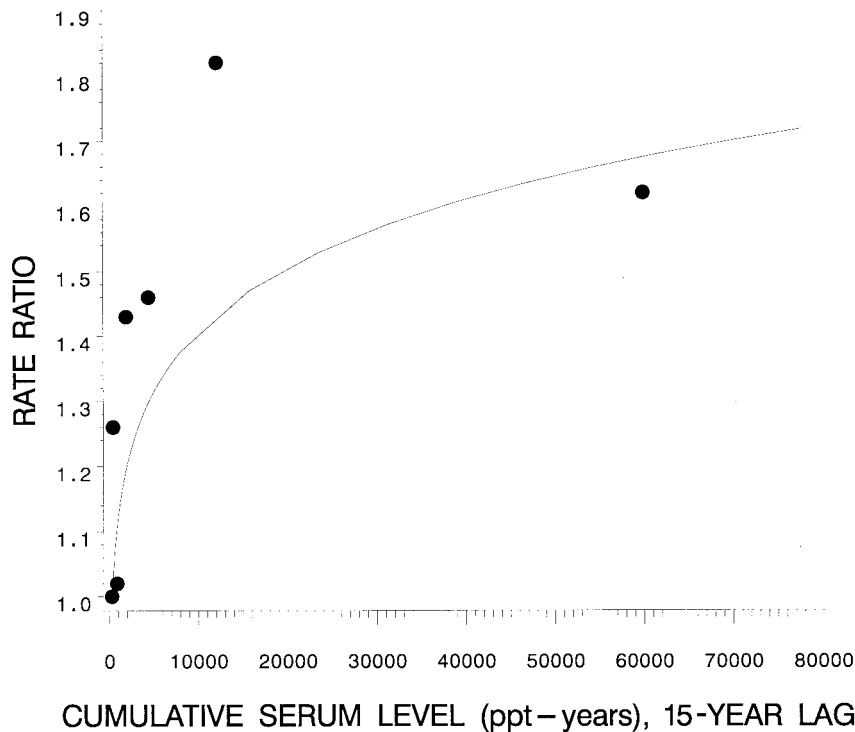
lead, under steady-state conditions, to a blood lipid level of 10 ppt TCDD (or 100 ppt TEQs). Japan and Canada recommend tolerable daily intake levels of 10 pg/kg per day of TEQs, approximately equivalent to an intake of 1 pg/kg per day of TCDD (1). The World Health Organization lowered its recommended daily intake of dioxins/furans to 1–4 TEQs in 1998 (19), equivalent to about 0.1–0.4 pg/kg per day of TCDD.

Results for estimates of lifetime excess risk are shown in table 3. When we used the model based on the log of cumulative serum level lagged 15 years, lifetime excess risk (as of age 75 years) for all cancers was 9 per 1,000 for males and 8 per 1,000 for females for a TCDD exposure of 1.0 pg/kg per day, above a background risk of cancer death of 11–12 percent at an assumed background intake of 0.5 pg/kg per day. The piecewise linear model gave a lower lifetime risk: 0.5 per 1,000 for males and females. These results illustrate the sensitivity of excess risk estimates in the low dose range to the model chosen.

Table 3 also shows the lifetime excess risks for an exposure of 10 pg/kg per day of TEQs, representing a doubling over background levels.

## DISCUSSION

We found an increasing cancer risk with increasing level of cumulative TCDD in the serum, paralleling our earlier findings (2) of a positive dose-response relation between cancer and cumulative (external) exposure score. This finding is not surprising given the correlation between estimated



**FIGURE 3.** Rate ratios vs. cumulative serum levels of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin for male chemical workers, United States.

serum level and external exposure score. The importance of the result is that it enables risk assessment for environmental exposures in units useful to public health authorities: TCDD intake per day.

