The Dow Chemical Company
Midland, MI 48667
May 6, 2004

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Dr. Garabrant,

As agreed during our last conference call on April 22, 2004, Dow is providing comments to you and all call participants on the criteria for membership to the Community Advisory Panel (CAP), rather than submitting names of specific individuals. Dow is also providing comments on the draft protocol you distributed April 16th.

While Dow is a stakeholder in the process, Dow will refrain from offering nominations to the Scientific Advisory Board (SAB), as agreed on the last conference call. Dow supports the concepts of independence, competency, and transparency in the selection of SAB members as well as SAB conduct.

At the next conference call, we expect you will identify the candidates that will be invited to serve on the SAB and clarify our collective understanding of the SAB, CAP, and protocol. Subsequent to this call, we anticipate that U of M will send letters of invitation to prospective SAB members that will be cosigned by U of M, MDCH, and ATSDR, as agreed during the last call.

We look forward to the upcoming conference call scheduled for 2:00pm on May 6th to discuss the SAB, CAP and the study protocol itself. If you have any questions about Dow's comments, please call me.

Sincerely,

John Phillips
Community Health Director
Dow Chemical
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Attachment

Dow Comments on U of M Proposal

Suggestions for a CAP: Dow supports the establishment of a new, study specific CAP, whose members are selected by you on the basis of pre-identified criteria. As selection criteria, Dow supports the concepts of independence, neutrality, and credibility as the basis for CAP membership, when considering representatives of the involved communities. Dow further supports a mix of community representatives who have been acknowledged as playing leadership roles within their communities. Dow suggests that the U of M team consider inviting as members to the CAP elected and appointed officials from the involved communities (Saginaw and Midland Cities and Counties and the Tittabawassee River townships), academics, public health officials, local physicians, representatives of the religious communities as well as individual residents to provide you and the SAB with a balanced perspective and appreciation of local community opinion and concerns. CAP members should be able to make the necessary time commitment to actively and constructively participate in the regular (monthly) meetings over the course of the study and who can effectively communicate with constituents between meetings.

Comments on the Protocol: The following comments are divided into two groups. First are general comments regarding study design, process, and procedures and second are specific comments on narrow topics.

General Comments: The following general comments focus on a single theme…which is to determine **if** there is an increase in D/F blood levels in the study population as compared to the referent populations, before further evaluations are conducted. If increased D/F blood levels are detected in the study populations, then a focused study or studies could be designed to determine the sources of exposure. Such focused study would allow for a more exhaustive investigation of exposure sources, including environmental parameters such as soil, vegetation, household dust, etc. If there is no relative increase in D/F blood levels, then it should be concluded that there is no need for the further analysis of the environmental parameters, because evaluation of those parameters are designed to determine **why** there is an increase, assuming one exists.

> **Blood Sampling and Analysis:** Dow supports the blood sampling and analysis as outlined in the protocol.
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> **Sampling and Analysis of Environmental Parameters:** We understand the intent of extensive soil and dust sampling in addition to blood sampling described in the protocol. However, we are concerned that the proposed level of effort required for obtaining and analyzing the very large number of soil, vegetation, and dust samples may unduly complicate the conduct of the study, operate as a distraction from the focus on obtaining a large population sample of blood data, and may not be needed, if there is no elevation in blood levels observed.
>
> Dow also understands that residents of the community who may be concerned about exposure to D/Fs are interested in learning, as soon as possible, whether

blood levels of people living in areas where soil levels are elevated are higher than in areas where soil levels are much lower. If a significant increase in D/F blood levels is detected in the study populations, then it may be concluded that the extensive soil and dust analysis proposed in the protocol would be useful to determine if soil levels are contributing to those differences.

