Meta-analysis of Dioxin Cancer Dose Response for Three Occupational Cohorts

Kenny S. Crump,[1] Richard Canady,[2] and Manolis Kogevinas[3]

[1]Environ International Corporation, Ruston, Louisiana, USA; [2]Center for Food Safety and Applied Nutrition, U.S. Food and Drug Administration, College Park, Maryland, USA; [3]Respiratory and Environmental Health Research Unit, Institut Municipal d'Investigació Mèdica, Barcelona, Spain

This article presents a meta analysis of data from three cohorts occupationally exposed to TCDD and related compounds. A statistically significant (p = 0.02) trend was found in total cancer mortality with increasing dioxin exposure. The trend tests show an increase in total cancer at cumulative TEQ (unit of measurement for TCDD-like compounds that is defined as the amount of TCDD that would produce the same toxicity as a mixture of TCDD-like compounds) serum levels that would result from lifetime intake of 7 pg TEQ/kg body weight/day, with no increase at 6 pg/kg/day. A linear dose response provided a good fit to the combined data and predicted an ED_{01} (dioxin exposure resulting in a 0.01 increase in lifetime risk of cancer mortality) of 45 pg/kg/day (95% confidence interval, 21–324). The U.S. Environmental Protection Agency estimates that current lifetime human exposures to dioxin average approximately 1 pg/kg/day (99% percentile: 3 pg/kg/day). Although it appears unlikely that current exposures through foods would reach either 7 pg/kg/day or the ED_{01}, our analysis argues for careful consideration of the upper ranges of long-term average exposures for dioxins. *Key words:* **carcinogen, dioxin, dose–response assessment, meta-analysis, occupational cohorts.** *Environ Health Perspect* **111:681–687 (2003). doi:10.1289/ehp.5831 available via** *http://dx.doi.org/* **[Online 30 October 2002]**

In 2000 the U.S. Environmental Protection Agency (U.S. EPA) released a draft risk assessment for 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) and other dioxin-like compounds that evaluated the current state of knowledge regarding exposures and health effects of these compounds (U.S. EPA 2000). Included in this assessment was an estimate derived from epidemiological data of the 1% effective dose, ED_{01}, defined as the lifetime average body burden of TCDD that would increase the lifetime risk of cancer (all kinds) mortality by 1%. Exposures to other dioxin-like compounds were accounted for by using toxicity equivalence factors (TEQ) to express the amount of all dioxin-like compounds in a mixture in TEQ units, defined as the amount of TCDD that would produce the same toxicity. The U.S. EPA risk assessment was criticized by Starr (2001), who showed that the epidemiologic data used by the U.S. EPA was consistent with an elevated background cancer risk of about 32% relative to comparison populations and no dioxin effect.

The U.S. EPA ED_{01} estimate was based on data from three occupational cohorts: 5,172 workers from 12 U.S. chemical plants studied by the National Institute for Occupational Safety and Health—the "NIOSH cohort" (Aylward et al. 1996; Fingerhut et al. 1991), 1,189 workers at a chemical plant in Hamburg, Germany—the "Hamburg cohort" (Flesch-Janys et al. 1998), and 243 workers exposed as a result of an uncontrolled release in 1953 of TCDD from an autoclave being used for trichlorophenol production at a BASF AG plant in Ludwigshafen, Germany—the "BASF cohort" (Ott and Zober 1996). The NIOSH cohort was by far the largest of the three, not only in terms of the number of workers exposed but also in terms of the number of cancers observed during follow-up.

Recently, an additional 6 years of follow-up was conducted for the NIOSH cohort (Steenland et al. 1999), and, more important, a new exposure assessment was developed that allowed an estimation of TCDD exposure for all members of the cohort (Steenland et al. 2001). This information was not available in time to be incorporated into the U.S. EPA (2000) assessment. We incorporated this new information from the NIOSH cohort, along with the information previously available for the Hamburg and BASF cohorts, into a risk assessment similar to that conducted by the U.S. EPA. We compared results of this risk assessment to those obtained by the U.S. EPA and by Starr (2001). We also compared our results to risk estimates based only on the NIOSH cohort (Steenland et al. 2001) and only on the Hamburg cohort (Becher et al. 1998). In addition, we applied an analysis to determine the lowest exposures for which there were statistically significant associations between dioxin exposure and cancer mortality.

Review of New Data for NIOSH Cohort

The data for the NIOSH cohort used in the U.S. EPA (2000) risk assessment were from the Fingerhut et al. (1991) study, which included follow-up through 1987. Steenland et al. (1999) extended follow-up of this cohort for an additional 6 years. They also developed a cumulative exposure score for each member of a subcohort of 3,538 workers (69% of total cohort) obtained by eliminating workers with inadequate exposure information or who were exposed to pentachlorophenol in addition to dioxin. This exposure score was based on work history, the concentration of TCDD in process materials, and a qualitative evaluation of the potential for dermal and inhalation exposure to TCDD-contaminated materials. More recently, Steenland et al. (2001) derived estimates of cumulative TCDD serum levels for this subcohort based on a regression analysis of exposure scores and serum lipid TCDD concentrations available for 170 workers at one of the NIOSH-studied facilities. This relationship was then used to estimate the cumulative serum lipid TCDD concentrations for all 3,538 workers based on the assumption that TCDD uptake and elimination obeys first-order pharmacokinetics. Steenland et al. (2001) observed a significant positive trend (p = 0.003) between all cancer mortality and the logarithm of cumulative serum lipid TCDD lagged 15 years.

Whereas Steenland et al. (2001) used worker-specific data on both the plant and the specific process, such information was not available to the U.S. EPA (2000) or to Starr (2001). Instead, the exposure analysis used by the U.S. EPA and Starr assigned all workers in broad categories of duration of exposure the same cumulative serum level regardless of the plant or job assignment within a plant or of when exposure took place in relation to the follow-up period. In the following sections we incorporate the new Steenland et al. (1999, 2001) data for the NIOSH cohort into a meta-analysis of the epidemiologic data for dioxin.

