Quantitative Cancer Risk Assessment for Dioxins Using an Occupational Cohort
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We consider a cohort of 1189 male German factory workers (production period 1952–1984) who produced phenoxy herbicides and were exposed to dioxins. Follow-up until the end of 1992 yielded a significantly increased standardized mortality ratio (SMR) for total cancer (SMR 141; 95% confidence interval 117–168). 2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD) concentrations up to 2252 ng/kg body fat were measured in 275 cohort members. Other higher chlorinated dioxins and furans also occurred in high concentrations. For quantitative analysis, the integrated TCDD concentration over time was used as an exposure variable, which was calculated using results from half-life estimation for TCDD and workplace history data. The other congeners were expressed as toxic equivalency (TEQ) and compared to TCDD using international toxic equivalency factors. Poisson and Cox regressions were used to investigate dose–response relationships. Various covariates (e.g., exposure to β-hexachlorocyclohexane, employment characteristics) were considered. In all analyses, TCDD and TEQ exposures were related to total cancer mortality. The power model yielded a relative risk (RR) function $RR(x) = (1 + 0.17x)^{0.326}$ for TCDD (in microgram/kilogram blood fat × years)—only a slightly better fit than a linear RR function—and $RR(x) = (1 + 0.023x^{0.795})$ for TEQ. Investigations on latency did not show strong effects. Different methods were applied to investigate the robustness of the results and yielded almost identical results. The results were used for unit risk estimation. Taking into account different sources of variation, an interval of $10^{-5}$ to $10^{-2}$ for the additional lifetime cancer risk under a daily intake of 1 pg TCDD/kg body weight/day was estimated from the dose–response models considered. Uncertainties regarding the dose–response function remain. These data did not indicate the existence of a threshold value; however, such a value cannot be excluded with any certainty. —Environ Health Perspect 106(Suppl 2):663-670 (1998). http://ehpnet1.niehs.nih.gov/docs/1998/Suppl-2/663-670becher/abstract.html

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Introduction

The most toxic dioxin congener, 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), was a contaminant in the production of phenoxy herbicides such as 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) and its derivatives. Cohorts of workers occupationally exposed to TCDD have been studied extensively (1–4). Kogevinas et al. (5) report results from a large international registry of persons occupationally exposed to phenoxy herbicides and contaminants (TCDD and other higher chlorinated dibenzodioxins and -furans). The studies showed a rather consistent picture of an increased cancer risk for all sites if cohorts with verified high exposures to TCDD are considered. However, the picture is not as clear if the focus is on specific cancer sites. The International Agency for Research on Cancer (IARC) recently reevaluated TCDD (6–7) and classified it as a Group 1 substance, i.e., carcinogenic to humans. This evaluation was based on studies conducted over the past 10 years in addition to broad knowledge on the mechanistic action of TCDD. However, a quantitative assessment of cancer risk associated with TCDD is difficult because the observed relative risks (RR) are low even in highly exposed occupational groups, potential confounding factors could not always be taken into account, and quantitative exposure assessment was not always possible. TCDD accumulates in the body fat with a half-life of about 7 years (8,9). Other congeners showed half-lives ranging from 3.0 years (1,2,3,4,6,7,8-heptachlorodibenzofuran) to 19.6 years (2,3,4,7,8-pentachlorodibenzofuran). Dioxins and furans therefore are among the few substances for which the past exposures can be assessed accurately even decades after exposure, making quantitative risk assessment more promising.

In this paper we describe a dose–response analysis for total cancer mortality and TCDD and toxic equivalency [a weighted sum of dioxins and furans; (7)] exposure based on a highly exposed occupational cohort from Germany, which has been studied previously (3,4,10). We know that risk assessment for dioxins is a complex issue that must take into account several lines of scientific research. The purpose of this paper is to use an epidemiologic data set, among the best available, to derive a quantitative estimate of cancer risk from human data.

Material and Methods

Cohort Description

The cohort studied consists of all 1189 regular male employees at the Boehringer chemical plant in Hamburg, Germany, that were employed for at least 3 months in the production period between 1952 and 1984. Exposure to polychlorinated dibenzo-p-dioxins/furans (PCDDs/Fs) in the plant occurred in the production of different herbicides and insecticides, as described in detail in Kauppinen et al. (11) and Manz et al. (10). A mortality follow-up was performed until 31 December 1992. Details can be found in Manz et al. (10) and Flesch-Janys et al. (3).
Exposure Assessment and Dose Variable

Exposure was verified by PCDD/F and beta-hexachlorocyclohexane (b-HCH) measurements in a sample of 275 workers. The mean TCDD was 101.3 ng/kg (range 2–2252 ng/kg). Half-life was estimated for all congeners using 48 individuals with multiple measurements, as described in Flesch-Janys et al. (8). These results were then used to backcalculate PCDD/F concentration at the end of each worker’s employment, taking into account the covariables (age and percent body fat). A regression model was then applied to estimate the dose rates for each congener for different occupations within the factory. This procedure is described in Flesch-Janys et al. (12) and led to dose–rate estimates that allow estimation of the PCDD/F concentration, \( y(t) \), from beginning of employment until end of follow-up for each member of the cohort using employment history data. Based on these concentration curves, we investigated different methods of constructing a dose variable. Although Flesch-Janys et al. (3) used the estimated concentration at the end of employment as a fixed covariable, we focused our analysis primarily on the cumulated dose (also called integrated dose or area under the curve (AUC)) as a time-dependent dose variable. This approach requires much more computation; however, according to Aylward et al. (13), “the appropriateness of the AUC for understanding the effects of drugs and chemicals that act through a receptor-mediated mechanism has been noted in pharmacology tests.” There is strong evidence that TCDD acts through binding to the aryl hydrocarbon receptor (7). The AUC can be converted to the lifetime average daily (or yearly) dose. Table 1 shows the relation between lifetime average yearly dose (dose rate), the associated blood level (concentration), and the AUC, assuming a lifetime of 70 years for selected doses.

