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Temporal trends in human TCDD body burden: Decreases over three decades and implications for exposure levels

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Data on lipid levels of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) in the general population in the United States, Canada, Germany, and France over the past 30 years were compiled from the literature. Mean lipid levels of TCDD exhibited a steady decrease by nearly a factor of 10 over this time period, with lipid-adjusted TCDD levels in 2000 about 2 parts per trillion (ppt). Pharmacokinetic modeling using a one-compartment model indicated that absorbed intake levels of TCDD must have decreased by more than 95% from levels in 1972 to result in the observed decrease in human lipid levels, with the bulk of this decrease occurring before 1980. Based on this modeling and the pharmacokinetic properties of TCDD in humans, we conclude that mean levels of TCDD in the general population are likely to decrease further over the next 15 years, to between 0.5 and 1 ppt, even if intake levels do not decrease further. Fewer data over a shorter time period are available for other dioxin and furan congeners in human lipid, but these data indicate substantial decreases as well, with general population TEQ lipid levels currently at least fourfold lower than in 1970 and still decreasing. Food sampling data are limited, but support these trends.
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Introduction

Over the past two decades, the U.S. Environmental Protection Agency (USEPA) and other regulatory agencies have promulgated numerous rules and measures specifically designed to reduce human exposure to polychlorinated dibenzodioxins and dibenzofurans (PCDD/Fs) in the environment, the food supply, consumer products, and the workplace. For example, in 1984, under the authority of the Clean Water Act, the USEPA published an ambient water quality criterion for 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD). In 1993, the USEPA proposed integrated rules for the pulp and paper industry, which included an effluent guideline for TCDD, and regulations passed in 1995 for municipal waste combustors and in 1997 for medical waste incinerators were expected to result in a 95% decrease in dioxin emissions from these two source categories. Other historical source control measures included cancellation of pesticide registration for compounds known to contain trace levels of TCDD and restrictions on the use of dioxin-containing pulp and paper sludges.

Implementation of and compliance with these regulations imposes a significant cost that is ultimately borne by the general public. Therefore, it is reasonable to assess whether and to what degree these control measures have effectively reduced our daily exposure to PCDD/Fs, and whether additional measures are required to further decrease PCDD/F body burdens in the general population. Clearly, this is a complex question that can be approached using several different techniques, including the following: estimating PCDD/F releases before and after sources were eliminated and regulations went into effect, making temporal measurements of PCDD/F levels in the environment, conducting exposure assessments, and/or actually measuring PCDD/F body burdens.

With respect to source elimination and emission control, USEPA's most recent analysis of the U.S. "dioxin inventory" concludes that quantifiable releases of dioxin-like compounds into the environment decreased by approximately 80% between 1987 and 1995, due primarily to a reduction in "point-source" emissions from municipal and medical waste incinerators (USEPA, 2000). It has been estimated that nonpoint combustion sources such as backyard burning are responsible for a significant fraction of the ongoing PCDD/F sources (USEPA, 2000), and that the contribution of these sources, either currently or in the past, cannot be quantified accurately. Temporal measurements of environmental PCDD/F levels are consistent with a general reduction in emissions and releases. Specifically, several

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sediment coring analyses have shown that PCDD/F levels began to increase around the 1930s time frame, peaked some time in the 1960s or early 1970s, and have generally been declining since the 1970s (e.g., Alcock and Jones, 1996), although the magnitude of decline is highly variable and depends on the surface-water body from which sediment samples are taken.

With respect to exposure assessment, it has typically been assumed that the vast majority of the general public is exposed to PCDD/Fs primarily via the diet — specifically, ingestion of animal fats in meats and dairy products. However, while reductions in PCDD/F emissions would be expected to ultimately result in lower levels in the food supply, and hence, in human intake, these changes may lag the emissions decline (USEPA, 2000). Unfortunately, there is a paucity of data to support accurate estimates of U.S. dietary PCDD/F intake over the last few decades. This is primarily due to the fact that large-scale, long-term, nationally representative monitoring of PCDD/F levels in the U.S. food supply has not been conducted. Short-term studies generally are not comparable because of differences in sampling protocols and analytical techniques. In addition, current data on PCDD/F levels in fish (farm-raised and wild), eggs, and milk are even more limited than the data available for meat products (Huwe, 2002).

Reports from European countries suggest that dietary PCDD/F intake rates have decreased severalfold since the 1970s (the Netherlands) and the 1980s (the United Kingdom) (Liem et al., 2000); however, the relevance of these findings to U.S. dietary intake is unclear. There is some limited quantitative evidence to suggest that PCDD/F levels in the U.S. food supply are decreasing. For example, Winters et al. (1998) analyzed all 2,3,7,8-substituted PCDD/Fs in preserved food samples from various decades of the 20th century, and reported that the PCDD/F TEQ levels in beef, pork, poultry, and dairy products during the 1950s–1970s were approximately two- to threefold higher than current levels.

While these results appear to be consistent and perhaps promising, it is important to note that they are all indirect measures of actual exposure and, accordingly, they all contain varying degrees of uncertainty. From a regulatory decision-making standpoint, they are less than ideal as a basis for reaching conclusions concerning the merits of past environmental PCDD/F legislation and/or the need for additional control measures. Measurements of PCDD/F concentrations in human tissues arguably provide the most direct and reliable estimates of PCDD/F exposure and uptake.

Over the past 20 years, there have been several reports of measured TCDD body burdens in populations with no known exposure to TCDD (other than exposure to trace levels in the diet, environment, and consumer products). In general, there appears to be a decreasing trend.