Meta-analysis methods. Our meta-analysis is based on the same three occupationally exposed cohorts as the U.S. EPA (2000) analysis: the NIOSH cohort, the BASF cohort, and the Hamburg cohort. Standardized mortality ratio (SMR; the ratio of observed to expected cancer deaths multiplied by 100) was the response measure used in these studies.

Address correspondence to K.S. Crump, Environ International Corp., 602 East Georgia Ave., Ruston, LA 71270 USA. Telephone: (318) 251–6085. Fax: (318) 255–2040. E-mail: kcrump@environcorp.com

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Mortality data for specific kinds of cancer were not evaluated, and the term "cancer" refers to mortality from all cancers. Cancer incidence data were not available, and consequently risks from nonfatal cancers were not reflected in the data, and risks from rapidly fatal cancers carried more weight than those from cancers with better survival rates.

Exposure assessment. To make comparisons among different epidemiologic studies, it is useful to have exposure quantified in a common metric that is plausibly related to risk. Because our analysis was based on published data, various aspects of the analysis, including selection of the dose metric, were constrained by the way in which data were presented in the published reports. Cumulative serum lipid concentration (CSLC; ppt-years) or area under the serum lipid concentration curve was selected as the exposure metric to relate to risk. By comparison, the U.S. EPA used average lifetime serum lipid concentration as the exposure measure in its analysis (U.S. EPA 2000). A time-dependent exposure such as CSLC allows one to distinguish potential differences in risks from different exposure patterns that result in the same lifetime average exposure.

Flesch-Janys (1998) categorized observed and expected cancer deaths in the Hamburg cohort (n = 1,189) by quartiles of TEQ (unit of measurement for TCDD-like compounds that is defined as the amount of TCDD that would produce the same toxicity as a mixture of TCDD-like compounds) CSLC (ppt-years) reduced by the cumulative TEQ contributed by background. Because only exposure ranges were provided in Flesch-Janys (1998), we specified average values within these ranges—the midpoint for bounded ranges and twice the lower bound for the highest (unbounded) range. Observed and expected numbers of cancer deaths, relative risks, and the estimated exposures for the Hamburg cohort are shown in Table 1.

Ott and Zober (1996) categorized cancer deaths and SMRs in the BASF cohort (n = 247) by total intake of TCDD (micrograms per kilogram body weight) as a result of the autoclave accident, estimated from detailed work activity analysis and from serum lipid TCDD concentrations measured in a subset of workers. M. A. Zober (personal communication) provided arithmetic average total doses for each of the four exposure categories (0.015, 0.485, 1.38, and 3.72 μg/kg body weight, respectively). To convert these total intakes to TCDD CSLC, we divided them by 0.25 (based on an assumed average percent body fat of 25%) and by the decay rate (0.099/year, corresponding to a half-life of 7 years, as assumed by Ott and Zober). The resulting data are shown in Table 1.

Steenland et al. (2001) computed risk ratios categorized by septiles of TCDD CSLC, including the contribution by background exposures, using a 15-year lag (i.e., defined so that exposures in the most recent 15 years did not contribute). These risk ratios used the low-exposure group as the reference group and consequently are not appropriate for our meta-analysis, which needs the risks relative to the normal background uncontaminated by occupational dioxin exposure. Also, these risk ratios depend on the observed risk in the low-exposure group, which might involve considerable uncertainty. However, Steenland et al. (1999) categorized observed cancer deaths and expected deaths for the NIOSH cohort by septiles of the cumulative exposure score also using a 15-year lag. As there was a high correlation between the cumulative exposure score and CSLC (Spearman correlation of 0.9; Steenland et al. 2001), the CSLC for the groups defined by septiles of cumulative exposure (Steenland et al. 2001) should be good approximations of exposures in the comparable groups defined by the septiles of the exposure index (Steenland et al. 1999). Consequently, in our meta-analysis the CSLC (lagged 15 years, TCDD half-life of 8.7 years assumed) from Steenland et al. (2001) were applied to the cancer mortality data in Steenland et al. (1999). Central values for the exposure ranges (antilogs of medians of log-transformed values) were provided by K. Steenland (personal communication). The resulting dose–response data are shown in Table 1.

Dose–response modeling. The dose–response data in Table 1 were modeled assuming that the SMR depends linearly on cumulative serum lipid concentration (CSLC, in units of parts per trillion-year),

$$\mathrm{SMR} = 100 \times \alpha \times (1 + \beta \times \mathrm{CSLC}), \qquad [1]$$

where $100 \times \alpha$ is the baseline SMR and β is a parameter that gauges the carcinogenic potency of dioxin. This model was fit both with the baseline SMR fixed at 100 ($\alpha \equiv 1$) and with variable baseline SMR (α estimated). The fitting was accomplished using maximum likelihood, assuming that the observed cancers in each exposure group were realizations of independent Poisson variables, each with a mean equal to the expected number of cancer deaths derived from the comparison population used by the original authors times the SMR predicted by Equation 1 divided by 100. The meta-analysis of the combined data from the three studies was accomplished via the combined likelihood of the three data sets in Table 1. We used likelihood ratio tests to test hypotheses, and we calculated confidence intervals using the profile likelihood method (Crump 1995; Kodell and West 1993; Venzon and Moolgavkar 1988). All hypothesis tests of individual parameters are two sided.

We used two types of analyses to evaluate the cancer dose response. First, a series of trend tests were applied to the data to determine the lowest dose for which there was a statistically significant trend in SMR using data from this dose and all lower doses, and the highest dose for which there was no statistically significant trend using data from this

Table 1. Dose–response data from three epidemiologic studies.

