**EPA**
September 2009

# REVIEW OF THE UNIVERSITY OF MICHIGAN DIOXIN EXPOSURE STUDY

National Center for Environmental Assessment
Office of Research and Development
U.S. Environmental protection Agency
Washington, DC 20460

Preferred citation:
U.S. EPA (Environmental Protection Agency). 2009. Review of the University of Michigan Dioxin Exposure Study. September 30, 2009. National Center for Environmental Assessment, Washington, DC. Available from http://www.epa.gov/ncea.

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## ABSTRACT

This document presents EPA's review of the University of Michigan Dioxin Exposure Study (UMDES). This is one of the largest studies of dioxin exposure ever conducted and is an important contribution to the understanding of levels of dioxin in human blood, house dust, and soils and the factors associated with dioxin exposure.

The design of the study was well-suited for meeting the objective of identifying patterns of serum dioxin, furan and PCB levels among adults living in the Midland-Saginaw region and provided the basis for making comparisons with a reference region in Jackson-Calhoun counties, 100 miles to the south. The relatively large number of participants and population based statistical sampling design are important strengths of this study. The data collected support reliable estimates of the distributions of dioxin concentrations in blood, soil and dust.

The UMDES design was only partially successful in meeting the objective of evaluating factors associated with serum dioxin concentrations. The associations between the observed serum levels and a variety of demographic factors (age, body mass index, where one lives, work history, etc.) were estimated; however, estimates of associations with other factors, particularly soil and dust concentrations, may be problematic. This was because subpopulations likely to be subject to high exposures (e.g., gardeners, fishers) were not specifically included in the sample design. Of particular note was that the UMDES study focused on exposure to individuals aged 18 years or older. The results are, therefore, not directly relevant to children, a sensitive subpopulation that is often the focus of studies of environmental exposure especially with regard to possible exposure through contact with soil and dust. Without increased focus on subpopulations likely to have high exposures, the study does not provide data that readily support analysis of the impacts of sources that may increase total exposure a relatively small amount relative to diet or other large sources of background exposures.

For risk-based decision-making, EPA's focus is typically on highly exposed and/or sensitive subpopulations, in addition to the general population. The UMDES did not target such subpopulations and coverage of groups of interest for risk-based decision-making is limited. Thus, the lack of emphasis on sampling of subpopulations likely to be most affected -- such as people living on properties with very high soil levels and people consuming large amounts of possibly contaminated fish and game -- is a significant drawback.

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**Acknowledgements:**

The development of this project benefited by conversations with Glenn Rice, USEPA, NCEA. We also acknowledge the assistance of David Garabrant and Al Franzblau from the University of Michigan who freely shared their time to discuss the University of Michigan Dioxin Exposure Study with us.

## EXECUTIVE SUMMARY

This document presents EPA's review of the University of Michigan Dioxin Exposure Study (UMDES). This is one of the largest studies of dioxin exposure ever conducted and is an important contribution to the understanding of levels of dioxin in human blood, house dust, and soils and factors associated with dioxin exposure. In recognition of the significance of this study, U.S. Environmental Protection Agency Administrator, Lisa P. Jackson, committed the Agency to conducting this review as a component of the EPA's *Science Plan for Activities Related to Dioxins in the Environment*, dated May 26, 2009 (www.epa.gov/dioxin/scienceplan).

The objectives of EPA's review were to comment on the design, implementation and results of the UMDES and the relevance of the study's findings to EPA's regulatory mission. The EPA review comments are summarized below and provided in detail in the attached report.

**Study Description:**

The University of Michigan (UM) conducted a field study of dioxin and dioxin-like compounds in the blood serum of the human population living in the area around Midland, Michigan. This is referred to as the "University of Michigan Dioxin Exposure Study" or UMDES. Financial support for the study was provided by the Dow Chemical Company through an unrestricted grant to the University. A large staff at the University of Michigan, and collaborators at several other academic institutions, has worked on the study for more than five years. All primary data collection was completed in 2005 and to date 20 journal articles and abstracts have been published or accepted for publication in scientific journals with many additional manuscripts under development. More than one hundred presentations based on the data have been made at scientific conferences and meetings. UM has constructed a comprehensive web site that provides ready access to the study protocol, publications, presentations, and review comments and responses (*http://www.sph.umich.edu/dioxin/index.html)*.

The objective of this study was described as follows: "to describe the pattern of serum dioxin, furan and PCB levels among adults and to understand the factors that explain variation in serum dioxin, furan and PCB levels." (Garabrant et al., 2005).

The data collection for the study was designed as a two-stage, area probability, household sample of the adult population living in five geographic regions in the area in and around Midland, Michigan. Four of the five geographic areas sampled are in the counties surrounding Midland and are thought to be most affected by releases from Dow. The fifth area was located in two counties 100 miles south of Midland and was intended to serve as a background or reference area. A total of 946 participants provided serum samples (695 in the four Midland study areas and 251 in the background area). Additionally, soil and household dust samples were collected from the residences of most of these participants. An extensive questionnaire was used to collect demographic and life style information from all participants.

**Comments on Study Design:**

The UMDES study focused on exposure to individuals aged 18 years or older. The results are, therefore, not directly relevant to children, a sensitive subpopulation that is often the focus of studies of environmental exposure especially with regard to possible exposure through contact with soil and dust. Additionally, other subpopulations likely to be subject to higher than typical exposures (e.g., gardeners, fishers, individuals living on more highly contaminated soils) were not specifically included in the sample design. Information was collected regarding such exposures, but limited sample sizes may limit the strength of study findings. The study design does not provide data that readily support analysis of the impacts of sources that may increase total exposure a relatively small amount relative to diet or other large sources of background exposures.

The first objective of the study was to identify patterns of serum dioxin, furan and PCB levels among adults, and EPA concludes that the design of the study was well-suited for meeting this objective. The relatively large number of participants and population based statistical sampling design are important strengths of this study. The data collected support reliable estimates of the distributions of dioxin concentrations in blood, soil and dust, reported as means, medians, lower and upper percentiles.

The second objective of the study was to evaluate factors associated with serum dioxin and EPA believes that the UMDES design may have been only partially successful in meeting this objective. The associations between the observed serum levels and a variety of demographic factors (age, body mass index, where one lives, work history, etc.) were estimated successfully. However, estimates of associations with other factors, particularly soil and dust concentrations may be problematic because contributions from typical background dietary exposures are usually much greater compared to typical contributions from soil and dust. The UMDES researchers attempted to address this by including in the sample two areas that would be more likely to have higher soil concentrations. These were an incinerator plume area and a 100 year floodplain area downstream of the plant. Further, they used a very high sampling rate in these areas (17% of the total population in the floodplain and 30% in the plume area). The final overall sample included a total of 23 properties out of 766 with maximum soil dioxin levels over 1,000 ppt TEQ (TEQ=Toxicity Equivalent[1]). The relatively low median soil levels in the floodplain (11 ppt TEQ), and suggestion of higher levels from other studies (ATS, 2009), support the concern that this representation of subjects from high soil properties was limited. A related design issue is how well the study represented individuals with specific behaviors (such as gardening, consuming local fish or game, or raising animals for local consumption) that could lead to elevated dioxin exposures. No design elements were used to ensure representation of these activities in the sample. However, the UMDES sample did identify two subjects with elevated

[1] Dioxin concentrations and exposures are presented in terms of toxic equivalents (TEQs). TEQs allow concentrations of dioxin mixtures to be expressed as a single value computed by multiplying each congener concentration by a toxicity weight (toxic equivalency factor or TEF) and summing across congeners. TEFs are expressed as a fraction equal to or less than 1 with 1 corresponding to the most toxic dioxin congener, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (2,3,7,8-TCDD).

serum levels who engaged in high soil contact activities (one gardener and one farmer) and the UMDES researchers have highlighted these findings.

The UMDES provided some unanticipated but useful findings. These involved the identification of several unexpected dioxin exposure scenarios. First was the discovery of soils containing elevated levels of dioxin outside the floodplain due to movement of soils from the floodplain to residences for fill or other purposes. Second was the discovery of elevated serum levels that appear to be associated with the activities of a ceramic clay hobbyist. Third was the discovery that polychlorinated biphenyls (PCBs) were the dominant contributors to high TEQ levels in soil at one residence (linked to past paint use) and in dust at nine residences (where one was linked to a carpet pad and others had unknown sources). In most other samples, dioxins and furans were the dominant contributors to TEQ levels.

A Quality Assurance Project Plan was drafted which, although not complete in all areas, addressed the key elements of quality assurance procedures. However, the publications to date have not included a report on quality assurance performance measures.

**Comments on Study Findings:**

EPA concludes that the following findings are supported by the UMDES data and analyses:

- Soils from properties in the Midland/Saginaw study areas contain higher concentrations of dioxin than soils in the reference area of Jackson/Calhoun.
- Higher concentrations of dioxins were found in the serum of residents living within the four study areas comprising the Midland/Saginaw region as compared to the reference Jackson Calhoun area.
- Dusts from households in the Midland Plume area contain higher dioxin levels than dusts from households in the other study areas.
- Living in the Midland/Saginaw study areas during the years 1960-1979 was associated with elevated serum dioxins.
- Working at Dow during the years 1940-1959 was associated with elevated serum dioxin levels. This does not appear to be a finding for TEQ, but it does appear to be a finding for 2,3,7,8-TCDD.

The most highlighted finding of this study is that age is positively associated with serum dioxin levels. EPA generally agrees that the analyses done on UMDES data support this finding. Indeed this is an expected result as other studies of U.S. populations show increase in average levels of serum dioxins and TEQs with age. However, while there is a tendency for blood levels to increase with age, many older people in the UMDES study had lower blood levels than many younger people. Age may have the strongest association with serum levels of all variables studied, but substantial variation apparent in the data indicated this to be a weak to moderate positive relationship. The value of $R^2$, a measure of the variation in the dependent variable (serum level) explained by variation in the explanatory variable (age) was not reported for serum level versus age alone. For serum TEQs versus an aggregate of nine demographic variables (including age) the $R^2$ was reported to be 0.396 (Garabrant et al., 2009b). This indicates that the nine demographic variables in the aggregate account for 39.6% of the variation in the observed

serum levels and that $R^2$ for age by itself would be smaller. Thus, the statements that imply that age is a strong predictor of serum levels appear overstated.

The relationship between blood serum dioxin and soil dioxin was less clear. Generally, weak relationships between various measures of soil and serum dioxin levels were noted but the overall conclusions in the more recent documents imply that there is not a meaningful relationship between these two key factors. EPA believes this finding is supported by the statistical analysis of the data presented in Garabrant et al (2009b). This is not an unexpected finding, given that dietary exposures explain over 90% of total exposures to the general population; direct soil impacts explain only about 1% of total exposures. A pharmacokinetic modeling exercise done as part of this evaluation showed that at the 95% soil concentration found in the Floodplain soils, 223 ppt TEQ, adult body burdens would only increase by 3 ppt TEQ or less (Appendix A). The impact to an adult body burden was more significant at a soil concentration of 1000 ppt TEQ, increasing body burden by about 11 ppt TEQ, which was a little less than half the median level in Midland Saginaw area of 27.3 ppt TEQ. However as noted above, the study design would be expected to result in limited coverage of high dioxin-concentration soils which would make evaluation of this relationship problematic. EPA also emphasizes that this finding should not be stated without the caveats about the study limitations. This is especially important with regard to possible effects due to soil exposure which are unlikely to occur unless soil concentrations are high.

UMDES found little association between household dust dioxin concentrations and serum dioxin levels. EPA notes the lack of strong or consistent findings regarding dust in the regression relationships. However, the design issues noted above for soils would also apply to dusts. Also, it is noted that two key documents, the 2006 report (University of Michigan, 2006) and the 2009 journal article (Garabrant, 2009b), have slightly different results. The 2006 report suggested that a relationship might exist between PCB 118 levels in serum and household dust, whereas Garabrant et al. (2009b) suggest that the relationship is with PCB 126.

A variety of findings addressed serum dioxin/fish relationships including: where the fish came from (store bought or from impacted water bodies), what kind of fish, whether the individuals recreationally fished, and so on. The overall comment that there is a relationship between consumption of fish and serum dioxin levels is generally supported by the findings that were outlined in the primary publication describing the statistical analysis of the data (Garabrant et al, 2009b). While the association was noted, the statistical relationship was weak. The UMDES reported somewhat mixed results with regard to eating fish from the contaminated waters (Tittabawassee River, Saginaw River, and Saginaw Bay). This is based on the statement in UM (2006) that people who eat fish from the contaminated water bodies have higher levels of dioxins in their blood compared to people who don't eat fish from these areas, while Garabrant et al (2009b) stated that there was no positive association between consumption of fish from these areas and serum dioxins.

Certain recreational activities were found to be associated with dioxin serum levels. This was supported by a positive association between recreational activities and dioxin body burden that appeared in the 2006 report (UM, 2006). However, like the conclusion noted above on

consuming fish from the impacted water bodies, this conclusion was not supported in the 2009 literature publication on predictors of serum levels.

**Implications for EPA:**

The UMDES study focused on exposure and included no health status information on those included in the study. Therefore, the UMDES data do not support analysis of the association between observed blood levels and possible health effects.

The direct relevance of the UMDES study to EPA's mission is uncertain. The UMDES is an overall population study. For risk-based decision-making, EPA's focus is typically on highly exposed and/or sensitive subpopulations, in addition to the general population. The UMDES did not target such subpopulations and coverage of groups of interest for risk-based decision-making is limited. Thus, the lack of emphasis on sampling of subpopulations likely to be most affected -- such as people living on properties with very high soil levels and people consuming large amounts of possibly contaminated fish and game -- is a significant drawback.

EPA's soil dioxin remediation goal of 1000 ppt TEQ is largely based on a scenario of childhood soil ingestion (i.e., based on a scenario of exposure in ages 1 to 30 years old with about two thirds of the dose occurring prior to age 18). With regard to the remediation goal, it is possible to examine the results for the subpopulation of subjects in the UMDES sample living on properties with soil concentrations greater than 1000 ppt. Interpretation of the results would be limited, however, by the absence of children and the likely sparse coverage by design of this subpopulation in the study.

Dioxin presents a significant concern for risk assessors and policymakers because the background exposure to dioxin is already at a level considered to be of concern (EPA, 2003). Food consumption explains 95% of total exposure. Any incremental exposure over the dietary background would be expected to increase the risk over the range of concern.

**Conclusions:**

The UMDES has produced a credible and valuable source of data on dioxin levels in adults. To the credit of the UM researchers, these data have been, and continue to be, used to support extensive analyses. EPA believes that the data will support additional analysis that may further clarify relationships between blood serum measurements and key factors, like soil concentrations. Specifically, EPA believes that further study of specific subpopulations in the UMDES sample – such as those exposed to high soil concentrations, high fish and game consumers, and those with high blood serum levels – may provide the basis for additional informative insights. For example, preliminary analysis of data from properties with maximum soil concentrations greater than 1000 ppt suggests that the subjects living on these properties have a distinctly different pattern of serum dioxin levels (see Appendix B).

## SECTION 1: INTRODUCTION

This document presents EPA's review of the University of Michigan Dioxin Exposure Study (UMDES). This is one of the largest studies of dioxin exposure ever conducted and is an important contribution to the understanding of levels of dioxin in human blood, domestic dust, and environmental soils, and factors associated with dioxin exposure leading to increased concentrations in blood. In recognition of the significance of this study, U.S. Environmental Protection Agency Administrator, Lisa P. Jackson, committed the Agency to conducting this review as a component of the EPA's *Science Plan for Activities Related to Dioxins in the Environment*, dated May 26, 2009 (www.epa.gov/dioxin/scienceplan).

The objectives of EPA's review were to comment on the design, implementation and results of the UMDES and the relevance of the study's findings to EPA's regulatory mission. In conducting this evaluation , EPA reviewed the study protocol (Garabrant et al., 2005) and August 2006 report (UM, 2006) published on the UMDES web site (www.sph.umich/edu/dioxin/index.html), and peer reviewed publications and in press papers, focusing on those emphasizing the primary findings (Garabrant et al., 2009a, 2009b; Hedgeman et al., 2009; Demond et al., 2008) Manuscripts in preparation, and other materials that became available after about August 1, 2009, have not been considered in the preparation of this report. EPA does acknowledge receipt of the presentations made by UMDES researchers at the August Dioxin 2009 conference in Beijing, China.

To gather information and ideas to assist with our review, we conducted a number of interviews with individuals who are knowledgeable about this study. These individuals included:

- Region V Staff (Mary Logan, Mario Mangino, Milt Clark, Wendy Carney) – meeting in Chicago, IL May 14, 2009
- Tracey Easthope (Ecology Center) and Ted Schettler (Science and Environmental Network) – phone interview July 20, 2009
- John Kern (Kern Statistical Services) – phone interview July 28, 2009
- Linda Dykema (MI Department of Health) – phone interview July 30, 2009
- Deborah MacKenzie-Taylor (MI Department of Environmental Quality) – phone interview July 30, 2009, with follow-up questions on September 9, 2009.
- Linda Birnbaum (NIEHS, chair of the UMDES Science Advisory Panel) – phone interview August 6, 2009
- David Garabrant and Alfred Franzblau (University of Michigan) – meeting in Alexandria, VA, August 10, 2009, with a follow-up data request on September 11, 2009
- David Kleinbaum, (Emory University, former member of the UMDES Science Advisory Panel) – phone interview August 18, 2009

Several of those contacted submitted written comments to us. Key points of comments included:

- The study purpose and hypotheses have not been clearly stated. This was an issue mostly near the beginning of the study when it was not made clear why it was being undertaken and the intended use of the results.
- There was not a focus on the "high end" of the potentially exposed population: children, those who consume locally produced foods (including fish and terrestrial animal food products) and game, and those who live on the most contaminated soil. Some suggested that these high end subpopulations, not including children, could have been better targeted in a stratified, or otherwise different, survey design.
- There was a common concern relating to the regression model used by the UMDES researchers to evaluate the data. Including a large number of possible explanatory variables in a single model can confound the results since many of the variables are known to have little or no effects on dioxin exposure. An alternate approach proposed was to establish a "base" model which included variables known to influence or be related to dioxin exposure, such as age, gender, dietary factors, body mass index, and so on, and to this model add one (or maybe two related) parameter to see the influence of this individual parameter. This model was termed "base + 1". With this approach, one can better evaluate and compare these individual factors.
- The soils on the sampled properties were not representative of the high end and given what was sampled, may not have been studied properly to date. Regarding representativeness, the study by Dow termed the Middle Tittabawassee River remedial investigation (ATS, 2009, also discussed in Section 3) identified many more areas and a higher percentage among areas sampled, of higher soil concentration. Regarding evaluations to date: a) UMDES used the most contaminated sample on the site and should have tested the average soil concentration, b) soil concentrations and years on properties could have been combined to obtain a new parameter similar to "pack years" that are used to evaluate the impacts of cigarette smoking, and c) the soil concentrations found suggest that a bimodal trend exists and that an attempt to separately evaluate the high portion of this data set instead of combining all the data may have been more informative.
- There was a concern that this study could be used to determine clean-up levels at this site and possibly other sites nationally.

The concerns described above parallel many of EPA's concerns and are addressed in the following discussions.

The EPA understands that the UMDES is not finished and is likely to continue for many years. Future reports will present new findings and may modify earlier ones. Thus our review should be regarded as a review of the findings to date with the understanding that these could change in the future.

## SECTION 2: DESCRIPTION OF STUDY

### 2.1 University of Michigan Dioxin Exposure Study (UMDES)

The University of Michigan (UM) conducted a field study of dioxin and dioxin-like compounds in the blood serum of the human population living in the area around Midland, Michigan. This is referred to as the "University of Michigan Dioxin Exposure Study" or UMDES. Financial support for the study was provided by the Dow Chemical Company through an unrestricted grant to the University. A large staff at the University of Michigan has worked on the study for more than five years. All data collection was completed in 2004, and to date 20 journal articles or abstracts have been published or accepted for publication in scientific journals with many additional manuscripts under development. More than one hundred presentations based on the data have been made at scientific conferences and meetings. UM has constructed a comprehensive web site that provides ready access to the study protocol, publications, presentations, and review comments and responses (*http://www.sph.umich.edu/dioxin/index.html)*.

### 2.2 Goals and Objectives

The motivation for this study has been described (with small variations among the articles and presentations) as: "The University of Michigan Dioxin Exposure Study (UMDES) was undertaken in response to concerns among the population of Midland and Saginaw Counties that dioxin-like compounds from the Dow Chemical Company facilities in Midland have contaminated areas of the City of Midland and sediments in the Tittabawassee River Floodplain."

The objective of the study is described in the protocol (Garabrant et al., 2005) as "to describe the pattern of serum dioxin, furan and PCB levels among adults and to understand the factors that explain variation in serum dioxin, furan and PCB levels."

### 2.3 Summary Description of Study

The design of the UMDES is a population-based two stage area probability household sample survey designed to select subjects from five regions in the state of Michigan. These five areas are discussed below (see Figure 1).

