

Remedial Investigation Work Plan

**Tittabawassee River and Upper Saginaw
River and Floodplain Soils
Midland, Michigan**

Volume 2 of 2

Prepared for:

**The Dow Chemical Company
1790 Building
Midland, Michigan 48674**

December 1, 2006

TABLE OF CONTENTS

SECTION NO.

TITLE

- 6. HUMAN HEALTH RISK ASSESSMENT**
- 7. SCREENING LEVEL ECOLOGICAL RISK ASSESSMENT**
- 8. BASELINE ECOLOGICAL RISK ASSESSMENT**

REMEDIAL INVESTIGATION WORK PLAN
TITTABAWASSEE RIVER AND UPPER SAGINAW RIVER AND
FLOODPLAIN SOILS
VOLUME 2 OF 2

SECTION 6: HUMAN HEALTH RISK ASSESSMENT

Remedial Investigation Work Plan

**Tittabawassee River and Upper Saginaw River
and Floodplain Soils
Midland, Michigan**

Volume 2 of 2

Section 6: Human Health Risk Assessment

Submitted by:

**The Dow Chemical Company
1790 Building
Midland, Michigan 48674**

December 1, 2006

6.	HUMAN HEALTH RISK ASSESSMENT	6
6.1	INTRODUCTION.....	6
6.1.1	Proposed Assessment Approach.....	8
6.1.1.1	Steps in Risk Assessment.....	8
6.1.1.2	Planned Assessment Elements.....	9
6.1.1.3	Applicable Risk Assessment Guidance.....	11
6.1.2	Derivation of Direct Contact Criteria for the Study Area.....	13
6.1.3	Prior Studies and Proposed Use of the UMDES Exposure Data.....	14
6.1.4	Comparison of PRA with UMDES Blood Concentrations.....	18
6.1.5	Studies Proposed to Support the HHRA.....	18
6.1.5.1	Activity Survey.....	19
6.2	CONCEPTUAL SITE MODEL: HUMAN HEALTH EXPOSURE PATHWAYS.....	21
6.2.1	Potential Human Receptors.....	21
6.2.1.1	Receptor Groups.....	21
6.2.1.2	Use of Probabilistic Techniques to Address Highly Exposed Receptors.....	22
6.2.2	Exposure Pathways and Scenarios.....	25
6.2.2.1	Residents.....	25
6.2.2.1.1	Exposure to CoPCs in Soil or Dust.....	25
6.2.2.1.2	Baseline Diet.....	27
6.2.2.1.3	Ingestion of Home-Grown Produce.....	28
6.2.2.1.4	Human Milk.....	29
6.2.2.2	Worker.....	29
6.2.2.3	Farmers.....	29
6.2.2.4	Recreational Use of Study Area.....	30
6.2.2.5	Anglers — Fish Consumption.....	30
6.2.2.5.1	Subpopulations with High Fish Consumption.....	31
6.2.2.6	Hunters — Consumption of Wild Game.....	32
6.3	ANALYTICAL CHEMISTRY DATA ANALYSIS AND IDENTIFICATION OF CoPCs.....	32
6.3.1	Summary of Concentration Data to Be Used for Identification of CoPCs.....	32
6.3.2	Methods for Screening of TAL to Determine CoPCs.....	34
6.3.2.1	Comparison to Background Concentrations.....	35
6.3.2.2	Comparison to MDEQ Benchmarks or EPA Risk-Based Concentrations.....	35
6.3.2.2.1	Soil and Sediment.....	35
6.3.2.2.2	Inhalation of Soil Particulates.....	35
6.3.2.2.3	Direct Contact with Sediment.....	36
6.3.2.2.4	Fish and Game.....	36
6.3.2.2.5	Surface Water.....	37
6.4	EXPOSURE ASSESSMENT.....	37
6.4.1	Receptors and Exposure Pathways.....	38
6.4.1.1	Receptors.....	38
6.4.1.2	Complete Exposure Pathways to be evaluated in the SLRA.....	39
6.4.1.3	Combinations of Receptors and Pathways for the PRA.....	40
6.4.2	Use of UMDES Data.....	40
6.4.3	Quantification of Exposure Variables in the SLRA.....	42
6.4.3.1	General Treatment of Variables with Known Distributions in the SLRA.....	42
6.4.3.2	Common Receptor Characteristics – Body Weight, Averaging Time, and Exposure Duration.....	43

6.4.3.2.1	Body Weight Assumption in SLRA	43
6.4.3.2.2	Averaging Time.....	43
6.4.3.2.3	Exposure Duration.....	44
6.4.3.3	Incidental Ingestion of Soil/Dust or Sediment	44
6.4.3.3.1	Estimates of Incidental Ingestion of Soil/Dust for Residents and Workers ...	45
6.4.3.3.2	Incidental Soil or Sediment Ingestion During Hunting, Fishing, and Other Recreational Visits.....	46
6.4.3.3.3	Residential Dust Findings From UMDES	48
6.4.3.4	Dermal Contact with Soil/Dust or Sediment.....	49
6.4.3.4.1	Dermal contact with soil for residents and adult workers	50
6.4.3.4.2	Dermal Contact with Soil or Sediments During Hunting, Fishing, and Other Recreational Use.....	50
6.4.3.5	Inhalation of Dust.....	51
6.4.3.6	Incidental Ingestion of Surface Water	53
6.4.3.7	Dermal Contact with Surface Water.....	54
6.4.3.8	Consumption of Sport-Caught Fish.....	56
6.4.3.9	Ingestion of Wild Game	59
6.4.3.10	Ingestion of Agricultural Animal Products	62
6.4.3.11	Ingestion of Homegrown Dairy Products.....	64
6.4.4	Quantification of Exposure Distributions in the PRA	65
6.4.4.1	Selection of Exposure Variable Values for Use in the PRA	65
6.4.4.2	Input Variable Sensitivity Analysis.....	67
6.4.4.3	Common Receptor Characteristics – Body Weight, Averaging Time and Exposure Duration.....	68
6.4.4.3.1	Body Weight in the PRA.....	68
6.4.4.3.2	Averaging Time.....	69
6.4.4.3.3	Exposure Duration in the PRA.....	69
6.4.4.4	Incidental Ingestion of Soil/Dust or Sediment	70
6.4.4.4.1	Soil Ingestion Rates for Residents and Workers in the PRA.....	70
6.4.4.4.2	Incidental Soil or Sediment Ingestion During Hunting, Fishing, and Other Recreational Visits.....	71
6.4.4.5	Dermal Contact with Soil/Dust or Sediment in the PRA	72
6.4.4.5.1	Skin surface area per event (SA) (cm^2 /event),.....	72
6.4.4.5.2	Event frequency (EV) (per day),	73
6.4.4.5.3	Soil adherence factor for this event (AF) (mg/cm^2)	73
6.4.4.6	Inhalation of Dust in the PRA	73
6.4.4.7	Incidental Ingestion and Dermal Contact with Surface Water	74
6.4.4.8	Consumption of Sport-Caught Fish.....	74
6.4.4.9	Ingestion of Wild Game in the PRA.....	75
6.4.4.10	Ingestion of Agricultural Animal Products and Homegrown Dairy Products, in the PRA	75
6.4.5	Chemical Specific Parameters	76
6.4.5.1	Cooking and Preparation Loss.....	76
6.4.5.2	Ingestion Absorption Efficiency.....	77
6.4.5.3	Dermal Absorption Efficiency from Soil	78
6.4.5.4	Physical Properties of CoPCs.....	79
6.4.6	Exposure Point Concentrations.....	79
6.5	TOXICITY ASSESSMENT.....	80
6.5.1	Toxicity Values for PCDD/Fs.....	81
6.5.1.1	Cancer Dose-Response Assessment.....	84
6.5.1.2	Critical Effect and Data Sets	85

6.5.1.2.1	Epidemiological or Animal Data.....	85
6.5.1.3	Dose Measure.....	87
6.5.1.3.1	Internal or External Dose.....	87
6.5.1.3.2	Body Burden or Tissue Dose.....	88
6.5.1.3.3	Dose Metric.....	88
6.5.1.3.4	Parent Chemical or Metabolite.....	88
6.5.1.4	Response Measure.....	89
6.5.1.4.1	Animal data.....	90
6.5.1.4.2	Point of Departure.....	90
6.5.1.4.3	Low Dose Extrapolation.....	90
6.5.1.4.4	Presentation of the Carcinogenic Slope Factor.....	92
6.5.2	Derivation of Toxicity Values for Non-Cancer Endpoints.....	93
6.5.2.1	Overview of Available Criteria.....	94
6.5.2.1.1	Applicability of Current Criteria.....	95
6.5.2.1.2	Scientific Shortcomings of the Current Criteria.....	96
6.5.2.2	Non-Cancer Criterion for the SLRA.....	98
6.5.2.3	Development of a Non-Cancer Criterion for the PRA.....	98
6.5.2.3.1	Selection of Toxicity Endpoints and Studies.....	98
6.5.2.3.2	Dose Metric and Point of Departure Selection.....	101
6.5.2.3.3	Additional Data for Consideration.....	101
6.5.2.3.4	Data-Derived Uncertainty Factors for Generation of Reference Doses.....	102
6.5.3	Toxicity Equivalency Factors for PCDD/Fs.....	103
6.6	RISK CHARACTERIZATION.....	108
6.6.1	Cancer risk.....	109
6.6.2	Non-Cancer Risk.....	110
6.6.3	Screening Level Deterministic Risk Assessment.....	110
6.6.4	Probabilistic Risk Assessment.....	111
6.6.4.1	Methodology.....	111
6.6.4.2	Probabilistic Risk Assessment Means to Present Findings.....	113
6.7	UNCERTAINTY ASSESSMENT.....	114
6.8	REFERENCES.....	114
6.9	ACRONYMS.....	150

LIST OF ATTACHMENTS

APPENDIX HHRA A – SUMMARY OF UNIVERSITY OF MICHIGAN DIOXIN EXPOSURE STUDY

APPENDIX HHRA B INDEPENDENT SCIENCE ADVISORY PANEL

APPENDIX HHRA C – STUDIES THAT WILL SUPPORT THE HHRA

APPENDIX C1 - DRAFT FISH SAMPLING WORK PLAN FOR THE TITTABAWASSEE RIVER STUDY AREA

APPENDIX C2 - DRAFT SAMPLING WORK PLAN FOR THE CONTINUED EVALUATION OF WILD GAME TAKEN FROM THE TITTABAWASSEE RIVER STUDY AREA

APPENDIX C3 - DRAFT GARDEN VEGETABLE SAMPLING WORK PLAN FOR THE TITTABAWASSEE RIVER STUDY AREA AND SELECT SURROUNDING LANDS

APPENDIX C4 - DRAFT DOMESTIC LIVESTOCK AND ANIMAL PRODUCT SAMPLING WORK PLAN FOR THE TITTABAWASSEE RIVER STUDY AREA

APPENDIX C5-1 - QUALITY ASSURANCE PROJECT PLAN - AMBIENT AIR DUST MONITORING TITTABAWASSEE RIVER FLOODPLAIN

APPENDIX C5-2 - QUALITY ASSURANCE PROJECT PLAN - WORKER DUST EXPOSURE MONITORING TITTABAWASSEE RIVER FLOODPLAIN

APPENDIX C6 - FOLLOW-UP STUDY REPORT: ORAL BIOAVAILABILITY OF DIOXINS/FURANS IN TITTABAWASSEE RIVER FLOODPLAIN SOIL

APPENDIX C7 - UNIVERSITY OF MASSACHUSETTS CHILD SOIL INGESTION PROJECT

APPENDIX HHRA D – ADDITIONAL SUPPORTING MATERIALS

D-1 SOIL ADHERENCE FACTOR FOR RECREATIONAL VISITORS IN THE PRA

D-2 EVALUATION OF EXPOSURES TO PCDD/FS IN HUMAN MILK IN THE HHRA

6. HUMAN HEALTH RISK ASSESSMENT

6.1 INTRODUCTION

The overall purpose of this proposed baseline human health risk assessment (HHRA) is to present an assessment of the potential human health risks associated with exposure to contaminants of potential concern (CoPCs)¹ in the Study Area. Potential human health risks associated with constituents in the Study Area attributable to historic Dow releases are being investigated pursuant to Condition XI.B.5 of the 2003 Hazardous Waste Management Facility Operating License (License) issued by MDEQ for Dow's Midland Plant in Midland, Michigan (Midland Plant) (MDEQ 2003a). This RIWP has been prepared to be generally consistent with the revised Scope of Work (SOW) for the Tittabawassee River and Floodplain Remedial Investigation developed and approved under the License (Dow 2005), MDEQ's Notices of Deficiency (NODs) issued in 2006, as well as subsequent meetings and discussions held between Dow and MDEQ. Dow and MDEQ have discussed working collaboratively on the refinement of the HHRA. The risk assessment approach described here was developed to be consistent with Part 201 of the Natural Resources and Environmental Protection Act (NREPA), Act 451 of 1994 as amended, and the Administrative Rules for Part 201 Environmental Remediation of NREPA, which is being used as a means to meet Dow's hazardous waste corrective action obligations under its License and under Part 111, Hazardous Waste Management, of NREPA.

In addition to MDEQ requirements, this risk assessment also draws from the scientific literature and from other guidance including U.S. Environmental Protection Agency (EPA) risk assessment guidance (*e.g.*, EPA 1989b, 1991a,b, 1992, 1997a,b,d; 2001, 2004a, 2005a) for sites being evaluated under the Comprehensive Environmental Response Compensation and Liability Act (CERCLA), and the National Contingency Plan. The HHRA will be an ongoing effort, requiring regular meetings and consultations between Dow and MDEQ. Early steps in the HHRA include the finalization of the CoPCs evaluated in the risk assessment, identification of the receptor populations along with the complete exposure pathways relevant to each, and establishment of the algorithms used to quantify exposure and the inputs variables needed. The HHRA also proposes to derive the needed toxicity criteria for cancer and non-cancer

¹ CoPCs for the human health risk assessment are defined as TAL chemicals from Dow operations present in soil, sediment, or another environmental medium at a concentration that is higher than background concentrations (*e.g.*, for naturally occurring metals) and higher than relevant risk-based screening values derived either by MDEQ or EPA, or where risk-based concentration are not available from either of these sources, through methods described further in this workplan for screening potential toxicity and exposure.

endpoints, and define where deterministic and probabilistic methods are to be used. The HHRA will address scientific information and recommendations that were not available at the time of MDEQ's promulgation of the Direct Contact Criteria for dioxin.

At present, the primary compounds of interest are certain polychlorinated dibenzofurans (furans or PCDFs). Low levels of polychlorinated dibenzodioxins (dioxins or PCDDs) are also found in the Study Area. Together, polychlorinated dioxins and furans are often referred to as PCDD/Fs and that terminology is used in this HHRA work plan. Although the text of this document reflects the primary focus to date on PCDD/Fs, as further described in Section 6.3, analytical data for a comprehensive list of chemicals potentially related to historic manufacturing activities (termed here the Target Analyte List [TAL]) will be evaluated to identify a complete list of CoPCs for consideration in the HHRA. If any of the additional identified CoPCs have properties that suggest the need for additional or differing risk assessment evaluation (e.g., through consideration of additional exposure pathways, toxicity values, or chemical specific exposure data) the approach presented herein will be modified accordingly.

Study Area populations may be exposed to CoPCs through ingestion, inhalation, or skin contact with these CoPCs in soil, sediment, or dust, or as the result of the ingestion of local foods (i.e., sport-caught fish or game, home-raised meat, milk, eggs, or garden plants). The HHRA will assess both the qualitative and quantitative aspects of all relevant completed exposure pathways using available and newly generated local data (e.g. the University of Michigan Dioxin Exposure Study [UMDES] data set (web site www.umdioxin.org) or media-specific measurements of chemical concentrations made in areas including the Study Area).

The recent National Academy of Sciences (NAS) report entitled *Health risks from dioxin and related compounds: Evaluation of the EPA reassessment* (NAS 2006) also will be relied upon for guidance. The HHRA will include assessment of the potential risk from Study Area exposures first using conservative point estimates of exposure and toxicity (i.e., a deterministic screening level evaluation) to eliminate CoPCs and exposures that contribute negligible risk. The HHRA will also include consideration of additional deterministic evaluations or a probabilistic risk characterization to more fully characterize the risk from major sources of exposure and illuminate the uncertainty and variability in the risk estimates. Dow will work with MDEQ to properly interpret the results of the risk assessment to risk managers and the public. MDEQ and EPA Region V expressed strong reservation to the December 2005 proposed RIWPs proposed use of probabilistic techniques to develop toxicity criteria from the complex database for TCDD and related compounds based on existing EPA risk assessment guidance. However, MDEQ and

Region V's comments were made in advance of the release of the NAS (2006) review of the Dioxin Reassessment that specifically called for use of such techniques. EPA has not yet formally responded to the NAS review to state whether it agrees or disagrees with the recommendations made by the NAS or to even explain the process that EPA will use to develop a response to the NAS recommendations. EPA's response may not complete its response before the HHRA is initiated or even completed.

Dow will work in concert with MDEQ to properly interpret the results of the risk assessment to risk managers and the public.

6.1.1 Proposed Assessment Approach

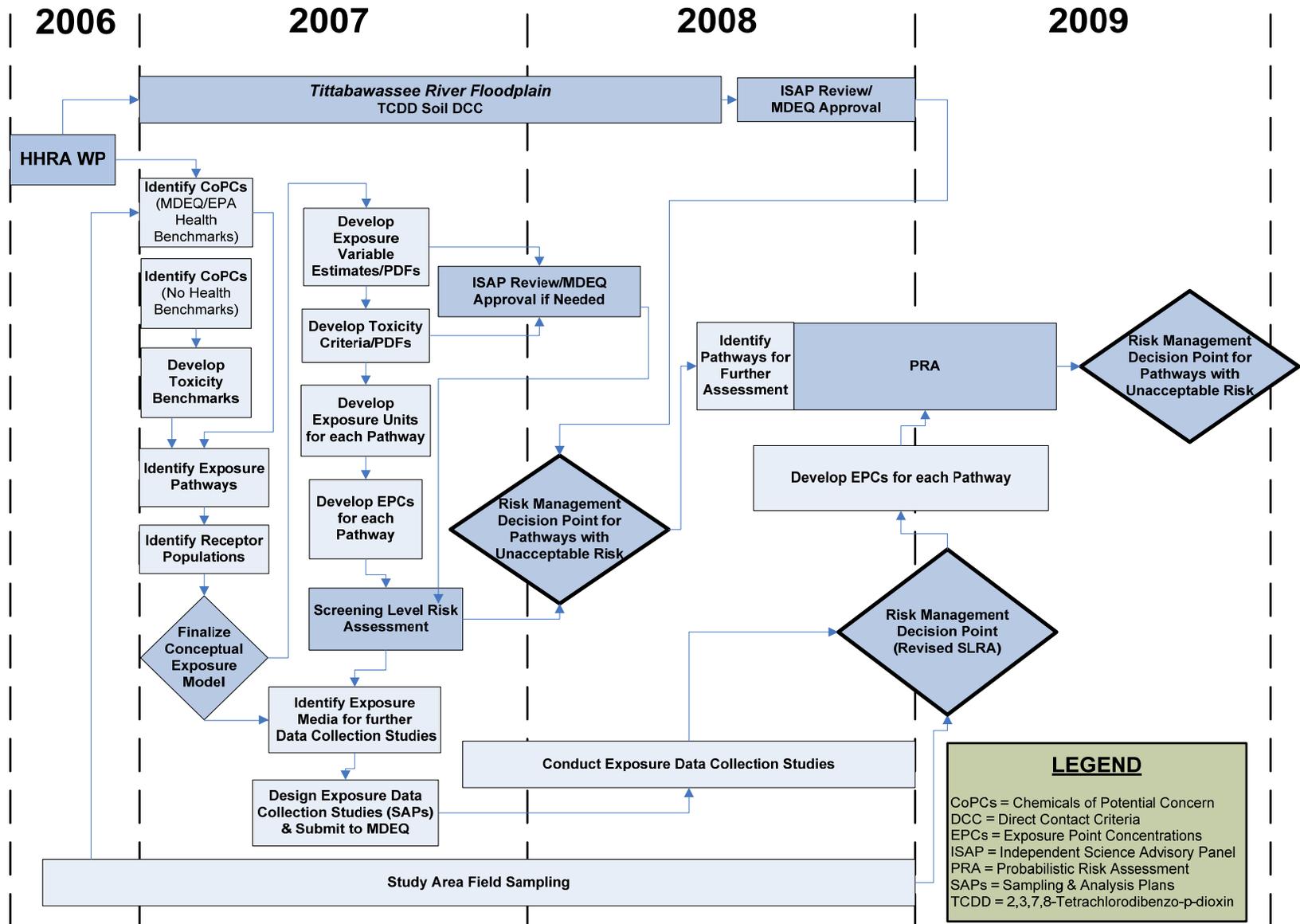
A proposed schedule (Figure 6.1) for the HHRA is provided, although such a schedule is dependent on many variables, including ISAP reviews and MDEQ approval(s) as well as on the completion of any scientific study identified as necessary for addressing specific data needs.

6.1.1.1 Steps in Risk Assessment

The HHRA will include the four steps identified by EPA guidance for risk assessment: (EPA 1989). Although MDEQ does not provide guidance for risk assessment, the Part 201 Rules have been applied, as appropriate. These rules describe the risk assessment methodology used in deriving cleanup criteria as well as considerations in toxicity assessment and these elements and assumptions have also been applied as appropriate. The four steps to be applied include:

- **Identification of contaminants of potential concern (CoPCs)**, through screening the Target Analyte List (See Section 6.3.2)
- **Exposure assessment** including an evaluation of all exposure pathways that are now complete, or are reasonably anticipated to be complete in the future. The exposure assessment will include collection and/or collation of the following: site-specific and (where appropriate) non-site-specific data considered to be representative of Study Area conditions (e.g. soil ingestion rates); CoPC concentrations in various media (soil, dust, fish, wild game and relevant agricultural products); behavioral and activity patterns (outdoor activities, soil ingestion, consumption of locally caught or grown foods, and the frequency and time spent for these activities); and chemical specific parameters (e.g., chemical properties published absorption values and bioavailability data gathered for PCDD/F and for any other CoPCs)
- **Toxicity assessment** including assembling appropriate EPA and MDEQ recommended toxicity values for all CoPCs; and deriving toxicity measures as appropriate, including the

Figure 6-1: Human Health Risk Assessment Decision Sequence (Timeline Approximate, See Figure 9-1) for Tittabawassee River Floodplain Soils.



toxicity criteria for PCDD/F to take into account new data available since the last MDEQ evaluation of cancer potency and development of Part 201 generic residential soil DCC of 90 ppt. In addition, CoPCs without recommended toxicity values may be evaluated, or existing values may be updated after discussions with MDEQ.

- **Risk characterization**, which will combine exposure and toxicity assessments to derive cancer risk estimates and noncancer hazard indices. The risk characterization will include assessment of variability and uncertainty in individual inputs and in overall risk estimates to evaluate the range of potential Study Area risks and limitations in our understanding of them. Delineation of the variability and uncertainty will be developed to assist efforts to place potential site risks in context and facilitate informed risk management decisions

6.1.1.2 Planned Assessment Elements

Since this is a large and complex Study Area and there may be a number of potential exposure pathways, a sequential approach is planned for the risk assessment as shown in Figure 6-1. Specifically the following steps are proposed:

- **Direct Contact Criteria:** There is a need for DCC for soil in the River and Midland Study Areas. These criteria will be used for early decision-making about sampling and early risk-management decision points. The methods proposed to derive these criteria are described in Section 6.1.2.
- **Screening Level Human Health Risk Assessment (SLRA):** An initial screening level risk assessment (SLRA) will be conducted to determine which CoPC—exposure pathway—receptor combinations require more thorough evaluation, which can be eliminated from further consideration because their contribution to potential risk is negligible (i.e., lifetime carcinogenic risk estimate $<10^{-7}$, or hazard index (HI) <0.001), and which may be incorporated in further refinement using screening level methods because their contribution is minor (i.e., lifetime carcinogenic risk estimate $<10^{-6}$, or $HI < 0.01$)².

² This risk range is based on the acceptable risk range (i.e., risks between 10^{-6} and 10^{-4} for carcinogenic effects and a hazard index of 1 for noncarcinogenic effects) cited in EPA's National Contingency Plan (NCP) (40 CFR 300) and the MDEQ risk level of 10^{-5} applied in derivation of cleanup criteria for carcinogens and hazard index of 1.0 identified for single chemicals pursuant to Part 201 Sec. 20120a(4). . The lower target risks and lower hazard index are provided to be protective of multiple CoPCs or pathways.

- Pathway-receptor combinations that have SLRA risk estimates that are negligible for all CoPCs will be omitted from any further consideration in the HHRA.
- CoPCs that have SLRA risk estimates that are negligible for all pathways for a given receptor will be omitted from further consideration for that receptor.
- Pathways and CoPCs not eliminated by the above two screens will be further evaluated in a probabilistic risk assessment (PRA):
 - CoPC/pathway/receptor combinations, while not required to be evaluated under Michigan's Part 201 statute and rules for the purposes of the development of criteria, will be evaluated as part of the HHRA as provided for in EPA's risk assessment guidance which provides for the consideration of exposure pathway combinations when it is likely that the same individuals will be exposed to CoPCs through more than one pathway. (EPA 1989).
 - CoPC/pathway/receptor combinations with minor contributions in the SLRA may be incorporated in the PRA using the SLRA screening methods and parameter values following discussion with MDEQ³
 - CoPC/pathway/receptor combinations with SLRA risk estimates greater than 10^{-6} , or HI 0.01 will be evaluated using PRA where possible. Where not possible, more detailed screening methods will be used to further evaluate these combinations.
- **Probabilistic Risk Assessment:** Those pathways identified to be of concern in the SLRA (see above), will be further evaluated in a forward-looking individual and population-based⁴ PRA to characterize the key aspects of variability and uncertainty in the calculated human risk estimates and ranges
- **Independent Science Advisory Panels:** Independent Science Advisory Panels (ISAPs) will be used to review the HHRA and HHRA components, as appropriate. In this regard, Dow contemplates working with the MDEQ to streamline the ISAP process. The involvement of an ISAP is not necessary nor beneficial in preliminary stages of the HHRA or during development of the HHRA process, and use of an ISAP at too many stages will unnecessarily delay progress. The HHRA proposes to use an ISAP to review only important substantive issues or determinations as agreed to by Dow and MDEQ, particularly development of site-

³ In implementing the PRA, it may be simpler to incorporate a CoPC/pathway/receptor combination probabilistically rather than attempt to maintain separate values for common variables used in both the SLRA and the PRA.

⁴ The PRA will evaluate synthetic individuals randomly chosen from within the population evaluated; an estimate of potential total population effects will be obtained by summing over all such individuals.

specific criteria, if any, as contemplated by the SOW. The independent review provided by these panels will provide a separate and autonomous technical evaluation. The ISAP review will also provide valuable technical feedback that will allow refinement of the HHRA technical approaches as needed. The ISAPs and the processes they use are intended to assist the public in understanding that the HHRA elements and also in ensuring that approaches applied are technically and scientifically sound. A description of the ISAP process is contained in Appendix HHRA B.

6.1.1.3 Applicable Risk Assessment Guidance

The risk assessment will be conducted in compliance with applicable methodology in the MDEQ Administrative Rules for Part 201 Environmental Remediation and in accordance with EPA guidance, including, but not limited to, as appropriate to the assessment, the following documents:

- *Table 4: Toxicological and chemical-physical data for Part 201 generic cleanup criteria and screening levels.* MDEQ R 299.5752. (MDEQ 2006).
- *Risk Assessment Guidance for Superfund: Volume 1 — Human Health Evaluation Manual (Part A)* (EPA 1989b)
- *Risk Assessment Guidance for Superfund Volume I: Human Health Evaluation Manual Supplemental Guidance “Standard Default Exposure Factors”* Interim Final (OSWER Directive # 9285.6-03) March 1991 (EPA 1991a)
- EPA Region IX preliminary remediation goals table (EPA 2006b) may be used in development of the CoPC list for chemicals that do not have MDEQ values and may also be consulted as an initial summary of toxicity values from the EPA Health Effects Assessment Summary Tables (HEAST) and the EPA National Center for Environmental Assessment (NCEA)
- *Risk Assessment Guidance for Superfund (RAGS) Volume 1: – Human Health Evaluation Manual (Part E, Supplemental Guidance for Dermal Risk Assessment)* Final. EPA/540/R/99/005, OSWER 9285.7-02EP, July 2004 (EPA 2004a).
- *Risk Assessment Guidance for Superfund (RAGS) Volume III –Part A, Process for Conducting Probabilistic Risk Assessment.* EPA 540-R-02-002, OSWER 9285.7-45. December 2001. (EPA 2001)

- *Supplemental Guidance to RAGS: Calculating the Concentration Term* (EPA 1992) and *Calculating Upper Confidence Limits for Exposure Point Concentrations at Hazardous Waste Sites* (EPA 2002a)
- *Exposure Factors Handbook* Volumes I through III (EPA 1997a)
- *Guidelines for carcinogenic risk assessment* 70FR17765-17817, Apr 7 2005. Reprinted as EPA/630/P-03/001F, March 2005 (EPA 2005a).
- *Supplemental guidance for assessing susceptibility from early-life exposure to carcinogens.* EPA/630/R-03/003F, March 2005 (EPA 2005b).
- *Approaches for the application of physiologically based pharmacokinetic (PBPK) models and supporting data in risk assessment* (EPA 2006c)
- Guiding principles for Monte Carlo analysis. EPA/630/R-97/001. March 1997. (EPA 1997b)
- Other sources as appropriate

The following guidelines will be followed if appropriate (generally, if CoPCs are identified that have toxicities of the appropriate nature):

- *Guidelines for neurotoxicity risk assessment.* 63FR26926-26954, May 14, 1998. Reprinted as EPA/630/R-95/001F, April 1998 (EPA 1998c).
- *Guidelines for developmental toxicity.* 56FR63798-63826, Dec 5, 1991. Republished as EPA/600/FR-91/001, December 1991 (EPA 1991d).
- *Guidelines for reproductive toxicity assessment.* 61FR56274-65322, Oct 31, 1996. Reprinted as EPA/630/R-96/009, October 1996 (EPA 1996).
- *Guidelines for the Health Risk Assessment of Chemical Mixtures.* 51FR34014-34025, Sept. 24, 1986. Reprinted as EPA/630/R098/002 September 1986 (EPA 1986).
- *Supplementary Guidance for conducting Health Risk Assessment of Chemical mixtures.* EPA/630/R-00/002. August 2000 (EPA 2000b).

Additional reference material relied upon include:

- *Health risks from dioxin and related compounds: Evaluation of the EPA reassessment.* National Research Council, Committee on EPA's Exposure and Human Health Reassessment of TCDD and Related Compounds. (NAS 2006)
- *Measuring people's exposure to dioxin contamination along the Tittabawassee River and surrounding areas: Findings from the University of Michigan dioxin exposure study.* University of Michigan (UM 2006). In addition, the associated questionnaire results and blood and soil data results, as published, will be extensively used, augmented by responses to queries to the UM team for more detailed information, particularly on questionnaire results. (Provided in Appendix HHRA A and available at www.umdioxin.org).

- *The 2005 World Health Organization Reevaluation of Human and Mammalian Toxic Equivalency Factors for Dioxins and Dioxin-Like Compounds* (van den Berg et al. 2006).
- *An examination of EPA risk assessment principles and practices.* Office of the Science Advisor, U.S. Environmental Protection Agency, Washington, D.C. 20460 EPA/100/B-04/001 March 2004 (EPA 2004b)

6.1.2 Derivation of Direct Contact Criteria for the Study Area

The MDEQ has developed generic soil DCC associated with different property uses (industrial, commercial, residential, etc.). For example, for PCDD/Fs (as TEQ), MDEQ has promulgated a generic residential soil DCC of 90 ppt. However, pursuant to Part 201 of NREPA, the Framework for an Agreement, the License, and the SOW, the work under the HHRA will include development of site-specific DCC, and other criteria, based upon the best available information, to better reflect local conditions and take into account updated information and science that has become available since the current DCC was established in 2002.

The draft HHRA will include a site-specific DCC to incorporate appropriate new scientific findings unavailable when the Part 201 generic DCC was created, site-specific information generated by the UMDES or as a result of site investigations, and development of new techniques to place this information in context. Following submission of the RI WPs, a series of collaborative meetings with MDEQ is planned to examine the inputs to the DCC and consider:

- Changes to default exposure parameters based on changes MDEQ has made elsewhere but not yet incorporated into the PCDD/F DCC (e.g., changes to dermal absorption, soil adherence and exposed surface area assumptions);
- Changes to default exposure parameters based on site-specific information (e.g., oral bioavailability, exposure frequency and duration, body weight and UMDES data, etc.);
- Changes to default exposure parameters based on best available science (e.g., soil ingestion rates, relative source contribution, etc.); and
- Changes to default toxicity criteria based on new toxicity data or the derivation of new criteria pursuant to MDEQ Part 201 R 299.5701(c) (e.g., use of the Department of Health and Human Services National Toxicology Program (NTP) 2004 bioassay for cancer slope factors, development of reference dose for endpoints of concern, etc.).

The HHRA will identify those parameters that can and should be up-dated for residential, commercial/industrial, agricultural, and recreational land uses as warranted. The final product, site-specific DCC for various land uses, will also be subject to third party ISAP review to provide transparency and ensure all values are scientifically justifiable and meet the public need.

6.1.3 Prior Studies and Proposed Use of the UMDES Exposure Data

The Dow Midland plant has been the subject of many investigations (See Section 6.3) that have generated considerable site-specific information available for use in the HHRA. These investigations, conducted by Dow, MDEQ, and EPA, have examined contaminants in soil, in fish, and others described in Section 6.3.1. These prior studies have helped to focus this investigation, and data from those studies are proposed for use the HHRA as determined through future discussions with MDEQ. The most informative and recent study is the UMDES, with an initial report in August of 2006 and with analyses still ongoing. This human exposure and biomonitoring study measured PCDD/Fs and PCBs congeners and reported these as well as a single combined TEQ in: blood serum, soil, household dust, and vegetation samples. The UMDES also administered detailed exposure surveys to elicit participants' reports of their consumption of various foods (both locally grown and store-bought) and participation in various activities expected to contribute to PCDD/F and PCB exposure.

The UMDES collected data from stratified random samples from five populations, consisting of persons resident in the following five mutually exclusive geographic areas:

1. Floodplain of the Tittabawassee River (defined as the floodplain of the river between the Dow Chemical plant in Midland and the confluence of the Tittabawassee and Shiawassee Rivers in Saginaw);
2. Near Floodplain (defined as census blocks adjacent to the Tittabawassee River Floodplain between the Dow Chemical plant in Midland and the confluence of the Tittabawassee and Shiawassee Rivers in Saginaw);
3. Midland Plume area (defined as an area downwind of the Dow plant in the city of Midland);
4. Other Midland/Saginaw areas (defined as other areas in Midland County, Saginaw County, and Williams Township in Bay County, excluding the previously defined areas and excluding also the flood plain of the Saginaw River and the confluence flood plain of the Shiawassee River);
5. Control area thought not to be affected by Dow Midland activities consisting of Jackson and Calhoun Counties over 100 miles away from the Dow Midland facility.

Persons who had lived at their current address for five years or longer and who were at least 18 years old were eligible for inclusion in the Study. Complete one-hour interview data were obtained for 1,324 persons, including 359 from the control area. Persons whose blood was sampled also had to meet medical eligibility criteria: weight at least 110 pounds, no chemotherapy within the last 6 months, no history of bleeding or clotting disorders, not currently taking blood thinner medications, not currently nursing (known to be) pregnant, not currently diagnosed or treated for anemia, and having not donated blood within the previous 8 weeks. Blood sample data were obtained from 946 of the interviewees, including 251 from the control area.

The UMDES study team went to substantial effort in the design and execution of the UMDES to ensure that the sample would be representative of the underlying population and to ensure that valid inferences could be drawn. The protocol (UMDES study protocol, 2005 [Appendix HHRA A]) defined the populations to be sampled, the method of sampling, and the many quality control procedures required. Extensive evaluation of the sampling approach and corrections for various biases were incorporated (Lepkowski 2006⁵) and great care taken in executing the design (Ward et al. 2006 and LaDronka et al. 2006). Cooperation and response rates were higher than expected (overall response rate 74.3%) (Lepkowski 2006). A follow-up survey of non-responders had a high response rate (50%), and indicated that nonresponders to the main study participated in fewer activities that are related to PCDD/F exposure (hunting or fishing in, and consuming game and fish from, Michigan and the Tittabawassee River or floodplain), but showed no significant differences in the most significant predictors of blood PCDD/F levels (age, sex, and BMI) (Olson et al. 2006). The study design and its preliminary results have all been reviewed and commented upon by an independent Scientific Advisory Board consisting of Linda Birnbaum, PhD, DABT (Diplomate of the American Board of Toxicology) (EPA), Paolo Boffetta, MD, MPH (Masters of Public Health) (International Agency for Research on Cancer), Ronald Hites, PhD (Indiana University) and David Kleinbaum, PhD (Emory University) (Franzblau 2006).

The study included analyses of the seventeen PCDD/F congeners substituted with chlorines at the 2,3,7, and 8 positions and the twelve polychlorinated biphenyls (PCBs) congeners identified by the World Health Organization (van den Berg et al. 2006) as having dioxin-like properties, and also calculated total TEQs using the PCDD/F and PCB congeners identified by World Health Organization (2006)⁶. The

⁵These papers are available at www.umdioxin.org and are attached as Appendix HHRA A to this report.

⁶ The toxic equivalent quotients (TEQs) so far reported by the UMDES were based on the World Health Organization 29 congeners, which includes coplanar PCB congeners. Additional analyses limited to PCDD/F

initial reports of the study evaluated the seven individual congeners contributing most to TEQ in blood together with the total TEQ values that combined dioxins, furans and PCBs. These analysis were collected and reported for the following:

- *Blood serum data* were reported for 946 persons, including 251 persons from the control area considered (because of its distance) to be unexposed to Dow activities;
- *Soil sample results* for 766 samples, including 194 from the control area, from the surface soil (0–1 inch) stratum around house perimeters; 449 samples, including 53 from the control area, for the 1–6 inch stratum around house perimeters; 484 samples, including 124 from the control area, of the 0–6 inch stratum in soil contact zones in gardens; and 191 soil samples each from 0–1 inch and 1–6 inch from garden areas in the Study Area.
- *Vegetation sample results* for 416 samples including 52 from the control area, associated with the house perimeter soil samples; and 163 vegetation samples associated with the soil samples from the Tittabawassee floodplain. All vegetation samples were opportunistic grab samples associated with the corresponding soil samples (UMDES protocol, 2005)
- *Household dust sample results* for 764 samples including 198 control area samples
- *Interview data* were obtained from 1324 participants, including 359 from the control area.
 - Interview data included demographic and general physical characteristics of study participants (e.g., body weight, age, years of residence)
 - Interviews also included extensive questions about exposure including: local and general consumption of local caught or grown foods as well as fish or game caught elsewhere or purchased, work history, years of residence in the area where studied, remediation at residence if any, activities involving soil contact including gardening, activities in and around the Tittabawassee River and other areas, and breast feeding history
- *A complete set of interview data, serum data, soil and dust sample data* were reported for 731 persons including 183 individuals from the control area.

UMDES has conducted statistical analyses of the sampling results to evaluate potential associations in four PCDD/F congeners, three PCB congeners, and TEQ concentrations between blood serum and soil concentrations, dust concentrations, and food consumption and other demographic characteristics,

TEQs have been or will be requested. The TEQ values used correspond to WHO (1998) TEF values, and UM are expected to update their report to WHO values (van den Berg et al. 2006).

personal characteristics, or residence locations.⁷ UMDES is continuing analyses on the other congeners that were measured.

Because the UMDES included 1324 interviews (including 965 in or near the area of interest), the investigation reports provide helpful and relevant site-specific information about food consumption rates, duration of residence, and demographic characteristics including ethnicity and body weight distributions in the Study Area.

The HHRA will integrate the relevant aspects of the UMDES conclusions and data, including exposure data gathered through these interviews into appropriate aspects of the HHRA. Dow plans to meet and collaborate with MDEQ and the University of Michigan on the use of the UMDES data. Dow together with MDEQ will identify the relevant questionnaire items and prepare a request to the UMDES Study Team for the following aspects of the relevant questionnaire items following submission of this work plan:

- For the four local areas, are there statistically significant differences in the responses to each of the relevant questionnaire items?
 - If not, a reporting of the weighted distribution for the aggregate of the four local area responses will be requested, for example in terms of specific percentiles or, if possible, in terms of a probability distribution function for the item.⁸
 - If significant differences among the four local areas are identified, the same request will be made for each of the four areas.
- For items such as consumption of local species of fish, are there positive or negative correlations among the behaviors (for example, are consumption rates of walleye and carp independent or correlated)?
 - If variables are correlated, the correlations among those behaviors will be quantified so all such behaviors can be incorporated in the PRA appropriately⁹

⁷ The seven congeners evaluated so far are the major contributors to TEQ in blood samples in the UMDES and in the United States generally (UMDES brochure, 2006 Appendix HHRA A).

⁸ Details have yet to be finalized. Preliminarily, distributions might be specified by UMDES providing 1st, 5th, 10th, 15th, ..., 95th, and 99th percentiles, and used in the PRA by fitting mathematically defined continuous distributions with infinite or semi-infinite support (to ensure in particular that upper tails are included). Alternatively, UMDES may perform such fitting using distribution shapes specified to them. The object is to provide the necessary estimates of variability distribution parameters and the corresponding uncertainty distributions and correlations for those parameters, while retaining complete confidentiality for all respondents in the UMDES.

In each instance of use within the HHRA, the UMDES interview data will be compared with any available parameter data provided by EPA or MDEQ sources, and where appropriate with US national or regional data. Where there are no statistically significant differences between UMDES distributions (known to be representative of the Study Area) and those obtained with lower uncertainties (generally using larger samples sizes), the lower uncertainty estimate will be used or suitably merged with the UMDES data using methods to be agreed upon with the ISAP. The HHRA may also use the results of an Activity Survey (Section 6.1.5.1) if one is conducted, to obtain additional site-specific data for algorithm inputs for various exposure pathways. Other requests may be made to the UMDES project team as additional questions are identified for which the information gathered during the UMDES may provide information useful in the HHRA. Where the UMDES distribution is incomplete for a particular requirement (e.g. because of the need to include children), the distribution obtained from UMDES will be merged with suitable other data (including possibly site-specific data or national data).

6.1.4 Comparison of PRA with UMDES Blood Concentrations

The PRA proposed here is designed to obtain the best estimates available for the distributions of doses and risks from the Study Area media. During the necessary calculations, the concentrations of PCDD/Fs in blood to be expected from such doses can also be calculated, and the sampling of blood concentrations performed during the UMDES will be simulated. The blood concentration distributions, and the potential relationships between blood concentration and environmental measurements (concentrations of PCDD/Fs in soil, fish, and game) will be evaluated from the results of this simulation exercise and compared with the results observed in the UMDES. A similar exercise will be performed using results from the SLRA; however, the SLRA is conservative by design, and moreover will be performed only on a pathway-by-pathway basis, so comparisons will be less direct. However, these comparisons may be able to detect extreme overestimates or underestimates of doses in particular pathways.

6.1.5 Studies Proposed to Support the HHRA

The HHRA will be supported by a number of exposure pathway specific data collection efforts. The work plans, and or protocols, for these studies are provided in Appendix HHRA-C. These include the following:

⁹ Again, precise details are not yet finalized. The method of incorporation of any correlations will likely depend on the method of specifying distributions.

- **Local-Grown Foods:** Analytical chemistry samples to evaluate potential concentrations of TAs in locally grown foods including: meats (chicken, beef, sheep), eggs, cow's milk, and garden vegetables, if available.
- **Fish and Game:** Analytical chemistry samples of fish and game from the Tittabawassee River Study Area
- **Dust:** Samples of PCDD/Fs in airborne dust collected adjacent to farm fields or from personal air monitors
- **Bioavailability:** A pilot study and a follow-up investigation were conducted to evaluate the potential oral absorption of PCDD/F in soil relative to absolute oral absorption potential (i.e., bioavailability). These data provide a basis to evaluate oral absorption of PCDD/Fs from local soil in the HHRA. The results of the pilot study are provided at the MDEQ web cite¹⁰, the results of the follow-up study are provided in Appendix HHRA C, and further discussion of this issue is provided in Section 6.4.5.2
- **Soil Ingestion Rates:** Soil ingestion rates are being further investigated by Drs. E.J. Calabrese and E.J. Stanek, III, at the University of Massachusetts (Hereafter UMass Soil Ingestion Project). These investigators are recognized as the primary international expert on soil ingestion. A general summary of the protocol for these investigations is provided in Appendix HHRA C and more discussion on soil intake assumptions for the HHRA is provided in Section 6.4.4.4.1.
- **Proposed Activity Survey:** An Activity Survey may be proposed if necessary to better characterize the exposure potential of the Midland and Tittabawassee Study Areas residents by administering questionnaires regarding the types of activities that could result in contact with CoPCs in Study Area media, potential contact rates, and consumption of local foods collected from within the Study Area. or observing activities within the Study Area The Activity Survey is discussed further in Section 6.1.5.1.

6.1.5.1 Activity Survey

There are certain exposure parameters for which site-specific information is not currently available, and for which generic or default values may be unsuitable or unavailable. These include some aspects of ingestion rates for various food items associated with the Study Area exposure pathways (e.g., ingestion rates of soil, fish, game, home-raised milk, meat, eggs, and garden vegetables) as well as estimates of

¹⁰ <http://www.deq.state.mi.us/documents/deq-whm-dioxin-PilotStudyReportFINALFeb24.pdf>

exposure frequency and duration of adult and child activities likely to bring these populations into contact with contaminated media (e.g., days spent outdoors, hours spent in contact with soil, etc.). To estimate these parameters, the HHRA may include developing and conducting an Activity Survey. If an Activity Survey is conducted it will build on and supplement data from the UMDES. The proposed approach would also be discussed with MDEQ and other stakeholder agencies, which will be asked to participate in the development of the survey instruments and interpretation of the results for risk assessment. Table 6-1 lists such information or values.

Table 6-1 Potential Information that May be Gained by an Activity Survey

Presence or absence of young children (except non-contact presence) in the Study Area
Recreational time spent in the Study Area by children/teens
Numbers of children/teens visiting recreational areas throughout the year
Direct observation of soil contact behavior by children in the Study Area
The fraction of the year with children/teens/adults performing activities with the potential for direct soil contact
Types of clothing (including footwear) observed throughout the year in residential and recreational areas and during residential and recreational activities
Types of clothing worn in the field by hunters and anglers.
Fish trimming and cooking methods
Game trimming and cooking methods
Types of fish consumed (if the UMDES is not sufficiently detailed)
Types of game consumed (if the UMDES is not sufficiently detailed)
Fish consumption rates and types of fish consumed by children and teens
Game consumption rates and types of game consumed by children and teens
The fraction of visitors who wade and/or swim in the Tittabawassee River, and the period spent wading and/or swimming
The fraction of anglers who wade (without waterproof waders) during fishing in the Tittabawassee River, and the period of time wading
Counting the number of cows and other livestock present in the Study Area
If necessary, evaluation of the distribution of fish meal sizes (for all ages)
If necessary, evaluation of the distribution of game meal sizes (for all ages)
More detailed information on homegrown meat and eggs (particularly total production and individual consumption rates)

6.2 CONCEPTUAL SITE MODEL: HUMAN HEALTH EXPOSURE PATHWAYS

The Conceptual Site Model (CSM) describes the network of relationships between CoPCs present at a site and the receptors that may be exposed to those CoPCs through various pathways leading from the site and ending with exposure through ingestion, inhalation, or dermal contact. The CSM incorporates the range of potential exposure pathways and identifies those that are present and may be important for human receptors. The CSM helps to identify main pathways and eliminate those pathways that are incomplete and therefore do not require further evaluation. Exposure pathways consist of the following four elements: 1) a source; 2) a mechanism of release, retention, or transport of a chemical to a given medium (e.g., air, water, soil); 3) a point of human contact with the medium (i.e., exposure point); and 4) a route of exposure at the point of contact (e.g., ingestion, dermal contact).

The sources and transport and fate mechanisms were described in Section 4 above; this section describes exposure pathways relevant for human exposure, which are depicted in Figure 6-2. The current exposure pathway model reflects emphasis on PCDD/Fs, which are the current CoPCs under consideration. This conceptual model may be modified depending on the CoPCs ultimately included in the HHRA. As land use mapping is completed during the RI, exposure scenarios will be associated with land uses to facilitate current and potential future use evaluations for the HHRA. All potentially exposed human receptor populations will be identified considering the land uses present in the Study Area to ensure that the media and exposure pathways that pose the greatest potential human health risk are identified and evaluated in the HHRA.

6.2.1 Potential Human Receptors

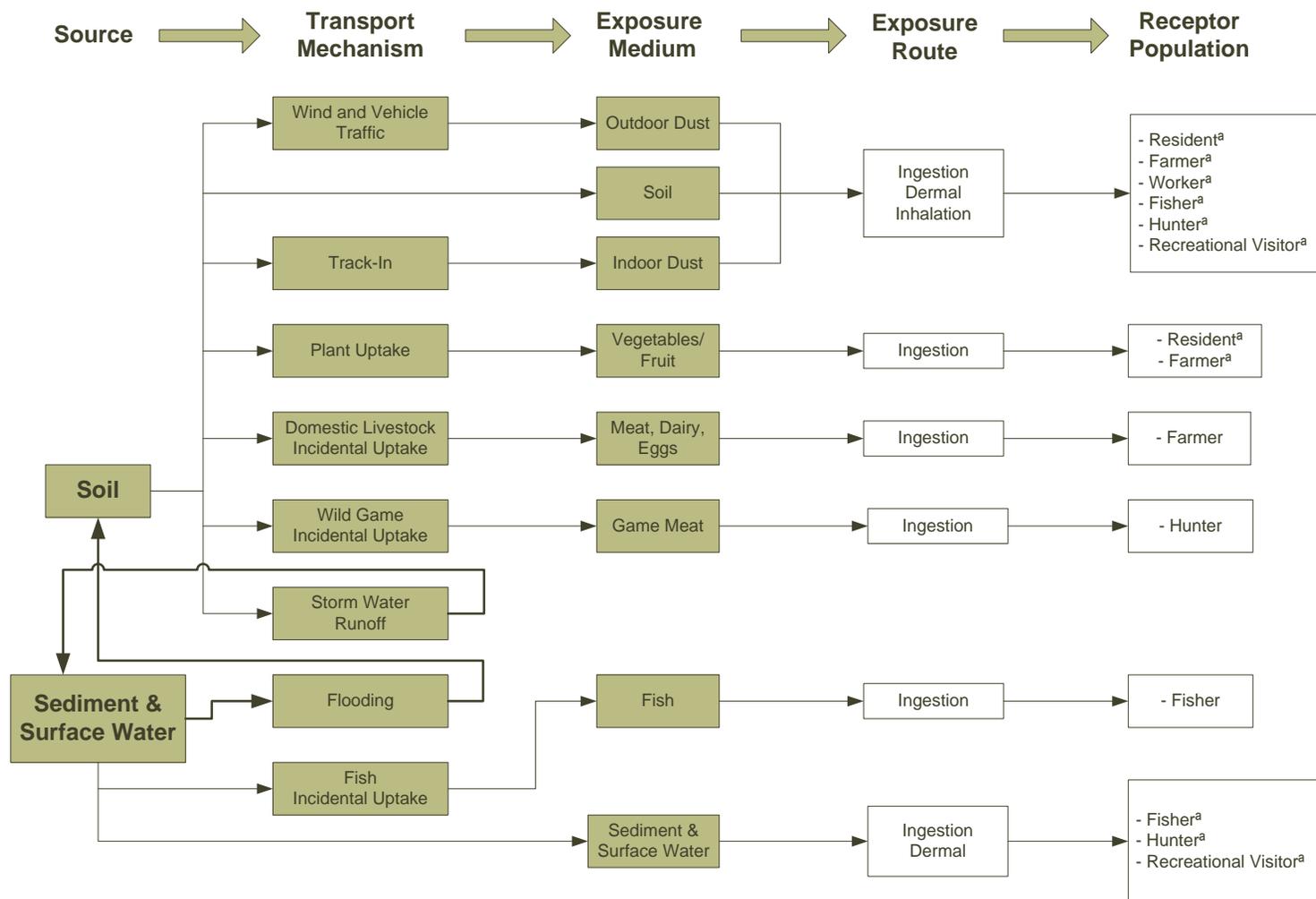
6.2.1.1 Receptor Groups

Receptor groups to be considered include residents, workers, farmers, anglers, hunters and recreational visitors¹¹. Both adults and children will be considered in the resident and recreational receptor groups. Potential pathways for each of these receptor groups are discussed further in the work plan

The HHRA will also address reasonably anticipated potential sensitive sub-populations which could include the developing fetus, young children, elderly people, and people with chronic diseases. The toxicity values and exposure assumptions applied in the SLRA are derived to be protective of the entire

¹¹ Three recreational scenarios are evaluated, hunting, fishing, and other recreation, which excludes hunting and fishing, even though those activities are primarily recreational.

