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The University of Michigan Dioxin Exposure Study: A Follow-Up Investigation of a Case with High Serum Concentration of 2,3,4,7,8-Pentachlorodibenzofuran

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RUNNING HEAD:

A Case with High Serum 2,3,4,7,8-pentaCDF

KEY WORDS:

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DISCLAIMERS/COMPETING INTERESTS DECLARATION

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ABBREVIATIONS

2,3,7,8-TCDF: 2,3,7,8-tetrachlorodibenzofuran

2,3,4,7,8-pentaCDF: 2,3,4,7,8-pentachlorodibenzofuran

BMI: body mass index

FP: floodplain

IAEA: International Atomic Energy Agency

I-TEQ: international TEQ

PCBs: polychlorinated biphenyls

PCDDs: polychlorinated dibenzodioxins

PCDFs: polychlorinated dibenzofurans

ppt: parts per trillion

TEFs: toxic equivalency factors

TEQ: toxic equivalency

TR: Tittabawassee River

UMDES: University of Michigan Dioxin Exposure Study

OUTLINE OF SECTION HEADERS:

Abstract

Introduction/Context

Case Presentation

Discussion

Relevance to Public Health Practice

ABSTRACT

CONTEXT: Polychlorinated dibenzo-*p*-dioxins, polychlorinated dibenzofurans and dioxin-like polychlorinated biphenyls that have toxic equivalency factors were measured in serum of 946 subjects in five Michigan counties. The study was motivated by concerns about human exposure to dioxin-contaminated sediments in the Tittabawassee River. Most of the toxic equivalency in Tittabawassee River sediments is from two furan congeners, 2,3,7,8-TCDF and 2,3,4,7,8-pentaCDF. **CASE PRESENTATION:** The individual with the highest adjusted (for age, age^2, and body mass index) serum level of 2,3,4,7,8-pentaCDF in the study (42.5 parts per trillion) reported a unique history of raising cattle and vegetables in the flood plain of the Tittabawassee River. Interviews and serum samples were obtained from the index case and 15 other people who ate beef and vegetables raised by the index case. 2,3,4,7,8-pentaCDF in beef lipid was estimated to have been more than three orders of magnitude greater than background (1,780 versus 1.1 parts per trillion). The mean, median, and 95^{th} percentile for serum 2,3,4,7,8-pentaCDF in the study control population were 6.0, 5.4, and 13.0 parts per trillion, respectively, and were 9.9, 8.4, and 20.5 parts per trillion among beef/vegetable consumers, respectively. Back extrapolation for the index case suggests that his increase in serum concentration of 2,3,4,7,8-pentaCDF over background may have been as high as 146 parts per trillion. **DISCUSSION:** Consumption of beef and/or vegetables raised on dioxin-contaminated soil may be an important completed pathway of exposure. **RELEVANCE TO PUBLIC HEALTH PRACTICE:** Animals and crops should not be raised for human consumption in areas contaminated with dioxins.

INTRODUCTION/CONTEXT

Polychlorinated dibenzodioxins (PCDDs) and polychlorinated dibenzofurans (PCDFs) are unintended byproducts of certain chemical processes involving chlorine, and incineration processes (ATSDR 1994, 1998). Some major examples include the bleaching processes involved in making white paper products, manufacture of chlorinated phenols, waste incineration, production of various metals, and combustion of fossil fuels (ATSDR 1994, 1998). PCDDs of natural origin have also been discovered in certain clays, and can lead to human exposure (Ferrario et al., 2000; Franzblau et al., 2008). Production and/or combustion of polychlorinated biphenyls (PCBs) is another a source of PCDFs (ATSDR 1994). Commercial production of PCBs ended in the United States in 1977 (ATSDR 2000). Collectively referred to as dioxins, or dioxin-like compounds, PCDDs, PCDFs and PCBs were spread widely in the environment during the last century largely as a result of human activities.