The U of M protocol indicates that two household dust samples (one from hard surfaces and one from soft surfaces) will be taken from each participant's home and as many as 9 vegetation/soil samples will be taken from each participant's property; i.e. a composite of vegetation, top 1" soil, and 2" to 6" soil samples from the residence parameter, soil contact area(s), and floodplain area. The protocol also indicates that these samples will be analyzed for the typical 17 D/F congeners used to calculate the TEQ as well as 12 Polychlorinated Biphenyls (PCBs) congeners. This dust and soil sampling may be justified if increased D/F blood levels are detected in residents near Dow or in the Tittabawasse floodplain. However, this has not been shown to be the case as of yet. Thus, the soil and dust sampling and analysis may be premature and/or unnecessary.

We question whether the proposed vegetation analysis would ever serve any useful purpose. Analysis of vegetation introduces numerous confounders, such as the impact of plant cell contents (exudate) on D/F concentrations. D/F concentrations in the varied plant types that may be randomly obtained in soil samples would not likely provide any insight or relation to residential D/F blood levels.

The protocol's proposal for Soil and dust sampling is complicated by the need to determine who can sign a release for sampling. By complicating the nature of who provides consent, the participation rate may become very low for soil and dust sampling. Low participation could make the limited information collected uninterpretable. This is exemplified by a situation where the land owner (landlord) is not the same person as the land occupant (tenant) and/or the adult aged child of the tenant selected for blood sampling. Determining which individual has the authority to approve soil (landlord?), dust (tenant?), and blood (adult aged child?) sampling and accept ownership of informed consent will be difficult. In addition, requiring a tenant to seek consent from a landlord for soil sampling may limit the confidentiality of the tenant's participation in the study, notwithstanding the existence of a Certificate of Confidentiality. At the very least having to obtain multiple consents may slow down the study considerably and ultimately have the effect of eliminating residents who cannot obtain the consent of their landlords or property associations. If these complications differentially impact participation rates, the results of the soil sampling may be uninterpretable.

Dow questions the scientific rationale behind the level of 8 ppt as proposed in the protocol for decision making in soil analysis. The state of Michigan (MI) is not well characterized for D/F soil levels, having only 16 results from the Upper

Peninsula and 52 results from the Lower Peninsula as reported by the Department of Environmental Quality (DEQ). [1] Dow does not have any reason to believe that the 8 ppt proposed by the U of M has any scientific basis as a background level for an industrialized urban area. For example, there are historical D/F sources unrelated to Dow that could impact D/F soil levels of the referent property; such as backyard burning and/or living in proximity to an industrial facility, waste water treatment plant, or hospital with historical incineration practices, etc.

If there is a need to confirm that the soil levels are below the state action level for the referent populations, then the study team should consider analysis of one soil sample (top 1") taken from public property in each referent census block, to confirm or refute the hypothesis that the referent census block did not exceed the state 90 ppt level. This approach would reduce the complexity of identifying land owners (in some cases landlords) to provide approval for soil sample collection, as well as any concerns on the part of participants associated with soil levels that may exceed the state action level and the subsequent possibility of being classified as a hazardous waste facility.

If it is deemed necessary to obtain dust samples, one household dust sample from soft surfaces (carpets) would be adequate. It would be very difficult to obtain the 10 grams of dust needed for analysis from hard surfaces, as exemplified in a study conducted by Lioy *et al.* in 1993[A], where only milligram quantities of dust could be obtained from hard surfaces.

Dow does not agree that the referent population of Saginaw and Midland Counties proposed in the protocol represents an exposed population. However, Dow is willing to support study of a second referent population, as long as it adds to the validity and interpretability of the study.

Dow is more supportive of U of M's initial proposal for blood, household dust, and soil sampling, presented at the meeting in Atlanta, GA. In that proposal, U of M suggested that one household dust sample and one blood sample be taken and analyzed per participant. The soil samples would be collected and stored. These samples would be analyzed later, if the study area residents showed higher D/F TEQ blood levels than the referent populations and if analysis of the stored soil samples would lead to a better understanding of soil as a possible source of these elevated blood levels. If there is difficulty with storing the dust and soil samples, alternatively, dust and soil samples could be obtained later if necessary.