For example, a constant intake of 1 ng/kg body weight/year yields a concentration of approximately 10 ng/kg body weight at age 70 and an AUC value of approximately 600 ng/kg body weight x years.

Choice of End Points

Standardized mortality ratio (SMR) results of the mortality follow-up are described in Flesch-Janys et al. (12). Of primary interest for possible dose–response analysis were those cancers for which a significantly increased risk was observed for the total cohort and the number of deaths was sufficiently large to allow a dose–response analysis. For example, we had to exclude lymphosarcoma from our analysis because the significantly increased SMR of 373 was based on only 5 cases. We therefore decided to base our dose–response analysis on total cancer mortality (124 cases; SMR 141; 95% confidence interval (CI) 117–168) and lung cancer mortality (38 cases; SMR 151; 95% CI 107–208). As will be discussed later, the main focus of the analysis lies on the total cancer mortality. This decision was supported by the fact that the IARC evaluation was also based on total cancer mortality, which has consistently increased in all occupational cohorts with high TCDD exposure, whereas the results are somewhat inconsistent for specific cancer sites.

Statistical Models

All analyses are based either on the disease end points total cancer or lung cancer. Poisson and Cox regression models with time-dependent covariables were used to investigate dose–response relationships between these disease end points and exposure levels of TCDD and TEQ (14).

For Poisson regression, an age (four levels) x calendar period (seven levels) x exposure level classification (10 levels, TCDD or TEQ) was performed. Expected number of deaths and person-years were calculated using West Germany mortality rates with the Fortran program "Person-Years" (15). Both models were applied with internal comparison (offset: person-years) and external comparison (offset: expected number of deaths). The TCDD and TEQ levels within each cell was taken as the geometric mean of cell limits and entered the Poisson model as a continuous covariable. As exposure variables in the Cox model we used the cumulated dose (AUC of TCDD, TEQ, and TCDD without TCDD [other congeners TEQ_O]). For TCDD, it was calculated as

\[ D(t) = \int_0^t y(t) dt, \]

where \( y(t) \) denotes the concentration of TCDD at time \( t \) and \( D(t) \) denotes the cumulated dose up to time \( t \). The procedure to estimate \( y(t) \) is given in Flesch-Janys et al. (12). For TEQ the dose was calculated as

\[ \sum TEF_i \times D_i(t), \]

where the sum is over all congeners \( i \) and \( TEF_i \) is the toxic equivalence factor for congener \( i \). Exposure variables were considered both separately and simultaneously within a model where applicable. To adjust for the coexposure to b-HCH, an estimate of the AUC dose for this substance was used in the Cox model. A mean background level for the German population of 3.4 ng/kg blood fat TCDD was taken into account (16–18). As further covariables we used age at employment entry, year of entry, and duration of employment. The following categories were used: years of age at entry (four categories: ≤20, <20 to ≤30, <30 to ≤40, and >40); year of entry (three categories: before 1 January 1954, 1 January 1954–31 December 1965, and after 1 January 1966); year of birth (six categories: ≤1900, 1900 to ≤1910, 1910 to ≤1920, 1920 to ≤1930, 1930 to <1940, and after 1940). An unexposed cohort (gas workers) described in Berger and Manz (19) was used for internal comparisons in most analyses. In these analyses an additional indicator was added into the model. The model may then be given as

\[ \lambda(t) = \lambda_0(t) \exp(\beta^T f(x)), \]

where \( x \) is a vector of covariables and \( f \) is an arbitrary function. Assuming a possible different baseline hazard function for different birth cohorts \( k \), \( \lambda_0(t) \), we use the model

\[ \lambda_k(t) = \lambda_0(t) \times \exp(\beta^T f(x)), \]

which can be fitted by defining different strata through the birth year, which we grouped as given above. This model is more flexible and also needs considerably
less computer time, as the risk sets are much smaller. We therefore focused primarily on this model.

### Dose–Response Modeling

Let \( X \) be the exposure variable of interest. From the Cox model the RR function

\[
RR(x) = \exp(f(x)\beta)
\]

can be derived. For modeling dose response, we investigated different shapes of the dose–response curve. A convenient method for defining a general model in which a linear relative risk function as well as concave and convex risk functions are covered is as follows. Let \( f \) be a transformation of the exposure variable with

\[
f(x) = \log(kx + 1),
\]

\( k \) constant. Then we have

\[
RR(x;\beta) = \exp(\beta\log(kx + 1))
\]

The value of \( \beta \) depends on \( k \). For \( \beta < 1 \) the dose–response curve is concave; for \( \beta > 1 \) it is convex. The model is therefore flexible enough to allow a rich set of monotone RR functions. If \( k \) is chosen such that \( \beta = 1 \), an additive (linear) dose–response curve is obtained. The best model is obtained by evaluating the goodness-of-fit statistic (deviance). A statistical evaluation of the method is given in Becher et al. (20).