The dominant source of exposure to dioxin-like compounds in the general population is food (>90%), mostly via consumption of animal products (ATSDR 1994, 1998, 2000). Farmers and other persons who consume foods raised in contaminated areas are at risk of exposure (Ewers et al. 1996, 1997).

As part of the University of Michigan Dioxin Exposure Study (UMDES) the 29 congeners of PCDDs, PCDFs and dioxin-like PCBs that have consensus toxic equivalency factors (TEFs) were measured in serum of 946 subjects who were a representative sample of the general population in five Michigan counties, including 251 subjects from two control counties located more than 100 miles away from the Dow facilities. The study was motivated because of concerns about possible human exposure to dioxin-contaminated sediments in the Tittabawassee River (TR) believed to be the result of historical industrial activities of the Dow Chemical Company (see Figure 1). Most (~80%) of the total toxic equivalency (TEQ) in TR floodplain sediments is due to two furan congeners, 2,3,7,8-TCDF and 2,3,4,7,8-pentaCDF (Demond et al. 2008; Hilscherova et al. 2003). The half life of 2,3,7,8-TCDF is short and thus it is less likely to accumulate in humans; 2,3,4,7,8-pentaCDF has a prolonged serum half life in humans (~7 years) (Milbrath et al. 2009). Because it can accumulate in human tissues, 2,3,4,7,8-pentaCDF can serve as a biomarker of remote exposure to contaminated TR sediment. The individual with the highest adjusted serum level of 2,3,4,7,8-pentaCDF in the UMDES (42.5 parts per trillion (ppt) lipid adjusted, or 4.29 studentized residuals above the log-normalized mean of the control population after adjustment for age, age^2, and body mass index (BMI)) reported a unique exposure history involving consumption of homegrown beef and vegetables raised in the floodplain (FP) of the TR. This report describes this person's results and results of a follow-up investigation of friends and family members who also reported regularly eating the beef and/or vegetables raised on his property.

The UMDES involved a two-stage clustered random sampling design to recruit subjects from five counties in the State of Michigan, USA. Eligible subjects were required to be at least 18 years old, and to have lived in their homes for at least 5 years. The main study involved an hour-long interview and obtaining blood, house dust and soil samples for chemical analyses from eligible subjects. Field data collection for the main study was completed in 2004-2005. Blood samples were obtained from 946 subjects and were analyzed for PCDDs, PCDFs and PCBs by Vista Analytical Laboratory (El Dorado Hills, California) using modified United States

Environmental Protection Agency methods 8290 and 1668, Revision A (USEPA 1994, 1999). Serum results are reported in parts per trillion (ppt) on a lipid adjusted basis and soil results are reported in ppt on a dry weight basis. Serum total lipids for each sample were calculated using Phillips formula summing triglycerides and total cholesterol. TEQ values are calculated using 2005 TEFs (Van den Berg et al. 2006). More complete details on the parent study methods are available elsewhere (Demond et al. 2008; Garabrant et al. 2009a, 2009b).

The person found to have the highest adjusted serum level of 2,3,4,7,8-pentaCDF in the UMDES was labeled as the index case. As part of an effort to better understand why his serum level of 2,3,4,7,8-pentaCDF was elevated, he underwent a follow-up interview to better understand his unique dietary history involving consumption of homegrown beef and vegetables from the TR FP. The index case identified the friends and family members who were most likely to have regularly consumed beef and/or vegetables raised on his property (n=15). These subjects were interviewed about diet (particularly consumption of beef and/or vegetables from the TR flood plain), occupation, residential history, personal habits (e.g., smoking), height, weight and change in weight, breast feeding, hobbies and recreational activities in or near the TR. Subjects were also invited to undergo phlebotomy for measurement of PCDDs, PCDFs and dioxin-like PCBs in serum except the index case and case 5 who had already undergone blood testing as part of the UMDES and were not retested. All subjects provided written consent that had been approved by the University of Michigan Health IRB.