***The Floodplain Area (FP):*** This area includes the 100-year Federal Emergency Management Agency (FEMA) floodplain of the Tittabawassee River as well as respondents who reported flooding of their home by the Tittabawassee River. The FP area was assumed to be the most impacted by contaminated sediments of the Tittabawassee River since flooding would transport dioxins onto surface soils of residential properties. Prior sampling has documented contamination of Tittabawassee sediments. Dow Chemical owns most waterfront property along the first six miles on the Tittabawassee River downstream from their facility. EPA was informed that no sampling occurred along these six miles (Garabrant, pers. comm.. 2009), although there

are residential properties within these first six miles (McKenzie, pers. comm., 2009). Given their location, these areas might be more impacted than locations further downstream from the Dow facilities.

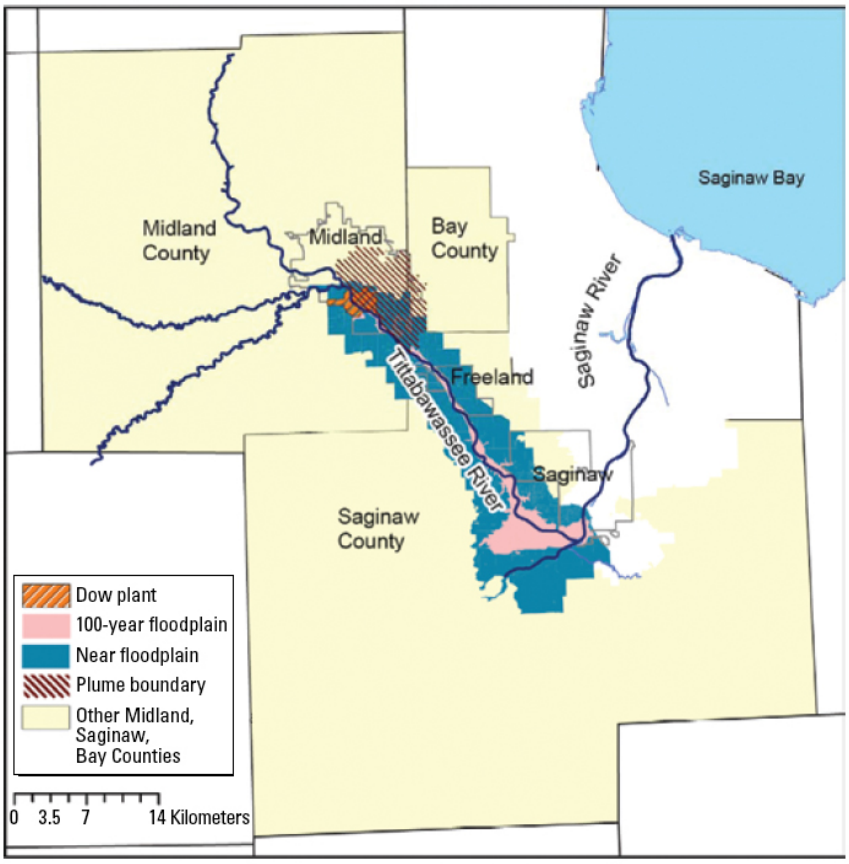


**Figure 1.** Map of Midland, Saginaw, and Bay counties, Michigan, showing the Dow Plant and the 100-year floodplain of the Tittabawassee River.

***The near-floodplain of the Tittabawassee River (NFP):*** The NFP area was assumed to be less impacted by flooding compared to the Floodplain area. Still, proximity to the river could influence soil concentrations and it might be a factor in recreational use of the river.

***The plume area in the City of Midland downwind from the historic incineration activities of the Dow plant (MP):*** The MP area was added to the study later during the planning and implementation of the study due to comment received by the UMDES research team during public meetings and consultations. Concern was expressed that individuals living in this area might be impacted from historical emissions from the Dow incinerator. The area was delineated by UMDES researchers who used an EPA air deposition model (the Industrial Source Complex Short Term (ISCST3) model) to identify an area where predicted soil concentrations would equal or exceed 75 ppt TEQ[2] based on modeled depositions from the Dow incinerator. Later on, the

[2] Dioxin concentrations and exposures are presented in terms of toxic equivalents (TEQs). TEQs allow concentrations of dioxin mixtures to be expressed as a single value computed by multiplying each congener

UMDES researchers verified their definition of the area with the use of a more recently developed EPA air deposition model (AERMOD).

**Elsewhere in Midland and Saginaw counties and parts of Bay County outside the floodplain, near-floodplain, and plume areas (MS)**. There was no explicit expectation of impacts in this area, and as noted below, the sampling weights were very low in this area; and

**Jackson and Calhoun counties as a control or referent population (JC)**. This area is located more than 100 miles away from the Dow facilities in Midland. The JC area was chosen as an area that was not impacted by activities of the Dow facilities, nor was otherwise impacted by specific known sources of dioxin. Results from soil and serum testing in the JC area have generally shown this was an accurate assessment.

Prior to selecting individuals within the five areas to participate in the study, a power calculation was conducted to determine a target number of individuals needed within each area to give the study adequate statistical power. Details of this power calculation have not been published, but the result was a target of 175 people (based on information provided in an EPA meeting with Garabrant and Franzblau on August 10, 2009) with the exception of the MP area. As noted, the decision to include this area came after other areas had been delineated. Decisions regarding study sample size and other design details had already been made, and interviews were already underway in other study areas when the MP area was added to the study. The final number of participants selected exceeded 175 within the four areas. As discussed below, while the number of people selected in the MP area was much less than this target population, the area in general was small and the sample weights demonstrate that the MP area was oversampled in comparison to other areas.

Study participants were selected using a 2-stage design. The first stage was a random selection of census blocks within the region. Census blocks are delineated based on population density. Generally all census blocks contain the same, or a similar, number of household units. Therefore, a census block in a densely populated region would be smaller in geographic size compared to a census block in an area of lower population density. Also, there would be a larger number of census blocks in areas of higher population density compared to areas of lower population density. With these characteristics, and the design to sample census blocks randomly, the study sampled at a higher rate in areas of high population density. Once a census block was selected, "clusters" of housing units within the blocks were identified by the UMDES researchers using a "drive-around" procedure. The second stage involved the random selection of clusters within the census block. The intent was to enlist each household within a cluster, assuming that the household was "eligible" and willing to participate. An "eligible" household was defined as one with at least one eligible subject residing. Eligible subjects were individuals who were at least 18 years old and had lived in their homes for at least 5 years. Repeated attempts were made to contact each household. UMDES researchers claim a participation rate of eligible households to be about 80%. If there was more than one eligible individual within a household willing to participate, only one individual was selected and that selection was made randomly.

concentration by a toxicity weight (toxic equivalency factor or TEF) and summing across congeners. TEFs are expressed as a fraction equal to or less than 1 with 1 corresponding to the most toxic dioxin congener, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (2,3,7,8-TCDD).

Interviews (lasting about one hour) were given to eligible individuals prior to blood sampling. Not all individuals who were interviewed consented to provide blood samples. A total of 1324 individuals deemed eligible were interviewed, and blood samples were obtained from 946 of these. In addition to a serum sample from the eligible individual within the selected household, there was also the intent to collect soil samples as well as dust samples representing that household. However, various issues precluded obtaining soil and dust samples at each residence, including whether the eligible individual rented or owned, whether the owner (living in the house or not) wanted soil and/or dust sampling, and who owns the dust in the house. In any case, there were a smaller number of households supplying soil and dust samples as compared to individuals supplying a serum sample. Vacuum house dust samples were obtained from 764 homes, and soil samples were obtained from 766 households. A summary of the final numbers and types of samples are shown in Table 1. Included in this table are the sample weights for the serum samples. Since individuals were randomly selected within each region, these weights can be understood as follows: each person's sample represents the sample weight number of similarly defined people within the region. For example, the sample weight of 6 in the FP region means that each person's serum results represent 6 other eligible individuals within that region.

**Table 1. Final numbers of study samples and sample weights***

| Description | Flood-plain | Near Flood-plain | Midland Plume | Other Midland/ Saginaw | Jackson/ Calhoun | Total |
|---|---|---|---|---|---|---|
| Blood samples | 243 | 205 | 43 | 204 | 251 | 946 |
| Household dust samples | 205 | 161 | 32 | 168 | 198 | 764 |
| Soil samples | 203 | 164 | 32 | 173 | 194 | 766 |
| Blood, Dust, and Soil | 195 | 156 | 30 | 167 | 183 | 731 |
| Serum Sample Weights | 6 | 6 | 3-4 | 300 | 600 | NA |

* The sample numbers are from UM (2006) and sample weights from verbal information provided at the August 10, 2009 EPA meeting with Garabrant and Franzblau.

Data collection for the main study was completed in 2004-2005. The chemical analyses of soil, blood, and dust, and the extensive questionnaire has resulted in a rich data base. The primary way these data have been analyzed is via a linear regression model that expressed blood serum levels as a function of multiple independent variables. A stepwise selection procedure was

used to identify which independent variables were statistically significant predictors of serum dioxin concentration. This methodology is summarized in Garabrant et al. (2009a).

The first report was published in 2006 (UM, 2006), and the first of ongoing public dissemination of materials at scientific conferences was also in 2006 at the annual dioxin international conference in Oslo, Norway. To date 20 journal articles have been published or accepted for publication in scientific journals with many additional manuscripts under development.

## 2.4 Personnel

The six principle investigators for UMDES are David Garabrant (Professor, Environmental Health Sciences), Alfred Franzblau (Professor, Environmental Health Sciences), Brenda Gillespie (Assistant Professor of Biostatistics), Peter Adriaens, (Professor and Director Fundamental and Applied Microbiology for the Environment), James Lepkowski (Associate Professor Department of Biostatistics) and Avery Demond (Associate Professor, Civil and Environmental Engineering). Numerous other faculty members and graduate students have been involved in this study. UM formed a Scientific Advisory Board for this study consisting of Linda Birnbaum (formerly Environmental Protection Agency now National Institute of Environmental Health Sciences), Paolo Boffetta (International Agency for Research on Cancer), Ronald Hites (Indiana University), and David Kleinbaum (Emory University).

## 2.5 Sample Collection

Detailed descriptions of the soil sampling protocol were provided in Appendix 8 of the Study Protocol (Garabrant et al., 2005). Soil samples were collected at up to 7 locations at each property: along the house perimeter, contact areas (i.e. gardens) and near the river for properties in the flood plain. At each location 3 cores were collected inside a 3 foot diameter ring. Each core had two vertical layers, a surface layer, 0 - 1 inch, and a lower layer, 1 - 6 inches, consistent with other dioxins studies. The reasons for sampling the surface layer are twofold: the surface layer best represents what individuals are exposed to, and dioxins are typically deposited onto the surfaces of soil from sources including air sources resulting in the highest soil concentrations. The samplers allowed for direct sample collection in the tube, sealing of the tube, and minimization of cross-contamination between samples. The removal of vegetation from the surface with means of a scissors is typical, and analysis of the vegetation provided a potentially useful data point for further analysis. All sealed sample cores were stored on ice (4° C) before transport to the University of Michigan Environmental and Water Resources Engineering (EWRE) laboratories.

Detailed descriptions of the dust sampling protocol were provided in Appendix 7 of the Study Protocol (Garabrant et al., 2005). The household vacuum dust samples were taken from two sampling locations that present the highest potential for human contact with household dust and dirt. A High Volume Small Surface Sampler (HVS3) was used to collect the sample. The dust sampling technicians attempted to collect a minimum of 10 grams of total dust in order to

yield an analytical detection limit of 1 part per trillion (ppt). If the amount of dust collected from the initial sampling area within each location was not sufficient, secondary areas were marked and sampled as needed. The total surface areas of all of the sampling areas that make up each sampling location were recorded, as well as the surface types from which the sample was taken. By measuring the sampling areas, results can also be provided in terms of "loadings", which are mass of dioxin per surface area. Loadings are often used in place of, or in addition to, concentrations in exposure studies. Samples were transported on ice to a dedicated 4° C cooler until delivery to Alta Analytical Laboratory for analysis.

Detailed descriptions of the blood sampling protocol were provided in Appendix 6 of the Study Protocol (Garabrant et al., 2005). Each participant was asked to give an 80 mL sample of blood. Blood samples were collected and handled by a mobile phlebotomy service. Blood was allowed to clot, centrifuged and the serum decanted. Serum was frozen at -20°C and shipped on dry ice to the analytic laboratory.

## 2.6 Data Management

Data management details are described in Garabrant et al., 2005. All data were stored as Microsoft Access datasets (separately for soil, dust, and blood) and were also converted to SAS datasets. All data were range-checked, and variable crosschecking performed as appropriate. Data were merged on the participant ID number, which appears in all records. Participant names are only available in interviewer and sample tracking databases, and are not included with the study data available for statistical analysis.

## 2.7 Statistical Analysis

The fundamental basis of the UMDES is a statistical survey of the populations of five geographic areas in the Midland and Saginaw region. The design used to collect the data for this survey is referred to as a "two-stage area probability household sample". Data collected in this manner are referred to as observational which means that a sample is drawn and characteristics of the sample are measured, i.e., observed. The data collected have been used by the University of Michigan team to support a wide range of statistical analyses which have been documented in numerous publications and presentations. The basic approach used by the UMDES to analyze the data was estimation of the distribution of serum dioxin levels in the adult population and multiple regression analysis to examine the relationship of the serum levels to a number of possible explanatory factors. This is consistent with the summary statement in the study protocol document: "This is the protocol for a study of dioxin, furan and coplanar PCB exposure among the population of Michigan to describe the pattern of serum dioxin, furan and PCB levels among adults and to understand the factors that explain variation in serum dioxin, furan and PCB levels." (Garabrant et al., 2005). Detailed descriptions of the sample design, sample size determination and plans for analyzing the data are provided in the protocol document.

The primary overall goal, "...to describe the pattern of dioxin, furan and PCB levels among adults..", in operational statistical terms, becomes one of using the observed data to estimate the

distribution of blood serum concentrations in the adult population of the geographic areas included in the study. The two-stage probability sample design yields data that support the estimation of the distribution of serum levels over all five areas and comparisons of the distributions among the five areas.

The phrase "…and to understand the factors that explain the variation…." expresses a second main goal to collect data that support investigation of the association of serum levels with a number of explanatory variables. The basic approach, which the UMDES has employed, is to use multiple regression analysis to estimate and examine associations between a dependent variable, such as blood serum levels, and a number of explanatory variables that are hypothesized to have an effect on or influence the dependent variable.

The statistical analysis plan provided in Section 4.7 of the protocol document describes in some detail appropriate statistical methods for using the UMDES data to estimate population distributions of blood serum levels and using multiple regression to evaluate and estimate relationships between the observed blood levels and explanatory variables. The methodology employed is commonly used for the analysis of large biomedical, sociological and environmental data sets and the description provided in the protocol is sound and thorough.

## 2.8 Quality Assurance and Quality Control

The Quality Assurance Project Plan (QAPP) is presented in Appendix 9 of the Study Protocol (Garabrant et al., 2005). The QAPP covers project management; data generation and acquisition; assessment and oversight; and data validation and usability activities.

## 2.9 Data Confidentiality and Human Subjects

This study was performed in compliance with University of Michigan policies and procedures governing the use of human subjects in research (Garabrant et al., 2005). The Consent forms are presented in Appendix 11 and the certificate of confidentially is presented in Appendix of 13 of the Study Protocol (Garabrant et al., 2005).

## SECTION 3: EVALUATION OF STUDY

### 3.1 Limitations of the Scope of the Study

The primary limitation of this exposure study is it was limited to individuals aged 18 years or older. Thus the study did not include children, a particularly sensitive subpopulation especially with regard to the possible exposure through contact with soil and dust

In addition the study has two design related limitations. First, this is an observational study. Observational studies provide the basis for examining relationships or associations between the variables. However, it is difficult, if not impossible, to establish reliable cause and effect relationships on the basis of observational studies. This is distinct from experimental studies where the values that variables assume and the assignment of those values to subjects are under the control of those conducting the experiment. The UMDES has produced credible estimates of the distribution of serum levels in the adult populations studied which is an important contribution. The concomitant environmental variables associated with each subject such as dioxin levels in soil and dust, fish and game consumed and so on are only observed. As a consequence, the full range of these variables or sampling rates within specified categories (e.g., high or low levels) for these variables are not guaranteed to be represented in the data. Second, the study does not specifically include as part of the design, focus on subpopulations who engaged in activities suspected to be associated with significant chance for elevated exposure (e.g., consumption of local fish and wild game; contact with highly contaminated soils; consumption of food grown in FP-NFP areas).

Although these limitations have been fully acknowledged by UMDES investigators, they may not have always been sufficiently emphasized in the presentation of results and findings.

### 3.2 Sample Collection, Analysis and Quality Assurance

Sample collection, handling and analysis was well described, appropriate and generally acceptable.

This QAPP was developed using the 1998 *EPA Guidance for Quality Assurance Project Plans, EPA QA/G5*. The UMDES QAPP addresses the critical elements identified in the guidance but does not provide the necessary detail that would allow one to evaluate and or validate the results. The publications to date have not included a report on quality assurance performance measures. Don Patterson (CDC) made a presentation to the UMDES Scientific Advisory Board on October 20, 2005 describing the results of a quality control exercise involving blinded serum samples. His lab and Alta (now Vista) analyzed 20 split serum samples for dioxins, furans, and PCBs (D/F/Ps). The presentation indicated that the two labs had very close agreement on these measurements.

### 3.3 Clarity of Study Goals and Objectives

The UMDES literature EPA reviewed has had slight variations in the wording of the goals, purposes, and objectives of the study. One statement implied that the relationship between soil and dust and blood levels was the primary objective of the study, with other relationships (eating fish, etc) also examined. Others stated that the primary objective was to determine what factors best explained blood levels found, with soil and dust among the list of factors. Consistent among all statements was the intent to correlate various factors to blood serum concentrations. The following is an example of the statement of purpose and/or objectives as they were similarly portrayed in the primary journal articles EPA reviewed for this evaluation:

> *The UMDES is a hypothesis-driven study designed to answer important questions about human exposure to dioxins in the environment of Midland, where the Dow Chemical Company has operated for > 100 years, and in neighboring Saginaw, Michigan. In addition, the UMDES includes a referent population from an area of Michigan in which there are no unusual sources of dioxin exposure and from which inferences regarding the general Michigan population can be derived. A central goal of the study is to determine which factors explain variation in serum dioxin levels and to quantify how much variation each factor explains (Garabrant et al, 2009a).*

This paper also describes the "hypothesis" as "whether the contamination of the environment by dioxins from the Dow Chemical Company's operation in Midland, MI is associated with increased body burdens of dioxins among some residents of the surrounding area of Midland, Saginaw and southwestern Bay counties." This is the only location in any of the publications where EPA could find statements regarding the description of the study being "hypotheses-driven". Additional hypotheses have been delineated in a PowerPoint response to comments from Dr. John Kern, a statistician consultant, as:

- *Soils and household dust in the Midland/Saginaw area are contaminated with DLCs (*dioxin like compounds*) having congener profiles that correspond to the congener profiles of Dow's historic contamination.*
- *Living on contaminated soil is associated with increased serum DLCs.*
- *Living in a house with contaminated household dust is associated with increased serum DLCs.*
- *Consumption of fish from contaminated water bodies is associated with increased serum DLCs.*
- *Consumption of game from the contaminated areas is associated with increased serum DLCs.*

- *Consumption of eggs, milk, dairy products, fruits, and vegetables raised on contaminated property is associated with increased serum DLCs. (Garabrant 2009c)*

This PowerPoint response then goes on to state, "The UMDES is a confirmatory observational study, the goal of which is to test the above hypotheses."

EPA concludes that the most appropriate objective statement, given the design of the study, is provided in the study protocol (Garabrant et al., 2005): "This is the protocol for a study of dioxin, furan and coplanar PCB exposure among the population of Michigan to describe the pattern of serum dioxin, furan and PCB levels among adults and to understand the factors that explain variation in serum dioxin, furan and PCB levels." The reason EPA favors this phrasing over others in the literature is that it is the only one that clearly states that a goal of the study is to "describe the pattern of serum dioxin, furan and PCB levels among adults." All others have focused only on the second of the two objectives noted here, "...and to understand the factors that explain variation in serum dioxin, furan and PCB levels." EPA interprets the phrase "describe the pattern of serum dioxin ….." to mean that the goal was to estimate the distribution of serum dioxin levels in the overall adult population living in the geographical areas studied. This is the primary goal supported by the data collected and detailed plans provided in the protocol. EPA interprets the phrase "…and to understand the factors that explain the variation…." to mean that a second main goal was to investigate the association of serum levels with a number of variables through multiple regression analysis.

### 3.4 Statistical Analysis

The UMDES is an observational study based on sound principles of statistical sampling design. The two-stage area probability household sample design is an appropriate design for this study. Accordingly, the data collected support the estimation of the overall distribution of blood levels in the populations of the areas sampled in the study and comparisons of the distributions among the areas sampled. The data also support estimation of the associations between blood levels and the various demographic and environmental factors measured in the study. The multiple regression methodology employed by UMDES to estimate these relationships and investigate associations is a standard general approach for the analysis of this kind of data. The multiple regression methodology involves modeling a dependant variable as a linear combination of a number of explanatory variables. In the UMDES study, the dependant variable is blood serum dioxin levels and the explanatory variables are several demographic and environmental factors. The blood serum measurement for each of the subjects in the study is associated with a set of explanatory variables and the methodology provides the mechanism for estimating associations between the dependant variable and the explanatory variables. The UMDES team has demonstrated considerable knowledge and skill in analyzing the data.