Cumulative lipid, TCDD or TEQ (ppt-year)	Cancer deaths Obs	Exp	SMR
Flesch-Janys (1998)			
180	25	23.3	107
988	34	20.8	164
3,416	31	23.3	133
10,425	34	20.8	164
Ott and Zober (1996)			
605	8	10.0	80
19,614	8	6.7	120
55,645	8	5.7	140
150,454	7	3.5	200
Steenland et al. (1999, 2001)			
260	67	68.4	98
402	27	30.0	90
853	31	27.2	114
1,895	30	25.4	118
4,420	34	25.6	133
12,125	33	19.5	169
59,838	34	22.1	154

Abbreviations: Exp, expected number of deaths; Obs, observed number of deaths.

Table 2. Results of fitting model 1 to data in Table 1.

		95% CI
Baseline SMR = 100 (α = 1)		
β (ppt-years)$^{-1}$ ($\times 10^6$)	11	5.1–19
p-Value for test of β = 0 (no dioxin effect)	0.00007	
Goodness-of-fit p-value	0.05	
ED_{10} (pg/kg/day)	266	161–587
ED_{05}	129	78–285
ED_{01}	25	15–56
Baseline SMR variable		
α	1.17	1.04–1.30
p-Value for test of α = 1	0.008	
β (ppt-years)$^{-1}$ ($\times 10^6$)	6.3	0.88–13
p-Value for test of β = 0 (no dioxin effect)	0.02	
Goodness-of-fit p-value	0.29	
ED_{10} (pg/kg/day)	475	223–3,401
ED_{05}	231	109–1,653
ED_{01}	45	21–324

dose and all lower doses (Tukey et al. 1985). Second, we made estimates of ED_{10}, ED_{05}, and ED_{01}, the lifetime average daily TEQ intakes (picograms per kilogram per day) corresponding to an increase of 0.1, 0.05, and 0.01, respectively, in the lifetime probability of mortality from cancer.

To develop the trend analyses, we ordered the data in Table 1 with respect to CSLC and applied a likelihood ratio test for a significant exposure-related trend (i.e., test for β in Equation 1 being significantly different from zero with α estimated) to the data. Then the data at the highest exposure were omitted, and the trend test was reapplied to the remaining data. This procedure was applied repeatedly until only the data for the lowest dose group remained.

To estimate ED_{10}, ED_{05}, and ED_{01}, we computed the cumulative lipid concentration, lagged 15 years, from a constant daily intake as a function of age, assuming *a*) a first-order elimination process with a 7.6 year half-life, *b*) a 50% systemic uptake of ingested dioxin, *c*) that dioxin concentration in serum lipid is an appropriate surrogate for dioxin concentration in total lipid, and *d*) that all dioxin is sequestered in lipid, which comprises 25% of body weight (U.S. EPA 2000). For a posited long-term average daily intake, the resulting cumulative age-specific lipid concentrations were applied in conjunction with model 1 to predict the age-specific mortality rates in the presence of dioxin exposure. These were then applied in a life-table analysis to predict the lifetime risk of cancer in the presence of dioxin exposure (Crump 1994). We calculated the additional risk posed by dioxin exposure by subtracting from this lifetime risk the corresponding risk assuming no additional exposure to dioxin above background. To calculate an ED_{01}, we adjusted the long-term average daily intake to make the additional lifetime risk equal to 0.01. This calculation used as baseline mortality rates for all-cause mortality and all-cancer mortality U.S. rates (both sexes and all races combined) for 1985–1990.

Whereas background exposures are not included in the exposures estimated for the Hamburg and BASF cohorts (Table 1), the NIOSH exposures include the contribution of an assumed background of 5 ppt TCDD in serum lipid. In the trend analyses, a background contribution of 3,000 ppt-years [e.g., 50 ppt for 60 years, as U.S. EPA (2000) reported that background TEQ lipid levels in North America were about 55 ppt in the late 1980s] was added to the Hamburg and BASF exposures in Table 1, and 2,700 ppt-years (45 ppt for 60 years, considering the 5 ppt already included in the NIOSH estimates) was added to the NIOSH exposures. Because the background mortality rates used to calculate ED_{01} already included any contribution to cancer mortality from background dioxin exposure, this adjustment for background was not made in the ED_{01} calculations. Consequently, the ED_{01} determined from our analysis are best interpreted as long-term average daily intakes of TCDD or TEQ above the current TEQ background that are predicted to increase the lifetime probability of cancer mortality by 0.01 above the current baseline probability. The latter was estimated as 0.125 in our analysis and includes any contribution by background levels of dioxin.

Results

Table 2 summarizes results of fitting model 1 to the data in Table 1. The hypothesis of no dioxin effect ($\beta = 0$) was rejected ($p = 0.00007$) when the baseline SMR was fixed at 100 and also when the baseline SMR was estimated ($p = 0.02$). Because the hypothesis that the baseline SMR = 100 ($\alpha = 1$) was rejected ($p = 0.008$), the results in Table 2 obtained with baseline SMR variable (α estimated, bottom half of Table 2) are preferred. The linear model provided an adequate fit to the data (goodness-of-fit $p = 0.29$), produced a baseline SMR estimate of $100\alpha = 117$ [95% confidence interval (CI), 104–130], and predicted that each part per trillion-year of cumulative lipid concentration increased the relative risk by $\beta = 6.3 \times 10^{-6}$ (95% CI, 8.8×10^{-7}–1.3×10^{-5}).

To test for potential nonlinearity in the dose response, model 1 was expanded by replacing CSLC with $CSLC^K$, $K \geq 1$. This expanded model is linear if $K = 1$ and is sublinear (threshold-like) if $K > 1$. The best estimate of K was 1, indicating there was no evidence of sublinearity in the dose response. Although models with $K < 1$ (supralinear models) provided even better fits (and higher risks), these were discounted because they produce an infinite slope to the exposure–response curve at zero exposure, which is not considered biologically plausible.