Figure 6-2. Conceptual Human Exposure Pathway Model for Tittabawassee River Sediment, Surface Water and Floodplain Soil.



^a Each receptor group is exposed to the medium within their respective exposure units to facilitate derivation of receptor-specific screening level risk estimates, such that the significance of each pathway exposure can be determined for each receptor group.

population including reasonably identified sensitive subpopulations; in the PRA, appropriate toxicity values will be developed and applied to the appropriate subpopulations. For PCDD/Fs, the toxicity values currently available for non-cancer endpoints are derived on the basis of potential impacts on the infant and fetus. Any new non-cancer toxicity values to be developed will consider exposures *in utero*, exposures resulting from breastfeeding in infancy, exposures during childhood, and subsequent exposures as an adult, as appropriate for the end point(s) examined.

Furthermore, the risk assessment will also address reasonably anticipated potential or actual highly exposed individuals. These are individuals whose activities or consumption rates result in much higher contact with CoPCs than those of the majority of the population. Examples include those with a high level of consumption of foods that may contain CoPCs such as avid anglers or persons whose cultural practices include high consumption of locally caught fish and game, or that have higher rates of soil ingestion as a group (e.g., children), or that have higher rates of soil ingestion due to behaviors that directly or indirectly increase soil intake. The exposure assessment used in the SLRA will be conducted to evaluate the reasonable maximum exposure (RME) scenario. The RME approach is intended to combine upper-bound and mid-range exposure assumptions so that the result represents an exposure scenario that is both protective and reasonable, not the worst possible case (EPA 1989). The ultimate estimates are intended to represent exposures generally in the 90th to 98th percentile range but possibly up to the 99.9th percentile of exposures, (EPA 1992, 1997a, 2003). The PRA will incorporate all available information on distributions of exposures (where SLRA estimates are deemed inadequate for characterization), allowing explicit evaluation of all exposure percentile(s).

6.2.1.2 Use of Probabilistic Techniques to Address Highly Exposed Receptors

All relevant exposed populations, including highly exposed subpopulations, will be included in the HHRA. The HHRA WPs propose a two-dimensional (variability and uncertainty) probabilistic assessment for the population at risk from the site now and in the future, using Monte Carlo techniques. The details will be expanded considerably to clarify this once meetings with MDEQ have been held and decisions have been made. This population assessment is constructed by evaluating risks to all the individuals (strictly, a constructed representative sample¹²) that is designed to be representative) within

¹² In the Monte Carlo procedure, a synthetic sample individual from the population is constructed by selecting a set of characteristics for that individual — just those characteristics needed for estimating that individual's dose and risk. The selection is done in a representative fashion, taking account of the probabilities for real individuals in the population to have each characteristic and each combination of characteristics.

that population (that is the variability component of a two-dimensional probabilistic assessment), while taking account of the uncertainty involved (that is the uncertainty component).

It is in this sense that the HHRA becomes both “population-based” and “individual-based.” By summing across all the individuals evaluated (that is, the whole hypothetical exposed population), the total population effect may be obtained in an unbiased fashion, together with the uncertainty on that total population effect. All sensitive or highly exposed subpopulations are incorporated in the total population involved, by appropriate incorporation in the variability distributions of the relevant parameters that describe factors accounting for such sensitivity, be they exposure factors (Section 6.4) or toxicity factors (Section 6.5). The approach described can obtain risk estimates in the exposed population, at any specified percentile of the variability distribution, and any specified percentile of the uncertainty distribution; in fact, for any statistic that can be defined on the variability and uncertainty distributions.

The Monte Carlo technique evaluates individuals with all possible combinations of exposure factors, weighted by the likelihood for these combinations occurring. This set of combinations necessarily incorporates the individual with “reasonable maximum exposure,” and the results of the Monte Carlo assessment therefore also incorporate such an individual. Indeed, the probabilistic approach is exactly what is required to estimate a “reasonable maximum exposure,” given the definition of that term as “the highest exposure that is reasonably expected to occur at a site” with the intent that it “is to estimate a conservative exposure case (i.e., well above the average case) that is still within the range of possible exposures” (EPA, 1989, Pages 6-4 to 6-5). It should be noted that the previous and following documents are also exactly those cited in MDEQ’s Part 201 generic soil direct contact criteria Technical Support Document (TSD), “More details on Dioxin 90 ppt value.” (MDEQ 1998). This intent has also been clarified by more recent guidance. For example, the EPA’s Guidance on Risk Characterization for Risk Managers and Risk Assessors (EPA, 1992; Memorandum from F. Henry Habicht II) clarifies that:

- The high-end risk descriptor is a plausible estimate of the individual risk for those persons at the upper end of the risk distribution. The intent of this descriptor is to convey an estimate of risk in the upper range of the distribution, but to avoid estimates that are beyond the true distribution. Conceptually, high-end risk means risks above about the 90th percentile of the population distribution, but not higher than the individual in the population who has the highest risk.
- This descriptor is intended to estimate the risks that are expected to occur in small but definable “high end” segments of the subject population. The individuals with these risks

may be members of a special population segment or individuals in the general population who are highly exposed because of the inherent stochastic nature of the factors, which give rise to exposure.

- In those few cases where the complete data on the population distributions of exposures and doses are available, high end exposure or dose estimates can be represented by reporting exposure or doses at selected percentiles of the distributions, such as the 90th, 95th, or 98th percentile.
- In the majority of cases where complete distributions are not available, several methods help estimate a high-end exposure or dose. If sufficient information about the variability in lifestyles and other factors are available to simulate the distribution through the use of appropriate modeling, e.g. Monte Carlo simulation, the estimate from the simulated distribution may be used.

It is only if “limited information on the distribution of the exposure or dose factors is available,” that “the assessor should approach estimating the high end by identify the most sensitive parameters and using maximum or near-maximum values for one or a few of these variables, leaving others at their mean values.”

More recent guidance from EPA in their *Guidance for Risk Characterization* (Science Policy Council, February EPA, 1995) confirms these points, and clarifies the guidance to provide more prominence to certain assumptions. Among the guiding principles emphasized is the necessity of distinguishing between variability and uncertainty (pointing out that the high end individual risk estimates are intended to capture the variability in exposure, lifestyles, and other factors that lead to a distribution of risk across a population). The guidance goes on to point out that:

- High-end descriptors are intended to estimate the exposures that are expected to occur in small, but definable, "high end" segments of the subject population. The individuals with these exposures may be members of a special population segment or individuals in the general population who are highly exposed because of the inherent stochastic nature of the factors that give rise to exposure. Where differences in sensitivity can be identified within the population, high end estimates addressing sensitive individuals or subgroups can be developed.
- In those few cases in which the complete data on the population distributions of exposures and doses are available, high end exposure or dose estimates can be represented by reporting

exposures or doses at a set of selected percentiles of the distributions, such as the 90th, 95th, and 98th percentile. High-end exposures or doses, as appropriate, can then be used to calculate high-end risk estimates.

The HHRA WPs envision that the high-end descriptors will be obtained in this manner, so that attempts to define hypothetical “sensitive subpopulations” are unnecessary; any such populations should (and will) be incorporated in the distributions used to represent population variability. The HHRA WP has been modified, however, to specify that where only particular subpopulations are at risk for particular endpoints, results for those subpopulations will be presented separately. An example of such a subpopulation would be neonates exposed as fetuses and subject to developmental risks.

6.2.2 Exposure Pathways and Scenarios

An exposure scenario is defined as the combination of potential exposure pathways that a receptor may experience over the course of a long-term exposure. Exposure pathways and scenarios for residents, workers, farmers, anglers, hunters, and other recreational visitors scenarios are discussed here, with reference to particularly highly exposed populations where relevant. An investigation of every conceivable pathway, use or exposure, is not required nor would such an investigation make sense or be effective. Instead, the draft HHRA will include evaluation of all relevant pathways that present a reasonable potential for exposure, given current, expected and reasonably anticipated property uses.

6.2.2.1 Residents

Current and potential future residents (adults and children) may potentially be exposed to CoPCs in Study Area soil, homegrown vegetables, and in human breast milk. Residents may also be exposed to CoPCs through recreational activities within the Study Area, which are discussed under their topic headings (i.e., angler, hunter, and other recreational activities).

6.2.2.1.1 Exposure to CoPCs in Soil or Dust

Current and future residents in the Midland and Tittabawassee River Study Areas might be exposed to CoPCs through incidental contact with soil and dust on their property. This contact may include incidental ingestion of soil, dermal contact with soil, and inhalation of airborne dust arising from soil. These potential exposure pathways will be incorporated in the HHRA for adults and for young children (ages 1 to 6).

6.2.2.1.1.1 *Unusual High Ingestion of Soil by Children*

The potential for ingestion of unusually high amounts of soil by a child will be considered in the HHRA. However, the approach to assess this potentially distinct receptor population has not been completely formulated. It will to be developed through future discussions with MDEQ as well as through a meta-analysis of soil ingestion studies by the University of Massachusetts. In addition, EPA risk assessment guidance provided in EPA's *Exposure Factors Handbook* (EPA 1997a) and the external review draft *Child-Specific Exposure Factors Handbook* (EPA 2006) will generally be followed, supplemented by analyses of the scientific literature.

The literature examined will include (but is not limited to) the following: Binder et al. (1986), Calabrese et al. (1989a,b, 1990, 1991, 1996, 1997a,b,c), Calabrese & Stanek (1991, 1992, 1995), Clausing et al. (1987), Davis et al. (1990, 2006), Bothe (2004), Stanek & Calabrese (1991, 1995a,b, 2000), Stanek et al. (1999, 2001a,b), van Wijnen et al. (1990), Wong (1988), Wong et al. (1988, 1990, 1991), Alexander et al. (1974), Beaver (1975), Juqdaohsinqh et al. (2002), Lawson (1977), Popplewell et al. (1998), Reffitt et al. (1999). In addition, the raw data from the mass-balance tracer studies by Calabrese et al. (1989b, 1997b), Davis et al. (1990, 2006), Bothe (2004), and any available other raw data will be examined for relevant information to this receptor population. The UMass soil ingestion project is also expected to provide additional information and guidance on how to address unusually high child soil ingestion estimates reported in a limited number of studies.

While EPA (2006) states that “the recurrent ingestion of unusually high amounts of soil (i.e., on the order of 1,000 to 5,000 milligrams per day)” is defined as soil pica, these relatively higher child soil ingestion estimates were reported in only one study, and are not clearly known to be attributable to soil pica. EPA (2006) noted that although information regarding the incidence of soil pica is limited, soil pica appears to be less common based on soil ingestion data from the five key tracer studies (Binder et al. 1986; Clausing et al. 1987; Van Wijnen et al. 1990; Davis et al. 1990; and Calabrese et al. 1989) in which only one child out of 600 children from these studies ingested an amount of soil significantly greater than the range for other children. EPA (2006) notes that while these studies represent only short-term soil ingestion and do not include data for all populations, “it can be assumed that the incidence rate of the recurrent ingestion of unusually high amounts of soil in the general population is low.” Consequently, EPA suggests developing a site-specific incidence rate estimate for this potential receptor population.

For the PRA, the incidence of unusually high soil ingestion events and the quantities of soil ingested will be estimated from the available information in soil ingestion studies, mineral balance studies, the Activity

Survey (if conducted) and any other literature information that may be available and relevant [see the soil ingestion references cited above]. Included in this evaluation will be an assessment of both the likely frequency and duration of this behavior. Relevant information generated through the UMass soil ingestion project will also be considered.

6.2.2.1.2 Baseline Diet

Concurrence on the inclusion of background dietary exposures was not reached by Dow and MDEQ. There was concurrence that background diet should be considered at some point, but not how. Both Dow and MDEQ are aware of the problems associated with including this exposure pathway to PCDD/Fs in the HHRA given that exposure via diet is not a media or land use-related exposure and is therefore not part of the standard RI process.

MDEQ indicates that background dietary exposures should be included in the HHRA, and points to its derivation of a soil clean-up criterion for lead as support for this position. However, background dietary exposures to and risks from dioxin-like compounds are not included in the HHRA WPs for the following reasons.

The purpose of the remedial investigation is to **assess site conditions** in order to select an appropriate remedial action, if one is required, that adequately **addresses those conditions**. The remedial investigation identifies the source or sources of any contamination and defines the nature and extent of contamination **originating from that source** (Mich. Admin. Code R. 299.5528(1) [emphasis added]).

Inclusion of background dietary or other background exposures, at this stage in the process, would hinder the clear assessment of site-related risks. Evaluation of background dietary exposures and risks as well as generation of cleanup criteria properly belongs in the Feasibility Study (FS) portion of the process, after site-related exposures and risks are clearly delineated. At that point, consideration of the need for and choices of remedial options can be informed by an accurate evaluation of background dietary exposures. That is, consideration of background exposures properly belongs in the risk management phase of the process.

The MDEQ's example of the selection of a criterion for lead in soil, which includes consideration of generic exposures to lead in diet, supports this interpretation: the example does not discuss a site risk assessment process (assessment of site-related exposures and risks), but rather demonstrates a risk management process (identification of a soil criterion that accounts for some background dietary

exposure). The goal of the risk assessment during the RIWP process is to characterize the site-related exposures and risks.

6.2.2.1.3 *Ingestion of Home-Grown Produce*

Current and future residents in the Midland and Tittabawassee River Study Areas may grow their own vegetables and may potentially ingest CoPCs by ingesting homegrown foods. However, soil to plant uptake of PCDD/F-like compounds is generally considered to be a minimal or insignificant (McCrary, et al. 1990), with atmospheric deposition being the more important means of exposure (Hites 1991; NAS 2006). Published literature on plant uptake is available for analyses and evaluation in the HHRA for homegrown vegetables (Hulster and Marschner 1993; Bacci et al. 1992; Hulster et al. 1994; Muller et al. 1994; Muller et al. 1993) if necessary. In the 2003 exposure assessment component of the EPA Dioxin Reassessment EPA did not include exposure through fruits and vegetables, as this exposure was considered insignificant. (EPA 2003, Volume II)

The UMDES evaluation of the influence of vegetable consumption determined that consumption of fruits and vegetables was associated with lower serum concentrations of PCDD/Fs and PCBs (UMDES brochure¹³ 2006 page 17). Specifically, the UMDES evaluated the effect of eating vegetables on blood concentrations of PCDD/Fs and PCBs, and found that “[i]n general, people who ate more fruit and vegetables have similar or lower levels of PCDD/Fs in their blood as compared to people who eat fewer fruit and vegetables” and that this “is largely true whether or not the fruit and vegetables come from the contaminated areas or are bought from a store.” In particular “[p]eople who ate root vegetables from the Tittabawassee River, Saginaw River, and Saginaw Bay Floodplains do not have higher levels of dioxins in their blood” [UMDES 2006, Findings]. Quantitatively, for TEQ and the seven specific congeners so far reported, for potentially non-random correlations between blood levels and consumption of fruits and vegetables, there were “[g]enerally negative associations for fruits, vegetables, and root vegetables, whether raised in the contaminated areas or raised elsewhere” although there were “[a] few positive associations for store bought fruits, vegetables, and root vegetables.”

In view of these entirely negative findings related to site conditions found in the UMDES regarding a potential impact of consumption of vegetables on blood levels of PCDD/Fs, and the low potential for PCDD/Fs to be taken up into plants (McCrary et al. 1990), it is proposed that the HHRA not incorporate

¹³ http://www.sph.umich.edu/dioxin/PDF/UMDES%20Brochure_FINAL_08042006.pdf

this pathway of exposure. Site-specific studies of vegetable uptake are proposed as described in Appendix HHRA C, but do not appear to be warranted given the findings of the UMDES study.

6.2.2.1.4 Human Milk

The developing offspring exposed *in utero* and postnatally through lactation, are the most sensitive receptors identified in laboratory (non-human animal) studies of PCDD/F. This was explicitly recognized by all of the agencies that have derived non-cancer criteria for TCDD and related compounds. Each of the available criteria was derived based on observed effects in offspring exposed to TCDD while *in utero* and postnatally via lactation. The criteria were all derived for chronic exposure scenarios with the goal of maintaining adult maternal exposures and body burdens below levels that could result in unacceptable exposures to the fetus *in utero* and the nursing infant. Because of this, these criteria are, by definition, protective of the nursing infant.

No explicit quantification of the daily intakes of PCDD/Fs through breast milk is required because that intake is accounted for by maintenance of maternal intake and body burdens below the levels identified in these non-cancer toxicity criteria, and application of such criteria to estimated intakes by infants would be inappropriate. This issue is discussed in more detail in Section 6.5.2. Further discussion on the means by which the human milk pathway will be evaluated in the assessment is provided in Appendix HHRA D.

6.2.2.2 Worker

A worker scenario evaluating potential exposures specific to adult workers will be conducted for areas that have land uses consistent with commercial II, III and IV and industrial land uses as these land uses are identified during land use mapping to be conducted in the RI. Exposure pathways to be considered are incidental ingestion and dermal contact with soil, and inhalation of soil particulates.

6.2.2.3 Farmers

Current and future farm residents in the Study Areas may be exposed to CoPCs in soil and dust and may raise and consume farm products including meat, dairy and eggs. The exposure pathways for such resident farmers will therefore include the exposure pathways for the resident (Section 6.2.2.1.), together with consumption of locally produced meat, dairy products and eggs. The only difference between farmers and residents in the HHRA is the difference in their exposure point concentrations (farmers will be exposed both to residential soils and to farm soils) and likelihood for farmers to consume locally produced meat, dairy products and eggs.

6.2.2.4 Recreational Use of Study Area

Visitors or residents may come to the Study Area for recreation¹⁴. Potential receptor populations may include, but are not limited to, hikers, bikers, water-sport enthusiasts, student athletes, out-of-area sportspeople, and other recreational users. Potential exposure pathways associated with these receptor groups include incidental ingestion and dermal contact with CoPCs in soil, sediment, and surface water. These pathways will be considered for adults and older children. Young children (under the age of 5) are not expected to visit areas directly adjoining the river without supervision because of the natural hazards of children playing near a river. Given this supervision, it is expected that exposures to river water and sediments would not occur for young children. Nevertheless, given concerns identified by MDEQ, a scenario will be developed that will include assumed visits to the River for a child under 6 years of age. As described below, exposures during gestation and infancy will be evaluated through the application of toxicity values derived to be protective of this life-stage.

6.2.2.5 Anglers — Fish Consumption

Anglers who fish the Tittabawassee River and consume the fish they catch will be evaluated in the HHRA using consumption rates to be developed primarily from the UMDES survey data. Specifically, the UMDES provided data on consumption of a wide variety of fish from the Tittabawassee River among adults who had lived at their current address within the Study Area for more than 5 years. These data will be evaluated to identify the degree of consumption of fish from the Tittabawassee River. The HHRA proposes to address childhood intake rates based on adult rates and if an Activity Survey is conducted it will include collection of children's intake data.

During fishing activities, incidental contact with river surface water, soil, and sediment may occur. In general, the limited frequency of contact with sediment and surface water by anglers is unlikely to result in significant exposure to CoPCs. This view is consistent with that determined by MDCH for PCB exposures in their *Health Consultation for Allied Paper/Portage Creek/Kalamazoo River* (MDCH 1997). In that document, it is stated: "moist sediments might adhere more strongly to skin than drier soil, but river water would tend to wash the sediments off before the soiled skin reaches the mouth or food." For surface water ingestion the amount of water intake (30ml/event) is also minimal and unlikely for an

¹⁴ For the purposes of this WP, "other recreation" excludes angling and hunting which are evaluated separately.

angler. Although exposure to CoPCs is expected to be low, the HHRA will include evaluation of exposure to CoPCs in soils, sediments, and surface water for anglers. .

6.2.2.5.1 Subpopulations with High Fish Consumption

An initial evaluation was completed to determine whether there are subpopulations with relatively higher fish consumption rates than the general population, and particularly whether there is a definable subpopulation that consumes fish at a subsistence level. Subsistence consumption is defined here as use of a self-caught food resource as a primary protein source in the diet. Native Americans living in settings where they engage in traditional lifestyle activities (EPA 1997a) have been identified as consuming higher amounts of fish than the general population or than Native Americans who are no longer living within a traditional community. In addition, Asian Americans have also been identified as a group with a high level of fish consumption, but much of this consumption was of grocery store fish (EPA 1999).

The UMDES collected comprehensive data regarding the demographics of the study populations. As indicated in the results of the UMDES analysis, no substantial population of Native Americans or Asian Americans was identified living in or near the Study Area. Specifically, the UMDES (Questionnaire H2) indicated that less than 3% of the population identified themselves as within the subset that could include Native American heritage or Asian and Pacific Islander heritage. Similarly, the U.S. Census for Midland indicates that 0.3% of Midland County residents are of Native American heritage, 1.7% are Asian American, and 95.9% are Caucasian.¹⁵ These demographics would suggest that subsistence consumption is unlikely in this area. However, this issue will be considered further with The Saginaw Chippewa Tribe of Michigan, which agrees that a smaller study with input from Ziibiwing Cultural Center and/or Seventh Generation and interviews with elders may be sufficient to evaluate if cultural/spiritual uses are different from general public uses.

In addition, the Michigan Department of Community Health suggests, in their Intercept Survey, that subsistence fishing on the Tittabawassee River is not likely or prevalent, e.g. in response to Question 8 of the survey inquiring about the number of meals in the last 7 days from “this water body,” (and the water body recorded was the Tittabawassee) the largest number was two (1 respondent; 9 respondents said one, all 270 others said zero or did not answer), and the largest claimed typical number was 10 meals per month (Question 11; one respondent, with one respondent each claiming 6, 5, 4, and 3 meals/month as typical, 4 two meals per month, 7 one meal per month, and 263 zero meals or not responding). Since such intercept surveys are typically biased to identifying individuals who spend more time fishing, these data

¹⁵ <http://quickfacts.census.gov/qfd/states/26/26111.html>

probably over-represents the average fish ingestion among the population using this resource. Consequently, there does not appear to be an identifiable subsistence subpopulation within the Tittabawassee River Study Area and thus the HHRA will develop a fish consumption rate representative for all fish consumers along the Tittabawassee River Study Area and this will be used as the basis for risk estimates in the HHRA. .

6.2.2.6 Hunters — Consumption of Wild Game

Individuals who hunt within the Study Area and consume the game they harvest will be considered in the HHRA. Potential exposure pathways include incidental ingestion and dermal contact with CoPCs in soil, sediment and surface water as well as consumption of CoPCs in game. Adults and children will be considered. In general, the limited frequency of contact with sediment and surface water by hunters is unlikely to result in significant exposure to CoPCs. The rationale given for the angler previously, that these exposure pathways are likely to be limited, is also relevant to this receptor group. In particular, exposure to sediment is considered likely to be insignificant. However, hunter's potential exposure to soil/sediment and surface water will be considered within the HHRA.

6.3 ANALYTICAL CHEMISTRY DATA ANALYSIS AND IDENTIFICATION OF CoPCs

This section describes the process used to screen analytical chemistry data to identify CoPCs to be carried through the HHRA. These processes are necessary to ensure that appropriate and reliable data are carried through the quantitative steps of the HHRA. Dow plans to meet and collaborate with MDEQ on analyses to be carried out to select CoPCs. This section discusses the sources of sampling and analytical data, and the criteria that will be considered in selecting the CoPCs. The analytical data will be grouped according to exposure media (e.g., soil) and land use, and then evaluated through a step-wise process described here to select the appropriate CoPCs to be assessed for each exposure scenario.

6.3.1 Summary of Concentration Data to Be Used for Identification of CoPCs

The HHRA will summarize all TAL data in tabular form (these data will be made available both in hard copy and electronically). The data will be categorized according to environmental medium, location, and land use (current and potential future). Considerations will include location relative to the Study Area and relative to the Midland plant (e.g., first river mile, next 3 miles, last 5 miles and by location relative to the river within 100-yr, outside 100-yr). Primary reliance will be placed on data to be gathered during this RI as described in prior WP sections and in Appendix HHRA C, but the HHRA will also include

review of historical data once these data are reviewed by Dow and MDEQ and determined to be representative and accurate for use in the HHRA. Site-specific data to be considered include the following:

Soil –Site-specific data available include:

For MIDLAND Study Area:

- (Dow 1984 Study): Agin et al. 1984. Point Sources and Environmental Levels of 2378-TCDD (2,3,7,8-Tetrachlorodibenzo-p-Dioxin) on the Midland Plant of The Dow Chemical Company and in the City of Midland, Michigan. November.
- EPA. 1985. Study of Dioxin and Other Toxic Pollutants, Midland, Michigan. Region IV. April
- MDEQ. 1997. Summary of 1996 Midland Dioxin Study Results. Working Draft of Document for Public Release. Waste Management Division. March.
- Dow. 2000. Soil Sampling Summary Report (Revised). March.

For River Study Area:

- MDEQ (2001). “Tittabawassee River Dioxin Study Area – Phase I Sampling Study” October 2001 (June 2002 revision).
- MDEQ (2002a). “Tittabawassee/Saginaw River Flood Plain – Information Bulletin” February
- MDEQ (2002b). “Tittabawassee/Saginaw River Flood Plain – Information Bulletin #2”.
- MDEQ (2002c) “Tittabawassee River Dioxin Study Area – Phase II Sampling Program (memo with data)”.
- MDEQ. (2002d) “Summary of Phase II Tittabawassee River Flood Plain Sampling (Report)”. June 2002.
- MDEQ. 2003. “Phase II Tittabawassee/Saginaw River Dioxin Flood Plain Sampling Study” (Final Report) June 2003.
- Taylor, A.B., and J.M. McCabe. “ Baseline Chemical Characterization of Saginaw Bay Watershed Sediments” MDEQ: August 2002.
- CH2M Hill. 2005a. Tittabawassee River Floodplain Scoping Study Work Plan-Revised. July.
- UMDES, 2006

Sediment (River Study Area)

- Amendola, G.A., and D.R. Barna. “Dow Chemical Wastewater Characterization Study – Tittabawassee River Sediments and Native Fish”. EPA-905/4-88-003: July 1986.

- MDEQ. (2003) “Phase II Tittabawassee/Saginaw River Dioxin Flood Plain Sampling Study” (Final Report) June 2003.
- Taylor, A.B., and J.M. McCabe. “Baseline Chemical Characterization of Saginaw Bay Watershed Sediments” MDEQ: August 2002.
- CH2M Hill. 2005b. Tittabawassee River Sediment Dioxin/Furan Concentration Variability. March.
- CH2M Hill. 2005c. Tittabawassee River Sediment Dioxin/Furan Concentration Vertical Variability – Revision 1. July.

Surface water

- MDEQ (2002b). “Tittabawassee/Saginaw River Flood Plain – Information Bulletin #2”.

Fish

- Tittabawassee River Aquatic Ecological Risk Assessment. Polychlorinated Dibenzo-p-Dioxins Polychlorinated Dibenzofurans. Galbraith Environmental Sciences LLC., October 2003.

Game

- Tittabawassee River Aquatic Ecological Risk Assessment. Polychlorinated Dibenzo-p-Dioxins Polychlorinated Dibenzofurans. Galbraith Environmental Sciences LLC., October 2003.

Vegetation

- UMDES 2006

Agricultural animal products

- MDEQ (2002b). “Tittabawassee/Saginaw River Flood Plain – Information Bulletin #2”)

6.3.2 Methods for Screening of TAL to Determine CoPCs

The CoPCs will be selected through comparison of the site TAL data to be gathered in the RI and any relevant data from sources summarized in Section 6.3.1 to available media and exposure pathway-specific screening concentrations to identify chemicals that could potentially pose a health risk. Concentrations of each TA in each exposure medium will be compared with the applicable and relevant Michigan and EPA human health-based cleanup values and metals concentrations will be compared to background concentrations. The purpose of the screening process is to focus the quantitative assessment on the chemicals that are site-related (i.e., not background), on the exposure pathway(s) that might pose a significant risk, and on the compounds that exceed the appropriate screening criteria.

6.3.2.1 Comparison to Background Concentrations

The first screening step will be to compare Study Area soil and sediment data for metals to State of Michigan derived background concentrations (MDEQ 2005b), and potentially to site-specific derived background concentrations. Background concentrations will only be used if the location where they were collected is determined to be representative of Study Site soils in terms of both the soil type and the area land use.

6.3.2.2 Comparison to MDEQ Benchmarks or EPA Risk-Based Concentrations

6.3.2.2.1 Soil and Sediment

Chemicals detected in soil or sediment at concentrations greater than background will be compared with the MDEQ or other generic cleanup criteria for soil. As noted above in Section 6.1.2, The HHRA will derive a site-specific residential DCC for PCDD/Fs. Once this process is completed, it is anticipated that this value would be used to screen site data for PCDD/Fs. TAs with a sample result greater than the applicable MDEQ pathway criteria or, where MDEQ criteria are not available, greater than EPA risk-based concentrations, will be carried forward in the HHRA as CoPCs. If a health-based cleanup or benchmark value is not available from MDEQ, health benchmarks will be considered from the following EPA sources.

- United States Environmental Protection Agency (EPA) Region 9 Preliminary Remediation Goals (PRG) Tables. These values can be accessed on the Internet at: <http://www.epa.gov/region09/waste/sfund/prg/index.htm>.
- EPA Region 6 Human Health Media-Specific Screening Levels. These values can be accessed on the Internet at: http://www.epa.gov/earth1r6/6pd/rcra_c/pd-n/screen.htm

Where chemicals do not have risk-based concentrations or cleanup criteria available in any of the above resources, the HHRA will attempt to identify appropriate risk-based concentrations based on toxicological literature or suitable surrogate chemicals for comparison (in that order). Where such risk-based concentrations are derived, the HHRA will provide all assumptions and data relied upon to MDEQ. Specifically, consistent with requirements in MDEQ Rule 706(3), the HHRA will provide the necessary data to calculate a criterion unless through coordination with MDEQ it is determined that a numerical criterion is not required to assure the remedial action will be protective.

6.3.2.2.2 Inhalation of Soil Particulates

As described further in Section, 6.4.3.5, MDEQ provides soil criteria derived to be protective of the inhalation of airborne dust (Part 201 Rule R 299.5726). These values will be used to screen TA soil

concentrations to identify CoPCs, which may pose unacceptable dust inhalation health risks. Where TA concentrations are greater than the MDEQ soil inhalation criteria, this pathway will be evaluated for the identified CoPCs.

6.3.2.2.3 *Direct Contact with Sediment*

Although there are no MDEQ criteria derived for sediments, the soil direct contact criteria available from MDEQ (Part 201 R 299.5720) provide a health protective means to evaluate direct contact with sediments and are proposed for use in screening sediment concentrations in the HHRA. TAs with a sediment concentration greater than the MDEQ soil direct contact criteria will be carried forward in the HHRA as a CoPCs.

6.3.2.2.4 *Fish and Game*

TAs detected in fish tissue will be compared with risk-based concentrations for fish tissue derived by EPA Region 3. These chemical specific, risk based concentrations are derived by Region 316 to be protective of lifetime consumption of 54 g/day of fish tissue assuming a 10⁻⁶ cancer risk or a hazard index of 1.0. TAs with a sample result greater than the risk-based concentration for that chemical, will be carried forward in the HHRA as CoPCs. Because the representative intakes for fish tissue in the Study Area have not been determined at this time, if the intake amount for fish tissue is determined to be more than 54 g/day, the EPA Region 3 risk-based concentrations will be adjusted downward to reflect the higher assumed fish consumption rate.

There are no known risk-based concentrations for game. It is proposed that the EPA Region 3 risk-based concentrations for fish be applied to chemical concentrations in game as well following any necessary adjustments of the risk-based concentrations to reflect the consumption rate for the game tissue being evaluated. Where chemicals do not have risk-based concentrations available in the Region 3 tables, the HHRA will attempt to identify appropriate risk-based concentrations based on toxicological literature or suitable surrogate chemicals for comparison (in that order). Where such risk-based concentrations are derived, the HHRA will document all assumptions and data relied upon. Any remaining TAs without risk-based concentrations will be considered in the uncertainty assessment.

¹⁶ <http://www.epa.gov/reg3hwmd/risk/human/info/cover.pdf>

6.3.2.2.5 *Surface Water*

TAs detected in Tittabawassee River water will be compared with MDEQ risk-based concentrations for drinking water, where available, or to EPA Region 9 risk-based concentrations for drinking water. This will provide a highly protective means to evaluate whether a chemical could pose a risk because both of these risk-based concentrations assume consumption of water as drinking water, whereas Tittabawassee River water is not used as drinking water and exposure is expected to consist of incidental ingestion and dermal contact related to recreational visits to the River. Screening of surface water will be determined collaboratively with MDEQ.

6.4 **EXPOSURE ASSESSMENT**

Exposure assessment is the process of identifying human populations that could potentially contact CoPCs and estimating their exposures, doses, exposure rates, or dose rates through evaluation of the magnitude, frequency, duration, and route(s) of potential exposures. Specifically, quantitative exposure estimates for the hypothetical RME will be derived for all complete exposure pathways identified above and summarized in Section 6.4.1. Section 6.4.1.3 provides an overview of proposed methods to use exposure data from UMDES in deriving exposure estimates. The proposed means to quantify exposures in the SLRA is provided in Section 6.4.3 and for the PRA in 6.4.4, with details regarding chemical specific parameters provided in Section 6.4.5. Sections, 6.4.1 through 6.4.6 provide the proposed parameters to be applied in the HHRA. Dow will work with MDEQ to refine the approach to exposure assessment including prioritizing data collection efforts and selecting appropriate exposure parameters for the assessment.

In the HHRA, potential site risks will be estimated using conservative exposure assumptions (i.e., assumptions designed not to underestimate risks, and which may overestimate risks). As described above in Section 6.1.1.2, two tiers of risk assessment are proposed:

- **Screening Level Risk Assessment (SLRA)** that will use RME variables (i.e., assumptions representing high end exposure and toxicity assumptions) and will be used to evaluate which CoPCs/receptor/pathway combinations to carry forward into the second tier assessment: Proposed risk targets to be used in deciding what will be further evaluated in the PRA are described above in Section 6.1.1.2.
- **Probabilistic Risk Assessment (PRA)** is the second, more refined view, of potential risks and will incorporate the distributions of inputs on all relevant exposure variables in order to

better characterize both the variability and uncertainties in the risk estimates. The PRA will encompass RME assumptions.

The SLRA and PRA will use the same basic algorithms for calculations, but will carry out estimates as point estimates (SLRA), or as distributions of risk estimates (PRA). The algorithms to be applied in exposure estimates draw from the methodology and apply the variables used in MDEQ Part 201 Administrative Rules cleanup criteria for pathways where cleanup criteria have been identified. For pathways where cleanup criteria are not available (i.e., recreational use pathways and food ingestion pathways) algorithms and variables have been proposed here based on standard mass-balance methodology to be as consistent as possible with MDEQ cleanup criteria and EPA risk assessment guidance. For site-specific exposure data, the HHRA proposes to draw from the UMDES data (see Section 6.4.1.3) as supplemented by additional analyses by UMDES and by data to be gathered in the Activity Survey.

6.4.1 Receptors and Exposure Pathways

6.4.1.1 Receptors

The draft HHRA will initially examine the following receptors:

- **Residents (Adults and Children)** Residents involved in activities within the Study Area boundaries, including activities around their homes and yards including vegetable gardening
- **Workers (Adults):** People who currently work within the Study Area now, or reasonably anticipated future workers will be considered.
- **Resident Farmers (Adults and Children):** Farmers within the Study Area who eat some of the food products they raise and or grow. Adults and children will be assumed to consume farm products from the Study Area
- **Anglers (Adults and Children):** Anglers who fish within the Tittabawassee River Study Area and eat the fish they catch at least occasionally. Adult and children will be assumed to consume fish caught within the River Study Area.
- **Hunters (Adults and Children):** Hunters within the Study Area, who eat the game they harvest at least occasionally. Adults and children will be assumed to consume game collected from the Study Area.
- **Recreational Visitors (Adults and Children):** People who visit the Study Area for recreation purposes other than fishing or hunting.

6.4.1.2 Complete Exposure Pathways to be Evaluated in the SLRA

For evaluation in the SLRA, each exposure pathway risk will be evaluated separately. The object of the SLRA is to identify receptor and pathway combinations that need to be more fully evaluated. Individual pathway/receptor combinations will therefore be evaluated, rather than attempting to combine multiple pathways. The following exposure pathways will be examined in the SLRA:

Resident exposure to soil (adults and children)

- Soil and dust ingestion (associated with the residence)
- Soil dermal contact (associated with the residence)
- Dust inhalation (associated with the residence)
- Dust inhalation (associated with adjacent farming)
- Consumption of home-grown vegetables, if needed

Worker exposure to soil (adults)

- Soil and dust ingestion (associated with the workplace)
- Soil dermal contact (associated with the workplace)
- Dust inhalation (associated with the workplace)

Farmers in River Study Area who consume farm products (Adults and Children)

- Soil and dust ingestion (associated with the farm residence)
- Soil dermal contact (associated with the farm residence)
- Dust inhalation (associated with farm residence)
- Soil and dust ingestion (associated with farming)
- Dust inhalation (associated with farming)
- Farm animal product ingestion (meat, dairy products, eggs)

Recreational visitor (adults and children) exposure to soil, sediment, Tittabawassee River water during recreation in the River Study Area:

- Soil, sediment, dust and surface water ingestion
- Soil, sediment, and surface water dermal contact
- Dust inhalation

Anglers on Tittabawassee River who consume fish (Adults and Children)

- Fish ingestion
- Soil, sediment, dust and surface water ingestion
- Soil, sediment, and surface water dermal contact

- Dust inhalation

Hunters in River Study Area who consume game (Adults and Children)

- Game ingestion
- Soil, sediment, dust and surface water ingestion
- Soil, sediment, and surface water dermal contact
- Dust inhalation

6.4.1.3 Combinations of Receptors and Pathways for the PRA

Receptor/pathway combinations that are not shown to be negligible in the SLRA will be incorporated in the PRA in a manner consistent with EPA risk assessment guidance. In the PRA, multiple combinations of pathways will be combined for single receptors, taking account of the correlations between exposure variables that are present (through, for example, there being only 24 hours per day), and that occur in the population as observed in the UMDES and the activity survey (e.g. hunter/anglers cannot spend all their time both hunting and fishing).

6.4.2 Proposed Use of UMDES Data

Many of the parameters needed for exposure assessment were measured in a subset of the target population by the UMDES. Future discussions with MDEQ and interaction with the UM researchers, will be used to develop exposure assessment inputs from the current UMDES data. If an Activity Survey is conducted it will also be used to fill exposure assessment data gaps. While confidentiality requirements preclude obtaining individual and/or property-specific data from the UMDES, these data are the best available for exposure assessment in the Study Area, since they were obtained from a stratified random sample from the local population with known probability weights for selection. The UMDES data so far published are limited in their detail, although in most cases they may be sufficient to define the upper end of exposure distributions.

Dow will work with MDEQ and the UMDES researchers to develop these data for use in the HHRA. More detailed (but still anonymous) information will be requested on selected UMDES exposure parameter distributions in the population in or near the contaminated area (excluding the Jackson/Calhoun county control area) for use in the SLRA and PRA. It is expected that the full distribution of the measured parameters, together with uncertainty estimates, can be obtained either in the form of percentiles (initially we envision using the 1%, 99%, and multiples of 5%; see also Footnote 8), or as parametric estimates for fits to distribution shapes. In the former case, parametric forms will be fitted to

the percentiles for use in the PRA. In either case, the parameter estimates obtained will be accompanied by uncertainty estimates and correlation matrices for the parameter and uncertainty estimates to ensure that the correct error and correlation structure is maintained. Parametric distributions will be used to ensure that potentially long tails to the distributions (not reflected in available percentiles, for example) are taken into account. Table 6-2 summarizes proposed types of information from the UMDES data to be applied in the HHRA.

Table 6-2- Proposed Types of Information from the UMDES to be Applied in the HHRA

Question(s) or derived results	Summary of information, and potential inferences (Other information or assumptions may also be necessary).
AA1; A1	Age and sex distribution
A3; A4; BMI	Height, weight, BMI distribution. Height vs. weight distribution.
B1	Years lived in Midland county, Saginaw County, or Williams township in Bay county. Residence period in local neighborhood.
B4b2-B4b1	Number of years in current residence. Distribution of residence periods.
C3	Vegetable gardens identified by participants. Distribution of period eating homegrown vegetables.
C5; C6; C6a	Current vegetable./flower garden present. Fraction of population actively using garden.
E1; E2–E8	Fishing in TR. Distribution of total period fishing in TR & other MI rivers & lakes.
E7; E8–E12	Hunting in TR FP. Distribution of total period hunting in TR FP & other MI areas.
E13; E14–E18	Recreational. Distribution of total periods recreating around TR & other MI rivers & lakes. ^a
F2, F3	Eating game meat and liver of game meat. Distribution of total period.
F10	Eating locally caught fish. Distribution of total period eating fish from TR, SR, SB.
F11–F13	Fish trimming methods. Fraction of fish eaters trimming in various ways.
G3–G10& ancillary	Homegrown and game meat from TR FP and other areas. Distributions of numbers of meals per year. G6c gives the fraction eating deer liver. G7a the fraction eating skin from various birds.
G13; G14	Fish from TR, SR, SB combined; fish from KR (<1%)
G19–G49	Fish consumption. Distributions of numbers of meals per year, by type of fish, and by area, including separately the TR.
G51	Eggs from TR FP and other areas. Distribution of numbers of meals per year.
G52; G53	Milk and dairy products from cows in the TR FP and other areas [probably only one person with positive response in the TR FP]. Probability for consumption; distribution of quantities may have to be extrapolated from elsewhere because of low numbers.
G54a; G54b	Root vegetables from own property or from TR FP. Distribution of number of root vegetable meals per year.

G55a; G55b	Other fruit/vegetables from own property or from TR FP. Distribution of number of other fruit/vegetable meals per year.
<p>TR: Tittabawassee River; SR: Saginaw River; SB: Saginaw Bay; KR: Kalamazoo river; FP: flood plain “Distributions” here include the fractions of the population involved. In all cases, it may be possible to infer information about distributions of numbers of meals per year for foodstuffs from the TR FP from the same questions asked for other areas.</p>	

^aThe UMDES definition of (non-fishing, non-hunting) recreational use (questions E13–E18) was all-inclusive. The questionnaire directed respondents to consider the following list of activities (UMDES, Respondent Booklet, Version 4-04-05). *Activities in the water*: Water skiing, Swimming, Snorkeling, Water tubing; *Activities on the water*: Boating, Canoeing, Kayaking, Rafting; *Activities in areas surrounding the water*: Camping, Jogging, Walking, Using parks along the river, Picnicking, Biking, Any other activity

For a further discussion of the UMDES data, and how the HHRA proposes to use these data, see Section 6.1.3

6.4.3 Quantification of Exposure Variables in the SLRA

6.4.3.1 General Treatment of Variables with Known Distributions in the SLRA

The SLRA is designed to be a screening level assessment, so exposure variables will be evaluated using an approach designed to evaluate RME (reasonably maximally exposed) receptors. To this end, two of the exposure variables (excluding the concentration term) in the exposure algorithms for each pathway will be selected at the mean of the uncertainty distribution of the 5th or 95th percentile value of their variability distributions, whichever corresponds to estimating higher risk. The variables to be selected will be chosen, as far as possible, to have a logarithmic sensitivity¹⁷ of +1 (*i.e.* to be direct multipliers of the dose estimate), otherwise to have as high a sensitivity as possible; and to have the largest relative variability.¹⁸

The exposure concentration term will also be selected at the upper 95th percentile of both its uncertainty and variability distributions (EPA 1989).¹⁹ All other exposure variables will be chosen at the mean of the uncertainty distribution for the mean of the variability distribution (*i.e.*, to represent central tendency

¹⁷ That is, the derivative of the logarithm of dose with respect to the logarithm of the variable, evaluated at the mean values of all variables.

¹⁸ This is necessarily a somewhat imprecise concept, since various useful measures (*e.g.* the ratio of 95th to 5th percentile) might be zero or infinity or not exist. For definiteness, the coefficient of variation (standard deviation divided by mean), or an estimate of it, will be used. For the variables used in risk assessment, this is expected to always exist.

¹⁹ In many cases, the appropriate concentration term is itself a time or space average; such averaging will be taken into account in defining the variability and uncertainty distributions.

values). The “mean” is understood to indicate an estimator of the mean value, chosen either to be as unbiased as available or to be a selected nominal value, and similarly as unbiased estimator of the 95th percentile as available will be chosen, or again a selected nominal value.²⁰ The most likely candidates for selection at upper 95th percentiles are: for cancer estimates, the exposure period and contact rate or frequency; for non-cancer estimates, the contact rate and frequency.

The following sections describe the proposed approach to quantifying all complete exposure pathways within the SLRA including proposed exposure algorithms, and input variables, or the means to derive input variables. Dow plans to meet and collaborate with MDEQ on the development and implementation of the exposure assessment including the selection of parameter values proposed here.

6.4.3.2 Common Receptor Characteristics – Body Weight, Averaging Time, and Exposure Duration

Since the approach to evaluation of body weight and averaging time is common to all pathways, the proposed approach to these elements is described here. Dow will work collaboratively with MDEQ to identify appropriate exposure assessment values.

6.4.3.2.1 Body Weight Assumption in SLRA

The nominal body weights of a 70 kg adult and a 15 kg child, as identified in the Part 201 soil direct contact criteria (R 299.5720), will be used in the SLRA. For a recreational scenario of an older child visiting the River Study Area, a body weight of 49 kg is proposed, corresponding to the average of the mean body weights of boys and girls ages 8 to 18 as calculated from data in the Exposure Factors Handbook (EPA 1997a, Table 7.3).

6.4.3.2.2 Averaging Time

As is typically done and scientifically required, the inputs and outputs for the algorithms are proposed to be time averaged as appropriate for evaluations of the adverse effects evaluated (EPA 1989). Thus, for example, cancer risk estimates for most CoPCs require dose rate estimates averaged over a lifetime, while estimates of acute risks require dose rates or total doses averaged or cumulated over periods ranging from minutes to years or longer, depending on the adverse effect and the CoPC in question.

²⁰ Selected nominal values will be used where these are specified by MDEQ for use in particular pathways; the same nominal values may also be used in other pathways for the same parameter.

Except as noted below, the averaging period for the SLRA is proposed as 30 years for non-carcinogens (corresponding to the exposure period of 30 years, 6 years as a child and 24 years as an adult), and 70 years for carcinogens (corresponding to the nominal lifetime used in extrapolation of carcinogenicity results to humans).

Where adverse effects occur only in particular sensitive subpopulations (or to a greater extent in such a subpopulation), such as fetuses, neonates, or children, the appropriate averaging time will be used to obtain the relevant dose metric that is causally connected to the relevant adverse effect. However, the averaging time and estimated intakes will be chosen to be consistent with the evaluation of the underlying toxicity criteria. For example, the current WHO TDI is specifically targeted at limiting long-term adult intake of PCDD/Fs to levels that will maintain maternal body burdens below levels of concern in order to protect the developing fetus and nursing infant. Therefore, these sensitive subpopulations (fetus, infants and children) are already accounted for in exposures that culminate in maternal body burdens. In this context, a risk assessment using this criterion should be based on long-term adult intake rates, not infant or childhood intake rate (except to the extent that such intake rates affected adult body burdens).

6.4.3.2.3 *Exposure Duration*

Exposure duration estimates in the SLRA are proposed to be those identified in the MDEQ cleanup criteria including 24 years for an adult, and 6 years for a young child. In addition, the older child scenario will assume 10 years of exposure. For the hunting, fishing, and other recreational scenarios where no MDEQ guidance is available, duration of exposure is proposed to correspond to duration of residence (evaluated from the UMDES data, national data, the Activity Survey (if conducted), other local data, or some combination, see Sections 6.4.3.1 and 6.4.4.3.3.); or of participation in the activity (see individual pathway discussions, below).

6.4.3.3 *Incidental Ingestion of Soil/Dust or Sediment*

Incidental ingestion of soil/dust by adults and children occurs presumably by mouthing hands, objects, and surfaces, including food and cigarettes that have soil or dust on them. Although sediment ingestion has not been directly studied, it is typically assumed that direct contact with sediments may also result in incidental ingestion through the same mechanisms. Exposures via the incidental ingestion pathway are expected to be higher in young children because childhood hand-to-mouth behavior is more frequent, and because on a body weight basis the amount of soil or dust ingested is greater than in either older children or adults.

6.4.3.3.1 Estimates of Incidental Ingestion of Soil/Dust for Residents and Workers

Assessment of the soil/dust ingestion pathways in the SLRA is proposed to be based on the exposure terms in algorithms identified in MDEQ R 299.5720 as follows:

Equation 1

$$\text{Average Daily Dose (ADD)} = (\text{Cs} \times \text{CF} \times \text{IR}_s \times \text{EF} \times \text{ED} \times \text{AE}_i) / (\text{AT} \times \text{BW})$$

- ADD = average daily dose (mg/kg-day)
- Cs = chemical concentration in soil (mg/kg)
- CF = 10⁻⁶ conversion factor: per kg soil to per mg soil
- IR_s = ingestion rate for soil (mg/day)
- ED = exposure duration (years)
- EF = exposure frequency (days/year)
- AE_i = chemical specific or default ingestion absorption efficiency as specified in R299.5720(3) except as noted in Section 6.4.5
- BW = body weight (kg)
- AT = averaging time (days)

For the SLRA, exposure to CoPCs through incidental soil ingestion is proposed to be calculated for each of the following receptors: child residents ages 1-6, adult residents; and adult workers using the following exposure terms as applied by MDEQ in the soil cleanup criteria. This includes assumed exposure frequencies for the resident, or worker of 350 days per year for an adult or a child resident, 245 days per year for a worker consistent with the MDEQ default assumptions as shown in Table 6-3.

Table 6-3: Exposure Assumptions for Residents’ and Workers’ Incidental Ingestion of Soil

Exposure terms	Receptors		
	Child resident (ages 1-6)	Adult resident	Adult worker
IR _s - Soil ingestion (mg/day)	200 mg/day	100 mg/day	100 mg/day
EF - Exposure frequency (days)	350 days	350 days	245 days
ED - Exposure duration (years)	6 years	24 years	21 Years

Source MDEQ Part 201 Rule R 299.5720

6.4.3.3.2 *Incidental Soil or Sediment Ingestion During Hunting, Fishing, and Other Recreational Visits*

Hunters, anglers, and other recreational visitors are also proposed to be evaluated in the SLRA and as described above recreational visitors may be expected to have incidental contact with soil and sediments in recreational areas near or in the Study Area. There are no MDEQ cleanup criteria for sediment direct contact or for soil or sediment contact in areas used for recreation. Instead, MDEQ Part 201, Section 20120(a)(2) indicates that site-specific risk assessments can be conducted for direct contact with sediments and to evaluate exposures to CoPCs in media during in recreational activities. Since sediment exposures would occur during hunting, fishing and other recreational visits to the River Study Area this exposure pathway is proposed to be evaluated in each of these scenarios. To evaluate exposures to soil and sediments during recreational uses (hunting, fishing, and other recreation), the same algorithm (Equation 1) proposed for use in the evaluation of incidental ingestion of soil in residential or worker scenarios is proposed for this pathway.

Exposure assumptions proposed here were modified to better represent likely recreational exposure frequencies. These proposed exposure frequencies will be drawn from the UMDES survey of recreational activities around the Tittabawassee River, from the EPA Exposure Factors Handbook (EPA 1997a) (for adults), and from ad-hoc assumptions possibly to be supplemented or replaced by the Activity Survey results (for children). Hunters in Michigan must generally be over the age of 17, although persons as young as 10 may obtain hunting licenses (through supervising adults) subject to special rules (MDNR, 2006a; Michigan Hunting and Trapping Guide). There is no limit on the age of anglers, although those over 17 must purchase a license (MDNR 2006b; Michigan Fishing Guide 2006). However, it is considered that younger hunters and anglers (less than 18) were likely to be incidentally exposed to soil or sediments substantially less than adults, so only adult incidental exposures are proposed to be evaluated.

As described above, it is anticipated that a young child would not engage in hunting, fishing, or other recreational activities near or in the Tittabawassee River due to the natural hazards of playing near a river. However, as indicated above, a scenario will be developed to evaluate potential exposure for a child under the age of 6. In addition, a scenario is provided here based on children ages 8 to 18 is proposed and includes the following proposed exposure terms 10 year exposure duration including 54 visits or days a year derived assuming 3 visits per week during the 3 summer months and 1 visit a week during two spring and two fall months. The older child scenario also assumes a body weight of 49 kg, which represents the average of the mean body weights of boys and girls ages 8 to 18. This scenario also assumes soil ingestion of 100 mg/day.

6.4.3.3.2.1 *Exposure frequency and duration assumptions for recreational visitors*

The UMDES survey provides information on exposure durations and frequencies for various recreational activities. Survey questions in the E series (UMDES, questionnaire #E14) provide results for the question of how many days per lifetime (up until the time of the survey) and years per lifetime individuals visited the Tittabawassee River for various forms of recreation. These data are proposed for use in evaluation of frequency of contact with soil, sediments, and surface water in the SLRA. The methodology to be adopted to correct the survey information to lifetime exposure duration is described in Section 6.4.4.3.3.