Pinsky and Lorber (1998) were the first to attempt to use information on temporal trends in sediment cores and body burdens to reconstruct historical exposures to 2,3,7,8-TCDD among the U.S. general population. The authors used information from the sediment core data to bound the time frame when exposures would have peaked, and used a simple pharmacokinetic (PK) model (coupled with a Bayesian framework) to analyze serum lipid-level data from five studies in an attempt to predict what exposure trends were through the late 1980s in the United States. Their results suggest that exposures in the United States peaked sometime around the late 1960s to early 1970s and dropped precipitously until the late 1980s (the latest time points for which they had body burden data). As a result, the authors were limited to making predictions into the late 1980s and were unable to say much about exposures that the U.S. population is experiencing today or what body burdens may be in the future.

Further evidence for this general decline in body burdens is evidenced in the study by Jackson and Michalek (2001) in which they reported serum lipid TCDD levels measured in 1987 and 1997 in a "control" group of Air Force veterans who did not handle Agent Orange and whose serum TCDD levels were similar to those in the general civilian population. The mean serum lipid TCDD levels in samples from this group of 1419 individuals decreased from 4.5 to 2.0 ppt over the 10-year period. The samples from this prospective cohort are perhaps the most convincing piece of evidence that the general population is experiencing a significant decline in TCDD body burdens.

In this analysis, we assemble additional serum and adipose lipid TCDD data from a variety of general population groups in North America and Western Europe. These data (more than 2800 individual samples) are used to estimate historical (ca. 1970), current, and likely future "background" TCDD body burdens in the general population. We use a simple one-compartment pharmacokinetic model, in conjunction with a variety of different intake and elimination assumptions, to develop a range of plausible TCDD doses for past, current, and future exposures. Based on the conclusions of this modeling and analysis, we make predictions regarding future body burden trends and provide perspectives on the effects of future changes in intake levels (e.g., via new control measures) on general-population body burdens.

Methods

Human Adipose and Serum Sampling Data

We surveyed the literature for studies reporting levels of TCDD in samples from the general populations of the United States, Canada, Germany, and France. Early studies, from the 1970s and most of the 1980s, reported levels of

TCDD in adipose tissue samples, because analytical techniques were not yet sensitive enough to allow detection and quantitation of TCDD in serum samples. Studies since the late 1980s have generally reported levels in serum lipids. As demonstrated by Patterson et al. (1988), human adipose tissue levels of TCDD on a lipid-adjusted basis are generally comparable to serum lipid-adjusted levels. Therefore, values reported in adipose tissue on a lipid-adjusted basis were compared directly with serum lipid-level measurements; values reported in adipose tissue on a whole-weight basis were adjusted using an assumption of 80% lipid in adipose tissue (Patterson et al., 1988) for comparison to both lipid-adjusted adipose tissue levels and serum lipid levels. We extracted from each study the mean, minimum, and maximum lipid-adjusted TCDD levels; the average age and age range of persons sampled; and the year(s) of sampling. Not all the studies provided all of these pieces of data.

The data from the various studies were plotted versus the median year of sampling to evaluate the temporal trend in lipid-adjusted TCDD levels in the general population. The earliest value found in the literature was for adipose tissue samples taken and stored in 1971–1973 and analyzed in the late 1980s (Kang et al., 1990). The latest values used were from studies reporting values from sampling conducted in 1999. The average age of the sampled populations was evaluated for possible correlation with sampling year by evaluating the Spearman rank correlation coefficient for those studies that reported age. Possible trends in age of sampled populations were also evaluated using nonparametric ANOVA of age versus decade using the Kruskal–Wallis test.

Modeling

A one-compartment pharmacokinetic model simulating the change in body burden (and therefore, serum lipid concentration) of TCDD was constructed to evaluate the effect on predicted serum lipid levels of various hypothetical scenarios of change in intake levels (absorbed dose). We assumed that a simple first-order elimination process, with a half-life of 7.5 years, governed the elimination of TCDD at levels within the range of typical background serum lipid levels over the entire time period of interest (less than 50 ppt). This value was chosen as a reasonable central estimate based on the literature (Poiger and Schlatter, 1986; Flesch-Janys et al., 1996; Michalek and Tripathi, 1999; Michalek et al., 2002). Change in body burden over time was modeled in an Excel® spreadsheet using an incremental model:

$$A_{t+1} = A_t - (k^* A_t) + I_{t+1}$$

where A is the total amount in the body, k is the elimination rate constant, and I is the incremental intake. Serum lipid concentration was calculated from total body amount at each time point assuming a 70-kg body weight and 25% body fat.

Modeling was performed for changes in body burden as a function of intake, beginning in 1972 and extending through the present and over the next decade. The purpose of the modeling was to explore different assumptions regarding changes in intake levels of TCDD since 1972. Pinsky and Lorber (1998) and Alcock and Jones (1996) have concluded that environmental levels of TCDD peaked sometime in the 1960s or early 1970s, based on data from lake sediment cores and other sources. Initial review of the data on lipid-adjusted TCDD levels in the general population appeared to show a steady decrease from the earliest samples (1971–1973) forward, indicating that the peak in body burdens occurred either at that time or sometime earlier, so assumptions about changes in intake level in the general population in our modeling were predicated on the general assumption that there has been some decline in intake since 1970.