As we argued in our earlier paper (2), the positive dose response is not likely to be due to other hypothetical occupational exposures or lifestyle factors. Other occupational exposures were not consistent between the eight plants we

**TABLE 3.** Estimates of lifetime (through age 75 years) excess risk of dying of any cancer due to exposure to TCDD\* or to TEQs\* at twice background levels, United States

Exposure level (pg/kg of body weight/day), sex	Model†	Lifetime excess risk above background	95% confidence interval	Background risk‡	Model chi-square statistic
1.0 TCDD, males	Log cumulative serum (ppt-years), 15-year lag	0.0094	0.0032, 0.0157	0.124	11.3, 4 df
1.0 TCDD, females	Log cumulative serum (ppt-years), 15-year lag	0.0080	0.0027, 0.0135	0.108	11.3, 4 df
10.0 TEQs, males	Log cumulative serum (ppt-years), 15-year lag	0.0018	0.0005, 0.0031	0.124	9.2, 4 df
10.0 TEQs, females	Log cumulative serum (ppt-years), 15-year lag	0.0015	0.0004, 0.0026	0.108	9.2, 4 df
1.0 TCDD, males	Piecewise linear, no lag	0.0005	0.0002, 0.0008	0.124	12.5, 5 df
1.0 TCDD, females	Piecewise linear, no lag	0.0004	0.0002, 0.0007	0.108	12.5, 5 df
10.0 TEQs, males	Piecewise linear, no lag	0.0005	0.0003, 0.0011	0.124	12.4, 5 df
10.0 TEQs, females	Piecewise linear, no lag	0.0005	0.0002, 0.0010	0.108	12.4, 5 df

\* TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin; TEQs, toxic equivalents.

† Based on a Cox regression exposure-response model in which the exposure is either the 1) log of the cumulative serum level (in ppt-years of TCDD or TEQs) with a 15-year lag or 2) cumulative serum level with no lag and the model is piecewise regression, in which two separate linear slopes are estimated. Excess risk is defined as risk above background risk. Background exposure is assumed to be either 0.5 pg/kg per day of TCDD, leading to a constant serum level of 5 ppt TCDD, or 5.0 pg/kg per day of TEQs, leading to a constant serum level of 50 ppt TEQs. TEQs are toxic equivalencies that represent the combined toxicity of all dioxins and furans based on toxic equivalency factors; TCDD is the most toxic dioxin/furan and has a toxic equivalency factor of 1.0. TCDD is presumed to represent 10% of all TEQs.

‡ Background risk of cancer death by age 75 years.

studied and would not be expected to be correlated with cumulative exposure to TCDD across all plants. Besides dioxin, only one known occupational carcinogen has been identified in this cohort, present at a single plant and affecting a single, relatively rare cancer (bladder). Excluding bladder cancer from all cancers did not alter the positive dose response for the remaining cancers. Important differences in smoking or socioeconomic status would not be expected between workers with different cumulative TCDD exposure levels. Non-smoking-related cancers showed the same dose response as smoking-related cancer.

To our knowledge, there has been only one previous risk assessment based on an epidemiologic study, which was conducted by Becher et al. in a cohort of German chemical workers (20). These authors used a methodology for estimating cumulative serum levels that was similar to ours. When a TCDD intake of 1.0 pg/kg per day and a 10-year latency were assumed, their three best-fitting models resulted in a range of excess lifetime risks for males (through age 70 years) of 0.0013–0.0056. Our estimate using our two best-fitting models through age 70 years (not age 75 years, as in table 3) are 0.007–0.0004 for males for a TCDD intake of 1.0 pg/kg per day, in the same range found by Becher et al.

Our estimates of lifetime risk are model dependent, as often occurs in assessing risks at low levels where the shape of the dose-response curve can have a large influence. Our estimate of lifetime risk by age 75 years using a piecewise linear model rather than the log of cumulative dose is an order of magnitude lower (0.0005 vs. 0.009). Although both models fit the data reasonably well, the piecewise linear model may be preferable to the log cumulative dose model because the latter is constrained to have its highest slope at low doses. This high slope predicts large increases in cancer rates for small increases in dose in the low dose region, which may be unrealistic. Results based on both models support a lifetime excess risk on the order of  $10^{-3}$ – $10^{-2}$  for an environmental exposure to TCDD (or TEQs) at twice background levels. This estimate lends support to a recent Environmental Protection Agency draft risk assessment for dioxin, which has similar estimates of lifetime excess risk at high levels of environmental exposure (Internet address: [www.epa.gov/ncea/dioxin.htm](http://www.epa.gov/ncea/dioxin.htm)).