Interpretation of the results of the analysis is, however, critically important. The data do not support the determination of causal relationships between blood levels and demographic and environmental factors. The presentation of the results does not always make clear that estimation of associations between blood levels and other factors is not the same as establishing causal relationships. For example, the following statements from UMDES (2006) could be

easily misinterpreted to assert that causal relationships have been established: "Older age is by far the most important factor related to higher levels of dioxins in people's blood. Eating fish from the Tittabawassee River, Saginaw River, and Saginaw Bay also leads to higher levels of dioxins in blood." That is, the phrase "also leads to higher levels" implies that the study has found that age and eating fish are direct causes of higher blood levels.

In response to the critical review by statistician consultant Dr. John Kern (2009), a presentation by Dr. Garabrant (2009c) refers to the UMDES as a "confirmatory observational" study. The UMDES protocol discusses model building to account for various demographic and environmental factors in general terms but does not identify specific models as would be expected in a confirmatory study. In fact, the UMDES team appears to have conducted a substantial amount of exploratory analysis in order to arrive at the results presented. This is a reasonable approach for analysis of observational data. In particular, presentation of results in Garabrant et al. (2009b) identifies an aggregate set of variables referred to as "demographic factors" which explain 39.63% of the observed variation in serum levels [Garabrant et al. (2009b), Table 1]. The aggregate set of variables in "demographic factors" is a compilation of a number of explanatory variables: age, age2, sex, BMI, BMI loss in the past 12 months, breast-feeding, number of pregnancies, race, smoking, and interaction terms. This finding, i.e., that a set of nine variables plus interaction terms are required to explain about 40% of the variation appears to be the result of considerable exploratory analysis. Interpretation of this finding is problematic because the effect on any one of the variables is difficult to discern from the summary listing of linear regression results in Table 2 of Garabrant et al. (2009b). In the interests of clarification, it would likely be helpful to examine the data separately for each possible explanatory variable in a descriptive manner. The plot of blood serum versus age in Figure 1 of Garabrant et al. (2009b) is an illustration of such an analysis. The plot shows a tendency for blood levels to increase with age but, from an overall perspective, the relationship is weak. Additionally, there is considerable variability apparent in the plot and it is clear that many older subjects have lower blood serum levels than younger subjects. The basis for the statement: "Age was strongly associated with serum TEQ and with all serum congener concentrations." in Garabrant et al. (2009b) is apparently the statistically significant p-values for the age variable in the first line of Table 2 of Garabrant et al. (2009b). The $R^2$ value for age, i.e., percent of variation in blood serum level explained by age is not provided but would appear to be substantially less than the 39.63% for all the demographic variables combined. The plot of the data in Figure 1 may be more informative with regard to the relationship. As stated elsewhere in this review, EPA believes that the importance of age as an explanatory factor for blood serum levels is overstated. As a general matter, the conclusions drawn by the UMDES appear to be overly dependent on regression statistics such as p-values and $R^2$ values. This approach, while technically valid, is not consistent with guidance provided in the literature. For example, Cummings and Rivara (2003) state: "*Much regression output serves little purpose in medical research publication; this usually includes the intercept coefficient, $R^2$, log likelihood, standard errors, and P values. Estimates of variance explained (such as $R^2$, correlation coefficients, and standardized regression coefficients (sometimes called effect size) are not useful measures of causal associations or agreement and should not be presented as the main results of an analysis. These measures depend not only on the size of any biological effect of an exposure, but also on the distribution of the exposure in the population."*

### 3.5 Study Design

As noted earlier, EPA concluded that the study objectives were best described in the protocol document (Garabrant et al, 2005) which indicated that the primary objective was to describe the pattern of serum dioxin levels among adults. In this regard the study design was adequate. The population based study design resulted in credible estimates of the distribution of serum levels in adults in the MS study areas. The sample from the JC reference area produced a distribution of adult serum levels that was shown to be consistent with the national NHANES survey (Hedgeman et al., 2009). The four survey areas identified in the MS area appear to be appropriately selected to represent the areas most likely impacted by activities of the Dow facilities. The analytical matrices evaluated in this study also appear appropriate. Blood is the best indicator of long term exposure to the dioxin-like compounds and soil and dust are also long term reservoirs for these compounds. Also, soil and dust were the matrices of concern with regard to deposition of contaminated floodplain sediments. The diets of the population in the five study areas were not sampled. However, diet is the primary source of dioxin exposures for the general population, and dioxin levels in food are declining. Even if diets were sampled in the UMDES, the data would not represent long term dietary exposure. Even representing current dietary levels would require collecting multiple meal samples over a long term for each participant, significantly increasing the cost of the study. UM chose instead to assess dietary issues via a questionnaire which was a practical choice.

The second part of the objective statement in the protocol document (Garabrant et al, 2005) was to understand the factors that explain variation in serum dioxin, furan and PCB levels. EPA concludes that the study design may have been sufficient to meet this objective for some factors, but may not have been sufficient for other factors, as will now be discussed.

With regard to general population exposures, the UMDES identified the key demographic factors that have been known to be associated with dioxin blood serum levels: age, sex, body mass index (BMI), breast-feeding, and so on. The NHANES studies on dioxin in blood have always found a relationship with age (higher serum concentrations tend to be associated with older individuals), while others (Lorber, 2002) have also studied temporal trends in dioxin exposure and concluded that higher levels of dioxins in the environment (and food) in the middle decades of the 20$^{th}$ century led to higher body burdens in current older individuals. Lakind et al (2001) and others have studied the decline in the mother's body burden of dioxins during the course of breast-feeding. Higher consumption of animal food products might lead to higher body weights (and higher BMI) and subsequent higher dioxin body burdens.

However, the population-based statistical sampling design of the UMDES survey does not guarantee that the "high end" of the population within the studied areas was adequately represented. The discussion below evaluates how well the UMDES design addressed high end exposures related to soil and activities such as fishing, hunting and gardening.

To fully evaluate the relationship between soil dioxin and serum dioxin, the study should represent properties containing high end soil contamination levels. UM recognized this issue and took some steps to address it. This involved identifying two areas that contained soils most

likely impacted by Dow activities (the FP and the plume area) and oversampling these areas. The success of this approach is difficult to judge but several discussion points are presented below for consideration.

There have been other soil surveys which suggest (but do not prove) that the UMDES did not identify the highest, or enough, properties with high dioxin soil levels. A study referred to as Dow's Middle Tittabawassee River (MTR) remedial investigation measured dioxin levels in MTR flood plain soils (ATS, 2009). This MTR investigation targeted areas most likely to have impacts from flooding and the deposition of river sediments contaminated with dioxins. It is expected that this subarea is part of the 100-year floodplain of the UMDES Floodplain study area. The two studies had soil sampling methodology differences (depth of sampling to describe the uppermost "surface" sample, for example). EPA has not conducted a detailed evaluation of the MTR study. However, visual inspection of satellite photographs and maps included in the study are informative. First, people living in the Tittabawassee FP generally reside on higher ground which is less often flooded than lower areas. Second, it appears that the majority of soil samples of the MTR study were collected in the river or near it in low-lying areas that were generally distant from residences. The maps also show that the higher concentrations were generally found in these low areas of little or no population near the river. Many of these samples were over 1000 ppt and some over 10,000 ppt.

However, the MTR also included several samples that were classified as having been obtained from "residential" parcels of land. The maps did show these samples. The MTR did not have a separate analysis of these samples, but all MTR samples are available in spreadsheet format. This spreadsheet was obtained by the Michigan Department of Environmental Quality (MDEQ). They separated out these residential samples from the full MTR dataset, and compared trends from this subset with findings of the UMDES (from an email dated 4/23/2008 from D. Mackenzie-Taylor to several individuals, supplied to EPA by Deborah MacKenzie-Taylor, MDEQ):

> *The UMDES estimates that 7% of the 203 properties with soil samples in the floodplain group (about 14 properties) have any soil samples exceeding 1,000 ppt dioxin and furan total toxic equivalency (TEQ). In contrast, the MTR residential top interval soil sample set had 47-67% (27 properties with only nearest to the river locations and 38 properties with all locations out of 57 residential properties) of the residential properties with any top interval location over 1,000 ppt estimated TEQ (ETEQ). In addition, the means and medians of the two data sets are very divergent. The mean values of the UMDES data nearest to the river samples are 237-285 ppt TEQ, while the MTR mean value nearest to the river is 1,300 ppt ETEQ. The medians of the UMDES data nearest to the river samples are 11-12.7 ppt TEQ, compared to the MTR median nearest to the river samples of 750 ppt ETEQ. The median of the topmost interval MTR residential samples is 780 ppt ETEQ.*

Visually inspecting the MTR maps, EPA also noted that they appear to show a much higher percentage of samples over 1000 ppt TEQ than 7%. Again, the designs of the UMDES and the MTR are very different, with different objectives and goals. Also, the UMDES

researchers have rebutted these comments with an analysis of their own which showed that, when looking at analogous subsets of the data, the two studies yielded similar percentages of properties over 90 and 1000 ppt TEQ (May 7, 2008 letter from Garabrant and Franzblau to MacKenzie-Taylor).

Another effort which sought to find residential properties that may have elevated dioxin concentrations was from a program conducted by the US EPA Region 5, who has investigated 20 "exposure units" along the Tittabawassee and Saginaw Rivers. Perhaps the most impacted of these units was at the confluence of the two rivers, on Riverside Boulevard. Eleven properties were sampled and elevated dioxin concentrations were found on all properties, many between 1000 and 10,000 ppt TEQ and some exceeding 10,000 ppt TEQ. Another exposure unit was West Michigan Park, which sampled some park area and 10 residential properties. Soil dioxin concentrations between 1000 and 10,000 ppt TEQ were observed throughout this exposure unit. Additional points to consider on how well high end soils are discussed below.

The median level of dioxins found in the surface soil samples was 11 ppt TEQ in the FP, 58 ppt TEQ in the Plume area and 4 ppt TEQ in JC (Demond et al, 2008). This suggests that the plume area was clearly elevated over JC, but much less elevation was seen for FP relative to JC. Half of the FP properties included in the study have soils less than the median value of 11 ppt TEQ, a relatively low value compared to the concern levels of 90 and 1000 ppt TEQ.

The maximum soil level found by UMDES in the FP was 7,258 ppt TEQ (Demond et al, 2008). ATS (2009) shows multiple soil samples over 10,000 ppt TEQ, although again the location of these elevations in low-lying unpopulated areas must be considered. Also, Garabrant and Franzblau (May 7, 2008 letter to MacKenzie-Taylor) stated that the greater sampling depth used in the MTR study (1.1 feet vs. 6 inches in MDES) would contribute to the higher levels.

The population-based, probability sampling design of the UMDES identified what is expected to be a reasonable result: that 7% (with appropriate error bounds) of properties on the flood plain contain soil concentrations above 1000 ppt TEQ. Given they sampled 203 properties with each having a sample weight of 6, one can surmise there were 1200 properties in all, 84 (plus or minus) of which had soil concentrations above 1000 ppt TEQ. They only sampled 14 of them, leaving perhaps about 70 residences not sampled, and given that their sampling scheme was population-based, they would have trended towards sampling locations of higher population density. If it is possible to generalize based on a visual inspection of maps in the MTR study, more densely populated areas are located in higher elevations, thus likely to be the less often flooded areas with lower concentrations.

EPA believes that further evaluation of the UMDES data may provide additional insight with regard to the impact that soil concentration can have on blood serum concentration. This is because other factors (primarily diet) are likely to overwhelm any contributions to serum from soil at low levels, making it very difficult to clearly identify relationships. For example, a comparison of the serum levels of the individuals living on soils over 1000 ppt TEQ to those living on background soils may be informative. In response to a request from EPA, UM identified the study participants living on soils over 1000 ppt TEQ in the age versus serum plot from Garabrant et al., 2009b (forwarded by email from Garabrant to Frithsen on September 11,

2009). This plot and further analysis of these data are presented in Appendix B. The plot shows that most of these participants had serum concentrations above the average levels for their age group. Appendix B also presents a separate serum versus age regression for these 23 individuals.

Considering the need for further data analyses and the uncertainties about whether the high end soils were adequately represented in the study, it is difficult to reach a definitive conclusion about the adequacy of the design to meet the second objective with regard to soil dioxin concentrations.

The potential for high end exposure is not only related to living on properties with high dioxin soil concentrations, but also to behaviors that lead to more exposures, such as fishing, gardening, consuming local game, raising animals used for home (or local) food consumption, and others. A fish consumption survey for the region has been conducted (MCDH, 2007), but it is unclear whether any of the "high end" patterns identified in this survey were adequately captured in the UMDES survey. The UMDES study design did not include any features aimed at ensuring that individuals engaged in these activities would be adequately represented. Also, the possibility exists that there simply are few high consumers of local fish or other individuals with high end behaviors that could be studied. It is noteworthy that UMDES researchers did identify one farmer who raised cattle for home consumption and one home gardener on a property with elevated dioxins, and both showed elevations in blood serum dioxins (Garabrant et al., 2009b).

It should also be noted that the random population based survey design provided some unanticipated but useful findings. These involved the identification of several unexpected dioxin exposure scenarios. One was the discovery of elevated soils outside the floodplain due to movement of soils from the floodplain to residences for fill or other purposes. Second was the discovery of elevated serum levels that appear to be associated with the activities of a ceramic clay hobbyist. Third was the discovery of several incidents of elevated soil and dust levels due to the use of PCB containing products.

In summary, EPA concludes that the UMDES study design was well suited for meeting the objective of describing the distribution of dioxins in the blood in the identified populations. On the other hand, EPA believes that the UMDES design may only have been partially successful in meeting the second objective, which was to identify factors associated with serum dioxin and to quantify their degree of influence. Key demographic factors that are known to be associated with dioxin body burden in the general population, including primarily age but also BMI, whether or not a woman breast-fed, and other factors, were identified in the UMDES. However, it is not clear whether individuals at the "high end" of the population, whose behaviors or residence location may lead to body burdens elevated over the general population, were adequately characterized. These include, for example, individuals living on properties with high dioxin soil concentrations, individuals fishing and consuming fish from the impacted water bodies, farmers and gardeners who produce a portion of their food on their own property, and so on. Because of the importance of soil in this region, discussions above focused mostly on this factor. Evidence was presented that there were a fair number of residences, perhaps about 70 residences in the FP, that contained dioxins above 1000 ppt TEQ that were not sampled. Given evidence presented above, one can at least hypothesize that UMDES under sampled the most heavily contaminated properties. This would have limited their ability to see relationships

between dioxins in soil and dioxins in blood serum. Still, data supplied by UMDES researchers for the individuals living on properties with soil concentrations above 1000 ppt TEQ did appear to suggest that these individuals had serum levels elevated over the central values for their ages (see Appendix B). To date, the UMDES researchers have not studied this specific subpopulation or similar subpopulations that may exist within the UMDES data set. Finally, one must consider the possibility that key subpopulations, such as high consumers of local fish, game or farm animals, simply could be very few in number or may not exist within the study areas, which would certainly limit the ability of the UMDES researchers to estimate relationships with these subpopulations.

## SECTION 4: EVALUATION OF MAJOR CONCLUSIONS

The major conclusions and findings from the UMDES were spread out in the various reports and journal articles. In this section, these conclusions/findings are first described in general terms, but then quotes from the key literature articles are provided so that the exact phrases developed by the UMDES researchers are identified. Then, a comment is provided on EPA's judgment on the statements made within these publications.

### 4.1 Nonserum Correlations Involving Soil and Dust

***Soil Versus Study Area:*** Soil from properties in the Midland/Saginaw study areas contain higher concentrations of dioxin than soils in the reference area, the Jackson/Calhoun area. Specific statements supporting this finding include:

> *Soil from properties in the Floodplain, Near Floodplain, Midland Plume, and Other Midland/Saginaw is more contaminated with dioxins than soil in Jackson/Calhoun (UM, 2006).*
>
> *More properties in Midland/Saginaw than in Jackson/Calhoun have soil TEQ levels at or above 90 parts per trillion, an important level set by the State of Michigan (UM, 2006).*
>
> *Levels of dioxins in soil in Jackson/Calhoun are similar to levels in soil across Michigan based on a small number of soil samples collected by the Michigan Department of Environmental Quality (UM, 2006).*
>
> *Soils in the Floodplain and Near Floodplain show patterns of dioxins suggestive of Dow's historical discharges. These patterns are not seen in Jackson/Calhoun (UM, 2006).*
>
> *On the basis of previous sampling campaigns, it was expected that the plume and floodplain areas had higher levels than background; this study indicates that the difference is statistically significant and is not based on convenience or targeted sampled. The higher levels in the near floodplain and other Midland/Saginaw samples were unanticipated and suggest either the movement of contaminated soils to those areas or the presence of additional sources other than the Tittabawassee river or the Dow incinerator.*
>
> *The mean $TEQ_{DFP\text{-}1998}$ of the HP (sic, house perimeter) 0-1 in. soil samples from Jackson and Calhoun Counties of 8.3 pg/g is similar to the mean value computed for the residential properties in the Denver Front range study of 8.8 pg/g $TEQ_{DFP\text{-}1998}$ suggesting that Jackson and Calhoun Counties are a suitable background comparison group (Demond et al., 2008).*

*This study employed a probabilistic sampling design that allowed for a statistical determination as to whether the soil concentrations in the target areas were above background. On the basis of this analysis, it was determined that the geometric mean soil concentrations in all four target areas in Midland, Saginaw, and Bay Counties, not just the Tittabawassee River floodplain and the incinerator plume in the City of Midland, were elevated relative to background. In addition, the probabilities of a soil sample having a concentration above the 75$^{th}$ and 95$^{th}$ percentiles of background were statistically greater in these areas (Demond et al., 2008).*

EPA COMMENT: This conclusion is supported by the data generated in UMDES. The medians of dioxin TEQ in the surface inch of soil in JC is 4 ppt, while for the FP it was 11 ppt and for the MP it was 58 ppt. It was also supported by the percentages of properties above the MDEQ soil criteria of 90 ppt TEQ: 36.5 % in floodplain 35.8% in plume, 9.7% in near floodplain, 1.7% in other Midland/Saginaw and 0.3% in Jackson/Calhoun (Demond et al., 2008). The finding relating to the pattern of dioxins in soil is supported by analysis showing that the congeners that contribute most to soil TEQs in the FP and NF were 23478-PeCDF, 2,3,7,8-TCDF, 2,3,7,8-TCDD, 1,2,3,7,8-PeCDD and 1,2,3,4,7,8-HxCDF (Demond et al., 2008). This pattern is similar to the pattern found by the Michigan Department of Environmental Quality in Tittabawassee River sediment which is believed to be the result of Dow's historic discharges into the river (UM, 2006). The congeners that contribute most to soil TEQs in the Jackson/Calhoun were PCB 126, 1,2,3,7,8-PeCDD, 1,2,3,4,6,7,8 HpCDD and 2,3,4,7,8-PeCDF (Demond et al., 2008).

***House Dust versus Study Area:*** Dusts from households in the Midland Plume area contain higher dioxin levels than dusts from households in the other study areas. Statements in the key documents which address this relationship include:

*Household dust from properties in the Midland Plume is more contaminated than household dust from properties in any other region (UM, 2006).*

*Living in the Midland Plume region (compared to living in the Jackson/Calhoun) was associated with higher 2,3,7,8-TCDD concentrations (Knutson et al., 2007).*

EPA COMMENT: This is supported by a comparison of median levels in household dust in ppt TEQ: Midland Plume — 35, Other Midland/Saginaw – 19, Floodplain – 17, Jackson/Calhoun - 14, Near Floodplain – 12 (UMICH, 2006). Also, it is supported by the percent of homes with dust levels > 35 ppt TEQ: Midland Plume – 50, Other Midland/Saginaw – 21, Floodplain – 27, Jackson/Calhoun – 26, Near Floodplain – 11 (UM, 2006). Although Knutson et al. (2007) report a positive correlation between dust levels in Midland Plume versus JC for 2,3,7,8-TCDD, they report a negative correlation for TEQs.

***Soil versus House Dust:*** Levels of dioxins in household dust are generally higher than levels of dioxins in soil around the house. Statements in the key documents which address this relationship include:

*Levels of dioxins in household dust are higher than levels of dioxins in soil in most of the study regions, suggesting that there are sources other than soil for dioxins in household dust (UM, 2006).*

*For both the TEQ and 2,3,7,8-TCDD models, soil concentration from around the house was the most important predictor in house dust concentrations – it explained the most variation in the models. Higher soil concentrations were associated with higher household dust (Knutson et al., 2007).*

EPA COMMENT: This is supported by presented linear regression analysis showing that soil around the house was found to be the most important predictor of house dust levels (Knutson et al., 2007). However, Franzblau et al. (2009) suggests other factors can also be important based on an investigation of homes with dust TEQ levels more than 2.5 standard deviations over the mean. Out of the 20 homes that met this criterion, only two appeared related to outdoor soils (based on profile comparisons). UM (2006) notes that commercial products can release dioxins indoors, such as wood preservatives and old electrical appliances. Franzblau et al. (2009) concluded that PCBs in an old carpet pad were the source in one house with high levels of PCBs in the dust. Although not noted in the UMDES reports, other possible indoor sources include cooking, wood combustion, track-in of soils from locations outside the residence and blow-in of dust which may be enriched in contaminants relative to bulk soils.