Initial conditions (body burden, intake level) were set for the modeling based on data from the literature review. Initial body burden in 1972 was set to correspond to a lipid-adjusted level of 20 ppt in a 70-kg person based on data from 1972 (Kang et al., 1990). Initial intake in 1972 was set at a level corresponding to the steady-state intake level required to produce a 20-ppt serum lipid level after an extended period of intake (four to five half-lives, or 30 to 37 years), a daily dose of 1.3 pg TCDD/kg/day (absorbed dose). This estimate could either underestimate or overestimate actual intake levels at this time point or in the time period shortly before 1972. If the observed 20-ppt serum lipid level was the peak population mean level, exposures at that time could have been much higher than 1.3 pg/kg/day, because the general population was unlikely to have been at steady state. Figure 1 illustrates how different intake rates

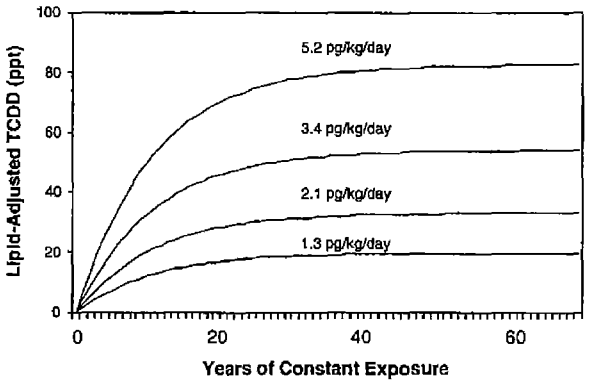

Figure 1. Pharmacokinetics of TCDD assuming a 7.5-year half-life for elimination. A 20-ppt lipid level of TCDD can be obtained at steady state assuming absorbed intake of 1.3 pg/kg/day; however, achieving steady state takes four to five half-lives (30 to 37.5 years). A 20-ppt lipid level can be achieved following shorter exposure durations if intake levels are higher than 1.3 pg/kg/day.

can result in a 20-ppt lipid-adjusted level depending on the time period of constant exposure. Intake of TCDD at the rate of 1.3 pg TCDD/kg/day over several decades will result in a serum lipid concentration approaching 20 ppt. Higher average intake rates can result in lipid levels of 20 ppt in a shorter period of time. Thus, 1.3 pg TCDD/kg/day represents a lower bound on the long-term average intake level needed to produce a general population level of 20 ppt, if this was the peak general population body burden.

If the observed level of 20 ppt in 1972 represented a level already on the decline from some higher average general population levels at an earlier time, the intake at 1972 could have been lower than the long-term average level of 1.3 pg/kg/day associated with a 20-ppt steady-state serum lipid level. However, earlier average intakes would have to have been higher than 1.3 pg/kg/day for some time period in order to have produced the higher peak serum levels.

In the absence of data to confirm that any higher general population levels had occurred at time points prior to 1972, we modeled the intake data assuming that general population levels prior to 1972 were no higher than those observed for 1972. We assigned an intake level of 1.3 pg/kg/day to year 1972 as the lowest average intake level over an extended time period (30 years or more) that could have produced a 20-ppt serum lipid level; we also evaluated the effect of assuming higher intake levels in 1972.

Using the one-compartment pharmacokinetic model, we explored different functions to describe the rate of change in the intake level (exponential and linear decreases) that would result in temporal trends in TCDD levels in humans that match the compiled sampling data. We used least sum of squares fitting for the parameters of these intake functions to identify the intake functions that produced predicted lipid TCDD levels that best fit the compiled sampling data. We

Table 1. Data sets reporting levels of TCDD in the general population of the United States, Canada, Germany, and France, 1972–1999.

Reference	Midpoint sampling year (range)	*n*	Mean TCDD level, ppt (range)	Population, sample type	Mean age (range)	Country
Kang et al., 1990	1972 (1971–1973)	27	19.8	Males, adipose tissue	NR (20–36)	U.S.
Kang et al., 1990	1975 (1974–1976)	29	17.3	Males, adipose tissue	NR (23–39)	U.S.
Schecter et al., 1986	1976	25	6.4 (2.0–13.0)[†,a]	Autopsy, adipose tissue	39.7	Canada
Gross et al., 1984	1978	4	5.1 (3.0–8.0)[†]	Veteran controls, adipose tissue		U.S.
Kang et al., 1990	1978 (1977–1979)	57	11.6	Males, adipose tissue	NR (26–42)	U.S.
Kang et al., 1990	1981 (1980–1982)	82	12.6	Males, adipose tissue	NR (29–45)	U.S.
Stanley, 1986	1982	46	6.2 (ND–14.0)	General population, adipose tissue composites	NR	U.S.
Patterson et al., 1986b	1984	35	7.1 (2.7–19.0)[†]	Autopsy, adipose tissue	55.8 (16–85)	U.S.
Graham et al., 1986	1984	35	7.2 (2.2–20.5)[†]	Autopsy, adipose tissue	41.5 (15–88)	U.S.
Patterson et al., 1986a	1985	128	7.0 (1.4–20.2)[†]	Surgical patients, adipose tissue	49.0 (18–85)	U.S.
Patterson et al., 1987	1985	21	7.6 (1.9–26.0)	Surgical patients, serum	42.5 (19–70)	U.S.
Patterson et al., 1994	1985	28	10.4 (1.6–38)	Adults, adipose tissue	49.2 (19–78)	U.S.
Kahn et al., 1988	1986	7	4.3 (1.0–5.0)	U.S. Army controls (non-Vietnam), serum		U.S.
CDC, 1988	1987	97	4.1 (ND–15.0)	U.S. Army controls (non-Vietnam), serum	39 (33–46)	U.S.
Stanley and Orban, 1991	1987	48	6.6 (ND–15.1)	General population, adipose tissue composites	NR	U.S.
Jackson and Michalek, 2001	1987	1058	4.5 (ND–26.6)	Ranch Hand comparisons, serum	49 (36.7–72.9)	U.S.
Fingerhut et al., 1991	1988	79	7 (2–20)	Males, serum		U.S.
Wittsiepe et al., 2000	1991	95	4.62 (1.2–12)	General population, serum	44.7 (12–82)	Germany
Jackson and Michalek, 2001	1992	244	3.2 (ND–12.2)	Ranch Hand comparisons, serum	53 (42.8–75.7)	U.S.
Papke, 1998	1996	47	2.1 (1–3.7)	Adults, serum	26.1 (18–30)	Germany
Papke, 1998	1996	48	2.2 (ND–3.6)	Adults, serum	36.6 (31–42)	Germany
Papke, 1998	1996	44	2.8 (ND–4.8)	Adults, serum	49.1 (43–71)	Germany
Wittsiepe et al., 2000	1996	95	2.34 (0.58–5.5)	Adults, serum	37.7 (9–67)	Germany
CDC (as reported in USEPA, 2000)	1996	316	2.1 (NR–4.2)	Adults, serum	NR	U.S.
Jackson and Michalek, 2001	1997	117	2.0 (ND–10.2)	Ranch Hand comparisons, serum	58 (47.2–79.8)	U.S.
Arfi et al., 2001	1999	16	2.8 (1.8–6.15)	Surgical patients, adipose tissue	55 (30–93)	France
Kang et al., 2001	1999	46	2.4[b] (NR)	U.S. Army controls (non-Vietnam), serum	49	U.S.