Figure 1 shows the SMRs from the three studies and corresponding 95% CIs, plotted against CSLC (log scale) in Table 1 after adjusting as described earlier to include background TEQ CSLC. The fit of the linear model 1 with variable baseline SMR is also displayed. This figure provides a visual confirmation of the adequacy of the linear model to describe these data.

Figure 1 suggests possible nonhomogeneity in the dose responses of the three studies because all four data points from Ott and Zober (1996) are below the predicted curve, and three of four data points from Flesch-Janys et al. (1998) are above the predicted curve. A likelihood ratio test of whether separate β for each study provided a better fit to the data was nonsignificant ($p = 0.13$, 2 df). A test of whether both separate β and separate α provided a better fit was also nonsignificant ($p = 0.17$, 4 df). These results suggest that perhaps some, but not extreme, heterogeneity exists among studies and consequently supports a combined analysis of data from all three studies using a common model.

Table 2 provides ED_{01}, ED_{05}, and ED_{10}, calculated with both the baseline SMR fixed at 100 and with the baseline SMR variable. As noted above, results from the latter model are preferred because the hypothesis that the baseline SMR = 100 was rejected ($p = 0.008$) and the model with the baseline variable provided a good fit to the data ($p = 0.29$). The model with variable baseline predicted ED_{10} = 475 pg/kg/day (95% CI, 223–3,401), ED_{05} = 231 pg/kg/day (95% CI, 109–1,653) and ED_{01} = 45 pg/kg/day (95% CI, 21–324).

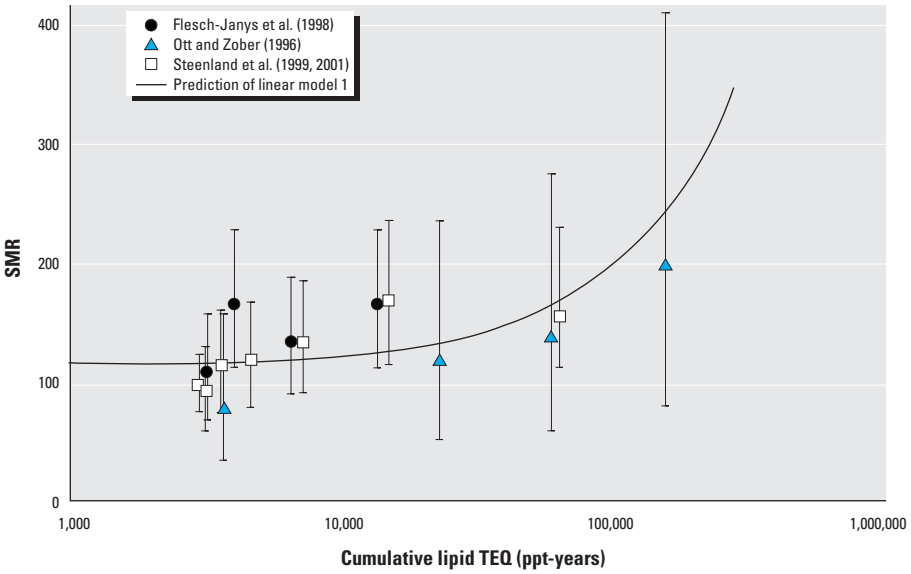

Figure 1. SMRs (with 95% confidence bounds) from three studies categorized by cumulative lipid concentration (Table 1), adjusted to include background TEQ.

It was noted earlier that exposures were lagged 15 years in the Steenland et al. (1999, 2001) study but not lagged in the remaining studies. In our calculations of ED_{10}, ED_{05}, and ED_{01} we used a 15-year lag. Some lag seemed appropriate because exposures immediately before death are not likely to influence the cancer response. Because Steenland et al. (1999, 2001) used a 15-year lag and the majority of the data were from this study, we decided to use a 15-year lag in the calculations. When no lag was used (results not shown), the estimated ED_{10}, ED_{05} and ED_{01} were smaller by roughly 40%.

Table 3 gives the results from the series of trend tests. The trend was significant (p = 0.02) when all the data were included. When the data at the highest exposure were omitted, the trend remained significant (p = 0.04) and the slope, β, increased. As the nine highest-dose groups were successively omitted, the dose–response slope, β, increased at each step until only doses of 3,988 ppt-years or lower remained. Also, as successive data points were omitted, the trend remained significant ($p \leq 0.05$) through the step at which only the data corresponding to a cumulative serum level of 7,120 ppt-years or lower were left. When the 7,120 ppt-years data point was omitted leaving 6,416 ppt-years as the highest dose, the trend became barely nonsignificant (p = 0.07) and remained so as the next data point was omitted. However, the trend again became significant (p = 0.04) when the highest exposure remaining was 3988 ppt-years. Statistical significance was not obtained when the 3,988 ppt-years group was omitted (leaving 3,853 ppt-years as the highest remaining exposure) or when subsequent dose groups were omitted. Thus, there is consistent statistical evidence of an exposure effect at 7,120 ppt-years and above. There is, however, also statistical support for an effect at 3,988 ppt-years and above.

Discussion

U.S. EPA analysis. The dose–response assessment methodology applied to epidemiology data in the U.S. EPA (2002) draft health effects dioxin document differed from our analysis in three main ways. First, rather than using the Steenland et al. (1999, 2001) study, the U.S. EPA used the Fingerhut et al. (1991) study, which included 6 fewer years of follow-up and a less detailed exposure assessment. Second, the U.S. EPA used average body burden as the exposure metric, whereas we used cumulative serum lipid concentration. Third, the U.S. EPA assumed a baseline SMR of 100, whereas we allowed the baseline SMR to increase above 100 because the hypothesis that SMR = 100 could be rejected. The U.S. EPA did not conduct a formal test of the hypothesis that SMR =100 nor did they report on the fit of the model to the data. However, Starr (2001) reproduced the U.S. EPA analysis and concluded that the model did not fit adequately. Based on their meta-analysis, the U.S. EPA estimated an ED_{01} = 47 ng/kg body burden (95% lower bound: 30 ng/kg). This body burden is estimated (Table 4) to correspond to a daily intake of 23 pg/kg/day (95% lower bound: 15 pg/kg/day).