For a hunter, in the SLRA assessment the fraction of time exposed for regular events (those assumed to occur on all hunting occasions) is proposed to be obtained from the results of the UMDES questionnaire (Question E8, number of days and years of hunting around the Tittabawassee flood plain). In the event further information from UMDES is not forthcoming, the fraction of time will be taken to be 20 days/year for the SLRA (the highest average for any distinct area is approximately 13 days/year in the UMDES questionnaire)

For an angler, in the SLRA the fraction of time exposed for regular events is proposed to be obtained from the results of the UMDES questionnaire (Question E2, number of days and years of fishing on the Tittabawassee River below the Tridge), in a similar fashion to that just described for the hunter. In the event further information is not forthcoming, the fraction of time is proposed as 40 days/year for the SLRA (the highest average for any distinct area is approximately 27 days/year in the UMDES questionnaire). For recreational activities other than fishing or hunting, in the SLRA duration of such activities and the fraction of time exposed for regular events is proposed to be obtained from the results of the UMDES questionnaire (Question E14 and E13, number of days and years of recreational activity in/around the Tittabawassee River below the Tridge). In the event further information is not forthcoming, the exposure frequency of 40 days/year in the SLRA (the highest average for any distinct area is 28 days/year in the UMDES questionnaire) is proposed for the SLRA.

Hunters in Michigan must generally be over the age of 17, although persons as young as 10 may obtain hunting licenses (through supervising adults) subject to special rules (MDNR 2006a; Michigan Hunting and Trapping Guide). There is no limit on the age of anglers, although those over 17 must purchase a license (MDNR 2006b; Michigan Fishing Guide 2006). However, it is considered that younger hunters

and anglers (less than 18) were likely to be incidentally exposed to soil or sediments substantially less than adults, so only adult incidental exposures are proposed to be evaluated.

Exposure duration for adults

Duration of exposure will be obtained from the published UMDES distribution for use in both the SLRA and the PRA (see Section 6.4.3.2.3).

Children

As described above, it is anticipated that a young child would not visit the Tittabawassee River due to the natural hazards of playing near a river; this anticipation may be confirmed or denied by the Activity Survey, if necessary. However, as indicated above, a scenario will be developed to evaluate potential exposure for a child under the age of 6. In addition, a scenario is provided here based on children ages 8 to 18 is proposed and includes the following proposed exposure terms for the SLRA: a 10-year exposure duration and exposure frequency of 54 visits a year. Table 6-4 summarizes proposed exposure assumptions for recreational visitors.

Table 6-4 Exposure Assumptions for Recreational Visitors' Incidental Ingestion of Soil and/ or Sediments

Exposure terms	Receptors Older child visitor (ages 8-18)	Adult Visitor
IR _s - Soil ingestion (mg/day)	100 mg/day	100 mg/day
EF - Exposure Frequency (days) older child	54 days ^a	--
EF - Exposure Frequency (days) hunter	--	20 days (UMDES Table E8)
EF - Exposure Frequency (days) angler	--	40 days (UMDES Table E2)
EF - Exposure frequency other (days)	--	28 days (UMDES E13 and E14)
ED - Exposure duration (years)	10 years SLRA	UMDES E8, E2, E13 and E14

^a Exposure frequency assumes 3 visits per week during the 3 summer months and 1 visit a week during two spring and two fall months

6.4.3.3 Residential Dust Findings From UMDES

People in the Study Area contact household dust within their residences and some part of this material could be ingested as part of soil ingestion rates. The TEQ concentration of dioxins, furans, and PCBs combined in dust is lower, on average, than soil around houses within the Tittabawassee floodplain (UMDES, 2000, data) although the pattern for individual congeners is mixed; the mean concentrations of all PCDF congeners except OCDF are lower in dust than in house perimeter soil, while the mean concentrations of all PCDD congeners except TCDD are higher in dust. Soil ingestion and contact rates

include any household dust ingestion or dust contact so the soil ingestion and soil contact pathways already incorporate dust ingested or contacted; and within the Study Area the soil ingestion and contact pathway algorithms will likely, therefore, on average overestimate ingestion of and contact with TEQs of dioxins, furans, and PCBs combined from household dust. Dow and MDEQ will discuss these issues further.

The UMDES results (UMDES 2000, results) find no correlation between household dust concentrations and blood concentrations of any evaluated PCDD/F congeners. Thus while some individuals may be mis-specified by treating the soil and household dust pathways together, the population distribution of total intakes through soil and dust is likely to be overestimated by the soil ingestion and contact pathway calculations. Residential dust ingestion, therefore, is assumed to be included with soil ingestion; and for non-residential receptors there is no distinction between soil and dust. Dow and MDEQ will discuss these issues further.

6.4.3.4 Dermal Contact with Soil/Dust or Sediment

Individuals in the Study Area could be exposed to CoPCs by dermal contact with soil, dust or sediment. This scenario is proposed to be evaluated for all receptors that have soil or sediment contact including residents, workers, and hunters, anglers and other recreational visitors. Assessment of the dermal contact with soil in the SLRA are proposed to be based on the exposure terms in algorithms identified in MDEQ R 299.5720 as follows:

Equation 2

$$\text{Average Daily Dose (ADD)} = (C_s \times CF \times SA \times EV \times EF \times AF \times ED \times AE) / (AT \times BW)$$

- C_s = chemical concentration in soil (mg/kg)
- CF = 10⁻⁶ conversion factor: per kg soil to per mg soil
- SA = surface area for dermal exposure (cm²/event)
- EV = event frequency (1 event per day)
- EF = exposure frequency (days/year)
- AF = adherence of soil mg/cm²
- ED = exposure duration (years)
- AE = dermal absorption fraction from soil (unitless) 10% for organic CoPCs 1% for inorganics, the defaults of R29.5720(3), except as indicated in Section 6.4.5.3
- BW = body weight (kg)
- AT = averaging time (days)

The event frequency is set to be 1 event per day in all scenarios, to be consistent with the methodology adopted for evaluation of event frequency, adherence of soil, and the dermal absorption fraction.

6.4.3.4.1 Dermal Contact with Soil for Residents and Adult Workers

Table 6-5 provides proposed exposure variables to be used for the SLRA for dermal contact with soil and dust for residential and worker receptors. These values are all consistent with the Part 201 exposure variables.

Table 6-5 Exposure Assumptions for Residents’ and Workers’ Dermal Contact With Soil

Exposure terms	Receptors		
	Child resident (ages 1-6)	Adult resident	Adult worker
SA . Skin surface area (cm ²)	2,670 cm ²	5,800 cm ²	3,300 cm ²
EF – Exposure frequency (days)	243 days	243 days	160 days
AF – Soil adherence factor (mg/cm ²)	0.2 mg/cm ²	0.07 mg/cm ²	0.2 mg/cm ² (industrial and commercial I)
ED - Exposure duration (years)	6 years	24 years	21 Years

Source MDEQ Part 201 Rule R 299.5720

6.4.3.4.2 Dermal Contact with Soil or Sediments During Hunting, Fishing, and Other Recreational Use

Hunters, anglers, and other recreational visitors are also proposed to be evaluated in the SLRA. As described above recreational visitors might be expected to have dermal contact with soil and sediments in recreational areas in the Study Area. There are no MDEQ cleanup criteria for sediment dermal contact or for incidental soil or sediment contact in areas used for recreation. Instead, Part 201 contains a provision in Section 20120(a)(2) and further in Part 201 Rule R 299.5730(1)(o) that allows for site-specific criteria, the equivalent of a site-specific risk assessment for human direct contact with sediments. Because soil or sediment exposures could occur during hunting, fishing and other recreational visits to the Tittabawassee River this exposure pathway is proposed to be evaluated in a hunting, a fishing, and an ‘other recreational use’ scenario (collectively recreational scenarios) using the same the same algorithm (Equation 2) provided above in Section 6.4.4.5. Exposure frequency and duration assumptions used for the soil ingestion pathway in the recreational scenarios are also proposed to be applied as described above in Section 6.4.3.3.2.1 will also be applied to the dermal contact pathway.

For the adult recreational visitors the adult skin surface area will be taken to be 3,300 cm²/event, corresponding to the industrial adult worker default (R299.5720.) considering the likelihood of a similar clothing scenario among these receptor types (this assumption may be modified based on observations during the Activity Survey). For the older child scenario a surface area of 3,278 cm² is assumed which represents 25% of the 50th percentile whole body surface area of children ages 6²¹ to 18 taken from Tables 6.6 and 6.7 of EPA (1997a). As indicated above, a scenario will be developed to evaluate potential exposure for a child under the age of 6. The adherence factors proposed for these pathways are those proposed for the residential scenarios (Table 6-5), with values for young children applied to the older children also.

It will also be assumed that hunters, anglers, or other recreational visitors will occasionally have a high exposure event in the form of “muddy hands” (corresponding to handling wet soil, soil-encrusted boats, soil-encrusted vegetation, or other intimate soil-hand contact. For anglers and hunters, such events will be assumed to occur every other day of the activity, while for recreational visitors such events are expected to be rare (once per year). In addition, a muddy feet event will be assumed to occur once per year for an angler. This would correspond to losing a shoe while traversing boggy ground (such events are expected to be unpleasant enough to discourage frequent recurrence). The adherence factors and surface areas for muddy hands and muddy feet events will be evaluated as described in Appendix HHRA D, part D-1. This assumption will also be further considered relative to site-specific conditions relative to the nature of the soil or sediment contact (e.g., contact with sand may be considered to result in less adherence than contact with clay).

6.4.3.5 Inhalation of Dust

There is potential for exposure to CoPCs in soil following re-suspension of dust from soil. However, much of the dust that is inhaled is ultimately swallowed, so soil ingestion estimates may already incorporate some inhaled dust. Soil ingestion studies that will be used in the HHRA are of this nature. Insofar as tracer concentrations are the same in soil and dust, soil ingestion studies necessarily cannot distinguish dust inhalation from soil ingestion. Similarly, because as exposure point concentrations of CoPCs in the study area are similar to exposure point concentrations used for soil and dust ingestion, soil and dust ingestion estimates will already incorporate inhalation dust exposures similar to those occurring during the ingestion studies that form the basis for soil ingestion rate estimates.

²¹ Data were not available in EPA (1997) to distinguish the 8-18 group so data from 6-18 were used here.

In normal circumstances where CoPC concentrations in soil and dust are likely similar, and dust generation is not excessive, dust exposures are much smaller than those due to soil ingestion, so the preceding argument becomes somewhat academic. This much smaller exposure is apparent in the MDEQ screening values for soil, where it is possible to compare such screening values for soil direct contact (ingestion plus dermal contact) versus dust inhalation. For 2,3,7,8-TCDD the MDEQ Table 2 (R299.5746) shows the residential particulate soil inhalation criterion (PSIC) as a concentration of 71 $\mu\text{g}/\text{kg}$ for 2,3,7,8-TCDD, while the corresponding criterion for the residential direct contact pathway is 0.09 $\mu\text{g}/\text{kg}$.

Nevertheless, there may be special exposure circumstances that might require special treatment of dust inhalation. Those relevant to the HHRA are:

- Farmers (dust inhalation while plowing)
- Other activities that involve generation of high amounts of dust such as earth moving in construction or road building.

However, the MDEQ soil screening value of 71 $\mu\text{g}/\text{kg}$ is much higher than any concentration identified to date in soil. Even when adjusted (R299.5726 (6)) for a 100-acre area (rather than the default 0.5 acre area), the PSIC is 30.5 $\mu\text{g}/\text{kg}$. The MDEQ derived this concentration to be protective of inhalation of particulates over long-term residential exposure and included consideration of erosion from wind and from vehicle traffic. Although potentially dust-raising farming activities or heavy earth moving activities may episodically raise more dust than the vehicular traffic and wind erosion included in the MDEQ screening assessment, these activities take place infrequently and do not always take place during dry periods. Moreover, while farmlands may be of larger area than the area (up to 100 acres) for wind erosion included in the MDEQ screening assessment, the relevant concentration would correspond to the average over that large area; and the amount of time that farmland is in a condition allowing wind erosion is very limited. Thus, although the degree of dust generated during some dry and windy periods may be higher than that assumed for calculation of the Part 201 PSIC, exposures would not last for as long a period.

Preliminarily, this pathway will not be further evaluated except for special circumstances if the Activity Survey indicates air long-term average concentrations of dust (e.g. for farmers or construction workers) exceeding those predicted by the R299.5726 generic algorithms.

If adjustments are needed to further evaluate this pathway, the MDEQ technical support document on derivation of the generic PSIC indicates how it can be modified. Dow would consider modifying it to better represent heavy equipment use as in farming if MDEQ concurs and assists in the modification. If additional CoPCs are identified, the concentrations of these CoPCs in soils will be compared with the Part 201 generic screening values for this pathway with particular emphasis on soils in current agricultural areas, or areas that could potentially be used for agriculture in the future, and taking account of any dust measurements made in the Activity Survey.

6.4.3.6 Incidental Ingestion of Surface Water

Surface water ingestion will be evaluated for any CoPCs for which it is relevant (that is, for CoPCs that are detected in dissolved form in surface water, or adsorbed to particulate material present in surface water). This route of exposure is expected to be negligible for exposure to PCDD/Fs; an initial bounding estimate will be performed to test that hypothesis, and to determine whether more complex analysis is needed for any other CoPCs. Surface water ingestion is only expected to occur incidentally during hunting, angling, or other recreational activities on the Tittabawassee River, since surface waters are not used for human consumption. Part 201 cleanup criteria are not available for assessment of recreational exposure to surface water. Consequently, the general exposure algorithm identified in MDEQ R 299.5710 ia proposed, with exposure assumptions derived from both MDEQ and EPA.

Assessment of recreational visitors' potential exposure to CoPCs through incidental ingestion of surface water in the SLRA is proposed to be based on the following algorithm:

Equation 3

$$\text{Average Daily Dose (ADD)} = (C_w \times IR_w \times EF \times ED) / (AT \times BW)$$

- ADD = average daily dose (mg/kg/day)
- C_w = chemical concentration in water (mg/L)
- IR_w = ingestion rate for water (L/day)
- ED = exposure duration (years)
- EF = exposure frequency (days/year)
- BW = body weight (kg)
- AT = averaging time (days)

Exposure to CoPCs through incidental ingestion of surface water will be calculated for older children and adults in the hunter, angler, and other recreational scenarios as provided in Table 6-6. However, as indicated above, a scenario will be developed to evaluate potential exposure for a child under the age of 6.

The ingestion rate for surface water is 10 ml/day based on Part 4 Water Quality Standards Rule R 323.1057(4). The exposure durations and frequencies for the hunter, angler, and recreational scenarios are described in Section 6.4.3.4.2. Proposed exposure assumptions are summarized in Table 6-6.

Table 6-6 Exposure Assumptions for Hunter, Angler, and Other Recreational Visitor’s Incidental Ingestion of Surface Water

Exposure terms	Receptors	
	Older child visitor (ages 8-18)	Adult Visitor
IRw . Surface water ingestion (L/day)	0.01 L/day ^a	0.01 L/day ^a
EF – Exposure Frequency (days/yr) older child	54 days ^a	--
EF – Exposure Frequency (days/yr) hunter	--	20 days (UMDES Table E8)
EF – Exposure Frequency (days/yr) angler	--	40 days (UMDES Table E2)
EF – Exposure frequency other (days/yr)	--	28 days (UMDES E13 and E14)
ED - Exposure duration (years)	10 years ^a	UMDES E8, E2, E13 and E14

^aIntake of 0.1 L/ day assumed based on Part 4 Water Quality Standards Rule R 323.1057(4). Older child exposure frequency assumes 3 visits per week during the 3 summer months and 1 visit a week during two spring and two fall months

6.4.3.7 Dermal Contact with Surface Water

Dermal contact with surface water is proposed to be evaluated if relevant for any CoPCs (that is, for CoPCs detected in dissolved form in surface water). This route of exposure is negligible for PCDD/Fs because of their low solubility (and predicted low skin permeability), and is not proposed to be evaluated for PCDD/Fs. (Reddy et al. 2000). As for other recreational pathways, no MDEQ cleanup value is available but the following algorithm is proposed consistent with the general exposure algorithm identified in Part 201 Rule R 299.5712 and EPA (2004) guidance for dermal contact with CoPCs in water.

Equation 4

$$\text{Average Daily Dose (ADD)} = (\text{Cw} \times \text{CF} \times \text{SA} \times \text{TD} \times \text{EF} \times \text{ED} \times \text{PC}) / (\text{AT} \times \text{BW})$$

ADD = average daily dose (mg/kg/day)

Cw = chemical concentration in surface water (mg/L)

CF = volumetric conversion factor for water 1 liter/1000 cm²

- SA = surface area for dermal exposure (cm²)
- TD = time of contact per day (hr/day)
- EF = exposure frequency (days/year)
- ED = exposure duration (years)
- PC = permeability constant (chemical specific cm/hr)
- BW = body weight (kg)
- AT = averaging time (days).

Recreational visitors, including children or adults wading in the River or contacting water during fishing are assumed to submerge the surface areas of their hands, forearms, feet, and lower legs, or approximately 25 percent of their total body surface area. Application of the 25 percent assumed surface area to total body surface areas provided by EPA (1997b) results in an exposure assumption of 4,500 cm² for an adult (i.e., 18,000 cm² adult total body surface area × 0.25) and 3,278 cm² for a child (i.e., 13,112 cm² older child total body surface area × 0.25). The exposure estimates for dermal contact with water incorporate a permeability coefficient, which reflects the rate of movement of the chemical across the skin. The permeability coefficient to be applied in the assessment will be taken from Appendix B, Tables B-3 and B-4, of EPA (2004) and are chemical specific. The daily time of contact will be assumed to be 1 hour for the SLRA. If screening estimates indicate this route of exposure might be non-negligible for any CoPCs, this value may be modified by the results of the activity survey. The exposure durations and frequencies for the hunter, angler, and other recreational scenarios are described in Section 6.4.3.3.2.1.

Table 6-7 summarizes proposed exposure assumptions for this pathway.

Table 6-7 Exposure Assumptions for Recreational Visitors' Dermal Contact With Surface Water

Exposure terms	Receptors	
	Older child visitor	Adult visitor
SA - Skin surface area (cm ²) ^a	3,278 cm ²	4,500 cm ²
EF – Exposure Frequency (days) older child	54 days ^a	--
EF – Exposure Frequency (days) hunter	--	20 days (UMDES Table E8)
EF – Exposure Frequency (days) fisher	--	40 days (UMDES Table E2)
EF – Exposure frequency other (days)	--	28 days (UMDES E13 and E14)
ED - Exposure duration (years)	10 years ^a	UMDES E8, E2, E13 and E14)

^a Surface area derived to represent 25% of the body surface area ^bOlder child exposure frequency assumes 3 visits per week during the 3 summer months and 1 visit a week during two spring and two fall months.

6.4.3.8 Consumption of Sport-Caught Fish

Consumption of sport-caught fish from the Tittabawassee River is expected to be an important potential pathway of exposure to the PCDD/PCDFs. At present, three different sources of information are available for evaluating consumption of fish specifically from the Tittabawassee River: The DNR creel surveys, the UMDES questionnaire data and the MDCH intercept survey. Other sources of data may also be used in a confirmatory or supplementary fashion, including but not limited to West et al. (1989, 1993), Hoehn et al. (1996a,b), Lupi (1998, 2004a,b). If conducted, the Activity Survey will add to the data from these prior studies so that sufficient input information concerning the fish exposure pathways will be available. The algorithm used for evaluation of the dose in the SLRA is proposed to be (based on EPA 1989 method, modified to incorporate meal size):

Equation 5

$$\text{Average Daily Dose (ADD)} = (\text{Cf} \times \text{CL} \times \text{IRf} \times \text{MSf} \times \text{ED}) / (\text{AT} \times \text{BW})$$

- ADD = average daily dose (mg/kg/day)
- Cf = chemical concentration in fish tissues eaten (mg/kg)
- CL = cooking and trimming loss (unitless)
- IRf = fish meal ingestion rate (meals/year)
- MSf = meal size for fish (kg/meal)
- ED = exposure duration (years)
- BW = body weight (kg)
- AT = averaging time (days).

The chemical concentration Cf may vary for different fish species. If this is the case, a weighted value will be obtained by using the fractions of various types of fish typically eaten, as measured in the UMDES questionnaire (questions G19–G49) for the Tittabawassee River. Since what is required is a long-term average concentration over many fish meals (since none of the CoPCs is expected to require evaluation of acute exposures), the appropriate fish tissue concentrations will be obtained as averages over measured concentrations in many fish of the appropriate type. The effect of variations with time of fish tissue concentrations will be taken into account in sensitivity analyses, extrapolating any observed time-trends, but the SLRA and main PRA analyses will assume constant fish concentration.

The cooking and trimming loss (CL) for PCDD/Fs is proposed to be taken as 50% in the SLRA, based on the value used for PCBs in the Kalamazoo Risk Assessment (CDM, 2003), since losses for these non-volatile, heat-stable, and fat-soluble compounds depend primarily on the loss of fat (Rose et al. 2001).

The *exposure duration* for the SLRA is proposed to be derived from the UMDES questionnaire results, using Q F10 (ate fish from any of the Tittabawassee River, Saginaw River, or Saginaw Bay), using the methodology described in Section 6.4.4.3.3 and 6.4.3.1. Since this question requested information about eating fish from any of three water bodies, it cannot give an underestimate of the period eating fish from the study area. As a double check, the exposure duration will be compared with the similar result obtained from UMDES Q E2 (the period spent fishing in the Tittabawassee).

The *Fish Meal Ingestion Rate* (IRf) is proposed to be obtained from the UMDES questionnaire results (questions G19–G49), which describe (*inter alia*) meal consumption within the last 5 years from the Tittabawassee River and from the combination of Saginaw River and Saginaw Bay. These data will be evaluated in conjunction with the data from questions E2 and F10. This information will also be supplemented with data derived from the Activity Survey. Since the UMDES evaluated only the fish meal ingestion rates for adults aged 18 or over, the fish meal ingestion rates for younger persons will be extrapolated from the UMDES data by assuming consumption within a household at the same rate (meals/year) for all persons within that household (a check will be performed using the Atkin, 1994 survey questions on children eating fish in the same household as the adult questioned). These analyses will be conducted together with MDEQ.

Species eaten: The species of fish that are eaten is proposed to be obtained from the UMDES questionnaire results (Section G). The UMDES questionnaire considered various broad combinations of fish species consumed (Walleye & perch; Bass; Pan fish; Steelhead, Trout or Salmon; Pike, Pickerel or Muskellunge). Whether this breakdown is adequate for the HHRA will depend on the results of fish sampling; if concentrations in the fish are not distinguishable between fish within these combinations, they will be used as in the UMDES survey, or combined to form even larger groups if concentrations are not distinguishable between those groups. If concentrations between fish within a group are significantly different (both statistically and in such a way as to affect the risk assessment, as judged by SLRA evaluations), it may be necessary to perform further activity surveying to obtain the breakdown in fish consumption at a more detailed level. Such information will be obtained with data derived from the Activity Survey. Sensitivity analyses will be performed when fish tissue concentrations are available to determine the necessity and value of further information.

Quantity consumed per meal. There are no direct measurements of meal size in the Tittabawassee River angler population, nor questions directed at obtaining estimates of meal sizes included in UMDES survey.

A prime source of information relevant to fishing in this region is a telephone interview survey (Atkin, 1994) of 690 anglers residing near the Kalamazoo River basin (out of 981 who were contacted).²² This survey obtained representative information on fish meal sizes. In that survey, anglers were asked how many meals of different types of self-caught fish they had eaten in the previous two weeks, and were asked to estimate their size as a “small portion... say, four or five ounces, or a large amount greater than ten ounces, or in between”. Atkin considered that the small portion could be adequately represented by 4 ounces, the in between portion by 8 ounces, and the large portion by 10 ounces. For the 177 anglers who had eaten self-caught fish and provided information on both number of meals and meal sizes, the distribution of average meal size is given in Table 6-8.

Table 6-8 Average meal size in a survey by Atkin (1994)

Avg. meal size ^a	No. of anglers
12	57
10.7	1
10.4	1
10	2
9	1
8	82
6.7	5
4	28
^a Meal sizes intermediate between 8, 10, and 12 oz. occur because some anglers reported different meal sizes for different types of fish; these averages are weighted by the relative amounts of fish eaten.	

Atkin (1994) did not explicitly specify whether the portion size was considered to be before or after cooking; it will be assumed that it is before cooking. Examination of Atkin’s data indicates that there was not much difference in the distribution of meal size by type of fish, so no differentiation will be made in the HHRA. The average serving size implied by the values from the Atkin (1994) survey is 8.7 ounces. Other potential sources of information relevant to the local area have been examined also. In Phase II of the Kalamazoo River Angler Survey (MDPH, 2000a,b,c;), 80 respondents gave estimates of serving size based on a 4-ounce model portion of fish on a 9-inch dinner plate. The responses were graded as 1, 4/3, 2, 3, 4, 6, 8, 10, 12, 14, 16, and >16 ounces. Taking >16 ounces to be represented by 20 ounces, the average serving size for the 80 respondents was 7.9 ounces. This appears to be entirely consistent with the

²² The data file for this survey contains records for just 689 anglers.

estimate from the Atkin survey. The Protocol for a Uniform Great Lakes Sport Fish Consumption Advisory (1993) advocates the use of a standardized meal size (8 oz for a 70 kg person) in evaluation of consumption advisories; with a variation in meal size proportional to body weight. While no formal data analysis is referenced for this recommendation, the meal size adopted appears consistent with the results found in Atkin’s survey. The 1989 evaluation of Michigan Sport Anglers fish consumption (West et al. (1989.) will also be examined for relevance and the results of that survey incorporated if it appears to be still representative of current conditions. The potential variation of meal size with age will be examined in Atkin’s survey, West et al. (1989), and using fish meals in the CSFII [USDA 2000] and the more recent National Institute of Health, Survey *What We Eat in America- National Health and Nutrition Examination Survey* [WWEIA-NHANES] 2001–2002, and 2003–2004²³).

In view of the agreement between Atkin’s survey and other sources, and the relatively local nature of Atkins’s observations, Atkin’s (1994) survey results are proposed for use in the HHRA to define a distribution of values to estimate variability between individuals in long-term average meal size. This information may also be bolstered, if required, by information derived from the Activity Survey.

6.4.3.9 Ingestion of Wild Game

Consumption of wild game in the vicinity of the Tittabawassee River is a pathway of exposure for the PCDD/Fs for those who hunt and consume game. The algorithm proposed for evaluation of the dose in the SLRA is a modification of MDCH (2005): *Petitioned Health Consultation: Dioxins in Wild Game Taken from the Tittabawassee River Floodplain South of Midland, Midland and Saginaw Counties, Michigan*:

Equation 6

$$\text{Average Daily Dose (ADD)} = (\text{Cg} \times \text{CL} \times \text{IRg} \times \text{MSg} \times \text{ED}) / (\text{AT} \times \text{BW})$$

- ADD = average daily dose (mg/kg/day)
- Cg = chemical concentration in the uncooked game tissues eaten (mg/kg)
- CL = cooking and trimming loss (unitless)
- IRg = game meal ingestion rate (meals/year)
- MSg = meal size for game (kg/meal)
- ED = exposure duration (years)

²³ What we eat in America – NHANES, see <http://www.ars.usda.gov/Services/docs.htm?docid=14018>

BW = body weight (kg)
AT = averaging time (days).

This algorithm may be modified if subsequent research and consultation between MDEQ and Dow indicates that a better estimator of intake can be obtained by explicitly accounting for the fat content of the game meat, as used in the beef consumption algorithm suggested in EPA (2004b).

The information needed for site-specific intake rate evaluation will be generally obtained from the UMDES questionnaire results, as detailed below. The approach proposed for selection of values for the SLRA is that described in Section 6.4.3. Where appropriate, the information from the UMDES may be augmented by Michigan DNR survey information (e.g. Frawley 2004, 2005a,b, c, d; and similar reports for other game or fowl and from other years).

The chemical concentration C_g is expected to vary for different game animals. The appropriate weighted value is proposed to be obtained by using the fractions of various types of game eaten, as measured in the UMDES questionnaire (questions G6–G10, including ancillary questions) for the Tittabawassee River flood plain.²⁴ Since a long-term average concentration over many game meals is required (i.e., none of the CoPCs is expected to require evaluation of acute exposures), the appropriate game tissue concentrations will be obtained as averages over measured concentrations in many game of the appropriate type, or by simulation of the numbers of animals taken.²⁵ The effect of (long-term) variations with time of game tissue concentrations will be taken into account in sensitivity analyses, extrapolating

²⁴ If concentrations differ materially between species lumped together in the UMDES questionnaire, appropriate averages will be constructed (and the uncertainties in those averages evaluated) using, so far as possible, national or regional surveys for consumption of the various individual species (e.g. using the CSFII, [USDA, 2000. Continuing survey of food intakes by individuals (CSFII) 1994-196, 1998. Agricultural Research Service], or the more recent WWEIA-NHANES 2001–2002, and 2003–2004 (What we eat in America – NHANES, see <http://www.ars.usda.gov/Services/docs.htm?docid=14018>), or notional estimates. Alternatively, better discrimination between game animals eaten may be generated in the Activity Survey.

²⁵ This takes into account the sentiment expressed in the statement in MDCH (2005; at page A-1) that “... wild game consumers will not randomly sample among several animals, but could instead harvest individual animals that could contain the higher levels of DLCs detected. ...” It is true that wild game consumers will not randomly sample among many animals at the same time, but over a sufficiently long period they will effectively sample from many animals, since they cannot repeatedly select the same animal. That sampling will be effectively random among animals, except insofar as concentrations in animals may correlate with their location. Any such effect will be taken into account by testing for such a correlation and including it if found; however, at any particular location, the appropriate concentration estimate corresponding to sufficiently long-term average intake is a mean over the animals harvested, provided sufficient animals are taken by a single hunter. The possibility to harvest multiple animals that have higher than average concentrations will be taken into account in the uncertainty distribution for the average concentration (for the high-end hunter), and/or by explicitly simulating the taking of individual animals (where the individual hunter does not take a relatively large number of animals in the exposure duration evaluated).

any observed time-trends, but the SLRA and main PRA analyses will assume a constant game concentration.

The proposed method to consider *cooking and trimming loss* (CL) for PCDD/Fs is to evaluate measurements reported in the literature for cooking loss in meat (see Section 6.4.5.1); all measurements on meats of any type are proposed to be combined if statistical analysis shows this is reasonable, as is expected since losses for these non-volatile, heat-stable, and fat-soluble compounds depend primarily on the loss of fat (Rose et al. 2001). For the same reason, trimming of fat is expected to reduce the amount of PCDD/PDFs intake. The SLRA will ignore trimming losses. Cooking methods are proposed to be inferred from other surveys (if others are located), or measured in the Activity Survey.

The proposed method to consider the *Game Meal Ingestion Rate* (IRg) is to obtain representative rates from the UMDES questionnaire results (questions G6–G10), which describe game meal consumption within the last 5 years for multiple species of game from the Tittabawassee River flood plain. The UMDES survey did not measure consumption by persons less than 18, so the game meal ingestion rate for such persons will be inferred from the UMDES survey on a household basis — children in a household will be assumed to eat game meals at the same rate as adults in that household. This extrapolation may be replaced by measurements in the Activity Survey.

The proposed method to evaluate *Exposure Duration* (ED) is to derive estimates from the UMDES questionnaire responses, by evaluation of questions E7–E12 (describing the period and number of days the respondent has hunted in the Tittabawassee River flood plain, Saginaw River flood plain, and areas surrounding Saginaw Bay) and F2–F3 (describing the total period during which the respondent has eaten game and liver of game). It will be assumed that the period of hunting in a given area corresponds to the period eating game from that area. The responses to questions F2–F3 will set an upper bound on period of eating game, and may be useable in conjunction with the responses to questions E7–E12 in estimating parameters of distributions (for an example of how this may be done in a distributional setting, see the evaluation of the distribution for vegetative cell concentration in Section 3.5.5 of Crouch and Golden (2005)).

Species eaten: The UMDES questionnaire considered various broad combinations of game species consumed (Whitetail deer or venison; Wild Turkey, Pheasant, Grouse, Quail or Woodcock; Wild Duck or Goose; Squirrel or Wild Rabbit; and any other game meat such as Raccoon, Opossum, Groundhog, Woodchuck, Muskrat, wild Turtle or Frog). Whether this breakdown is adequate for the HHRA will

depend on the results of game sampling; if concentrations in the game are not distinguishable between game within these combinations, they will be used as in the UMDES survey, or combined to even larger groups if concentrations are not distinguishable between those groups. If concentrations between game within a group are significantly different (both statistically and in such a way as to affect the risk assessment, as judged by SLRA evaluations), it may be necessary to perform further activity surveying to obtain the breakdown in game consumption at a more detailed level; or national or regional surveys may be used (such as the CSFII [USDA 2000], the more recent WWEIA-NHANES 2001–2002, and 2003–2004²⁶), or notional estimates of the relative contributions of different game species may be used. Sensitivity analyses will be performed when game tissue concentrations are available to determine the necessity and value of further information. This work will be done with input from MDEQ.

Quantity consumed per meal. There are no direct measurements of game meal size in the Tittabawassee River flood plain hunter population, nor questions directed at obtaining estimates of meal sizes included in UMDES survey. There appear to be few data on meal sizes enjoyed by hunters. The MDCH (2005) used a 4 oz meal size for adults, and a 2 oz meal size for children, together with notional meal consumption rates. However, it seems likely that some game eaters would eat larger portions. The CSFII or WWEIA-NHANES (op. cit.) will be investigated for any information they may provide on a distribution of typical meal sizes for particular types of game meat. In addition, searches will be conducted for other surveys providing meal size estimates. An overall total game meat consumption rate should be obtainable from the known annual take of some game animals; and attributing this consumption to hunters alone should provide an upper bound on average consumption rates; estimates along these lines will be evaluated. This approach is proposed pending MDEQ approval.

6.4.3.10 Ingestion of Agricultural Animal Products

The HHRA proposes to evaluate potential risks if any related to consumption of homegrown agricultural animal products. “Homegrown” is here simply meant to designate production within the Tittabawassee River flood plain, rather than being produced outside the area and brought in. Consumption of meats and eggs produced in the Study Area is not expected to be a major pathway of exposure, although for some individuals this route may be a contributor to risks. The algorithm proposed used for evaluation of the dose in the SLRA is a modification of MDCH (2005):

²⁶ What we eat in America – NHANES, see <http://www.ars.usda.gov/Services/docs.htm?docid=14018>

Equation 7

For meats:

$$\text{Average Daily Dose (ADD)} = (\text{Cm} \times \text{CL} \times \text{IRm} \times \text{MSm} \times \text{ED}) / (\text{AT} \times \text{BW})$$

For eggs

$$\text{Average Daily Dose (ADD)} = (\text{Ce} \times \text{Me} \times \text{IRe} \times \text{ED}) / (\text{AT} \times \text{BW})$$

- ADD = average daily dose (mg/kg/day)
- Cm = chemical concentration in the homegrown meat tissues eaten (mg/kg)
- Ce = chemical concentration in homegrown eggs (mg/kg)
- CL = cooking and trimming loss for homegrown meat (unitless)
- IRm = homegrown meat meal ingestion rate (meals/year)
- MSm = meal size for homegrown meat (kg/meal)
- IRe = homegrown egg consumption rate (eggs/year)
- Me = average mass of homegrown eggs (kg)
- ED = exposure duration (years)
- BW = body weight (kg)
- AT = averaging time (days).

The SLRA and PRA propose to use the data obtained in the UMDES survey to estimate the fraction of people who eat homegrown meat and eggs in the Study Area (and the rate of eating such meat and egg meals (questions G3, G4, and G51). While the positive response rate in the UMDES survey was low (the estimated fraction of the population eating homegrown meat from the Study Area was less than 3% in any area, and the fraction eating eggs less than 5%) these data provide the site-specific information required for the exposure assessment. It is also proposed that evaluations for children be based on the assumption that children eat meals at the same rate as adults in the same household. This information may be supplemented with data derived from the Activity Survey.

Meal size distributions for meats and eggs are proposed to be assumed similar to those in the national or regional diet, as evaluated from national or regional surveys (such as the CSFII [USDA 2000] or WWEIA-NHANES 2001–2002, and 2003–2004²⁷).

²⁷ What we eat in America – NHANES, see <http://www.ars.usda.gov/Services/docs.htm?docid=14018>

If different homegrown meats are found to have significantly different concentrations of contaminants, the ingestion concentration term will be evaluated as an intake-weighted average of those concentrations; if necessary the intake proportion of the various meats treated together in the UMDES survey (questions G3, G4) will be estimated from national data (CSFII, 1994-1996, 1998; and NHANES, 2003, 2004) or from further information obtained on production or consumption of meat in the flood plain in the Activity Survey.

Proposed assumptions for the exposure duration are the same as those for residence duration (Section 6.4.3.2.3).

6.4.3.11 Ingestion of Homegrown Dairy Products

As in Section 6.4.3.10, “homegrown” is here simply meant to designate milk or products obtained from milk produced within the Study Area, rather than from milk produced outside the area and brought in. The algorithm proposed for evaluation of doses is a modification of that suggested for beef consumption in EPA (2004b), in that it is based on the fat content of the dairy products. PCDD/Fs partition primarily into the fat components in such foods, so basing the evaluation on fat content, and normalizing all measured concentrations to fat content, will provide a better estimate than using total weight or volume. If other CoPCs are determined to be of potential importance for this route, the algorithm will be modified appropriately for those CoPCs.

Equation 8

$$\text{Average Daily Dose (ADD)} = (\text{Ca} \times \text{IRa} \times \text{MSa} \times \text{ED}) / (\text{AT} \times \text{BW})$$

- ADD = average daily dose (mg/kg/day)
- Ca = chemical concentration in the fat of dairy products (mg/kg fat)
- IRa = ingestion rate of dairy products (meals/year)
- MSa = meal size for dairy products (kg fat/meal)
- ED = exposure duration (years)
- BW = body weight (kg)
- AT = averaging time (days).

The distributions of ingestion rates for milk and other dairy products are proposed to be obtained from the UMDES (questions G52 and G53). Since only one respondent indicated consumption of homegrown milk (as defined here, from the Study Area), the distribution of ingestion rates will be inferred from consumers

of milk from elsewhere (the distributions of consumption appear to be independent of source or consumer location; this hypothesis will be tested). For persons below the age of 18, the fraction of the population exposed is proposed to be estimated by assuming that all persons in any given household use the same source of milk, and the distribution of ingestion rates assumed similar to the national or regional diet, as evaluated from national or regional surveys (such as CSFII [USDA 2000] or WWEIA-NHANES 2001–2002, and 2003–2004²⁸).

It is also proposed that the distribution of meal size (amount of fat per milk or milk product meal) be assumed similar to that in the national or regional diet, as evaluated from national or regional surveys (op. cit.).

The data just described is proposed to be augmented by the results of the Activity Survey — for example, the mean of the product of the distributions defined by the methodology just described (which product is just the distribution of intakes of fat from dairy products) may be checked by evaluation of the total milk production of the Study Area region obtained by counting the number of Study Area cows and estimating their milk production. Where possible, such checks will be performed, and the estimates adjusted accordingly (that is, the estimation procedures will take into account all available methods for estimating any distributional parameters, and the uncertainties associated with those methods).

All elements of the SLRA exposure assessment will be developed in coordination with MDEQ.

6.4.4 Quantification of Exposure Distributions in the PRA

6.4.4.1 Selection of Exposure Variable Values for Use in the PRA

Prior to initiating any PRA analyses, Dow will meet with MDEQ to discuss general principals and to develop consensus on the approach. The approach provided here should be considered to be the proposed methodology subject to discussion with MDEQ. In the PRA, all variables will in general be treated as having both uncertainty and variability distributions, although the estimate for the variance of either one may be zero in particular cases either through a formal analysis of data or by choice. Technically, every potentially non-constant input to a PRA is or may be considered as a (mathematical) distribution, even though some non-constant inputs may be approximated as point distributions (i.e., even a point estimate for a non-constant input may be considered a distribution, both mathematically and in some practical

²⁸ What we eat in America – NHANES, see <http://www.ars.usda.gov/Services/docs.htm?docid=14018>

implementations). PRA implementation methodology is available that is capable of handling arbitrary numbers of distributions; and every input to such implementations can be (although it need not be) defined to be a distribution, even if that distribution is represented at run time as a point distribution (see, for example, the Risk Assessment for *Clostridium perfringens* in Ready-to-Eat and Partially Cooked Meat and Poultry Products (Sep 2005), and the associated model files and source codes, http://www.fsis.usda.gov/Science/Risk_Assessments/index.asp).

Variables that are shown by sensitivity analysis to have little effect on the variability or uncertainty distributions of the risk estimate (see Section 6.4.4.2) may be input to the PRA as point estimates with respect to variability or uncertainty or both. The methodology proposed by the HHRA WP does not depend on such prioritization, so if scientifically justifiable distributions are readily available, they may be used even if they are of low priority. Thus, if it is simpler to implement such variables as distributions, and the data are readily available to support the use of such distributions, they will be input as distributions (see also Footnote 3). This approach is consistent with the EPA guiding principles on probabilistic risk assessment (Guiding Principles for Monte Carlo Analysis, EPA/630/R-97/001, March 1997b) and includes prioritization for development of probability distributions based on the sensitivity of the results to the inputs, and on the resource costs of developing such distributions. The Draft HHRA will include identification of variables that would benefit from the evaluation of distributions as well as those that would not and streamline this process as much as possible.

MDEQ recommended placement of each exposure variable into categories to clearly identify the type of investigation needed to develop a distribution for each:

- (a) Parameters having a quantitative variation that is expected to be well known or of relatively low uncertainty (e.g., body weight variation) for which published data are readily available and collection of site-specific data is not needed.
- (b) Parameters having a quantitative variation that is less well known or may be subject to significant uncertainty, therefore, requiring an extensive literature review; or a combination of published literature values, default values, or professional judgment.
- (c) Parameters for which the quantitative variation is intended to be fully described by site-specific data or information and, therefore, will require collection of field data and a specific plan for field data collection.

The data sources for any input distributions to be developed and the methodology that will be applied to obtain variability and uncertainty distributions from those data sources will be described and justified. That explanation will include specification of the type of investigation that is needed to provide the data, and the subsequent analysis of the data obtained. The descriptions will incorporate and will be in some cases more graded than the categorical specification suggested here, since some parameters may involve aspects of more than one category. For example, a parameter such as length of residence may be considered type (a), since the quantitative variation of length of residence is well known and there are readily available published data for this parameter; however, site-specific information may be used to confirm that length of residence for the affected population does not differ significantly from published information on larger populations that include the affected population. Nevertheless, a table of the recommended categories will be developed in future discussions with MDEQ to be held after the December 1st, 2006 RIWP submittal

6.4.4.2 Input Variable Sensitivity Analysis

For each exposure pathway included in the PRA, a sensitivity analysis is proposed to be performed on all the variables involved. A measure of the importance of each variable for both variability and uncertainty in the overall dose estimates will be evaluated by computing the product of a relative variability or uncertainty (see Footnote 18),²⁹ the logarithmic sensitivity (see Footnote 17) for each pathway,³⁰ and a risk estimate obtained using the SLRA procedure with mean estimates for all variables for each pathway,³¹ and summing across pathways for each receptor.³² Where necessary, approximate and in some cases subjective estimates for the relative variability or uncertainty will be used in this sensitivity analysis (since the object of the exercise is partially to determine which variables need further analysis, accurate estimates for the relative variability or uncertainty may not be available).

The variables will be ordered by the resultant measure to indicate the relative importance of obtaining variability and/or uncertainty distributions for use in the PRA, and most effort will be devoted to developing distributions for the variables at the top of this list (see also Footnote 3)

²⁹ This accounts for the size of the variation or uncertainty of the individual variable.

³⁰ This accounts for the standardized effect of the particular variable on the particular pathway.

³¹ This accounts for the relative size of the risk from a particular pathway to a particular receptor.

³² This takes account of the occurrence of the same variable in multiple pathways; if that variable does not occur in a particular pathway, the logarithmic sensitivity for the variable in that pathway is zero.

6.4.4.3 Common Receptor Characteristics – Body Weight, Averaging Time and Exposure Duration

6.4.4.3.1 Body Weight in the PRA

For the probabilistic risk assessment the UMDES data have been preliminarily reviewed to evaluate any differences between the local population and national population. The distribution of body mass index in the UMDES study population (UMDES Questionnaire results, A4) is essentially identical to that in the corresponding US population as a whole, as measured by the NHANES (2003-2004; http://www.cdc.gov/nchs/about/major/nhanes/nhanes2003-2004/nhanes03_04.htm). (Figure 6-3: no statistical test for similarity has yet been performed). The US distribution of body weight with age and sex is proposed to be used for the whole population in the area unless further analysis shows significant differences. In particular, the US distribution will be used for those aged less than 18.

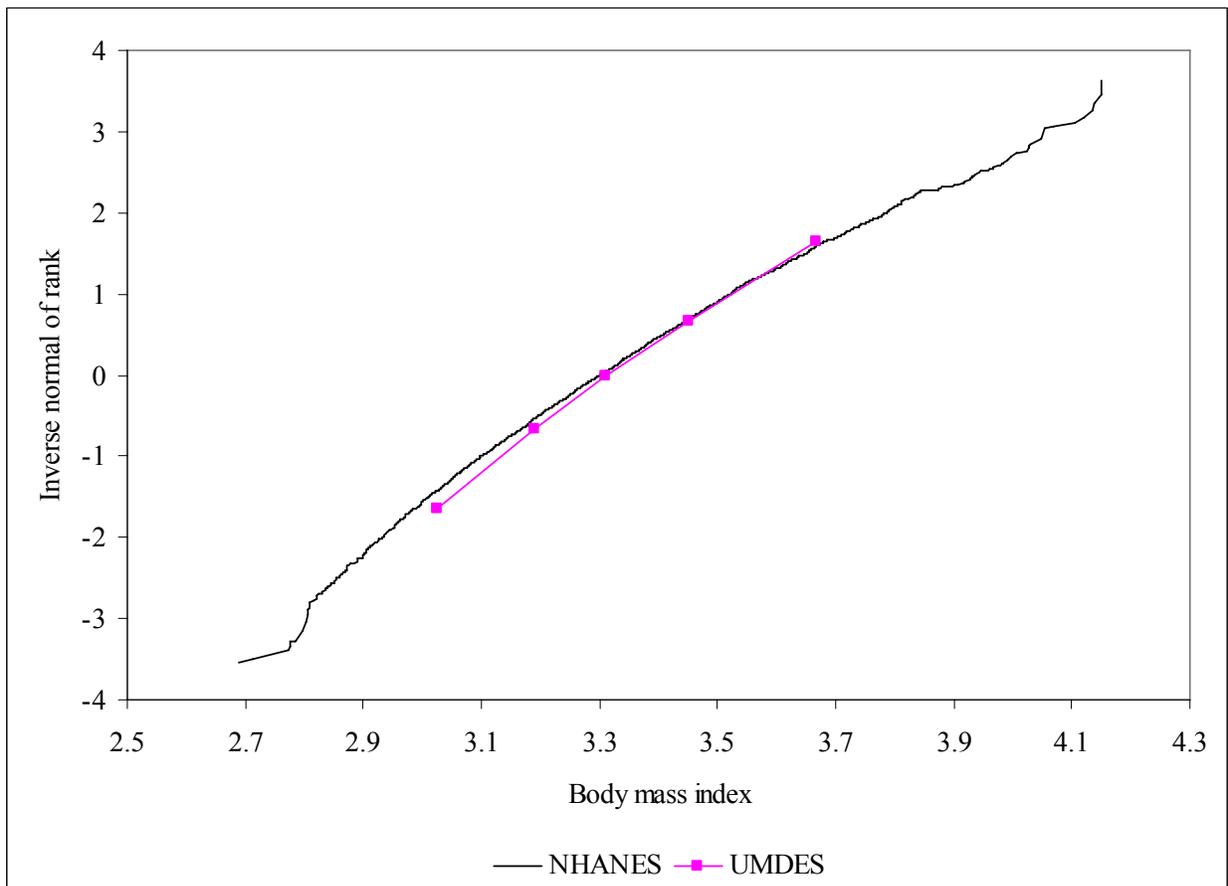


Figure 6-3 Distribution of body mass index for the US population observed in NHANES (2003-2004) for the 18+ population (weighted), and in the UMDES study (weighted).

6.4.4.3.2 *Averaging Time*

As described in Section 6.4.3.2.2 the inputs and outputs for the algorithms are proposed to be time averaged as appropriate for evaluations of the adverse effects evaluated. In the PRA, the averaging period for carcinogens will be the age range 0 to 70 years, and longer exposure durations will be truncated at 70 years. For non-carcinogens, the averaging period will be ages 0 to 30 years, and longer calculated exposure durations will be truncated at 30 years of age. In a sensitivity analysis, the averaging period for exposure durations shorter than 30 years (and occurring below age 30) will be set equal to the larger of the exposure duration or 7 years, to evaluate the intake rates during exposure, but averaged over at least 7 years.

6.4.4.3.3 *Exposure Duration in the PRA*

For several of the receptor/pathway combinations, exposure duration is proposed to be set equal to duration of residence. In the PRA, to evaluate duration of residence, the UMDES data on residential history (UMDES Q results, B1 and B4b2-B4b1 together with more detail expected to be obtained by requests to UMDES) will be compared with similarly censored (lived >5 years in current residence and aged 18 or more at the time of the interview) versions of similar statistics from the whole US population, or from a more local subset population (see below for available datasets). If they are similar, the US distribution for residential period will be used. If distinct, a suitably re-scaled version of the US distribution for the population censored below 5 years residence period and below age 18 will be added to the UMDES distribution. If there are significant differences between the UMDES data and US distribution data, a draft approach will be provided for review by MDEQ.

From these distributions of residence times in current residences (or within Midland/Saginaw/Bay counties), the distributions of total residence times will be derived using the same methodologies as used for the US population (Israeli and Nelson 1999 and Johnson and Capel 1992). These publications are those used by EPA (1997a). The values obtained in the two references cited are now more than 19 years old (the first used data from 1985 and 1987, and the second from 1987), so the methodologies will be applied to more current data and any differences in results obtained using the two methodologies (which use independent survey data) will be reconciled. Those references also used summary data from, respectively, the American Housing Survey and the Current Population Survey, whereas now microdata are more readily available (<http://www.census.gov/hhes/www/housing/ahs/nationaldata.html>, and <http://dataferrett.census.gov/>, respectively) so such microdata will be used to refine the distributions obtained. Additional site-specific information may be obtained from the Activity Survey. By examining any changes since around 1985, it should also be possible to evaluate the fundamental assumptions made

by the two methods (stability of the distributions over calendar time) in the first reference, and constancy of probability to move in the second reference); such an evaluation will be made.

For the hunting, fishing, and recreational exposure pathways discussed below, the distributions of duration of exposure are proposed to be obtained as discussed in the individual pathways, either below or in the relevant pathway description for the SLRA (Section 6.4.3), except that the full distribution will be used rather than the point estimate selected for the SLRA.

6.4.4.4 Incidental Ingestion of Soil/Dust or Sediment

It is considered likely that the ingestion of soil or dust is a pathway that will be considered in the PRA, while it is quite plausible that sediment ingestion will be screened out in the SLRA. Soil/dust or sediment ingestion will be evaluated using the algorithm provided in Equation 1 in all cases.

6.4.4.4.1 Soil Ingestion Rates for Residents and Workers in the PRA

Exposure frequency assumptions for residents and workers are proposed to be those shown in Table 6-3, unless scientifically defensible relationships can be developed between exposure opportunities and weather variables like temperature, rainfall, or soil conditions (like snow cover or freezing temperatures). In the latter case, such relationships (to be discussed with MDEQ) would be used to select exposure frequencies, with weather data from Midland Bay City Saginaw airport (WBAN 726379 14845³³). Although the soil/dust ingestion pathway includes dust, the lack of any correlation between concentrations of PCDD/F in blood and household dust (albeit in adults) in the UMDES study suggests that soil would be the major contributor to intake, so that outdoor weather and soil conditions may be controlling factors; the sensitivity of the UMDES study to detect a difference between household dust and soil will be examined.

Exposure duration is proposed to be the same as duration of residence (Section 6.4.4.3.3).

³³ Hourly records from 1973 to the present are available through <http://www.ncdc.noaa.gov/oa/climate/climatedata.html>. Incomplete records may be augmented by reference to other Michigan weather records.

6.4.4.4.2 *Incidental Soil or Sediment Ingestion During Hunting, Fishing, and Other Recreational Visits*

If exposure pathways related to incidental ingestion of soil or sediments for recreational visitors are identified as pathways to be evaluated in the PRA, this exposure pathway is proposed to be quantified using the algorithm set out in Equation 2,. As described above in 6.4.3.3.2.1, exposure measurements drawn from UMDES survey of recreational activities around the Tittabawassee River and from the EPA Exposure Factors Handbook (EPA 1997a) are proposed. The following describe the origin of the exposure duration and frequency measurements that are proposed for use:

- Adult anglers –the distribution of total numbers of days/year fishing and duration fishing in the Tittabawassee River will be used (from Question E2 of the UMDES survey), and the fraction of persons fishing are proposed to be incorporated in the distribution.
- Adult hunters - the distribution of total numbers of days/year hunting and duration hunting in the surrounding areas of the Tittabawassee River flood plain below the Tridge are proposed to be used (from Question E8 of the UMDES survey), and the fraction of persons hunting incorporated in the distribution.
- For recreational activities other than fishing or hunting - the distribution of total numbers of days/year and duration of partaking in recreational activities in or around the Tittabawassee River below the Tridge are proposed to be used (from Question E14 of the UMDES survey), and the fraction of persons taking part in recreational activities (Questions E13 and E14) will be incorporated in the distribution.
- Teen recreational exposures - For the PRA, the UMDES exposure frequency distributions for recreational activity are proposed to be used as though they applied also to the teenage group. This extrapolation will be tested and augmented (or possibly replaced) by the observations collected during the Activity Survey.