ND=not detected; NR=not reported.
[†]Values reported on an adipose whole-weight basis; for use in analysis, these values were adjusted to a lipid basis assuming that adipose tissue is 80% lipid.
[a]Mean is of 25 positive samples; 21 samples were NDs.
[b]Geometric mean.

also evaluated different assumptions about how quickly the intake must have decreased and what current intake levels would be required to be consistent with the compiled sampling data. We examined the effect on the conclusions of the modeling of omitting the data set with the earliest and highest measured TCDD levels (Kang et al., 1990). We also examined the implications of the modeling results for future general-population levels of TCDD based on two assumptions: continued exposure at current intake levels predicted by the modeling, or additional reduction in modeled intake levels by a factor of 10 beginning in 2003.

Finally, we assessed the effect of our assumption regarding population half-life by varying the value for half-life of elimination over the range from 6.5 to 8.5 years, a range of values that encompasses most literature estimates of the central tendency for half-life of elimination for TCDD. While individuals may exhibit half-lives of elimination that are outside this range, the mean elimination half-life in the general population is unlikely to be less than 6.5 years or greater than 8.5 years.

Results

We reviewed articles reporting TCDD levels in persons from the general population with no known occupational or other specific exposures to TCDD. From these studies, we identified data sets that contained the necessary data on year of sampling and mean TCDD levels for the temporal trend analysis, representing over 2800 individual samples. These studies and data are presented in Table 1, and the data are plotted in Figure 2. There is a trend of decreasing lipid-adjusted TCDD levels, with a nearly 10-fold decrease in levels from the earliest data point to levels reported in the most current studies.

Several studies have noted that, within a group of people sampled at a given time, TCDD levels tend to increase with age due to the tendency to accumulate TCDD (Kang et al., 1990; Patterson et al., 1990; Michalek et al., 1998; Papke, 1998). It is possible that the observed temporal trend of decreasing TCDD levels could be exaggerated if sampling from the 1970s was from older populations than the sampling in later decades. Data on the age of the persons sampled were not available in all studies included in this analysis, but for those studies for which age data were available, there was no statistically significant correlation between average age of the sampled population and year of sampling (for data sets that provided only an age range, the midpoint of that age range was used for comparisons). For the 23 data sets that provided information on age, the Spearman rank correlation coefficient for age versus year of sampling was 0.331 (not significantly different from zero, $P=0.94$). When compared based on decade of sampling, the Kruskal–Wallis test indicated a borderline significant difference among the ages of the sampled populations in the three decades ($P=0.53$), but the trend was for increasing age in each successive decade. The average age of the subjects from the 1970s was approximately 33 years, compared to 46 and 44 years for the 1980s and 1990s, respectively. The average age of the sampled groups from the 1970s was statistically significantly less than from the 1980s, but not significantly different from that of the 1990s based on a Tukey pairwise comparison. Thus, the observed trend in the collected data is unlikely to be due to a trend of sampling of younger persons in the later time periods.

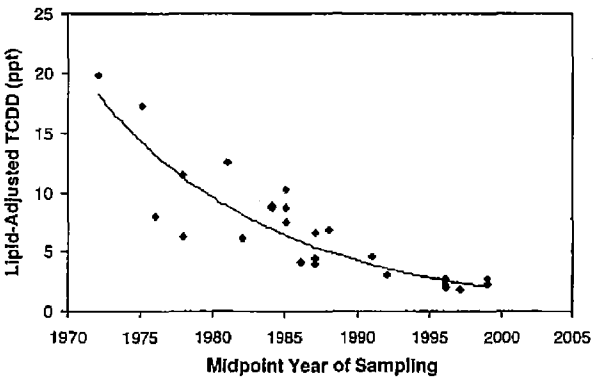

Figure 2. Mean lipid-adjusted TCDD levels from general population samples in the United States, Canada, and Western Europe. Data points represent mean values from studies listed in Table 1. Trend line is the best-fit exponential function to the data.