Starr analysis. Starr (2001) conducted a critique of the U.S. EPA (2000) risk assessment for dioxin that included a meta-analytic evaluation of the same dose–response data from the NIOSH, Hamburg, and BASF studies as was used by the U.S. EPA in its meta-analysis. Starr concluded that the data from these three studies were consistent (goodness-of-fit p-value = 0.31) with an elevated background (SMR = 132) and no exposure effect. In contrast, our comparable analysis, based upon the updated NIOSH data, found a significant dose–response trend (p = 0.01).

Applying the same linear model for relative risk as the U.S. EPA (constraining the background SMR = 100), Starr (2001) estimated an ED_{01} body burden concentration of 47 ppt (95% lower bound: 28 ppt), which agrees with the U.S. EPA results. However, Starr noted that this model did not describe the data adequately (goodness-of-fit p-value = 0.0003). When the background SMR was estimated, the linear model provided an adequate fit (goodness-of-fit p-value = 0.31) and an ED_{01} = 145 ppt (95% lower bound: 49 ppt). This body burden is estimated (Table 4) to correspond to a daily intake of 72 pg/kg/day (95% lower bound: 24 pg/kg/day). However, the fit of the intercept-only model was equally as good as that of the linear model.

Steenland et al. analysis. Steenland et al. (2001) conducted a quantitative risk assessment using only the updated data from the NIOSH study. A significant (p = 0.003) positive dose–response trend was found between estimated log cumulative TCDD serum level and all-cancer mortality. Steenland et al. estimated additional lifetime risk of cancer from TCDD exposure using two models. One model assumed that relative risk was a linear

Table 3. Tests results for dose–response trend applied to data ranked by CSLC, adjusted to include background TEQ.

CSLC (ppt-year)	Cancer deaths Obs	Exp	SMR	Study	β (Slope)[a] (ppt-year)$^{-1}$	Trend p-value[a]
153,434	7	3.5	200	Ott and Zober (1996)	5.7×10^{-6}	0.02**
62,538	34	22.1	154	Steenland et al. (1999, 2001)	7.6×10^{-6}	0.04**
58,645	8	5.7	140	Ott and Zober (1996)	1.6×10^{-5}	0.05**
22,614	8	6.7	120	Ott and Zober (1996)	4.6×10^{-5}	0.005***
14,825	33	19.5	169	Steenland et al. (1999, 2001)	6.7×10^{-5}	0.001***
13,435	34	20.8	164	Flesch-Janys (1998)	7.8×10^{-5}	0.008***
7,120	34	25.6	133	Steenland et al. (1999, 2001)	1.2×10^{-4}	0.05**
6,416	31	23.3	133	Flesch-Janys (1998)	1.9×10^{-4}	0.07*
4,595	30	25.4	118	Steenland et al. (1999, 2001)	6.4×10^{-4}	0.08*
3,988	34	20.8	164	Flesch-Janys (1998)	1.7×10^{-1}	0.04**
3,605	8	10.0	80	Ott and Zober (1996)	4.8×10^{-5}	0.78
3,553	31	27.2	114	Steenland et al. (1999, 2001)	4.0×10^{-4}	0.49
3,180	25	23.3	107	Flesch-Janys (1998)	0	1
3,102	27	30.0	90	Steenland et al. (1999, 2001)	0	1
2,960	67	68.4	98	Steenland et al. (1999, 2001)		

[a]Slope and two-sided p-value for dose–response trend obtained using data from given exposure group and all groups with lower CSLC. *p = 0.1; **p = 0.05; ***p = 0.01.

Table 4. Summary of ED_{01} estimated from linear or piecewise linear dose–response models.[a]

Study and model	Background SMR	pg/kg/day intake ED_{01}	95% LB	95% UB	Steady-state body burden, ppt ED_{01}	95% LB	95% UB	Goodness-of-fit p-value
Becher et al. (1998), linear	Effectively estimated	4.5	NR	NR	9.1	NR	NR	NR
U.S. EPA (2000), linear	Fixed (=100)	23	15	NR	47	30	NR	NR
Starr (2001), linear	Fixed (=100)	24	14	NR	47	28	NR	0.003
	Estimated	72	24	Infinite	145	49	Infinite	0.31
Steenland et al. (2001), piecewise linear	Effectively estimated	7.7	5.0[b]	19[b]	15[b]	10[b]	37[b]	NR
Present study, linear	Fixed (=100)	25	16	47	51	33	95	0.08
	Estimated	45	23	173	91	47	346	0.29

Abbreviations: LB, lower bound; NR, not reported; UB, upper bound.
[a]The relationship between daily intake and steady-state body burden was determined assuming first-order pharmacokinetics, half-life of 7.6 years, 50% systemic uptake of TCDD, TCDD sequestered only, and homogeneously, in lipid, which forms 25% of human body by weight. [b]97.5% bounds rather than 95%.

function of log TCDD CSLC lagged 15 years, and the second assumed that relative risk was a piecewise linear function of (untransformed) TCDD CSLC with no lag.

The piecewise linear model selected by Steenland et al. had a change in slope at a cumulative serum level of 40,000 ppt-years; this break-point was determined by a process of elimination. A threshold model was found not to significantly improve the fit. The use of the piecewise model caused the risk estimates to be larger than what would be obtained using a purely linear model.