The distributions may need modification for use in the HHRA to account for their censored nature, as described in Section 6.4.4.3.3 for exposure duration.

As described in Section 6.4.3.3.2.1 it is considered unlikely that young children will take part in recreational activities that are conducive of exposure in the Study Area, and hunters and anglers younger than 18 are also excluded for these pathways.

In the PRA, any observed correlations between hunting, fishing, and recreational activity are proposed to be incorporated (assuming such information is obtained from the UMDES), both in the individuals partaking in any activities and the fractions of times spent on each activity.

The soil ingestion rate used for these pathways in the PRA are proposed to be those derived for adults, see Section 6.4.4.4.1. These are proposed to be applied to soil (for hunters) or a weighted combination of sediment and soil (for anglers and recreational visitors), the weights being chosen to match the observations in the Activity Survey of the relative times spent on soil or in the river.

6.4.4.5 Dermal Contact with Soil/Dust or Sediment in the PRA

Any evaluation of exposures to CoPCs through dermal contact with soil or dust are proposed to be evaluated using the algorithm shown in Equation 2. The exposure frequency, duration, and body weights to be applied in assessment of dermal contact are the same as described above (Section 6.4.3.3.2.1) for evaluation of incidental ingestion of soil or sediments (but additionally, the muddy hands and feet events will be incorporated as described in Section 6.4.3.4.2). Additional values needed for the dermal contact algorithms are skin surface area (SA), event frequency (EV) and soil adherence (AF).

6.4.4.5.1 Skin Surface Area per Event (SA) (cm^2 /event),

To obtain surface area estimates for the PRA, the age variation of height from the NHANES 2003-2004 examination is proposed to be used, using the covariance of weight and height obtained from these US population data. The distributions of weights and heights at any age are indistinguishable from lognormal based on preliminary analysis of these NHANES data; see also Burmaster (1998) and Burmaster and Crouch (1997a). Median weights and heights, and the standard deviations of their logarithms, will be parameterized by age and sex using suitable formulae, and the variance co-variance matrix of the distributions about these medians similarly parameterized. The height squared will act as a surrogate for body surface area using standard correlations between surface area, body weight, and height (Burmaster, 1998; EPA 1997a, Appendix 6A).

The fraction of skin surface area exposed is proposed to be hands only at 45 °F, increasing linearly to hands, lower legs, forearms, and face for adults & children at 70 °F+ in the residential and recreational scenarios, where the temperature is based on the maximum daily temperature. Surface area fractions corresponding to particular body parts will be taken from the Exposure Factors Handbook (EPA 1997a). Weather records will be obtained for Midland-Bay City-Saginaw airport (WBAN 726379 14845³⁴). For the angler scenarios, surface areas exposed will be taken to be hands, arms, lower legs, and face (and feet

³⁴ Hourly records from 1973 to the present are available through <http://www.ncdc.noaa.gov/oa/climate/climatedata.html>. Incomplete records may be augmented by reference to other Michigan weather records.

during muddy feet episodes), while the hunter will be assumed to have hands and face exposed, but lower legs and arms covered (again, with feet exposed during muddy feet events); these selections may be modified by observations during the activity survey.

The approach taken to exposed fractions of various body parts is proposed to be similar to that used in the EPA Stochastic Human Exposure and Dose Simulation (SHEDS) model (Zartarian et al. 2005). For children, Wong et al. (2000) provide a default estimate for surface areas exposed during play, and such information will be augmented if necessary by the activity survey. The methodology to be adopted for estimation of average soil adherence is one recommended in EPA (1997a) Exposure Factors Handbook — measured values for soil accumulation on all the appendages are summed. The torso is considered unexposed in any of the activities for the hunter or angler scenario — hunting would take place principally in fall, requiring appropriate dress for both warmth and protection while pushing through brush, and anglers here are unlikely to have consistently exposed torsos.

6.4.4.5.2 *Event Frequency (EV) (per day),*

The event frequency is proposed to be set at 1/day during actual exposure periods for all types of event. This approach is consistent with the methodology used in dermal contact pathways that use the adherence factor (*AF*) (MDEQ 2005a), so will be used for both SLRA and PRA.

6.4.4.5.3 *Soil Adherence Factor (AF) (mg/cm²)*

Long-term average mean values are proposed to be estimated from the measurements of Kissel et al. (1996, 1998) and Holmes et al. (1999), as also reported in EPA (1997a). There are insufficient data to evaluate whether long term mean soil adherence factors differ between individuals, so no variability will be incorporated in the analysis. The derivation of a representative range of adherence factors for use in the probabilistic assessment is described in Appendix HHRA D, D-3. Raw data will be obtained from Prof. Kissel's web site (<http://depts.washington.edu/jkspage/index.html>).

6.4.4.6 *Inhalation of Dust in the PRA*

If inhalation of dust is an exposure pathway that requires further evaluation in the PRA, a method to derive appropriate distributions for exposure variables will be proposed. Provisionally, the methodology used for particulates in Rule 726 will be used, with Study Area specific vegetation cover and field areas.

6.4.4.7 Incidental Ingestion and Dermal Contact with Surface Water

If ingestion or dermal contact with surface water are pathways requiring further evaluation in the PRA, a method to derive appropriate distributions for exposure variables will be proposed. Provisionally, exposure frequency and duration for hunters, anglers, and recreational visitors will be estimated from the UMDES for adults.

6.4.4.8 Consumption of Sport-Caught Fish

Consumption of sport-caught fish from the Tittabawassee River Study Area may be further evaluated in the PRA and if so evaluations will be conducted following discussion with MDEQ. The algorithm shown in Equation 5 is proposed to be applied as described in Section 6.4.3.8 except that distributions will be applied for all exposure variables where available including the following:

- The *fish meal ingestion rate* (IRf) is proposed to be obtained from the UMDES questionnaire results (questions G19–G49) It was observed in a probabilistic analysis of the Kalamazoo River Survey (Crouch, E., Ames, M., and Green, L. 2002) that the fish ingestion rate on the Kalamazoo had a slight positive correlation with reported length of time eating fish, so such a correlation will be examined here if possible.
- The *cooking and trimming loss* (CL) for PCDD/Fs is proposed to either be taken as 50% as in the SLRA, or a distribution of values will be applied based on measurements of cooking losses and trimming (see Section 6.4.5.1), taking in account trimming methods used locally as measured in the UMDES (questions F11–F13), together with cooking methods inferred from other surveys or measured in the Activity Survey.
- *Quantity consumed per meal*. Proposed to be based on a comprehensive interview survey (Atkin, 1994) of 690 anglers residing near the Kalamazoo River basin. A summary of some of the data is given in Section 6.4.3.8.
- The *Exposure Duration* (ED) is proposed to be estimated from the UMDES questionnaire as described in Section 6.4.3.8
- The *Species consumed*: proposed to be obtained from the UMDES questionnaire results (Section G). The UMDES questionnaire breakdown of species eaten will be applied if concentrations in the fish are not distinguishable between fish within the combination of species in the UMDES questionnaire and fish species eaten may be combined to form even larger groups if concentrations are not distinguishable between those groups. If concentrations between fish within a group are significantly different (both statistically and in such a way as to affect the risk assessment, as judged by SLRA evaluations), it may be

necessary to perform further activity surveying to obtain the breakdown in fish consumption at a more detailed level. Such information will be obtained with data derived from the Activity Survey. Sensitivity analyses will be performed when fish tissue concentrations are available to determine the necessity and value of further information.

6.4.4.9 Ingestion of Wild Game in the PRA

Consumption of wild game is a pathway of exposure for the PCDD/Fs for those who hunt and consume game collected from within the Tittabawassee River Study Area. The algorithm proposed for evaluation of the dose in the PRA is a modification of MDCH (2005) and is shown in Equation 6. As indicated in Section 6.4.3.9, this algorithm may be modified if subsequent research indicates that a better estimator of intake can be obtained by explicitly accounting for the fat content of the game meat, as used in the beef consumption algorithm suggested in EPA (2004b).

The discussions of Section 6.4.3.9 generally apply to the PRA evaluation, except that the full distributions will be used rather than the point estimates required in the SLRA. In addition, an additional cooking loss will be taken into account:

Cooking loss. As opposed to the SLRA, the PRA proposes to also take account of trimming losses using a distribution based on measurements of trimming losses (Section 6.4.5.1), taking account of trimming methods used locally as measured in the UMDES (specifically, the likelihood to eat the skin of wild Turkey, Pheasant, Grouse, Quail, or Woodcock, as measured in question G7a) or in the Activity Survey.

6.4.4.10 Ingestion of Agricultural Animal Products and Homegrown Dairy Products, in the PRA

The HHRA proposes to evaluate potential risks if any related to consumption of homegrown agricultural animal and dairy products including meat, milk and eggs. “Homegrown” is here simply meant to designate production within the Study Area, rather than being produced outside the area and brought in. If ingestion of home-grown animal products are pathways requiring further evaluation in the PRA the methods described above in Sections 6.4.3.10 and 6.4.3.11, but using the full distributions rather than the point estimates of the SLRA, will be applied.

6.4.5 Chemical Specific Parameters

Chemical-specific parameters used in risk assessment include data for the degree of cooking and preparation loss for foods, oral absorption from soil, dermal absorption from soil, and other physical-chemical parameters. These are discussed here and this approach will be discussed further with MDEQ.

6.4.5.1 Cooking and Preparation Loss

Cooking loss accounts for contaminant mass loss as the result of preparation practices and is applied in the exposure assessment to adjust the concentrations in raw foods to account for concentrations taken in as cooked food. Trimming of fat and removal of skin from fish or game can result in a significant reduction in contaminant mass even before cooking, and cooking may remove contaminants from food portions either by destruction of the contaminants or by their loss in (uneaten) water or fat. For example, catfish typically has the skin removed before eating, as do most game animals and some game birds. Walleye is often prepared skin-off and the dark belly fat removed to achieve a white fillet. Fatty tissue is also often removed from meats and fish in response to health messages advocating decreased fat in the diet or cooking advisory information. Information on common preparation methods will be collected during the Activity Survey and incorporated into the HHRA as feasible.

For evaluation of cooking loss of PCDD/Fs for fish and for game meat, a 50% loss is proposed as was applied in the Kalamazoo risk assessment for PCBs in fish (CDM 2003). Cooking loss for dioxins, furans, and PCBs is essentially due to loss of fat during cooking (Rose et al. 2001), so similar losses can be expected for all these fat-soluble contaminants.

Alternatively, in consultation with MDEQ, uncertainty distributions for cooking and trimming losses (separately) for PCDD/Fs will be identified, extending the methodologies of Sherer and Price (1993) and Wilson et al. (1998). References to be considered for cooking loss from fish tissues include the following: Armbruster et al. (1989, 1987), Bayen et al. (2005), Cichy et al. (1979), Gruemping et al. (2004), Hora (1981), Hori et al. (2005), Khanna et al. (1997), Lee, and Lee (1985), Lewis and Makarewicz (1985), Moya et al. (1998), Niimi and Oliver (1989), Petroske et al. (1998), Puffer and Gossett (1983), Reinert et al. (1972), Roseberry and Burmaster (1991), Salama et al. (1998), Sanders and Haynes (1988), Skea et al. (1979, 1981), Smith et al. (1973), Stachiw et al. (1988), Trotter et al. (1989), Voiland et al. (1991), Wan et al. (2003), Wanderstock et al. (1971), Zabik (1974), Zabik and Zabik (1995, 1996, 1997, 1999). and Zabik et al. (1978, 1979a,b, 1982, 1993, 1995a,b, 1996). References to be

considered for cooking loss for meat and poultry include the following: Ritchey et al. (1967, 1969), Rose et al. (2001), Schecter et al. (1998, 1996), and Smith et al. (1977).

In addition, if any further evaluation of vegetables is necessary Tsutsumi et al. (2002) provides a basis for evaluation of cooking loss from vegetables. If additional CoPCs are identified, appropriate cooking loss assumptions will be derived using methods discussed with MDEQ.

6.4.5.2 Ingestion Absorption Efficiency

The HHRA proposes to develop a bioavailability value (or PDF) based on the currently available swine and rat data, the bioaccessibility data, and information available in the published literature from other dioxin-related bioavailability studies.

For the SLRA, the MDEQ default value of 50% (Part 201 Rule R 299.5720(3)(b)(i)) is proposed for evaluation of PCDD/Fs in the algorithm for soil ingestion, Equation 1. For ingestion from foods in the other algorithms, no explicit ingestion absorption efficiency is incorporated, because the absorption efficiency is considered to be equivalent to that used for derivation of toxicity values based on intake. For CoPCs for which no site-specific data are available, the ingestion absorption efficiencies used in the SLRA will be the default values specified by the Part 201 regulations (Table 4 of R299.5752), and for chemicals not listed, the default values specified at R299.5720(3) will be used.

Dow sponsored a pilot bioavailability study and follow-up study that evaluated the bioavailability of PCDD/F from Tittabawassee River floodplain soils. The results of the pilot study are provided at the MDEQ web cite³⁵ and the results of the follow-up study are provided in Appendix HHRA C. For the PRA, these results will be used where possible to derive uncertainty distributions for the site-specific ingestion bioavailability of the PCDD/PCDFs from floodplain soil, and the resulting uncertainty distributions used. Preliminary analysis indicates absolute absorption efficiency from soils of approximately 25%, which corresponds closely with the 50% relative absorption efficiency used in the SLRA in Equation 1, since absolute absorption from typical diets is expected to be about 50% (JECFA, 2001). It is expected that further discussions with MDEQ will proceed to agree on the precise methodology used for evaluation of the bioavailability data. Uncertainty distributions for other CoPCs (if

³⁵ <http://www.deq.state.mi.us/documents/deq-whm-dioxin-PilotStudyReportFINALFeb24.pdf>

any) will be obtained from literature studies of bioavailability from soil, or the default values of the SLRA (Section 6.4.3.4) used if no published studies are located.

6.4.5.3 Dermal Absorption Efficiency from Soil

There are no site-specific studies of the dermal bioavailability of PCDD/Fs from Midland soil. In a letter MDEQ (1999) recommends using a dermal absorption efficiency of 1.75%, based on an EPA study of dermal absorption in rats (EPA 1991) cited in EPA's Dermal Exposure Assessment document (EPA, 1992). The EPA (1991) study resulted in adjusted dermal absorption efficiency values for TCDD across human skin of 0.95 and 2.5% for low organic carbon content soil similar to typical Michigan soil (except for high organic carbon content soils present as sediments or wetland soils). Michigan DEQ's recommended value of 1.75% represents the midpoint of the two values from the EPA study and this value is proposed for use in the SLRA.

For analyses in the PRA, EPA's *Draft Dioxin Reassessment* (2003) and the Dermal Exposure Assessment (EPA 1992) cite a few additional studies of dermal absorption of TCDD across rat skin. Poiger and Schlatter (1980) concluded that approximately 2% of the administered dose of TCDD in a soil/water paste was found in the liver of the rats. Shu et al. (1988) find that after 24 hours of contact with rat skin, the degree of dermal uptake from contaminated soil was approximately 1% of the administered dose. A limitation of these studies is the extrapolation of results in the rat to absorption across human skin. EPA (2003) notes that in vitro permeation of TCDD across human skin was significantly lower than in mouse skin. EPA (2003) also cites one study of 1,2,3,7,8-PeCDF in monkeys that concluded that less than 1% of the administered dose was absorbed after 6 hours. If possible, a distribution for dermal absorption efficiency will be developed based on the studies cited above and on any further studies of PCDD/F absorption from soil identified in the literature; alternatively the default value of 1.75% will be used. The distribution will be primarily an uncertainty distribution reflecting the uncertainty in the true value for the dermal absorption efficiency of PCDD/Fs from Study Area soil.

For CoPCs for which no further data are available, the dermal absorption efficiencies used in the SLRA will be the default values specified by the Part 201 regulations (Table 4 of R299.5752), and for chemicals not listed, the default values specified at R299.5720(3) will be used.

6.4.5.4 Physical Properties of CoPCs

The following hierarchy of sources are proposed as resources to gather chemical specific data on physical properties needed for the HHRA: First, the National Institute of Standards and Technology (NIST) Webbook³⁶ for properties that have been critically evaluated (for properties with reference collations only in the NIST Webbook, e.g. Henry's law values, see the subsequent hierarchy). Second, review articles that critically assemble and evaluate original data, and provide recommendations. Third, original published articles reporting experimental results. Finally, for properties with inadequate or absent information in these sources, values will be inferred from structure-activity relationships, with preference given to those structure-activity relationships included in critical review articles that assemble and evaluate original data.

6.4.6 Exposure Point Concentrations

An exposure point concentration (EPC) is an estimate of the appropriate average chemical concentration in a medium that a receptor is likely to contact over their exposure duration. Typically for SLRAs an appropriate estimate is the 95 percent upper (uncertainty) confidence limit on a mean concentration (EPA, 1989), since the mean (e.g. over an area, for soil contact scenarios; or over a number of fish, for fish intake scenarios) usually adequately represents the time average; and taking an upper uncertainty confidence limit gives a conservative estimate. Where there is a distribution of exposures across a population, the appropriate 95th confidence percentile should (for SLRAs) be on an upper percentile of that population variation. In SLRAs, however, selecting sub-populations expected to have high exposures may substitute for selection of an upper percentile of the population variation.

As mentioned, due to the uncertainty associated with estimating a true average concentration, EPA recommends calculating the 95% upper confidence limit (UCL) of the arithmetic mean concentration in an exposure unit (EPA 1992). The methods that will be considered for calculation of the 95% UCLs are provided in *Calculating Upper Confidence Limits for Exposure Point Concentrations at Hazardous Waste Sites* (EPA 2002). Sampling data from previous and ongoing studies and investigations as explained in Section 6.3.1 will be considered for calculation of the media- and exposure pathway-specific EPCs.

³⁶ <http://webbook.nist.gov/chemistry/>

The distributional shape of the concentration datasets can be tested using the Shapiro-Wilk ‘W’ Test or other appropriate test as described for example by Gilbert (1987) or EPA (2000) if particular (mathematical) functional forms are selected as potentially representing the empirical distributions. Generally, functional form fits to such distributions will be used to adequately represent them, and statistical methods used to estimate confidence limits. In the SLRA, if the estimated 95% upper confidence limit (UCL) on the mean of the appropriately selected data distribution is lower than the maximum concentration, the 95% UCL will be used as the EPC; otherwise the maximum value will be used as the EPC. The method for calculating the 95% UCL will depend on the distribution of the dataset. When the data are normally distributed, the Student’s *t*-statistic can be used to calculate the 95% UCL. The *H*-statistic will be used to calculate the 95% UCL for log-normally distributed datasets. For datasets that fit neither lognormal nor normal distribution curves, parametric or non-parametric methods described by EPA (EPA, 2000) or others will be employed.

Dow anticipates using the Geomorph data generated by ATS to the extent possible to derive representative EPCs for exposure units defined for each of the land use categories. Further discussion with MDEQ is also anticipated to facilitate decisions on how exposure units are developed.

6.5 TOXICITY ASSESSMENT

Methods to be applied in the toxicity assessment will be agreed upon with MDEQ. The toxicity assessment will quantitatively evaluate the hazards associated with CoPCs in Study Area media using the best available information and science. For noncarcinogenic chemicals, EPA has developed a specific toxicity value called a reference dose (RfD). EPA defines an RfD as ‘An estimate (with uncertainty spanning perhaps an order of magnitude) of a daily oral exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime.’ Non-cancer risk assessment can also consider using a tolerable daily intake (TDI) or margin of exposure (MOE) approach for characterizing risk. Potential carcinogenic effects are evaluated through application of a carcinogenic slope factor (CSF). This work plan is currently focused on the identified CoPC for the Study Area the PCDD/Fs. Any additional CoPCs identified in the screening process will be considered in the risk assessment through application of toxicity values available from the following sources (shown here in priority of use), or other sources as appropriate:

- EPA’s Integrated Risk Information System (IRIS; www.epa.gov/iris),
- EPA’s Provisional Peer Reviewed Toxicity Values (PPRTVs)

- Additional EPA sources (e.g. the historic Health Effects Assessment Summary Tables, HEAST and NCEA provisional values as they are summarized in the EPA Region 9, EPA. [2006]³⁷) and non-EPA sources of toxicity values (e.g. California EPA toxicity values)
- Other guidance as appropriate

As recommended by Region 9, all values will be checked against the original sources to verify their correctness. All toxicity values used in the assessment will be clearly identified and provided in tabular form for MDEQ approval in the draft HHRA.

6.5.1 Toxicity Values for PCDD/Fs

Based on an initial review of the sources listed above, there are no current EPA toxicity criteria for PCDD/Fs for use in either cancer or non-cancer risk assessment. The CSFs previously available for TCDD are based on a 30-year old study (Kociba et al. 1978) and do not reflect current scientific understanding or substantial additional available data on cancer risk. Thus, toxicity criteria for PCDD/Fs for use in the risk assessments in the Study Areas must be derived. This derivation will be aided by recent scientific reviews — the NAS committee review of EPA’s reassessment has been completed (NAS 2006), and in addition, the World Health Organization has completed a review of the toxicity equivalence factors (TEFs) for dioxin-like compounds, which are also integral to the risk assessment process for PCDD/Fs other than TCDD (van den Berg et al. 2006). Dow and MDEQ will meet after the December 1st 2006 submission of the RI WPs to chart a course of action for the development of these toxicity criteria, and the scientific recommendations of the NAS (2006) and WHO TEF reports will be included in those discussions.

Michigan 201 rules provide that the best available information be used as the basis for derivation of toxicity criteria for use in risk assessment (Part 201, Rule 701(c)). The recent expert consensus reviews by the NAS and WHO-IPCS committees should be given significant weight and credibility in the derivation of toxicity values for use in the risk assessments of the Study Areas because they represent the current state of the science for toxicity of PCDD/Fs. Given the primary focus in this risk assessment on PCDD/Fs and the lack of MDEQ or any currently recommended EPA toxicity values for cancer or noncancer assessment of PCDD/F toxicity, the remainder of this section is focused on approaches to derive appropriate and representative toxicity values for PCDD/Fs to be used in the HHRA.

³⁷ see <http://www.epa.gov/region9/waste/sfund/prg/whatsnew.htm>

Currently, a 30-year old study (Kociba et al. 1978) is used as the sole basis for cancer potency estimates. EPA has no national standards or toxicity criteria for PCDD/Fs aside from the 1000 ppt soil level used by CERCLA³⁸. Independent derivation of toxicity values for PCDD/Fs by states, other countries, or other organizations has been on going. Numerous other states (e.g., California) develop and utilize their own toxicity criteria. The draft HHRA will include proposed cancer and non-cancer toxicity values for purposes of assessing local risks.

As indicated above, substantial new information and scientific guidance has become available since the development of the CSF for 2,3,7,8-TCDD based on Kociba et al. (1978) and even since the comments made by the regulatory authorities in the March 2006 NOD. These include the recently published National Toxicology Program cancer bioassays on 2,3,7,8-TCDD and 2,3,4,7,8-PeCDF which provide state-of-the-art cancer bioassay information for determining cancer potency values, and also allow a direct evaluation of the TEF value for 4-PeCDF (Walker et al. 2005; Budinsky et al. 2006). The National Academy of Sciences (NAS 2006) provided numerous and extensive recommendations to the EPA directed at increasing the scientific content of EPA's risk characterizations for dioxin. The WHO-IPCS expert committee has published an update to their recommended TEFs (van den Berg et al. 2006) and simultaneously provided further guidance on their intended range of uses in PCDD/F risk assessment, and desirable extensions of the methodology to include a probabilistic treatment of the TEFs. Additional publications have addressed appropriate use of TEFs in risk assessment and evaluation of impacts of uncertainty in TEFs (Haws et al. 2006; Finley et al. 2003).

Discussion over derivation of toxicity criteria was deferred until the NAS review of the EPA Dioxin Reassessment was completed in the hopes that it would eliminate the need to pursue an independent derivation of the CSFs and RfDs for PCDD/Fs. However, the NAS review was critical of EPA's efforts, suggested major revisions of the document, but did not derive toxicity criteria for TCDD. Since it is unknown whether EPA will respond to the NAS criticisms soon enough to be useful in this HHRA, to the draft HHRA will include derivation of the toxicity criteria values taking into account the recommendations of the NAS and the specific characteristics of the local PCDD/F profile. Because of the unique furan-dominated TEQ fingerprint in the Tittabawassee River Study Area, the development of toxicity criteria for these furans may also be regarded as a site-specific effort that would support a site-

³⁸ Timothy Fields, Jr. Acting Administrator /s/ Office of Solid Waste and Emergency Response "Approach for Addressing Dioxin in Soil at CERCLA and RCRA Sites" (April 13, 1998) OSWER Directive 9200.4-26. <http://www.epa.gov/superfund/resources/remedy/pdf/92-00426-s.pdf>

specific soil criterion, provided adequate dose-response assessment can be done. Ultimately, new toxicity values may not be needed, if for example, risk management decisions made pursuant to the RIWPs are made without reliance upon numeric criteria. The important issues raised by the NAS 2006 review included: use of a non-linear (threshold) dose-response model in development of estimates of the CSF; use of different dose metrics (e.g., body burden, organ doses) that incorporate the kinetics of the PCDD/Fs; incorporation of probabilistic techniques for estimating uncertainty and variability in the values derived (including TEFs), development of a RfD based on appropriate endpoints, and taking into account human and animal data, relevant dose-response models and use of appropriately defined uncertainty factors. Concurrent with release of the NAS report, the WHO published an update on their TEF estimates (van den Berg et al. 2006) and simultaneously provided useful guidance on the use of TEFs in dioxin risk assessment complementary to other publications regarding the use of TEFs in risk assessment (Haws et al. 2006; Finley et al. 2003). As with the cancer and non-cancer toxicity criteria, the ability to incorporate new data and best information into the TEFs will be subject to future discussions with MDEQ as well as use of an Independent Science Advisory Panel (ISAP) process.

Dow and MDEQ will meet after the December 1st 2006 submission of the RI WPs to chart a course of action for the development of these toxicity criteria, and the scientific recommendations of the NAS (2006) and WHO TEF (van den Berg et al. 2006) reports will be included in those discussions. The draft HHRA proposes to include development of deterministic toxicity criteria. However, it remains possible that a probabilistic derivation may be necessary to address the complexity and uncertainty inherent in the PCDD/F database.

Regardless of how they are derived, the final toxicity criteria value or values will subject to third party external review to ensure transparency of the process and quality of the values. The following discussion provides an overview of the scientific issues that need to be considered in derivation of appropriate toxicity criteria for cancer, non-cancer and TEFs.

1. Critical Effect/Data Set
2. Dose Measure
3. Response Measure
4. Dose-Response Model
5. Point of Departure
6. Extrapolating to Low Doses
7. Inter-species extrapolation (if necessary)
8. Presentation of Toxicity Value

Where possible, information regarding the mode of action (MOA) for the chemical should be used to guide the decisions made at each point (Cohen et al. 2004; Cohen et al. 2003; Bolt et al. 2004; Butterworth 2006; Meek et al. 2003; Byrd et al. 1998 Purchase and Auton 1995; Dellarco and Baetcke 2005; Holsapple et al. 2006). Also, because the seven steps are common to non-cancer and cancer risk assessment, efforts to harmonize both assessments are encouraged by ongoing initiatives.

6.5.1.1 Cancer Dose-Response Assessment

Although PCDD/F, and particularly 2,3,7,8, -tetrochlorodibenzo-p-dioxins are known to be carcinogenic in animal bioassays and are suspected to be human carcinogens based on limited evidence in human populations (Kociba et al. 1978; NTP 2004; Cole et al. 2003), there has been considerable debate since the mid 1980s regarding the most appropriate data set(s) and methodology to apply in evaluating carcinogenic risks associated with PCDD/Fs in risk assessment (NAS 2006; Starr 2001 and 2003).

The NAS review rejected the EPA's proposed CSF ("Use of this approach was not supported by a scientifically rigorous argument, nor was there a balanced presentation of arguments using the same data to support the calculation and interpretation of an MOE." NAS 2006, Conclusions and Recommendations, p. 186), urged EPA to consider non-linear extrapolation methods to extrapolate to low-dose exposures ("The committee unanimously agrees that the current weight of evidence on TCDD, other dioxins, and DLCs carcinogenicity favors the use of nonlinear methods for extrapolation below the point of departure (POD) of mathematically modeled human or animal data", NAS, 2006, p 135) and urged EPA to consider the NTP studies (NTP 2004a, 2006) that were not available to review at the time the 2003 reassessment was completed. They also emphasized the benefit of a probabilistic approach to best characterize the range of plausible values (NAS 2006, see Attachment HHRA A for NAS report).

NAS (2006) urged EPA to complete the derivation of toxicity values. However, this process includes several internal and external review steps and will likely not be complete by the time the HHRA for the Tittabawassee River or Midland Study Areas is initiated (or even by the time it is completed). Therefore, in order to carry out the risk assessment in the Study Area, CSFs will be derived deterministically for both 2,3,7,8-TCDD and 2,3,4,7,8-PeCDF from bioassays performed by the National Toxicology Program (NTP) in 2004 (NTP 2004a, 2006). In addition to standard default approaches for developing CSFs, this effort will include the development and consideration of a non-linear dose-response approach, as explicitly endorsed by the NAS committee, and which is consistent with the mode of action of dioxins

leading to cancer in laboratory animals, as determined by a large body of scientific information (Popp et al. 2006). The deterministic CSFs will be used in the SLRA process to conservatively estimate added lifetime cancer risk for purposes of screening pathways or exposures that do not contribute markedly to the hypothetical risk. These deterministic CSFs may also be used in assessing cancer risks in a forward-looking, PRA. However, the development and use of probabilistic CSFs to fully explore and explain the range of hypothetical cancer risks associated with site-related exposures has not been entirely ruled out based on the NAS recommendations and the information contained in Appendix D. A number of steps are required to properly develop CSFs and these will be further discussed with MDEQ. These steps are discussed in more detail below.

Cancer risks associated with other identified PCDD/Fs will be estimated using the TEF approach as discussed in the recent WHO TEF revisions (van den Berg et al. 2006) and NAS recommendations (NAS2006) as well as Michigan's Part 201 rules. More discussion on the TEFs and the potential issues associated with their use can be found in Section 6.5.3.

6.5.1.2 Critical Effect and Data Sets

This decision point requires the selection of both an endpoint (i.e., type of effect) and source (i.e., study/studies). The carcinogenic effects of TCDD have been well studied in epidemiological studies and animal cancer bioassays. Established quantitative dose-response data are available from cancer bioassays in laboratory animals and these serve as the current means to conduct cancer risk assessment for PCDD/Fs. The methods by which to estimate cancer potency information from the newer data are also available and these methods include the use of non-linear estimates as recommended by NAS and other scientists. In contrast, the epidemiological data are not useful for establishing a CSF for TCDD due to large uncertainties in exposure estimates and potential confounding exposures (Aylward et al. 2005).

6.5.1.2.1 Epidemiological or Animal Data

Both epidemiological and laboratory animal studies have associated strengths and limitations (Cheng et al. 2006, Aylward et al. 2005; Bodner et al. 2003; Ketchum and Michalek (2005); Walker et al. 2006, Ott and Zober 1996; Flesch-Janys et al. 1998; Steenland et al. 1999; Steenland et al. 2001; Fingerhut et al. 1991; Bertazzi et al. 2001). The human data sets are most certainly relevant to hazard assessment; however, the exposure estimates are highly uncertain, the modeling of "all-cancer" mortality is unusual, unprecedented in its lack of biological plausibility, and causal inference from these studies is problematic for a variety of reasons (Starr 2003; Cole et al. 2003). In addition, use of epidemiology data generally

will increase the complexity of the dose-response assessment (because of the problems involved in dose estimation).

The NAS (2006) has stated: “EPA used linear extrapolation from the POD, the ED01, derived from the cancer epidemiological studies to calculate a CSF. The resulting cancer risk estimate of 1×10^{-3} per pg TEQ/kg of body weight per day for both background intakes and incremental intakes above background was considered by EPA to be the most appropriate approach. Using a linear extrapolation approach in the Reassessment was one of the most critical decisions by EPA. Use of this approach was not supported by a scientifically rigorous argument, nor was there a balanced presentation of arguments using the same data to support the calculation and interpretation of an MOE.” (NAS 2006, p186). In view of the lack of scientific support for use of epidemiological data in this way, the HHRA proposes initially to use data from animal bioassays in a standard (default) way. Other options may be explored in sensitivity and uncertainty analyses.

A number of animal cancer bioassays are available for TCDD that describe dose-response relationships for several tissue sites, most notably in the liver (NTP 1982; NTP, 2006; Kociba et al. 1978; Van Miller et al. 1977; Toth et al. 1979; Della Porta et al. 1987; Rao et al. 1988). As opposed to epidemiological studies exposures (or doses) are known with a high degree of certainty for the animal data sets; however, the relevance of results to human health is uncertain. Species differences in toxicokinetics and toxicodynamics complicate interspecies extrapolation, as exemplified by the well-known differences in sex and species sensitivity demonstrated by TCDD (e.g. humans are known to be less sensitive to some effects of TCDD than even closely related animal species³⁹). Another factor to consider is the life-stage

³⁹ Direct comparison between laboratory animal and human sensitivity to dioxin toxicity can be made for several endpoints. The human Ah receptor (AhR) expresses a mutation that is identical to that observed in the “non-responsive” DBA mouse strain. This mutation results in reduced binding affinity for dioxin and conveys a fundamental reduction in sensitivity compared to responsive mouse and rat strains of approximately 10-fold (reviewed in Connor and Aylward 2006). With respect to acute lethality, several poisoning incidents have resulted in measured body burdens substantially in excess of the lower end of the range of LD50 values for laboratory rodents (Geusau et al. 2001; Ryan et al. 1990; Brouwer et al. 2005). German researchers have examined the relationship between dioxin exposure and immune system endpoints in marmosets (a non-human primate) and in occupationally exposed workers. Specific alterations in lymphocyte subsets were observed in marmosets at body burdens similar to those found in the workers, who demonstrated no alterations in lymphocyte subsets related to exposures (Neubert et al. 1993, 1994a, 1994b). Human embryonic palatal shelves are several hundred times less sensitive than mouse palatal shelves to cleft palate induction from dioxin exposures (Abbot et al. 1999). Finally, induction of expression of mRNA for and induction of activity of CYP1A1 and CYP1A2 enzymes are endpoints that have consistently been observed to be the most sensitive responses to dioxin exposures. Multiple studies of exposed human populations have demonstrated that in persons with body burdens up to about 250 ng TEQ/kg (corresponding to serum lipid concentrations of approximately 1,000 ppt TEQ), no significant induction of mRNA, protein, or enzyme activity is observed, while significant changes in enzyme activity are clearly observable in laboratory rodents at body burdens below 50 ng TEQ/kg (reviewed in Connor and Aylward 2006; see also Lambert et al. 2006).

at which exposure occurs. In epidemiological studies of occupationally exposed cohorts, exposure to PCDD/Fs occurs exclusively during adulthood. On the other hand, in animal cancer bioassays, exposure to these compounds begins much earlier in life. Since TCDD is widely recognized as a tumor promoter (rather than a tumor initiator), this difference in exposures may affect the occurrence of cancer and its extrapolation between species and ages. The findings from well-conducted animal studies, which included exposure during earlier life stages, suggest that the animal data are the most technically supportable basis for derivation of a CSF.

6.5.1.3 Dose Measure

A number of decisions are necessary in selecting an appropriate dose measure for characterizing the dose-response relationship. For purposes of generating a deterministic CSF for TCDD and 4-PeCDF for this risk assessment, the dose measure selected will be the applied dose, in keeping with standard EPA approaches to developing such toxicity criteria. However, other dose measures recommended by NAS or other authoritative bodies and discussed in the following sections may be considered in sensitivity and uncertainty analyses.

6.5.1.3.1 Internal or External Dose

The selection of an appropriate dose measure for the dose response assessment should consider the relevance of the endpoint, the quality of the data and the study from which the data are derived, the persistence, mode of action, and target tissue of the compound under consideration. Because of the persistence of many PCDD/Fs, use of an external dose measure (e.g., lifetime average daily dose or LADD in terms of mg/kg-day for oral exposure; ppm or ppm-years for inhalation exposure) is not preferred (NAS 2006). Instead, NAS (2006) recommended implementing pharmacokinetic modeling in the dose-response assessment to estimate internal dose measures. Internal dose measures (i.e., body burden, tissue dose, etc.) can be estimated using a variety of available pharmacokinetic (PK) or physiologically based pharmacokinetic (PBPK) models, or can be estimated based on measurements of tissue concentrations in experimental studies (e.g., the recent NTP bioassays contain measured tissue concentration data at several time points during the experiments).

A wide variety of pharmacokinetic models are available to describe the behavior of TCDD in laboratory rodents and in humans. These models incorporate varying degrees of physiological representation of the phenomena that govern distribution and elimination of TCDD (Aylward et al. 2005; Carrier et al. 1995a,

b; Emond et al. 2004; Kim et al. 2002; Maruyama et al. 2002, 2003; NTP 2006). However, only Carrier et al. (1995a, b) and Maruyama et al. (2003) have parameterized models for 4-PeCDF, and none of the available models have been parameterized, implemented, validated, or otherwise developed for the other major furan compound present in the Study Area, TCDF. Because the distribution behavior of TCDF is substantially different than that of TCDD and 4-PeCDF (i.e., no significant hepatic sequestration), these models may have limited applicability and usefulness for modeling tissue burdens in the local risk assessment. While PBPK models are useful for addressing dose- and species-dependent factors that can complicate a dose-response assessment and are considered the “gold standard” for internal dosimetry, the lack of validated models for the major congeners of interest in the Study Area may limit their usefulness in the current risk assessment. The benefits and issues associated with applying PK and PBPK approaches towards development of toxicity criteria including the cancer potency values will be discussed with MDEQ prior to selecting the approach to be used. If PK models predict the relevant dose metric as well as PBPK then the relatively more straightforward PK approach will be used.

6.5.1.3.2 *Body Burden or Tissue Dose*

The NAS (2006) review recommended body burden as a better dose measure than administered dose. Body burden may be an appropriate dose measure for assessing total cancer risk or risk from combined tissue sites for PCDD/Fs, but it also has a tendency to distort the risks to human health due to species differences in distribution (i.e., adipose versus hepatic sequestration). For this reason, a tissue dose (e.g., liver burden) may be a better internal dose measure for specific endpoints. Again, the use of a PK or PBPK model may be useful to develop appropriate dose estimates for some congeners.

6.5.1.3.3 *Dose Metric*

PK and PBPK models can also be used to calculate several metrics for tissue dose including peak, average, and area-under-the-curve or AUC. Because of its persistence in tissues, a cumulative dose measure (AUC) is generally recommended over other measures of internal dose for dioxins and furans.

6.5.1.3.4 *Parent Chemical or Metabolite*

Based upon the current understanding of the mode of action for TCDD (involving an initial interaction of parent chemical with Ah receptors), a dose metric based on the parent chemical in tissues is recommended for cancer and non-cancer risk assessments. There is some evidence to support a potential role for metabolites for some endpoints (Smith and De Matteis 1990); however, the general scientific consensus on the mode of action for PCDD/Fs is one of parent compound binding to the Ah receptor and activating gene expression. However, the PCDD/Fs that are more rapidly metabolized may also have

limited toxicological relevance as the result of clearance and elimination from the body. For example, TCDF's well-known metabolic clearance and inability to bioaccumulate (Olson et al. 1994; Tai et al. 1993; McKinley et al. 1993) has important ramifications for TCDF as confirmed by the Pilot bioavailability Study, the Wild Game Study, and mink data from the Tittabawassee River Study Area. These local, site-specific tissue data for TCDF clearly show the absence of TCDF in the liver. Therefore, while TCDF may contribute to a hypothetical risk based on administered dose, TCDF's absence in a key target organ argues against its inclusion in a cancer risk assessment conducted on a target organ concentration or body burden basis.

6.5.1.4 Response Measure

Risk can be calculated using one of several metrics:

$$\text{Relative Risk} = [\text{Observed Cancer Response}]/[\text{Expected Cancer Response}]$$

$$\text{Extra Risk} = [P(d)-P(0)]/[1.0-P(0)]$$

$$\text{Added Risk} = P(d)-P(0)$$

Where,

d = dose

P(d) = Probability of a cancer response at dose d

P(0) = Probability of cancer response at zero dose

Although information for the likely Mode of Action (MOA) might be used to support a decision for response measure (depending upon relationship between treatment related and spontaneous tumors), the default decisions for human (relative risk) and animal (extra risk) are recommended and will be used in the deterministic derivation of TCDD and 4-PeCDF CSFs. There are multiple lines of evidence indicating a threshold approach to cancer risk assessment for TCDD. These include: 1) TCDD's mode of action (ligand-AHR binding to DRE with recruitment of co-activators and repressor proteins), clearly a mass-action receptor phenomenon, 2) TCDD's biology of disrupting cell cycle kinetics with enhancement of cellular growth characteristics, another threshold phenomenon, 3) the histopathological time course of TCDD-induced lesions with clear progression of liver hypertrophy and accompanying necrosis into adenomas and carcinomas, and, 4) the reversibility of various end points, as evidenced by the NTP Start-Stop studies. Simply put, absent cell, tissue and organ toxicity, no cancer risk appears to exist from low TCDD tissue concentrations. The same issues could be easily accounted for if a probabilistic derivation

of the CSF was developed. The implications of these factors in deciding on how to develop the CSFs will be discussed with MDEQ.

6.5.1.4.1 *Animal data*

EPA's Benchmark Dose Software (BMDS, version 1.3.2) includes a number of models available for dichotomous data collected from cancer bioassays: Multistage, Gamma, Logistic, Probit, Quantal Linear, Quantal Quadratic, Weibull. Alternative dose-response models can also be considered. The model or models used to develop the CSF for the dose-response assessment will be selected based upon a consideration of visual inspection, p-value for goodness of fit test, and AIC value. Preliminary evaluation shows that selection of any particular model, provided it fits adequately, has negligible effect on estimates.

For purposes of the deterministic CSFs for TCDD and 4-PeCDF, the Linearized Multistage Model (LMS) will be used since it is the EPA default model. and it provides an adequate fit to all the animal data available for TCDD and 4-PeCDF. For threshold evaluation, an LMS model that incorporates a threshold will be used.

6.5.1.4.2 *Point of Departure*

Consistent with EPA guidelines (EPA 2005a), a point of departure is selected to separate the "range of observation" from the "range of extrapolation". The range of observation should consider both the range of doses tested, and the range where increased risk can be reliably observed as defined by specific data set. A number of response levels serve as potential candidates for the point of departure with the default for animal data being the effective dose producing a 10% increase in response (ED10) and its lower confidence limit (LED10). Animal data sets generally do not support points of departure lower than 5%, since test groups typically do not have sufficient power to detect a 1% increase in risk. This has been specifically shown for TCDD (Gaylor and Aylward 2004). Lower points of departure are possible when large exposure groups are used (e.g., >100 tested/group) or when data sets are pooled together such as might be done in a meta-analysis or a probabilistic treatment of the CSF. At the moment, the POD selected will be based on the characteristic of the data set chosen to develop the CSF.

6.5.1.4.3 *Low Dose Extrapolation*

The decision regarding the most appropriate method for extrapolating to low doses requires a careful consideration of the mode of action (MOA). Options for low-dose extrapolation include linear (default),

nonlinear/threshold (MOE or RfD approach), or through use of a biologically based model. EPA (2005a) considers agents to be linear at low doses when either of the following conditions is met:

- (1) Agents that are DNA-reactive and have direct mutagenic activity, or
- (2) Agents for which human exposures or body burdens are high and near doses associated with key precursor events in the carcinogenic process, so that background exposures to this and other agents operating through a common mode of action are in the increasing, approximately linear, portion of the dose-response curve.

As a matter of science, and consistent with NAS (2006) recommendations, TCDD does not meet the first requirement for linear low-dose extrapolation. However, the second requirement is subject to debate, and will depend upon the dose measure used (body burden vs. tissue burden) and definition of the low end of the range of observation (ED01 versus ED10). The choice for this decision will be based on the data set and the manner in which it is to be treated. Further, substantial evidence exists that humans are fundamentally less sensitive to many biological responses to TCDD than rats and other laboratory species¹ (See footnote 39). Therefore, the exercise of comparing human body burdens to (animal based) NOAEL/LOAEL body burdens derived from rat studies is likely to overestimate human risks.

EPA may ultimately revise its assessment to include both linear and nonlinear extrapolations, which would be consistent with NAS recommendations. Popp et al. (2006) recently came to the same conclusion supporting the use of a threshold approach for TCDD carcinogenicity. Again, unless a threshold for tissue response is achieved, i.e., CYP1A induction or liver injury revealed by elevated liver enzymes, a risk for TCDD-induced cancer does not exist. According to the current UMDES data, local residents do not have dioxin concentrations sufficient to elicit these basic phenomena that occur prior to downstream cellular, tissue and organ events that cause cancer (Connor and Aylward 2005; Guzelian et al. 2006). Because this is such a critical and controversial decision point, this may be an area where expert elicitation such as an Independent Science Advisory Panel (ISAP) (consistent with EPA guidelines) may be useful. To reiterate, the deterministic CSF developed for both TCDD and 4-PeCDF will be based on a linear, non-threshold response, as has been the standard default assumption for cancer risk assessments; however, the assumptions inherent in this choice, the impact of an alternative, more likely extrapolation, and the comparison to available site-specific data must be included in the risk characterization. If undertaken, a probabilistic treatment of the CSF would include both threshold and non-threshold models.

Low dose extrapolation should take into account potentially susceptible subpopulations such as nursing infants. Based upon the likely MOA (tumor promotion), the additional adjustments defined by EPA (2005a) for genotoxic carcinogens are not applicable for the PCDD/F (Anderson 2006; Anderson 2004a, 2004b; Preston 2004; Bunin 2004). Further, the epidemiological data do not support a need to incorporate additional uncertainty factors related to higher breast milk intake since epidemiological studies of breast fed individuals with body burdens comparable to today's young people find no evidence of increased lifetime cancer risk compared to those not breastfed (Martin et al. 2005a) a finding consistent with risk evaluations performed for both breast-fed and formula-fed infants (Maruyama et al. 2004). Epidemiological evidence shows that the incidence of childhood tumors is reduced in breast fed children (Kwan et al. 2004; Martin et al. 2005b). Therefore, there is little evidence to factor in either a breast milk exposure pathway or additional protective uncertainty factors when considering cancer risk and childhood exposures. This line of reasoning is further developed in Appendix D. Limited animal data are available to address early-life susceptibility in mice (Della Porta et al. 1987). However, since PCDD/Fs act as tumor promoters, late-life exposures are expected to be more important. Late life exposures are already addressed in both epidemiological and cancer bioassay data sets. Ah receptor polymorphisms exist in humans, but most do not impact phenotype/response to ligands (Harper et al. 2002; Okey et al. 2005)

6.5.1.4.4 *Presentation of the Carcinogenic Slope Factor*

Although past dose-response assessments have relied upon deterministic point estimates for characterizing cancer potency (upper bound estimate when based upon animal data; central tendency estimate when based upon human data), EPA (2005a) guidelines and NAS (2006) recommendations include presentation of central tendency, upper bound, and lower bound estimates of cancer potency. The EPA (2005a) guidelines are intended to be flexible enough to incorporate additional approaches for characterizing uncertainty that have less commonly been used by regulatory agencies in the past. This could include presentation of a probability density function for CSF using Monte Carlo or probabilistic methods. Such methods have been applied to exposure assessment for years, and more recently to toxicity assessment (Crouch 1996; Crouch 2005; Crouch et al. 2005). The SLRA will use a deterministic approach (single sensitive endpoint scaled to the $\frac{3}{4}$ body weight with the CSF determined using the LMS for both TCDD and 4-PeCDF from the recent NTP bioassays) in order to be conservative and only screen out exposures that carry a low theoretical risk. The CSF used in the forward looking PRA will also initially use a deterministic CSF, but then may move to probabilistic estimates of the CSF that would serve to define the full range of theoretical cancer risks and their uncertainty and variability more completely.

6.5.2 Derivation of Toxicity Values for Non-Cancer Endpoints

The most sensitive endpoints observed in experimental animals should be used as the basis for the derivation of cancer or non-cancer toxicity criteria when adequate human data is not readily available or interpretable. Discussions with MDEQ on the animal and human data will be necessary to develop proper characterization of non-cancer risks based upon concerns over sensitive subpopulations such as the fetus and infant. However, in the specific case of dioxins, numerous issues must be accounted for in selecting appropriate non-cancer toxicity criteria: Some of these issues are:

- The presence of an extensive database of studies using TCDD in which all studies examine the same sensitive endpoints but which identify substantially different quantitative estimates of LOAELs and NOAELs for these endpoints in the same species. A critical review of these data, evaluation of the possible sources of the discrepancies in results, and a comprehensive approach to including these data is both necessary and appropriate for a scientifically sound risk assessment.
- A review of issues related to deriving appropriate and scientifically justified toxicity criteria including endpoints of concern, species sensitivity dosimetry and kinetics, dose-response models and extrapolation, uncertainty factors (including data -derived uncertainty factors), and so forth
- A review of the available epidemiological data to determine if such data are useful for deriving toxicity criteria or for providing supporting data in a weight of evidence approach
- The necessity and methodology for extrapolation from TCDD to other PCDD/Fs for the Study Area. Scientific evidence on specificity of particular toxic endpoints may affect such extrapolations and should be considered carefully.

These points are expanded on below, and must be resolved before development of non-cancer toxicity criteria can be completed and used to identify issues and solutions to the broader problem of accurately assessing human health risk. The HHRA will be modified to include any additional CoPCs identified in the draft HHRA. If they are identified as chemicals of concern for this site, these compounds will be treated in such a manner to ensure that developmental effects (or other relevant non-cancer endpoints) are included in the risk assessment with appropriate time averaging for model inputs and outputs.

The development of a TCDD RfD was not attempted by EPA in its Dioxin Reassessment and this was a source of criticism by NAS (2006). The draft HHRA will propose a means to scientifically address this issue and derive an RfD for use in the HHRA as well as in the development of a DCC as previously discussed in Section 6.1.2. The derivation of an RfD will include identification of endpoints and data sets, application of appropriate dose-response models, and selection of appropriate uncertainty factors.

The final value or values will be subject to third party external review by an ISAP to ensure transparency of the process and quality of the results obtained.

6.5.2.1 Overview of Available Criteria

Several non-cancer toxicity criteria are available for TCDD. Each of these values is conventionally applied to all PCDD/Fs by use of the Toxicity Equivalency (TEQ) method. Table 1 summarizes each of these criteria and describes the basis for the values. Each of these criteria was derived from animal data on effects in offspring exposed to TCDD while *in utero* and postnatally via lactation. The criteria were all derived with the goal of maintaining adult maternal exposures below levels associated with effects in offspring. While all of the major criteria are reported on an intake basis, only two of them, the Agency for Toxic Substances and Disease Registry (ATSDR) and Great Lakes criteria, were actually derived on an intake basis. The World Health Organization/UN Food and Agriculture Organization Joint Expert Committee on Food Additives (WHO/FAO JECFA) value were derived on the basis of maternal body burden, after continuous exposure until after childbirth and lactation.

Table 6-9 Overview of non-cancer toxicity criteria

Organization	Value	Toxicity Study/Endpoint	Comment
Great Lakes Acceptable Daily Exposure (ADE) (1995)	1.3 pg/kg/d	Bowman et al. (1989). Reproductive toxicity in rhesus monkeys.	Estimate of maternal intake rate of 0.13 ng/kg/d NOAEL, interspecies and intraspecies uncertainty factors of 10 each for a total factor of 100.
ATSDR Minimal Risk Level (MRL) (1998)	1 pg/kg/d	Schantz et al. (1992). Neurobehavioral changes in offspring.	Estimate of maternal intake rate of 0.12 ng/kg/d LOAEL. Uncertainty factors of 3 for minimal LOAEL to NOAEL, 3 for interspecies extrapolation, and 10 for intraspecies sensitivity, for a total of 100.