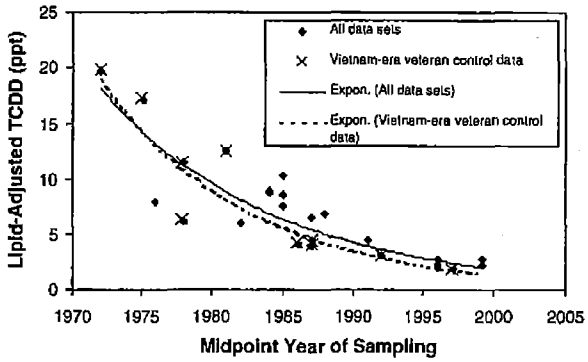

Figure 3. Comparison of data from Vietnam-era veteran control groups to full data set. Trend lines represent best-fit exponential functions to the two data sets.

A number of the studies over the entire time period reported data for veterans from the Vietnam era or age-matched controls for Vietnam veterans. These data represent sampling over time from men of service age during the Vietnam era but without direct exposure to herbicides or dioxins in Vietnam. The trend in decline in lipid-adjusted TCDD levels in this subset of the data is similar to that of the full data set (Figure 3). This indicates that, although the full data set was compiled from sampled groups with a range of ages, the overall trend is not substantially changed by inclusion in the more recent data sets of younger persons who did not experience the higher exposures of the 1960s.

Both linear and exponential functions for the decreases in absorbed intake level can produce model results that are consistent with the observed decrease in lipid-adjusted TCDD levels in the general population. For an intake function to result in predicted lipid levels that fit the observed decreases in the collected data, the mathematical form of the function for intake was less important than the general characteristic that intake levels drop by more than about 95% before 1980. Indeed, the best fit for both the linear and exponential functions for decrease in intake levels results in intake levels that drop by 1976 to levels of less than 5% of the estimated intake levels in 1972. Figure 4A and B illustrate the compiled sampling data and the predicted lipid-adjusted TCDD values paired with the best-fit intake function for the exponential decline function.

Changing the assumed half-life over the range from 6.5 to 8.5 years does not significantly affect the basic conclusion of this analysis — that levels of intake must have declined by more than 95% from peak values before 1980 — the main effect of changes in the assumed half-life is a shift in the bottom of the curve to somewhat later time periods (Figure 4B). For the assumption of an 8.5-year half-life, the best-fit intake function resulted in intakes of zero required from 1973 forward to produce declines in human lipid levels that match those observed in the compiled data.

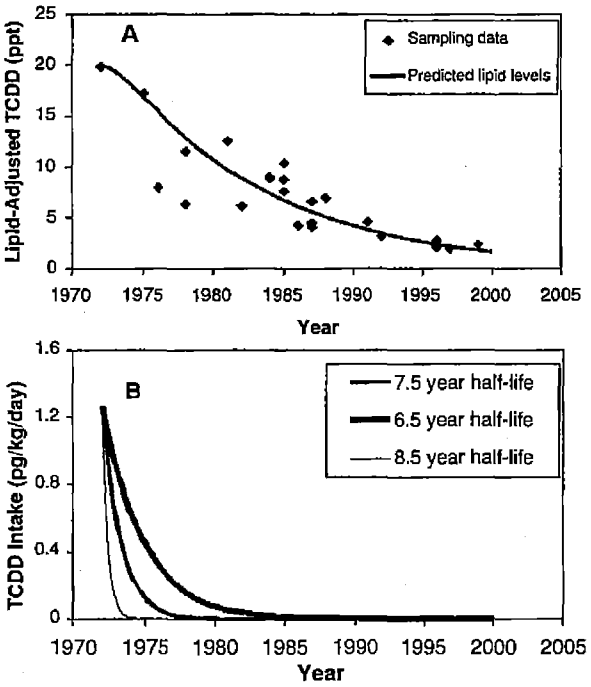

Figure 4. Modeling results for the assumption of an exponential decline in intake levels. (A) Actual lipid-adjusted TCDD levels (data points) and predicted lipid-adjusted TCDD level decline curve based on intake function illustrated in (B), 7.5-year elimination half-life. (B) Exponential decline function for intake producing the best fit of predicted TCDD levels versus measured TCDD levels, illustrated in (A), for elimination half-lives of 6.5, 7.5, and 8.5 years.

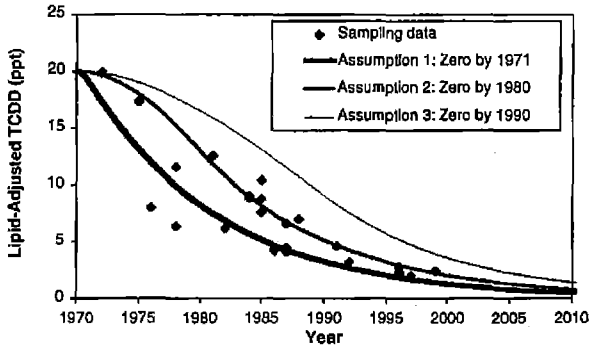

Figure 5. Effect of bounding assumptions on shape of predicted lipid-adjusted TCDD levels. Curves illustrate the effect of assuming a linear decrease in intake with intake decreasing and ceasing by 1971, 1980, and 1990. Cessation of intake by 1990 did not produce declines in predicted lipid-adjusted TCDD levels as dramatic as those observed in the sampling data.