### 4.2 Serum Correlations with Soil and Dust

***Serum versus Soil:*** Many statements appear in the various documents relating to this key relationship. Generally, weak relationships between various measures of soil and serum dioxin levels were noted but the overall conclusions in the more recent documents imply that there is not a meaningful relationship between these two key factors. Statements in the key documents which address this relationship include:

*People who have higher levels of dioxins in their soil have a higher TEQ (total dioxin-like activity) and higher levels of some specific dioxins in their serum (UM, 2006).*

*In some cases there is a direct relationship between higher levels of dioxins in soil and higher levels of dioxins in people's serum. This relationship is small and applies to some, but not all of the specific dioxins (UM, 2006).*

*The region in which people live, soil contamination, and household dust contamination combined account for about one percent of the variability in levels of 2,3,7,8-TCDD, 1,2,3,7,8-PeCDD, PCB-118, and PCB-126 in people's serum. For the other types of dioxins and the TEQ, region, soil and household dust contamination combined account for less than 0.2 percent of the variability in levels of dioxins in people's serum (UM, 2006).*

*Four of the seven specific types of dioxins examined showed no relationship between levels of dioxins in soil and levels of dioxins in serum. People who have higher levels of 2,3,4,7,8-PeCDF, 1,2,3,7,8-PeCDD, 1,2,3,6,7,8-HxCDD, and PCB-156 in their soil do not have higher levels of these dioxins in their serum (UM, 2006).*

*Three of the seven specific types of dioxins plus the TEQ showed some relationship between levels of dioxins in soil and levels of dioxins in serum. People who have higher TEQ levels and higher levels of 2,3,7,8-TCDD, PCB-118, and PCB-126 in some of their soil samples have higher levels of these dioxins in their serum (UM, 2006).*

*We looked at the highest level of dioxins in soil out of all the soil samples taken on each property. This value, the highest soil value measured on the property, is related to the TEQ level in people's serum. For a person living on a property with a soil TEQ of 1,000 parts per trillion, the serum TEQ is about 0.7 parts per trillion higher than that for a person living on a property with a soil TEQ of four parts per trillion (which is the median soil TEQ in Jackson/Calhoun) (UM, 2006).*

*We also looked at levels of dioxins in soil from vegetable and flower gardens. People whose gardens have higher levels of 2,3,7,8-TCDD or higher levels of PCB-118 have higher levels of these dioxins in their serum. For a person living on a property with a garden soil 2,3,7,8-TCDD level of 22 parts per trillion (which is the median level of soil from homes in the Midland Plume), the serum 2,3,7,8-TCDD level is 0.7 parts per trillion higher than that for a person living on a property with garden soil at the median level of Jackson/Calhoun (0.1 parts per trillion). People who have higher levels of PCB-126 and PCB-118 in soil from around the house have slightly higher levels of these two specific dioxins in their serum. For example, a person whose soil around the house has a PCB-118 level of 1000 parts per trillion has a less than 1 percent increase (about 18 parts per trillion) of this chemical in their serum compared to someone whose soil has a lower level of this chemical (UM, 2006).*

*Soil and household dust dioxin content explained only a small part of the variation in serum dioxin levels: 0.5% for TCDD, 1% for PCB-126, and < 0.01% for the other congeners (Garabrant et al., 2009b).*

*A principal focus of our study was to assess activities that might involve contact with contaminated soils, river sediments, and household dust. These included living on contaminated soil, living with contaminated household dust, and pursuing activities in the contaminated water bodies and floodplain (boating, swimming, picnicking, hiking, etc.). We found little evidence in the general population that these activities were associated with increased serum dioxins (Garabrant et al., 2009b).*

*The TCDD concentration in garden soil was statistically significantly associated with higher serum TCDD. This association was due to a single observation that was highly influential (Garabrant et al., 2009b).*

*The house perimeter top 1 in. (2.5 cm) soil PCB-126 concentration was associated with serum PCB-126 (parameter estimate = 1.001 ppt PCB-126 in serum/ppt PCB-126 in soil; p = 0.0002). This association was due to two influential observations. When we excluded these, we found no statistically significant relationship (Garabrant et al., 2009b).*

*With the exception of results described above, no soil variable was statistically significantly associated with serum dioxins (Garabrant et al., 2009b).*

*There are statistically significant positive associations between serum dioxin concentrations and soil dioxin concentrations for TEQ, 2,3,4,7,8-PCDF, 2,3,7,8-TCDD and PCB-126 (Chang et al., 2007).*

*The variation in serum dioxin levels explained by the soil parameter did not exceed 1.3% for any soil parameter (Chang et al., 2007).*

*In most instances, soil concentrations had little effect on the serum levels for TEQ, 2,3,7,8-TCDD, 2,3,4,7,8-PCDF, or PCB-126. The one exception to this was the relationship between 2,3,7,8-TCDD in serum and garden soil (soil contact zone), for which serum TCDD increased by approximately 50% as soil TCDD increased by 22 ppt (Chang et al., 2007).*

*Soil and household dust were not important contributors to serum TEQ, PCDDs, PCDFs, or PCBs (Garabrant, 2008).*

EPA COMMENT: EPA offers several comments on this finding:

This overall general finding is supported by the statistical analysis that is presented in Garabrant et al (2009b). When measures of household dust and soil concentrations were combined, these explained 0% of the variation for TEQ, 1,2,3,7,8-PCDD, 1,2,3,6,7,8-PCDD, and 2,3,4,7,8-PCDF. It explained only 0.51% of the variation for 2,3,7,8-TCDD and 0.96% of the variation for PCB 126.

This general finding pertains to the full adult populations sampled in the 5 areas of the study, or as noted in a quote from Garabrant et al (2009b), "*We found little evidence in the general population that these activities were associated with increased serum dioxins*." However, as discussed earlier, the study may not have adequately represented high end soil levels. Therefore it is uncertain if this general statement applies to individuals living on these properties containing the highest levels of dioxin. Even more importantly, EPA believes that making these statements without also noting that it does not pertain to children is misleading.

The messages have not been consistent among the documents EPA gathered for this review. The 2006 report did have general conclusions, along with some statistical results, that suggest that relationships exist. Like in other cases, PCB 118 along with PCB 126 were identified as congeners for which relationships exist in the 2006 report, but only PCB 126 was identified in later documents. The poster by Chang et al. (2007) did note weak associations between certain congeners in soil and serum concentrations. Interestingly, TEQ and 2,3,4,7,8-PCDF, noted as having associations in the poster were also noted as explaining 0% variation in the Garabrant et al. (2009b) journal article.

EPA is not convinced that the statistical analysis and results in Garabrant et al. (2009b) provide the final word on the UMDES data base. A statistician, Dr. John Kern, contracted by the Michigan Department of Environmental Quality, has argued that the overall statistical model employed by the UMDES research team is not the best model for use at this site. Rather, he proposes a model which includes a "base" set of parameters already known to be related to dioxin body burden (age, diet, etc), and to this base, add only one or two additional parameters in independent analyses to see the influence of these other parameters on body burdens. He calls this approach the "base + 1" approach and EPA sees potential merit in that approach. EPA asked for and received additional data regarding serum levels of individuals living on properties with soil over 1000 ppt TEQ., These data were discussed in Section 3 and in more detail in Appendix B. These data suggest that these individuals had serum levels elevated over the central values for their ages The UMDES team has not studied this specific subpopulation or others that may exist that could be characterized as "high end" subpopulations. With further study, EPA believes that additional relationships could be unearthed within the UMDES data base.

An independent pharmacokinetic modeling exercise was conducted by EPA as part of the evaluation of the UMDES study (details are provided in Appendix A and further comments in Section 5). The purpose of the exercise was to model the difference between a population having only background exposures, dominated by food and having soil-related exposures based on a soil concentration of 11 ppt TEQ, and another with the same background exposures except the soil-related exposures were based on soils at 223 ppt TEQ. This level corresponds to the 95$^{th}$ percentile of surface soils at residences in the FP. Those exposed to the higher soil had a body burden that was only 3 ppt higher than those exposed to background soils. This suggests that perhaps 95% of all adult individuals in the FP would have serum level increases less than 3 ppt TEQ due to soil ingestion. This would be a small increase for most individuals considering that the median serum level was 23.2 ppt TEQ. Therefore, it is not unexpected and consistent with this external modeling exercise that UMDES would find little influence of soil dioxins on their measured dioxin body burdens.

The same PK analysis described above showed much more impact to a child. A child of 5 sampled in the early 2000s would have a 6 ppt TEQ difference if living on soils at 223 ppt TEQ: their body burden is modeled to be 17 ppt TEQ at background soils but 23 ppt TEQ at 223 ppt TEQ soils. The modeling also showed a difference of nearly 19 ppt if living on soils at 1000 ppt TEQ: 17 versus 36 ppt TEQ.

Soils and sediments are recognized reservoirs for dioxins that result in ongoing impacts to food chains. While the direct pathway of soil ingestion may alone explain only a small part of

body burden, certainly soil and sediment dioxins are the sources for animal concentrations of dioxins, and, as found worldwide in the study of exposure to dioxin, there is a direct correlation with animal food consumption and dioxin body burdens.

***Serum versus House Dust:*** Little association was found between household dust concentrations of dioxins and serum. Statements in the key documents which address this relationship include:

> *People who have higher levels of dioxins in their household dust have higher levels of one of the specific dioxins (PCB-118) in their serum (UM, 2006).*
>
> *Soil and household dust dioxin content explained only a small part of the variation in serum dioxin levels: 0.5% for TCDD, 1% for PCB-126, and < 0.01% for the other congeners (Garabrant et al., 2009b).*
>
> *We found no statistically significant associations between household dust dioxins and serum dioxins (Garabrant et al., 2009b).*
>
> *The lack of evidence that contaminated household dust was associated with serum dioxin concentrations is also reassuring in that even though soil contamination contributes to household dust contamination, it does not contribute appreciably to the body burden of dioxins (Garabrant et al., 2009b).*

EPA COMMENT: Here is yet another example where the two key documents, the 2006 report (UM, 2006) and the 2009 journal article (Garabrant, 2009b), have slightly different results. The 2006 report suggested that a relationship might exist between PCB 118 levels in serum and household dust, whereas Garabrant et al. (2009b) suggest that the relationship is with PCB 126. Generally, the findings on the influence of household dust and serum concentrations, and between household dust and outdoor soil, appear supported by the analyses presented in the journal articles. In Garabrant et al. (2009b), combining soil and dust together showed a possible relationship only for PCB 126, with that congener in dust explaining 0.96% of the variation in serum PCB 126. The only other congener which showed a relationship was with 2,3,7,8-TCDD, which explained 0.51% of the variation. However, this finding appeared to have been driven by a single household showing a high concentration of 2,3,7,8-TCDD in garden soil. Without this data point, the relationship was not statistically significant.

### 4.3 Serum Correlations with Other Factors

***Serum versus Study Area:*** Higher concentrations of dioxins were found in the serum of residents living within the four study areas comprising the MS region as compared to the reference JC area. The following statements have been made supporting this finding:

> *People who live in some regions of Midland/Saginaw have higher levels of some dioxins in their serum than do people in Jackson/Calhoun (UM, 2006).*

*The median serum $TEQ_{DFP\text{-}2005}$ varied by 6.4 ppt among the five populations, was significantly elevated in the floodplain compared with the referent population (23.2 ppt vs. 18.5 ppt, p >0.01), and was lowest in the Midland plume population (16.8 ppt). Maximum $TEQ_{DFP\text{-}2005}$ concentrations varied by more than 130 ppt across the five populations, with the most elevated serum concentration in the floodplain (211 ppt) and the near-floodplain (154 ppt) populations, and the lowest maximum serum concentration in the Midland plume (78.5 ppt) (Hedgeman et al., 2009).*

EPA COMMENT: This conclusion is supported primarily by analysis provided in Hedgeman et al, 2009. This publication provides key percentiles for the full distributions in the two regions. The analysis showed that the distributions are fairly similar up until the 50th percentile (the median), but that the MS concentrations (combining all results from the 4 study areas comprising the M/ region) then were higher than the JC region. Specifically, the medians for the two populations were 20.7 and 18.5 pg/g TEQ lipid weight (ppt lwt) for the MS and JC populations, respectively. The 75th, 95th, and maximum concentrations were 32.3, 62.9, and 211 ppt TEQ lwt for MS and 25.3, 46.5, and 109 ppt TEQ lwt for JC.

***Serum versus Living in the MS Region***: Living in the MS region during the middle decades of the 20th century was associated with elevated serum dioxins. Statements in the key documents which address this relationship include:

*People who lived in Midland/Saginaw between 1940 and 1959 have higher levels of 2,3,7,8-TCDD in their serum. We believe this is suggestive of Dow's operations during that time period. Other types of dioxins and TEQ do not have this kind of relationship. Other time periods do not have this relationship (UM, 2006).*

*Residence in Midland and Saginaw counties was examined in three different historic periods, 1940–1959, 1960–1979, and 1980–2005, with the duration of residence during each period handled as a continuous variable. Residence in the area during 1960–1979 was positively associated with TEQ, TCDD, and 1,2,3,7,8-PeCDD, but not with other congeners….Neither residence in 1940–1959 nor residence in 1980–2005 was associated with any congener (Garabrant et al., 2009b).*

*After adjustment for all other factors in the model, including historical residence in Midland or Saginaw counties as described above, living currently in the floodplain or near the floodplain of the Tittabawassee River or in the plume area downwind of the Dow facility was not associated with either TEQ or any of the PCDD or PCDF congeners. We found a significant positive association for serum PCB-126 and living currently in the near floodplain compared with living in Jackson/Calhoun counties. However, we are not aware that PCB-126 was manufactured or used at Dow (Garabrant et al., 2009b).*

EPA COMMENT: This is an instance where the two primary reports we reviewed have a different message altogether. It is noted that the statement attributed to the 2006 report (UM, 2006) was not included as a primary finding – all other findings from the 2006 report originated on page 2 of the summary whereas the quote above was from page 10 in the body of the report. Based on other information, we believe that the later findings are more supported and we cannot understand this disparity in the two documents. New work that was presented at the Dioxin 2009 conference (Hong et al., 2009; Garabrant et al., 2009d) concluded that the number of years living in the MS area between 1960-79 resulted in elevations in certain dioxin measures, and that this effect is most pronounced with 2,3,7,8-TCDD. The UMDES researchers hypothesize that this is due to emissions from the Dow incinerator during those years. In Garabrant et al. (2009b), this factor was part of a category called "residence factors" (defined as, "Number of years in MS in 1960-1979", but also including "reside in Near Floodplain"), and it was shown that these factors explained only about 0.6% of TEQ, but 3.4% of 2,3,7,8-TCDD variation.

***Serum versus Age:*** A primary finding from this study is that age is positively associated with serum dioxin levels. The following statements have been made supporting this finding:

> *The most important factor related to levels of dioxins in people's serum is age. We found that older people have higher levels of dioxins in their serum. This effect was found in both Midland/Saginaw and Jackson/Calhoun and has been found in other studies for people across the United States (UM, 2006).*
>
> *The largest part of the variation (31-44%) was explained by what we have labeled demographic factors: age, age$^2$, sex, BMI, BMI loss in the past 12 months, breast-feeding, number of pregnancies, race, smoking, and interaction terms. (The amount of variation associated with age alone is not provided.) (Garabrant et al., 2009b)*
>
> *Age was strongly associated with serum TEQ and with all serum congener concentrations. In addition, age$^2$ was negatively associated with serum TEQ, 1,2,3,6,7,8-HxCDD, and 2,3,4,7,8-PCDF, indicating that the relationship between age and serum concentrations was slightly less than exponential for these dioxins (Garabrant et al., 2009b).*
>
> *TEQ increased more dramatically among females than among males (Various statements similar to this TEQ statement were made on a congener-specific basis) (Garabrant et al., 2009b).*

EPA COMMENT: This finding is supported by the analysis conducted to date. However, while age may be the most important variable relating to serum levels, plots of serum level versus age show substantial scatter or variability, yielding a significant, but weak positive correlation. The $R^2$ for age alone was not reported. However, the lumped demographic factors have an $R^2$ of 0.396 for serum TEQs (Garabrant et al., 2009b), so age by itself would be lower. Thus, the statements that age is a strong predictor of serum levels appear overstated.

***Serum versus Fish:*** Aside from the demographic factors, perhaps the factor otherwise most correlated with serum measurements was consumption of fish. Various statements of findings addressed issues including: where the fish came from (store bought or from the impacted water bodies), what kind of fish, whether the individuals recreationally fished, and so on. Specific statements relating to the relationship of serum levels with fish consumption and/or recreational fishing activities, include:

> *Eating fish, no matter whether it is sport-caught, store-bought, or from a restaurant, is related to higher levels of dioxins in people's serum. This applies to fish both from the contaminated area in Midland/Saginaw and from outside the contaminated area (UM, 2006).*
>
> *People who eat fish from the Tittabawassee River, Saginaw River, and Saginaw Bay have higher levels of dioxins in their serum than people who do not eat fish from these areas. Most of these people live in Midland/Saginaw. For example, 65 percent of people who live in the Floodplain have eaten fish from the Tittabawassee River, Saginaw River, or Saginaw Bay at some point during their lives, compared to only 8 percent in Jackson/Calhoun (UM, 2006).*
>
> *Fishing and fish consumption explained 0.5–3% of the variation in serum dioxin concentrations (Garabrant et al., 2009b).*
>
> *Consumption of fish after 1980, regardless of their source (store-bought, restaurant, or sport caught), was positively associated with TEQ, TCDD, and PCB-126. We found no positive associations between consumption of fish from the contaminated areas (Tittabawassee River, Saginaw River, or Saginaw Bay) and serum PCDD or PCDF levels. There were equivocal results for eating fish from the Saginaw River or Saginaw Bay in the past 5 years (positive association for consumption less than once per month, but a negative association for consumption of more than once per month). We found positive associations for serum 1,2,3,6,7,8-HxCDD and 2,3,4,7,8-PeCDF and consumption of walleye or perch from other sources (other water bodies, restaurants, and grocery stores). All other variables related to consumption of fish from the contaminated water bodies were either significantly negatively associated with serum dioxins or not associated. Overall, consumption of fish was positively associated with increased serum levels of a number of dioxins, but the findings were not related to fish from the contaminated areas, with the exception of PCB-126 (Garabrant et al., 2009b).*
>
> *Fishing in the Saginaw River and Saginaw Bay after 1980 was positively associated with serum TEQ, 1,2,3,7,8-PeCDD, and 2,3,4,7,8-PeCDF, and fishing in the Tittabawassee River between 1960 and 1979 was positively associated with 1,2,3,6,7,8-HxCDD (Garabrant et al., 2009b).*
>
> *The overall pattern of findings in this population suggest little contribution from exposures in Midland and Saginaw counties during the last 25 years to serum*

*dioxins from either contaminated soil, household dust, consumption of fish and game from contaminated areas, or recreational habits (Garabrant et al., 2009b)..*

*Our model suggests that fishing in the Saginaw River or Bay at least once per month since 1980 multiplies the serum 2,3,4,7,8-PeCDF concentration by a factor of 1.3 (an increase of 1.6 ppt compared with the median level of 5.4 ppt in Jackson and Calhoun counties). In contrast, consumption of fish from the contaminated areas was not associated with increased serum 2,3,4,7,8-PeCDF. It is possible that a larger sample of people who consumed contaminated fish regularly might have shown an association (Garabrant et al., 2009b).*

EPA COMMENT: The general comment that there is a relationship between consumption of fish and serum dioxin levels is generally supported by the several findings that were outlined in the primary publication detailing the statistical correlation analysis of the data set (Garabrant et al, 2009b). While the correlation was noted, the statistical relationship was weak as overall fishing and fish consumption appeared to explain only about 1% of the variation in serum TEQ levels, and less than 3% for any of the individual congeners (Table 1 in Garabrant et al, 2009b). There appeared to be some slight differences and inconsistencies between the 2006 report (UM, 2006) and the 2009 journal article (Garabrant et al., 2009b) which are summarized here. The 2006 report (UM, 2006) included the conclusion: "People who eat fish from the Tittabawassee River, Saginaw River, and Saginaw Bay have higher levels of dioxins in their serum on average than people who do not eat fish from these areas." However, the 2009 publication states, "We found no positive associations between consumption of fish from the contaminated areas (Tittabawassee River, Saginaw River, or Saginaw Bay) and serum PCDD of PCDF levels" (Garabrant et al, 2009b, p. 822). Also, the 2006 report seemed to promote the notion of a clear relationship between fish consumption and serum levels, while the later EHP report was more equivocal about this, as they stated, "The overall pattern of findings in this population suggest little contribution from exposures in Midland and Saginaw counties during the last 25 years to serum dioxins from either contaminated soil, household dust, consumption of fish and game from contaminated areas, or recreational habits."