[1] In addition, these results were likely biased toward areas not expected to have elevated D/F soil levels. Even so, 14 of 52 or 27% of samples analyzed for D/Fs from the Lower Peninsula are essentially at or exceed 8 ppt. Thus, there is a random chance of 1 in 3 of obtaining a level at or greater than 8 ppt. The MI background levels reported by DEQ are as high as 34.7 ppt in the Lower Peninsula and 35.0 ppt in the Upper Peninsula. Thus, if a level is to be set for background, Dow recommends a range at least as high as 35.0 ppt and preferably the state level of 90 ppt.

Dow's Specific Comments:

Data Interpretation:

- There is little discussion in the protocol about how the data will be analyzed to determine if residents within the Tittabawassee floodplain near Dow have serum dioxin levels above or below background levels. The study team should consider specifically which congeners or groups of congeners (e.g. TEQ) are likely to be most important for such a causal assessment. Since serum dioxin, furan and PCB levels have such large variability in humans, evaluating all 29 congeners listed on an individual basis along with the TEQ could yield statistically significant differences that have no causal basis. This is further complicated by statistical analysis of the values used for the limit of detection for results of congeners that are below the limit of detection. At the very least, the study team should discuss the criteria they will use for making a causal assessment from these data.

  Furthermore, the multiple regression analyses of each D/F and PCB congener will likely produce false positive associations due only to the large number of comparisons being made (i.e. produce artifactual statistical variation), that will need to be explained. Dow suggests that U of M focus its regression analysis on the congeners most likely to be related to local potential exposure; i.e. 2,3,7,8-TCDD, PCDD (Midland only), the two penta-furans (most valuable in the Tittabawassee River area), PCB 126, and TEQ. This more focused evaluation on the congeners of interest and TEQ should reduce the number of false positive associations.

- A study by Fingerhut *et al.*, 1991[B] is referenced in the section on Power Calculations (4.7). These researchers reported referent population D/F levels at 20 ppt maximum. It should be noted that this study reported 2,3,7,8-TCDD levels only, such that the referent population had a maximum of 20 ppt 2,3,7,8-TCDD not TEQ, making it less useful for comparative purposes to the U of M study. This study was also based on data from the mid-1980s. Levels would be anticipated to be lower today. Dow suggests U of M conduct their power calculations on more contemporaneous population data and based on TEQ, such as reported for the German population by Wittsiepe *et al*., 2000[C].

Chemical Analysis:

- In the protocol under the *Soil Sampling and Analysis*, Section 4.5 at the top of page 13 the protocol indicates that "*Sediment extraction will be performed under high temperature and pressure using a multisample FMS Powerprep Sample Extraction and Cleanup System*"…technically this step will be a cleanup not an extraction step. Also, we believe U of M meant to indicate "*Soil*" verse "*Sediment*" extraction. Further in this section at the bottom of page 13 at the end

of the first sentence…HPGC/HPMS should actually be HRGC/HRMS (underlining of Ps and Rs added for clarity only).

Similarly in Appendix 6 *Soil Sampling Protocol*, section 6.1 *Sample Analysis Introduction,* page 9, second paragraph the "*Sediment extraction…*" with "*…a multisample FMS…*" is technically a cleanup step, not an extraction step.

Dust Sampling Protocol:

- In the protocol, Section 4.4 *Dust Sampling and Analysis*, Page 9, at the end of the second paragraph, the procedure indicates that dust samples will be "sieved", although, there is no indication that the sieves will be cleaned between samples to avoid cross contamination. Dow recommends a cleaning series of distilled water, followed by methanol, followed by acetone for collection equipment to avoid cross contamination.

- Appendix 5 *Household Dust Sampling Protocols*, page 3, item 6 *Reagents*, Dow recommends a cleaning series of distilled water, followed by methanol, followed by acetone for collection equipment to avoid cross contamination. Same appendix, 7.5 *EWRE Laboratory Observations*, page 6, item 6 the "*camel's hair brush*" to be used "*to ensure compete transfer of the sample*" should also be cleaned after each use to avoid cross contamination. Same appendix, 7.6 *Equipment Decontamination,* item 3, Dow suggests the cleaning series described above (with distilled water, followed by methanol, followed by acetone) be followed to avoid cross contamination. Spraying with methanol will likely have no impact on cleaning and distilled water alone is not sufficient to avoid cross contamination. Same appendix, *Hard Surface Household Dust Sampling Protocol*, page 5, item 7.6 Dow suggests the cleaning series described above to avoid cross contamination.