There are a number of limitations to our approach, which introduced imprecision. For example, we used a constant estimate of half-life for TCDD; in practice, half-life is likely to vary by body weight, about which we had limited data. More importantly, we were restricted to a sample of 170 people at one chemical plant for estimating the relation between exposure score and serum level, and these workers may not have been representative of all those in the study. Work history at this plant was not as detailed as at some other plants, which hampered the original development of external exposure scores at this plant. This limitation in turn introduced inaccuracy when estimating the relation between serum levels and exposure scores at this plant, which then affected the accuracy of estimating serum levels from exposure scores at all of the other plants. Nevertheless, the cumulative serum levels proved to be a reasonably good predictor of cancer and provided a reasonable fit to the data.

Furthermore, use of cumulative serum levels enabled us to estimate the risk in units of intake (picograms per kilogram per day) that, unlike external exposure scores, are useful to public health and regulatory agencies.

The workers we studied were heavily exposed to TCDD and had exposure levels on the average of three orders of magnitude higher than background (1,589 ppt at the time of last exposure vs. a background of 5–10 ppt). However, the average was dominated by those workers in the top 10 percent of the exposure distribution. The estimated median level at time of last exposure was considerably lower, 98 ppt. A good number of subjects had relatively low estimated exposure levels. In our cohort, the 5th, 10th, and 25th percentiles of estimated serum levels at time of last exposure were 18, 21, and 37 ppt, respectively. Given that significant numbers of subjects had exposure levels only several times those of background, extrapolation of our exposure-response data to estimate risk at background levels might not be considered unreasonable. However, the shape of the overall dose-response curve was still driven by those workers with the highest exposures who had higher cancer rates. This dilemma is typical in many risk assessments.

Animal data, primarily from rats, do not provide consistent evidence regarding whether the carcinogenic response to TCDD has a threshold at low dose levels (19). In our own data, models with thresholds (assuming no increase in risk at low doses) did not fit as well as models without them.

Note that, in our data, the relative risk (rate ratio) of cancer due to a doubling of background exposure, over a 75-year lifetime, is very small, ranging from 1.005 to 1.07. However, this small relative risk is sufficient to result in excess lifetime risks on the order of  $10^{-2}$  or  $10^{-3}$  of dying of cancer, because the background risk of cancer mortality by age 75 years is high (12 percent).

Our exposure-response results, in conjunction with similar results from a German cohort (20), provide support for the recent Environmental Protection Agency risk assessment for dioxin. The use of human data for risk assessment, when quantitative estimates of exposure are available, offers advantages over animal data in estimating risk for humans by avoiding the uncertainties involved in extrapolating from rodents to humans (21). In our case, we were fortunate to have reasonably good data to estimate human exposure, superior to those available in many epidemiologic studies; we were able to take advantage of the long half-life of TCDD in humans and the availability of serum TCDD levels in a sample of our cohort.

## ACKNOWLEDGMENTS

The authors acknowledge Drs. Sue Nowlin and Amy Feng, who provided valuable programming help. Valuable comments on the draft manuscript were received from Drs. Linda Birnbaum, Dieter Flesch-Janys, Dave Dankovic, Leslie Stayner, Manolis Kogevinas, and Kenny Crump.