WHO/FAO JECFA (2001) Provisional Tolerable Monthly Intake (PTMI)	70 pg/k/month (2.3 pg/kg/d)	Gray et al. (1997); effects on male rat reproductive system development following in utero exposure (decreases in sperm counts)	Background body burden in rats was accounted for in the evaluation. Dose metric used was maternal body burden after acute administration, adjusted for differences in distribution to fetus after chronic rather than acute administration. Committee judged that humans were likely to be no more sensitive than the most sensitive laboratory rodents to the effects of dioxin. Value was judged to be protective for carcinogenesis as well based on an assumed threshold mechanism. Total uncertainty factors were: 3.2 (inter-individual variability) * 3.2 (sensitive endpoint, considered close to a NOEL for a marginal effect, LOEL to NOEL factor) * 1 (interspecies toxicokinetic factor because of use of body burden) * 1 (interspecies toxicodynamic factor, humans no more sensitive than most sensitive animal) = 9.6.
ECSCF (2001)	14 pg/kg/week (2 pg/kg/d)	Male rat reproductive system developmental effects	Similar to JECFA derivation

6.5.2.1.1 Applicability of Current Criteria

The developing offspring, exposed *in utero* and postnatally through lactation, are the most sensitive receptors identified in laboratory studies of non-cancer effects of dioxin. This was explicitly recognized by all of the agencies that have derived non-cancer criteria for TCDD and related compounds. All of the current criteria were derived with the goal of keeping long term adult maternal intake levels below levels that would accumulate to body levels that could produce adverse effects in offspring. As such, these criteria should be applied to assessing maternal adult, not childhood, intakes of dioxins.

In general children may experience greater intake rates of contaminants on a body weight basis due to a greater food intake rate and contact with the environment. However, the body concentrations of dioxins decline more rapidly in children than in adults due to both growth and dilution and faster elimination rates (Leung et al. 2006; Lorber and Phillips 2002). This is reflected in the pattern of body burdens noted in the general population, where children demonstrate substantially lower body burdens than adults (see, for example, Link et al. 2005) despite higher daily exposure on a per kg bodyweight basis (Lorber and

Phillips 2002). Existing non-cancer criteria are directed explicitly to protect children through preventing elevated *in utero* and breast milk exposures by controlling the **adult** maternal body levels of these compounds. Comparison of estimated childhood intake rates (from breastfeeding or other sources) to these criteria is inappropriate and incorrect without accounting for the more rapid elimination of dioxin and furan compounds in children (See Appendix D for further discussion).

6.5.2.1.2 *Scientific Shortcomings of the Current Criteria*

There are significant shortcomings in the scientific basis for each of the current non-cancer criteria for TCDD and associated chemicals. Some of these shortcomings have particular relevance to the risk assessments for the Study Areas. The major issues are as follows:

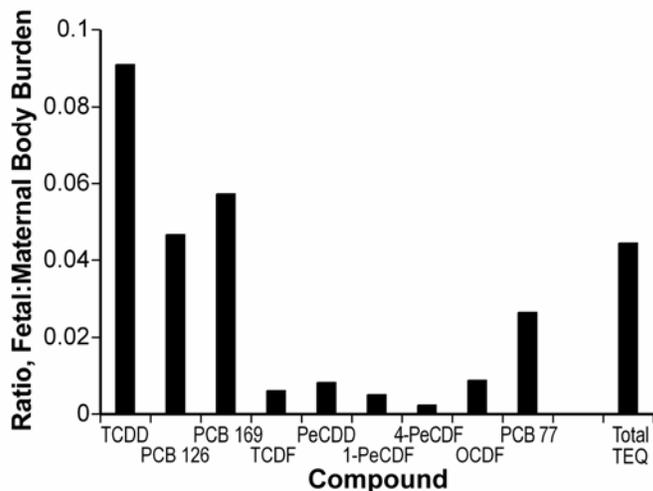
- Rats appear to be more sensitive to TCDD than humans and this sensitivity is further complicated by the difference in rat reproductive physiology compared to humans including differences in placental biology, immaturity of birth for rat pups versus humans, and the much higher transfer of dioxins/furans to the rat pup since rat breast milk is higher in lipid than human breast milk. Arguably, the rat reproductive/developmental findings represent the most sensitive highly conservative animal effect known for TCDD and a risk not shared by humans to the same degree
- A recent publication (Rier et al. 2001) presented new data that demonstrate that the major studies that underlie the ATSDR and Great Lakes criteria, Bowman et al. (1989) and Schantz et al. (1992), are critically confounded because of high co-exposure to polychlorinated biphenyls (PCBs) and cannot be relied upon as the basis for quantitative risk assessment for dioxins. These data were relied upon by the ECSCF and WHO/FAO JECFA committees, in their decisions to exclude the Bowman et al. (1989) and Schantz et al. (1992) data from their quantitative assessments. With regards to past MDEQ guidance, the use of the Great Lakes reference dose of 1.3 pg/kg/day is no longer scientifically based given the confounding by PCB exposure.
- The rodent studies that form the basis for the WHO/FAO JECFA criterion used acute or repeated bolus dosing regimens that may over predict effects from the chronic environmental exposure situation. The fact that some of the rat studies reporting developmental effects relied upon acute gavage dosing to achieve a body burden a young woman would achieve over 20 to 30 years of daily, dietary ingestion of much smaller dosages, raises serious questions about the relevance and validity of the rat data in predicting human risk. It is expected that these bolus body burden dosages achieve higher short-term levels of TCDD in the fetal compartment than would occur following low-level chronic exposures leading to the same maternal body burdens. The

WHO/FAO JECFA committee acknowledged this shortcoming and adjusted their assessment to partially account for this issue, but the full impact may not have been accounted for.

- The endpoints of concern identified in the small rat studies that underlie the WHO/FAO JECFA criterion have been examined in much greater detail in more recent studies (including one evaluated in the WHO/FAO JECFA process, Ohsako et al. 2001). The original endpoint of concern, effects on spermatogenesis in male rats exposed in utero, have not been confirmed in the more recent studies which used larger numbers of animals and modern sperm counting and evaluation techniques (Ohsako et al. 2001; Bell et al. presentation at MSU, July 18th, 2006). Other, subtle effects of questionable biological relevance have been observed in these studies at similar dosages, but the original more adverse findings of Gray et al. (1997), Mably et al. (1992), and Faqi et al. (1998) have not been confirmed in these larger, more recent studies.

All of the available studies examined the effects of TCDD. However, other TEQ-contributing compounds are distinctly different from TCDD in their ability to distribute to the developing fetus the developing animal. Figure 6-4 shows the ratio between rat fetal and maternal body burdens for different dioxin-like compounds that were studied in a mixture. While the rat fetus experienced body concentrations of TCDD nearly 10% of those in the maternal animal, other compounds were overwhelmingly sequestered in the maternal liver and were not available for distribution to the fetus. In particular, 2,3,4,7,8-pentachlorodibenzofuran (4-PeCDF) and 2,3,7,8-tetrachlorodibenzofuran (TCDF) were less than 1/10th as available to the fetus as TCDD. In a risk assessment in which the predominant exposures are to these compounds rather than TCDD, an evaluation based on TCDD-derived criteria may significantly overestimate the risk of adverse effects. However, because no comparable animal studies have been done with either 4-PeCDF or TCDF, this hypothesis cannot be evaluated at this time. It is of note that the WHO-IPCS committee (van den Berg et al. 2006) cautioned about the use of TEFs in application to body burden and tissue concentration-based assessments because of their failure to take account of pharmacokinetics. 4-PeCDF and TCDF, in particular, do not distribute to the fetal compartment to the same extent as TCDD. One could argue that the TEF value for non-cancer risk assessment for 4-PeCDF and TCDF should be adjusted 10-fold lower based on this knowledge of tissue distribution kinetics. A 10-fold reduction in the current WHO TEF for 4-PeCDF from 0.3 to 0.03 is consistent with the approximate 0.03 TEF for 4-PeCDF when derived with internal dose metrics of liver concentration and body burden (Budinsky et al. 2006; Gray et al. 2006).

Figure 6-4: Ratio of fetal to maternal body burden of dioxin-like compounds in a rat mixture study (data from Chen et al. 2001, figure from Aylward et al. 2005).



6.5.2.2 Non-Cancer Criterion for the SLRA

As discussed above, all available non-cancer criteria suffer from scientific shortcomings that limit their validity for the application to the HHRA. Despite these shortcomings, for the purposes of the SLRA, The WHO/FAO JECFA Provisional Tolerable Monthly Intake of 70 pg TEQ/kg/month (WHO/FAO JECFA 2001) will be used as the non-cancer toxicity criterion along with further information used to update this value including the published epidemiological data.

6.5.2.3 Development of a Non-Cancer Criterion for the PRA

The following section describes the proposed approach for development of a non-cancer toxicity criterion (RfD) for use in the full risk assessment and discusses the available data sets for this process. The final approach and development of an RfD will be developed following discussions with MDEQ.

6.5.2.3.1 Selection of Toxicity Endpoints and Studies

Human Developmental Effects Data. The endpoints of concern for non-cancer risk assessment of dioxins are focused on potential developmental effects in infants exposed *in utero* and lactationally (See Table 6-10). Numerous human data sets are available for evaluating dose-response for potential developmental effects on the immune, hematological, hormone, neurological, and other organ systems in

children after perinatal (*in utero*, lactational, or childhood) exposure to TCDD and related compounds. These studies are identified in Table 2 and include:

- Two longitudinal cohort studies of children examining a variety of developmental endpoints to *in utero* and/or lactational exposures to dioxin and furan compounds in the Netherlands (the Rotterdam/Groningen and the Amsterdam cohorts; together, the “Dutch studies”);
- A recent study of German infants (the “Duisburg cohort”)
- Studies of children exposed to TCDD in Seveso examining developing teeth (a sensitive endpoint in rodent studies) age at puberty (also a sensitive endpoint in rodent studies), and menstrual cycle characteristics after puberty.
- Studies of infants from Japan with quantified dioxin and furan exposures.

The Dutch and Japanese studies provide quantitative measures of exposure in terms of prenatal exposures (estimated from measurements in milk samples from the mother, which, on a lipid basis, have been shown to be highly correlated with maternal serum lipid dioxin TEQ levels; Wittsiepe et al. 2004) and postnatal exposures due to breastfeeding estimated by multiplying the concentrations of “dioxin-like” compounds (PCDDs, PCDFs for all studies, and including non-ortho PCB compounds for the Rotterdam/Groningen cohort and the Japanese studies) in human milk by the duration of breast feeding.

The data from these studies will be described, tabulated, and extracted to identify candidate data sets with information on responses observed consistently in response to dioxin exposures and that provide sufficient detail to allow identification of NOAEL/LOAELs and benchmark dose analysis of the observed responses. Existing reviews of these data will be utilized (for example, Schantz et al. 2003; Giacomini et al. 2006) to streamline this process where appropriate.

Table 6-10: Developmental endpoints evaluated in human studies with quantified dioxin TEQ exposures

Endpoint Description	Study	Dose Metric
Thyroid hormone alterations in infants	Koopman-Esseboom et al. 1994	Maternal serum lipid TEQ concentration (estimated from milk lipid concentration); Infant dioxin intake
	Pluim et al. 1993	Infant dioxin intake
	Nagayama et al. 1998	Infant dioxin intake
	Matsuura et al. 2001	Maternal serum lipid TEQ (estimated from human milk lipid

		concentration)
	Nagayama et al. 2004	Infant dioxin intake
	Wilhelm et al. 2006	Maternal serum lipid TEQ concentration; milk lipid TEQ concentration; Infant dioxin intake
Neurodevelopmental effects	Huisman et al. 1995	Maternal serum lipid TEQ concentration (estimated from milk lipid concentration)
	Lanting et al. 1998	Maternal serum lipid TEQ concentration (estimated from milk lipid concentration); Infant dioxin intake
	Patandin et al. 1999	Maternal serum lipid TEQ concentration (estimated from milk lipid concentration); Infant dioxin intake
	Ilse et al. 1996	Infant dioxin intake
	Wilhelm et al 2006	Maternal serum lipid TEQ concentration; milk lipid TEQ concentration; Infant dioxin intake
Infant growth and development	Ilse et al. 1996	Infant dioxin intake
	Pluim et al. 1996	Infant dioxin intake
	Patandin et al. 1998	Maternal serum lipid TEQ concentration (estimated from milk lipid concentration); Infant dioxin intake
Platelet alterations in infants	Pluim et al. 1994	Infant dioxin intake
Lymphocyte subset alterations	Nagayama et al. 1998	Infant dioxin intake
	Weisglas-Kuperus et al. 1995	Maternal serum lipid TEQ concentration (estimated from milk lipid concentration); Infant dioxin intake
	Kaneko et al. 2006	Maternal serum lipid TEQ (estimated from human milk lipid concentration)
Other immune system endpoints	Weisglas-Kuperus et al. 2000	Maternal serum lipid TEQ concentration (estimated from milk lipid concentration); Infant dioxin intake
	Weisglas-Kuperus et al. 2004	Maternal serum lipid TEQ concentration (estimated from milk lipid concentration); Infant dioxin intake

ALT and AST alterations	Pluim et al. 1994 Ilsen et al. 1996	Infant dioxin intake
Developmental dental enamel anomalies	Alaluusua et al. 2004	Peak childhood body burden of TCDD
Age at puberty	Warner et al. 2004	Peak childhood body burden of TCDD
Menstrual cycle characteristics	Eskenazi et al. 2002	Peak childhood body burden of TCDD
Existing reviews of these data will be utilized (for example)	Schantz et al. 2003; Giacomini et al. 2006) to streamline this process where appropriate.	Existing reviews of these data will be utilized (for example)

6.5.2.3.2 *Dose Metric and Point of Departure Selection*

In several studies, exposure to all TEQ-contributing congeners was not measured (for example, studies of the Amsterdam cohort, which evaluated only PCDD and PCDF congeners and studies from Seveso, in which only TCDD exposure was quantified). For these studies, exposure estimates reported in the study will be adjusted to account for missing TEQ-contributing congeners based on contemporaneous data sets. For example, data from the Rotterdam cohort will be used to estimate PCB contributions to the Amsterdam cohort, and data reported by the Seveso researchers on non-exposed Italian controls will be used to estimate non-TCDD contributions to body burdens in Seveso residents.

For all studies other than the Seveso reports, the dose-response data available in the study will be used to identify a point of departure (NOAEL, LOAEL, or benchmark dose if supported by the reporting of data). This point of departure will be converted to an equivalent maternal serum lipid TEQ concentration, and then to an equivalent long-term adult maternal TEQ intake rate associated with that point of departure using first-order kinetic assumptions (see, for example, Lorber 2002).

For the Seveso data set(s), the point of departure for each endpoint will be identified in terms of peak and average serum lipid TEQ concentrations. Childhood intake rates associated with the identified point(s) of departure will be identified using age-specific first-order kinetics (Kerger et al. 2005; Leung et al. 2005; Leung et al. 2006).

6.5.2.3.3 *Additional Data for Consideration*

Because existing non-cancer criteria for TCDD TEQs have been based on animal data, the relevant animal toxicology data will also be evaluated in this effort and the results will be compared to those obtained from the human data sets.

For TCDD TEQs, the United Nations Food & Agriculture Organization / World Health Organization Joint Expert Committee on Food Additives (JECFA, 2002) estimated a tolerable (human) monthly intake value of 70 pg/kg, corresponding effectively to an RfD of about 2.3 pg TEQ/kg-day. The approach and experimental data selected by JECFA will be evaluated in this analysis, augmented by accounting for variability and uncertainty and the inclusion of data published since their review. The studies to be evaluated include those examining adverse effects on male rat reproductive system development and immunological deficits after *in utero* and lactational exposure. These include studies by: Mably et al. (1992a, b, c), Gray et al. (1995), Gehrs and Smialowicz (1997), Gehrs et al. (1997), Gray et al. (1997a, b), Faqi & Chahoud (1998), Faqi et al. (1998), Gehrs and Smialowicz (1999), Ostby et al. (1999), Ohsako et al. (2001), Chen et al. (2001), Hamm et al. (2003), and Bell et al. (2005, 2006). These studies will be evaluated for relevant points of departure for the endpoints of interest using appropriate dose-response models and recommendations for dioxins and reproductive endpoints (NAS 2006; Allen et al. 1994a, 1994b; Gaylor and Aylward 2004). Point of departure estimates from the available animal data will be developed based on these studies. The initial studies on developmental neurobehavioral effects and endometriosis in monkeys (Schantz et al. 1992; Rier et al. 1993) will not be considered, in view of the later findings of unexplained high PCB exposures in these monkeys (Rier et al. 2001).

Other data that will be considered in assessing risks of PCDD/F exposure in children and adults include:

- Data regarding the relative expression of the aryl hydrocarbon receptor (AhR) in fetal and adult tissues (Yamamoto et al. 2004);
- Data regarding the intrinsic function of the AhR in healthy reproduction (Baba et al. 2005)
- Data regarding the intrinsic structure and binding affinity of the human AhR compared to the AhRs in laboratory rodents used as the basis for risk assessment (Connor and Aylward 2006);
- Data regarding the expression of key, early biological responses to binding to the AhR in humans and rodents (Guzelian et al. 2005);
- Studies of potential health effects in highly and moderately exposed human populations (for example, Bacarelli et al. 2005);
- Data regarding measured body burdens in adults in the Study Area from the UMDES in the context of current and historical data on body burdens in the general US population and in the context of exposed study groups from other areas.

6.5.2.3.4 *Data-Derived Uncertainty Factors for Generation of Reference Doses*

Appropriate uncertainty factors will be identified and applied to the points of departure identified from the available human or animal data to derive safe intake levels for adults (to prevent maternal body burdens exceeding levels that are safe for infants exposed *in utero* or through breast feeding) and safe childhood exposure intake rates. This will take advantage of the increased knowledge of inter- and intraspecies sensitivity, mechanisms of action, and detailed evaluation of databases to develop “data-derived” uncertainty factors that result in better overall confidence in the risk assessment. EPA and Health Canada have employed such techniques to support the selection of uncertainty factors other than the default value of 10 (Dourson et al. 1996; Pelekis et al. 2003; Dorne and Renwick 2005; WHO 2005). In such cases, the types of data that are used to support a change in the default value would be explicitly reviewed to determine why the data support a different uncertainty factor, how the uncertainty is reduced, and what assumptions have been satisfied or replaced.

6.5.3 Toxicity Equivalency Factors for PCDD/Fs

The draft HHRA proposes to evaluate risks for PCDD/s using the WHO (2005) TEF values recently updated by the WHO-IPCS committee (van den Berg et al. 2006) to comply with Part 201 regulatory requirements. As stressed by that committee and by the NAS committee (NAS 2006) the use of these TEFs can only be justified for dietary exposures, so their use in assessing risks from non-dietary exposures must be done carefully, if at all. Further, there are substantial uncertainties inherent in the TEF values that need to be taken into account (Finley et al. 2003; Haws et al. 2006; van den Berg et al. 2006; NAS 2006). The use of the WHO (2005) TEFs without such scrutiny would not reflect utilization of the best information in the HHRA. Therefore, the HHRA will incorporate a thorough review, discussion and presentation of the variability and uncertainty (as well as their underlying and supporting relative potency [REP] factors) of the TEFs that are of principle importance in the Study Area. Applying the best science and information into the HHRA will be discussed with MDEQ following the December 1st, 2006 RI WP submissions.

The PCDD/Fs contributing most to TEQs (as defined by either the WHO-1998 system (van den Berg et al. 1998) or the WHO 2005 system (van den Berg et al. 2006)) in the Tittabawassee River Study Area are 4-PeCDF and TCDF. Since the toxicity of these congeners is conventionally estimated from the toxicity of TCDD by use of the TEFs, any bias or uncertainty in such TEFs will contribute directly to the overall bias and uncertainty of the HHRA. Uncertainty enters into the picture through the uncertainty in the derivation of the TEFs, and also when rodent or other data are extrapolated to humans since it is largely unknown if the same relative potencies for PCDD/Fs found in rodent or other studies apply to humans.

The TEFs presented by van den Berg et al. (1998) were based on a subjective evaluation of multiple end-points measured in many organisms or experimental systems, notably excluding (because data were not available) the end-points and organisms that are of direct interest in a risk assessment. The values presented by van den Berg et al. (2006) are also somewhat subjective, although objective initial selections were made. The subjectivity and the lack of rigorous mathematical and statistical analyses in developing the WHO TEFs is a significant problem with the use of these values in risk assessment. For any particular congener, there is a substantial variation in the values of REP obtained for different experimental systems, a variation that translates into a substantial uncertainty in the value of the TEF that is most representative of potential human toxicity for various end points. The WHO (1998) committee selected point estimates based on the multiple REP values available, using a subjective system and acknowledging the large uncertainties. Finley et al. (2003) illustrated the large uncertainties involved, and demonstrated how the original data used by the WHO committee could be used to define uncertainty distributions for TEFs, hence potentially leading to an objective estimate for TEFs.

Since the introduction of the WHO (1998) TEFs substantial new data have become available. In particular, for 4-PeCDF there are now available long-term rat bioassays (NTP 2004, 2006) that allow a direct measurement of 4-PeCDF's TEF for cancer and many non-cancer end points of primary interest in risk assessment. The newly available data allowed a re-evaluation of the WHO (1998) TEF system by the WHO-IPCS committee (van den Berg et al. 2006), and the REP2004 database of REP values upon which the committee largely relied has been published (Haws et al. 2006). This database incorporated data from the NTP (2004) bioassay on PeCDF, and included more data on TCDF. The WHO-IPCS (2005) committee selected point estimates for TEFs based on the multiple REP values available, but using a slightly less subjective approach than in 1998, and guided by the objective summary of the available published REPs (Haws et al. 2006).

The WHO-IPCS committee made several suggestions for improvement of the process used to estimate or use TEFs, including the use of probabilistic methods advocated by Finley et al. (2003) and Haws et al. (2006) and the evaluation of systemic (body burden based, or tissue concentration based) TEFs in addition or alternatively to the current system based on intakes. The committee also considered the possibility of using (even for the derivation of the WHO 2005 system) a weighted version of the REP distribution to set a single TEF value; but decided that would require more effort than was available to obtain a consensus on weighting methodology and method of selection of the point value. In addition, neither the WHO-IPCS committee nor Haws et al. (2006) re-evaluated the REPs given in literature

sources (or derived internally in 1998) to ensure that they were consistently, systematically and correctly derived.

The NAS Committee (NAS 2006) examined the use of TEFs and, while agreeing “that the TEF method is reasonable, scientifically justifiable, and widely accepted for the estimation of the relative toxic potency of TCDD, other dioxins, and DLCs” (NAS 2006, p 14), did point out various shortcomings, including the necessity of careful evaluation before applying the intake-based TEFs to body-burden-based measures of toxicity (“it remains to be determined whether the current WHO TEFs, which were developed to assess the relative toxic potency of a mixture to which an animal is directly exposed by dietary intake, are appropriate for the assessment of internal TEQ concentrations and potential toxic effects” [NAS 2006, p67]). However, the NAS Committee specifically recommended “EPA should acknowledge the need for better uncertainty analysis of the TEF values and should, as a follow-up to the Reassessment, establish a task force to begin to address this uncertainty by developing 'consensus probability density functions' for TCDD, other dioxins, and DLCs” (NAS 2006, p 14). The NAS committee recommendation could eliminate some of the concerns raised by the WHO-IPCS committee on the use of TEF in risk assessment involving contaminated soils and sediments and application of TEFs to body burden-based assessments (van den Berg et al. 2006). In particular, the NAS Committee recommended, “that EPA clearly address TEF uncertainties in the Reassessment.” In a related activity, a recent ToxForum workshop discussed issues related to TEFs with discussion identifying the problems and future directions needed for improving TEFs and their application (Budinsky 2005)

The realization that the WHO systems of TEFs apply only to intake-based measures of toxicity is of substantial importance for the TCDF and 4-PeCDF congeners contributing the majority of the TEQs in soil samples in the Study Area. This is significant because, for induction of EROD and ACOH activities in mice, the relative potencies for TCDF and 1-PeCDF, which have much shorter half-lives than TCDD in mice (hence lower tissue concentrations for equal intake dose rates), were found to be increased on a tissue concentration basis (DeVito et al. 1997). In contrast, in Sprague-Dawley rats, it was found that 4-PeCDF (and PeCDD) has a substantially lower relative potency on a tissue concentration basis for induction of tumor promoting activity (Waern et al. 1991). The same is true for 4-PeCDF as a complete carcinogen and for other end points, as is seen in the NTP bioassays (Budinsky et al. 2006). The effect of differences in metabolism of TCDF and 4-PeCDF is seen in animal tissue samples from the floodplain, where it is 4-PeCDF that dominates the TEQ concentrations, with TCDF playing a minor role, despite intake doses that should approximately reflect soil concentrations with both congeners contributing substantially. The application of WHO TEFs therefore requires the use of intake-based toxicity estimates,

particularly for the PCDFs; TEFs for systemic (e.g. body-burden-based or tissue-concentration-based) measures of toxicity would require a complete re-evaluation of the entire TEF system on that basis, something that poses a significant challenge for the HHRA.

The point estimate of TEF for TCDF selected by the WHO-IPCS committee in the new WHO (2005) system (van den Berg et al. 2006) is 0.1. This is a point estimate based primarily on the distribution of values in the REP2004 database (Haws et al. 2006), and cannot by itself indicate the (substantial) uncertainty contributed to risk estimates due to the uncertainty in the relative toxicity of TCDF. Importantly (unlike for 4-PeCDF), no cancer or cancer mode of action studies are available for TCDF, whereas there are a few teratology studies of relevance for non-cancer endpoints.

To derive an uncertainty distribution for TCDF TEF for use in this HHRA, and correctly incorporate this additional uncertainty (which is independent of the uncertainty in the toxicity of TCDD), the HHRA proposes to re-evaluate the REP2004 database values to ensure consistency and correctness in their derivation, and the results used as the basis for an uncertainty distribution. Additional published values meeting the inclusion criteria for the REP2004 database, but that were either inadvertently omitted (Haws, personal communication 2006) from the database or published after it will also be included in this re-evaluation. When necessary and possible, the original data will be obtained from the authors to allow re-evaluation. Only REPs based on studies performed on TCDF, and using TCDD as the reference material, will be included.

REPs derived from data published in the following studies are to be included: *REP 2004 database* (in all cases, the original papers will be consulted; so the references to Bols et al. and Waern in Haws et al. 2006, have been replaced with the original authors, primarily Clemons et al. 1994, 1996, and 1997). Citations to be reviewed include: Bandiera (1984), Birnbaum (1987), Birnbaum (1995), Brown (2001), Clemons (1997), Clemons (1994), Clemons (1996), Davis (1988), Davis (1991), DeVito (1993), DeVito (1994), DeVito (1995), DeVito (1997), Gierthy (1985), Harris (1990), Krishnan (1993), Li (1999), Mason (1985), McConnell (1978), McKinney (1985), Moore (1973), Takagi (2003), Tillit (1991), Tysklind (1994), van Birgelen (1996a,b), Weber (1984), Weber (1985), Wiebel (1996), Yoon (2000). *Additional papers* that will be evaluated (others may be located later and added to this list): Abnet (1999), Bradlaw (1979), Harper (1993), Harris (1989), Heid (2001), Jansing (1985), Nagayama (1985), Vecchi (1983), Xu (2000), Zacharewski (1989).

The re-evaluation and re-calculation of REP values will use a consistent set of dose-response curves; for biochemical endpoints the Hill equation, for toxic and teratogenic end points the log-probit. All data from each single study on TCDF will be simultaneously evaluated with the corresponding reference study on TCDD, in order to ensure that the conditions required for the definition of a REP (parallel dose-response curves that differ only by a scale factor in dose) can be tested for acceptability, and used in the derivation of the REP (studies in which the conditions for a valid REP are statistically unlikely will nevertheless be evaluated for a REP under those conditions, but they may subsequently be given lower weight). The re-calculation of the REP values will include a statistically reliable evaluation of the uncertainties in each REP value. Both the re-calculation and evaluation of uncertainties will use likelihood methods.

Further analysis of the REP values may also be performed, for example to detect any correlations with bioassay conditions such as length of dosing, period since dosing ended, methodology (*e.g.* in vitro *vs.* in vivo). This analysis may be used to extrapolate REP values to standard conditions relevant to human exposure conditions; and those conditions may be varied depending on the metric(s) used for estimating human exposures. REPs are generally derived for in-vivo studies on the basis of intake dose; and will be assumed to apply to human intake doses (the high likelihood that the conditions of in-vitro studies do not match the metabolic conditions in humans provides one potential reason for giving low weight to REPs estimated from in vitro studies); however, for different human dose metric(s), different analyses or extrapolations may have to be applied to the TEF analysis to ensure consistency with the dose metric to be used.

The REP values and their uncertainties will be used to define a distribution for the TEF for TCDF. Preliminary investigation suggests that the distribution may be adequately approximated by a parametric (probably lognormal) distribution; if this turns out to be the case, the parameters of such a distribution (including their uncertainties) will be estimated from the REP estimates, taking into account the uncertainties for each REP estimate. The effect of differing weighting schemes for the REP estimates, to reflect expert opinion on their relevance to humans, will also be considered; *e.g.* REP estimates obtained from (partially or wholly) in-vivo studies may be given higher weight over those obtained from purely in-vitro studies. The resulting distribution for TCDF TEF will be interpreted as an uncertainty distribution for application in the HHRA.

For 4-PeCDF, the WHO-IPCS committee selected an estimate of 0.3 for the TEF in the new WHO (2005) system, as opposed to 0.5 in the WHO (1998) system, primarily reflecting the improved information available from the NTP bioassays for cancer endpoints. The NTP bioassay data may be used to evaluate a

distribution for the TEF for PeCDF (Budinsky et al. 2006) on either an intake or systemic basis. When the 4-PeCDF cancer dose-response data are compared to TCDD on a body burden basis, a relative potency of approximately 0.036 is obtained. Based on tumor initiation and promotion relative potency estimates for 4-PeCDF, an even lower relative potency of 0.007 was obtained when using liver concentration as the dose metric – a useful mode of action assessment related to 4-PeCDF’s carcinogenic mechanism (Waern et al. 1991). Since no specific non-cancer TEF for 4-PeCDF has been derived, a review and analysis of the published non-cancer studies on 4-PeCDF will be undertaken with specific interest in any reproductive/developmental studies that may be available. In working collaboratively with MDEQ on this effort, it is hoped that a more scientifically justified non-cancer relative potency for 4-PeCDF can be derived that better characterizes the uncertainty and variability for 4-PeCDF exposure and risk estimates.

In summary, TEFs are required under the Part 201 regulations for characterizing exposure and risk for the 2,3,7,8-chlorinated PCDD/Fs other than 2,3,7,8-TCDD. However, currently available TEFs do not always represent the best information for scientifically assessing the risk from exposure to these PCDD/Fs. Current TEF values for the PCDDs/Fs generally represent a fairly conservative deterministic estimate of relative potency based on a wide range of relative potency factors derived from the available toxicological studies comparing specific PCDD/Fs to TCDD. These relative potency factors can represent a diverse collection of endpoints, some related to toxic end points, and some not. Furthermore, the TEF estimates are not currently derived using robust criteria, dose-response modeling or statistical assessments. The lack of objective criteria, dose-response modeling and statistical assessment undermines the scientific validity of TEFs for accurately depicting risks from exposure to PCDD/Fs mixtures. It could be argued that relative potency estimates from specific studies are in fact superior to the TEF estimate for a specific PCDD/Fs congener. The TEF values can be considered expedient but not necessarily the best science or the best information for conducting a HHRA. In particular, because of the importance of the two-furan congeners (TCDF and 4-PeCDF) to the Tittabawassee River Study Area, and the available scientific information available on both congeners, it is necessary to thoroughly evaluate this information to provide “best information” in the risk assessment.

6.6 RISK CHARACTERIZATION

In the risk characterization, quantitative exposure estimates and toxicity factors will be combined to calculate numerical estimates of potential health risk. In this section, potential cancer and noncancer health risks will be estimated assuming long-term exposure to CoPCs Study Area media. Dow will work

with MDEQ to ensure application of appropriate approaches in the risk characterization. The risk characterization approaches applied in MDEQ cleanup criteria and used in EPA guidance will be applied as appropriate to calculate potential RME and typical excess lifetime cancer risks for carcinogens and hazard indices for contaminants with noncancer health effects. These methods to be used in both the SLRA and the probabilistic risk assessment are described below.

6.6.1 Cancer risk

Quantifying total excess cancer risk requires calculating risks associated with exposure to individual carcinogens (summed across pathways of exposure) and aggregating risks associated with simultaneous exposure to multiple carcinogenic CoPCs. Of course, consideration of additional chemicals in the cancer risk assessment is dependent on what is found in the TAL analyses and eliminated in the SLRA. A cancer risk estimate for a single carcinogen will be calculated by multiplying the lifetime average daily intake of the contaminant by its carcinogenic slope factor.

$$\text{Excess lifetime cancer risk} = \text{Intake} \times \text{Cancer slope factor.}$$

Cancer risks are assumed to be additive, so risks associated with simultaneous exposure to more than one carcinogen in a given medium can be aggregated to determine a total cancer risk for each exposure pathway. However, exposure and risk *estimates* are not necessarily additive; and this is true for the exposure and risk estimates obtained in the SLRA, since they are all upper bound estimates. Thus risk estimates obtained in the SLRA will not be summed across pathways or chemicals, but used solely to select pathway/receptor combinations for inclusion in the PRA. Exposure estimates obtained in the PRA will be additive, so they will be summed across pathways to produce total exposure estimates for each receptor; risk estimates from these total exposures may then be obtained by multiplying by cancer slope factors (although strictly a probabilistic product is required to maintain the correct probability interpretations).

For the SLRA cancer risk estimates, the likelihood that actual risks are greater than estimated risks is very low because of the conservative assumptions used to develop both exposure and cancer slope factor estimates; in fact, actual risks may be significantly less than predicted values and may be zero. EPA's *Guidelines for Cancer Risk Assessment* state “. . . the linearized multistage procedure (typically used to calculate CSFs) leads to a plausible upper limit to the risk that is consistent with proposed mechanisms of carcinogenesis The true value of the risk is unknown, and may be as low as zero” (51 Fed. Reg. 185:33992, 33998). For the PRA, if a probabilistic approach is used for the cancer slope factor, the known uncertainties will all be incorporated in the estimates, so the degree of conservatism may be

chosen. There will still be uncertainties due to lack of knowledge, and they will be described in the uncertainty assessment (Section 6.7). With a deterministic cancer slope factor applied in the PRA, however, the risk estimates at any given percentiles of the distributions obtained will all be upper bounds, since the deterministic cancer slope factor is itself an upper bound.

6.6.2 Non-Cancer Risk

Intakes of a given CoPC by various pathways may be additive, although once again exposure estimates may not be (and in particular, SLRA exposure estimates are not additive). A hazard quotient less than 1 for a given CoPC implies that exposure is below a level that is expected to be free of any deleterious effect with high probability. A hazard quotient greater than 1 does not necessarily mean that an effect would occur, rather that exposure may exceed a level that calls for more investigation of potential health effects in sensitive populations. Exposures resulting in a hazard quotient less than or equal to 1 are very unlikely to result in noncancer adverse health effects. EPA states that the range of possible uncertainty around RfDs is “perhaps an order of magnitude” (EPA 2006).

Because the SLRA intake estimates are not additive, hazard quotients for individual CoPCs will not be summed across pathways. Instead the values for each pathway will be used to determine whether to evaluate that pathway more fully in the PRA. Intakes estimates evaluated in the PRA will be additive, so will be added across pathways to evaluate a total hazard index for each CoPC. If the RfD estimates are derived deterministically, they are lower bounds, so the resultant distributions of hazard quotient will all be upper bounds; but if the RfD estimates are evaluated probabilistically, the hazard quotient distributions will have probabilistic interpretations (subject, as always, to the unknown uncertainties to be listed in the uncertainty evaluation).

Summing hazard indices across different CoPCs is more problematic, unless the mechanism of action is the same for all the CoPCs included in the sum. Conventionally, such a sum is computed as a summary measure; but it has very little meaning if the CoPCs have different mechanisms of action.

6.6.3 Screening Level Deterministic Risk Assessment

As described in Section 6.1.1.2 all potentially complete exposure pathways will be evaluated in the SLRA. The SLRA will be conducted to determine which require more thorough evaluation, which ones can be eliminated completely from further consideration because their contribution to potential risk is negligible (lifetime carcinogenic risk estimate $<10^{-7}$, or hazard index (HI) <0.001), and which ones will be

incorporated in further refinement using screening level methods because their contribution is minor (lifetime carcinogenic risk estimate $<10^{-6}$, or HI <0.01).

6.6.4 Probabilistic Risk Assessment

6.6.4.1 Methodology

Probabilistic risk assessment (PRA) generally characterizes and describes variability and uncertainty, as opposed to deterministic or point-estimate methods of assessing that generally can only be used to evaluate bounding estimates of risk. Therefore, following discussions with MDEQ the HHRA proposes to use PRA as appropriate to inform risk decisions. The probabilistic risk assessment will be carried out using the Monte Carlo methodology based on selection of random individuals in a (synthetic) population designed to match the whole population of individuals (“receptors”) potentially exposed to CoPCs in site media now or in the future, or some specific subset of that population defined by their characteristics. These specific subsets include the receptor populations described above (residents, hunters, anglers, and recreational visitors). The algorithms given in previous sections allow calculation of dose rates during exposure and an effective lifetime average dose rate for the selected individual (and any other dose metric may also be computed from the dose rate and characteristics of the individual). For any individual, however, any or all the terms (e.g. body weight, number of game meals eaten per year, number of fish eaten per year) in these algorithms are likely to be uncertain, and that uncertainty is measured by the uncertainty distributions associated with each term.

The Monte Carlo methodology takes into account such uncertainty by sampling multiple times from the uncertainty distributions for all the terms. On each (uncertainty) iteration of the Monte Carlo procedure the uncertainty distribution for each of the terms in all the algorithms applicable to any calculation of dose is sampled to obtain a value (it may be necessary to also incorporate other characteristics of the individual, e.g. age and location, that do not explicitly appear in the algorithms but may affect the selection of random values for the terms), and all the calculations of doses performed to obtain one estimate in the uncertainty distribution for dose which, when combined with a toxicity estimate provides one estimate in the uncertainty distribution for risk. Sufficient repetition of this procedure allows evaluation of the uncertainty distribution for doses and risks, building them up one-by-one from those estimates.

Each term in the algorithms may, however, also vary between individuals. The variability of individual terms is measured by the variability distributions calculated for each such term. Any particular individual

is then distinguished by the characteristic set of values for all those terms (and possibly other characteristics, like age and location, that do not appear explicitly but may affect the distributions for each term). Variability is also handled by a Monte Carlo procedure either wrapped around or packaged within the Monte Carlo procedure for uncertainty. On each of the variability iterations, some individual is selected by random sampling from the variability distributions for the characteristics of that individual (taking account of any correlations between the characteristics sampled); and the characteristics of the individual are, in most part, just the terms of the algorithms (there may be other characteristics that affect the terms). For each selected individual, a dose and risk estimates are calculated using the algorithms; and the whole procedure is repeated many times to build up a picture (variability distribution) of how the dose varies between individuals in the population.

The usual approach for this two-dimensional type of Monte Carlo procedure, and which is intended to be used here, is to perform the variability loop inside the uncertainty loop. That way, a set of values is selected from the uncertainty distributions, then the complete variability distribution describing how doses or risks vary across the population may be obtained using a one-dimensional Monte Carlo procedure; and population parameters (like expected values of dose, or the total expected number of effects in the population) may be obtained by integrating over the variability distribution (summing over the selected synthetic individuals). Repeating the procedure multiple times builds up an uncertainty distribution for the variability distribution, and the uncertainty distribution for the derived population parameters.

In the PRA, the uncertainty and variability distributions for each exposure term will be evaluated as described in the preceding sections, keeping track of any correlations between the various distributions (there may even be correlations linking the uncertainty and variability distributions; for example, the parameters describing an uncertainty distribution may depend on the parameters describing the variability distribution for the same term).

The Monte Carlo algorithm for the combined uncertainty and variability analysis can then be summarized, using a simple pseudo-computer-language in which each pair of braces {} indicates a block of operations, as:

Repeat a large number of times: (start of outer, uncertainty, repetition)

- Choose a sample from the uncertainty distribution for each term in the algorithms, taking account of correlations.

Repeat a large number of times (start of inner, variability, repetition)

- Choose a sample from the variability distribution of each term in the algorithms taking account of correlations
- Calculate the corresponding sample value for dose rate, any other required dose metric, and risk
- Calculate any required averages of dose rates (e.g. lifetime average dose rate) or other dose metrics, (e.g. body burdens).
- Store the calculated values.

} (end of the inner repetition)

From the stored values, construct the variability distributions for average dose rates, other dose metrics, and risks.

- Calculate population averages from the variability distribution
- Store the variability distribution (for example, store a set of percentiles of the distribution), and the population averages.

} (end of outer repetition)

From the stored variability distributions for average dose rates, construct the uncertainty distribution for those distributions (for example, construct the uncertainty percentiles for each stored variability percentile), and for the stored population averages.

- Calculate any desired averages over the uncertainty distributions.
- Print out the results in a convenient way and interpret them.

6.6.4.2 Probabilistic Risk Assessment Means to Present Findings

The results of the probabilistic methodology are distributions of results, the distributions showing both variability and uncertainty. Risk estimate results will be presented using graphs of the cumulative distributions, graphs of (smoothed versions of) the differential distributions, and tables showing percentage points of the distributions. Results will be presented for individuals (variability and uncertainty distributions) and for the population as a whole (uncertainty distributions – the population values are obtained by integrating over the variability distributions). The risk assessment output most useful to risk managers will be presented.

6.7 UNCERTAINTY ASSESSMENT

The uncertainties present in any HHRA are of at least three forms – uncertainties that are known to exist, and whose size can be estimated; uncertainties that are known to exist, but whose size cannot be estimated; and unknown uncertainties. To the extent possible the first category have been incorporated in the SLRA (but using upper bound values) and in the probabilistic assessment (using distributions of values). This section of the HHRA will discuss the uncertainties that are known to exist but that are of unknown size, indicating why they are known to be uncertainties, whether anything is known about the direction and size of the uncertainty, and any potential effect on the HHRA. Uncertainties related to exposure assumptions, toxicity assumptions and risk characterization will be addressed.

6.8 REFERENCES

Abbott, B.D., G.A. Held, C.R. Wood, A.R. Buckalew, J.G. Brown, and J. Schmid. 1999. AhR, ARNT, and CYP1A1 mRNA quantitation in cultured human embryonic palates exposed to TCDD and comparison with mouse palate in vivo and in culture. *Toxicol. Sci.* 47:62-75.

Abnet, C.C., R.L. Tanguay, W. Heideman, and R.E. Peterson. 1999. Transactivation activity of human, zebrafish, and rainbow trout aryl hydrocarbon receptors expressed in COS-7 cells: greater insight into species differences in toxic potency of polychlorinated dibenzo-p-dioxin, dibenzofuran, and biphenyl congeners. *Toxicol. Appl. Pharmacol.* 159(1):41-51.

Agin, R.J., V.A. Atiemo-Obeng, W.B. Crummett, K.L. Krumel, L.L. Lamparski, T.J. Nestruck, C.N. Park, J.M. Rio, L.A. Robbins, S.W. Tobey, D.I. Townsend, and L.B. Westover. 1984. Point Sources and Environmental Levels of 2378-TCDD (2,3,7,8-Tetrachlorodibenzo-p-Dioxin) on the Midland Plant Site of The Dow Chemical Company and in the City of Midland, Michigan. November 1984. The Dow Chemical Company, Midland, MI.

Alaluusua, S., P. Calderara, P.M. Gerthoux, P.L. Lukinmaa, O. Kovero, L. Needham, D.G. Patterson, Jr., J. Tuomisto, and P. Mocarelli. 2004. Developmental dental aberrations after the dioxin accident in Seveso. *Environ Health Perspect* 112:1313-1318.

Alexander, F.W., B.E. Clayton, and H.T. Delves. 1974. Mineral and trace metal balances in children receiving normal and synthetic diets. *Q. J. Med.* 43(169):89-111.

Allen, B.C., R.J. Kavlock, C.A. Kimmel and E.M. Faustman. 1994a. Dose-response assessment for developmental toxicity. II. Comparison of generic benchmark dose estimates with No Observed Adverse Effect Levels. *Fund. Appl. Toxicol.* 23:487-495.

Allen, B.C., R.J. Kavlock, C.A. Kimmel and E.M. Faustman. 1994b. Dose-response assessment for developmental toxicity. III. Statistical Models. *Fund. Appl. Toxicol.* 23:496-509.

- Allen, C., K.S. Crump, and A.M. Shipp. 1988a. Correlation between carcinogenic potency of chemicals in animals and humans. *Risk Analysis* 8(4):531–544.
- Allen, C., K.S. Crump, and A.M. Shipp. 1988b. Response to Comments on Correlation Between Carcinogenic Potency of Chemicals in Animals and Humans. *Risk Analysis* 8(4):559–561.
- Amendola, G.A. and D.R. Barna. 1986. Dow Chemical Wastewater Characterization Study – Tittabawassee River Sediments and Native Fish. EPA-905/4-88-003. July 1986. U.S. Environmental Protection Agency.
- Anderson, H.A., J.F. Amrhein, P. Shubat, and J. Hesse. 1993. Protocol for a Uniform Great Lakes Sport Fish Consumption Advisory. Great Lakes Sport Fish Advisory Task Force, Council of Great Lakes Governors, Chicago, IL.
- Anderson, L.M. 2004a. Predictive values of traditional animal bioassay studies for human perinatal carcinogenesis risk determination. *Toxicol. Appl. Pharmacol.* 199:162-174.
- Anderson, L.M. 2004b. Introduction and overview: Perinatal carcinogenesis: growing a node for epidemiology, risk management, and animal studies *Toxicol. Appl. Pharmacol.* 199: 85-90.
- Anderson, L.M. 2006. Environmental genotoxicants/carcinogens and childhood cancer: Bridgeable gaps in scientific knowledge. *Mut. Res.* 608:136-156.
- Armbruster, G., K.G. Gerow, W.H. Gutenmann, C.B. Littman, D.J. and Lisk. 1987. The effects of several methods of fish preparation on residues of polychlorinated biphenyls and sensory characteristics in Striped Bass. *J. Food Safety* 8:235–243.
- Armbruster, G., K.L. Gall, W.H. Gutenmann, and D.J. Lisk. 1989. Effects of trimming and cooking by several methods on polychlorinated biphenyls (PCB) residues in Bluefish. *J. Food Safety* 9:235–244.
- Atkin, C. 1994. A survey study of anglers residing near the Kalamazoo River basin. Michigan State University, East Lansing, MI.
- ATSDR. 1998. Toxicological Profile for Chlorinated Dibenzo-p-Dioxins. <http://www.atsdr.cdc.gov/toxprofiles/tp104.html>. Agency for Toxic Substances and Disease Registry
- Aylward, L.L., J.C. Lamb and S.C. Lewis. 2005. Issues in Risk Assessment for Developmental Effects of 2,3,7,8-Tetrachlorodibenzo-p-Dioxin and Related Compounds. *Tox Sci* 87(1):3-10.
- Aylward, L.L., R.C. Brunet, T.B. Starr, G. Carrier, and E. Delzell. 2005. Exposure Reconstruction for the TCDD-Exposed NIOSH Cohort Using a Concentration- and Age-Dependent Model of Elimination. *Risk Anal.* 25(4):945-956.

- Baba, T., J. Mimura, N. Nakamura, N. Harada, M. Yamamoto, K. Morohashi, and Y. Fujii-Kuriyama. 2005. Intrinsic function of the aryl hydrocarbon (dioxin) receptor as a key factor in female reproduction. *Mol Cell Biol* 25:10040-10051.
- Baccarelli, A., A.C. Pesatori, D. Consonni, P. Mocarelli, D.G. Patterson, Jr., N.E. Caporaso, P.A. Bertazzi, and M.T. Landi. 2005. Health status and plasma dioxin levels in chloracne cases 20 years after the Seveso, Italy accident. *Br J Dermatol* 152:459-465.
- Bacci, E., M.J. Cerejeira, C. Gaggi, G. Chemello, D. Calamari, and M. Vighi. 1992. Chlorinated dioxins: Volatilization from soils and bioconcentration in plant leaves. *Earth Environ. Sci.* 48(3):401-408.
- Baird, S.J.D., J.T. Cohen, J.D. Graham, A.I. Shlyakhter, and J.S. Evans. 1996. Noncancer risk assessment: A probabilistic alternative to current practice. *Hum. Ecol. Risk Assess.* 2:79-102.
- Baker, B. 2006. Personal communication (letter to G.W. Bruchmann, Michigan Department of Environmental Quality, Lansing, MI, dated May 1, 2006, regarding Dow responses to the Michigan Department of Environmental Quality's (MDEQ) March 2 and April 13, 2006 notices of deficiency). The Dow Chemical Company, Midland, MI. [NOT CITED]
- Bandiera, S., T. Sawyer, M. Romkes, B. Zmudzka, L. Safe, G. Mason, B. Keys, and S. Safe. 1984. Polychlorinated dibenzofurans (PCDFs): Effects of structure on binding to the 2,3,7,8-TCDD cytosolic receptor protein, AHH induction and toxicity. *Toxicology* 32(2):131-144.
- Bayen, S., P. Barlow, H.K. Lee, and J.P. Obbard. 2005. Effect of cooking on the loss of persistent organic pollutants from salmon. *J. Toxicol. Environ. Health A*68:253-265.
- Beaver 1975. *Health Lab Sci* 12(2):116-125.
- Bell et al. presentation on their recently completed TCDD reproduction/developmental study at MSU, July 18th, 2006 – (MSU's Center for Integrated Toxicology seminar series)
- Bell, D.R., G. Loizou, S. White, A. Fernandes, M. Rose, B.G. Miller, L. Tran, S. Clode, P.M. Foster, and A. MacNicoll. 2005. A robust examination of effects of TCDD on the developing male reproductive system. Abstract 681. *Toxicological Sciences* 84.
- Bertazzi, P.A., D. Consonni, S. Bachetti, M. Rubagotti, A. Baccarelli, C. Zocchetti, and A.C. Pesatori. 2001. Health effects of dioxin exposure: a 20-year mortality study. *Am. J. Epidemiol.* 153(11):1031-1044.
- Binder, S., D. Sokal, and D. Maughn. 1986. Estimating soil ingestion: the use of tracer elements in estimating the amount of soil ingested by young children. *Arch. Env. Health* 41(6):341-345.
- Birnbaum, L.S., and M.J. DeVito. 1995. Use of toxic equivalency factors for risk assessment for dioxins and related compounds. *Toxicology* 105(2-3):391-401.

Birnbaum, L.S., M.W. Harris, D.D. Crawford, and R.E. Morrissey. 1987. Teratogenic effects of polychlorinated dibenzofurans in combination in C57BL/6N mice. *Toxicol. Appl. Pharmacol.* 91(2):246–255.

Bnin, G. 2004. Nongenetic causes of childhood cancers: evidence from international variation, time trends, and risk factor studies. *Toxicol. Appl. Pharmacol.* 199:91-103.

Bodner, K.M., J.J. Collins, L.J. Bloemen, M.L. Carson. 2003. Cancer risk for chemical workers exposed to 2,3,7,8-tetrachlorodibenzo-p-dioxin. *Occup. Environ. Med* 60:672–675.

Bolt, H.M., H. Foth, J.G. Hengstler and G. H. Degen. 2004. Carcinogenicity categorization of chemicals – new aspects to be considered in a European perspective. *Toxicol. Letters* 151: 29-41.

Bothe, M. 2004. Quantifizierung der Ingestion von Boden durch Kinder [Quantification of the Ingestion of Soil by Children]. Verein für Kernverfahrenstechnik und Analytik, Rossendorf e.V. (VKTA), Postfach 51 01 19, 01314 Dresden. BMU–2004–647

Bowman, R.E., S.L. Schantz, N.C.A. Weerasinghe, M.L. Gross, D.A Barsotti. 1989. Chronic dietary intake of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) at 5 or 25 parts per trillion in the monkey: TCDD kinetics and dose-effect estimate of reproductive toxicity. *Chemosphere* 18(1-6):243-252.

Bradlaw, J.A. and J.L. Casterline, Jr. 1979. Induction of enzyme activity in cell culture: a rapid screen for detection of planar polychlorinated organic compounds. *J Assoc Off Anal Chem.* 62(4):904–916.

Brown, D.J., M. Chus, I. Van Overmeire, A. Chu, and G.C. Clark. 2001. Determination of REP values for the Calux® bioassay and comparison to the WHO TEF values. *Organohalogen Compounds* 53:211–214.

Bruchmann, G.W. 2006a. Personal communication (letter to B. Baker, The Dow Chemical Company, Midland, MI, dated March 2, 2006, regarding notice of deficiency for Tittabawassee River and floodplain remedial investigation work plan and Midland area soils remedial investigation work plan). Michigan Department of Environmental Quality, Lansing, MI.

Bruchmann, G.W. 2006b. Personal communication (letter to B. Baker, The Dow Chemical Company, Midland, MI, dated April 13, 2006, regarding response to comments and notice of deficiency for Tittabawassee River and floodplain remedial investigation work plan and Midland area soils remedial investigation work plan). Michigan Department of Environmental Quality, Lansing, MI. [NOT CITED]

Budinsky, R.A. 2005. Workshop Report: A summary of the 2005 Winter Toxicology Forum session on dioxin toxic equivalency factors *Reg. Toxicol Pharmacol* 43: 324-326

Budinsky, R.A., D. Paustenbach, D. Fontaine, B. Landenberger, and T.B. Starr. 2006. Recommended Relative Potency Factors for 2,3,4,7,8-Pentachlorodibenzofuran: The Impact of Different Dose Metrics. *Toxicol. Sci.* 91(1):275-285.