We performed modeling using bounding assumptions to evaluate whether the observed decreases in lipid levels of TCDD could have occurred under a range of scenarios for changes in exposure level, assuming a 7.5-year half-life. Using a linear function for the decrease in intake levels, we evaluated the effect of assuming that intake decreased and ceased completely by 1971, 1980, and 1990 (Figure 5). While the curves based on the assumption of decreases to zero by 1980 and 1971 fell within the observed sampling data, the predicted lipid levels resulting from intake that continued until 1990 were too high at every time point. The assumption that intake decreased to zero was used as a bounding assumption. Because this is not a realistic assumption, we also evaluated decreases to low but nonzero levels. The results of this modeling indicated that the observed decreases in lipid levels of TCDD are consistent with intake functions that exhibit rapid decreases to levels less than 5% of 1970 intake levels before 1980, with continuing low-level exposure. However, because of the long half-life of TCDD and the lack of a "bottom" in the observed body burdens, the data set does not have the sensitivity to allow the model to distinguish what the lowest dose truly is around the time frame of the year 2000 (Figure 6). However, assuming intake levels as high as 0.08 pg/kg/day appears to overpredict the most recent available sampling data; an average daily intake of 0.04 pg/kg/day or less provides a closer match to the recent data.

The Ranch Hand control population offers a unique data set to explore temporal trends in exposures required to yield the decline observed in this group of people. The Ranch Hand control group represents U.S. servicemen from the Vietnam era who were not exposed to elevated levels of TCDD through handling Agent Orange. Furthermore, this data set represents a prospective cohort identified in 1980 and tracked over time, unlike the whole compiled data set

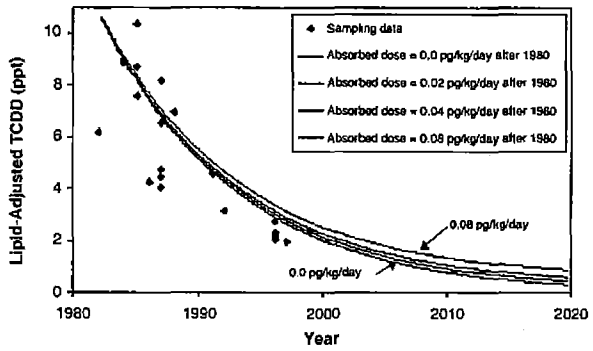

Figure 6. Predicted lipid-adjusted TCDD levels from 1980 forward based on a decline to constant 0, 0.02, 0.04, or 0.08 pg/kg/day intake after 1980. Constant post-1980 intake rates as high as 0.04 pg/kg/day result in predicted trends that are consistent with the observed sampling data.

presented in this study, which is a cross section of different people at different times. We modeled this data set with several different assumptions (linear and exponential decline in exposure, and constant exposure, over the time period from 1987 to 1997) to determine whether it provided more insight into the potential decline in exposures experienced by the general population over the time period from 1987 to 1997. If a constant daily intake was assumed over this time period, the reduction in serum lipid levels from 4.5 ppt in 1987 to 2.0 ppt in 1997 could be achieved only with an absorbed dose no higher than 0.04 pg/kg/day (modeling not shown). Modeling assuming that the dose was decreasing over this time period resulted in even lower absorbed doses at the final time point. This result is consistent with the simulations performed on the whole data set presented here.

This modeling assumed that intake levels in 1972 were equal to 1.3 pg/kg/day, the constant intake rate required to achieve a long-term steady-state body burden of 20 ppt. As discussed above, a 20-ppt body burden could be achieved in a short time if the average intake rates were higher. If higher initial intake rates in 1972 are assumed, corresponding to the possibility that the general population was not at steady state at this time, the rate of decrease in intake required to produce the predicted changes in lipid levels of TCDD is steeper. Conversely, if the body burden levels observed for 1972 were already decreased from some earlier peak levels due to decreasing intake rates, the intake rates in 1972 might have been lower than the average intake level associated with steady state at 20 ppt, but would have to have been even higher than that steady-state level (1.3 pg/kg/day) at some earlier time period.

The values for midpoint sampling years 1972, 1975, 1978, and 1981 from Kang et al. (1990) represented the earliest data points for this analysis, and also exhibited the highest serum lipid levels. Because these data were generated from the analysis of adipose tissue samples that had been stored for as long as 18 years, it is possible that these data could be unreliable in some way. We evaluated the trend in the lipid level data with and without these data. The overall trend was similar, although the predicted lipid levels in 1972 based on the data set excluding the Kang et al. (1990) data were somewhat lower (about 17 ppt rather than 20 ppt) (Figure 7). Exclusion of the Kang et al. (1990) data from the modeling would modify somewhat the degree of decrease in intake predicted by the model, but does not change the major conclusion that substantial decreases in intake to much lower intake levels would have been required before 1980 to produce the trend exhibited by the remaining data sets.

We evaluated the effect of accepting the hypothesis that elimination rate is a function of TCDD concentration (Michalek et al., 2002) by varying the elimination rate to range from an elimination half-life of 7.0 years at a lipid-adjusted concentration of 20 ppt to 8.0 years at 2 ppt. This assumption did not change the basic shape of the predicted intake functions or the conclusion that intake must have decreased rapidly before 1980 (modeling not shown).