### Latency

Latency for cancer varies from a few years to several decades. Different methods are available to address latency in epidemiologic studies (21). Here we chose to consider lagged exposure as

\[
D(t) = \int_0^t f(t)dt,
\]

\( k = 0, 5, 10, 15, \) or \( 20 \) years, where \( f(t) \) denotes concentration at time \( t \). With this definition, the last \( k \) years of exposure are not considered. This procedure "has the particular advantage of including the entire enumerated cohort and all members' complete exposure histories" (21).

### Attributable and Absolute Risk Estimation

The dose–response functions can be used to estimate the impact for a population with a given background level. Both the absolute risk for a given (unit) level and the attributable risk (AR) can be estimated. The attributable risk for TCDD exposure is

\[
AR = \frac{P(D = 1) - P(D = 1)_{TCDD = 0}}{P(D = 1)}
\]

\[
= 1 - \frac{1}{RR(TCDD)}\frac{f(TCDD)}{f(0)}
\]

where \( f \) is the density of TCDD distribution in the population. This formula reduces to

\[
AR = \frac{RR - 1}{RR},
\]

if the RR function is linear in the dose range observed in the population, where RR is that for the mean exposure level of TCDD in the population. Information on background exposure to TCDD, TEQ, and \( \beta \)-HCH and resulting blood levels in Germany (16–18) were used for calculation. The attributable risk is given for the accumulated dose at age 70 under background exposure, which is approximately 240 ng/kg·years (Table 1).

For absolute risk estimation we consider the absolute additional cancer risk associated with a constant exposure to a predefined dose, known as the unit risk (UR). It is defined as \( UR = P\text{(disease lifetime constant exposure of unit dose)} - P\text{(disease no exposure)} \). This quantity may be estimated using background mortality rates and the derived RR function (20). Here we use the German rates for total cancer mortality and total mortality (22). In accordance with previous risk assessments, we use the daily dose 1 pg/kg body weight/day as the unit. Assuming a body fat proportion of 25% this daily dose corresponds to 4 pg/kg fat/day or \( 365 \times 4 = 1.46 \) ng/kg fat/year. According to Table 1 this yields a cumulative dose of 869 ng/kg fat·years after a 70-year exposure to TCDD.

To calculate the UR based on ambient air exposure, we need additional considerations. Assuming a daily respiratory volume of \( 20 \) m\(^3\) and absorption of 50% (20), we get an intake of 10 pg/day from a unit ambient air concentration level of 1 pg/m\(^3\), i.e., 0.14 pg/kg body weight/day (assuming a mean body weight of 70 kg). This corresponds to 0.56 pg/kg fat/day = 0.204 ng/kg fat/year and equals 14% of the unit value obtained from an intake of 1 pg/kg body weight/day.

We used the SAS software package for all calculations. Cox regression models were fitted using PROC PHREG. The software package EGRET was used for Poisson regression (23).

### Results

As shown in Flesch-Janys et al. (12), SMR analyses yielded significantly increased overall SMR for all cancers and lung cancer in the total cohort (SMR 1.41; 95% CI 1.17–1.68 and SMR 1.51; 95% CI 1.07–2.08, respectively) and an increasing SMR with TCDD and TEQ dose levels. A dose–response analysis therefore seems justified. Our results are presented below.

#### Poisson Regression

Results of the Poisson model are presented in Table 2. The results with external rates reflect the observation in Flesch-Janys et al.

| Model | \( \chi^2 \) | df | \( \hat{\beta}_{GM} \) | \( \hat{\beta}_{TCDD} \) | \( p \)-Value, \( \hat{\beta}_{TCDD} \) |
|-------|-----------|----|-----------------|-----------------|-----------------|
| Internal comparison, offset: person-years | | | | | |
| Intercept only (GM) | | | | | |
| GM + TCDD | 10.0 | 1 | -5.62 | 0.0272 | 0.001 |
| GM + TCDD + age + calendar period | 210.1 | 9 | -8.38 | 0.0156 | 0.070 |
| External comparison, offset: expected number of deaths | | | | | |
| Intercept only (GM) | | | | | |
| GM + TCDD | 3.3 | 1 | 0.34* | 0.0163 | 0.055 |
| Internal comparison, offset: person-years | | | | | |
| Intercept only (GM) | | | | | |
| GM + TEQ | 11.4 | 1 | -6.57 | 0.0274 | <0.001 |
| GM + TEQ + age + calendar period | 208.9 | 9 | -8.38 | 0.0107 | 0.175 |

Abbreviations: \( \chi^2 \), difference of deviances to model with intercept only; df, degrees of freedom; GM, general mean. *The overall SMR in the cohort is \( \exp(\hat{\beta}_{GM}) = 1.40 \).
Table 3. Results of Cox regression analyses for TCDD with categorized exposure levels, latency 0 years, all cancers combined.

| TCDD categories | RR | 95% CI | p-Value |
|-----------------|----|--------|---------|
| 0 ≤ TCDD < 1    | 1.00 | -      | -       |
| 1 ≤ TCDD < 4    | 1.12 | 0.70–1.80 | 0.63          |
| 4 ≤ TCDD < 8    | 1.42 | 0.70–2.85 | 0.33          |
| 8 ≤ TCDD < 16   | 1.77 | 0.81–3.86 | 0.15          |
| 16 ≤ TCDD < 64  | 1.83 | 0.73–3.64 | 0.23          |
| ≥ 64 TCDD       | 2.19 | 0.76–6.29 | 0.15          |

Results are adjusted for year at entry, age at entry, duration of employment, and stratified for birth cohort (p[trend] = 0.03). *Measured in μg/kg blood fat x years.