## REFERENCES

1. Polychlorinated dibenzo-*para*-dioxins and polychlorinated dibenzofurans. IARC monographs on the evaluation of carcinogenic risks to humans. Vol 69. Lyon, France: International Agency for Research on Cancer, 1997.
2. Steenland K, Piacitelli L, Deddens J, et al. Cancer, heart disease, and diabetes in workers exposed to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD): an update and exposure-response analysis of the NIOSH TCDD cohort. *J Natl Cancer Inst* 1999;91:779–86.
3. Piacitelli L, Marlow D, Fingerhut M, et al. A retrospective job exposure matrix for estimating exposure to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin. *Am J Ind Med* 2000;38:28–39.
4. Michalek M, Pirkle J, Caudill S, et al. Pharmacokinetics of TCDD in veterans of Operation Ranch Hand: 10 year follow-up. *J Toxicol Environ Health* 1996;47:209–20.
5. Piacitelli L, Sweeney M, Fingerhut M, et al. Serum levels of 2,3,7,8-substituted PCDDs among workers exposed to 2,3,7,8-TCDD contaminated chemicals. *Chemosphere* 1992;25:251–4.
6. Flesch-Janys D, Steindorf K, Gurn P, et al. Estimation of the cumulated exposure to polychlorinated dibenzo-*p*-dioxins/furans and SMR analyses of cancer mortality by dose in an occupationally exposed cohort. *Environ Health Perspect* 1998;106(suppl 2):655–62.
7. Tomaseth K, Salvan A. Estimation of occupational exposure to 2,3,7,8-TCDD using a minimal physiologic toxicokinetic model. *Environ Health Perspect* 1998;106(suppl 2):743–55.
8. Pirkle J, Wolfe W, Patterson D, et al. Estimates of the half-life of 2,3,7,8-TCDD in Vietnam veterans of Operation Ranch Hand. *J Toxicol Environ Health* 1989;27:165–71.
9. SAS Institute, Inc. SAS user's guide: statistics, version 6.07 ed. Cary, NC: SAS Institute, Inc, 1991.
10. Harrell F, Lee K, Pollock B. Regression models in clinical studies: determining relationships between predictors and response. *J Natl Cancer Inst* 1988;80:1198–202.
11. World Health Organization. Assessment of the health risk of dioxins: re-evaluation of the Tolerable Daily Intake (TDI). WHO Consultation May 25–29, 1998. Geneva, Switzerland: WHO European Centre for Environmental Health and International Programme on Chemical Safety, 1988.
12. Gail M. Measuring the benefits of reduced exposure to environmental carcinogens. *J Chronic Dis* 1978;28:135–47.
13. US Department of Health and Human Services (HHS). Health 1999. Washington, DC: US Department of Health and Human Services, 1999. (HHS publication 99-1232).
14. Stayner L, Smith R, Thun M, et al. A dose-response analysis and quantitative assessment of lung cancer risk and occupational cadmium exposure. *Ann Epidemiol* 1992;2:177–94.
15. Hornung R, Meinhardt T. Quantitative risk assessment of lung cancer in US uranium miners. *Health Physics* 1987;52:417–30.
16. Steenland K, Deddens J, Stayner L. Diesel exhaust and lung cancer in the trucking industry: exposure-response analyses and risk assessment. *Am J Ind Med* 1998;34:220–8.
17. Hertz-Picciotto I, Smith A. Observations on the dose-response curve for arsenic exposure and lung cancer. *Scand J Work Environ Health* 1993;19:217–26.
18. Lubin JH, Pottern LM, Stone BJ, et al. Respiratory cancer in a cohort of copper smelter workers: results from more than 50 years of follow-up. *Am J Epidemiol* 2000;151:554–65.
19. Sewall C, Lucier G. Receptor-mediated events and the evaluation of the EPA dioxin risks. *Mutat Res* 1995;333:111–22.
20. Becher H, Steindorf K, Flesch-Janys D. Quantitative cancer risk assessment for dioxins using an occupational cohort. *Environ Health Perspect* 1998;106(suppl 2):663–70.
21. Hertz-Picciotto I. Epidemiology and quantitative risk assessment: bridge from science to policy. *Am J Public Health* 1995;85:484–91.