- Bunge, A.L., and A.L. Bunge. 1995. A new method for estimating dermal absorption from chemical exposure: 2. Effect of molecular weight and octanol-water partitioning. *Pharmaceutical Research* 12(1):88–95.
- Bunge, A.L., R.L. Cleek, and B.E. Vecchia. 1995. A new method for estimating dermal absorption from chemical exposure: 3. Compared with steady-state methods for prediction and data analysis. *Pharmaceutical Research* 12(7):972–982.
- Bunin, G. 2004. Nongenetic causes of childhood cancers: evidence from international variation, time trends, and risk factor studies. *Toxicol. Applied Pharmacol.* 199(2):91-103.
- Burmester, D.E. 1998. Lognormal distributions for skin area as a function of body weight. *Risk Anal.* 18(1):27–32.
- Burmester, D.E., and E.A. Crouch. 1997. Lognormal distributions for body weight as a function of age for males and females in the United States, 1976–1980. *Risk Anal.* 17(4):499–505.
- Butterworth, B.E. 2006. A classification framework and practical guidance for establishing a mode of action for chemical carcinogens. *Reg. Toxicol. Pharmacol.* 45:9-23.
- Byrd, D.M., D.O. Allen, R.L. Beamer, H.R. Besch, D.B. Bylund, J. Doull, W.W. Fleming, A. Fries, F.P. Guengerich, R. Hornbrook, L. Lasagna, B.K.B. Lum, E.K. Michaelis, E.T. Morgan, A. Poland, K.K. Rozman, J.B. Smith, H.I. Swanson, W. Waddell, and J.D. Wilson. 1998. The dose—response model for dioxin. Letter to the editor. *Risk Analysis* 18(1):1-2.
- Calabrese, E.J., and E.J. Stanek, III. 1991. A guide to interpreting soil ingestion studies. II. Qualitative and quantitative evidence of soil ingestion. *Regul. Toxicol. Pharmacol.* 13(3):278–292.
- Calabrese, E.J., and E.J. Stanek, III. 1995. Resolving intertracer inconsistencies in soil ingestion estimation. *Environ. Health Perspect.* 103(5):454-457.
- Calabrese, E.J., and E.S. Stanek. 1992. Distinguishing outdoor soil ingestion from indoor dust ingestion in a soil pica child. *Regul. Toxicol. Pharmacol.* 15(1):83–85.
- Calabrese, E.J., E.J. Stanek, and C.E. Gilbert. 1991. Evidence of soil-pica behaviour and quantification of soil ingested. *Hum. Exp. Toxicol.* 10(4):245–249.
- Calabrese, E.J., E.J. Stanek, C.E. Gilbert, and R.M. Barnes. 1990. Preliminary adult soil ingestion estimates: results of a pilot study. *Regul. Toxicol. Pharmacol.* 12(1):88–95.
- Calabrese, E.J., E.J. Stanek, III, P. Pekow, and R.M. Barnes. 1997a. Soil ingestion estimates for children residing on a superfund site. *Ecotoxicol. Environ. Saf.* 36(3):258–268.
- Calabrese, E.J., E.J. Stanek, P. Pekow, and R.M. Barnes. 1997c. Soil Ingestion Estimated for Children Residing on a Superfund Site. *Ecotoxicol. Environ. Saf.* 36:258-268.

- Calabrese, E.J., E.J. Stanek, R. Barnes, D.E. Burmaster, B.G. Callahan, J.S. Heath, D. Paustenbach, J. Abraham, and L.A. Gephart. 1996. Methodology to estimate the amount and particle size of soil ingested by children: implications for exposure assessment at waste sites. *Regul. Toxicol. Pharmacol.* 24(3):264–268. Erratum in: *Regul. Toxicol. Pharmacol.* 25(1):87.
- Calabrese, E.J., E.J. Stanek, R.C. James, and S.M. Roberts. 1997b. Soil ingestion: a concern for acute toxicity in children. *Environ. Health. Perspect.* 105(12):1354–1358.
- Calabrese, E.J., H. Pastides, R. Barnes, C. Edwards, P. Kostecki, E.J. Stanek, III, P. Veneman, and C.E. Gilbert. 1989a. How much soil do young children ingest: an epidemiologic study. pp.363–397. In: *Petroleum Contaminated Soils, Vol. 2.* E.J. Calabrese and P.T. Kostecki (eds). Lewis Publishers, Chelsea, MI.
- Calabrese, E.J., R. Barnes, E.J. Stanek, III, H. Pastides, C.E. Gilbert, P. Veneman, X.R. Wang, A. Lasztity, and P.T. Kostecki. 1989b. How much soil do young children ingest: an epidemiologic study. *Regul. Toxicol. Pharmacol.* 1989 10(2):123–137.
- Carrier, G., R.C. Brunet, and J. Brodeur. 1995a. Modeling of the Toxicokinetics of Polychlorinated Dibenzo-p-Dioxins and Dibenzofurans in Mammalians, Including Humans. I. Nonlinear Distribution of PCDD/F Body Burden Between Liver and Adipose Tissues. *Toxicol. Appl. Pharmacol.* 131:253-266.
- Carrier, G., R.C. Brunet, and J. Brodeur. 1995b. Modeling of the Toxicokinetics of Polychlorinated Dibenzo-p-Dioxins and Dibenzofurans in Mammalians, Including Humans. II. Kinetics of Absorption and Disposition of PCDDs/PCDFs. *Toxicol. Appl. Pharmacol.* 131:267-276.
- CDC. 2005. Third National Report on Human Exposure to Environmental Chemicals. July 2005. Centers for Disease Control and Prevention, Atlanta, GA.
- CDM. 2003. Final (Revised) Human Health Risk Assessment for the Allied Paper, Inc./Portage Creek/Kalamazoo River Superfund Site. Camp Dresser & McKee.]
- CH2M Hill. 2005b. Tittabawassee River Sediment Dioxin/Furan Concentration Variability. March.
- CH2M Hill. 2005a. Tittabawassee River Floodplain Scoping Study Work Plan-Revised. July.
- CH2M Hill. 2005c. Tittabawassee River Sediment Dioxin/Furan Concentration Vertical Variability – Revision 1. July. Chen, J.J. and D.W. Gaylor. 1987. Carcinogenic risk assessment: comparison of estimated safe dose for rats and mice. *Environ. Health Perspect.* 72:305–309.
- Chen, C.Y., J.T. Hamm, J.R. Hass, and L.S. Birnbaum. 2001. Disposition of polychlorinated dibenzo-p-dioxins, dibenzofurans, and non-ortho polychlorinated biphenyls in pregnant Long Evans rats and the transfer to offspring. *Toxicol. Appl. Pharmacol.* 173: 65–88.
- Cheng, H., L. Aylward, C. Beall, T.B. Starr, R.C. Brunet, G. Carrier, E. Delzell. 2006. TCDD exposure-response analysis and risk assessment. *Risk Anal.* 26(4):1059–1071.

- Cheng, H., L. Aylward, C. Beall, T.B. Starr, R.C. Brunet, G. Carrier, E. Delzell. 2006. TCDD exposure-response analysis and risk assessment. *Risk Anal.* 26(4):1059–1071.
- Cichy, R.F., M.E. Zabik, and C.M. Weaver. 1979. Polychlorinated biphenyl reduction in Lake Trout by irradiation and broiling. *Bull. Environ. Contam. Toxicol.* 22:807–812.
- Clausing, P., B. Brunekreef, and J.H. van Wijnen. 1987. A method for estimating soil ingestion by children. *Int. Arch. Occup. Environ. Health.* 59(1):73–82.
- Cleek, R.L., and A.L. Bunge. 1993. A new method for estimating dermal absorption from chemical exposure. 1. General Approach. *Pharmaceutical Research* 10(4):497–506.
- Clemons, J.H., D.G. Dixon, and N.C. Bols. 1997. Derivation of 2,3,7,8-TCDD toxic equivalent factors (TEFs) for selected dioxins, furans and PCBs with rainbow trout and rat liver cell lines and the influence of exposure time. *Chemosphere* 34(5-7):1105-1119.
- Clemons, J.H., L.E.J. Lee, C.R. Myers, D.G. Dixon, and N.C. Bols. 1996. Cytochrome P4501A1 induction by polychlorinated biphenyls (PCBs) in liver cell lines from rat and trout and the derivation of toxic equivalency factors. *Can. J. Fish. Aquat. Sci.* 53:1177-1185.
- Clemons, J.H., M.R. van den Heuvel, J.J. Stegeman, D.G. Dixon, and N.C. Bols. 1994. Comparison of toxic equivalent factors for selected dioxin and furan congeners derived using fish and mammalian liver cell lines. *Can. J. Fish. Aquat. Sci.* 51:1577–1584.
- Cohen, S.M., J. Klaunig, M.E. Meek, R.N. Hill, T. Pastoor, L. Lehman-McKeeman, J. Bucher, D.G. Longfellow, J. Seed, V. Dellarco, P. Fenner-Crisp and D. Patton. 2004. Evaluating the human relevance of chemically induced animal tumors. *Toxicol Sci.* 78: 181-186.
- Cohen, S.M., M.E. Meek, J. E. Klaunig, D.E. Patton and P.A. Fenner-Crisp. 2003. The human relevance of information on carcinogenic modes of action: Overview. *Crit Rev Toxicol.* 33:581-589.
- Cole, P., D. Trichopoulos, H. Pastides, T. Starr, and J.S. Mandel. 2003. Dioxin and cancer: a critical review. *Regul. Toxicol. Pharmacol.* 38(3):378-88.
- Connor, K.T. and L.L. Aylward. 2006. Human response to dioxin: aryl hydrocarbon receptor (AhR) molecular structure, function, and dose-response data for enzyme induction indicate an impaired human AhR. *J Toxicol Environ Health B Crit Rev* 9:147-171.
- Crouch, E. and N.J. Golden. 2005. A Risk Assessment for *Clostridium perfringens* in Ready-to-Eat and Partially Cooked Meat and Poultry Products. September 2005. Available at: http://www.fsis.usda.gov/Science/Risk_Assessments/index.asp).
- Crouch, E. and R. Wilson. 1979. Interspecies comparison of carcinogenic potency. *J. Toxicol. Environ. Health* 5:1095–1118.

Crouch, E., M. Ames, and L. Green. 2002. A Quantitative Health Risk Assessment for the Kalamazoo River PCB site. Prepared for the Kalamazoo River Study Group. June 1, 2001, with errata and addenda, July 31, 2002. Cambridge Environmental, Inc., Cambridge, MA.

Crouch, E.A.C. 1983. Uncertainties in interspecies extrapolations of carcinogenic potencies. *Environ. Health Perspect.* 50:321–327.

Crouch, E.A.C. 1996. Uncertainty distributions for cancer potency factors: laboratory animal carcinogenicity bioassays and interspecies extrapolation. *Hum. Ecol. Risk Assessment* 2(1):103–129.

Crouch, E.A.C. 1996. Uncertainty distributions for cancer potency factors: combining epidemiological studies with laboratory bioassays — the example of acrylonitrile. *Hum Ecol. Risk Assessment* 2(1):130–149.

Crump, K., B. Allen, and A. Shipp. 1989. Choice of dose measure for extrapolating carcinogenic risk from animals to humans: an empirical investigation of 23 chemicals. *Health Physics* 57(Suppl. 1):387–393.

Davis, D. and S. Safe. 1988. Immunosuppressive activities of polychlorinated dibenzofuran congeners: quantitative structure–activity relationships and interactive effects. *Toxicol. Appl. Pharmacol.* 94(1):141–149.

Davis, D. and S. Safe. 1991. Halogenated aryl hydrocarbon–induced suppression of the in vitro plaque–forming cell response to sheep red blood cells is not dependent on the Ah receptor. *Immunopharmacology* 21(3):183–190.

Davis, S. and D.K. Mirick. 2006. Soil ingestion in children and adults in the same family. *J. Expo. Sci. Environ. Epidemiol.* 16(1):63–75.

Davis, S., P. Waller, R. Buschbom, J. Ballou, and P. White. 1990. Quantitative estimates of soil ingestion in normal children between the ages of 2 and 7 years: population-based estimates using aluminum, silicon, and titanium as soil tracer elements. *Arch. Environ. Health.* 45(2):112–122.

Della Porta, G., T.A. Dragani, and G. Sozzi. 1987. Carcinogenic effects of infantile and long-term 2,3,7,8-tetrachlorodibenzo-p-dioxin treatment in the mouse. *Tumori.* 73(2):99–107.

Dellarco, V.L. and K. Baetcke. 2005. A risk assessment perspective: Application of mode of action and human relevance frameworks to the analysis of rodent tumor data. *Toxicol. Sci.* 86:1–3.

DeVito, M.J. and L.S. Birnbaum. 1995. The importance of pharmacokinetics in determining the relative potency of 2,3,7,8-tetrachlorodibenzo-p-dioxin and 2,3,7,8-tetrachlorodibenzofuran. *Fundam. Appl. Toxicol.* 24(1):145–148.

DeVito, M.J., J.J. Diliberto, D.G. Ross, M.G. Menache, and L.S. Birnbaum. 1997. Dose–response relationships for polyhalogenated dioxins and dibenzofurans following subchronic

treatment in mice. I. CYP1A1 and CYP1A2 enzyme activity in liver, lung, and skin. *Toxicol Appl Pharmacol.* 147(2):267–280.

DeVito, M.J., W.E. Maier, J.J. Diliberto, and L.S. Birnbaum. 1993. Comparative ability of various PCBs, PCDFs, and TCDD to induce cytochrome P450 1A1 and 1A2 activity following 4 weeks of treatment. *Fundam. Appl. Toxicol.* 20(1):125–130.

DeVito, M.J., X. Ma., J.G. Babish, M. Menache, and L.S. Birnbaum. 1994. Dose-response relationships in mice following subchronic exposure to 2,3,7,8-tetrachlorodibenzo-p-dioxin: CYP1A1, CYP1A2, estrogen receptor, and protein tyrosine phosphorylation. *Toxicol. Appl. Pharmacol.* 124(1):82–90.

Dorne, J. L.C. M., and A.G. Renwick. 2005. The Refinement of Uncertainty/Safety Factors in Risk Assessment by the Incorporation of Data on Toxicokinetic Variability in Humans *Toxicol Sci* 86:20-26.

Dourson, M.L., S.P. Felter, and D. Robinson. 1996. Evolution of science-based uncertainty factors in noncancer risk assessment. *Regul. Toxicol. Pharmacol.* 24:108-120.

Dow. 2000. Soil Sampling Summary Report (Revised). March. The Dow Chemical Company, Midland, MI.

ECSCF. 2001. Opinion of the Scientific Committee on Food on the risk assessment of dioxins and dioxin-like PCBs in food. Update based on new scientific information available since the adoption of the SCF opinion of 22nd November 2000. Rep. CS/CNTM/DIOXIN/20 final. Available at: [http://europa.eu.int/comm/food/fs/sc/scf/out90_en.pdf]. European Commission Scientific Committee on Foods, Brussels, Belgium.

Emond C., L.S. Birnbaum, and M.J. DeVito. 2004. Physiologically based pharmacokinetic model for developmental exposures to TCDD in the rat. *Toxicological Sciences* 80(1):115–133.

EPA. 1985. Study of Dioxin and Other Toxic Pollutants, Midland, Michigan. April 1985. U.S. Environmental Protection Agency, Region IV.

EPA. 1986a. Guidelines for the Health Risk Assessment of Chemical Mixtures. EPA/630/R-98/002. September 1986. Published: [51FR34014-34025, September 24, 1986]. U.S. Environmental Protection Agency, Risk Assessment Forum, Washington, DC.

EPA. 1988. Response to public comments on risk assessment for dioxin contamination at Midland, Michigan (EPA-905/4-88-005) and proposed risk management actions for dioxin contamination at Midland, Michigan. Appendices A, B, and C. EPA 905/4-88-005. December. U.S. Environmental Protection Agency, Region V, Chicago, IL.

EPA. 1989b. Risk assessment guidance for Superfund. Volume 1: Human health evaluation manual (Part A). Interim Final Report. U.S. EPA 540/1-89/002. U.S. Environmental Protection Agency, Office of Emergency and Remedial Response, Washington, DC.

- EPA. 1991a. Risk assessment guidance for Superfund. Volume I: Human health evaluation manual supplemental guidance. Standard default exposure factors. Interim Final. OSWER Directive 9285.6-03. U.S. Environmental Protection Agency, Office of Emergency and Remedial Response, Washington, DC.
- EPA. 1991b. Risk assessment guidance for Superfund. Volume I: Human health evaluation manual (Part B, development of risk-based preliminary remediation goals). Interim Report. U.S. Environmental Protection Agency, Office of Emergency and Remedial Response, Washington, DC.
- EPA. 1991c. Role of the baseline risk assessment in Superfund remedy selection decisions. U.S. Environmental Protection Agency, Office of Solid Waste and Emergency Response (OSWER), Directive 9355.30, Washington, DC.
- EPA. 1991d. Guidelines for developmental toxicity. EPA/600/FR-91/001. December 1991. Published: [56FR63798-63826, December 5, 1991]. U.S. Environmental Protection Agency, Risk Assessment Forum, Washington, DC.
- EPA. 1991e. Percutaneous absorption of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) and 3,3',4,4'-tetrachlorobiphenyl (TCB) applied in soil. U.S. Environmental Protection Agency, Office of Health and Environmental Assessment. Available from Exposure Assessment Group, Washington, DC. OHEA-E-453.
- EPA. 1992a. Supplemental guidance to RAGS: Calculating the concentration term. U.S. Environmental Protection Agency, Office of Solid Waste and Emergency Response, Washington, DC.
- EPA. 1992b. Guidelines for exposure assessment. [FRL-4129-5] Effective May 29, 1992. U.S. Environmental Protection Agency, Office of Health and Environmental Assessment, Washington, DC.
- EPA. 1992c. Dermal exposure assessment: principles and applications. Interim Report. EPA/600/8-91/011B. January 1992. U.S. Environmental Protection Agency, Office of Health and Environmental Assessment, Exposure Assessment Group, Washington, D.C.
- EPA. 1995. Criteria documents for the protection of human health. EPA-820-B-95-006. Available on the web at http://www.trwnews.net/Documents/MDEQ/epa_GL_QIC.pdf United States Environmental Protection Agency, Office of Water, Great Lakes Water Quality Initiative, Washington, D.C.
- EPA. 1995. Guidance for risk characterization. February 1995. U.S. Environmental Protection Agency Science Policy Council, Washington, DC.
- EPA. 1996a. Guidelines for Reproductive Toxicity Risk Assessment. EPA/630/R-96/009. October 1996. Published: [61FR56274-56322, October 31, 1996]. U.S. Environmental Protection Agency, Risk Assessment Forum, Washington, DC.

- EPA. 1997a. Exposure factors handbook. Volume I: General factors. Volume II: Food Ingestion factors; Volume III: Activity factors. U.S. EPA/600/P-95/002Fa. U.S. Environmental Protection Agency, Office of Research and Development, Washington, DC.
- EPA. 1997b. Guiding Principles for Monte Carlo Analysis. U.S. EPA/630/R-97/001. U.S. Environmental Protection Agency, Office of Research and Development, Washington, DC.
- EPA. 1997d. Policy for the use of probabilistic analysis in risk assessment. U.S. Environmental Protection Agency, Office of Research and Development, Washington, DC.
- EPA. 1998b. Report of the workshop on selecting input distributions for probabilistic assessments, April 21-22, 1998. EPA/630/R-98/004. U.S. Environmental Protection Agency New York, NY.
- EPA. 1998c. Guidelines for neurotoxicity risk assessment. EPA/630/R-95/001F. May 14, 1998. U.S. Environmental Protection Agency New York, NY.
- EPA. 1999. Asian and Pacific Islander seafood consumption study in King County, Washington. Exposure information obtained through a community-centered approach. Study results and education outreach. EPA 910/R-99-003. Office of Environmental Assessment, Risk Evaluation Unit, US Environmental Protection Agency Region 10, Seattle, WA.
- EPA. 2000a. Options for development of parametric probability distributions for exposure factors. EPA/600/R-00/058. U.S. Environmental Protection Agency.
- EPA. 2000b. Supplementary Guidance for Conducting Health Risk Assessment of Chemical Mixtures. EPA/630/R-00/002. August 2000. U.S. Environmental Protection Agency, Risk Assessment Forum, Washington, DC.
- EPA. 2001. Risk assessment guidance for Superfund: Volume III, Part A: Process for conducting probabilistic risk assessment. EPA 540-R-02-002. December 2001. Available at www.epa.gov/oswer/riskassessment/rags3adt/index.htm. U.S. Environmental Protection Agency, Office of Emergency and Remedial Response, Washington, DC.
- EPA. 2002a. Calculating upper confidence limits for exposure point concentrations at hazardous waste sites. OSWER 9285.6-10. December 2002. U.S. Environmental Protection Agency, Office of Emergency and Remedial Response, Washington, D.C.
- EPA. 2003. Exposure and Human Health Reassessment of 2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin (TCDD) and Related Compounds National Academy Sciences (NAS) Review Draft. Part I: Estimating Exposure to Dioxin-Like Compounds. Available at: <http://www.epa.gov/ncea/pdfs/dioxin/nas-review/>. Accessed October 24, 2006. U.S. Environmental Protection Agency, Office of Research and Development, National Center for Environmental Assessment, Exposure Assessment and Risk Characterization Group, Washington, DC.
- EPA. 2004a. Risk assessment guidance for Superfund, Volume 1: Human health evaluation manual (Part E, supplemental guidance for dermal risk assessment). Final, July 2004.

EPA/540/R/99/005. U.S. Environmental Protection Agency, Office of Emergency and Remedial Response, Washington, DC.

EPA. 2004b. An Examination of EPA Risk Assessment Principles and Practices. March 2004. EPA 100/B-04/001. U.S. Environmental Protection Agency, Office of the Science Advisor, Washington, D.C.

EPA. 2004c(b). Example exposure scenarios. EPA/600/R-03/036. April 2004. U.S. Environmental Protection Agency, National Center for Exposure Assessment, Washington, DC.

EPA. 2005a. Guidelines for carcinogenic risk assessment. EPA/630/P-03/001F. March 2005, posted April 7, 2005 in 70FR17765-17817. U.S. Environmental Protection Agency, Risk Assessment Forum, Washington, DC.

EPA. 2005b. Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens. EPA/630/R-03/003F. March 2005. U.S. Environmental Protection Agency, Risk Assessment Forum, Washington, DC.

EPA. 2005c. Guidance on selecting age groups for monitoring and assessing childhood exposures to environmental contaminants. EPA/630/P-03/003F. Available at: <http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=146583>. U.S. Environmental Protection Agency, Risk Assessment Forum, Office of Research and Development, Washington, D.C.

EPA. 2006a. Integrated Risk Information System. Chemical files. U.S. Environmental Protection Agency, Office of Research and Development, Cincinnati, OH.

EPA. 2006b. U.S. EPA Region IX preliminary remediation goals. Revision date: December 28, 2004. Accessed on _____, 2006 at <http://www.epa.gov/region09/waste/sfund/prg/files/04prgtable.pdf> U.S. Environmental Protection Agency Region IX, San Francisco, CA.

EPA. 2006c. Approaches for the application of physiologically based pharmacokinetic (PBPK) models and supporting data in risk assessment. EPA/600/R-05/043F. U.S. Environmental Protection Agency, National Center for Environmental Assessment, Office of Research and Development, Washington, DC.

EPA. 2006d. Child-Specific Exposure Factors Handbook (External Review Draft). EPA/600/R/06/096A. September 2006. U.S. Environmental Protection Agency, Washington, DC.

EPA. 2006e. Region 6 Human Health Media-Specific Screening Levels. Revised December 22, 2005. Accessed on Nov 27, 2006 at http://www.epa.gov/earth1r6/6pd/rcra_c/pd-n/screen.htm last updated November 6, 2006. U.S. Environmental Protection Agency, Region VI, Dallas, TX.

Eskenazi, B., M. Warner, P. Mocarelli, S. Samuels, L.L. Needham, D.G. Patterson, Jr., S. Lippman, P. Vercellini, P.M. Gerthoux, P. Brambilla, and D. Olive. 2002. Serum dioxin concentrations and menstrual cycle characteristics. *Am J Epidemiol* 156:383-92.

- Faqi, A. S. and I. Chahoud. 1998. Antiestrogenic effects of low doses of 2,3,7,8-TCDD in offspring of female rats exposed throughout pregnancy and lactation. *Bull Environ Contam Toxicol* 61:462-469.
- Faqi, A.S., P.R. Dalsenter, H.J. Merker, and I. Chahoud. 1998. Reproductive toxicity and tissue concentrations of low doses of 2,3,7,8-Tetrachlorodibenzo-p-dioxin in male offspring rats exposed throughout pregnancy and lactation. *Toxicol and Applied Pharmacology*, 150(2):383-392.
- 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. Cancer mortality in workers exposed to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin. *New England Journal of Medicine* 324:212-218.
- Finley, B.L., K.T. Connor, and P.K. Scott. 2003. The use of toxic equivalency factor distributions in probabilistic risk assessments for dioxins, furans, and PCBs. *J. Toxicol. Environ. Health, Part A*, 66(6):533–550.
- Flesch-Janys, D., K. Steindorf, P. Gurn, and H. Becher. 1998. Estimation of the cumulated exposure to polychlorinated dibenzo-*p*-dioxins/furans and standardized mortality ratio analysis of cancer mortality by dose in an occupationally exposed cohort. *Environ. Health Perspect.* 106(Suppl. 2):655-662.
- Franzblau, A. 2006. The University of Michigan Dioxin Exposure Study: project overview. August 21, 2006. Presentation at the Dioxin 2006 Conference. University of Michigan, Ann Arbor, MI.
- Frawley B.J. 2004. Demographics, recruitment, and retention of Michigan hunters. Michigan DNR Wildlife Division Report No. 3426. September 2004. Michigan Department of Natural Resources, Wildlife Division, Lansing, MI.
- Frawley, B.J. 2005a. Michigan Deer Harvest Survey Report, 2004 Seasons. Michigan DNR Wildlife Report No. 3444. August 2005. Michigan Department of Natural Resources, Wildlife Division, Lansing, MI.
- Frawley, B.J. 2005b. Small game harvest and characteristic of small game hunters in Michigan, 2004. Michigan DNR Wildlife Report No. 3449. December 2005. Michigan Department of Natural Resources, Wildlife Division, Lansing, MI.
- Frawley, B.J. 2005c. 2004 Michigan Fall turkey hunter survey. Michigan DNR Wildlife Report No. 3434. April 2005. Michigan Department of Natural Resources, Wildlife Division, Lansing, MI.
- Frawley, B.J. 2005d. 2005 Michigan Spring turkey hunter survey. Michigan DNR Wildlife Report No. 3450. December 2005. Michigan Department of Natural Resources, Wildlife Division, Lansing, MI.
- Freedman, D.A., L.S. Gold, and T.H. Lin. 1996. Concordance between rats and mice in bioassays for carcinogenesis. *Regul. Toxicol. Pharmacol.* 23:225–232.

Galbraith. 2003a. Tittabawassee River Aquatic Ecological Risk Assessment. Polychlorinated Dibenzo-p-Dioxins Polychlorinated Dibenzofurans. October 2003. Galbraith Environmental Sciences LLC., Newfane, Vermont.

Galbraith. 2003b. Tittabawassee River Aquatic Ecological Risk Assessment. Polychlorinated Dibenzo-p-Dioxins Polychlorinated Dibenzofurans. October 2003. Galbraith Environmental Sciences LLC., Newfane, Vermont.

Garabrant, D.H., A. Franzblau, B. Gillespie, X. Lin, J. Lepkowski, P. Adriaens, and A. Demond. 2005. The University of Michigan Dioxin Exposure Study - Study Protocol, revised. January 2005. Available online at: <http://www.sph.umich.edu/dioxin/protocol.html> University of Michigan School of Public Health, Ann Arbor, MI.

Gaylor, D.W. and J.J. Chen. 1986. Relative potency of chemical carcinogens in rodents. *Risk Analysis* 6(3):283–290.

Gaylor, D.W. and L.L. Aylward. 2004. An evaluation of benchmark dose methodology for non-cancer continuous-data health effects in animals due to exposure to dioxin (TCDD) *Reg. Toxicol. Pharmacol.* 40:9-17.

Gaylor, D.W., J.J. Chen, and D.M. Sheehan. 1993. Uncertainty in cancer risk estimates. *Risk Analysis* 13(2):149–154.

Gehrs, B.C. and R.J. Smialowicz. 1997. Alterations in the developing immune system of the F344 rat after perinatal exposure to 2,3,7,8-tetrachlorodibenzo-p-dioxin I. Effects on the fetus and the neonate. *Toxicology* 122:219–228.

Gehrs, B.C. and R.J. Smialowicz. 1999. Persistent suppression of delayed-type hypersensitivity in adult F344 rats after perinatal exposure to 2,3,7,8-tetrachlorodibenzo-p-dioxin. *Toxicology* 134:79-88.

Gehrs, B.C., M.M. Riddle, W.C. Williams, and R.J. Smialowicz. 1997. Alterations in the developing immune system of the F344 rat after perinatal exposure to 2,3,7,8-tetrachlorodibenzo-p-dioxin: II. Effects on the pup and the adult. *Toxicology* 122:229-240.

Geusau, A., S. Schmaldienst, K. Derfler, O. Papke, and K. Abraham. 2002. Severe 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) intoxication: kinetics and trials to enhance elimination in two patients. *Arch. Toxicol.* 76:316-325.

Geusau, A., K. Abraham, K. Geissler, M.O. Sator, G. Stingl, and E. Tschachler. 2001. Severe 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) intoxication: Clinical and laboratory effects. *Environ Health Perspect.* 109:865–869

Giacomini, S.M., L. Hou, P.A. Bertazzi, and A. Baccarelli. 2006. Dioxin effects on neonatal and infant thyroid function: routes of perinatal exposure, mechanisms of action and evidence from epidemiology studies. *Int Arch Occup Environ Health* 79:396-404.

- Gierthy, J.F. and D. Crane. 1985. In Vitro Bioassay for dioxinlike activity based on alterations in epithelial cell proliferation and morphology. *Fundam. Appl. Toxicol.* 5(4):754–759.
- Gilbert, R.O. 1987. *Statistical Methods for Environmental Pollution Monitoring*. John Wiley & Sons, Inc., New York, NY
- Gold, L.S., L. Bernstein, R. Magaw, and T.H. Slone. 1989. Interspecies extrapolation in carcinogenesis: prediction between rats and mice. *Environ. Health Perspect.* 81:211–219.
- Gold, L.S., N.B. Manley, and B.N. Ames. 1992. Extrapolation of carcinogenicity between species: qualitative and quantitative factors. *Risk Analysis* 12(4):579–588.
- Gray, Jr., L.E., W.R. Kelce, E. Monosson, J.S. Ostby, and L.S. Birnbaum. 1995. Exposure to TCDD during development permanently alters reproductive function in male Long Evans rats and hamsters: reduced ejaculated and epididymal sperm numbers and sex accessory gland weights in offspring with normal androgenic status. *Toxicol. Appl Pharmacol* 131(1):108-118.
- Gray, L.E., J.S. Ostby, and W.R. Kelce. 1997. A dose-response analysis of the reproductive effects of a single gestational dose of 2,3,7,8-tetrachlorodibenzo-p-dioxin in male Long Evans Hooded rat offspring. *Toxicol. Appl Pharmacol* 146(1):11-20.
- Gray, M.N., L.L. Aylward, and R.E. Keenan. 2006. Relative cancer potencies of selected dioxin-like compounds on a body-burden basis: Comparison to current toxic equivalency factors (TEFs). *J. Toxicol. Environ. Health, Part A*, 69:907-917.
- Gruemping, R., S. Hamm, D. Stegemann, A. Maulshagen. 2004. Levels of polychlorinated dibenzo(p)dioxins, dibenzofurans and dioxin-like PCBs in Irish farmed salmon. *Organohalogen Compounds* 66:1977–1984.
- Guzelian, P., L. Quattrochi, N. Karch, L. Aylward, and R.Kaley. 2006. Does dioxin exert toxic effects in humans at or near current background body levels?: An evidence-based conclusion. *Hum Exp Toxicol* 25:99-105.
- Guzelian, P.S., M.S. Victoroff, N.C. Halmes, R.C. James, and C.P. Guzelian. 2005. Evidence-based toxicology: a comprehensive framework for causation. *Hum. Exp. Toxicol.* 24(4):161-201.
- Habicht II, F.H. 1992. Memorandum to assistant and regional administrators re: Guidance on Risk Characterization for Risk Managers and Risk Assessors. February 26, 1992. Available at: <http://www.epa.gov/oswer/riskassessment/habicht.htm>. U.S. Environmental Protection Agency, Office of Solid Waste and Emergency Response, Washington, DC.
- Hamm, J.T., C.Y. Chen, and L.S. Birnbaum. 2003. A mixture of dioxin, furans, and non-ortho PCBs based upon consensus toxic equivalency factors produces dioxin-like reproductive effects. *Toxicol. Sci.* 74:82-191.

- Harper, M., J. Piskorska-Pliszczynska, T. Zacharewski, M. Romkes, and S. Safe. 1989. Structure-dependent induction of aryl hydrocarbon hydroxylase in human breast cancer cell lines and characterization of the Ah receptor. *Cancer Res.* 49(16):4531-4535.
- Harper, N., K. Connor, and S. Safe. 1993. Immunotoxic potencies of polychlorinated biphenyl (PCB), dibenzofuran (PCDF) and dibenzo-p-dioxin (PCDD) congeners in C57BL/6 and DBA/2 mice. *Toxicol.* 80(2-3):217-227.
- Harper, P.A., J.Y. Wong, M.S. Lam, and A.B. Okey. 2002. Polymorphisms in the human AH receptor. *Chem. Biol. Interact.* 141(1-2):16.
- Harris, M., J. Piskorska-Pliszczynska, T. Zacharewski, M. Romkes, and S. Safe. 1989. Structure-dependent induction of aryl hydrocarbon hydroxylase in human breast cancer cell lines and characterization of the Ah receptor. *Cancer Res.* 49(16):4531-4535.
- Harris, M., T. Zacharewski, J. Piskorska-Pliszczynska, R. Rosengren, and S. Safe. 1990. Structure-dependent induction of aryl hydrocarbon hydroxylase activity in C57BL/6 mice by 2,3,7,8-tetrachlorodibenzo-p-dioxin and related congeners: mechanistic studies. *Toxicol. Appl. Pharmacol.* 105(2):243-253.
- Hawley, J.K. 1985. Assessment of health risk from exposure to contaminated soil. *Risk Anal.* 5(4):289-302.
- Haws, L.C., S.H. Su, M. Harris, M.J. Devito, N.J. Walker, W.H. Farland, B. Finley, and L.S. Birnbaum. 2006. Development of a refined database of mammalian relative potency estimates for dioxin-like compounds. *Toxicol. Sci.* 89(1):4-30.
- Heid, S.E., M.K. Walker, and H.I. Swanson, 2001. Correlation of cardiotoxicity mediated by halogenated aromatic hydrocarbons to aryl hydrocarbon receptor activation. *Toxicol. Sci.* 61(1):187-196.
- Hites, R.A. 1991. Atmospheric transport and deposition of polychlorinated dibenzo-p-dioxins and dibenzofurans. Prepared for the U.S. Environmental Protection Agency, Methods Research Branch, Atmospheric Research and Assessment Laboratory, Office of Research and Development, Research Triangle Park, NC. EPA/600/3-91/002.
- Hoehn, J.P., Tomasi, T., Lupi, F., and Chen, H.Z. 1996a. An economic model for valuing recreational angling resources in Michigan. Volume 1: Main Report. Department of Agricultural Economics, Michigan State University. December 1996.
- Hoehn, J.P., Tomasi, T., Lupi, F., and Chen, H.Z. 1996b. An economic model for valuing recreational angling resources in Michigan. Appendix 2: Survey of Michigan Anglers. Department of Agricultural Economics, Michigan State University. December 1996.
- Holmes K.K., J.H. Shirai, K.Y. Richter, and J.C. Kissel. 1999. Field Measurement of Dermal Soil Loadings in Occupational and Recreational Activities. *Environ. Research* 80(2):148-157.

- Holsapple, M.P., H.C. Pitot, S.H. Cohen, A.R. Boobis, J.E. Klaunig, T. Pastoor, V.L. Dellarco and Y.P. Dragan. 2006. Mode of action in relevance of rodent liver tumors to human cancer risk. *Toxicol. Sci.* 98:51-56.
- Hora, M.R. 1981. Reduction of polychlorinated biphenyl (PCB) concentrations in carp (*Cyprinus carpio*) fillets through skin removal. *Bull. Environ. Contam. Toxicol.* 26:364–366.
- Hori, T., R. Nakagawa, K. Tobiishi, T. Iida, T. Tsutsumi, K. Sasaki, and M. Toyoda. 2005. Effects of cooking on concentrations of polychlorinated dibenzo-p-dioxins and related compounds in fish and meat. *J. Agric. Food Chem.* 53(22):8820–8828.
- Huisman, M., C. Koopman-Esseboom, C. I. Lanting, C.G. van der Paauw, L.G. Tuinstra, V. Fidler, N. Weisglas-Kuperus, P.J. Sauer, E.R. Boersma, and B.C. Touwen. 1995. Neurological condition in 18-month-old children perinatally exposed to polychlorinated biphenyls and dioxins. *Early Hum Dev* 43:165-176.
- Huisman, M., C. Koopman-Esseboom, V. Fidler, M. Hadders-Algra, C.G. van der Paauw, L.G. Tuinstra, N. Weisglas-Kuperus, P.J. Sauer, B.C. Touwen, and E.R. Boersma. 1995. Perinatal exposure to polychlorinated biphenyls and dioxins and its effect on neonatal neurological development. *Early Hum Dev* 41:111-127.
- Hulster, A., and H. Marschner. 1993. Transfer of PCDD/PCDF from contaminated soils to food and fodder crop plants. *Chemosphere* 27:439–446.
- Hulster, A., J.F. Muller, and H. Marschner. 1994. Soil–plant transfer of polychlorinated dibenzo-*p*-dioxins and dibenzofurans to vegetables of the cucumber family (*Cucurbitaceae*). *Environ Sci Technol.* 1994;28:1110–1115.
- IARC Monographs, Volume 69 Polychlorinated dibenzo-*para*-dioxins and polychlorinated dibenzofurans. 1997 IARC, Lyon France.
- Ilsen, A., J.M. Briet, J.G. Koppe, H.J. Pluim, and J. Oosting. 1996. Signs of enhanced neuromotor maturation in children due to perinatal load with background levels of dioxins. Follow-up until age 2 years and 7 months. *Chemosphere* 33:1317-1326.
- IOM. 2003. Human foods and food-consumption patterns. pp. 110–149. In: *Dioxins and Dioxin-like Compounds in the Food Supply, Strategies to Decrease Exposure*. Available at: <http://fermat.nap.edu/openbook/0309089611/html/110.html>. Accessed October 24, 2006. Institute of Medicine of the National Academies, Food and Nutrition Board, Committee on the Implications of Dioxin in the Food Supply. The National Academies Press, Washington, DC.
- Israeli, M. and C. Nelson. 1992. Distribution and expected time of residence of U.S. households. *Risk Analysis* 12:65-72.
- Jansing, R.L. and W. Shain. 1985. Aryl hydrocarbon hydroxylase induction in adult rat hepatocytes in primary culture by several chlorinated aromatic hydrocarbons including 2,3,7,8-tetrachlorodibenzo-*p*-dioxin. *Fund. Appl. Toxicol.* 5(4):713–720.

JECFA. 2001. Summary and conclusions. Fifty-seventh meeting. Rome, 5-14 June 2001. Section 3: Polychlorinated dibenzodioxins, polychlorinated dibenzofurans, and coplanar polychlorinated biphenyls http://www.who.int/ipcs/food/jecfa/summaries/en/summary_57.pdf. Joint Food and Agriculture Organization of the United Nations/World Health Organization (FAO/WHO) Expert Committee on Food Additives.

JECFA. 2002. Evaluation of certain food additives and contaminants. WHO Technical Report Series: 909. December 27, 2002. Prepared by the 57th Meeting of the Joint FAO/WHO Expert Committee on Food Additives. World Health Organization, Geneva. 96 pp.

Johnson, T. and J. Capel. 1992. A Monte Carlo Approach to Simulating Residential Occupancy Periods and Its Application to the General U.S. Population. EPA 450/3-92-011. August 1992. U.S. Environmental Protection Agency, Office of Air Quality Planning and Standards, Emissions Standards Division, Research Triangle Park, NC.

Jugdaohsingh, R., S.H.C. Anderson, K.L. Tucker, H. Elliott, D.P. Kiel, R.P.H. Thompson, and J.J. Powell. 2002. Dietary silicon intake and absorption. *Am. J. Clin. Nutr.* 75(5):887–893.

Kaneko, H., E. Matsui, S. Shinoda, N. Kawamoto, Y. Nakamura, R. Uehara, N. Matsuura, M. Morita, H. Tada, and N. Kondo. 2006. Effects of dioxins on the quantitative levels of immune components in infants. *Toxicol Ind Health* 22:131-136.

Ketchum, N.S., and J.E. Michalek. 2005. Postservice Mortality of Air Force Veterans Occupationally Exposed to Herbicides during the Vietnam War: 20-Year Follow-Up Results. *Military Medicine* 170(5)406-413.

Kerger, B. D., H.W. Leung, D.J. Paustenbach, L.L. Needham, D.G. Patterson, Jr., P.M. Gerthoux, and P. Mocarelli. 2005. Age- and concentration dependent TCDD elimination kinetics in Seveso children. *Organohalogen Compounds* 67:1722-1725.

Kerger, B.D., H.W. Leung, P. Scott, D.J. Paustenbach, L.L. Needham, D.G. Patterson Jr., P.M. Gerthoux, and P. Mocarelli. 2006. Age- and Concentration-Dependent Elimination Half-Life of 2,3,7,8-Tetrachlorodibenzo-p-dioxin in Seveso Children. *Environ. Health Perspect.* 114(10):1596–1602.

Ketchum, N.S., and J.E. Michalek. 2005. Postservice Mortality of Air Force Veterans Occupationally Exposed to Herbicides during the Vietnam War: 20-Year Follow-Up Results. *Military Medicine* 170(5)406-413.

Khanna, N., C.R. Santerre, D. Xu, and Y.W. Huang. 1997. Changes in dieldrin and p,p'-DDE residues following cooking of Channel Catfish. *J. Food Protection* 60(3):300–304.

Kim H.S., B.H. Kim, S.J Lee and Y.S. Chang. 2002. Levels of PCDD/Fs and dioxin-like PCBs in the blood of Korean workers and residents. *Organohalogen Compd* 58:257–260.

Kissel, J.C., J.H. Shirai, K.Y. Richter, and RA. Fenske. 1998. Investigation of Dermal Contact with Soil in Controlled Trials. *J. of Soil Contamin.* 7(6):737-752.

- Kissel, J.C., K.Y. Richter, and R.A. Fenske. 1996. Factors affecting soil adherence to skin in hand-press trials. *Bull. Environ. Contam. Toxicol.* 56:722-728.
- Kociba, R.J., D.G. Keyes, J.E. Beyer, R.M. Carreon, C.E. Wade, D.A. Dittenber, R.P. Kalnins, L.E. Frauson, C.N. Park, S.D. Barnard, R.A. Hummel, and C.G. Humiston. 1978. Results of a two-year chronic toxicity and oncogenicity study of 2,3,7,8-tetrachlorodibenzo-p-dioxin in rats. *Toxicol. Appl. Pharmacol.* 46:279-303.
- Kodell, R.L., J.J. Chen, R.R. Delongchamp and J.F. Young. 2006. Hierarchical models for probabilistic dose-response assessment. *Reg. Toxicol. Pharmacol.* 45:265-272.
- Koopman-Esseboom, C., D.C. Morse, N. Weisglas-Kuperus, I. J. Lutkeschipholt, C.G. Van der Paauw, L.G. Tuinstra, A. Brouwer, and P. J. Sauer. 1994. Effects of dioxins and polychlorinated biphenyls on thyroid hormone status of pregnant women and their infants. *Pediatr Res* 36: 468-473.
- Krablin, R. 1989. [Letter to Jonathon Z. Cannon concerning soil ingestion rates.] Denver, CO: Arco Coal Co.; October 13, 1989. As referenced in EPA, 1997 (EFH).
- Krishnan, V. and S. Safe. 1993. Polychlorinated biphenyls (PCBs), dibenzo-p-dioxins (PCDDs), and dibenzofurans (PCDFs) as antiestrogens in MCF-7 human breast cancer cells: quantitative structure-activity relationships. *Toxicol Appl Pharmacol* 120(1):55-61.
- Kwan, M.I., P.A. Buffler, B. Abrams and V.A. Kiley. 2004. Breastfeeding and the risk of childhood leukemia: a meta-analysis. *Public Health Reports* 119:521-535.
- LaDronka, K., B.L. Ward, K. Olson, S. Freeland, J. Sinibaldi, E. Hedgeman, L. Zwica, T. Towey, A. Demond, A. Franzblau, D. Garabrant, P. Arianes, and J.M. Lepkowski. 2006. Cross-Organizational Training on the University of Michigan Dioxin Exposure Study: Ensuring Consistency, Confidentiality and Cooperation in Data Collection. Poster presented at Dioxin 2006 conference. University of Michigan, Ann Arbor, MI.
- Lambert, G.H., L.L. Needham, W. Turner, T.J. Lai, D.G. Patterson, Jr., and Y.L. Guo. 2006. Induced CYP1A2 activity as a phenotypic biomarker in humans highly exposed to certain PCBs/PCDFs. *Environ Sci Technol* 40:6176-6180.
- Lanting, C.I., S. Patandin, V. Fidler, N. Weisglas-Kuperus, P.J. Sauer, E.R. Boersma, and B.C. Touwen. 1998. Neurological condition in 42-month-old children in relation to pre- and postnatal exposure to polychlorinated biphenyls and dioxins. *Early Hum Dev* 50:283-292.
- Lawson, M.S. 1977. Trace element balances in children. *J. Hum. Nutr.* 31(5):354-355.
- Lee, C-K. and E-H. Lee. 1985. Heat stability of organochlorine pesticide residues in loach. *Bull. Nat. Fish. Univ. Pusan* 25:85-91.
- Lepkowski, J.M. 2006. Survey methodology in an environmental exposure study: methods to assure sound inference. August 21, 2006. Presentation at the Dioxin 2006 Conference. University of Michigan, Ann Arbor, MI.

- Leung, H., B.D. Kerger, and D.J. Paustenbach. 2006. Elimination half-lives of selected polychlorinated dibenzodioxins and dibenzofurans in breast-fed human infants. *J. Toxicol. Environ. Health Part A* 69(6):437-443.
- Leung, H.W., B.D. Kerger, D.J. Paustenbach, J.J. Ryan, and Y. Masuda. 2005. Age- and concentration-dependent elimination half lives of chlorinated dibenzofurans in Yusho and Yucheng patients. *Organohalogen Compounds* 67:1589-1592.
- Lewis, T. and J. Makarewicz. 1985. Effects of smoking on mirex levels in brown trout from Lake Ontario. *N.Y. Fish and Game J.* 31:84-86.
- Li, W., W.Z. Wu, K.-W. Schramm, Y. Xu, and A. Kettrup. 1999. Toxicity of Mixtures of Polychlorinated Dibenzo-p-dioxins, Dibenzofurans, and Biphenyls Determined by Dose-Response Curve Analysis. *Bull Environ Contam Toxicol* 62(5):539-546.
- Link, B., T. Gabrio, I. Zoellner, I. Piechotowski, O. Paepke, T. Herrmann, A. Felder-Kennel, V. Maisner, K.H. Schick, M. Schrimpf, M. Schwenk, and J. Wuthe. 2005. Biomonitoring of persistent organochlorine pesticides, PCDD/PCDFs and dioxin-like PCBs in blood of children from South West Germany (Baden-Wuerttemberg) from 1993 to 2003. *Chemosphere* 58:1185-1201.
- Lorber, M. 2002. A pharmacokinetic model for estimating exposure of Americans to dioxin-like compounds in the past, present, and future. *Sci. Tot. Environ.* 288: 81-95.
- Lorber, M. and L. Phillips. 2002. Infant exposure to dioxin-like compounds in breast milk. *Environ. Health Perspect.* 110(6):A325-A332.
- Lupi, F. 2004a. Fishing sites visited by anglers in the Michigan panel survey. Report to Fisheries Division of the Michigan DNR. September 2004.
- Lupi, F. 2004b. A profile of recreational anglers in Michigan. Staff paper No 04-17. Department of Agricultural Economics, Michigan State University, East Lansing, Michigan 48824
- Lupi, F., Hoehn, J.P., Chen, H.Z., and Tomasi, T.D. 1998. The Michigan Recreational Angling Demand Model. Staff Paper Number 97-58, Department of Agricultural Economics, Michigan State University. March, 1998.
- Mably, T.A., D.L. Bjerke, R.W. Moore, A. Gendron-Fitzpatrick, and R.E. Peterson. 1992. In utero and lactational exposure of male rats to 2,3,7,8-tetrachlorodibenzo-p-dioxin. 3. Effects on spermatogenesis and reproductive capability. *Toxicol. Appl. Pharmacol.* 114:118-126.
- Mably, T.A., R.W. Moore, and R.E. Peterson. 1992. In utero and lactational exposure of male rats to 2,3,7,8-tetrachlorodibenzo-p-dioxin. 1. Effects on androgenic status. *Toxicol. Appl. Pharmacol.* 114:97-107.
- Mably, T.A., R.W. Moore, R.W. Goy, and R.E. Peterson. 1992. In utero and lactational exposure of male rats to 2,3,7,8-tetrachlorodibenzo-p-dioxin. 2. Effects on sexual behavior and

the regulation of luteinizing hormone secretion in adulthood. *Toxicol. Appl. Pharmacol.* 114:108-117.

Martin, R.M., D. Gunnell, C.G. Owen and G.D. Smith 2005b Breast-feeding and childhood cancer: A systemic review with metaanalysis. *Int. J. Cancer* 117:1020-1031.

Martin, R.M., N. Middleton, D. Gunnell, C.G. Owen, G. D. Smith 2005a Breast-feeding and cancer: The Boyd Orr cohort and a systematic review with meta-analysis. *J. Natl. Cancer Inst.* 97:1446-1457.

Maruyama, W. and A. Yasunobu. 2006. Estimated cancer risk of dioxins to humans using a bioassay and physiologically based pharmacokinetic model. *Toxicol Appl. Pharmacol* 214: 118-198.

Maruyama, W., K. Yoshida, and Y. Aoki. 2004. Dioxin health risk to infants using simulated tissue concentrations *Environ Toxicol Pharmacol* 18:21-37.

Maruyama, W., K. Yoshida, T. Tanaka, and J. Nakanishi. 2002. Possible range of dioxin concentration in human tissues: simulation with a physiologically based model. *J. Toxicol. Environ. Health, Part A*, 65:2053-2073.

Maruyama, W., K. Yoshida, T. Tanaka, and J. Nakanishi. 2003. Simulation of dioxin accumulation in human tissues and analysis of reproductive risk. *Chemosphere* 53: 301–13.

Mason, G., T. Sawyer, B. Keys, S. Bandiera, M. Romkes, J. Piskorska-Pliszczyńska, B. Zmudzka and S. Safe. 1985. Polychlorinated dibenzofurans (PCDFs): correlation between in vivo and in vitro structure-activity relationships. *Toxicology* 37(1):1-12.

Matsuura, N., T. Uchiyama, H. Tada, Y. Nakamura, N. Kondo, M. Morita, and M. Fukushi. 2001. Effects of dioxins and polychlorinated biphenyls (PCBs) on thyroid function in infants born in Japan--the second report from research on environmental health. *Chemosphere* 45:1167-1171.

McConnell, E.E., J.A. Moore, J.K. Haseman, and M.W. Harris. 1978. The comparative toxicity of chlorinated dibenzo-p-dioxins in mice and guinea pigs. *Toxicol. Appl. Pharmacol.* 44(2):335–356.

McCrary, J.K., C. McFarlane, and L.K. Gander. 1990. Transport and Fate of 2,3,7,8-TCDD in Soybean and Corn. *Chemosphere* 21:359-376.

McKinley, M.K., L.B. Kedderis, and S. Birnbaum. 1993. The effect of pretreatment on the biliary excretion of 2,3,7,8-tetrachlorodibenzo-p-dioxin, 2,3,7,8-tetrachlorodibenzofuran, and 3,3,4,4-tetrachlorobiphenyl in the rat. *Fund. Appl. Toxicol.* 21:425-432.

McKinney, J.D., K. Chae, E.E. McConnell, and L.S. Birnbaum. 1985. Structure–induction versus structure–toxicity relationships for polychlorinated biphenyls and related aromatic hydrocarbons. *Environ. Health. Perspect.* 60:57–68.

MDCH (Klaviter, E., Humphrey, H., Bloomer, A.W., and Welch, R.). 2000a. Kalamazoo River Angler Survey and Biological Testing Study, Final Report. May 2000. Michigan Department of Community Health, Community Public Health Agency, Environmental Epidemiology Division, Lansing, MI.

MDCH. 2000a. Fish Consumption Advisory. Michigan Department of Community Health, Lansing, MI.