Since the index case stopped raising beef in 1996 and the follow-up investigation was performed in 2008, there were no beef samples available for analysis. The 2,3,4,7,8-pentaCDF beef concentration was therefore estimated on the basis of local environmental concentrations in vegetation and soil, and experimental biotransfer factors from the literature. The cattle were raised for an average of 18 months, but because of variation in dietary sources of fodder (see below) it was assumed (conservatively) that cattle only consumed fodder from the floodplain for six months. The daily intake of 2,3,4,7,8-pentaCDF by the cattle in the floodplain (I) was estimated as:

$$I = Q_{soil} \cdot C_{soil} + Q_{vegetation} \cdot C_{vegetation} \quad [1]$$

where C_{soil} and $C_{vegetation}$ ($pg/g_{dry\ weight}$) are the observed soil and vegetation concentrations in the floodplain, and Q_{soil} and $Q_{vegetation}$ ($g_{dry\ weight}/d$) are the daily quantities of local soil and fodder ingested by the cattle. Since the cattle roamed widely on the property of the index case, and only one sample of soil and vegetation from the flood plain was taken from each property in the flood plain, the concentration of 2,3,4,7,8-pentaCDF in soil and vegetation eaten by the cattle was estimated by averaging flood plain results from six properties (including the index case and the five closest properties in the study that front on the river within approximately one kilometer of the index case's property on the same side of the river). Daily intake of fodder by cattle was estimated as $Q_{vegetation}$ = 7,200 $g_{dry\ weight}/d$ with an expected range of 5,000 to 10,000 $g_{dry\ weight}/d$ (IAEA 1994). Soil ingestion is expressed as a fraction of feed or forage intake of 6% for grazing cattle, yielding Q_{soil} = 432 $g_{dry\ weight}/d$ (IAEA 1994).

Feil et al. (2000) reported that intake by cattle of a daily dose of 83.3 ng/d for 4 months resulted in an average increase in lipid adjusted concentration of 2,3,4,7,8-pentaCDF of 105 pg/g lipid in beef at the end of the experiment (based on Figure 2 and Tables 4 and 5, Feil et al. 2000). Considering that the cattle raised in the floodplain had been grazing at least 6 months in the floodplain, the estimates from Feil et al. can be used to calculate a conservative estimate of the resulting increase in the 2,3,4,7,8-pentaCDF beef concentration (ΔC) for a given intake level (I):

$$\Delta C = I * (105 / 83.3) \qquad [2]$$

Since the human serum concentrations in this study were measured nine or more years after beef consumption had ended, the decrease in serum concentration that may have occurred following cessation of consumption was estimated. An attenuation factor can be calculated using the following equation:

$$f_{attenuation} = \frac{\Delta C_{human\ serum}^{consumption\ end}}{\Delta C_{human\ serum}^{time\ of\ sampling}} = e^{+\frac{\ln(2)}{\tau_{1/2}}\Delta t} \qquad [3]$$

where Δt *(year)* is the elapsed time between the end of the beef ingestion and measurement of serum concentration, ΔC is the increase in serum concentration of 2,3,4,7,8-pentaCDF either at the time consumption of contaminated food ended (numerator) or the time that serum was sampled (denominator), and $\tau_{1/2}$ *(years)* is the average elimination half-life during this period, calculated according to Milbrath et al. (2009).