Table 4. Results of Cox regression analyses for TCDD, exponential risk function, latency 0 years, all cancers combined.

| Variable | Parameter estimate | Standard error | p-Value | RR |
|----------|--------------------|----------------|---------|----|
| TCDD, μg/kg x years | 0.0089 | 0.0047 | 0.056 | 1.01 |
| TEQ_O | -0.024 | 0.06 | 0.70 | 0.98 |
| β-HCH | 0.14 | 0.10 | 0.17 | 1.15 |
| Cohort, gas workers vs Boehringer chemical plant workers | 0.11 | 0.22 | 0.63 | 1.11 |

Table 5. Results of time-dependent Cox regression analyses for TEQ with categorized exposure levels, latency 0 years, all cancers combined.

| TCDD categories | RR | 95% CI | p-Value |
|-----------------|----|--------|---------|
| 0 ≤ TEQ < 1     | 1.00 | -      | -       |
| 1 ≤ TEQ < 4     | 1.12 | 0.70–1.80 | 0.63          |
| 4 ≤ TEQ < 8     | 1.42 | 0.70–2.85 | 0.33          |
| 8 ≤ TEQ < 16    | 1.77 | 0.81–3.86 | 0.15          |
| 16 ≤ TEQ < 64   | 1.83 | 0.73–3.64 | 0.23          |
| ≥ 64 TEQ        | 2.08 | 0.61–7.03 | 0.23          |

Results are adjusted for year at entry, age at entry, duration of employment, and stratified for birth cohort (p[trend] = 0.06). *Measured in μg/kg blood fat x years.

Table 6. Results of Cox regression analyses for TCDD, exponential risk function, latency 0 years, all cancers combined.

| Variable | Parameter estimate | Standard error | p-Value | RR |
|----------|--------------------|----------------|---------|----|
| TEQ, μg/kg x years | 0.0078 | 0.0042 | 0.066 | 1.01 |
| β-HCH | 0.109 | 0.086 | 0.20 | 1.12 |
| Cohort, gas workers vs Boehringer chemical plant workers | -0.07 | 0.21 | 0.74 | 0.93 |

Cox Regression: General Models

A first investigation with the Cox model of TCDD levels grouped into five categories yielded the results in Table 3. As in the SMR analysis, increasing RR was observed with increasing dose level.

Table 4 lists results of the full Cox regression model with the all cancers end point, TCDD, TEQ_O, and β-HCH as time-dependent continuous exposure covariates, with all other covariates. This model yields RR(TCDD) = exp(0.0089 TCDD), TCDD in μg/kg x years with a p-value of 0.06. Few of the adjustment factors had separate effects. However, year at entry before 1954 was associated with a significantly increased risk (RR = 1.54; 95% CI 1.12–2.09).

Investigation of TEQ levels grouped into five categories yielded results similar to those for TCDD; however, there was a somewhat less pronounced increase in risk with increasing dose levels (Table 5).

Table 6 lists results of the Cox regression model with the all cancers end point, TEQ and β-HCH as time-dependent continuous exposure covariates, and all other covariates. This model yields RR(TEQ) = exp(0.0078 TEQ), TEQ in μg/kg x years with a p-value of 0.07. Again, few of the adjustment factors had separate effects. Entry into the plant before 1954 again was associated with a significantly increased risk (RR = 1.53; 95% CI 1.12–2.09). Duration of employment and age at entry had no additional effect. Birth cohort effects were accounted for in this model by stratification.

Analysis for lung cancer using either TCDD or TEQ as the exposure variable yielded almost the same regression estimates as that for the total cancer analysis (β_{TCDD} = 0.0096; β_{TEQ} = 0.01). However, because the number of cases was much lower, these estimates have low precision and result in p-values of 0.28 and 0.22, respectively. This indicates that the effect of the exposures may be similar for lung cancer and all cancer sites. The degree of uncertainty appears to be too high, however, to give explicit dose–response functions for TCDD or TEQ exposure and lung cancer risk.

Cox Regression: Latency Effects

Table 7 shows the results of the investigation of possible latency effect on total cancer mortality. The regression coefficients for TCDD and TEQ, the associated p-values, and the goodness-of-fit

### Table 4. Results of Cox regression analyses for TCDD, exponential risk function, latency 0 years, all cancers combined.

| Variable | Parameter estimate | Standard error | p-Value | RR |
|----------|--------------------|----------------|---------|----|
| TCDD, μg/kg x years | 0.0089 | 0.0047 | 0.058 | 1.01 |
| TEQ_O | -0.024 | 0.06 | 0.70 | 0.98 |
| β-HCH | 0.14 | 0.10 | 0.17 | 1.15 |
| Cohort, gas workers vs Boehringer chemical plant workers | 0.11 | 0.22 | 0.63 | 1.11 |

### Table 5. Results of time-dependent Cox regression analyses for TEQ with categorized exposure levels, latency 0 years, all cancers combined.

| TCDD categories | RR | 95% CI | p-Value |
|-----------------|----|--------|---------|
| 0 ≤ TEQ < 1     | 1.00 | -      | -       |
| 1 ≤ TEQ < 4     | 1.12 | 0.70–1.80 | 0.63          |
| 4 ≤ TEQ < 8     | 1.42 | 0.70–2.85 | 0.33          |
| 8 ≤ TEQ < 16    | 1.77 | 0.81–3.86 | 0.15          |
| 16 ≤ TEQ < 64   | 1.83 | 0.73–3.64 | 0.23          |
| ≥ 64 TEQ        | 2.08 | 0.61–7.03 | 0.23          |

Results are adjusted for year at entry, age at entry, duration of employment, and stratified for birth cohort (p[trend] = 0.06). *Measured in μg/kg blood fat x years.