Because it takes decades to achieve steady state, any decreases in intake level over the past 20–30 years have

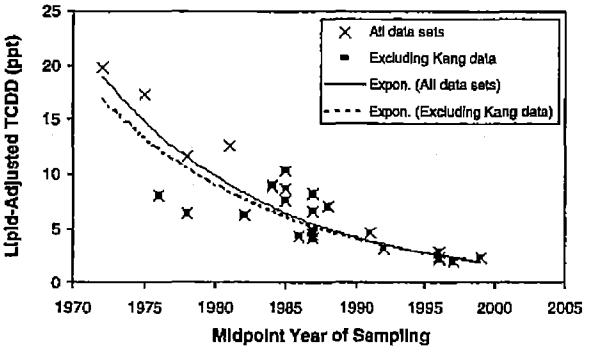

Figure 7. Comparison of temporal trends with and without data from Kang et al. (1990). Lines are best-fit exponentials to the data sets.

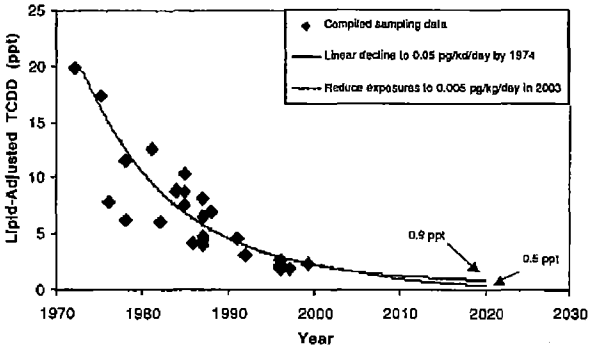

Figure 8. Predicted time course of lipid-adjusted TCDD levels due to immediate decline to 0.05 pg/kg/day in 1974 and showing the effect of an additional 10-fold reduction in intake levels beginning in 2003. The effect of future reductions in TCDD intake rates on body burden will be small compared to reductions that have already occurred.

not yet had their full effect on general-population body burden, and any recent decreases in intake that might have occurred due to regulatory actions of the past decade have had little effect on body burden. However, because lipid levels of TCDD have already declined so much, further declines will be much less dramatic. Figure 8 illustrates the predicted general-population body burden trend over the next 20–25 years at the current intake level predicted by our modeling, and also at an intake rate one-tenth as high. In either case, predicted serum lipid TCDD levels in 2020 are below 1 ppt.

Discussion

The sampling data collected here illustrate a steady and substantial drop in lipid levels of TCDD in the general population over nearly three decades, from 1972 to 2000. The long half-life for elimination of TCDD in humans implies that such decreases can only have occurred as a result of substantial decreases in intake level. The results of the simple pharmacokinetic modeling conducted in this analysis indicate that these decreases must have been substantial (that is, more than a 95% decrease in absorbed intake levels) and rapid, with the bulk of the decreases having occurred by 1980.

The heterogeneity in the sampled populations and in the general population (age, diet, and other factors), coupled with the long half-life of TCDD, makes this analysis insensitive to the details of the changes in exposure levels over the time period studied, beyond the conclusion that exposures have declined by more than 95%. However, a few conclusions can be drawn regarding the implications of these data for serum lipid levels of TCDD over the next one to two decades. Based on trends in the sampling data, our modeling of intake levels, and basic pharmacokinetics of TCDD in humans, we estimate that mean serum lipid TCDD levels in the general population will be between 0.5 and 1 ppt by the year 2015, representing a reduction of up to fourfold over current serum lipid levels, even if intake levels do not decrease further. This result is the consequence both of the long period of time needed for body burdens to respond to changes in intake levels (due to the long elimination half-life) and of the fact that younger cohorts in the population who never experienced the higher exposures of the 1960s will constitute a greater proportion of the general population as time goes on.

Identifying the causes for the decline in exposure levels since the early 1970s is beyond the scope of this work. However, potential reasons include the phasing out of leaded gasoline (Marklund et al., 1987); reductions in open burning practices at municipal landfills, homes, and apartment buildings (Gullett et al., 2001); reduction in TCDD levels in herbicides used in the United States and subsequent suspension of the use of these herbicides (USEPA, 2000); reductions in incinerator emissions due to new regulations and equipment (USEPA, 2000); changes in how the food supply is produced (for example, the shift to farm-raised versus wild fish); and lifestyle changes such as changes in dietary patterns. Further moderate or even extreme decreases in emissions of TCDD from environmental sources may not produce detectable effects in reducing body burdens of TCDD in the general population beyond the trend already expected during this time period.

Based on the bounding exercises we performed, it is our best estimate that current averaged absorbed intake levels of TCDD are no higher than 0.04 pg TCDD/kg/day. This estimate is in reasonable agreement with a recent USEPA estimate of intake of dioxins and furans on a TEQ basis (Schaum et al., 1999). The USEPA estimate was based on analysis of food samples in the United States from the early and mid-1990s, and resulted in an estimated daily intake of 0.65 pg TEQ/kg/day. If TCDD accounts for 10% of the TEQ intake of dioxins and furans, as is often found to be the case, the USEPA estimate would imply daily intake of about 0.065 pg TCDD/kg/day. This level may have dropped further, because much of the food sampling data on which it is based are now 5–10 years old. In addition, this estimate is for intake, not absorbed dose as was the case for our modeling; this makes the two estimates even more similar. This concordance of intake estimates based on two different approaches supports the validity of the modeling used in this analysis, and also supports our conclusion that daily intake levels before 1980 were as much as 20 times higher than current estimated intake levels (and possibly 40 to 100 times higher than current estimated intake levels).