***Serum versus Recreational Activities:*** There was evidence that certain recreational activities may be related to dioxin serum levels. Statements in the key documents which address this relationship include:

*People who do recreational activities in the Tittabawassee River, Saginaw River, and Saginaw Bay have higher levels of dioxins in their serum than people who do not do recreational activities in these areas (UM, 2006).*

*A principal focus of our study was to assess activities that might involve contact with contaminated soils, river sediments, and household dust. These included living on contaminated soil, living with contaminated household dust, and pursuing activities in the contaminated water bodies and floodplain (boating, swimming, picnicking, hiking, etc.). We found little evidence in the general population that these activities were associated with increased serum dioxins. Participating in water activities on the Tittabawassee River more than once per*

*month in 1980–2005 was associated with increased TCDD, but less frequent activities and activities before this period were not. We found no relationship between these activities and any other dioxin in any historic era (Garabrant et al., 2009b).*

*The overall pattern of findings in this population suggest little contribution from exposures in Midland and Saginaw counties during the last 25 years to serum dioxins from either contaminated soil, household dust, consumption of fish and game from contaminated areas, or recreational habits (Garabrant et al., 2009b).*

EPA COMMENT: This was supported by a positive association between recreational activities and dioxin body burden that appeared in the 2006 report (UM, 2006). However, like the conclusion noted above on consuming fish from the impacted water bodies, this conclusion was not supported in the 2009 literature publication on predictors of serum. A category of "Water activities factors" was included in Table 1 in Garabrant et al (2009b). This table provided the percentages of variation for several factors for explaining serum dioxin, and the percentages of variation for water activity factors ranged from 0.00 to 0.77 for TEQ and several congeners. To at least show some positive correlation may have been enough to have motivated the UMDES researchers to list the finding the in 2006 report, but the conclusions in the later journal article did not echo that sentiment.

***Serum versus Working at Dow:*** A relationship was found between working at Dow during the middle decades of the 20th century and serum dioxin levels. Statements in the key documents which address this relationship include:

*People who worked at the Dow plant from 1940 to 1959 have higher levels of dioxins in their serum than people who did not work at Dow during that period (UM, 2006).*

*Even though 6% of the subjects reported ever having worked at Dow, we found little evidence that such work was associated with increased serum dioxin levels…Work at Dow in 1940–1959 was positively associated with TCDD; however, working at Dow in 1980–2005 was inversely associated with 1,2,3,6,7,8-HxCDD and 2,3,4,7,8-PeCDF. None of the other variables that explored work at Dow, work with chlorophenol derivatives, or likely occupational exposure to dioxins was associated with increased serum dioxins (Garabrant et al., 2009b).*

EPA COMMENT: Interestingly, this does not appear to be a finding for TEQ, but it does appear to be a finding for 2,3,7,8-TCDD. In Garabrant et al. (2009b), it is noted that this factor explained only 0.18% of the variation in TEQ serum levels, but 1.82% of the variation in 2,3,7,8-TCDD. The UMDES researchers have recently conducted analyses (Garabrant et al. 2009d) that show that impacts from the Dow facilities, including to workers and importantly also to nearby residents, may have had the most impact during the middle decades of the 20th century (1940 to 1959 for workers, and 1960 – 1979 for residents), but not the later decades (1980 – 2005 for any subset of individuals), and furthermore, that this impact is seen most with 2,3,7,8-TCDD. It is

interesting to note that, once again, a slight change of tone from the 2006 report the 2009 journal article is present, even though both are based on the same analysis.

## SECTION 5: UNANSWERED QUESTIONS ABOUT EXPOSURE

### 5.1 Can Pharmacokinetic Modeling Help to Inform Study Results?

Simple pharmacokinetic (PK) modeling was used to study the potential impact from living on soil with elevations in dioxin. This exercise is described in detail in Appendix 1. The basic structure of the exercise was to simulate the lifetime accumulation of dioxins in a 20 year-old, a 40 year-old, and a 60 year-old who might have been sampled for dioxin-like compounds in 2007. Doing these simulations entailed constructing their lifetime exposures, considering the years they were living (the 40 year-old lived from 1968 to 2007, for example) as well as how exposures would change over their specific lifetimes (children have a higher body-weight based exposure due to elevated soil ingestion rates, etc). In this exercise, there were, two 20 year-olds, two 40 year-olds, and two 60 year-olds, in two distinct populations. In one, the 20, 40, and 60 year-old had all background exposures including soil-related exposures (ingestion plus dermal contact) at background soil levels. This level, as ascertained by the Dioxin Reassessment (EPA, 2003a), was assumed to be 11 pg/g TEQ (dioxins, furans, and PCBs: D/F/P). In the other, the three individuals had all of the background exposures and the soil-related exposures were based on a soil concentration of 223 pg/g TEQ (D/F/P), which was the 95% concentration found in properties measured on the flood plain. The principal output from this exercise was the body burden of the six individuals in simulated year 2007. Available body burden data to compare this with include age-related NHANES survey results from 2001-2002 and 2003-2004, as well as data from the study area. The principal findings from this exercise are summarized below.

The medians for the age ranges in the measured data from JC appear quite comparable to the analogous (not exactly the same) age ranges and metrics from the NHANES survey (geometric mean from NHANES 2001-2002 and median from the NHANES 2003-2004). For example, the median concentrations in the 45-59 and >60 age ranges in JC of 20.8 and 31.3 pg/g TEQ, respectively, compare well to geometric means of 20.7 and 33.7 pg/g TEQ from the same two age ranges in NHANES 2001-2002. Interestingly, the lower median from Jackson/Calhoun of 7.8 pg/g TEQ for the 18-29 age range compares better to the NHANES 2003-2004 results (7.1 and 8.9 pg/g TEQ medians for 12-19 and 20-39 ages, respectively) than the NHANES 2001-2002 results (12.5 geometric means for 20-29 year olds).

The modeled concentrations for the 20, 40, and 60 year-old with background exposures including background soils are certainly within the range of the Jackson/Calhoun and NHANES data. The concentrations for the 20, 40, and 60 year-old were 13.6, 16.4, and 19.7 ppt TEQ lipid weight. The span of concentrations, from 13.6 to 19.7 or about a 6 ppt span, is similar to the span of about 8 ppt TEQ for both NHANES surveys up until age 60. However, for both NHANES data sets, the concentration for ages >60 then jump somewhat, to 33.7 pg/g TEQ for NHANES 2001-2002 and 26.9 for NHANES 2003-2004. It is unclear whether the model would simulate this high a body burden for individuals older than 60, but that remains untested.

Assuming the above finding suggests credibility with the model for characterizing the varying body burdens of individuals living in the US in background settings, one can then use the model to study the impact to body burdens from exposures higher or lower than the

background scenario crafted. The exposure examined here was to elevated soil. The modeled difference between body burdens of individuals exposed to background only compared to background plus elevated soils, at 223 ppt TEQ, appears to be only about 3 ppt TEQ lipid weight. This difference was consistent for all three ages.

This analysis is preliminary with several uncertainties, which were identified in the appendix. Still, given the uncertainties, limitations, assumptions, and so on, this at least begins to provide supportive evidence that exposures to elevated soils, by themselves (i.e., no secondary impacts such as elevated fruit/vegetables, elevated fish or terrestrial food animal products) may not provide that great an impact to body burdens of adults of all ages who may be surveyed during the 2000s.

This same modeling structure can now be used to study other issues that may be of concern, such as potential exposures to children, potential exposures to soils even higher than 223 ppt TEQ, and other scenarios.

### 5.2 What About Children and Exposure to Contaminated Soils and Dust?

It was stated in the UMDES study documentation that children were not measured because the volume of blood required for laboratory analysis was evaluated as being too high for them. However, of all populations, children might be deemed the most exposed to dioxins in soils.

The pharmacokinetic modeling structure described above and in the appendix can provide an initial sense of what the body burden difference might be for a child living on elevated soils versus background soils. As part of the simulation of lifetime accumulation of dioxins in the PK exercise, children aged 1-6 were assumed to ingest 100 mg/day of soil. This was reduced to 50 mg/day for all later ages. For the fully background scenario, the soil concentration was 11 ppt TEQ, while for the background plus elevated soil, this was increased to 223 ppt. The difference in the two 20 year-olds when they turned 5 was examined; this is because the 20 year-old turned 5 in 1993, and based on the structure of the historical intake model, background exposures to dioxin leveled off at about 1980, so this prediction of 5 year-old body burdens in 1993 would be comparable to simulating an individual being born in 2002 and turning 5 in 2007. The modeling suggests about a 6 ppt TEQ difference in the body burdens of the two 5 year-olds in 1993: it is 23.4 ppt TEQ for the child living on elevated soil and 17.4 for the child living on background soils. Besides noting the 6 ppt TEQ difference, one might also characterize the difference at about 33% from living on soils at about 223 ppt TEQ; i.e., an increase from 17 to 23 ppt TEQ is about a 33% increase.

### 5.3 Were all Populations of Interest Adequately Represented in the Study? What About Highly Exposed Individuals and Areas with Highly Elevated Soil Concentrations?

This issue was discussed in detail in Section 3.1. Basically, it was concluded that although UMDES took steps to increase the likelihood that impacted soils would be represented

in the survey, the success of this effort is unclear. Data presented in ATS (2009) suggest that high soil levels may be more prevalent than found in UMDES. Section 3.1 also concludes that UMDES did not include any special features to ensure representation of activities related to high end exposures such as farming, fishing, hunting and gardening. The study did end up including one farmer who consumed his own beef and one gardener with elevated soils. In both these cases, the individual was found to have elevated serum dioxin concentrations (Garabrant et al., 2009b).

### 5.4 Is it Reasonable that the Correlations Between Soil and Blood Were Weak?

Yes, this is a reasonable expectation, given the arguments presented above. As noted, 95% of the properties on the floodplain have topsoil concentrations at 223 ppt TEQ and lower, and yet the PK exercise suggested living on soils this elevated compared to living on background soils would only raise body burden TEQ by about 3 ppt TEQ. Without the use of rigorous survey statistics, and given the range of serum levels found in the UMDES survey, it is at least intuitive to surmise that a weak association between soil and blood would be expected when over 95% of the individuals that could be sampled might have body burden impacts at 3 ppt TEQ and less. Indeed, had a strong correlation been found (given the range of soil concentrations found in the FP and other areas), EPA's own evaluations (here and in EPA, 2003, for example) suggesting a small impact from soil exposure compared to all other exposures, particularly food exposures, would need to be reassessed.

EPA cautions that the findings in the UMDES are not general findings, for at least two important reasons: they do not address children's exposures, and they may not address living on properties with high dioxin soil concentrations. EPA asked UMDES investigators and received data for properties with soil concentrations exceeding 1000 ppt TEQ. Twenty-three properties were identified. Inspection of those data suggests that blood serum dioxin levels tended to be elevated for subjects living on those properties (See Appendix B).

## SECTION 6: RELEVANCE TO EPA

EPA acknowledges that many stakeholders are concerned about the implications of this study for risk assessment, particularly with regards to dioxin levels in soils. Current EPA soil dioxin remediation goals are largely based on a scenario of childhood soil ingestion. The Superfund-supported benchmark of 1000 ppt TEQ, for example, is based on a scenario of exposure for ages 1 to 30 years old with about two-thirds of the dose estimated to occur prior to age 18. No children (<18 years) were sampled in the study, so no insights as to the potential impacts to children as measured by body burdens can be gained from the UMDES.

The ability of the UMDES to accurately capture "high end" scenarios was questioned (see discussions in Section 3). Conclusions in the UMDES study about the relationship between soil concentrations and serum concentrations pertain to the general adult population. The study design did not guarantee inclusion of the properties with the highest soil concentrations, the fishers with the highest consumption rate of recreationally caught fish, or those with highest exposure from gardening in soils with elevated dioxin concentrations. New data supplied to EPA on individuals living on properties at concentrations above 1000 ppt TEQ may suggest a relationship between high dioxin soil concentrations and body burdens.

Regulatory benchmarks such as dioxin remediation goals or fish advisories are based on high end exposure scenarios. They are based on factors that have uncertainties and variabilities, such as soil and fish ingestion rates, years of exposure, cancer potency factors, and so on. None of these features are addressed in the UMDES study. Any discussion on the usefulness of the UMDES results on regulatory activities must first recognize this fact.

Perhaps the most interesting findings from the UMDES, with regard to this discussion, are the findings that some individuals have elevated serum dioxins that can be associated with specific activities that are linked to higher exposures. One individual in the FP who had elevated dioxin levels in his blood (Franzblau et al, 2009b) raised cattle for consumption (for himself, family, and friends). Interestingly, the elevations were in the furan congeners and these congeners are elevated in FP soils. Therefore, the pathway of soil to cattle to humans was likely in this case. In another instance, a gardener with elevated dioxin serum levels (Garabrant et al., 2009b) also had elevated garden soil (Franzblau et al, 2009c). EPA suggests that these individuals support the contention that contact with soils, directly or via the food chain, may be associated with elevated blood dioxin concentrations.

Finally, dioxin presents a challenge for risk assessors and policymakers because the background exposure to dioxin is already at a level considered to be of concern. This was a finding of EPA's draft Dioxin Reassessment (EPA, 2003), and another finding was that animal food consumption explained 95% of the exposure and that resulting risk level. Therefore, any incremental exposure over the dietary background will increase the risk over the range of concern.

## SECTION 7: CONCLUSIONS

The most important limitations to the scope of this study are that it addresses exposure only (i.e. no health status or outcomes data were collected) and participants were limited to individuals aged 18 years or older. A design limitation is that as an observational study it provides the basis for examining associations between the variables, but cannot be relied on for determining cause and effect relationships.

EPA concludes that the UMDES study design was well-suited for meeting its first objective of characterizing distributions and identifying patterns of exposure. The relatively large number of participants and the population-based statistical sampling design are important strengths of this study. They provide reliable estimates of the distributions of dioxin concentrations in blood, soil and dust, and the study provides several measures of those distributions (i.e. means, medians, lower and upper percentiles).

EPA believes that the UMDES design may only have been partially successful in meeting the second objective, which was to evaluate factors associated with serum dioxin. EPA concludes that the UMDES identified the associations between serum levels and a variety of demographic factors (age, sex, body mass index, where one lives, work history). However, EPA is uncertain that the UMDES evaluated the full impact on serum levels of soils or dust, or of various activities, including dietary choices. Determining the incremental effect on serum levels of dioxin exposures from soil or dust is problematic because soil and dust contributions to total exposure are generally small compared to background dietary exposures. Pharmacokinetic modeling done as part of this review indicates that direct ingestion of soil and dust would not be expected to contribute significantly to adult serum levels except at relatively high soil and dust concentrations (i.e. over 1000 ppt TEQ).

The UMDES researchers recognized this need and took steps to address it. They targeted sampling areas that most likely had soil impacts from the Dow facility (an area impacted by the incinerator plume and the 100 year floodplain downstream of the plant). Further, they used a very high sampling rate in these areas (17% of the population in the floodplain and 30% of the population in the plume area) and ultimately included 23 properties with dioxin levels over 1,000 ppt TEQ. Judging whether this is an adequate representation is difficult. The relatively low median soil levels in the floodplain (11 ppt TEQ) and suggestion of higher levels from other studies (ATS, 2009) support the concern that it may not be adequate.

A related design issue is how well the data represented behaviors occurring on contaminated soils that could lead to elevated dioxin exposures such as gardening, consuming local fish and game or raising animals for local consumption. No design elements were used to ensure representation of these activities. However, two such scenarios were identified in the study (one gardener and one farmer) and the UMDES researchers have highlighted these findings.

The UMDES data provided some unanticipated but useful findings. These involved the identification of several unexpected dioxin exposure scenarios. First, was the discovery of soils

containing elevated levels of dioxin outside the floodplain due to movement of soils from the floodplain to residences for fill or other purposes. Second was the discovery of elevated serum levels that appear to be associated with the activities of a ceramic clay hobbyist. Third was the discovery that polychlorinated biphenyls (PCBs) were the dominant contributors to high TEQ levels in soil at one residence (linked to past paint use), and in dust at nine residences (where one was linked to a carpet pad and others had unknown sources.

A Quality Assurance Project Plan was drafted which, although not complete in all areas, addressed the key elements of quality assurance procedures. However, the publications to date have not included a report on quality assurance performance measures.

The points discussed above represent EPA's conclusions regarding the study design. EPA's primary comments on the study findings are summarized below.

EPA concludes that the following findings are well supported by the UMDES data and analyses:

- Soils from properties in the Midland/Saginaw study areas contain higher concentrations of dioxin than soils in the reference area, the Jackson/Calhoun area.
- Higher concentrations of dioxins were found in the serum of residents living within the four study areas comprising the Midland/Saginaw region as compared to the reference Jackson/Calhoun area.
- Dusts from households in the Midland Plume area contain higher dioxin levels than dusts from households in the other study areas.
- Living in the Midland/Saginaw study areas during the years 1960-1979 was associated with elevated serum dioxins.
- Working at Dow during the years 1940-1959 was associated with elevated serum dioxin levels. This does not appear to be a finding for TEQ, but it does appear to be a finding for 2,3,7,8-TCDD.

The most highlighted finding of this study is that age is positively associated with serum dioxin levels. EPA agrees that the analysis done on UMDES data support this finding. However, while age may have the strongest correlation with serum levels of all variables studied, plots of serum level versus age show substantial scatter or variability, yielding a significant, but weak to moderate positive correlation. The $R^2$ for age alone was not reported. However, the correlation between serum TEQs and an aggregate of nine demographic factors, including age, was reported to have an $R^2$ of 0.396 (Garabrant et al., 2009b), so age by itself would be lower. Thus, the assertion that age is a strong predictor of serum levels appear overstated.

Many findings appear in the various documents relating to the key relationship between serum dioxin and soil dioxin. Generally, weak relationships between various measures of soil and serum dioxin levels were noted but the overall conclusions in the more recent documents imply that there is not a meaningful relationship between these two key factors. EPA believes this general finding of a weak association between soil and dioxin serum dioxin levels is supported by the statistical analysis that is presented in Garabrant et al (2009b). This may be associated with the large relative contribution from diet, which would be expected to overwhelm

contributions from soils at background concentrations. The study design may not have fully represented the soils with high concentrations of dioxin making it difficult to fully evaluate this relationship. EPA also emphasizes that it is important that this finding not be stated alone without the caveats about the study limitations.

Similarly, UMDES found little association between household dust concentrations of dioxins and serum. EPA agrees that the analysis done on UMDES data support this finding. However, the issues about the relative contribution of diet and the design issues noted above for soils would also apply to dusts. Also, it is noted that two key documents, the 2006 report (UM, 2006) and the 2009 journal article (Garabrant, 2009b), have slightly different results. The 2006 report suggested that a relationship might exist between PCB 118 levels in serum and household dust, whereas Garabrant et al. (2009b) suggest that the relationship is with PCB 126.

A variety of findings addressed serum/fish relationships including: where the fish came from (store bought or from the impacted water bodies), what kind of fish, whether the individuals recreationally fished, and so on. The general comment that there is a relationship between consumption of fish and serum dioxin levels is generally supported by the several findings that were outlined in the primary publication detailing the statistical correlation analysis of the data set (Garabrant et al, 2009b). While the correlation was noted, the statistical relationship was weak. There appeared to be some slight differences and inconsistencies between the 2006 report (UM, 2006) and the 2009 journal article (Garabrant et al., 2009b).

Certain recreational activities were found to be associated with dioxin serum levels. This was supported by a positive association between recreational activities and dioxin body burden that appeared in the 2006 report (UM, 2006). However, like the conclusion noted above on consuming fish from the impacted water bodies, this conclusion was not supported in the Garabrant et al., 2009.

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## APPENDIX A.

## EVALUATION OF THE IMPACT OF SOIL CONCENTRATIONS ON BODY BURDENS OF INDIVIDUALS

### Introduction and Approach:

The Dioxin Reassessment (US EPA, 2003) included pharmacokinetic (PK) modeling which predicted the lipid concentration of dioxin-like compounds during an individual's life, starting from the impacts of breast-feeding through adulthood and old age. This simple PK model was retrieved and used to model the body burdens of individuals who lived in two settings which differed only in the soil concentration to which the individuals were exposed. Specifically, the individuals that are modeled here live in: a fully background setting with regard to lifetime intakes including intakes via ingestion of soil at background levels, and a setting where intakes are the same as the first scenario except the soil-related intakes (ingestion plus dermal contact) is based on living on a soil that has a toxic equivalent (TEQ) concentration of 223 pg/g (ppt).