Based on the piecewise linear model, Steenland et al. estimated an increased lifetime risk of 0.0005 in males and 0.0004 in females from an incremental exposure of 1 pg/kg/day TCDD over the risk at a background exposure to 0.5 pg/kg/day. Using the same model, they estimated an increased lifetime risk of 0.0071 in males and 0.0060 in females from an incremental exposure of 10 pg/kg/day TEQ over the risk at a background exposure to 5 pg/kg/day. Because the background TEQ exposure of 5 pg/kg/day is the more realistic scenario, we focus on the average risk in males and females under this scenario. Because the model is linear in this exposure range, an additional lifetime risk of 0.0065 from an additional exposure to 5 pg/kg/day is equivalent to an $ED_{01} = 5 \times (0.01/0.0065) = 7.7$ pg/kg/day (95% CI, 5.0–19).

The log-linear model used by Steenland et al. predicted risks of up to 20-fold higher than those predicted by the piecewise linear model. However, Steenland et al. noted that this model may be unrealistic and expressed a preference for the piecewise linear model. Results from the log-linear model are not considered further here.

Becher et al. analysis. Becher et al. (1998) conducted a quantitative dose–response assessment using only the data from the Hamburg study. Cumulative lipid concentration over time, with a lag of either 0 of 10 years, was used as the exposure variable. A number of Poisson and Cox regressions were used to investigate dose–response relations, and in each analysis TCDD and TEQ exposures were significantly related to total cancer.

To evaluate the shape of the dose response, Becher et al. considered three mathematical forms for relative risk: the multiplicative model: relative risk (RR) = $e^{\beta d}$, where d is cumulative TCDD or TEQ exposure; the additive model: RR = $1 + \beta d$ (equivalent to our linear model, Equation 1); and the power model: RR = $(1 + \beta d)^k$, which is an extension of the additive model. In the basis of each of these models, a linear relationship between exposure and lifetime risk was assumed by Becher et al. in the low-dose range. Similar risks were estimated for males and females separately and combined, and for no exposure lag and for a 10-year lag; consequently, only results for males and females combined using a 10-year lag are discussed here. Using these models, Becher et al. estimated the additional lifetime risk of mortality from total cancer from lifetime daily intake of 1 pg/kg dioxin to be 0.0012 (multiplicative model), 0.0022 (additive model) and 0.0052 (power model).

The additive model provided a slightly better fit (higher likelihood) than the multiplicative model, and the power model predicted a supralinear dose response that provided only a very minor, statistically insignificant improvement over the fit provided by the additive model. The lifetime risk of 0.0022 from intake of 1 pg/kg dioxin per day (additive model) is equivalent to an $ED_{01} = 0.01/0.0022 = 4.5$ pg/kg/day. Although this analysis was based on TCDD serum levels, the slope Becher et al. obtained ($\beta = 0.018$ ppt^{-1}) was similar to the slope they obtained using TEQ serum levels ($\beta = 0.0175$ ppt^{-1}). Consequently, it appears that a similar ED_{01} would have been obtained using TEQ serum levels.

Present analysis. The new NIOSH data (Steenland et al. 1999, 2001), which incorporates 6 additional years of follow-up and a detailed exposure analysis, provides new information on the potential carcinogenicity of dioxin. Based on a meta-analysis of data from three epidemiological cohorts, including the old NIOSH data, Starr (2001) did not find a statistically significant relationship between dioxin exposure and total cancer. However, using the data from the same three cohorts but incorporating the new NIOSH data, we did find a statistically significant relationship between dioxin exposure and cancer ($p = 0.02$).

Because we lacked the necessary data, we were not able to evaluate the likelihood that confounding with lifestyle factors or occupational exposures to other chemicals may have been responsible for the observed responses in the individual studies. However, fitting model 1 with the background SMR as an estimated parameter effectively compared the responses of workers exposed to different amounts of dioxin. Thus, confounding as an explanation for the association is less of a concern for the comparison in the present analysis than it would be if direct comparisons were made of exposed workers to an external comparison group. Similarly, Steenland et al., using internal comparisons based on Cox regression, found significant trends in cancer in the NIOSH data with logarithm of cumulative exposure score, cumulative exposure score after omitting the highest 1% of exposure scores (Steenland et al. 1999), and logarithm of cumulative serum level (Steenland et al. 2001).

The trend analysis (Table 3) demonstrates statistical evidence of an association between dioxin TEQ exposure and cancer mortality for TEQ CSLCs of 3,988 ppt-years and higher. The highest dose where a trend was not supported by the analysis is a TEQ CSLC of 3,605 ppt-years. In addition, this analysis does not support the frequently quoted observation that the human evidence for dioxin carcinogenicity is limited to populations with very high exposures. If anything, our analysis suggests the contrary because the slope of the dose–response curve increased as higher doses were successively omitted (Table 3). The lack of statistical significance at the lowest doses does not necessarily indicate the absence of a dioxin effect in this dose range because this could be the result of a reduction in statistical power as higher doses are omitted.

The estimated long-term average daily intake corresponding to a cumulative lifetime (to age 70) exposure of 3,988 ppt-years is 7 pg/kg/day. By comparison, based on combined analysis of fat intake, estimates of average dioxin intake, and variation in serum dioxin levels, current average human daily intake is estimated to be about 1 pg/kg/day TEQ, with a 99% percentile of 3 pg/kg/day (U.S. EPA 2000). Thus, while current U.S. foodborne exposures are not likely to range up to the levels where our analysis found significant associations with cancer mortality, our analysis provides some evidence that TEQ exposures near current background levels are carcinogenic.

The linear dose–response model based on cumulative exposure described the data well (goodness-of-fit p-value = 0.29), despite the fact that the cohort members experienced patterns of exposure ranging from acute (e.g., from the autoclave accident in the BASF plant) to longer-term exposures. Moreover, there was no statistical evidence of a sublinear dose response or threshold. Our trend analysis (Table 3) taken at face value indicates that if a threshold for the carcinogenicity of dioxin exists, it is likely below a cumulative serum level of 4,000 ppt-years.