Soil Sampling:

- If U of M is intent on the soil sampling approach described in the protocol, consideration needs to be given to how alternates will be identified for those who are willing to participate, yet decline soil sampling or cannot obtain the necessary consents for soil sampling in a timely manner, if at all.

- In the protocol in Section 4.4 *Dust Sampling and Analysis*, page 9 at the bottom on the second paragraph the dust will be sieved "*…with particle size separation of 150 microns.*" The soil fraction considered applicable for skin contact/absorption should be evaluated from 150 microns to 250 microns. This is because the only soil particle size relevant for dermal exposure is < 250 microns in size. Soil particles of >250 microns are less adherent to skin and are only available for a hand-to-mouth exposure pathway.[D]

- In the protocol in Section 4.5 *Soil Sampling and Analysis* in the text on the bottom of page 11 and items 2, 5, and 8 at the top of page 12, Dow believes U of M meant to indicate that samples would be taken at 2-6 inch composites verses 1-6 inch composites, since the top one inch was already removed and composited.

Blood Sampling:

- In Appendix 4 *Blood Collection and Analysis*, page 1, middle of the second paragraph the veinapuncture will be conduced using a "*…19 gauge or 21 gauge needle with an attached butterfly assembly and luer-lock adapter…*". Blood should be collected with a direct needle connection (e.g. Vacutainer) using the standard CDC protocol. Use of butterfly assemblies or other materials could result in a loss of D/Fs in the sample due to adsorption to other surfaces.

  Similarly in this section the third paragraph fourth sentence indicates that "*Using a disposable serological pipette, all serum will be transferred to a 50 milliliter polystyrene sample mailing tube…*". Dow recommends the use of glass pipettes and glass vials to reduce the possibility of D/F adsorption onto other surfaces.

Survey:

- In the protocol in Section 4.2 *Interviews* the list of information solicited includes fish consumption from the Tittabawassee River, Saginaw River/Bay, and stores, although, does not question fish consumption from other Michigan rivers, lakes, and streams. This should be considered, since recreational anglers likely fish in multiple locations throughout the state.

- In the survey, question set F 23, page 44, asks about bass fish consumption. Dow suggests U of M try to obtain input on consumption of the three different types of bass found in the Tittabawassee River (i.e. small mouth bass, large mouth bass, and white bass), because they vary widely on D/F concentrations. Also, there is a fish advisory in place for small mouth bass.

References

A Lioy *et al.*, 1993, Journal of Exposure Analysis and Environmental Epidemiology, volume 3, pages 315-330: *A wipe sampler for the quantitative measurement of dust on smooth surfaces: Laboratory performance studies.*

B Fingerhut, M.A., W.E., Halperin, D.A. Marlow, L.A. Piacitelli, P.A. Honchar, M.H. Sweeney, A.L. Greife, P.A. Dill, K. Steenland and A.J. Suruda, 1991, New England Journal of Medicine, Volume 324, pages 212-218: *Cancer mortality in workers exposed to 2,3,7,8-tetrachlorodibenzo-p-dioxin.*

C Wittsiepe *et al.*, 2000, Chemosphere Volume 40, pages 1103-1109, *Decrease of PCDD/F levels in human blood from Germany over the past ten years (1989 – 1998).*

D Christopher T. De Rosa, David Brown, Rosaline Dhara, Woodrow Garrett, Hugh Hansen, James Holler, Dennis Jones, Denise Jordan-Izaguirre, Ralph O'Connor, Hana Pohl, and Charles Xintaras. *Dioxin and Dioxin-Like Compounds in Soil, Part 1: ATSDR Interim Policy Guideline* VOL. 13, No. 6, pp. 759-768, 1997.

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