MDCH. 2000b. Kalamazoo River Angler Survey and Biological Testing Study, Database for Phase I. Provided by Dr. Robert L. Wahl, Environmental Epidemiology Division, August 31, 2000, in response to a Freedom of Information Request from Dr. Edmund Crouch, Cambridge Environmental Inc. Michigan Department of Community Health, Community Public Health Agency, Environmental Epidemiology Division, Lansing, MI.

MDCH. 2000b. Kalamazoo River Angler Survey and Biological Testing Study, Database. [Provided by the Environmental Epidemiology Division, MDCH, in response to a Freedom of Information Request. Cover letter dated August 31, 2000, from Dr. Robert L. Wahl to Dr. Edmund Crouch.] Michigan Department of Community Health, Environmental Epidemiology Division, Lansing, MI.

MDCH. 2000c. Kalamazoo River Angler Survey and Biological Testing Study, Database for Phase II. Provided by Dr. David R. Wade, Division of Environmental Epidemiology, December 23, 1998, in response to a Freedom of Information Request from Ms. Dawn E. Penniman, Blasland, Bouck & Lee, Inc. Michigan Department of Community Health, Community Public Health Agency, Environmental Epidemiology Division, Lansing, MI.

MDCH. 2004. Fish Consumption Advisory. Michigan Department of Community Health, Lansing, MI.

MDCH. 2005. Petitioned Health Consultation: Dioxins in Wild Game Taken from the Tittabawassee River Floodplain South of Midland, Midland and Saginaw Counties, Michigan. EPA ID# MID980994354. April 29, 2005. Prepared under a cooperative agreement with Agency for Toxic Substances and Disease Registry. Michigan Department of Community Health, Lansing, MI.

MDCH. 1997. Health consultation for Allied Paper/Portage Creek/Kalamazoo River/Allegan Counties, Michigan. CERCLIS No. MID006007306. July 2, 1997. Michigan Department of Community Health, Lansing, MI.

MDEQ. 1991. Letter to Dow re: dermal absorption efficiency of 1.75%

MDEQ. 1997. Summary of 1996 Midland Dioxin Screening Study Results, 3/25/97. Working DRAFT of Document for Public Release. Michigan Department of Environmental Quality, Waste Management Division, Lansing, MI.

MDEQ. 2001a. Unpublished: Greenpoint - Tittabawassee River Dioxin Study Area, Phase I Sampling Study Report. October 2001. Michigan Department of Environmental Quality, Environmental Response Division, Lansing, MI.

MDEQ. 2002. Administrative Rules for Part 201, Environmental Remediation of the Natural Resources and Environmental Protection Act, 1994 PA 451, as amended. Filed with the Secretary of State on December 13, 2002. Michigan Department of Environmental Quality, Lansing, MI.

MDEQ. 2002. Greenpoint – Tittabawassee River Dioxin Study Area Phase I Sampling Study Report. October 2001 (June 2002 revision) Michigan Department of Environmental Quality, Environmental Response Division, Lansing, MI.

MDEQ. 2002a. Information bulletin - Tittabawassee/Saginaw River Flood Plain Environmental Assessment Initiative Midland, Saginaw counties. February 2002. Michigan Department of Environmental Quality, Environmental Response Division, Lansing, MI.

MDEQ. 2002b. Information bulletin #2 - Tittabawassee/Saginaw River Flood Plain Environmental Assessment Initiative Bay, Midland, Saginaw counties. August 2002. Michigan Department of Environmental Quality, Environmental Response Division, Lansing, MI.

MDEQ. 2002c. Tittabawassee River Dioxin Study Area – Phase II Sampling Program (memo with data). April 2002. Michigan Department of Environmental Quality, Environmental Response Division, Lansing, MI.

MDEQ. 2002d. Summary of Phase II Tittabawassee River Flood Plain Sampling. June 2002. Michigan Department of Environmental Quality, Environmental Response Division, Lansing, MI.

MDEQ. 2003a. 2003 Hazardous Waste Management Facility Operating License for the Dow Chemical Company, Michigan Operations, Midland, MI. MID 000 724 724. Effective date: June 12, 2003. Michigan Department of Environmental Quality, Lansing, MI.

MDEQ. 2003b. Final Report Phase II Tittabawassee/Saginaw River Dioxin Flood Plain Sampling Study. June 2003. Michigan Department of Environmental Quality, Lansing, MI.

MDEQ. 2004. Preliminary Analytical Results for Soil Samples taken at Residential Properties in the Tittabawassee River Floodplain by the DEQ in June through December of 2003. February 2004. Michigan Department of Environmental Quality, Lansing, MI.

MDEQ. 2005a. Technical Support Document – Attachment 6. Part 201 Soil Direct Contact Criteria, Part 213 Tier 1 Soil Direct Contact Risk-Based Screening Levels. Operational Memorandum No. 1. Remediation and Redevelopment Division. April. <@@@ See page 80>

MDEQ. 2005b. Michigan Background Soil Survey. Waste and Hazardous Materials Division. July. MDEQ. 2006. Table 4: Toxicological and chemical-physical data for Part 201 generic cleanup criteria and screening levels. www.michigan.gov/deq/0%2c1607%2c7-135-3311_4109_9846_30022-101581--%2c00.html. Accessed September 28, 2006. Last updated January 23, 2006. Michigan Department of Environmental Quality, Remediation and Redevelopment Division, Lansing, MI.

- MDNR. 2006a. 2006-2007 Michigan Hunting and Trapping Guide. Michigan Department of Natural Resources, Lansing, MI.
- MDNR. 2006b. 2006-2008 Michigan Fishing Guide. Michigan Department of Natural Resources, Lansing, MI.
- Meek, M.E., J.R. Bucher, S.M. Cohen, V. Dellarco, R.N. Hill, L.D. Lehman-McKeeman, D.G. Longfellow, T. Pastoor, J. Seed and D.E. Patton. 2003. A framework for human relevance analysis of information on carcinogenic modes of action. *Crit. Rev. Toxicol.* 33: 591-653
- Moore, J.A., B.N. Gupta, J.G. Zinkl, and J.G. Vos. 1973. Postnatal effects of maternal exposure to 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD). *Environ. Health Perspect.* 5:81-85.
- Moya, J., K.G. Garrahan, T.M. Poston, and G.S. Durell. 1998. Effects of cooking on levels of PCBs in the fillets of Winter Flounder. *Bull. Environ. Contam. Toxicol.* 60:845-851.
- Muller, J.F., A. Hulster, O. Papke, M. Ball, and H. Marschner H. 1993. Transfer pathways of PCDD/PCDF to fruits. *Chemosphere* 27:195-201.
- Muller, J.F., A. Hulster, O. Papke, M. Ball, and H. Marschner. 1994. Transfer of PCDD/PCDF from contaminated soils into carrots, lettuce and peas. *Chemosphere* 29:2175-2181.
- Nagayama, J., C. Kiyohara, Y. Masuda, and M. Kuratsune. 1985. Genetically mediated induction of aryl hydrocarbon hydroxylase activity in human lymphoblastoid cells by polychlorinated dibenzofuran isomers and 2,3,7,8-tetrachlorodibenzo-p-dioxin. *Arch Toxicol* 56(4):230-235.
- Nagayama, J., H. Tsuji, T. Iida, H. Hirakawa, T. Matsueda, K. Okamura, M. Hasegawa, K. Sato, H.-Y. Ma, T. Yanagawa, H. Igarashi, J. Fukushima, and T. Watanabe, 1998. Postnatal exposure to chlorinated dioxins and related chemicals on lymphocyte subsets in Japanese breast-fed infants. *Chemosphere* 37:1781-1787.
- Nagayama, J., H. Tsuji, T. Iida, R. Nakagawa, T. Matsueda, H. Hirakawa, A. Shiraha, T. Yanagawa, J. Fukushima, and T. Watanabe. 2004. Effects of lactational exposure to organochlorine pesticides, PCBs and dioxins on immune response and thyroid hormone systems in Japanese male and female infants. *Organohalogen Compounds* 66:3217-3222.
- Nagayama, J., K. Okamura, T. Iida, H. Hirakawa, T. Matsueda, H. Tsuji, M. Hasegawa, K. Sato, H.-Y. Ma, T. Yanagawa, H. Igarashi, J. Fukushima, and T. Watanabe. 1998. Postnatal exposure to chlorinated dioxins and related chemicals on thyroid hormone status in Japanese breast-fed infants. *Chemosphere* 37:1789-1793.
- Nakano, S., T. Noguchi, H. Takekoshi, G. Suzuki and M. Nakano. 2005. Maternal-fetal distribution and transfer of dioxins in pregnant women in Japan, and attempts to reduce maternal transfer with *Chlorella* (*Chlorella pyrenoidosa*) supplements. *Chemosphere* 61:1244-1255.
- NAS. 2006. Health risks from dioxin and related compounds: evaluation of the EPA reassessment. National Academies of Science, National Research Council, Committee on EPA's Exposure and Human Health Reassessment of TCDD and Related Compounds. Board on

Environmental Studies and Toxicology, Division on Earth and Life Studies. The National Academies Press, Washington, D.C.

NCHS. 2005. National Health and Nutrition Examination Surveys (NHANES) 2003-2004 public data general release file documentation. June 2005. Available at: <http://www.cdc.gov/nchs/nhanes.htm>. Centers for Disease Control and Prevention, National Center for Health Statistics, Division of Health Examination Statistics, Hyattsville, MD.

Neubert, R., G. Golor, H. Helge, and D. Neubert. 1994. Risk assessment for possible effects of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) and related substances on components and functions of the immune system. *Exp Clin Immunogenet* 11:163-171.

Neubert, R., G. Golor, L. Maskow, H. Helge, and D. Neubert. 1994. Evaluation of possible effects of 2,3,7,8-tetrachlorodibenzo-p-dioxin and other congeners on lymphocyte receptors in *Callithrix jacchus* and man. *Exp Clin Immunogenet* 11:119-127.

Neubert, R., L. Maskow, J. Webb, U. Jacob-Muller, A.C. Nogueira, I. Delgado, H. Helge, and D. Neubert. 1993. Chlorinated dibenzo-p-dioxins and dibenzofurans and the human immune system. 1. Blood cell receptors in volunteers with moderately increased body burdens. *Life Sci* 53:1995-2006.

Niimi, A.J. and B.G. Oliver. 1989. Distribution of polychlorinated biphenyl congeners and other halocarbons in whole fish and muscle among Lake Ontario salmonids. *Environ. Sci. Technol.* 23:83-88.

NTP. 1982a. Carcinogenesis bioassay of 2,3,7,8-tetrachlorodibenzo-p-dioxin (CAS no. 1746-01-6) in Swiss-Webster mice (dermal study). Bethesda, MD: Carcinogenesis Testing Program, National Cancer Institute, National Institute of Health. Research Triangle Park, NC: National Toxicology Program. (NIH) DHHS publication no 82-1757.

NTP. 1982b. Carcinogenesis bioassay of 2,3,7,8-tetrachlorodibenzo-p-dioxin (CAS no. 1746-01-6) in Osborne-Mendel rats and B6C3F1 mice (gavage study). Bethesda, MD: Carcinogenesis Testing Program, National Cancer Institute, National Institute of Health. Research Triangle Park, NC: National Toxicology Program. (NIH) DHHS publication no 82-1765.

NTP. 2004. Report on Carcinogens. Eleventh Edition. Research Triangle Park, NC: National Toxicology Program. Available: <http://ntp.niehs.nih.gov/go/19914> [accessed November 9, 2006].

NTP. 2004. DRAFT NTP Technical Report on the Toxicology and Carcinogenesis Studies of 2,3,4,7,8-Pentachlorodibenzofuran (PeCDF) (CAS No. 57117-31-4) in Female Harlan Sprague-Dawley Rats (Gavage Study) (NTP TR 525), National Toxicology Program.

NTP. 2006. NTP Technical Report on the Toxicology and Carcinogenesis Studies of 2,3,7,8-Tetrachlorodibenzo-P-Dioxin (TCDD) (CAS No. 1746-01-6) in Female Harlan Sprague-Dawley Rats (Gavage Studies). National Institutes of Health, Public Health Service, U.S.DHSS. NTP TR 521. NIH Publication No. 06-4468. April 2006.

- Ohsako, S., Y. Miyabara, N. Nishimura, S. Kurosawa, M. Sakaue, R. Ishimura, M. Sato, K. Takeda, Y. Aoki, H. Sone, C. Tohyama, and J. Yonemoto. 2001. Maternal exposure to a low dose of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) suppressed the development of reproductive organs of male rats: dose-dependent increase of mRNA levels of 5alpha-reductase type 2 in contrast to decrease of androgen receptor in the pubertal ventral prostate. *Toxicol Sci* 60:132-143.
- Okey, A.B., P.C. Boutros, and P.A. Harper. 2005. Polymorphisms of human nuclear receptors that control expression of drug-metabolizing enzymes. *Pharmacogenet. Genomics* 15:371-379.
- Olson, J.R., B.P. McGarrigle, P.J. Gigliotti, S. Kumar, and J.H. McReynold. 1994. Hepatic uptake and metabolism of 2,3,7,8-tetrachlorodibenzo-p-dioxin and 2,3,7,8-tetrachlorodibenzofuran. *Fund. Appl. Toxicol.* 22:631-640.
- Olson, K., J. Sinibaldi, J. Lepkowski, B.L. Ward, and K. LaDronka. 2006. Examination of Nonresponse Bias in the University of Michigan Dioxin Exposure Study. Poster presented at Dioxin 2006 Conference. University of Michigan, Ann Arbor, Michigan, USA.
- Ostby, J., M. Price, O. Huey, C.H. Hurst, L.S. Birnbaum, and L.E.J. Gray. 1999. Developmental and reproductive effects of low-dose, steady-state maternal 2,3,7,8 tetrachlorodibenzo-p-dioxin (TCDD) administration. *The Toxicologist* 48:147.
- Ott, M.B. and A. Zober. 1996. Cause specific mortality and cancer incidence among employees exposed to 2,3,7,8-TCDD after a 1953 reactor accident. *Occup. Environ. Med.* 53(9):606-612.
- Patandin, S., C. Koopman-Esseboom, M.A. de Ridder, N. Weisglas-Kuperus, and P.J. Sauer. 1998. Effects of environmental exposure to polychlorinated biphenyls and dioxins on birth size and growth in Dutch children. *Pediatr Res* 44:538-545.
- Patandin, S., C.I. Lanting, P.G.H. Mulder, E.R. Boersma, P.J.J. Sauer, and N. Weisglas-Kuperus. 1999. Effects of environmental exposure to polychlorinated biphenyls and dioxins on cognitive abilities in Dutch children at 42 months of age. *J. Pediatrics* 134(1):33-41.
- Pelekis, M., M.J. Nicolich, and J.S. Gauthier. 2003. Probabilistic Framework for the Estimation of the Adult and Child Toxicokinetic Intraspecies Uncertainty Factors. *Risk Analysis* 23(6):1239-1255.
- Petroske, E., R.G. Zaylskie, and V.J. Feil. 1998. Reduction in polychlorinated dibenzodioxin and dibenzofuran residues in hamburger meat during cooking. *J. Agric. Food Chem.* 46:3280-3284.
- Pluim, H. J., J.G. Koppe, K. Olie, J.W. van der Slikke, P.C. Slot, and C.J. van Boxtel. 1994. Clinical laboratory manifestations of exposure to background levels of dioxins in the perinatal period. *Acta Paediatr* 83: 583-7.
- Pluim, H. J., J.J. de Vijlder, K. Olie, J.H. Kok, T. Vulsma, D.A. van Tijn, J.W. van der Slikke, and J.G. Koppe. 1993. Effects of pre- and postnatal exposure to chlorinated dioxins and furans on human neonatal thyroid hormone concentrations. *Environ Health Perspect* 101:504-508.

- Pluim, H. J., M. van der Goot, K. Olie, J.W. van der Slikke, and J.G. Koppe. 1996. Missing effects of background dioxin exposure on development of breast-fed infants during the first half year of life. *Chemosphere* 33:1307-1315.
- Pluim, H.J., J. Wever, J.G. Koppe, V.J.W. Slikke, and K. Olie. 1993. Intake and Faecal Excretion of Chlorinated Dioxins and Dibenzofurans in Breast-Fed Infants at Different Ages. *Chemosphere* 26(11):1947-1952.
- Poiger, H. and C. Schlatter. 1980. Influence of Solvents and Adsorbents on Dermal and Intestinal Absorption of TCDD. *Food Cosmet. Toxicol.* 18:477-481.
- Popp, J.A., E. Crouch, and E.E. McConnell. 2006. A weight-of-evidence analysis of the cancer dose-response characteristics of 2,3,7,8-tetrachlorodibenzodioxin (TCDD). *Tox. Sci.* 89(2):361-369.
- Popplewell, J.F., S.J. King, J.P. Day, P. Ackrill, L.K. Fifield, R.G. Cresswell, M.L. di Tada, and K. Liu. 1998. Kinetics of uptake and elimination of silicic acid by a human subject: a novel application of ³²Si and accelerator mass spectrometry. *J. Inorg. Biochem.* 69(3):177-180.
- Preston, R.J. 2004 Children as a sensitive subpopulation for the risk assessment process. *Toxicol Appl Pharmacol.* 199:132-141.
- Puffer, H.W. and R.W. Gossett. 1983. PCB, DDT, and Benzo(a)pyrene in raw and pan-fried White Croaker (*Genyonemus lineatus*). *Bull. Environm. Contam. Toxicol.* 30:65-73.
- Purchase, I.F.H. and T.R. Auton. 1995. Thresholds in chemical carcinogenesis. *Reg. Toxicol. Pharmacol.* 22:199-205.
- Rao, M.S., V. Subbarao, J.D. Prasad, and D.G. Scarpelli. 1988. Carcinogenicity of 2,3,7,8-tetrachlorodibenzo-p-dioxin in the Syrian golden hamster. *Carcinogenesis* 9(9):1677-1679.
- Reddy, M.B., R.H. Guy, and A.L. Bunge. 2000. Does epidermal turnover reduce percutaneous penetration? *Pharmaceutical Research* 17(11):1414-1419.
- Reffitt, D.M., R. Jugdaohsingh, R.P. Thompson, and J.J. Powell. 1999. Silicic acid: its gastrointestinal uptake and urinary excretion in man and effects on aluminium excretion. *J. Inorg. Biochem.* 76(2):141-147.
- Reinert, R.E., Stewart, D., and Seagran, H.L. (1972). Effects of dressing and cooking on DDT concentrations in certain fish from Lake Michigan. *J. Fish Res. Board Can.* 29:525-529.
- Rier, S. E., D.C. Martin, R.E. Bowman, W.P. Dmowski, and J.L. Becker. 1993. Endometriosis in Rhesus Monkeys (*Macaca mulatta*) Following Chronic Exposure to 2,3,7,8-Tetrachlorodibenzo-p-dioxin. *Toxicol. Sci.* 21:433-441.
- Rier, S.E., W.E. Turner, D.C. Martin, R. Morris, G.W. Lucier and G.C. Clark. 2001. Serum Levels of TCDD and Dioxin-like Chemicals in Rhesus Monkeys Chronically Exposed to Dioxin: Correlation of Increased Serum PCB Levels with Endometriosis. *Toxicol. Sci.* 59:147-159

Ritchey, S. J., Young, R.W., and Essary, E.O. (1967). The effects of cooking on chlorinated hydrocarbon pesticide residues in chicken tissue. *J. Food Sci.* 32:238–240.

Ritchey, S. J., Young, R.W., and Essary, E.O. (1969). Cooking methods and heating effects on DDT in chicken tissues. *J. Food Sci.* 34:569–571.

Rose, M., S. Thorpe, M. Kelly, N. Harrison, and J. Startin. 2001. Changes in concentration of five PCDD/F congeners after cooking beef from treated cattle. *Chemosphere* 43:861–868.

Roseberry, A.M., and D.E. Burmaster. 1991. A note: estimating exposure concentrations of lipophilic organic chemicals to humans via raw finfish fillets. *J. Expos. Anal. Environ. Epidemiol.* 1(4):513–521.

Ryan, J. J., T.A. Gasiewicz, and J.F. Brown, Jr. 1990. Human body burden of polychlorinated dibenzofurans associated with toxicity based on the yusho and yucheng incidents. *Fundam Appl Toxicol* 15:722-731.

Salama, A.A., M.A.M. Mohamed, B. Duval, T.L. Potter, and R.E. Levin. 1998. Polychlorinated biphenyl concentration in raw and cooked North Atlantic bluefish (*Pomatomus saltatrix*) fillets. *J. Agric. Food Chem.* 46:1359–1362.

Sanders, M., and B.L. Haynes. 1988. Distribution patterns and reduction of polychlorinated biphenyls (PCB) in Bluefish *Pomatomus saltatrix* (Linnaeus) fillets through adipose tissue removal. *Bull. Environ. Contam. Toxicol.* 41:670–677.

Santerre, C.R., R. Ingram, D.H. Xu, G.W. Lewis, and L.G. Lane. 2000. Chlordane and Toxaphene Residues following Cooking of Treated Channel Catfish Fillets. *J. Food Protection* 63(6):763–767.

Schantz, S. L., J. J. Widholm, and D.C. Rice. 2003. Effects of PCB exposure on neuropsychological function in children. *Environ Health Perspect* 111:357-576.

Schantz, S.L., S.A. Ferguson, and R.E. Bowman. 1992. Effects of 2,3,7,8-tetrachlorodibenzo-p-dioxin on behavior of monkeys in peer groups. *Neurotoxicol. Teratol.* 14(6):433-446.

Schechter, A., M. Dellarco, O. Pöpke, and J. Olson. 1998. A comparison of dioxins, dibenzofurans and coplanar PCBs in uncooked and broiled ground beef, catfish, and bacon. *Chemosphere* 37:1723–1730.

Schechter, A., O. Pöpke, M. Dellarco, and J. Olson. 1996. A comparison of dioxins and dibenzofurans in cooked and uncooked food. *Organohalogen Compounds* 28:166-170.

Shafer, M.A.M., and M.E. Zabik. 1975. Dieldrin, fat and moisture loss during cooking of beef loaves containing texturized soy protein. *J. Food Sci.* 40(5):1068–1071.

Sherer, R.A. and P.S. Price. 1993. The effect of cooking processes on PCB levels in edible fish tissue. *Qual. Assur. Good Practice Regul. Law* 2(4):396–407.

- Skea, J. C., S. Jackling, J. Symula, H.A. Simonin, E.J. Harris, and J.R. Colquhoun. 1981. Summary of fish trimming and cooking techniques used to reduce levels of oil soluble contaminants. Unpublished technical report, Field Toxicant Research Unit, Rome, NY and Hale Creek Field Station, New York State Dept of Env. Conservation, Sept. 1981.
- Skea, J.C., H.A. Simonin, E.J. Harris, S. Jackling, J.J. Spagnoli, J. Symula, and J.R. Colquhoun. 1979. Reducing levels of Mirex, Aroclor 1254, and DDE by trimming and cooking Lake Ontario Brown Trout (*Salmo Trutta Linnaeus*) and Smallmouth Bass (*Micropterus Dolomieu* lacepede). *J. Great Lakes Res.*, Internat. Assoc. Great Lakes Res. 5(2):153–159.
- Slob, W. and M.N. Pieters. 1998. A probabilistic approach for deriving acceptable human intake limits and human health risks from toxicological studies: General framework. *Risk Analysis* 18:787-798.
- Smith, A.G. and F. De Matteis. 1990. Oxidative injury mediated by the hepatic cytochrome P-450 system in conjunction with cellular iron. Effects on the pathway of haem biosynthesis. *Xenobiotica* 20(9):865-877.
- Smith, D.B., W.F. Cannon, L.G. Woodruff, R.G. Garrett, R. Klassen, J.E. Kilburn, J.D. Horton, H.D. King, M.B. Godlhaber and J.M. Morrison. 2005. Major- and trace-element concentrations in soils from two continental-scale transects of the United States and Canada. U.S. Department of the Interior, U.S. Geological Survey. Open File Report 2005-1253.
- Smith, S.K., M.E. Zabik, and L.E. Dawson. 1977. Polybrominated biphenyl levels in raw and cooked chicken and chicken broth. *Poultry Sci.* 56(4):1289–1296.
- Smith, W.E., K. Funk, and M.E. Zabik. 1973. Effects of cooking on concentrations of PCB and DDT compounds in Chinook (*Oncorhynchus tshawytscha*) and coho (*O. kisutch*) salmon from Lake Michigan. *J. Fish. Res. Board Can.* 30:702–706.
- Stachiw, N.C., M.E. Zabik, A.M. Booren, and M.J. Zabik. 1988. Tetrachlorodibenzo-p-dioxin residue reduction through cooking/processing of restructured carp fillets. *J. Agric. Food Chem.* 36(4):848–852.
- Stanek III, E.J., E.J. Calabrese and M. Zorn. 1999. Development of exposure distribution parameters for use in Monte Carlo risk assessment of exposure due to soil ingestion. Final Report. December 1999. Department of Biostatistics and Epidemiology. Department of Environmental Health University of Massachusetts at Amherst, Amherst, Massachusetts. Sponsor: U.S. Environmental Protection Agency Region VIII, Ecosystems Protection & Remediation. Contract: LOR056 1998 T 08L, TIN:043-16-7352
- Stanek III, E.J. and E.J. Calabrese. 1991. A guide to interpreting soil ingestion studies. I. Development of a model to estimate the soil ingestion detection level of soil ingestion studies. *Regul. Toxicol. Pharmacol.* 13(3):263-277.
- Stanek III, E.J. and E.J. Calabrese. 1995a. Daily estimates of soil ingestion in children. *Environ. Health. Perspect.* 103(3):276–285.

- Stanek III, E.J. and E.J. Calabrese. 1995b. Soil ingestion estimates for use in site evaluations based on the best tracer method. *Health Ecol. Risk. Assess.* 1(2):133–157.
- Stanek III, E.J. and E.J. Calabrese. 2000. Daily soil ingestion estimates for children at a Superfund site. *Risk Anal.* 20(5):627–635.
- Stanek III, E.J., E.J. Calabrese, and M. Zorn. 2001a. Biasing factors for simple soil ingestion estimates in mass balance studies of soil ingestion. *Hum. Ecol. Risk. Assess.* 7(2):329–355.
- Stanek III, E.J., E.J. Calabrese, and M. Zorn. 2001b. Soil ingestion distributions for Monte Carlo risk assessment in children. *Hum. Ecol. Risk. Assess.* 7(2):357–368.
- Stanek, E.J. and E.J. Calabrese. 2006. Response. *Risk Analysis* 26(4):865.
- Stanek, E.J., Calabrese, E.J., Barnes, R., and Pekow, P. 1997. Soil ingestion in adults — results of a second pilot study. *Exotoxicol. Env. Safety* 36:249–257.
- Starr, T.B. 2001. Significant shortcomings of the U.S. Environmental Protection Agency's latest draft risk characterization for dioxin-like compounds. *Toxicol. Sci.* 64:7-13.
- Starr, T.B. 2003. Significant issues raised by meta-analyses of cancer mortality and dioxin exposure. *Environ. Health Perspect.* 111(12):1443–1447.
- Steenland, K., J. Deddens, and L. Piacitelli. 2001. Risk assessment for 2,3,7,8-p-dioxin (TCDD) based on an epidemiologic study. *Am. J. Epidemiol.* 154:451-458.
- Steenland, K., L. Piacitelli, J. Deddens, M. Fingerhut, and L.I. Chang. 1999. Cancer, heart disease, and diabetes in workers exposed to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin. *J. Natl. Cancer Inst.* 91(9):779–786.
- Stifelman, M. 2006. Letter to the editor. *Risk Analysis* 26(4):863.
- Tai, H.L., J.H. McReynolds, J.A. Goldstein, H.P. Eugster, C. Sengstag, W.L. Alworth, and J.R. Olson. 1993. Cytochrome P04501A1 mediates the metabolism of 2,3,7,8-tetrachlorodibenzofuran in the rat and human. *Toxicol Appl. Pharmacol.* 123:34-42.
- Takagi, A., A. Hirose, Y. Hirabayashi, T. Kaneko, M. Ema, and J. Kanno. 2003. Assessment of the cleft palate induction by seven PCDD/F congeners in the mouse fetus. *Organohalogen compounds* 64:336-338.
- Taylor, A.B. and J.M. McCabe. 2002. Baseline chemical characterization of Saginaw Bay watersehd sediments. August 29, 2002. Michigan Department of Environmental Quality, Waste Management Division, Lansing, MI.
- Tillitt, D.E., J.P. Giesy, and G.T. Ankley. 1991. Characterization of the H4IIE rat hepatoma cell bioassay as a tool for assessing toxic potency of planar halogenated hydrocarbons in environmental samples. *Environ. Sci. Technol.* 25(1):87–92.

Toth, K., S. Somfai-Relle, J. Sugar, and J. Bence. 1979. Carcinogenicity testing of herbicide 2,4,5-trichlorophenoxyethanol containing dioxin and of pure dioxin in Swiss mice. *Nature* 278(5704):548–549.

Travis, K.Z., I. Pate, and Z.K. Welsh. 2005. The role of the benchmark dose in a regulatory context. *Regul. Toxicol. Pharmacol.* 43(3):280-291.

Trotter, W.J., P.E. Corneliussen, R.R Laski, and J.J. Vannelli. 1989. Levels of polychlorinated biphenyls and pesticides in bluefish before and after cooking. *J. Assoc. Off. Anal. Chem.* 72(3):501–503.

Tsutsumi, T., T. Iida, T. Hori, R. Nakagawa, K. Tobiishi, T. Yanagi, Y. Kono, H. Uchibe, R. Matsuda, K. Sasaki, and M. Toyoda. 2002. Recent survey and effects of cooking processes on levels of PCDDs, PCDFs and Co-PCBs in leafy vegetables in Japan. *Chemosphere* 46(9-10):1443–1449.

Tuomisto, J. 2005. Dose mechanistic understanding help in risk assessment – the example of dioxins. *Toxicol. Appl. Pharmacol.* 207:S2-S10.

Tysklind, M., D. Tillitt, L. Eriksson, K. Lundgren, and C. Rappe. 1994. A toxic equivalency factor scale for polychlorinated dibenzofurans. *Fundam. Appl. Toxicol.* 22(2):277–285.

UKCOT. 2001. Statement on the tolerable daily intake for dioxins and dioxin-like polychlorinated biphenyls. <http://www.food.gov.uk/science/ouradvisors/toxicity/statements/cotstatements2001/dioxinsstate>. United Kingdom Committee on Toxicology.

UMDES. 2000. Data: University of Michigan Questionnaire Data; and Blood, Dust and Soil Sampling Data. Available at <http://www.sph.umich.edu/dioxin/handouts.html> (Accessed Nov. 27, 2006).

UMDES. 2006. Measuring people's exposure to dioxin contamination along the Tittabawassee River and surrounding areas: Findings from the University of Michigan dioxin exposure study. August 2006. University of Michigan. 44 pp.

USDA. 2000. Continuing survey of food intakes by individuals (CSFII) 1994-1996, 1998. Available at: <http://www.ars.usda.gov/SP2UserFiles/Place/12355000/pdf/Facts1.pdf>. U.S. Department of Agriculture, Agricultural Research Service (ARS), Beltsville, MD.

USDA. 2006. What we eat in America – NHANES: 2001–2002 and 2003–2004. Available at: <http://www.ars.usda.gov/Services/docs.htm?docid=14018>. U.S. Department of Agriculture, Agricultural Research Service (ARS), Beltsville, MD.

Van Birgelen, A.P., K.M. Fase, J. van der Kolk, H. Poiger, A. Brouwer, W. Seinen, and M. van den Berg. 1996. Synergistic effect of 2,2',4,4',5,5'-hexachlorobiphenyl and 2,3,7,8-tetrachlorodibenzo-p-dioxin on hepatic porphyrin levels in the rat. *Environ Health Perspect.* 104(5):550-557

- Van Birgelen, A.P., M.J. DeVito, J.M. Akins, D.G. Ross, J.J. Diliberto, and L.S. Birnbaum. 1996. Relative potencies of polychlorinated dibenzo-p-dioxins, dibenzofurans, and biphenyls derived from hepatic porphyrin accumulation in mice. *Toxicol. Appl. Pharmacol.* 138(1):98–109.
- Van den Berg, M., L. Birnbaum, A.T.C. Bosveld, B. Brunstrom, P. Cook, M. Feeley, J.P. Giesy, A. Hanberg, R. Hasegawa, S.W. Kennedy, T. Kubiak, J.C. Larsen, F.X. van Leeuwen, A.K. Liem, C. Nolt, R.E. Peterson, L. Poellinger, S. Safe, D. Schrenk, D. Tillitt, M. Tysklind, M. Younes, F. Waern, and T. Zacharewski. 1998. Toxic equivalency factors (TEFs) for PCBs, PCDDs, PCDFs for humans and wildlife. *Environ. Health Perspect.* 106(12):775-792.
- Van den Berg, M., L.S. Birnbaum, M. Denison, M. De Vito, W. Farland, M. Feeley, H. Fiedler, H. Hakansson, A. Hanberg, L. Haws, M. Rose, S. Safe, D. Schrenk, C. Tohyama, A. Tritscher, J., Tuomisto, M. Tysklind, N. Walker, and R. Peterson. 2006. The World Health Organization Re-Evaluation of Human and Mammalian Toxic Equivalency Factors for Dioxins and Dioxin-Like Compounds. *Toxicological Sciences.* 93(2):223–241 (doi:10.1093/toxsci/kfl055)..
- Van Miller, J.P., J.J. Lalich, and J.R. Allen. 1977. Increased incidence of neoplasms in rats exposed to low levels of 2,3,7,8-tetrachlorodibenzo-p-dioxin. *Chemosphere* 6(9):537–544.
- Van Wijnen, J.H., P. Clausing, and B. Brunekreef. 1990. Estimated soil ingestion by children. *Environ. Res.* 51(2):147–162.
- Vecchi, A., M. Sironi, M.A. Canegrati, M. Recchia, and S. Gaartini. 1983. Immunosuppressive effects of 2,3,7,8-tetrachlorodibenzo-p-dioxin in strains of mice with different susceptibility to induction of aryl hydrocarbon hydroxylase. *Toxicol. Appl. Pharmacol.* 68(3):434–441.
- Voiland, Jr., M.P., K.L. Gall, D.J. Lisk, and D.B. MacNeill. 1991. Effectiveness of recommended fat trimming procedures on the reduction of PCB and mirex levels in brown trout (*Salmo trutta*) from Lake Ontario. *J. Great Lakes Res.* 17(4):454–460.
- Waern, F., S. Flodstrom, L. Busk, T. Kronevi, I. Nordgren and U.G. Ahlbog. 1991. Relative liver tumour promoting activity and toxicity of some polychlorinated dibenzo-p-dioxin- and dibenzofuran-congeners in female Sprague-Dawley rats. *Pharmacol. Toxicol.* 69(6):450-458.
- Walker, N. J., P.W. Crockett, A. Nyska, A.E. Brix, M.P. Jokinen, D.M. Sells, J.R. Hailey, M. Easterling, J.K. Haseman, M. Yin, M.E. Wyde, J.R. Bucher, and C.J. Portier. 2005. Dose-additive carcinogenicity of a defined mixture of "dioxin-like compounds". *Environ. Health Perspect.* 113:43–48.
- Walker, N.J., M.E. Wyde, L.J. Fischer, A. Nyska, and J.R. Bucher. 2006. Comparison of chronic toxicity and carcinogenicity of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) in 2-year bioassays in female Sprague-Dawley rats. *Mol. Nutr. Food Res.* 50:(advanced publication).
- Walker, S. and S. Griffin. 1998. Site-Specific Data Confirm Arsenic Exposure Predicted by the U.S. Environmental Protection Agency. *Environ Health Perspect.* 106(3):133–139.

- Wan, P., C.R. Santerre, P.B. Brown, and D.C. Deardorff. 2003. Chlorpyrifos residues before and after cooking of catfish fillets. *J. Food Sci.* 68(1):12–15.
- Wanderstock, J.H., W. Iskat, W. Gutenmann, and D. Lisk. 1971. Effects of several cooking methods on concentration of DDT residues in lake trout and coho salmon. *N.Y. Fish and Game J.* 18:70–71.
- Ward, B.L., K. LaDronka, M. Skoman, K. Olson, J. Sinibaldi, J. Lepkowski, Z. Blackburn, S. Freeland, A. Franzblau, E. Hedgeman, L. Zwica, T. Towey, A. Demond, and D. Garabrant. 2006. Considerations for managing a large, multi-faceted study involving multiple organizations. Poster presented at Dioxin 2006 conference. University of Michigan, Ann Arbor, MI.
- Warner, M., S. Samuels, P. Mocarelli, P.M. Gerthoux, L. Needham, D.G. Patterson, Jr., and B. Eskenazi. 2004. Serum dioxin concentrations and age at menarche. *Environ Health Perspect* 112:1289-1292.
- Weber, H., J.C. Lamb, M.W. Harris, and J.A. Moore. 1984. Teratogenicity of 2,3,7,8-tetrachlorodibenzofuran (TCDF) in mice. *Toxicol. Lett.* 20(2):183–188.
- Weber, H., M.W. Harris, J.K. Haseman and L.S. Birnbaum. 1985. Teratogenic potency of TCDD, TCDF and TCDD–TCDF combinations in C57BL/6N mice. *Toxicol. Lett.* 26(2–3):159–167.
- Weisglas-Kuperus, N., H.J. Vreugdenhil, and P.G. Mulder. 2004. Immunological effects of environmental exposure to polychlorinated biphenyls and dioxins in Dutch school children. *Toxicol. Lett.* 149(1–3):281–285
- Weisglas-Kuperus, N., S. Patandin, G.A.M. Berbers, T.C.J. Sas, P.G.H. Mulder, P.J.J. Sauer, and H. Hooijkaas. 2000. Immunologic Effects of Background Exposure to Polychlorinated Biphenyls and Dioxins in Dutch Preschool Children. *Environ. Health Perspect.* 108(12):1203-1207.
- Weisglas-Kuperus, N., T.C. Sas, C. Koopman-Elseboom, C.W. van der Zwan, M.A. De Ridder, A. Beishuizen, H. Hooijkaas, and P.J. Sauer. 1995. Immunologic effects of background prenatal and postnatal exposure to dioxins and polychlorinated biphenyls in Dutch infants. *Pediatr Res* 38: 404-410.
- West, P.C., J.M. Fly, R. Marans, and F. Larkin. 1989. Michigan Sport Anglers Fish Consumption Survey. A report to the Michigan Toxic Substance Control Commission. Natural Resource Sociology Research Lab, Technical Report #1. May 1989. University of Michigan, School of Natural Resources, Ann Arbor, MI.
- West, P.C., J.M. Fly, R. Marans, F. Larkin, and D. Rosenblatt. 1993. 1991-92 Michigan sport anglers fish consumption study. Technical Report #6, prepared for the Michigan Department of Natural Resources. May 1993. University of Michigan, School of Natural Resources, Ann Arbor, MI.

WHO. 1998. Assessment of the health risk of dioxins: re-evaluation of the Tolerable Daily Intake (TDI). WHO Consultation. May 25-29, 1998. WHO European Centre for Environment and Health, International Programme on Chemical Safety.

Wiebel, F.J., M. Wegenke, and F. Kiefer. 1996. Bioassay for determining 2,3,7,8-tetrachlorodibenzo-p-dioxin equivalents (TEs) in human hepatoma Hepg2 cells. *Toxicol. Lett.* 88(1-3):335-338.

Wilhelm, M., U. Ranft, J. Wittsiepe, F. Lemm, P. Furst, M. Greshake, G. Eberwein, and G. Winneke. 2006. Influence of prenatal exposure to PCDDs/PCDFs and PCBs on thyroid hormones in newborns and neurodevelopment of infants: Results from the birth cohort study in Duisburg (2000-ongoing) compared to the Dusseldorf PCB cohort study. *Organohalogen Compounds*. [this title shows up on the Dioxin 2006-Oslo program for August 24]

Wilson, N.D., N.M. Shear, D.J. Paustenbach, and P.S. Price. 1998. The effect of cooking practices on the concentration of DDT and PCB compounds in the edible tissue of fish. *J. Exp. Anal. Environ. Epidemiol.* 8:423-440.

Wittsiepe, J., P. Furst, P. Shrey, F. Lemm, M. Kraft, G. Eberwein, G. Winneke, and M. Wilhelm. 2004. PCDD/F and dioxin-like PCB in human blood and milk from German mothers. *Organohalogen Compounds* 66: 2865-2872.

Wong, E.Y., J.H. Shirai, T.J. Garlock, J.C. Kissel. 2000. Adult proxy responses to a survey of children's dermal soil contact activities. *J. Expo. Anal. Environ. Epidemiol.* 10:509-517.

Wong, M.S. 1988. The role of environmental and host behavioral factors in determining exposure to infection with *Ascaris Lumbricoides* and *Trichuris Trichiura*. Thesis. Department of Zoology, University of the West Indies, Mona Campus.

Wong, M.S. and D.A. Bundy. 1990. Quantitative assessment of contamination of soil by the eggs of *Ascaris lumbricoides* and *Trichuris trichiura*. *Trans. R. Soc. Trop. Med. Hyg.* 84(4):567-570.

Wong, M.S., D.A. Bundy, M.H. Golden. 1988. Quantitative assessment of geophagous behaviour as a potential source of exposure to geohelminth infection. *Trans. R. Soc. Trop. Med. Hyg.* 82(4):621-625.

Wong, M.S., D.A. Bundy, M.H. Golden. 1991. The rate of ingestion of *Ascaris lumbricoides* and *Trichuris trichiura* eggs in soil and its relationship to infection in two children's homes in Jamaica. *Trans. R. Soc. Trop. Med. Hyg.* 85(1):89-91.

Xu, L., A.P. Li, D.L. Kaminski and M.F. Ruh. 2000. 2,3,7,8 Tetrachlorodibenzo-p-dioxin induction of cytochrome P4501A in cultured rat and human hepatocytes. *Chem. Biol. Interact.* 124(3):173-189.

Yamamoto, J., K. Ihara, H. Nakayama, S. Hikino, K. Satoh, N. Kubo, T. Iida, Y. Fujii, and T. Hara. 2004. Characteristic expression of aryl hydrocarbon receptor repressor gene in human

tissues: organ-specific distribution and variable induction patterns in mononuclear cells. *Life Sci* 74: 1039-49.

Yoon, B.I., T. Inoue, and T. Kaneko. 2000. Teratological effect of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD): induction of cleft palate in the ddY and C57BL/6 mouse. *J. Vet. Sci.* 1(2):113-119.

Zabik, M.E. 1974. Polychlorinated biphenyl levels in raw and cooked chicken and chicken broth. *Poultry Sci.* 53(5):1785-1790.

Zabik, M.E. and M.J. Zabik. 1995. Tetrachlorodibenzo-p-dioxin residue reduction by cooking/processing of fish fillets harvested from the Great Lakes. *Bull. Environ. Contam. Toxicol.* 55:264-269.

Zabik, M.E. and M.J. Zabik. 1996. Influence of processing on environmental contaminants in foods. *Food Technol.* 50:225-229.

Zabik, M.E. and M.J. Zabik. 1999. Polychlorinated biphenyls, polybrominated biphenyls, and dioxin reduction during processing/cooking food. In *Impact of Processing on Food Safety*, eds. L.S. Jackson, M.G. Knize, and J. F. Morgan, New York: Plenum Press. *Adv. Exp. Med. Biol.* 459:213-231.

Zabik, M.E., A. Booren, M.J. Zabik, R. Welch, and H. Humphrey. 1996. Pesticide residues, PCBs, and PAHs in baked, charbroiled, salt boiled, and smoked Great Lakes lake trout. *Food Chem.* 55(3):231-239.

Zabik, M.E., C. Merrill, and M.J. Zabik. 1982. PCBs and other xenobiotics in raw and cooked carp. *Bull. Environm. Contam. Toxicol.* 28:710-715.

Zabik, M.E., M.J. Zabik, A.M. Booren, M. Nettles, J-H. Song, R. Welch, and H. Humphrey. 1995b. Pesticides and total polychlorinated biphenyls in Chinook Salmon and Carp harvested from the Great Lakes: effects of skin-on and skin-off processing and selected cooking methods. *J. Agric. Food Chem.* 43:993-1001.

Zabik, M.E., M.J. Zabik, A.M. Booren, S. Daubenmire, M.A. Pascall, R. Welch, and H. Humphrey. 1995. Pesticides and total polychlorinated biphenyls residues in raw and cooked walley and white bass harvested from the Great Lakes. *Bull. Environm. Contam. Toxicol.* 54:396-402.

Zabik, M.E., M.J. Zabik, and H. Humphrey. 1993. Assessment of contaminants in five species of Great Lakes fish at the dinner table. Final Report, Part 1. March 1, 1993. [To the Great Lakes Protection Fund, Grant #LOI6903004]

Zabik, M.E., P. Hoojjat, and C.M. Weaver. 1979. Polychlorinated biphenyls, dieldrin, and DDT in Lake Trout cooked by broiling, roasting or microwave. *Bull. Environm. Contam. Toxicol.* 21:136-143.

Zabik, M.E., S.K. Smith, and R. Cala. 1979. Polybrominated biphenyl isomer distribution in raw and cooked chicken and chicken broth. *Poultry Sci.* 58(6):1435–1438.

Zabik, M.E., T.M. Johnson, and S. Smith. 1978. Effects of processing and cooking on PBB residues. *Environ. Health Perspect.* 23:37–41.

Zacharewski, T., M. Harris, and S. Safe. 1989. Induction of cytochrome P450–dependent monooxygenase activities in rat hepatoma H–4–IIE cells in culture by 2,3,7,8–tetrachlorodibenzo–p–dioxin and related compounds: mechanistic studies using radiolabeled congeners. *Arch. Biochem. Biophys.* 272(2):344–355.

Zartarian, V.G., J. Xue, H. Özkaynak, W. Dang, G. Glen, L. Smith, and C. Stallings. 2005. A Probabilistic Exposure Assessment for Children Who Contact CCA-Treated Playsets and Decks Using the Stochastic Human Exposure and Dose Simulation Model for the Wood Preservative Exposure Scenario (SHEDS-Wood). Final Report. February 2005. U.S. Environmental Protection Agency, ORD/OPP and ManTech Environmental Technology, Inc.

6.9 ACRONYMS

ACOH	Acetanilide 4-hydroxylase
ADD	Average Daily Dose
ADE	Acceptable Daily Exposure
Ah	Aryl Hydrocarbon
AhR	Aryl Hydrocarbon Receptor
AHR	Aryl Hydrocarbon Receptor
AIC	Aitken Information Criterion
ALT	Alanine Aminotransaminase (a liver enzyme)
AST	Aspartate Aminotransaminase (a liver enzyme)
ATS	Ann Arbor Technical Service Inc.
ATSDR	Agency for Toxic Substances and Disease Registry
AUC	Area Under (the) Curve
BMDS	Benchmark Dose Software
BMI	Body Mass Index
BW	Body Weight
CDM	Camp Dresser & McKee
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CFR	Code of Federal Regulations
CL	Cooking Loss
cm	Centimeter
CoPC	Chemical of Potential Concern
CSF	Cancer Slope Factor
CSFII	Continuing Survey of Food Intakes by Individuals
CSM	Conceptual Site Model
CYP1A	Cytochrome P450 1A
CYP1A1	Cytochrome P450 1A1
CYP1A2	Cytochrome P450 1A2

d	Day
DABT	Diplomate of the American Board of Toxicology
DBA	An inbred mouse strain: "DBA mouse"
DCC	Direct Contact Criterion
DEQ	Department of Environmental Quality
DLCs	Dioxin-Like Compounds
DNA	Deoxyribonucleic Acid (the molecule that encodes genetic information in the nucleus of cells)
DNR	Department of Natural Resources
DRE	Dioxin Responsive Element (in nuclear genetic material)
ECSCF	European Commission Scientific Committee on Foods
ED01	Effective Dose for 1% response
ED10	Effective Dose for 10% response
EPA	U.S. Environmental Protection Agency
EPC	Exposure Point Concentration
EROD	7-Ethoxyresorufin-O-deethylase
EV	Event Frequency
FAO	Food and Agriculture Organization of the United Nations
FP	Flood Plain
FS	Feasibility Study
GM	Geometric Mean
GSD	Geometric Standard Deviation
HEAST	Health Effects Assessment Summary Tables
HHRA	Human Health Risk Assessment
HI	Hazard Index
hr	Hour
IPCS	International Program on Chemical Safety
IRf	Fish meal ingestion rate
IRg	Game meal ingestion rate
IRIS	U.S. EPA Integrated Risk Information System

ISAP	Independent Science Advisory Panel
JECFA	Joint FAO/WHO Expert Committee on Food Additives
kg	Kilogram
KR	Kalamazoo River
L	Liter
LADD	Lifetime Average Daily Dose
LD50	Lethal Dose 50% (dose causing 50% mortality)
LED10	Lower confidence limit on the ED10 (q.v.)
LMS	Linear multistage model
LOAEL	Lowest Observed Adverse Effect Level
LOEL	Lowest Observed Effect Level
MBS	Midland Bay City Saginaw International Airport
MDCH	Michigan Department of Community Health
MDEQ	Michigan Department of Environmental Quality
MDNR	Michigan Department of Natural Resources
MDPH	Michigan Department of Public Health
mg	Milligram
ml	Milliliter
MOA	Mode of Action
MOE	Margin of Exposure
MRL	(ATSDR) Minimal Risk Level
mRNA	Messenger RNA (q.v.) [RNA that serves as a template for protein synthesis]
MSU	Michigan State University
NAS	The National Academy of Sciences
NCEA	U.S. EPA's National Center for Environmental Assessment
NCP	National Contingency Plan
ng	Nanogram
NHANES	National Health and Nutrition Examination Survey
NIST	National Institute of Standards and Technology

NOAA	National Oceanic and Atmospheric Administration
NOAEL	No Observed Adverse Effect Level
NOD	Notice of Deficiency
NOEL	No Observed Effect Level
NREPA	Natural Resources and Environmental Protection Act
NTP	National Toxicology Program
OCDF	Octachloro dibenzofuran
OSWER	Office of Solid Waste and Emergency Response
PAH	Polyaromatic Hydrocarbon
PBPK	Physiologically Based Pharmacokinetic
PCB	Polychlorinated Biphenyl
PCCD/F	Polychlorinated dibenzo-p-dioxins and polychlorinated dibenzofurans
PCDD	Polychlorinated dibenzo-p-dioxin
PCDF	Polychlorinated dibenzofuran
PDF	Probability Density Function
PeCDD	Pentachloro dibenzo-p-dioxin
PeCDF	Pentachloro dibenzofuran
pg	picogram
PK	Pharmacokinetic
POD	Point Of Departure
PPRTV	EPA's Provisional Peer Reviewed Toxicity Values
ppt	parts per trillion
PRA	Probabilistic Risk Assessment
PRG	Preliminary Remediation Goal
PSIC	Particulate Soil Inhalation Criterion
PTMI	Provisional Tolerable Monthly Intake
RAGS	Risk Assessment Guidance for Superfund
RCRA	Resource Conservation and Recovery Act
REP	Relative Effect Potency

RfD	Reference Dose
RI	Remedial Investigation
RIWP	Remedial Investigation Work Plan
RME	Reasonable Maximum Exposure
SLRA	Screening Level Risk Assessment
SOW	Statement of Work
TA	Target Analyte
TAL	Target Analyte List
TCDD	Tetrachloro dibenzo-p-dioxin
TCDF	Tetrachloro dibenzofuran
TDI	Tolerable Daily Intake
TEF	Toxic Equivalency Factor
TEQ	Toxic Equivalents
TR	Tittabawassee River
TSD	Technical Support Document
UCL	Upper Confidence Limit
UKCOT	United Kingdom Committee on Toxicology
UM	University of Michigan
UMass	University of Massachusetts
UMDES	University of Michigan Dioxin Exposure Study
UN	United Nations
USDA	U.S. Department of Agriculture
WBAN	Weather Bureau, Air Force, and Navy
WHO	World Health Organization
WP	Work Plan
Yr	Year

REMEDIAL INVESTIGATION WORK PLAN
TITTABAWASSEE RIVER AND UPPER SAGINAW RIVER AND
FLOODPLAIN SOILS
VOLUME 2 OF 2

SECTION 7: SCREENING LEVEL ECOLOGICAL RISK ASSESSMENT
RESPONSE TO MDEQ COMMENTS



December 1, 2006

The Dow Chemical Company
Midland, Michigan 48674
USA

George W. Bruchmann, Chief
Waste and Hazardous Materials Division
Michigan Department of Environmental Quality
Constitution Hall
525 W. Allegan
Lansing, MI 48909-7741

Re: Submittal of response to comments received to date on the Tittabawassee River
Screening-Level and Baseline Ecological Risk Assessment Work Plans.