The concentration of 223 ppt TEQ was selected since this is the level that was characterized as the 95% percentile flood plain soils (Demond et al, 2008). This compares to the 11.6 ppt TEQ (17 D/Fs, 13 PCBs) assumed for background exposures in the Reassessment (US EPA, 2003). At this soil level, background soil impacts explained about 1% of total exposures for the various age ranges of individuals, with the exception of breast-feeding, which dominated exposures when it was modeled. It was above 1% for the children 1-5 whose soil ingestion rate was 100 mg/day, but below 1% for older age ranges, where ingestion rates were 50 mg/day. For example, the Reassessment estimated a total exposure of 50 pg TEQ/day for children ages 1-5. Of that total, soil ingestion (100 mg/day) plus soil dermal contact (2.2 mg/day) explained 1.2 pg TEQ/day (102.2 mg/day * 11.6 pg TEQ/g * 0.001 g/mg = 1.19 pg TEQ/day), which was over 2% of the total. If instead the child was living on a property whose soil level was 223 ppt TEQ, then his/her total exposure between ages 1-5 would be:

50 pg/day – 1.2 pg/day + (102.2 mg/day * 223 pg/g * 0.001 g/mg) = 71.5 pg/day

In this exercise, we will model the body burdens of a 20 year-old, a 40 year-old, and a 60 year-old whose blood was sampled in 2007. Therefore, the 20 year-old was born in 1988, the 40 year-old was born in 1968, and the 60 year-old was born in 1948. We will model the impacts of being raised in two settings: a background setting with all exposures similar to that of the Reassessment, and another background setting with all exposures the same except the soil-related exposures which are based on a concentration of 223 ppt TEQ. This results in a total of 6 scenarios:

20 year-old, 11.6 ppt TEQ soils
20 year-old, 223 ppt TEQ soils

40 year-old, 11.6 ppt TEQ soils

40 year-old, 223 ppt TEQ soils

60 year-old, 11.6 ppt TEQ soils
60 year-old, 223 ppt TEQ soils

The outcome of interest in these scenarios is simply the predicted body burdens of total dioxins in these individuals as though they were sampled in 2007.

In order to do this exercise, and also to be clear on the steps necessary to model the doses to which these individuals are exposed to, the construct of the exercise will be described in the following series of steps:

*1) Step 1: Develop a "multiplier" for converting current doses to past doses*

This exercise must consider the differences in environmental levels of dioxins in past years; specifically, higher exposures occurred in the past because of higher environmental levels. This was studied in Lorber (2002), who modeled the exposure of Americans to dioxins throughout the 20$^{th}$ into the 21$^{st}$ century using a simple pharmacokinetic model. He found that individuals in America who lived in the second half of the 20$^{th}$ century had higher body burdens than currently because of much higher exposures in the past. Table 1 is reproduced from Lorber (2002) and it shows the results from various blood monitoring studies of Americans in background settings throughout the 20$^{th}$ century. The earliest studies measuring the 17 dioxin and furan congeners (this table did not include dioxin-like PCBs) in background settings was a control group for a systematic study of Vietnam Veterans in sampling which occurred in several years in the 1970s. As seen in Table 1, background body burdens in the 1970s was consistently higher than 50 ppt TEQ, while in later years, it was under 30 ppt TEQ. The latest NHANES data from the early 2000s shows body burdens mostly near and under 20 ppt TEQ, except for the oldest in the population. In any case, Lorber (2002) studied temporal trends in exposure using the simple pharmacokinetic model used in this exercise. He calibrated a dose which was able to reproduce body burdens that were seen in Table 1. Figure 1 is from Lorber (2002) and it shows this calibrated background dose of dioxins and furans that was derived for adults for exposures which occurred in the past. While this calibration curve may suggest a degree of certainty in the knowledge of past exposure, Lorber (2002) describes the uncertainties associated with its generation, including (for example) the use of the simple pharmacokinetic model, the modeling of TEQ as though it were a single compound, the lack of data for historical serum and exposure media data to back up this historical intake, and so on. In any case, use of this intake did result in a good fit between model predictions and past body burdens compared against those that are shown in Table 1. As seen in Figure 1, the dose in the past was modeled to peak at about year 1964 and to decline steadily from that point until 1980. Then, the decline was more gentle until year 2000 and then flattened out past that. Specifically and for current purposes, the CDD/F dose in the year 1948 was 4.1 pg TEQ/kg-day, it peaked in 1964 at 6.5 pg TEQ/day, in 1968 the dose was 5.5 pg TEQ/kg-day, in 1980 the dose was 1.0 pg TEQ/kg, and in 2000, the dose flattened at 0.65 pg TEQ/kg-day. This 0.65 pg TEQ/kg-day was, in fact, derived in Lorber (2002) to be the same as current CDD/F background dose of 43 pg CDD/F TEQ/day that was developed as part of the Dioxin Reassessment effort. In the Reassessment, the current background dose of PCBs was derived as 23 pg PCB TEQ/day, resulting in a total current dose

of 66 pg CDD/F/PCB TEQ/day. The dose of PCBs turned out to be about 33% of total adult dose. If we assume the ratio between dioxin/furan and dioxin-like PCBs to be constant over time, then the total doses (CDD, CDF and PCB) over time for an adult can be derived as the CDD/F dose times 1.5. The results of this multiplication are: 6.15 pg TEQ/kg-day in 1948, 9.75 pg TEQ/kg-day in 1964, 8.25 pg TEQ/kg-day in 1968, 1.5 pg TEQ/kg-day in 1980, and 1.0 pg TEQ/kg-day in 2000. These "total doses" can now be used as "multipliers" that correlate current dose levels to past levels. For example, the adult dose in 1980 is calculated as the current adult total dose, 66 pg TEQ/day, times the 1980 multiplier, 1.5, and in 1968, the total adult dose is calculated as 66 pg TEQ/day * 8.25 = 545 pg TEQ/day. Needless to say, the doses from 2000 on are the same as derived in the Reassessment, since the multiplier is 1.0.

*2) Step 2: Use the "multiplier" with current background exposures to model past exposures*

This step will now map out the strategy to model past background exposures, not yet considering being raised on elevated soil levels. First, the Dioxin Reassessment provided these background D/F/P exposures, on a mass/day basis (not on a body weight basis) as a function of age:

| | | |
|---|---|---|
| Age | 1-5 | 50 pg TEQ/day |
| | 6-11 | 54 pg TEQ/day |
| | 12-19 | 61 pg TEQ/day |
| | >19 | 66 pg TEQ/day |

If we neglect breast-feeding, we can assume that the dose from year 0-1 equals the dose for the 1-5 year-old, even though the dose from 1-5 has a soil ingestion component. This is obviously a simplification for this exercise. However, the Reassessment showed with modeling that while breast-feeding greatly impacted the body burden of an infant and child, the body burdens of a breast-fed versus a formula-fed individual were very similar by the time the individuals reached 20 years old or thereabouts. If an individual was born in 1968, their initial exposure is calculated as 50 pg TEQ/day * 8.25 = 412.5 pg TEQ/day. This calculation employs the unitless multiplier of 8.25 derived above. When this individual turns 6 years old, their dose is recalculated as 54 pg TEQ/day times a new multiplier, extrapolated downward from 8.25 to be about 6.0. Similarly when the individual turns 12 in 1980, his/her dose is now calculated as 61 pg TEQ/day times a multiplier of 1.5. We can continue this calculation for all ages up until 2007 when the individual turns 40. Doing these calculations entailed a linear decline in the multiplier, as well as linear changes in dose as a function of age. This procedure was repeated for an individual born in 1948 and 1988.

*3) Step 3: Incorporate elevated soil levels into these calculations*

Step 2 above described the derivation of daily doses for an individual born in 1948 (the 60 year-old), 1968 (the 40 year-old), and 1988 (the 20 year-old), being exposed to background levels of dioxins, furans, and PCBs. Reconstructing the past exposures was accomplished by using the temporal dose regime constructed by Lorber (2002) in combination with the Dioxin Reassessment's evaluation of current dose for different age ranges. This procedure was laid out in steps 1 and 2 above. The next step will be to amend the three dose scenarios developed (i.e.,

for the 20, 40, and 60 year-old) to consider the impact of being raised on soils typical of the 95% soil concentration of floodplain soils: 223 ppt TEQ. For the background scenarios, exposures via soil ingestion plus dermal contact was 102.2 mg soil/day contact for children ages 1-5, and about 51 mg soil/day thereafter. In the Introduction above, it was shown how the daily exposure for a child ages 1-5 rose from 50 pg TEQ/day to 72 pg TEQ/day considering being raised on soil at concentrations of 223 ppt TEQ. If we now change the exposures for the other age ranges, we arrive at:

| Age | 11.6 ppt TEQ | 223 ppt TEQ |
|---|---|---|
| 1-5 | 50 pg TEQ/day | 72 pg TEQ/day |
| 6-11 | 54 pg TEQ/day | 65 pg TEQ/day |
| 12-19 | 61 pg TEQ/day | 74 pg TEQ/day |
| >19 | 66 pg TEQ/day | 78 pg TEQ/day |

If we repeat the analysis as outlined in steps 1 and 2 above, we arrive at exposures for the three age ranges over time.

***It is important to note*** *that this three-step procedure results in past exposures that were uniformly higher in all pathways as compared to today's exposure. Specifically, the "multiplier" gets applied to the intakes displayed above. The proportion of soil intakes to total intakes remains the same throughout time. What this means, however, is that this simulation assumes higher soil concentrations in the past (assuming that the soil exposure factors of soil ingestion and soil dermal contact remain the same over time). With a multiplier of 8, for example, it is assumed that back in the 1960s, soil that is today at 223 ppt TEQ was more like 2000 ppt TEQ then. At the very least, this is conservative, but it is also plausible. Dioxins do degrade in surface soils with a half-life of roughly 25 years (Paustenbach et al. 1992), so with minimal inputs over the past 25 years, a concentration of 223 ppt TEQ today might have been 450 ppt TEQ 25 years ago. It is plausible as well that emissions into the air as well as into the river by the Dow facility were much higher in the 1960s as compared to today, leading to higher depositions to soil from the atmosphere and higher sediment concentrations, and hence higher surface soil concentrations in affected areas. In any case, the discussion of all results on impacts to body burdens of living on soils at 223 ppt TEQ is really a discussion on living on soils that are at that level today but were higher in the past. If the soil in fact had been constant at 223 ppt TEQ, than the predicted impacts to body burdens increments would be lower than presented in this Appendix.*

Table 2 shows the final results of this procedure to develop daily doses for the six scenarios. The table includes the daily doses in 5-year increments for each of the 6 scenarios.

*Step 4: Run simulations incorporating all PK assumptions as previously developed*

The Dioxin Reassessment provides details on the simple 1$^{st}$ order, single-compartment pharmacokinetic (PK) model used to simulate the accumulations of dioxins throughout a lifetime of exposure, including breast-feeding. The simplified modeling approach treats "TEQ" as though it were a single compound with a half-life (and elimination rate) that varies over time as a function of the person's age. Also varying over a person's age are body weight and body lipid

reservoir. Table 3 shows how these key parameters vary over the course of a lifetime. Another key parameter for PK modeling is the absorption fraction. Intakes are multiplied by this factor to consider what portion of the intake dose gets absorbed into the body. Simplifications were made in this exercise to consider absorption. First, here is how it was done in the Reassessment. Food and inhalation ingestion amounts were multiplied by an absorption fraction of 0.8 before doing PK modeling. Soil ingestion exposures were multiplied by 0.5. The dermal contact factor of 2.2 mg/day described above considers several parameters including surface area of skin which contacts dirt, contact events per day, adherence of soil to skin, and most importantly, it also considers absorption at 3%. In other words, the value of 2.2 mg/day already considers absorption and an additional factor is not needed. For this exercise, the total doses derived above were all simply multiplied by 0.8 before doing PK modeling. This results in a slight overprediction, as compared to the Reassessment approach, because soil ingestion exposures were not reduced by 50%, but only by 20%. As in other aspects of this simulation, values between the dates shown in Tables 2 and 3 are interpolated in order to arrive at (somewhat) smooth simulations. The model was incorporated into a spreadsheet using a 1-month time-step, with interpolations as necessary.

**Results:**

The results from the simulation are shown in Figures 2-4 and Table 4. Figures 2-4 show the body burdens from birth to 20 (Figure 2), 40 (Figure 3), and 60 (Figure 4), given that these individuals reached these ages in 2007. The ages at that last point are reproduced in Table 4, along with comparisons to NHANES data and to data from the Jackson/Calhoun cohort of the UMDES. The NHANES data are from 2001-2002 (Scott et al, 2008) and also from 2003-2004 (Lakind et al, 2008). All NHANES data are derived using the 2005 TEF scheme and include the 17 CDD/Fs and 9 coplanar PCBs that have been measured in NHANES. A quick evaluation of the NHANES data show that about ¼ of total TEQ is comprised of the 9 dioxin-like PCBs. This is not an exact match with the assumption that 1/3 of dose is derived from these PCBs, but given the simplicity and generality of the overall approach (modeling TEQs as one compound, assuming the 1/3 contribution by PCBs to total dose is consistent over time, etc), the important aspect is that past exposures to CDD/F/PCB TEQ is meaningfully higher than just CDD/F TEQ. In any case, some immediate observations from the information presented in Table 4 include:

1. Although the age breakdown of NHANES 2001-2002 is not the same as NHANES 2003-2004, and the available metric for NHANES 2001-2002 – geometric mean, is not the same as the metric for NHANES 2003-2004 – median, it does appear that body burdens for the later survey date are meaningfully lower. For example, the geometric mean for 20-29 year olds in NHANES 2001-2002 is 12.5 pg/g TEQ while for medians 12-19 and 20-39 ages are both under 10 pg/g TEQ for NHANES 2003-2004. Similar trends are noted for the other two age categories shown in Table 4.

2. Although again not a one-to-one correspondence, the medians for the age ranges in Jackson/Calhoun appear quite comparable to the similar age ranges from the NHANES survey. For example, the median concentrations in the 45-59 and >60 age ranges in Jackson/Calhoun of 20.8 and 31.3 pg/g TEQ, respectively, compare well to geometric means of 20.7 and 33.7 pg/g

TEQ from NHANES 2001-2002. Interestingly, the lower median of 7.8 pg/g TEQ for the 18-29 age range compares better to the NHANES 2003-2004 results (7.1 and 8.9 pg/g TEQ medians for 12-19 and 20-39 ages, respectively) than the NHANES 2001-2002 results (12.5 geometric means for 20-29 year olds).

3. The modeled concentrations for the 20, 40, and 60 year-old are certainly within the range of the Jackson/Calhoun and NHANES data. Further, the span of concentrations seem to be comparable to both sets of NHANES data. Specifically, the three modeled body burdens are 13.6 (for the 20 year-old), 16.7 (40 year-old), and 19.4 pg /g TEQ (60 year-old), which is about a 6 pg/g TEQ spread. This is similar to the range implied by the 7.1-8.9 pg/g TEQ medians for the lower ages in NHANES 2003-2004 to the 15.0 pg/g TEQ as the median for the 40-59 age range. For NHANES 2001-2002, the range appears to be from about 12.5 to 20.7 pg/g TEQ, also similar to the modeled range. However, for both NHANES data sets, the concentration for ages >60 then jump somewhat, to 33.7 pg/g TEQ for NHANES 2001-2002 and 26.9 for NHANES 2003-2004. It is unclear whether the model would simulate this high a body burden for older individuals, but that remains untested. I suspect it would not.

This brief analysis focused only on the model predictions, the Jackson/Calhoun data, and the NHANES data. What is missing is the listing of the appropriate data from the Midland/Saginaw cohorts. Strictly speaking, what is required are data for individuals in these locations who live on soils that are elevated in concentration, say greater than 200 pg/g TEQ as an example. What is missing even still are the overall population summaries broken out by age and TEQ for the 4 Midland/Saginaw cohorts. There does appear to be a difference between the Jackson/Calhoun cohort and the Midland/Saginaw cohorts. The overall TEQ of these two populations are broken out by overall quartile (not age) in Hedgeman et al (2009). From their summary, it does appear that the upper percentiles in the Midland/Saginaw population diverge from both NHANES and Jackson Calhoun. Hedgeman et al (2009) make this observation: "The population serum data from the present study bracket the NHANES 2001–2002 serum data published by Ferriby et al. (2007). With the exception of the maximum TEQ(DFP- 1998) observation, serum percentiles from the Jackson/Calhoun population vary from the U.S. adult population by < 5 ppt. Within the Midland and Saginaw county populations, serum concentrations are similar to the NHANES 2001–2002 data up to the 50th percentile, but then diverge from the U.S. population data with an increase of 10–30 ppt."

It is noted that the overall summary report from 2006 does contain Figure 2 which shows the age breakdown comparison between Jackson/Calhoun and the Floodplain cohort. This figure is in TEQ-1998, which makes a difference: they have shown in separate publications that it can mean several ppt TEQ depending on what system is used. Since both are in the same TEF, both populations would be adjusted similarly when going to the newer TEF, so it would be expected that the general trends would not change. In any case, this figure is curious in that it suggests little difference in the compared cohorts, not like the 10-30 ppt TEQ noted above. This could be due to the fact that the statement above covers all 4 cohorts in the Midland/Saginaw region while Figure 2 only looks at the Floodplain cohort. Certainly, there is no 10-30 ppt TEQ spread in the data shown in Figure 2. It is a curious result that merits further investigation – why would the Floodplain as a cohort be similar to Jackson/Calhoun while the other 3 cohorts seem to significantly drive up the concentrations by the overall Midland/Saginaw 4-cohort group?

So besides getting clarity on the entire Midland/Saginaw age range breakdown, as a whole group and then by each of the four subgroups perhaps, an important next step in this evaluation is to retrieve the data in detail so the blood levels of individuals in homes with high soil concentrations can be separated from the rest of the population. Initial evaluations of this type are provided in Appendix B of this report, where individuals living on properties with a soil concentration greater than 1000 ppt TEQ were retrieved and studied. But it would appear that a majority of individuals from the Floodplain did not live on elevated soils. As noted in Hedgeman et al (2009), the median soil level in the floodplain is 11 ppt TEQ (CDD/F/PCB). This is the same as the national background soil level used in the Reassessment and in these simulations to characterize background exposures. Even though the median soil level in the floodplain is the same concentration, it cannot be surmised that the median blood level corresponds to the median soil level. To complete the evaluation, we need to retrieve the detailed data and then we need to compare, by age range ideally, the blood concentrations of individuals living in homes with elevated soils, perhaps 200 ppt and greater, with the model predictions for individuals exposed to 223 ppt TEQ soils.

It is also noted that the median soil levels in the Jackson/Calhoun cohort is 3.6 ppt TEQ (Hegeman et al, 2009). The difference in modeling impacts from living on 11.6 ppt TEQ versus 3.6 ppt TEQ is miniscule – there would be 0.1 ppt TEQ lipid difference in predicted lipid levels (I did a quick test to confirm this). Again, the most valid comparison of modeling and measured data can come once we retrieve the detailed data and look at blood levels only for individuals living on soils with elevated dioxin levels.

Notwithstanding the absence of this more valid comparison, it can be stated that the approach appears reasonable in its ability to capture the variation in a central tendency measure of dioxin body burdens by age for a cross section of adult ages for a survey that might occur in the 2000s. This statement is mainly supported by the comparison of model results with NHANES as well as the Jackson/Calhoun referent population. This does not necessarily mean, however, that the procedure to characterize exposures to dioxins in soil is accurate. Rather, it is a statement that the general procedure to derive a history of total dose (including mainly food intakes, but also soil intakes, inhalation, etc), and the impact of that dose on body burden over a lifetime, might be reasonable.

Even though we do not yet have the more detailed and appropriate data to compare the model results with those from the UMDES, we can still make some observations. It can be stated, for example, that the modeled difference between body burdens of individuals exposed to background only compared to background except with exposures to elevated soils (equal to the 95% soil found in the floodplains, at 223 ppt) appears to be only about 3 ppt TEQ body burden, on a lipid basis. As was noted earlier, this finding may be conservative because it assumed that all exposures in the past were proportionally higher, including soil exposures. A simple exercise can be done to show that constant exposure to soils at 223 ppt TEQ would result in an increment even less than 3 ppt TEQ. First, the aannual dioxin uptake from ingested soil is calculated as 223 pg/g * 0.05 g/d * 365d/yr * .8 absorption = 3256 pg/yr. The total amount of dioxin that would be deposited into the body over 30 years is given as:

$$TD = (ANN/k)(1 - e^{-kt})$$

Where TD = total amount of dioxin remaining in the body over a period of exposure, pg
ANN = the annual intake at 3256 pg/yr
k = first order elimination rate, 0.0815/yr (given a half-life of 8.5 yr, Table 2)
t = years of exposure, yr

If we assume 30 years of exposure, the TD is solved above as 36486 pg. If this gets deposited into an adult at 70 kg at about 0.25 body fat (see Table 2), than the resulting incremental body lipid concentration would be 2.1 pg/g.

Questions remain that could be answered with PK modeling, with further evaluation of data from the UMDES study area, or maybe never answered because specifically-desired data is not available. For example, monitoring did not occur for young children. Figure 2 showing differences for the 20 year-old may be useful to hypothesize about possible impacts to children. It is seen that the peak body burden occurs for about a 5 year-old. At that age, the difference in body burdens is about 6 ppt TEQ, at 23.4 ppt TEQ for the child living on elevated soil and 17.4 for the child living on background soils. Although the simulation was set up for the 5 year-old in this figure to have turned 5 years old in 1993, in fact this is about what the model would predict for an individual who was born in 2002 and turned 5 in 2007. This is because, as seen in Figure 1, background doses to dioxins were surmised to have largely diminished to near current levels at about 1980. Therefore, the body burdens modeled in Figure 2 are nearly what would be predicted to occur from birth to age 20 given today's background dose levels.