Despite the statistical significance of the test for dose–response trend in our meta-analysis ($p = 0.02$), the data were marginally consistent, according to a goodness-of-fit test, with no effect of exposure and a background SMR of 124 (goodness-of-fit p-value = 0.08). However, a goodness-of-fit test does not specifically evaluate the hypothesis of increasing response with increasing exposure to dioxin. In contrast, a trend test provides a specific and statistically more powerful evaluation of this hypothesis.

There are several differences in the exposure estimates for the three epidemiological studies used in our meta-analysis. First, the NIOSH estimates used a 15-year lag, whereas no lag was used with the other cohorts. Given that follow-up in the Steenland et al. (2001) cohort extended for many years past the time

at which exposures were most significant, results based on cumulative exposure lagged 15 years should not differ greatly from those based on unlagged exposure.

A second difference in the exposure estimates is that those for the Hamburg cohort included total TEQ (Flesch-Janys et al. 1998), whereas estimates for the NIOSH (Steenland et al. 1999, 2001) and BASF (Ott and Zober 1996) cohorts quantified only TCDD. Based on the available lipid samples from workers, total TEQ exposures in the Hamburg cohort appear to have been primarily a result of exposure to TCDD (Ott et al. 1993; Ott and Zober 1996; Piacitelli et al. 1992), whereas total lipid TEQ in the Hamburg cohort were estimated to be about twice that resulting from TCDD alone (Flesch-Janys et al. 1998). Steenland et al. omitted (and, consequently, so does this analysis) all workers in the NIOSH cohort who were exposed to pentachlorophenol, which is contaminated with dioxins other than TCDD. Thus, it appears that the exposure estimates available for each cohort are reasonable estimates of total TEQ exposures.

A third difference in the exposure estimates is that the exposures for the NIOSH cohort included 2,3,7,8-TCDD background exposures, whereas the exposures for the Hamburg and BASF cohorts did not include any background. In the trend analysis (Table 3, Figure 1), the exposures in Table 1 were modified (2,700 ppt-years added to NIOSH exposures and 3,000 ppt-years to Hamburg and BASF exposures) to include TEQ contributions to background. However, we obtained similar results (not shown) in the trend analysis when no background adjustment was made and also when 300 ppt-years was subtracted from NIOSH exposures. No adjustment for background was made in the calculations of ED_{01}, and these are best interpreted as pertaining to additional risk over any that may exist from background exposures. However, these estimates are based on a linear model and consequently will be insensitive to how background exposures are handled as long as the CSLC background is small relative to $1/\beta$, which is the case here. As a verification of this, the analysis leading to our ED_{01} of 45 pg/kg/day (Tables 2, 4) was repeated using the exposures adjusted for background (Table 3, Figure 1); the resulting change in the ED_{01} was less than 3%.

There is some evidence that at high exposures liver enzymes are induced that increase the elimination rate of dioxin compounds (Carrier et al. 1995). Such an effect was not accounted for in the analyses discussed here, but rather in each case first-order pharmacokinetics was assumed. Based on the estimated maximum body burdens in these studies, the amount of underestimation of the cumulative exposures from not accounting for enzyme induction is expected to be at most a factor of 1.5 for the upper dose levels (Van der Molen et al. 2000; Zeilmaker et al. 1998).

Table 4 summarizes ED_{01} estimates derived from linear (or piecewise linear) models. The U.S. EPA (2000) ED_{01} estimate and the estimate by Starr (2001) with baseline SMR = 100 agree closely (23–24 pg/kg/day), as expected since Starr's calculation is intended as a reproduction of that of the U.S. EPA. However, Starr showed that this model provided an inadequate fit to the data ($p < 0.003$). It is interesting that our meta-analysis with SMR = 100 also predicted a similar ED_{01} (25 pg/kg/day), as there are a number of differences between our calculations and those of the U.S. EPA and Starr. We used the updated follow-up and exposure data for the NIOSH cohort and used cumulative lipid serum concentration as the exposure measure, whereas the U.S. EPA and Starr used the earlier NIOSH data and used average body burden as the exposure metric.

Because the hypothesis that background SMR = 100 was rejected ($p = 0.008$), the model with background SMR estimated is the preferred one from our meta-analysis. This model predicted an ED_{01} = 45 pg/kg/day and was based on a statistically significant linear trend ($p = 0.02$). This estimate is also preferred over Starr's estimate of 72 pg/kg/day because it reflects the updated follow-up and more precise exposure estimates for the NIOSH cohort.

The estimate of ED_{01} = 4.5 pg/kg/day from the linear model applied by Becher et al. (1998) to the Hamburg data is 10-fold smaller than our preferred estimate of ED_{01} = 45 pg/kg/day based on data from all three cohorts. This difference is mainly attributable to differences in the underlying data. When we restricted our analysis to just the Hamburg data, we obtained an ED_{01} = 11 pg/kg/day, and when we repeated this analysis using Hamburg TCDD exposures rather than TEQ exposures, we obtained an ED_{01} = 4 pg/kg/day.

Our preferred ED_{01} of 45 pg/kg/day is 6 times higher than the Steenland et al. (2001) estimate of 7.7 pg/kg/day. We have not determined the full basis for this difference, although contributing factors are known. Both analyses estimate cancer risk above that of an unexposed worker population rather than of an external comparison population. Effects of different assumptions regarding pharmacokinetic parameters (uptake fraction, half-life, and percent lipid) and background exposures appear minor. Part of the difference is attributable to the fact that the Steenland et al. analysis was based only on the NIOSH cohort, and our analysis also incorporated the data from the BASF and Hamburg cohorts. However, when we repeated our analysis using only the NIOSH data, our ED_{01} estimate only decreased from 45 pg/kg/day to 32 pg/kg/day. The most likely reason for the remaining difference is that, whereas we used a purely linear model, Steenland et al. used a piecewise linear model with a break in the slope at a CSLC of 40,000 ppt. Use of the piecewise linear model resulted in a smaller ED_{01} than would have been obtained using a linear model. However, it should be kept in mind that none of these models can be verified at low exposure levels.