### Table 6. Results of Cox regression analyses for TCDD, exponential risk function, latency 0 years, all cancers combined.

| Variable | Parameter estimate | Standard error | p-Value | RR |
|----------|--------------------|----------------|---------|----|
| TEQ, μg/kg x years | 0.0078 | 0.0042 | 0.066 | 1.01 |
| β-HCH | 0.109 | 0.086 | 0.20 | 1.12 |
| Cohort, gas workers vs Boehringer chemical plant workers | -0.07 | 0.21 | 0.74 | 0.93 |

### Table 7. Results of Cox regression analyses for TCDD, exponential risk function, latency 0 years, all cancers combined.

| Variable | Parameter estimate | Standard error | p-Value | RR |
|----------|--------------------|----------------|---------|----|
| TEQ, μg/kg x years | 0.0078 | 0.0042 | 0.066 | 1.01 |
| β-HCH | 0.109 | 0.086 | 0.20 | 1.12 |
| Cohort, gas workers vs Boehringer chemical plant workers | -0.07 | 0.21 | 0.74 | 0.93 |
Table 7. Influence of latency on different models for TCDD and TEQ.

| Latency, years | TCDD $\beta$Value, $p$-Value | TEQ $\beta$Value, $p$-Value |
|---------------|-------------------------------|----------------------------|
| 0             | 0.0096 0.026                  | 0.0093 0.024               |
| 5             | 0.0104 0.023                  | 0.0101 0.020               |
| 10            | 0.0116 0.021                  | 0.0113 0.018               |
| 15            | 0.0132 0.020                  | 0.0130 0.017               |
| 20            | 0.0160 0.020                  | 0.0157 0.018               |

Results are adjusted for year at entry, age at entry, duration of employment, and stratified for birth cohort.

statistic for the total model are given. The regression coefficients gradually increase with increasing latency time. There is a slight improvement of the fit with increased latency time, but the $p$-values for $\beta_{\text{TCDD}}$ and $\beta_{\text{TEQ}}$ remain almost constant. It is noteworthy that for the estimation of the lifetime risk the choice of the latency period has little effect because the smaller dose associated with a longer latency period is outweighed by the larger regression coefficient.

Cox Regression: Dose–Response Modeling

Most emphasis was placed on assessing the dose–response curve. We investigated the class of models $RR(x, \beta) = \exp(\beta \log(kx + 1)) = (kx + 1)^\beta$ using the deviance as measure for goodness of fit. In these models, $\log(kx + 1)$ is the transformation function for the dose variable and $\beta$ is the estimated parameter. Values for $k$ were chosen arbitrarily. Figure 1 compares deviation and $k$ for the Cox model, with TCDD as the exposure variable and all other variables used as covariates as before. The maximum of the curve is the model with the best fit to the data among the class of RR functions considered. Figure 2 shows corresponding results with a latency of 10 years. Table 8 gives the results of three selected models: the model with the best fit, the additive RR function, and the exponential RR function, all with latency times of 0 and 10 years.

The differences in respective fits are small; therefore we cannot justify selection of a particular model on statistical grounds. The model with the best fit has a concave shape and therefore yields higher risks for low exposures. The dose–response curves are displayed in Figure 3.

The same procedure was applied for TEQ. Again, the differences in goodness of fit were small. In this case, the model with the best fit is rather close to the additive RR function. Results of the analysis are given in Table 8 and the dose–response curves are displayed in Figure 4.

Attributable Risk and Unit Risk Estimates

Because the dose–response analysis yielded stronger results for TCDD than for TEQ, and because there was no indication of a separate effect of congeners other than TCDD in either the present cohort or in other epidemiologic studies, we present attributable risk and UR estimates for TCDD only. As shown previously, based on the data, no clear distinction can be made as to the function on which absolute risk estimation should be based. Under the additive RR function we estimate an attributable risk of 0.0038 (95% CI 0.0004–0.007) for TCDD assuming a constant dose rate of 0.35 ng/kg/year.

UR estimates both for a unit intake of 1 pg/kg body weight/day and a unit concentration value of 1 pg/m³ in ambient air are given in Table 9. For the unit intake 1 pg/kg body weight/day these values range from $1.2 \times 10^{-3}$ to $7.7 \times 10^{-3}$. For the unit concentration value of 1 pg/m³, values ranging from $1.65 \times 10^{-4}$ to $1.1 \times 10^{-3}$ are observed. These ranges reflect the degree of variation associated with the respective models; they are not interpretable as confidence intervals.

Discussion

We have presented an extensive analysis of a single cohort of workers with high exposure to TCDD and other chlorinated dioxins and furans. This cohort is among the most studied dioxin-exposed cohorts in the world. Nevertheless, there are several limitations to this type of analysis and these are discussed below.