CASE PRESENTATION

The index case owned property in the TR FP that fronted on the river. His recollection, as corroborated by the friends and family members, was that in about 1984 or 1985 he began to raise cows on his land. Each year in the spring he bought 2-3 calves from local farms (not in the FP) and typically raised them for ~18 months. He had 4-6 cows on the property at a time, and the cows routinely roamed and grazed in areas that flooded annually. They ate a mixture of FP grass, grain not grown in the FP, and hay from a nearby field that was near the FP but did not flood. The cattle were slaughtered at a local commercial abattoir. The meat always passed federal inspection (based on visual inspection – no chemical testing), but the livers never passed (for unknown reasons), and no organ meats were consumed. The meat was never sold, but was distributed to friends and family members. He stopped raising beef in about 1996. At the time of this follow-up investigation (2008) no meat samples were available for chemical analyses. Beginning in the early 1980's he started a vegetable garden in an area of the TR FP that regularly flooded. Vegetables included: asparagus, tomatoes, cucumbers, green beans, corn, radishes, potatoes, beets, green peppers, onions, Swiss chard, watermelon and pumpkins. Many vegetables were canned and consumed year-round. The vegetables were shared with the same friends and family members. Use of the vegetable garden was largely discontinued in about 1997, except for occasional tomato plants and asparagus. No one else among the 946 subjects in the parent study (who were a representative sample of the adult population in the regions studied) reported such regular and prolonged consumption of beef from the FP of the TR.

UMDES study participants who lived along the TR had one near-river soil and vegetation sample analyzed for PCDDs, PCDFs and PCBs. Since the cattle grazed over a relatively wide area along the river floodplain, it was felt that averaging of soil and vegetation measurements obtained from properties in the vicinity of the index case (including the index case) would provide a better index of exposure of cattle to floodplain contamination. Mean 2,3,4,7,8-pentaCDF concentrations in soil and vegetation based on 6 near-river samples obtained from the vicinity of the index case's property were 1250 $pg/g_{dry\ weight}$ for soil (range: 14.4 to 3790 $pg/g_{dry\ weight}$) and 122 $pg/g_{dry\ weight}$ for vegetation (range: 4.66 to 315 $pg/g_{dry\ weight}$). The corresponding concentration of 2,3,4,7,8-pentaCDF in beef calculated according to equations (1) and (2) amounts to 1780 pg/g_{lipid} in beef lipid (range: 30 to 6820 pg/g_{lipid}) or 180 $pg/g_{wet\ weight}$ in beef meat (range: 3 to 680 $pg/g_{wet\ weight}$). The beef lipid mean value is more than three orders of magnitude greater than the maximum concentration of 1.1 pg/g_{lipid} observed for commercial beef in the United States, indicating that the beef raised by the index case were likely heavily contaminated (Ferrario et al. 1996).

The index case had the greatest disparity between his serum concentration of 2,3,4,7,8-pentaCDF and the predicted value for someone of his age and BMI (42.5 ppt, or 4.29 studentized residuals above the predicted value based on the UMDES referent population). One other subject (#2) had a serum concentration of 2,3,4,7,8-pentaCDF that was more than 3 studentized residuals above the predicted value (14.7 ppt, or 3.48 studentized residuals above the mean for those of comparable age and BMI); all remaining subjects' serum concentrations of 2,3,4,7,8-pentaCDF were less than 2.5 studentized residuals above their respective predicted values (see Table 1; see Supplemental Material, Table 1, for complete serum results for all 16 subjects). The mean serum concentration of 2,3,4,7,8-pentaCDF was 12.0 ppt among the 16 subjects (9.94 excluding the index case). For comparison, the overall mean, median, 95th percentile and maximum for serum 2,3,4,7,8-pentaCDF in the UMDES control population were 6.0 ppt, 5.4 ppt, 13.0 ppt, and 26.2

ppt, respectively (not adjusted for age or BMI). The serum 2,3,4,7,8-pentaCDF levels among the 16 cases are displayed in Figure 2, along with quantile curves based on the control population (median, 75th percentile and 95th percentile curves). None of the 16 subjects had an occupational history that might have provided opportunity for exposure to 2,3,4,7,8-PeCDF, and none of them ever lived near a source of aerosol emission of furans or other dioxins. Previous work has shown that merely living on soil with 2,3,4,7,8-PeCDF (and/or house dust with contamination) makes no contribution to serum (Garabrant et al., 2009b).