Another key question is, what might the impact be if living at much higher soil levels, say at 1000 ppt TEQ? This can be initially answered with the PK modeling framework developed here. Results for a 20 year-old using this framework, making all relevant changes to dose, are shown in Figure 5. Here the peak concentration for the 5 year-old is 36.1 ppt TEQ, now more than double that of a child of that age living in a background setting. Even at age 20, the individual living on 1000 ppt soil has a body burden of 24.5 ppt, compared to 13.6 and 16.5 ppt TEQ for the other two scenarios. This is yet another question that might be asked of the UMDES data – we can look at blood levels of individuals who not only lived in soils greater than 223 ppt TEQ, but of only those who lived on soils greater than 1000 ppt TEQ.

This exercise was a start at using PK models to "ground truth" the body burden results that have come out of the UMDES. If an acceptable measure of validity can be obtained with use of the PK model, in addition to or other than what this exercise has already shown, than the "bottom line" finding of the UMDES that living in soils elevated in dioxins would not greatly impact body burdens, can be supported. Also, the model can be used to do further "what if" scenarios and answer questions about exposure not necessarily captured with the monitoring data. Two questions that this exercise has already looked at are the impacts to the 5 year-old and impacts to having lived on soils as high as 1000 ppt TEQ.

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Table 1 from Lorber (2002)

Table 1
Summary of studies with body burden data of dioxins and furans

| Year | Mean TEQ, pg/g lipid | *N* | Ages | Reference; Location |
|---|---|---|---|---|
| 1972 | 87 | 7 | 18–45 | Kang et al., 1991; USEPA, 1990. Vietnam veterans, non-Vietnam veterans and Civilians. |
| 1973 | 89 | 14 | | |
| 1974 | 70 | 14 | | |
| 1975 | 68 | 14 | | |
| 1976 | 129 | 5 | | |
| 1977 | 69 | 17 | | |
| 1978 | 69 | 17 | | |
| 1979 | 67 | 22 | | |
| 1980 | 55 | 42 | | |
| 1981 | 54 | 26 | | |
| 1983 | 34 | 4 | NA | Schecter et al., 1986; Binghamton, NY |
| 1985 | 47 | 35 | $\bar{x}$=43 (21–88) | Graham et al., 1986; St. Louis, MO |
| 1986 | 31 | 4 | $\bar{x}$=34 (19–55) | Patterson et al., 1994; Atlanta, GA |
| 1987 | overall: 37<br>15–44: 27.5<br>>45: 53.4 | 666 | NA | Orban et al., 1994; EPA,1991 |
| 1988 | 30 | 26 | NA | Schecter et al., 1989; Massachusetts |
| 1988 | 37 | 57 | $\bar{x}$~50 (12–88) | Stanley et al., 1989; San Francisco and Los Angeles, CA |
| 1989 | 50 | 100 | NA | Schecter, 1991; Syracuse, NY |
| 1991 | 29 | 44 | $\bar{x}$=48 (41–66) | Schecter et al., 1993; Michigan Vietnam veterans |
| 1996 | 32 | 100 | NA | Schecter et al., 1997; Binghamton, NY |
| 1996 | 20 | 316 | $\bar{x}$=45 (20–70) | Personal communication from D. Patterson, Center for Disease Control, Atlanta, GA, to M. Lorber, US EPA, Washington, DC. April, 2000; background populations from site-specific studies in MO, OR, WS, AK and NC. |
| 1998 | 25 | 45 | $\bar{x}$=45 (28–67) | Petreas et al. 2000; San Francisco, CA |

Table 2. Daily background dose, described in 5-year increments, for each of the individuals in the 6 scenarios; dose in pg TEQ/day.

| Year | Scenario | | | | | |
|---|---|---|---|---|---|---|
| | 60 year-old, bkgrnd soil | 60 year-old, elevated soil | 40 year-old, bkgrnd soil | 40 year-old, elevated soil | 20 year-old, bkgrnd soil | 20 year-old, elevated soil |
| 1948 | 200 | 288 | | | | |
| 1953 | 282 | 376 | | | | |
| 1958 | 405 | 524 | | | | |
| 1963 | 544 | 685 | | | | |
| 1968 | 572 | 643 | 413 | 594 | | |
| 1973 | 396 | 424 | 290 | 360 | | |
| 1978 | 210 | 248 | 154 | 186 | | |
| 1983 | 96 | 113 | 90 | 108 | | |
| 1988 | 88 | 103 | 86 | 101 | 65 | 94 |
| 1993 | 79 | 94 | 78 | 92 | 63 | 78 |
| 1998 | 71 | 84 | 69 | 82 | 62 | 75 |
| 2003 | 66 | 78 | 66 | 78 | 63 | 76 |
| 2007 | 66 | 78 | 66 | 78 | 65 | 78 |

Table 3. Modeling parameters for pharmacokinetic modeling.

| Time After Birth | Body Weight (kg) | Body Lipid Fraction | TEQ Half-life (yrs) |
|---|---|---|---|
| At birth | 3.3 | 0.14 | 0.40 |
| 1 year | 11.3 | 0.23 | 1.06 |
| 2 years | 13.3 | 0.20 | 1.72 |
| 5 years | 19.7 | 0.15 | 3.70 |
| 12 years | 41.1 | 0.15 | 7.12 |
| 19 years | 65.1 | 0.13 | 7.54 |
| 35 years | 71.5 | 0.21 | 8.50 |
| 60 years | 73.8 | 0.27 | 10.00 |

Table 4. Final results of PK modeling exercise including lipid concentrations of 6 modeled individuals: 20, 40, and 60 year-old individuals living on background and elevated soil concentrations, compared against the UMDES results (from Hedgeman et al, 2009), NHANES 2001-2002 (from Scott et al, 2008; 17 CDD/Fs, 9 PCBs), and NHANES 2003-2004 (Lakind et al, 2008).

| | Serum Lipid Levels (ppt TEQ) | | |
|---|---|---|---|
| **Description** | **Modeled** | **UMDES** | **NHANES** |
| 20 yr old exposed to background including soils at 11.6 ppt TEQ | 13.6 | 7.8 (median for 18-29 yr olds in Jackson/Calhoun) | 13.5 (geometric mean for 20 -29 yr olds) 7.1 and 8.9 (median for 12-19 and 20-39 in NHANES 2003-2004) |
| 20 yr old exposed to background but soils at 223 ppt | 16.5 | Comparable data not yet available | No comparable data |
| 40 yr old exposed to background including soils at 11.6 ppt TEQ | 16.7 | 14.0 (median for 30-44 yr olds in Jackson/Calhoun) | 17.1 (geometric mean for 30-44 yr olds in NHANES 2001-2002) 8.9 and 15.0 (median for 20-39 and 40-59 in NHANES 2003-2004) |
| 40 yr old exposed to background but soil at 223 ppt. | 20.0 | Comparable data not yet available | No comparable data |
| 60 yr old exposed to background including soils at 11.6 ppt TEQ | 19.4 | 20.8; 31.3 (median for 45-59 & >60 yrs in Jackson/Calhoun) | 20,7, 33.7 (geometric mean for 45-59 and >60 yrs; NHANES 2001-2002) 15.0 and 26.9 (median for 40-59 and >60 in NHANES 2003-2004 ) |
| 60 yr old exposed to background but soils at 223 ppt | 22.7 | Comparable data not yet available | No comparable data |

Figure 1. The variation in adult exposures exposure levels as a function of time (from Lorber, 2002).

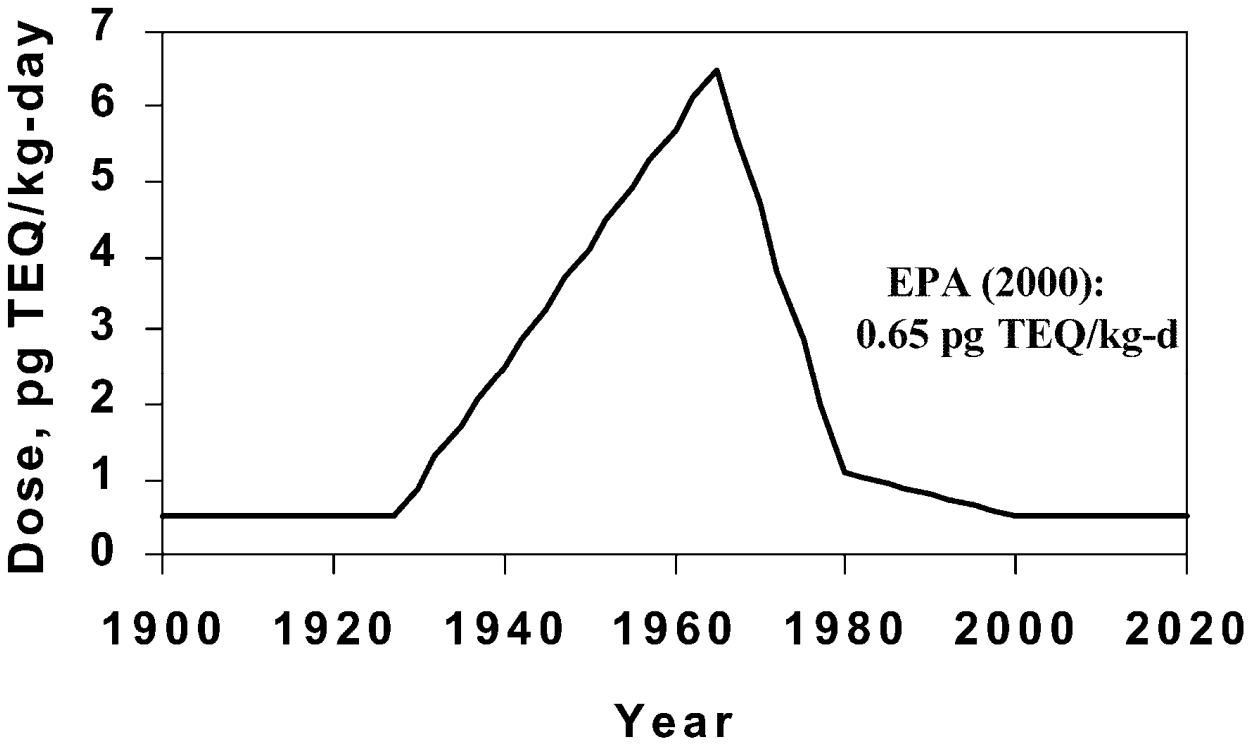


Figure 2. Difference in the body burden of a 20 year-old sampled in 2007 as a result of being exposed to soil at two concentration levels, along with all other background exposures.

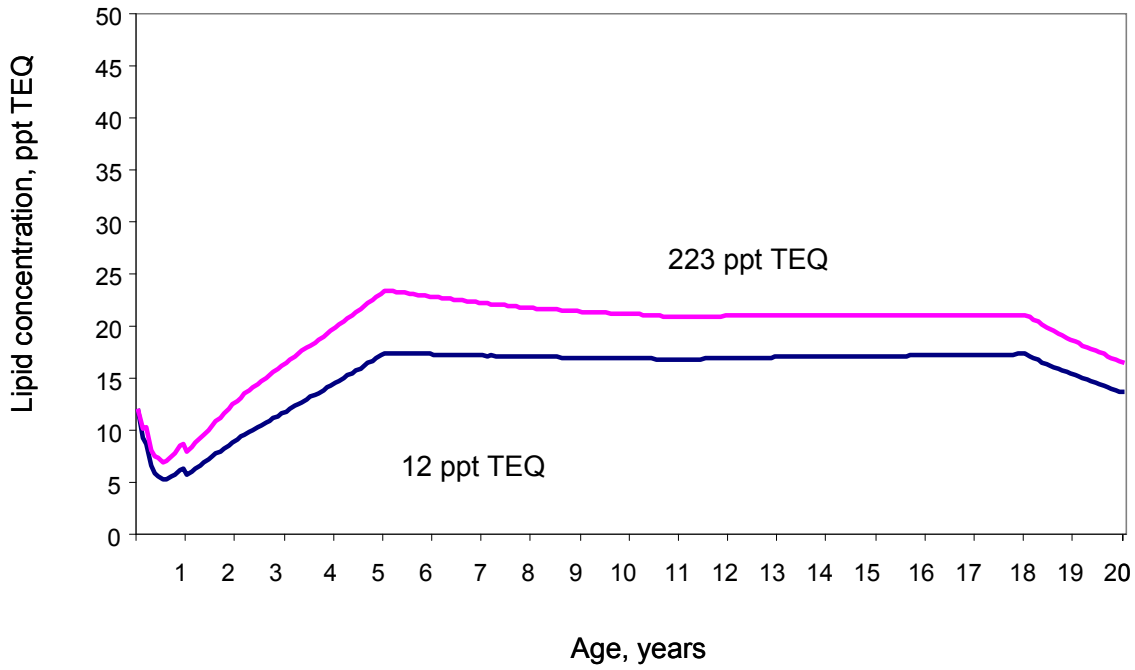


Figure 3. Difference in the body burden of a 40 year-old sampled in 2007 as a result of being exposed to two different soil levels, along with all other background exposures.

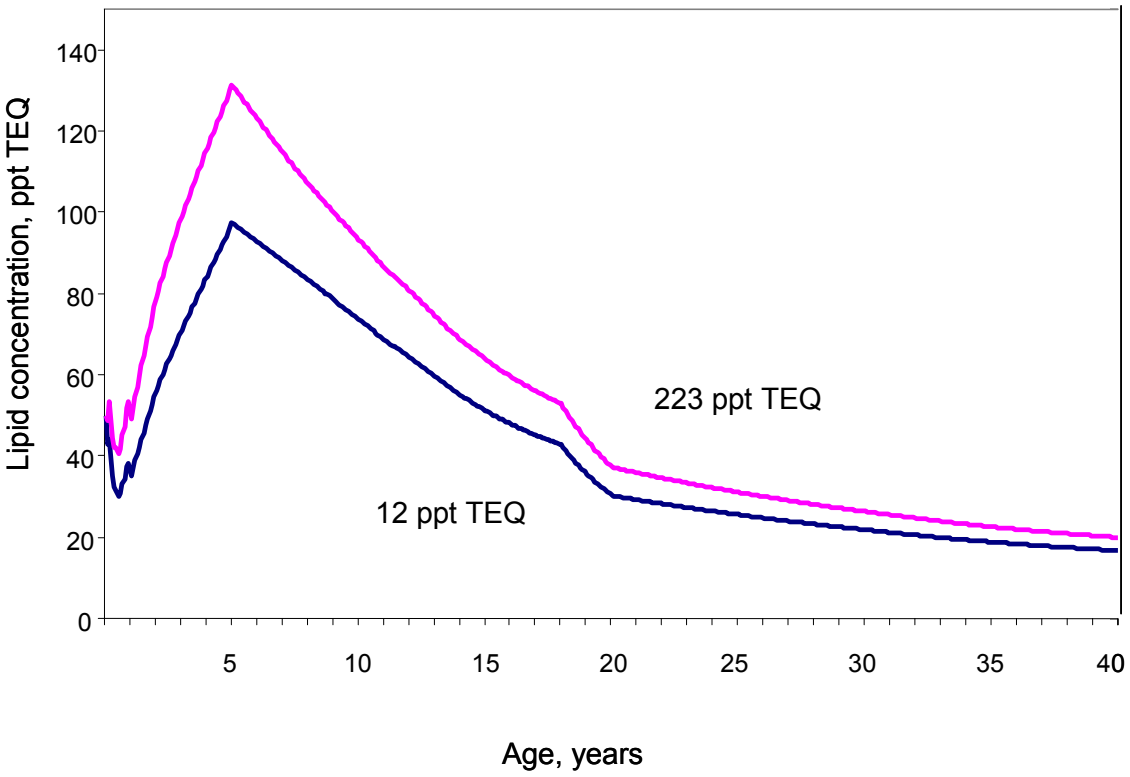


Figure 4. Difference in the body burden of a 40 year-old sampled in 2007 as a result of being exposed to two different soil levels, along with all other background exposures.

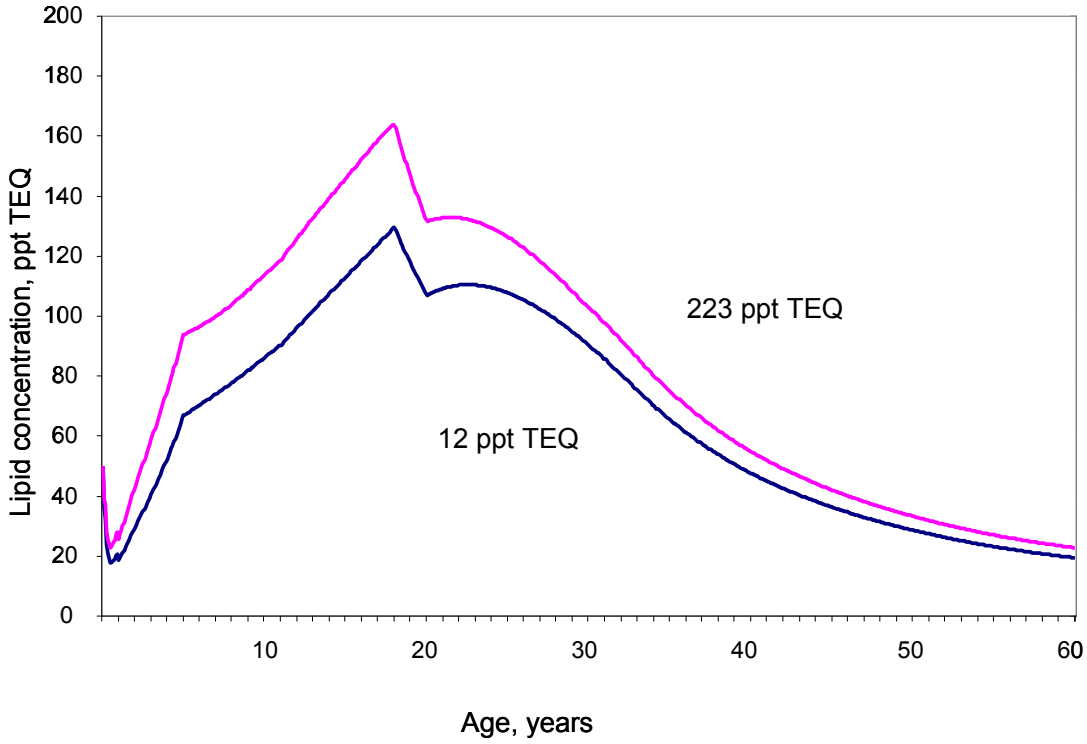
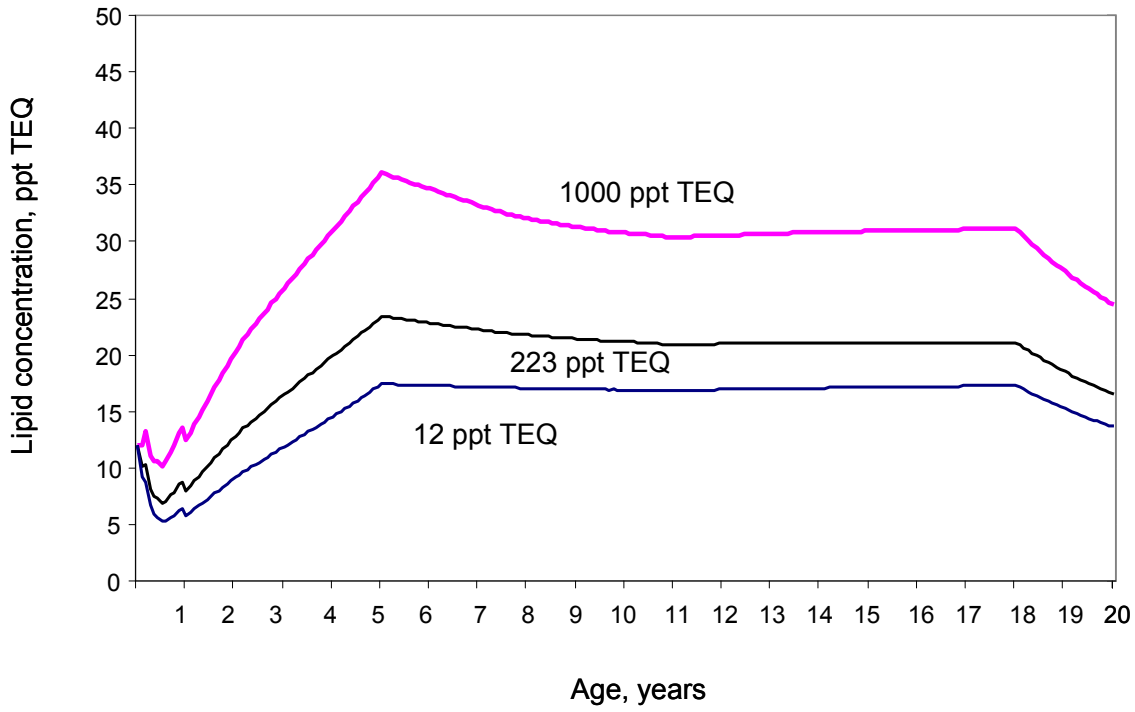



Figure 4. Difference in the body burden of a 40 year-old sampled in 2007 as a result of being exposed to two different soil levels, along with all other background exposures.