Table 8. Results of different dose–response models for TCDD and TEQ, in μg/kg blood fat.

| Model                     | Relative risk equation | Estimate | Likelihood ratio statistic | $p$-Value of $\beta$ |
|---------------------------|------------------------|----------|----------------------------|----------------------|
| **TCDD**                  |                        |          |                            |                      |
| Latency time: 0 years     |                        |          |                            |                      |
| Multiplicative model      | $RR(x) = \exp(\beta x)$ | $\beta = 0.00869$ | 30.2                     | 0.043                |
| Additive model            | $RR(x) = 1 + \beta x$  | $\beta = 0.016$  | 30.8                     | 0.031                |
| Power model               | $RR(x) = \exp(\beta \log(kx + 1)) = (kx + 1)^\beta$ | $\beta = 0.326$, $k = 0.17$ | 31.2                     | 0.026                |
| Model without TCDD        |                        |          |                            |                      |
| Latency time: 10 years    |                        |          |                            |                      |
| Multiplicative model      | $RR(x) = \exp(\beta x)$ | $\beta = 0.0098$ | 34.0                     | 0.048                |
| Additive model            | $RR(x) = 1 + \beta x$  | $\beta = 0.018$  | 34.4                     | 0.038                |
| Power model               | $RR(x) = \exp(\beta \log(kx + 1)) = (kx + 1)^\beta$ | $\beta = 0.398$, $k = 0.11$ | 34.6                     | 0.036                |
| Model without TCDD        |                        |          |                            |                      |
| **TEQ**                   |                        |          |                            |                      |
| Latency time: 0 years     |                        |          |                            |                      |
| Multiplicative model      | $RR(x) = \exp(\beta x)$ | $\beta = 0.00863$ | 30.2                     | 0.045                |
| Additive model            | $RR(x) = 1 + \beta x$  | $\beta = 0.015$  | 30.5                     | 0.040                |
| Power model               | $RR(x) = \exp(\beta \log(kx + 1)) = (kx + 1)^\beta$ | $\beta = 0.7847$, $k = 0.023$ | 30.5                     | 0.040                |
| Model without TEQ         |                        |          |                            |                      |
| Latency time: 10 years    |                        |          |                            |                      |
| Multiplicative model      | $RR(x) = \exp(\beta x)$ | $\beta = 0.00946$ | 34.0                     | 0.048                |
| Additive model            | $RR(x) = 1 + \beta x$  | $\beta = 0.0175$  | 34.2                     | 0.046                |
| Power model               | $RR(x) = \exp(\beta \log(kx + 1)) = (kx + 1)^\beta$ | $\beta = 0.8754$, $k = 0.022$ | 34.2                     | 0.046                |
| Model without TEQ         |                        |          |                            |                      |

Results are adjusted for year at entry, age at entry, duration of employment, $\beta$-HCH, and stratified for birth cohort.
Magnitude of Effect and Assessment of Dose

The overall effect of exposure to cancer risk was not very large, and it was therefore unlikely that a clear picture of the shape of the dose–response curve could emerge. This cohort, however, was unique in that exposure assessment based on blood measurements was available for many cohort members. We have shown that the work histories can be used to estimate concentrations of substances during exposure and after exposure has ceased, and therefore we were able to get sufficiently reliable estimates for the exposures of all cohort members (12). Nevertheless, there are several sources of variation within this estimation procedure. These, however, are not likely to be related to cause of death and therefore would yield underestimations rather than overestimations of the effect.

Robustness of Results

Additional analyses were performed to investigate the robustness of the results. Because categorizing continuous covariables is always arbitrary, we investigated different procedures, for example, using more refined categories. All models were calculated with and without the gas worker cohort as an unexposed control cohort. No substantial differences were observed in the estimates; however, the standard errors were somewhat higher when the gas workers were excluded. We performed subgroup analyses using the year of employment entry to divide the cohort into different subcohorts. We used the upper and lower confidence limit to estimate the half-life of TCDD as obtained from Flesch-Janys et al. (8) for dose calculation. We excluded workers from specific production departments because they may have been exposed to other substances (e.g., lindane). A possible effect for using the unexposed comparison cohort was investigated by omitting it from the dataset. All these analyses yielded only slight changes in the overall results. This was true for both TCDD and TEQ as the dose variable. Using exposure to β-PCH as an additional covariable did not alter the risk estimates for TCDD or TEQ. In some analyses β-PCH showed an independent effect; however, this finding needs further investigation. A full account of the results from these analyses are given in the technical report of this study.

The observed effect of the variable year of entry before 1954 is difficult to interpret. This effect holds for both cohorts, which indicates that it is independent of TCDD exposure. However, the possibility cannot be excluded that exposure before that date actually was higher than predicted by our models. Duration of employment and age at entry had no additional effects. Birth cohort effects were accounted for in this model by stratification (see "Materials and Methods"). Using birth cohort as a covariable yielded almost identical results (data not shown).

Threshold versus Nonthreshold Level

Some authors [e.g. Aylward et al. (13)] consider the possible existence of a threshold level for TCDD. It is almost impossible to obtain conclusions concerning a possible threshold level from epidemiologic data.
The fact that the dose–response curve with the best fit has a concave shape may be interpreted as an indication of the absence of a threshold. A similar dose–response curve has been reported very often. One example is cumulative dose of inhaled arsenic and lung cancer for which Enterline et al. (25) found a similar dose–response curve. In this study, cumulative exposure as air concentration \times time of exposure was used as a dose variable. Arsenic, however, is rapidly excreted from the body, and therefore this dose variable may be considered the AUC with a very low half-life in the body. A direct comparison of the results is therefore not possible. Both the kinetics of these two substances and the suspected mechanism in cancer development are different. The data from this study do not indicate the existence of a threshold level. However, no definite conclusions can be drawn on that issue from these data.