Table 1 includes an estimate of the percentage contribution to each subject's total serum TEQ from 'extra' 2,3,4,7,8-pentaCDF, i.e., the amount of 2,3,4,7,8-pentaCDF in each individual's serum above his/her predicted value based on the referent population after adjustment for age, age^2 and BMI. The percentage contribution of extra 2,3,4,7,8-pentaCDF to the TEQ ranges from -1.7% to +20.4%, with a mean and median contribution of 4.9% and 2.6%, respectively, among the 16 cases.

Subjects were asked about the average number of beef and vegetable meals consumed per week or per month during the time period in which they ate the beef or vegetables from the index case. The estimated number of beef meals ranged from zero to 2248, with a mean and median of 1109 and 1056 beef meals, respectively (see Supplemental Material, Table 2). The estimated number of meals with vegetables from the garden of the index case ranged from 44 to 1350, with a mean and median of 570 and 506 meals, respectively.

Since consumption of potentially contaminated beef stopped in 1996 (and most consumption of vegetables stopped in about 1997), but serum measurements were not performed until 2008 (2005 for the index case, 2004 for case #5) it is possible that the present results underestimate past serum levels of 2,3,4,7,8-pentaCDF. To illustrate the potential magnitude of such attenuation with time, the 'excess' serum level of 2,3,4,7,8-pentaCDF in 1996 was estimated for the index case. Considering the body mass index, the age and the smoking status of the index case yields an estimated average elimination half-life of $\tau_{1/2} = 4.4$ years. With this half-life estimate, the steady-state serum 2,3,4,7,8-pentaCDF concentration in 1996 was estimated to be 4.1 times higher than when it was measured in 2005. His serum concentration increase of 2,3,4,7,8-pentaCDF in 1996 due to prior consumption of contaminated beef and/or vegetables was therefore estimated to be ΔC_{serum} = 4.1*(2,3,4,7,8-pentaCDF in 2008 – predicted based on UMDES controls) = 4.1*(42.5-6.8) = 146 pg/g lipid, corresponding to a potential increase of 146*0.3 (the TEF for 2,3,4,7,8-pentaCDF) = 44 pg/g_{lipid} in total serum TEQ.

DISCUSSION

Most cases included in this follow-up investigation had higher serum concentrations of 2,3,4,7,8-pentaCDF than predicted from the control population (adjusted for age, age^2 and BMI), but, with two exceptions, all were less than 2.5 studentized residuals above their mean values. The estimated mean extra or excess contribution of 2,3,4,7,8-pentaCDF to the TEQ was 4.9%, and was less than 21% in all cases. The results suggest that prolonged regular consumption of beef and/or vegetables raised in the flood plain of the Tittabawassee River, a region documented to have widespread and high levels of dioxin contamination of flood plain sediments, can be a completed pathway of human exposure. In the present case, due to attenuation linked to the elapsed time between beef consumption and serum measurements, the estimated contribution of such past exposure to current TEQ above background appears to be modest (less than 21% in all cases), adding, on average, less than 5% to the serum TEQ. However, estimated steady-state serum 2,3,4,7,8-pentaCDF concentrations in 1996 would have been as much as 4.1 times higher than in 2005, and would have added 44 ppt to the total serum TEQ of the index case.

A key element of this study was reliance on the remote dietary recall of consumption of beef and/or vegetables raised on the property of the index case. Subjects were asked to recall the frequency of meals consumed per week or per month with the beef and/or vegetables from 12 to 22 years prior to the interviews. While subjects' recall of whether they ever ate the beef and/or the vegetables, and the approximate time frame of such consumption, may be reasonably reliable, recall of frequency of remote consumption of specific foods is known to be less reliable and may explain some of the observed variation in serum levels of 2,3,4,7,8-pentaCDF (Wu et al. 1988). This uncertainty appears to be unavoidable in the present circumstance.