Food consumption is generally considered to be the primary pathway for human exposure to TCDD and other dioxin and furan compounds (USEPA, 2000; Liem et al., 2000). The sampling data and modeling results shown here cannot distinguish between a rapid drop to an intake level of less than 0.04 pg TCDD/kg/day by 1980 and a drop to zero intake. A reasonable assumption is that, over the time period of interest, levels in food dropped dramatically and continued to decline at some smaller rate. We attempted to identify data that would allow us to evaluate the temporal trends of TCDD levels in foods over time against the intake predictions from this analysis, with a focus on dairy fat as an indicator food type. However, a quantitative evaluation of the temporal trends in food is much more difficult than for human lipid levels due to a number of factors related to the data that are available on food levels. Few systematic monitoring programs for dioxins in foods have been in place for more than a few years. Isolated data on levels in specific foods or on total intake level are available in the literature, but evaluation and comparison of these data is complicated by lack of consistent protocols, limited analytical sensitivity resulting in a preponderance of nondetectable levels in

many studies, changes in TEQ definitions over time, and the lack of detailed, congener-specific reporting of results.

The United Kingdom Food Standards Agency (FSA, formerly the Ministry of Agriculture, Fisheries and Food, or MAFF) has monitored estimated intake levels of dioxin, furan, and selected PCB congeners in the United Kingdom on a TEQ basis periodically since 1982 (FSA, 2000). This monitoring has indicated a decrease in upper-bound intake levels from 7.5 pg TEQ/kg bodyweight per day in 1982 to 1.7 pg TEQ/kg bodyweight per day in 1997 (estimates include dioxins, furans, and selected PCB congeners). This is approximately an 80% decrease in estimated TEQ intake. Because these estimates are based on measurements in food, they are estimates of total intake, not absorbed dose. Congener-specific intake data are more limited in the FSA survey, but TCDD levels in milk fat decreased by 85% over this time period (samples with nondetectable levels were assumed to have TCDD present at the detection limit).

Liem et al. (2000) presented a comprehensive review of data on intake levels from food from studies in several countries. In general, these data were available only from the late 1980s to the present. Liem et al. (2000) concluded that levels of intake on a TEQ basis had decreased in the United Kingdom, Germany, and the Netherlands by a factor of about 2 over the 7 years from 1992 to 1999, but they did not draw conclusions regarding changes in intake levels before the 1990s.

While the data and modeling in this analysis evaluated only TCDD levels in human lipids, other studies indicate that levels of other dioxin and furan congeners in human lipids have also been decreasing. Data for other congeners are available for a much more limited time period and in a smaller number of studies (based on a smaller number of individual samples). Kang et al. (1990) reported mean levels of PCDDs from samples taken during 1971 to 1973 of 63 ppt TEQ; the corresponding value from the CDC sampling in 1996 was approximately 17 ppt TEQ, or a fourfold decrease (USEPA, 2000). Wittsiepe et al. (2000) reported that most PCDD/F congeners decreased by approximately one-half over the period from 1991 to 1996 in samples from the general population in Germany; Papke (1998) reported similar decreases. Quantitative evaluation of the changes in intake levels that caused these changes in lipid levels in humans is more difficult for congeners other than TCDD, because the pharmacokinetics of other PCDD/F congeners have been studied less than those of TCDD. Also, there are many fewer data on changes in the levels of dioxin-like PCBs in human lipids and on the pharmacokinetics of these PCB compounds, and these data are available over a shorter time period. Thus, overall conclusions regarding changes in intake levels for PCDD/F and PCB compounds other than TCDD are less certain.

However, despite the lack of data on total TEQ body burdens from before the 1980s, data compiled since then clearly show a decrease of more than 50% in total TEQ body burden (Wittsiepe et al., 2000; Papke, 1998). These and other data suggest a substantial decrease in the TEQ body burden, which may parallel that observed for TCDD.

Such high body-burden levels in 1972 suggest that the ongoing regulatory concern regarding potential health effects of current TEQ body burdens, as expressed in the recent USEPA dioxin reassessment process, should be tempered by the recognition that substantial reductions in body burden and general population exposures, and therefore increases in the margin of exposure, have already been made. These historical data also suggest that the regulatory hypothesis that humans may experience adverse effects at or near current TEQ body burdens could be tested. If there are specific health endpoints of concern associated with current body burdens of dioxin-like compounds, the decrease in body burdens since 1970 suggests that a significant decreasing trend in these adverse health outcomes (improvement in health status) should be detectable from historical data. A test of this hypothesis would require identification of specific health endpoints in humans that are believed to be related to TCDD exposure, and would depend on the availability of statistics related to these endpoints. Control for confounding factors such as changes in lifestyle factors over time (e.g., changes in smoking rates, increases in rates of obesity, etc.) would be important, but difficult, for such an analysis.

The data compiled and analyzed in this paper do not constitute a statistically representative sampling of general population body burdens over time. The data are samples of opportunity collected in various locations and for various purposes, and they represent groups of different sizes, and predominantly come from males. Despite these limitations, the consistent, steady, and substantial decreases in human lipid TCDD levels in these samples over the previous three decades are indicative of substantial decreases in intake. Modeling based on known pharmacokinetics of TCDD indicates a reduction in intake by more than 95%, with the bulk of these decreases occurring before 1980. These decreases in intake and body burden have implications that should be accounted for in current regulatory assessments of potential hazards from dioxins.

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