### Dioxin and Other Air Pollutants

Cancer risks from seven ambient air pollutants (arsenic, asbestos, cadmium, diesel exhaust, polycyclic aromatic hydrocarbons, TCDD, benzene) have been estimated and compared for Germany (26). In this study the additional lifetime cancer risk from constant exposure to 1 ng TCDD/m³ in ambient air was given as 1.4 \times 10^{-3} based on animal data. Our estimated values range from 3 \times 10^{-4} to 3 \times 10^{-3}, slightly lower but in the same order of magnitude. Taking the absolute concentration of TCDD in the ambient air into account, in the range 1 to 10 fg/m³, it is reasonable to suggest that the cancer risk from ambient air TCDD concentration is very low and almost negligible. In the LAI report (26) it was concluded that the relative importance of TCDD in relation to other air pollutants is very low, a statement that can be made with a somewhat larger degree of certainty based on our results.

### Effect of Different Congeners

A separate effect for other PCDD/Fs other than TCDD could not be established. This was partly because exposure was highly correlated with \(\text{B-HCH}\) exposure. Although in the dose–response analysis we observed a relationship between cancer risk and both TCDD and TEQ exposure, we feel less confident about the result for TEQ. The dose–response curve for TCDD is similar to that for TEQ, as seen in Table 7. The background level of TEQ is about 5 to 10 times larger than that of TCDD and absolute risks could easily be calculated. However, because no separate effects for dioxins other than TCDD were identified in this or any other occupational cohort, we did not present URs for TEQ.

### Childhood Exposure

It must be noted that with our data it is not possible to address the effect of dioxin exposure in childhood. Although it is likely that metabolism at younger ages yields a shorter half-life for dioxins, data on adverse health effects, in particular cancer development later in life, are not available and cannot be deduced. It is possible that such effects may become visible after a long-time observation time of Seveso, Italy, cohort (27). One cannot exclude the possibility that exposure to TCDD in early childhood poses a higher risk than predicted from the models given here. Although it is possible to employ some safety factors for childhood exposure levels to address this fact, such factors must be arbitrary and would not be based on scientific knowledge.

### Dose Metric and Latency

The question of the appropriate dose metric is difficult to answer. In previous analyses with this cohort, concentration at end of employment was used. This analysis also demonstrated a positive relationship to cancer. There is no clear supporting evidence for a specific dose metric; however, for environmental risk assessment it appears that cumulative dose is accepted as an appropriate metric. The results on latency are interesting. In terms of absolute risk estimates, the results are almost identical for any latency period used. This is because the increasing regression coefficient with increasing latency time is outweighed by decreasing cumulative dose with latency. Therefore, the question of the true latency is of less importance for quantitative risk assessment.

### Other Risk Assessments

The U.S. Environmental Protection Agency currently is performing quantitative risk assessment for TCDD based on published data from three occupational cohort studies (1,10,28). No dose–response analyses using individual data are performed. These results were available only in a draft version at the time this paper was written and therefore were not available for comparison with our results. In general, analyses based on tabulated summary data are less precise than those based on individual measurements. In addition, it is not possible to adjust for potential confounders. On the other hand, analyses based on such grouped data may be more robust because extreme data points may have less impact.

In summary, our risk assessment is based on an occupational cohort with a large number of individual dioxin measurements. The result, which was not included in the IARC evaluation because it was not published at that time, supports the recent classification of TCDD as an IARC Group 1 substance. The estimated risks at environmental levels are on the same order of magnitude as those obtained from previous animal experiments using a linearized multistage model. Several assumptions were made to bridge data gaps that hampered interpretation of the findings. Thus, all results should be considered with caution, as the risk levels in the low-dose range are strongly dependent on the underlying model and the appropriateness of the underlying assumptions. This study is not a final risk estimate for dioxins but we believe that it contributes a relevant body of information that might help solve the dioxin–cancer puzzle.

### REFERENCES AND NOTES

1. Fingerhut MA, Halperin WE, Marlow DA, Piacitelli LA, Honchar PA, Sweeney MH, Greife AL, Dill PA, Steenland K, Suruda AJ. Cancer mortality in workers exposed to 2,3,7,8-tetrachlorodibenzo-p-dioxin. New Engl J Med 199:212–218 (1991).
2. Saracci R, Kogevinas M, Bertazzi PA, Bueno de Mesquita BH, Coggon D, Green LM, Litterin M, Lynge E. Cancer mortality in workers exposed to chlorophenox herbicides and chlorophenols. Lancet 338:1027–1032 (1991).
3. Flesch-Janys D, Berger J, Gurn P, Manz A, Nagel S, Walzgrott H, Dwyer JH. Exposure to polychlorinated dioxins and furans (PCDD/F) and mortality in a cohort of workers from a herbicide-producing plant in Hamburg, Federal Republic of Germany. Am J Epidemiol 142:1165–1175 (1995).
4. Becher H, Flesch-Janys D, Kauppinen T, Kogevinas M, Steindorf K, Manz A, Wahrendorf J. Cancer mortality in Germany: Migrant workers exposed to phenoxy herbicides and dioxins. Cancer Causes Control 7:312–321 (1996).