Cattle that forage on dioxin-contaminated soil can take up and bioaccumulate such contamination, which can then be passed on to the human consumers (Chang et al. 1989). For most vegetables, transfer and bioaccumulation of dioxins in contaminated soil to the leaves or fruit is generally low (Hulster et al. 1993, 1994; Muller et al. 1994). However, for some vegetables in the family *Cucurbitaceae*, such as pumpkin and zucchini, up-take from soil can be considerable (Hulster et al., 1994). No measurements of dioxins in meat or vegetables were performed as part of this investigation, and information about frequency of consumption of specific vegetables from the garden of the index case was not obtained. Based on the knowledge that most vegetables do not become significantly contaminated from soil, we assume that consumption of the beef raised on the property of the index case was the dominant pathway of exposure to dioxins in flood plain soil for the subjects of this study. Other investigators have also suggested that animal products are more important (Ewers et al. 1997).

Food is the dominate route of exposure to dioxins for most people. A number of studies have documented levels of PCDDs, PCDFs, and/or PCBs in fish destined for human consumption and/or higher serum levels in people from consuming fish raised in contaminated regions (Hites et al. 2004; Lee et al. 2006). In other cases, animal feed was contaminated from one of a variety of sources (e.g., ball clay added as an anti-caking agent to soy meal in feed; citrus pulp used in cattle feed; oil contaminated with PCDDs/PCDFs/PCBs added to recycled fat added to animal feed), which resulted in contamination of chicken, beef, and/or cat fish, and subsequent human exposure (Huwe 2002). Contamination of cooking oil with PCBs and PCDFs resulted in outbreaks of illness in Taiwan and Japan (Rogan 1982). There have also been a few investigations of human exposure to dioxins from consumption of farm animals raised on contaminated soil (Ewers et al. 1996, 1997).

RELEVANCE TO PUBLIC HEALTH PRACTICE

The subjects in the present study reported regular consumption beef and/or vegetables raised in a region heavily contaminated with dioxins. Their dietary practices were unusual if not unique: no one else among the 946 subjects in the parent study (a representative sample of the adult population in the regions studied) reported such regular and prolonged consumption of beef and/or vegetables raised in the FP of the TR. The dietary practices of the index case (and friends and family members who also ate the beef and/or vegetables) appear to be a 'worst case scenario' in terms of completing a pathway of exposure to dioxin contamination in TR FP soil and achieving the highest serum level of 2,3,4,7,8-pentaCDF (after adjustment for age, age^2, and BMI) in the entire study. Though this is a case study and other exposure sources and pathways cannot be excluded, the estimated impact of consumption of these homegrown foods on current serum TEQ was modest (i.e., contributed, on average, less than 5% to the serum TEQ, and less than 21% to the serum TEQ in all cases); it likely was much greater in the past. Animals and crops should not be raised for human consumption in areas contaminated with dioxins.

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Table 1. TEQ and 2,3,4,7,8-pentaCDF Concentrations in Serum Among People Who Consumed Beef and Vegetables

Case	Age at Blood Draw	WHO-TEQ (ppt)	WHO-TEQ Studentized Residuals[a]	2,3,4,7,8-PentaCDF (ppt)	PentaCDF Studentized Residuals[a]	Predicted PentaCDF[b] (ppt)	Percent Contribution of 'excess' 2,3,4,7,8-pentaCDF to TEQ
1[c]	≥60	52.4	2.22	42.5	4.29	6.8	20.4
2	30-44	17.6	1.21	14.7	3.48	3.5	19.3
3	30-44	18.1	1.02	9.5	2.25	3.8	9.4
4	≥60	44.0	0.32	21.4	1.79	9.9	7.9
5	≥60	69.4	1.45	20.1	1.59	10.2	4.3
6	≥60	33.1	0.81	12.9	1.47	7.2	5.1
7	45-59	24.1	0.53	8.84	1.02	6.0	3.5
8	45-59	24.3	0.21	8.42	0.63	6.7	2.1
9	45-59	13.7	-0.41	6.34	0.69	4.9	3.1
10	45-59	31.0	1.02	7.11	0.41	6.4	0.7
11	45-59	19.6	0.02	6.72	0.46	5.9	1.3
12	≥60	22.5	-0.29	8.45	0.45	7.3	1.5
13	45-59	14.8	-0.46	6.03	0.38	5.4	1.4
14	45-59	20.4	0.10	6.29	0.21	6.0	0.5
15	≥60	19.3	-0.72	6.94	-0.05	7.3	-0.6
16	45-59	19.2	-0.28	5.34	-0.37	6.4	-1.7