Figure 5. Impact of being exposed to 1000 ppt TEQ rather than 223 or 12 ppt TEQ.

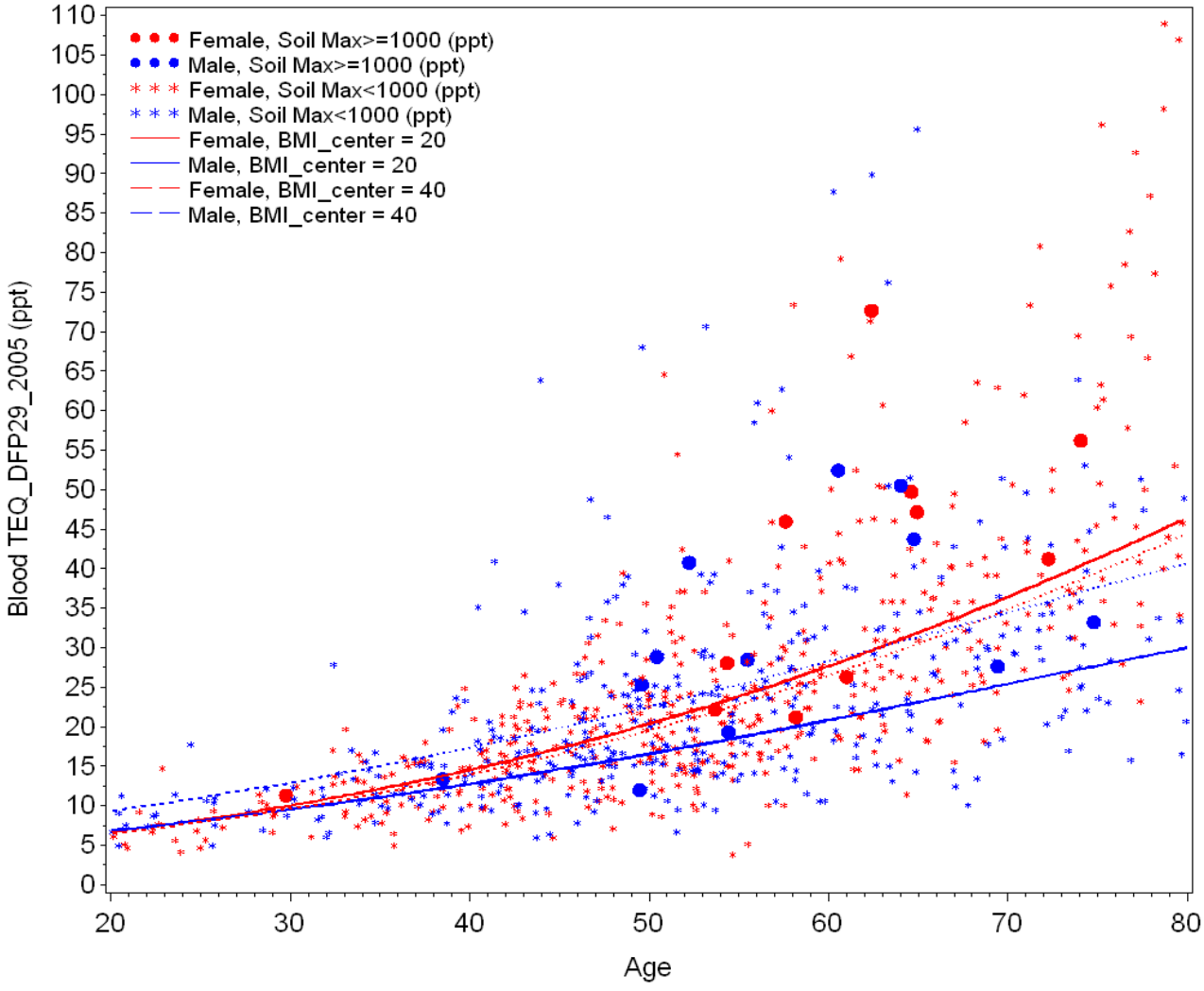


## APPENDIX B

## EVALUATION OF THE BLOOD SERUM DATA FROM SUBJECTS LIVING ON PROPERTIES WITH MAXIMUM SOIL TEQ VALUES GREATER THAN 1000 PPT .

In response to an EPA request, Dr. Garabrant provided (September 11, 2009 email from Garabrant to Dr. Frithsen) a graph of the data presented in Figure 1 from Garabrant et al., 2009b which had been modified to identify the data points associated with subjects living on properties with a maximum soil TEQ concentration greater than 1000 ppt. The graph provided, labeled as 'Plot 1' is copied below. Data for subjects living on properties with maximum soil TEQ concentration greater than 1000 ppt are identified in the plot by the large blue and red dots. There are 23 of these in the data set.

**Plot 1:** Serum TEQDFP29-2005 by age, identifying subjects whose maximum soil TEQ DFP29-2005 is > 1000 ppt. (without Clay Lady)




***Notes:***

*1. The maximum soil is the soil sample that has the highest TEQ of all soil samples taken on the participant's property.*
*2. This plot shows all data points except for the "Clay Lady" whose serum TEQ was 210.7 ppt. She did not have a soil value > 1000 ppt. She was omitted from the graph so that the Y axis was not compressed by her high value.*

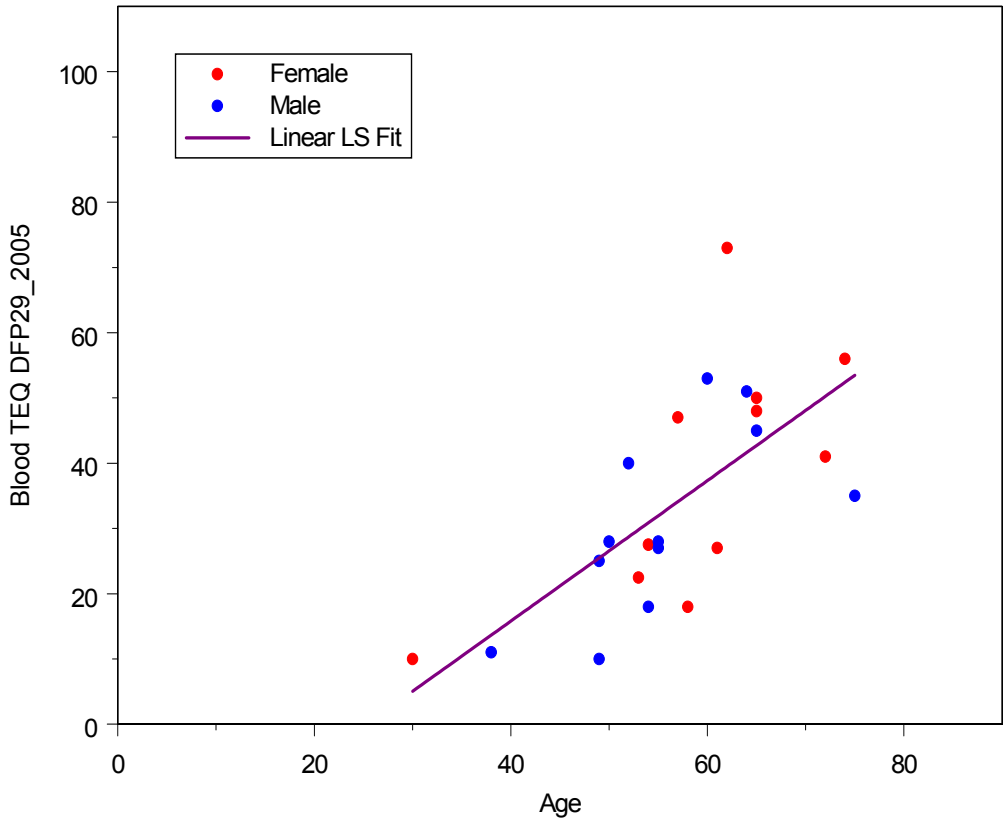
Visual examination of this plot indicates a pattern in the greater than 1000 ppt subset that is distinct from the overall data set. That is, the relationship between serum levels and age in the subset is visually different from the overall data in that the majority of the points lie above the averages represented by the lines in the plot and appear to increase with age at a greater rate. In stable populations, such as the communities in the UMDES, time in a residence would be generally expected to increase with age which would suggest that age is likely to be a surrogate measure for time lived on the property. This, in turn, suggests that these data are an indication of an effect on serum levels due to extended exposure to high soil levels.

The specific data for the 23 subjects were not provided but it was possible to read approximate values for these data from the plot. The blood serum and age values read from the plot for the 23 subjects living on soils with greater than 1000 ppt TEQ concentrations are shown below in the graph titled “Figure: Serum TEQ DFP29-2009 vs. Age for subjects whose maximum soil TEQDFP29-2009 is > 1000 ppt”. The line overlaying the plot is the least squares fit to the data of the linear model

$Y= B_0 + B_1X,$

where Y= blood serum TEQ, X = Age, $B_0$ = intercept and $B_1$ = coefficient for Age.

Figure: Serum TEQ DFP29-2009 vs Age for subjects whose maximum soil TEQDFP29-2009 is > 1000 ppt

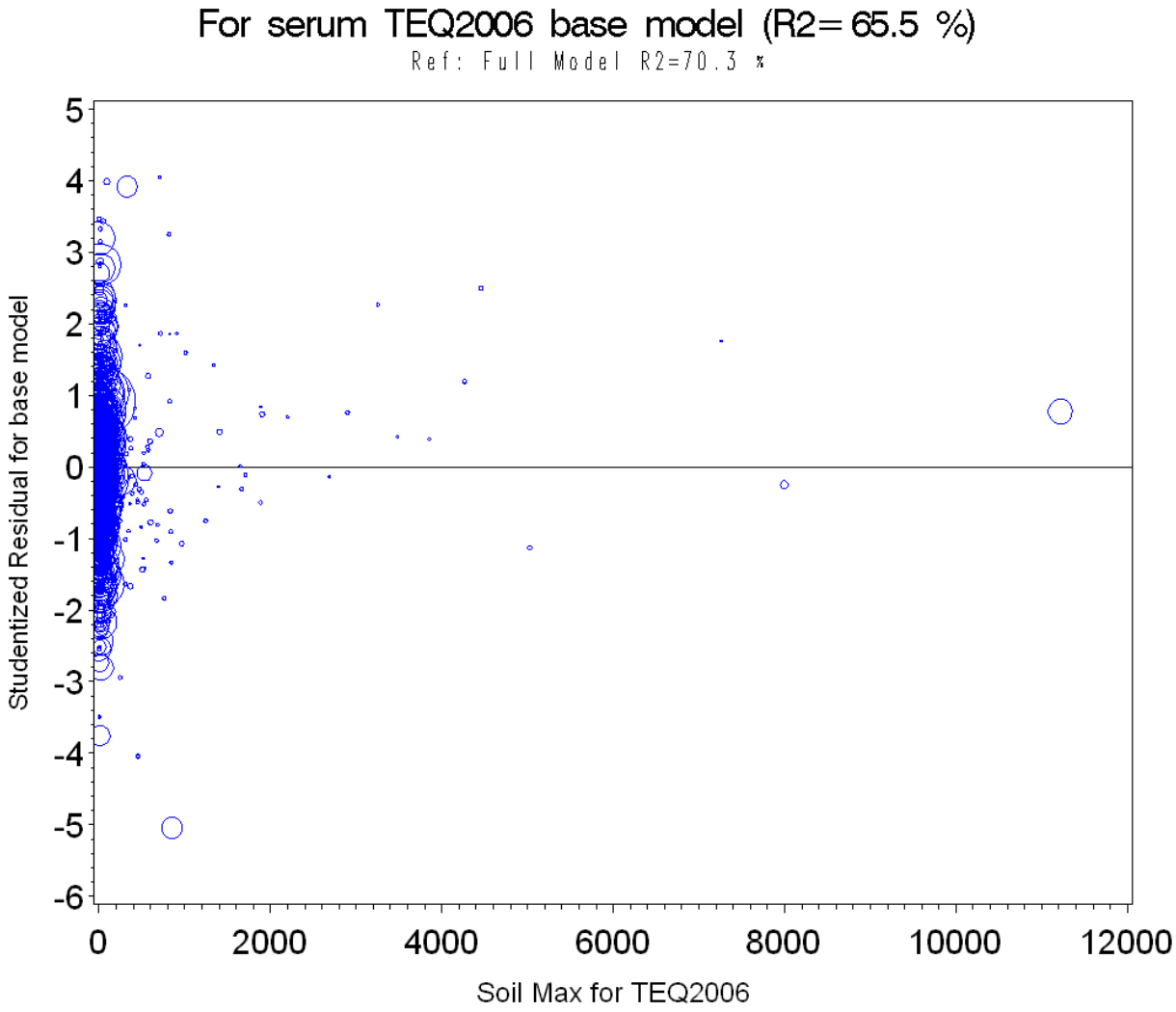



The results are approximate because the data were read from the graphic provided by Dr. Garabrant. Never the less, the estimated regression relationship between blood serum level and age is strong. The regression is highly significant, and R-squared is 0.44. The statistics for this regression are shown in Table 1, below. Garabrant et al. (2009b) reported an $R^2$ of 0.396 for serum levels versus a set of nine demographic factors of which age was only one, for the overall data set. More importantly, the graph in the Figure shows a reasonable regression relationship in the subset data, i.e., a relatively narrow pattern of data points clustered around an increasing regression line. Regardless of the approximate nature of the data used in this analysis, there is an apparent relationship in the subset that should be investigated further.

| Table 1. Regression Statistics: Blood Serum TEQ versus Age for Adults Living on Properties with Maximum Soil Concentrations Greater than 1000 TEQ | | | | |
|---|---|---|---|---|
| Regression Coefficients: | Estimate | Std. Error | t value | Pr(>\|t\|) |
| (Intercept) | -27.2347 | 14.5782 | -1.868 | 0.075754 |
| Age | 1.0762 | 0.2505 | 4.296 | 0.000320 *** |
| Residual standard error: 12.43 on 21 degrees of freedom | | | | |
| Multiple R-squared: 0.4677, Adjusted R-squared: 0.4424 | | | | |
| F-statistic: 18.45 on 1 and 21 DF, p-value: 0.0003203 | | | | |
| *** Significant at less than 0.001 level | | | | |

In the September 11, 2009 email, Dr. Garabrant also provided the graph shown below, labeled as **Plot 2** which shows residuals from the base regression model of serum $TEQ_{DFP29\text{-}2005}$ versus maximum soil $TEQ_{DFP29\text{-}2005}$. The residuals are the differences between the actual measured blood values and the values predicted by the model. Notes for this plot included the following statement: "This plot shows that after accounting for the factors in the base model, there is no relationship between maximum soil TEQ and serum TEQ". The basis for this statement is not clear from the information provided in the email although it would likely be difficult to discern an effect in a subset of 23 subjects in an overall analysis of the data. It is clear that the base model referred to in the email is somewhat different from that in Garabrant et al. (2009b). It is also clear from the pattern of the residuals that the model tends to under predict blood levels for the high soil concentration subset. Specifically, residuals for 15 of the 23 serum levels predicted for subjects living on soils with greater than 1000 ppt concentration are greater than zero. If the fitted model was correct, the residuals should be equally distributed about zero. Furthermore, Plot 2 shows an overall pattern of increasing residuals as soil concentration increases. This is an indication of a fundamental error in the regression model [e.g., Draper and Smith, *Applied Regression Analysis* (1996)].

**Plot 2:** *Bubble plot of studentized residuals from base regression model of serum TEQDFP29-2005 versus maximum soil TEQDFP29-2005.*




***Notes:***

*1. The maximum soil is the soil sample that has the highest TEQ of all soil samples taken on the participant's property.*

*2. The base model is the linear regression model in which $\log_{10}$(serum TEQ) is the outcome variable, and age, age$^2$, sex, BMI, pack-years of smoking, lifetime breast feeding, sex by age interaction, and sex by BMI interaction are independent variables.*

*3. The size of the bubble is proportional to the survey sample weight of the observation.*

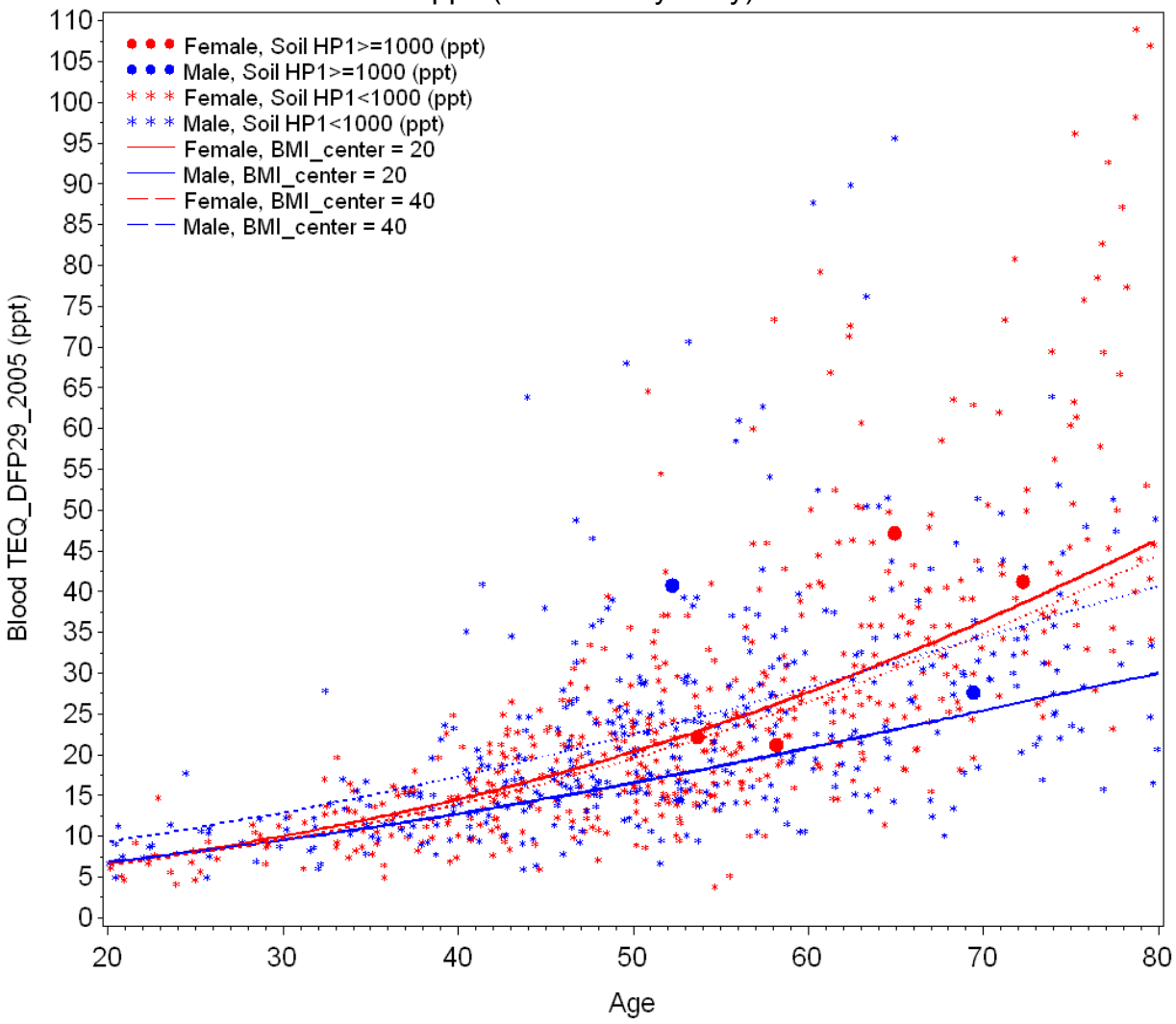
*4. This plot shows that after accounting for the factors in the base model, there is no relationship between maximum soil TEQ and serum TEQ.*

*5. This plot shows all data points including the "Clay Lady".*

In his email of September 11, 2009, Dr. Garabrant also provided the graph shown below identified as Plot 4 which shows the data from Figure 1 from Garabrant et al., 2009b modified to

highlight the subjects in the overall data living on properties with homogenized perimeter soil samples that were measured at greater than 1000 ppt TEQ. The blood serum values for these six subjects appear to be somewhat higher than the average but no analysis was attempted with these data.

**Plot 4:** Serum $TEQ_{DFP29-2005}$ by age, identifying subjects whose house perimeter top 1 inch soil $TEQ_{DFP29-2005}$ is > 1000 ppt. (without Clay Lady)




***Notes:***

*1. The house perimeter top 1 inch soil is the homogenized sample of the top 1 inch soil from all soil cores taken on four sides around the house on the participant's property.*

*2. This plot shows all data points except for the "Clay Lady" whose serum TEQ was 210.7 ppt. She did not have a soil value > 1000 ppt. She was omitted from the graph so that the Y axis was not compressed by her high value.*