5. Kogevinas M, Becher H, Benn T, Bertazzi P-A, Boffetta P, Bueno-de-Mesquita B, Coggon D, Colin D, Flesch-Janys D, Fingerhut M et al. Cancer mortality in workers exposed to phenoxy herbicides and dioxins. An expanded and updated international cohort study. Am J Epidemiol 145:1061–1075 (1997).

6. McGregor DB, Partensky C, Wilbourn J, Rice JM. An IARC evaluation of polychlorinated dibenzo-p-dioxins and polychlorinated dibenzofurans as risk factors in human carcinogenesis. Environ Health Perspect 106(Suppl 2):755–760 (1998).

7. IARC. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Vol 69: Polychlorinated Dibenzo-para-Dioxins and Dibenzofurans. Lyon:International Agency for Research on Cancer, 1997.

8. Flesch-Janys D, Becher H, Gurn P, Jung D, Konietzko J, Manz A, Päpke O. Elimination of polychlorinated dibenzo-p-dioxins and dibenzo-furans (PCDD/F) in occupationally exposed persons. J Toxicol Environ Health 47:363–378 (1996).

9. Michalek JE, Pirkle JL, Caudill SP, Tripathi RC, Patterson DG, Needham LL. Pharmacokinetics of TCDD in veterans of Vietnam War: results of a 10-year follow-up. J Toxicol Environ Health 47:209–220 (1996).

10. Manz A, Berger J, Dwyer JH, Flesch-Janys D, Nagel S, Waltsgott H. Cancer mortality among workers in chemical plant contaminated with dioxin. Cancer 338:959–964 (1991).

11. Kauppinen T, Kogevinas M, Johnson E, Becher H, Bertazzi PA, Bueno de Mesquita HB, Coggon D, Green L, Littorin M, Lyng E. Chemical exposure in manufacture of phenoxy herbicides and chlorophenols and in spraying of phenoxy herbicides. Am J Ind Med 23:903–920 (1993).

12. Flesch-Janys D, Steindorf K, Gurn P, Becher H. Estimation of the cumulative 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):655–662 (1998).

13. Aylward LL, Hay SM, Karch NJ, Paustenbach DJ. 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 (1996).

14. Breslow NE, Day NE. Statistical Methods in Cancer Research. Vol II: The Design and Analysis of Cohort Studies. IARC Sci Publ No 82. Lyon:International Agency for Research on Cancer, 1987.

15. Coleman M, Douglas A, Hermon C, Peto J. Cohort study analysis with a Fortran computer program. Int J Epidemiol 15:134–137 (1986).

16. Päpke O, Ball M, Lis ZA, Scheuert K. PCDD/PCDF in whole blood samples of unexposed persons. Chemosphere 19:941–948 (1989).

17. Päpke O, Ball M, Lis A. PCDD/PCDF in humans - an update of background data. Dioxin '93. Organohalogen Compounds 13:81–84 (1993).

18. Päpke O, Ball M, Lis A. PCDD/PCDF in humans, a 1993 update of background data. Chemosphere 29:2355–2360 (1994).

19. Berger J, Manz A. Cancer of the stomach and the colon-rectum among workers in a coke gas plant. Am J Ind Med 22:825–834 (1992).

20. Becher H, Steindorf K, Wahrendorf J. Epidemiological Methods of Risk Assessment with Applications [in German] (Umweltbundesamt Berlin, ed). Berlin:Erich Schmidt Verlag, 1995.

21. Checkoway H, Pearce N, Crawford-Brown DJ. Research Methods in Occupational Epidemiology. New York:Oxford University Press, 1989.

22. Becker N, Wahrendorf J. Atlas of the cancer mortality in the Federal Republic of Germany. 3rd edition. Heidelberg/New York:Springer Berlin, 1997.

23. Statistic and Epidemiology Research Corporation. EGRET User's Manual, Seattle, WASERC, 1989.

24. Becher H, Flesch-Janys D, Gurn P, Steindorf K. Risikoabschätzung für das Krebsrisiko von polychlorierten Dibenodioxidin- und Furanen (PCDD/Fs) auf der Datenbasis epidemiologischer Krebsmortalitätstudien. Tech Rpt 3/97. Heidelberg, Germany:German Cancer Research Center, Division of Epidemiology, 1997.

25. Enterline PE, Henderson VL, Marsh GM. Exposure to arsenic and respiratory cancer. A reanalysis. Am J Epidemiol 125:929–938 (1987).

26. LAI. Beurteilungsmaßstäbe zur Begrenzung des Krebsrisikos durch Luftverunreinigungen. Abschlußbericht der Arbeitsgruppe "Krebsrisiko durch Luftverunreinigungen" des Länderausschusses für Immissionsschutz. Düsseldorf:Ministerium für Umwelt, Raumordnung und Landwirtschaft des Landes NRW (Hrsg.), 1992:1–158.

27. Bertazzi PA, Bernucci I, Brambilla G, Consolini D, Pesatori AC. The Seveso studies on early and long-term effects of dioxin exposure: a review. Environ Health Perspect 106(Suppl 2):625–633 (1998).

28. Zober A, Messerer P, Huber P. Thirty-four year mortality follow-up of BASF employees exposed to 2,3,7,8-TCDD after the 1953 accident. Int Arch Occup Environ Health 62:139–157 (1990).