[a]Distance from the lognormal mean of the referent population after adjustment for age, age^2 and BMI

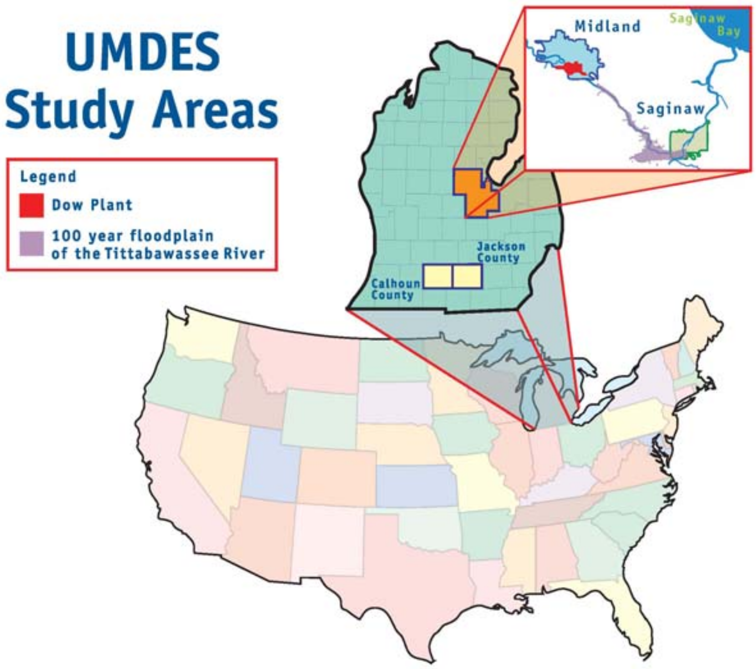
[b]Predicted mean 2,3,4,7,8-pentaCDF (in ppt) for persons with the same age and BMI of each subject based on the referent population

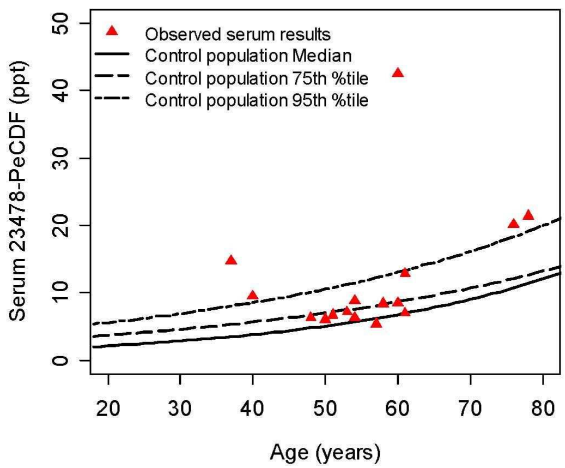
[c]Index case

Figure Legends:

FIGURE 1: Map of University of Michigan Dioxin Exposure Study Areas

FIGURE 2: Serum 2,3,4,7,8-pentaCDF Results by Age with Quantile Curves Based on the UMDES Control Population


UMDES
Study Areas
Legend
Dow Plant
100 year floodplain
of the Tittabawassee River
Midland
Saginaw Bay
Saginaw
Jackson County
Calhoun County



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