At present we do not see a clear choice between our ED_{01} estimate of 45 pg/kg/day and the Steenland et al. (2001) estimate of 7.7 pg/kg/day. Our estimate has the advantage of drawing from three different studies. On the other hand, the Steenland et al. estimate has the advantage of being based on individual worker data from the largest of the three studies rather than summarized data. If the different policy implications of the two estimates are large, it could be worthwhile to conduct an analysis that combines the best features of each and perhaps includes data from other cohorts with extensive TCDD exposure evaluation, such as the Dutch accident cohort (Hooiveld et al. 1998).

Overall, the available dose–response assessments for dioxin and cancer indicate that dioxin TEQ exposures within roughly 3-fold of current background levels may be carcinogenic. The proximity of foodborne dioxin exposure levels to those associated with cancer argues for careful consideration of both the cancer mechanism and the upper ranges of long-term average exposures for dioxins.

References

Aylward LL, Hays SM, Karch NJ, Paustenbach DJ. 1996. Relative susceptibility of animals and humans to the cancer hazard posed by 2,3,7,8-tetrachlorodibenzo-*p*-dioxin using internal measures of dose. Environ Sci Technol 30:3534–3543.

Becher H, Steindorf K, Flesh-Janys D. 1998. Quantitative cancer risk assessment for dioxins using an occupational cohort. Environ Health Perspect 106(suppl 2):663–670.

Carrier G, Brunet RC, Brodeur J. 1995. Modeling of the toxicokinetics of polychlorinated dibenzo-*p*-dioxins and dibenzofurans in mammalians, including humans. I. Nonlinear distribution of PCDD/PCDF body burden between liver and adipose tissue. Toxicol Appl Pharmacol 131:253–266.

Crump KS. 1994. Risk of benzene-induced leukemia: a sensitivity analysis of the Pliofilm cohort with additional follow-up and new exposure estimates. J Toxicol Environ Health 42:219–242.

———. 1995. Calculation of benchmark doses from continuous data. Risk Anal 15:79–89.

Fingerhut M, Halperin WE, Marlow DA, Piacitelli LA, Houchar PA, Sweeney MH, et al. 1991. Cancer mortality in workers exposed to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin. N Engl J Med 324:212–218.

Flesch-Janys D, Steindorf K, Gurn P, Becher H. 1998. Estimation of the cumulated exposure to polychlorinated dibenzo-*p*-dioxins/furans and standardized mortality ratio analysis of cancer mortality by dose in an occupationally exposed cohort. Environ Health Perspect 106(suppl 2):665–662.

Hooiveld M, Heederik DJJ, Kogevinas M, Boffetta P, Needham LL, Patterson DG, Bueno-de-Mesquita HB. 1998. Second follow-up of a Dutch cohort occupationally exposed to phenoxy herbicides, chlorophenols, and contaminants. Am J Epidemiol 147:891–901.

Kodell RL, West RW. 1993. Upper confidence limits on excess risk for quantitative responses. Risk Anal 13:177–182.

Ott MG, Messerer P, Zober A. 1993. Assessment of past occupational exposure to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin using blood lipid analyses. Int Arch Occup Environ Health 65:1–8.

Ott MG, Zober A. 1996. Cause specific mortality and cancer incidence among employees exposed to 2,3,7,8-TCDD after a 1953 reactor accident. Occup Environ Med 53:606–612.

Piacitelli LA, Sweeney MH, Fingerjut MA, Patterson DG Jr, Turner WE, Connally, LB, et al. 1992. Serum levels of PCDDs and PCDFs among workers exposed to 2,3,7,8-TCDD contaminated chemicals. Chemosphere 25:251–254.

Starr TB 2001. Significant shortcomings of the U.S. Environmental Protection Agency's latest draft risk characterization for dioxin-like compounds. Toxicol Sci 64:7–13.

Steenland K, Deddens J, Piacitelli L. 2001. Risk assessment for 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) based on an epidemiologic study. Am J Epidemiol 154:451–458. [Published erratum: Am J Epidemiol 155:189 (2002).]

Steenland K, Piacitelli L, Deddens J, Fingerhut M, Chang LI. 1999. Cancer, heart disease, and diabetes in workers exposed to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin. J Natl Cancer Inst 91:779–786.

Tukey J, Ciminera J, Heyse J. 1985. The consultant's forum. Testing the statistical certainty of a response to increasing doses of a drug. Biometrics 41:295–301.

U.S. EPA. 2000. Exposure and Human Health Reassessment of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) and Related Compounds. Part III. Integrated Summary and Risk Characterization for 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) and Related Compounds. September 2000 SAB Review Draft. EPA/600/P-00/001Bg. Washington, DC:U.S. Environmental Protection Agency.

Van der Molen GW, Kooijman BALM, Wittspepe J, Schrey P, Flesch-Janys D, Slob W. 2000. Estimation of dioxin and furan elimination rates with a pharmacokinetic model. J Expo Anal Environ Epidemiol 10:579–585.

Venzon D, Moolgavkar S. 1988. A method for computing profile-likelihood-based confidence intervals. Appl Stat 37:87–94.

Zeilmaker MJ, van Eijkeren. 1998. The Calculation of Human Toxicity Thresholds of 2,3,7,8-TCDD: A Physiologically-Based Pharmacokinetic Modeling Approach. RIVM Report 601503.010. Bilthoven, the Netherlands:National Institute of Public Health and the Environment.