Dear Mr. Bruchmann:

The MDEQ has provided comments on the response submittals for the MDEQ review of the Tittabawassee River Screening-Level and Baseline Ecological Risk Assessment Work Plans. In addition, there were comments in the Notice of Deficiencies (NODs) that are relevant to the Tittabawassee River ecological risk assessment. Responses to the MDEQ comments on response submittals, and NODs are included with this RIWP. MDEQ has indicated that further comments from US EPA on prior response submittals remain outstanding. The text of the Screening-Level and Baseline Ecological Risk Assessment Work Plans, as submitted on January 17, 2006, has not been modified and so are not being resubmitted with the RIWP. These revised work plans are flexible enough to accommodate the adjustments proposed by the agencies as responded to in the attached memos. In particular, the BERA work plan was written to allow inclusion of additional receptors as necessary. A summary of the adjustments to the ERA approach in response to agency comments follows:

- Dietary item sampling has been expanded to include a site in Shiawassee National Wildlife Refuge and as well as two sites on the Saginaw River downstream of the confluence of the Tittabawassee and Shiawassee Rivers.
- Existing trustee data and newly acquired MSU data for wood ducks and hooded mergansers will be included in the ERA using the multiple lines of evidence approach.
- A mammalian top predator will be included as a receptor of concern.
- A theoretical dietary exposure for woodcock will be calculated from the dietary items that are already being collected.
- Sample splits can be obtained by contacting Matthew Zwiernik at 517-749-5243 or zwiernik@msu.edu

It is our objective to work collaboratively with the MDEQ to resolve any further outstanding differences and address the final US EPA comments upon their receipt.

Sincerely,

Ben Baker
Senior Environmental Project Leader
Sustainable Development
1790 Building
Midland, MI 48674

November 22, 2006

**Memo re: Response to Michigan Department of Environmental Quality
(MDEQ) Comments on Response Submittals for the MDEQ review of
the Draft Screening-Level Ecological Risk Assessment Work Plan**

In this memo, we provide a disposition of comments including responses and/or clarifications pertaining to each of the comments presented in the MDEQ review of the Response Submittals (ENTRIX) for the Draft Screening-Level Ecological Risk Assessment (SLERA) Work Plan. MDEQ considered most of the comments satisfactorily resolved by the ENTRIX response dated January 17, 2006. Only the three comments not considered satisfactorily resolved are addressed in this memo.

MDEQ comments, numbered 1 through 3, on the original draft work plan, the ENTRIX response, and the current MDEQ comments (1a, 2a, and 3a) on ENTRIX response submittals are presented in the format shown below in italicized and indented font. For clarity, ENTRIX responses to the current MDEQ comments follow in Arial font.

1. Title of Original Comment

MDEQ Original Comment

ENTRIX First Response (to original comment)

MDEQ Comment on ENTRIX Response

ENTRIX Second Response

1. The need, or otherwise, for further risk assessment activities and the failure to recognize previous activities.

MDEQ Original Comment: *Two ecological risk assessments have already been performed for the Tittabawassee River and its floodplain. In GES (2003) risks posed by PCDDs and PCDFs in the aquatic environment and its associated food chains were evaluated. In GES (2004) the same was done for the terrestrial floodplain environment. Since it included a relatively large amount of site-specific data (sediments, fish, bird eggs), the former ecological risk assessment can be considered as being closer to the definitive end of the risk assessment scale (as distinct from the screening-level end). The terrestrial ecological risk assessment performed by MDEQ should be considered screening-level.*

While there is clearly a need for a more definitive analysis of risks on the floodplain, and there is likewise a need for the assessment of aquatic risks posed by contaminants other than PCDDs and PCDFs, the perceived need for further aquatic risk estimates for PCDDs and PCDFs in the Tittabawassee River is doubtful. Furthermore, as discussed below, sediment sampling in the Saginaw River and Saginaw Bay has clearly indicated that ecological risk may be “exported” out of the Tittabawassee River and into downriver areas. As yet, these downriver risks have not been adequately examined. I regard this as a more appropriate focus for future aquatic risk assessment activities, rather than a re-examination of the Tittabawassee River aquatic system.

ENTRIX First Response: *The text has been updated to more clearly recognize previous ERA activities. We agree with MDEQ that there is clearly a need for a more definitive analysis of risks on the floodplain and aquatic environments for chemicals of potential ecological concern (COPECs) other than PCDDs and PCDFs. We disagree that the perceived need is “doubtful” for further aquatic risk estimates for PCDDs and PCDFs. MDEQ’s prior assessments focused only on piscivorous ecological receptors, with many simplifying assumptions and relatively great uncertainties. Further evaluations of aquatic risks of PCDDs and PCDFs are consistent with current guidance for conducting ERAs which recommends tiered evaluations for complex sites such as the Tittabawassee River.*

MDEQ Comment on ENTRIX First Response: *It is encouraging that both MDEQ and ENTRIX agree on the need for more detailed ERA in the Tittabawassee River Floodplain. However, it is not my opinion that the level of effort proposed by ENTRIX for their aquatic ERA is necessary. This is dealt with at greater length in my comments on their Baseline Ecological Risk Assessment Work Plan.*

ENTRIX Second Response: Because the level of effort proposed for the aquatic ERA is related to the evaluation of aquatic risks of PCDDs and PCDFs described in the BERA Work Plan, further discussion of this topic will, as suggested, be reserved for the comments on the BERA Work Plan.

2. *Geographic scope of the proposed analysis.*

MDEQ Original Comment: *At several places in the document (including the map in Figure 2-1, p.2-3) the geographical area of investigation is defined as the reach of the Tittabawassee River and its floodplain from Midland downriver to the confluence with the Saginaw River. Discussions with Dow and ENTRIX personnel on September 16, 2005 confirmed that no risk assessment activities are planned for downriver of the confluence. The September 16 discussions also confirmed that the reason for this geographical truncation is regulatory, rather than scientific: Dow and ENTRIX maintain that, under the terms of the permit with the State, the reaches further downriver do not need to be addressed in the current round of risk assessment activities.*

Regardless of the regulatory issues, sediment sampling by the Army Corp of Engineers in 1998 and 1999 detected TCDD-EQ concentrations of up to 610 ppt (WHO avian TEFs) in the inner Saginaw Bay and exceeding 2,000 ppt in Saginaw River. More recent sampling in the Saginaw River by MDEQ and by Dow identified TCDD-EQ concentrations that were greatly elevated above background (approaching 50,000 ppt – WHO avian TEFs). The congeners that make the greatest contributions to this toxicity are the same as those in the Tittabawassee River, indicating the likelihood of a common source. Furthermore, preliminary evaluations performed by MDEQ (GES, 2003) on the Army Corp of Engineers data set indicate that the possibility that these concentrations pose unacceptable risks to ecological receptors cannot be disregarded.

Ignoring the permit and regulatory issues and concentrating solely on the implications of the risk assessment, it is obvious that the ecological risk assessment activities proposed in the ENTRIX work plan will not capture or address all of the potential watershed ecological risks due to PCDDs and PCDFs originating in Midland. Specifically, risks posed by these contaminants transported downriver of the confluence of the Tittabawassee and Saginaw Rivers will not be included.

ENTRIX First Response: *The draft SLERA Work Plan includes the geographical scope as defined in the Operating License. The potential need for expansion of the geographic scope of the studies will be addressed in future studies as necessary to meet the requirements of the Operating License.*

MDEQ Comment on ENTRIX First Response: *While the ENTRIX response may accurately state the case from a permitting viewpoint, the NRDA trustees and MDEQ staff should be aware that the results of the proposed SLERA are unlikely to capture the entire spatial extent of risk (or injury to natural resources).*

ENTRIX Second Response: Dow and the Trustees have agreed that a downstream expansion of the geographic scope of the ERA would be beneficial. Dow has provided Michigan State University with funding to collect additional samples on the Shiawassee National Wildlife Refuge as well as two sites on the Saginaw River downstream of the confluence of the Tittabawassee and Shiawassee Rivers, Veterans Memorial Park and the Dow Lighthouse Property. The sampling scheme builds on and complements the current Tittabawassee River ecological food web studies to provide insight into conditions on the Saginaw River. For additional information, see the June 7, 2006 memo from Ben Baker, DOW, to George Bruchmann, MDEQ.

3. *The omission of PCDDs and PCDFs from the screening-level assessment.*

***MDEQ Original Comment (part 1):** ENTRIX (2005) proposes that PCDDs and PCDFs not be included in the screening-level assessment. Before discussing this issue further, I acknowledge that I agree with ENTRIX that the results of a SLERA should not be regarded as rigorously predictive of risk, and its primary purpose is to identify and eliminate from further analyses contaminants that can be safely regarded as not likely to pose unacceptable risks. Nevertheless, the relative magnitudes of SLERA hazard indices can provide at least an order of magnitude comparative assessment of the potential contributions to risk by each of the contaminants. Thus, a SLERA, in addition to eliminating contaminants from unnecessary analysis, may also provide a useful early indication of the relative importances of each of the contaminants that fail the “SLERA test”.*

***ENTRIX First Response:** The ERA activities described in both the SLERA and BERA draft work plans are intended to build upon the data and results of all relevant historical activities, including those conducted previously by MDEQ. The screening results, as correctly characterized by MDEQ, “should not be regarded as rigorously predictive of risk [but rather] its primary purpose is to identify and eliminate from further analyses COPECs that can be safely regarded as not likely to pose unacceptable risks.” That is exactly the approach that is taken in the draft ERA work plans.*

However, the suggestion that the relative magnitudes of SLERA hazard quotients can provide an assessment of the potential contributions to risk by each of the COPECs is not scientifically defensible as there are varying degrees of uncertainty in the hazard quotient calculation for each COPEC. These uncertainties include the use of maximal (single point) concentrations and screening benchmarks that may not be particularly relevant to the assessment endpoints of a particular site. Therefore the SLERA results should only be used to identify COPECs that will be evaluated further in the BERA.

***MDEQ Original Comment (Part 2):** The reasons for the omission of PCDDs/PCDFs from the proposed ENTRIX SLERA are not stated fully in the SLERA work plan, but only vaguely described as (for example) “based on historical data, it is assumed thatPCDDs and....PCDFs will continue to be COPECs” (my italics). In verbal discussions with Dow and ENTRIX personnel on September 16, they clarified their position by explaining that the reason that PCDDs and PCDFs are not to be included in the SLERA is because they accept the results of the State’s previous efforts to evaluate risks posed by these contaminants in the Tittabawassee River and its floodplain. Dow and ENTRIX apparently believe that since the State has already*

concluded that PCDD/PCDFs pose unacceptable risks to biota, they need not be included in their proposed screening-level assessment. If my interpretation of what was communicated is correct, and if Dow and ENTRIX accept the State's conclusions, it should be clearly stated in the ENTRIX (2005) work plan. Otherwise, I would recommend (for the reasons given at the beginning of this paragraph) that PCDDs and PCDFs should be included in the screening-level evaluation.

ENTRIX First Response: *The sentence quoted in this comment from MDEQ has been modified within the SLERA work plan text to read "Previously, two preliminary ERAs were performed for the Tittabawassee River and its floodplain focusing on the aquatic environment (GES 2003) and the terrestrial environment (GES 2004) and their associated food chains. Based on these analyses, it is appropriate to conclude that polychlorinated dibenzo-p-dioxins (PCDDs) and dibenzofurans (PCDFs) will continue to be COPECs and are currently the focus of ongoing studies that will be used in the BERA." It is our position that it is premature to draw conclusions regarding whether the current conditions within the study area present unacceptable risk to ecological receptors of concern.*

MDEQ Comment on ENTRIX First Response. *ENTRIX have now agreed that the previous MDEQ ERA are valid bases for pursuing further work. While I would make greater claims for them, this may be a step forward.*

ENTRIX Second Response: We agree that is important to move forward. New data and information will be incorporated into the BERA as they become available to iteratively build upon existing PCDD and PCDF data.

REMEDIAL INVESTIGATION WORK PLAN
TITTABAWASSEE RIVER AND UPPER SAGINAW RIVER AND
FLOODPLAIN SOILS
VOLUME 2 OF 2

SECTION 8: BASELINE ECOLOGICAL RISK ASSESSMENT

RESPONSE TO MDEQ COMMENTS
RESPONSE TO NOTICE OF DEFICIENCIES



December 1, 2006

The Dow Chemical Company
Midland, Michigan 48674
USA

George W. Bruchmann, Chief
Waste and Hazardous Materials Division
Michigan Department of Environmental Quality
Constitution Hall
525 W. Allegan
Lansing, MI 48909-7741

Re: Submittal of response to comments received to date on the Tittabawassee River
Screening-Level and Baseline Ecological Risk Assessment Work Plans.

Dear Mr. Bruchmann:

The MDEQ has provided comments on the response submittals for the MDEQ review of the Tittabawassee River Screening-Level and Baseline Ecological Risk Assessment Work Plans. In addition, there were comments in the Notice of Deficiencies (NODs) that are relevant to the Tittabawassee River ecological risk assessment. Responses to the MDEQ comments on response submittals, and NODs are included with this RIWP. MDEQ has indicated that further comments from US EPA on prior response submittals remain outstanding. The text of the Screening-Level and Baseline Ecological Risk Assessment Work Plans, as submitted on January 17, 2006, has not been modified and so are not being resubmitted with the RIWP. These revised work plans are flexible enough to accommodate the adjustments proposed by the agencies as responded to in the attached memos. In particular, the BERA work plan was written to allow inclusion of additional receptors as necessary. A summary of the adjustments to the ERA approach in response to agency comments follows:

- Dietary item sampling has been expanded to include a site in Shiawassee National Wildlife Refuge and as well as two sites on the Saginaw River downstream of the confluence of the Tittabawassee and Shiawassee Rivers.
- Existing trustee data and newly acquired MSU data for wood ducks and hooded mergansers will be included in the ERA using the multiple lines of evidence approach.
- A mammalian top predator will be included as a receptor of concern.
- A theoretical dietary exposure for woodcock will be calculated from the dietary items that are already being collected.
- Sample splits can be obtained by contacting Matthew Zwiernik at 517-749-5243 or zwiernik@msu.edu

It is our objective to work collaboratively with the MDEQ to resolve any further outstanding differences and address the final US EPA comments upon their receipt.

Sincerely,

Ben Baker
Senior Environmental Project Leader
Sustainable Development
1790 Building
Midland, MI 48674

November 22, 2006

**Memo re: Response to Michigan Department of Environmental Quality (MDEQ)
Comments on Response Submittals for the MDEQ review of the
Draft Baseline Ecological Risk Assessment Work Plan**

In this memo, we provide a disposition of comments including responses and/or clarifications regarding each of the comments that were raised by the MDEQ review of the Response Submittals (ENTRIX) for the Draft Baseline Ecological Risk Assessment (BERA) Work Plan.

MDEQ comments on the original work plan, numbered 1 through 13, the ENTRIX response, and the current MDEQ comments, numbered 1a through 13a, on the ENTRIX Response Submittals are presented in the format shown below in italicized and indented font. For clarity, ENTRIX responses to the current MDEQ comments follow in Arial font. Entrix responses to additional comments from MDEQ, numbered 14 through 16, follow the original comments.

Format:

1. Title of Original Comment

MDEQ Original Comment

ENTRIX First Response (to original comment)

MDEQ Comment on ENTRIX Response

ENTRIX Second Response

1. *The relationship of the BERA to previous studies and data collection and analyses, and the need for further ecological risk assessment.*

MDEQ Original Comment: Since about 1980, a large quantity of data has been gathered characterizing the degree and extent of environmental contamination in the Tittabawassee River watershed. These data sets describe contaminant concentrations in sediments, surface water, soils, and biota. Based on these data, two ecological risk assessments have already been performed for the Tittabawassee River watershed (GES, 2003; GES 2004). The former focused on the aquatic environment, while the latter addressed risks to biota on the floodplain of the Tittabawassee River. Since it included a relatively large amount of site-specific data (sediments, fish, bird eggs), the former ecological risk assessment can be considered as being closer to the definitive end of the risk assessment scale (as distinct from the screening-level end). The floodplain (terrestrial) ecological risk assessment performed by MDEQ should be considered screening-level.

Reading the ENTRIX (2005a) work plan, one could be forgiven for concluding that comparatively little information was available regarding contamination of the study area by organochlorines, bioaccumulation in food chains, or exposure and risks to predatory wildlife. This is because the ENTRIX work plan fails to acknowledge, to an adequate extent, the fact that a large amount of data has already been gathered and analyzed. In fact, the Tittabawassee Watershed is a comparatively well-characterized system. It is also the case that contaminant concentrations in many of the components of the aquatic and terrestrial ecosystems have been assessed and in each the result is the same – high levels of contamination that greatly exceed baseline. During the September 16 discussions, ENTRIX personnel stated that their proposed work should be regarded as “building on” or “extending” previous studies (including MDEQ studies). If this is the case, a more comprehensive acknowledgement of previous studies and their contributions to our understanding of environmental risks should form part of the BERA work plan.

The previous studies notwithstanding, there are three outstanding risk assessment “data needs” for the Tittabawassee River watershed:

- 1. There is a need for a more definitive analysis of risks on the floodplain (where the MDEQ assessment is at the screening level).*
- 2. There is a need for the assessment of aquatic risks posed by contaminants other than PCDDs and PCDFs in the aquatic environment.*
- 3. Sediment sampling in the Saginaw River and Saginaw Bay (discussed below) has clearly indicated that ecological risk may be “exported” out of*

the Tittabawassee River and into downriver areas. As yet, however, these downriver risks have not been adequately examined. They could be a much-needed focus of future risk assessment.

The studies described in the ENTRIX BERA clearly focus on data need numbers 1 and 2. They do not, however, address data need number 3 (see below). Moreover, a large component of the BERA work plan describes studies that revisit an issue that the State has already completed much work on: the risks to ecological receptors in aquatic food chains in the Tittabawassee River from PCDD/PCDFs. Future time and resources would be better spent if the BERA focused mainly on the three data needs identified above.

ENTRIX First Response: *The text has been revised to provide more details on previous studies, including the limitations of previous studies and data gaps. The aquatic study by GES (2003) made substantial contributions to the body of fish residue data available for the Tittabawassee River. However, the limitations of this study are that it focused exclusively on PCDDs and PCDFs, piscivorous exposure pathways were the only pathways directly assessed, the specimens of fish were generally large, and dietary risks were calculated from an overly simplified diet that does not account for species-specific and site-specific dietary exposures. The draft BERA Work Plan will address risks from PCDDs and PCDFs and other COPECs that are retained after the SLERA is completed. This will allow a direct comparison of relative risks for each COPEC and receptor of concern. In addition, aquatic-based receptors, both piscivorous and non-piscivorous, will be evaluated using site-specific dietary information from field studies, and residue concentrations in receptor tissues. The terrestrial study by GES (2004) is acknowledged to be at a screening-level, clearly providing a basis for a more definitive analysis of risks on the floodplain. (See also the response to Comment #2 regarding geographic scope.)*

MDEQ Comment on ENTRIX Response: *The 2005 version of the BERA work plan claimed that there was minimal information available on residues of PCDD/PCDFs in biota in the aquatic environment. The 2006 version of the work plan uses the term limited, rather than minimal. This may be a slight improvement; however, overall, it is disappointing that rather than acknowledge the strengths and value of the previous MDEQ/USFWS sampling effort and use those data fully, ENTRIX chooses instead to overemphasize “limitations”. One could be forgiven for wondering just how serious ENTRIX is about “building on” or “extending” the State and USFWS studies.*

ENTRIX Second Response: All available data that meet the project data quality objectives will be considered for use in the ERA and will be used if technically appropriate. The studies named above along with all other available historical data will be evaluated for inclusion in the ERA analysis. It is not possible to specifically state *a priori* the extent to which the existing data sets will have a role in the final analysis.

2. Geographic scope of the proposed analyses.

MDEQ Original Comment: *At several places in the document (e.g., p. 1-1 first para., p. 1-4 first para., Appendix C, Figure C-1) the main geographical area of investigation (“the Site”) is defined as the reach of the Tittabawassee River and its floodplain from Midland downriver to the confluence with the Saginaw River. A work plan for a screening-level risk analysis that I previously reviewed (ENTRIX 2005b) also restricted the study area to the Tittabawassee River and its floodplains. This definition of the area of investigation is, however, not entirely consistent: in the package of BERA materials that I received from MDEQ there were three alternative versions of Appendix C, one of which includes plans for sampling on the Saginaw River close to Saginaw Bay. During discussions with ENTRIX personnel on September 16, it was made clear that the BERA will only cover the Tittabawassee River as far downriver as its confluence with the Saginaw River and that Saginaw River and Bay would not be included. During the September 16 discussions ENTRIX and Dow stated that under the terms of the permit with the State the reaches further downriver need not be addressed.*

Sediment sampling by the Army Corp of Engineers in 1998 and 1999 detected TCDD-EQ concentrations of up to 610 ppt (WHO avian TEFs) in the inner Saginaw Bay and exceeding 2,000 ppt in Saginaw River. More recent sampling in the Saginaw River by MDEQ and by Dow identified TCDD-EQ concentrations that were greatly elevated above background (approaching 50,000 ppt – WHO avian TEFs. This last maximum concentration is almost an order of magnitude greater than the sediment samples gathered in the Tittabawassee River. The congeners that make the greatest contributions to this toxicity are the same as those in the Tittabawassee River, indicating the likelihood of a common source in Midland. Furthermore, preliminary evaluations performed by MDEQ (2003) on the Army Corp of Engineers data indicate that the possibility that these concentrations pose unacceptable risks to ecological receptors cannot be disregarded.

Ignoring the permit and regulatory issues and concentrating solely on the implications of the risk assessment, it is clear that the ecological risk assessment activities proposed in the ENTRIX BERA work plan will not capture or address all of the potential watershed ecological risks due to PCDDs and PCDFs originating in Midland. Specifically, risks posed by these contaminants transported downriver of the confluence of the Tittabawassee and Saginaw Rivers will not be included.

ENTRIX First Response: *The draft BERA Work Plan includes the geographical scope as defined in the Operating License. The potential need for expansion of the geographic scope of the studies will be addressed in*

future studies as necessary to meet the requirements of the Operating License.

***MDEQ Comment on ENTRIX Response:** While the ENTRIX response may accurately state the case from a permitting context, MDEQ staff should be aware that the results of the proposed ERA are unlikely to capture the entire spatial extent of risk.*

ENTRIX Second Response: Dow and the Trustees have agreed that a downstream expansion of the geographic scope of the ERA would be beneficial. Dow has provided Michigan State University with funding to collect additional samples on the Shiawassee National Wildlife Refuge as well as two sites on the Saginaw River downstream of the confluence of the Tittabawassee and Shiawassee Rivers, Veterans Memorial Park and the Dow Lighthouse Property. The sampling scheme builds on and complements the current Tittabawassee River ecological food web studies to provide insight into conditions on the Saginaw River. For additional information, see the June 7, 2006 memo from Ben Baker, DOW, to George Bruchmann, MDEQ.

3. *Multiple lines-of-evidence approach.*

MDEQ Original Comment: *Throughout the BERA work plan (ENTRIX, 2005a) it is repeatedly stated that the intended approach to assessing risks to wildlife will be via multiple lines-of-evidence. In effect, this will mean that estimated and measured exposures, and the resulting calculated risks, to wildlife species will not be the only factors used in assessing risk to biota. Using data that is expected to be provided by the Dow-funded Michigan State University Studies, ENTRIX will also incorporate (for example) population abundance, reproductive success, and individual health data into its overall evaluation of risk.*

The intent in using a lines-of-evidence approach, particularly one involving measures of population “health”, in risk assessment, is typically to address the question “are impacts really occurring among receptors for which risk may or may not be predicted”? Thus, the BERA, as proposed, combines two separate concepts – risk and impact. The reason for utilizing such an approach in risk assessment is often given as being intended to reduce the uncertainty inherent in risk modeling. While uncertainty does exist in the estimation of risk from exposures (modeled or measured), the important question is: to what extent are the results of field studies free from uncertainty? In a multiple lines-of-evidence approach to risk assessment there is often a temptation to regard the results of field studies as free from uncertainty and, therefore, the ultimate arbiters of whether or not risk actually exists. This may not be appropriate since it fails to recognize that the results of field studies may be as fraught with uncertainty as risk assessment modeling and, by disregarding the results of the latter in favor of the former, we may only be replacing one set of uncertainties with another. In effect: field studies may not be “silver bullets” that pierce through uncertainty to provide unambiguous or clear results.

The uncertainties inherent in the interpretation of the results of field studies largely grow out of the uncontrolled or only partially controlled nature of such studies. For example, spatial or temporal differences in the breeding productivity of a wildlife species may arise from factors not controlled for (and potentially uncontrollable) in the study design. Such factors may include: the intermittent presence of a predator in the study area, local weather variability, localized disturbance by humans, or local short-term disruption in the food supply. All of these factors may be likely to go unrecognized by researchers. Nevertheless, it is typical that such factors result in a considerable amount of “noise” in field study results. Against this background of noise, it can be very difficult to unambiguously distinguish the “signal” being sought after. Thus the interpretation of productivity data from the field may be as fraught with as much uncertainty as that of model results.

If the variable being measured in the field is density or abundance a whole new set of uncertainties is introduced. It is well known among population biologists that the densities of organisms measured at specific sites in the field may have little or no relationship to the local presence or lack of stressors. So called “sink populations” of organisms may exist in an area where their population “health” and productivity is low, but they are supported and maintained by immigration from “source” areas where productivity is high.

The concerns that I have outlined above are not intended to imply that field studies do not have a role in ecological risk assessment. They do. However, the results of field studies should not be viewed as unambiguous data that “trump” the predictions of ecological risk prediction. I maintain that, while they may provide useful supporting information, they should be treated as circumspectly as the modeled predictions. If a situation arises where risk modeling predicts unacceptable risk, but field studies fail to show an impact, it should not be regarded as axiomatic that there is no risk, only that the field impacts may not have been detected. This is especially the case with PCDDs and PCDFs which do not usually result in “kills” in wildlife species, but are expressed in much more subtle and difficult to detect effects, including reductions in fecundity, and morphological and behavioral abnormalities.

In the September 16 discussion, ENTRIX personnel agreed that the field study results would not be used to trump risk assessment predictions but that each line of evidence would be weighted and a final evaluation derived from the integration of these weighted results. This raises the question: how will the various elements be weighted? This should be addressed in the BERA.

ENTRIX First Response *Utilization of all available lines of evidence is important in understanding the complex interactions that may occur when assessing exposures and potential effects. The text has been modified to clarify how this information will be utilized. It is not a question of whether the field study results may or may not “trump” the risk assessment predictions. Among other types of information the field studies will obtain concentrations of tissue residues in receptors of concern, which integrate their exposures spatially and temporally. These concentrations can be compared to what is predicted from modeled exposure estimates, but more importantly, can be compared to tissue residue-based effect levels available from the scientific literature. The alternative is to rely almost exclusively on a single line of evidence, estimates of dietary exposures, for which risk assessors must make significant assumptions regarding bioavailability, temporal and spatial utilization of the site, and dietary composition. Note that this approach is not a direct assessment of effect, but is a direct measure of exposure. Uncertainties of this approach will be presented in the BERA. Comparison of both approaches may reveal site-specific deviations from generic dietary*

models. Thus, these field studies are critical to “ground truth” model estimates. An additional aspect of the field studies includes an assessment of potential “impact”. While such assessments have uncertainties as suggested by GES, these uncertainties will be discussed in the BERA. Furthermore, the field studies were designed in such a way as to minimize these uncertainties. For example, while weather events might influence productivity measurements in birds, the use of multiple years of data and multiple locations may allow an evaluation of the impact of such events on the results.

***MDEQ Comment on ENTRIX Response:** The ENTRIX comment above and the revisions and additions to the text [in the revised draft BERA Work Plan] are valuable in that they add detail to what is intended in the forthcoming ERA. However, the main point that I made in my previous review of the work plan still stands: field effects or impact studies may provide valuable contributions to an ERA, however, despite all the precautions that may be taken, interpretation of their results is rarely clear and unambiguous. The many uncertainties that often plague field studies should be fully recognized and the likelihood of alternative explanations acknowledged.*

In light of the above, I consider that the ENTRIX assertion that “Site-specific measures of productivity and other field-effects data... provide a direct assessment of the effects of COPECs on receptor species...” (pages 5-7) may be unrealistically optimistic. While such studies might provide important supporting information, they are often beset with problems of interpretation.

ENTRIX Second Response: We agree that there are inherent uncertainties in each of the proposed lines of evidence. That is exactly why the multiple lines of evidence approach has been recognized as so valuable, and is recommended in the Guidance for Ecological Risk Assessment (USEPA, 1997) as the most effective approach to developing a scientifically credible ERA. We agree that each line of evidence present in the BERA will require careful consideration and discussion of the associated uncertainties.

4. Protection of all receptors.

MDEQ Original Comment: Presumably, the intent of the BERA is to provide results that will be protective of all, or at least the great majority, of receptors at the site. However, the BERA focuses on only a small subset of receptors. How will the risk assessors ensure adequate levels of protection for all exposed species? For the great majority of birds and mammals that inhabit the assessment area we have little or no information regarding their potential sensitivity or insensitivity to PCDDs or PCDFs. There is no a priori reason to assume that some of these species could not be as, or more, sensitive than the most sensitive species that have thus far been tested. It is not clear how the ENTRIX study will extrapolate from the selected receptor species to the ecological community as a whole.

ENTRIX First Response: The draft BERA Work Plan incorporates an uncertainty approach regarding development of toxicity reference values (TRVs) that is consistent with applicable guidance. Uncertainty concerning interpretation of the toxicity test information among different species, different laboratory endpoints, and differences in experimental design, age of test animals, duration of test, etc., are addressed by applying uncertainty factors (UFs) to toxicological data in order to derive the final TRV.

MDEQ Comment on ENTRIX Response: This is a valid approach to the issue that I raised. However, it will be important for MDEQ to closely watch the UFs that are used and how they are used in order to make sure that the risk estimations are adequately protective.

ENTRIX Second Response: It is our intention to work with the MDEQ throughout the ERA process including opportunities for MDEQ review of draft documents.

5. Receptor species.

MDEQ Original Comment: *Why are some highly exposed organisms that MSU is already collecting data for (hooded merganser and wood duck) not included in this (receptors of concern) list?*

ENTRIX First Response: *Data have been collected for the hooded merganser and wood duck, however they are not currently receptors of concern because other birds that have been identified at the site as receptors are more representative of site-specific conditions and have more potential for exposure. The existing data for merganser and wood duck can be incorporated into the BERA and the toxicological significance of any chemicals measured in these samples will be evaluated using the multiple lines of evidence approach that has been outlined in the BERA Work Plan. Furthermore, data on concentrations of PCDD/DF in eggs of these birds suggests that they are not present at concentrations that would be expected to exceed the most conservative estimation of hazard (Augsburger, T.P. et. al. 2005 poster # RP092, SETAC North America 26th Annual meeting).*

MDEQ Comment on ENTRIX Response: *It is not apparent from the ENTRIX response above whether wood ducks or hooded mergansers will be included in the ERA, it seems that they “can” be. I would recommend that they should be.*

ENTRIX Second Response: Existing trustee data and newly acquired MSU data for wood ducks and hooded mergansers will be included in the ERA using the multiple lines of evidence approach outlined in the BERA Work Plan. Population health measurements will also be determined for two piscivorous birds (king fisher and great blue heron) that have been observed to have greater site usage and thus, greater exposure to site conditions.

MDEQ Original Comment: *Why are mammalian top predators on the floodplain absent from the list? Assuming that mink is at least partly aquatic in its diet, there should be animals such as red fox included?*

ENTRIX First Response: *A mammalian top predator has not been included in the list of receptors of concern because the likely candidates, red fox, long-tailed weasel, and coyotes, have mitigating factors that reduce the potential for exposure. For example, red fox diet can include up to approximately 31% herbaceous material (USEPA, 1993). In addition, field observations from the MSU research team and local trappers suggest that the floodplain does not*

offer significant areas of suitable habitat for the red fox or long-tailed weasel and thus these species are rarely seen on site. The coyote represents an alternative terrestrial carnivore since they are abundant on the floodplain and are frequently trapped along the river. However, the coyote has a larger foraging range than the red fox. This expanded foraging range likely extends outside of the area of concern.

***MDEQ Comment on ENTRIX Response:** Regarding the comments about the red fox: red foxes have highly flexible habitat preferences (from suburban areas to agricultural land to pristine wilderness), and to claim that habitat does not exist in the Tittabawassee River floodplain cannot be supported. Also, while it is true that some red foxes might feed outside the floodplain, some may not and are, therefore, suitable candidates for evaluation.*

ENTRIX Second Response: A mammalian top predator will be included as a receptor of concern. The coyote as been selected as the most suitable species for evaluation because of its greater potential for exposure via dietary items and documented presence in the Tittabawassee River floodplain.

***MDEQ Original Comment:** Why are no vermivorous animals (e.g., American woodcock) included in the list of receptors?*

***ENTRIX First Response:** American robins have been documented to consume up to 15% earthworms in their diets with a greater proportion of worms being consumed during the sensitive life stages in the spring when eggs are developed and nestlings are fed (USEPA, 1993; MSU field team observations). Site specific data will be available for American robin dietary exposure and tissue residues in the Tittabawassee River floodplain. The short-tailed shrew is also included as a receptor of concern and consumes soil dwelling insects and worms. In addition, while it would be possible to include the woodcock in a theoretical exposure evaluation, ongoing field studies indicate that woodcock is not a resident species on the site. Therefore consideration would have to be given to the transient nature of this migratory species that spends minimal time on the site, a few days per year, based on field observations.*

***MDEQ Comment on ENTRIX Response:** Entrix has responded to my comment about American woodcock by asserting that since woodcock are recorded relatively infrequently from the Shiawassee NWR there must be no habitat for them there. However, in the Atlas of Breeding Birds in Michigan project performed in the 1980s*

(Brewere et al., 1991) woodcocks were found to be widely distributed as a breeding species throughout the state and in the general area of the Tittabawassee. Also, personal observations in the Tittabawassee River floodplain and familiarity with the species habitat requirements leads me to believe that it is not the case that suitable woodcock habitat (woodlots, forested wetland, etc.) does not exist there.

While it is true that woodcock are classified as a relatively uncommon species in the Shiawassee NWR bird list, this is not likely to be due to lack of habitat. It could be due to the fact that since the species is crepuscular and nocturnal they are not typically recorded, or to the fact that (as MSU studies have shown) their food supply is so highly contaminated by TCDD-EQ. I would advise that DEQ should continue to recommend to DOW that American woodcocks be included in their list of study species.

ENTRIX Second Response: As previously stated, a theoretical dietary exposure for woodcock will be calculated from the dietary items that are already being collected. Other currently selected receptors including the American robin and short-tailed shrew have much greater site usage and may be more representative of the exposure of animals that consume soil dwelling insects and worms at this site. In addition, evaluation of woodcock exposure will be limited to one line of evidence (dietary) whereas there will be multiple lines of evidence (dietary, tissue, and reproductive) and hence less uncertainty involved in the evaluation of American robin and short-tailed shrew.

6. Assessment and measurement endpoints.

MDEQ Original Comment: *In Section 3.4 of the BERA work plan “Reproductive Success and Population Sustainability” is identified as the overall assessment endpoint. To actually put this into use, quantifiable measurement endpoints (e.g., Toxicity Reference Values) must be developed. In Section 5.2 of the BERA work plan there is some discussion about how measurement endpoints may be developed. However, it is still unclear how these will relate back to the assessment endpoints. Can it be assumed that if (for example) the endpoint is avian reproductive success and population sustainability, and that the egg tissue residue threshold (the TRV) is exceeded, resulting in a hazard index of greater than unity, that the standard of the assessment endpoint has not been met?*

Also, PCDD/PCDF toxicosis may result in a suite of effects that are not immediately translatable into population effects. For example, edema in embryos, limb malformations. Will these be looked for and will it be assumed that if they are found in study animals they will automatically result in embryo mortality?

ENTRIX First Response: *To evaluate whether the reproductive success and population sustainability assessment endpoint has been met, multiple lines of evidence will be evaluated as suggested in the USEPA 1997 guidance for ecological risk assessment. Table 3-5 has been added to the BERA work plan to better demonstrate the relationship between the measurement endpoints and the assessment endpoints. Exceedance of a criterion for a single measurement endpoint may not ultimately lead to the conclusion that an assessment endpoint has not been met.*

As part of the field studies with certain avian species, embryos will be evaluated for a number of endpoints including abnormalities and deformities as well as growth rates. For specific endpoint measures, please refer to the appropriate study plans. Observations of abnormalities, deformities, or inhibited growth in embryos will not automatically be inferred to result in embryo death. Rather, the severity and occurrence of such observations will be evaluated in terms of incidence in natural populations as documented in the scientific literature or by observations in reference areas; and the potential for embryo death or reduced long-term survival will be discussed in the risk characterization section of the BERA.

MDEQ Comment on ENTRIX Response: *This is an important issue and MDEQ should be prepared to look closely at how ENTRIX actually relates measurement*

endpoints to population attributes. My own position is that reproductive success is one of the key factors in population demography and sustainability. That being so, a very good argument would have to be presented to convince me that sub-acute effects such as embryo deformations, or edema, should not be treated as the equivalent of embryo mortality.

ENTRIX Second Response: We agree that reproductive success is a key factor in population sustainability. As mentioned in ENTRIX's first response, information presented in Table 3-5 of the BERA work plan is designed to demonstrate the relationship between the measurement endpoints and the assessment endpoints. An immense field effort is being put forth by the MSU team to acquire the data necessary to appropriately address this important question.

7. Use of existing data sets.

MDEQ Original Comment: *Several important data sets already are available to describe contamination at the site. These include data sets for sediments, soils, water, and biota. It is not clear from the BERA work plan, however, which, if any, of these data sets will be incorporated into the proposed analyses. The work plan needs a clear statement about which of these data sets are likely to be used.*

ENTRIX First Response: *The text has been revised to more clearly describe which data sets will be utilized.*

MDEQ Comment on ENTRIX Response: *Despite the ENTRIX response, it is still not apparent to me whether existing non-Dow data sets will be used in the proposed ERA. For example, will the MDEQ fish data set be utilized? Will the MDEQ/FWS wood duck and hooded merganser data set be utilized?*

ENTRIX Second Response: All available data that meet the project data quality objectives will be considered for use in the ERA and will be used if technically appropriate. The studies named above along with all other available historical data will be evaluated for inclusion in the ERA analysis. It is not possible to specifically state *a priori* the extent to which the existing data sets will have a role in the final analysis.

8. Inclusion of wood ducks and hooded mergansers in the ERA.

***MDEQ Original Comment:** Why are wood duck and hooded merganser not included in this list or receptors? We already have data that characterizes their exposure and MSU has already gathered eggs of both species.*

***ENTRIX First Response:** Data have been collected for the hooded merganser and wood duck, however they are not currently receptors of concern because other birds that have been identified at the site as receptors are more representative of site-specific conditions and have more potential for exposure. The existing data for merganser and wood duck can be incorporated into the BERA and the toxicological significance of any chemicals measured in these samples will be evaluated using the multiple lines of evidence approach that has been outlined in the BERA workplan. Furthermore, data on concentrations of PCDD/DF in eggs of these birds suggests that they are not present at concentrations that would be expected to exceed the most conservative estimation of hazard (Augsburger, T.P. et. al. 2005 poster # RP092, SETAC North America 26th Annual meeting).*

***MDEQ Comment on ENTRIX Response:** Hooded mergansers and wood ducks should be included in the proposed ERA. Excluding them on the basis of some a priori assumptions about whether or not they are “representative of site-specific conditions”, or on the results of a poster presentation (which may have not undergone appropriate levels of scientific peer-review) is not valid. Furthermore, the MDEQ/USFWS control data from Rose Lake demonstrate conclusively that the hooded merganser data are likely to be representative of site-specific conditions.*

ENTRIX Second Response: Existing trustee data and newly acquired MSU data for wood ducks and hooded mergansers will be included in the ERA using the multiple lines of evidence approach outlined in the BERA Work Plan. Population health measurements will also be determined for two piscivorous birds (king fisher and great blue heron) that have been observed to have greater site usage and thus, greater exposure to site conditions.

9. p. 3-5, Section 3-4. *Individual and population endpoints.*

***MDEQ Original Comment:** Can we infer from this section that if unacceptable risks are shown to apply to reproductive endpoints that this axiomatically implies risk to population sustainability?*

***ENTRIX First Response:** While measures of reproductive success are sensitive indicators of contaminant toxicity and are indicators of population sustainability, they are not direct measures of how populations behave in ecological systems. Evaluation of population sustainability includes consideration of multiple factors including reproduction, growth, and survival. Density-dependent and density-independent factors all have a role in determining whether a population is sustainable at any given location and must be taken into account when assessing the potential impact of COPECs on a particular receptor. For this reason, a multiple line of evidence approach will be used to assess the impact of COPECs in which toxicological and ecological data will be used to assess the health and sustainability of receptor populations and to apportion the potential causes for any alterations in populations characteristics found at different locations within the reference and down river sites.*

***MDEQ Comment on ENTRIX Response:** While it is true that a number of demographic and ecological factors mediate the relationships between individual reproductive effects and population processes, it is also true that it can be extremely difficult to quantify the contribution of these factors. In practice, and appropriately adhering to the Precautionary Principle, it may be necessary to make the assumption that unacceptable risks to reproductive performance are also unacceptable risk to populations sustainability.*

ENTRIX Second Response: The Precautionary Principle applies to situations where uncertainty is high due to lack of data or scientific understanding. This BERA work plan is written to preclude this outcome. Through extensive site-specific sampling and analysis that will include measures of reproduction, growth, and survival wherever possible, uncertainty will be kept to a minimum. These data will then be interpreted using the best available science to minimize the need for such assumptions.

10. p. 5-3, final para. Statistical extrapolation.

It is stated that the results obtained from the MSU sampling grids will be extrapolated to the wider environment of the site. However, since the sample sites that were chosen for the grids were subjectively selected (i.e. they were not, apparently, based on a random model or a systematic grid with randomized start point) any statistical inferences from a grid should be confined to that grid, or perhaps, to comparisons between grids. How will the risk assessors address this limitation?

ENTRIX First Response: *The use of data collected from the grids will not be extrapolated to the wider site, rather the data collected from these grids will be used to derive parameters that can be used in models to assess the potential exposure of receptors found at other locations within site and reference locations. The exposure model, using site-specific parameters along with chemical data from soils collected as part of the nature and extent studies will be used to estimate exposures for targeted receptors throughout the site. This approach is commonly used along with GIS methodologies to “map” areas of potential risk based on soil chemical concentrations.*

MDEQ Comment on ENTRIX Response: *The ENTRIX response does not fully resolve this issue. The non-randomized sampling design does not allow the extrapolation of variables such as tissue residues to the wider environment. Model factors such as bioaccumulation rates are no different. A model factor developed in one plot cannot be applied widely to the floodplain unless it is assumed that the processes outside the plot are similar or identical to those within it. A randomized sampling design would have better addressed this issue.*

ENTRIX Second Response: In designing any sampling strategy, tradeoffs have to be made between number of sites and the number of samples analyzed per site. In this study, relationships between contaminant concentrations in soil and dietary items were determined through intensive sampling of fewer sites with a greater priority given to factors that are critical for long-term wildlife studies including presence of habitat, co-location of food web items, ability to access locations, and potential for elevated concentrations of COPECs. Biological sampling is often more restricted in relation to sediment or soil sampling due to the effort required to collect biological samples and the inherent destructiveness in such sampling. There is nothing unusual about such a sampling approach as it is widely used by agencies and researchers to provide input to bioaccumulation models. The six locations where extensive food-web sampling has been conducted are not intended to characterize conditions on the entire floodplain, but rather to establish site-specific congener-specific trophic-level relationships that can then be applied to predict

receptor exposure based on the extensive soil and sediment concentration measurements taken in the floodplain during the remedial investigation.

Another consideration is that although the lower trophic levels such as invertebrates and small mammals were taken from within the sampling plots, the higher trophic level receptors were taken opportunistically at many locations along the river. These higher trophic level receptors that are the focus of this ecological risk assessment (e.g. mink and great horned owl), effectively integrate exposure from their entire home range allowing us to relate exposure to large areas of the floodplain.

11. p. 5-5. Section 5.2.1.

MDEQ Original Comment: Why explicitly is doubt being cast on the Saginaw Bay carp mink feeding study in a work plan? Is it being contended that the study has no predictive value elsewhere? Or is that the TCDD-EQ approach to evaluating risk is being questioned?

ENTRIX First Response: The Saginaw Bay mink study is not flawed when interpreted relative to the risk question that was being asked at the time of the study. That is, what are the risks posed to mink populations that consume fish from the Saginaw Bay? However, this study is not appropriate for use in the current assessment due to the presence of co-contaminants in the feeding study. For example, when total TEQs derived from a biological assay (H4IIE) were compared to those derived from chemical analyses, the chemically derived TEQ values only accounted for approximately 40 to 50% of the total TEQ quantified by the biological assay. The remaining TEQs were never identified chemically. Finally, since the carp used in the feeding study were collected in the 1980's from Saginaw Bay, an area with numerous industrial inputs, it is likely that other non-AhR contaminants were present. Taken together, the use of data from these studies tends to overestimate potential risks.

The Saginaw Bay mink feeding study has been used in many ERAs because it was one of the only studies that was available at the time of those assessments. Currently, however, there are other studies that have fewer co-contaminant issues.

MDEQ Comment on ENTRIX Response: It is my understanding that this issue is to be addressed by performing a mink feeding study. This is laudable. However, based on my understanding of the proposed study it may not answer the crucial risk question: does consumption of Tittabawassee River fish pose risks to mink (because the experimental animals will be fed dosed chow rather than fish from the river). I would urge that a valid feeding study would utilize fish from the river.

ENTRIX Second Response: Discussions of a potential laboratory mink feeding study have included consideration of using Tittabawassee River dietary items as feed. If the decision is made to proceed with the study, the details will be established and consideration will be given to this concept. The collection of >20 mink directly from the Tittabawassee River gives insight to the exposure of and effects to mink that consumed diets of Tittabawassee River fish, small mammals, and other dietary items. Results from this study suggest that mink from the Tittabawassee River floodplain downstream of Dow are in good condition.

12. p. 6-1, Section 6.1.1.

MDEQ Original Comment: *There is an inconsistency in the logic and terminology in the 2nd complete paragraph. If it is to be assumed that HQ values less than unity indicate that unacceptable risks are unlikely, then it should be assumed if the HQ values are greater than unity that unacceptable risks are likely. Also, what can be deduced if the HQ value is exactly one?*

ENTRIX First Response: *The logic used in the BERA work plan relative to the interpretation of HQ values is not inconsistent in that HQ values less than 1 indicate that the potential for unacceptable risk is not likely to occur. However, for HQ values greater than or equal to 1, the potential for unacceptable risk cannot be ruled out, and the magnitude of the effect on a particular receptor cannot be inferred based on the magnitude of the HQ. This is due to the fact that HQ values are not statistical probabilities of adverse effects but rather an indicator of the level of concern regarding the potential of unacceptable risks. EPA has clearly described some of the limitations of assessing HQ values (USEPA, 1998, p. 96): “A number of limitations restrict application of the quotient method. While a quotient can be useful in answering whether risks are high or low, it may not be helpful to a risk manager who needs to make a decision requiring an incremental quantification of risks. For example, it is seldom useful to say that a risk mitigation approach will reduce a quotient value from 25 to 12, since this reduction cannot by itself be clearly interpreted in terms of effects on an assessment endpoint.” Additional information and discussion of the HQ concept has been added to the revised BERA work plan.*

MDEQ Comment on ENTRIX Response: *If “HQ values less than 1 indicate that the potential for unacceptable risk is not likely to occur”, then is it not axiomatic that HQ values greater than 1 indicate (at the least) that the potential for unacceptable risk is not unlikely? ENTRIX is correct in stating that the magnitude of the HQ may not reflect the magnitude of effect, but it certainly reflects magnitude of risk. For this reason it would be more accurate to rephrase the text: “HQ values less than 1 indicate that the potential for unacceptable risk may be unlikely. However, for HQ values greater than or equal to 1, it should be assumed that the potential for unacceptable risk may be likely.” This is not the same as saying that unacceptable risk is a given at HQs>1, only that unity is a threshold that needs to be taken seriously.*

ENTRIX Second Response: Given the conservative nature of ecological risk assessment, the HQ is akin to a one-tailed test used to rebut the presumption of risk when the value is less than unity. As such, HQs less than one indicate that risk is

unlikely. HQs greater than 1 do not imply that risk is likely, but rather that potential risk may exist that requires additional site- and receptor-specific data and analysis before actual risk can be assessed.

13. Study Plans. Exposure Pathway Analysis (p. C-4).

***MDEQ Original Comment:** The stated rationale for this study largely ignores the results of previous studies. We know that various species of predatory and forage fish have bioaccumulated PCDD/PCDFs. We know what their tissue residues are. We know that at least two species of duck have bioaccumulated PCDD/PCDFs, and that their eggs have high levels of contamination. Every ecosystem component that has been thus far investigated has proven to be contaminated to relatively high levels. It is disingenuous to describe the information that has been collected thus far as “limited”.*

***ENTRIX First Response:** The study plans from MSU were included with the BERA work plan as supporting evidence for the type of data that will be collected for inclusion in the BERA. These are not ENTRIX work plans and as a result changes have not been made to these documents.*

***MDEQ Comment on ENTRIX Response:** This may be the case but it is not apparent from the revised work plan that existing data sets will be given the full weight that they deserve in the proposed ERA (see my comments on issues 1, 7, and 8 above).*

ENTRIX Second Response: All available data that meet the project data quality objectives will be considered for use in the ERA and will be used if technically appropriate. The studies named above along with all other available historical data will be evaluated for inclusion in the ERA analysis. It is not possible to specifically state *a priori* the extent to which the existing data sets will have a role in the final analysis.

Additional new comments included in the MDEQ May 22, 2006 review:

14. Receptor Species:

MDEQ Original Comment: Throughout the BERA Work Plan it is repeatedly stated that birds and mammals will be the main foci of the investigations. Is it the intention on the risk assessors to not evaluate risks to other groups, such as invertebrates and fish? If so, what is the rationale behind those decisions?

ENTRIX Response: Section 3.3.2 of the BERA Work Plan addresses species that were not selected as receptors of concern. *“Terrestrial and aquatic invertebrates will be collected in order to estimate COPEC exposures to organisms that feed on them. However, since such invertebrate organisms lack a functional AhR-mediated pathway, they are not expected to be directly affected by COPECs, such as PCDDs and PCDFs. Thus, the main reason for exclusion of terrestrial and aquatic invertebrates as ROCs is their lack of sensitivity to PCDDs and PCDFs.”* Insensitivity of invertebrates to dioxin is well documented (West et al. 1997) and fish are less sensitive to dioxin than birds and mammals (Hecker et al. 2006).

The work plan focuses resources on wildlife with the greatest potential risk and thus the most likely potential risk drivers in the evaluation of the Tittabawassee River and floodplain. Given our current knowledge of the site this is most likely piscivorous wildlife rather than invertebrates or fish. Avian and mammalian piscivores were also selected as assessment endpoints in the previous Tittabawassee River Aquatic Ecological Risk Assessment provided by MDEQ and authored by Galbraith Environmental Sciences “because these endpoints represent protection of the ecological receptors that are likely to be most vulnerable to PCDDs and PCDFs within the assessment area, they are likely to be protective of the other, less vulnerable, exposed ecological resources.” In this prior study, risks to fish or aquatic invertebrates were not considered.

There is existing evidence indicating that COPECs, such as PCDDs and PCDFs, are not adversely affecting the health of the Tittabawassee River fisheries, including harvest data from DNR creel surveys and the fact that walleye eggs spawned in the Tittabawassee River are being used to stock other fisheries in the DNR fish hatchery program. Eggs and larval fish are considered much more sensitive to dioxin than adult fish (Walker et al. 1991), and the highly successful propagation of walleye from Tittabawassee River stocks suggest that risk to fish is unlikely.

15. Information on background conditions:

***MDEQ Original Comment:** Two reference sampling sites are identified in the RIWP; these are the sample sites selected by MSU as part of their field studies. One is on the upper Tittabawassee River above Midland, while the other is adjacent to the Pine River. While it is important to be able to characterize “baseline” conditions in the ERA, there are three main reasons why the data that will be gathered from these sites is less than optimal:*

- 1. A sample size of two is not adequate to characterize soil/sediment, food chain transfer, or other resource conditions or processes.*
- 2. There are problems associated with statistical extrapolation from these sites (see comment 10 above).*
- 3. the selection of the Pine River site as a source for “background” data is problematic. The Pine has point sources of industrial contaminants including PBBs, DDT, and petroleum hydrocarbons. These contaminants may affect the measurements of background concentrations or ecosystem/food chain processes.*

ENTRIX Response: Intense sampling of food-web dietary items has occurred at one site on the Pine river and one site on the Tittabawassee River upstream of Dow. To date, the MSU field team has collected many more than their targeted 2 sediment and soil samples at each reference location. A minimum of 10 samples have been collected for each type at each location. In addition, top-level receptors such as mink and great horned owl that integrate exposure to chemicals over time and space are being sampled throughout the Pine, Chippewa, and upper Tittabawassee Rivers. Rather than extensive characterization of soils and sediments throughout these reference locations, chemical residues in the tissue of top-level receptors will indicate the presence or absence of bioaccumulative compounds.

Reference sites were selected on the main tributaries of the Tittabawassee River, upstream of the Dow facility. These sites were selected as the most relevant reference sites for evaluating contaminants and ecology prior to any impacts of Dow. As the trustees state, the Pine River drainage does contain point sources of PBBs and DDT and its metabolites, however, this drainage does serve as reference to conditions present upstream of Dow. It also allows for the evaluation of potential loading of contaminants to the Tittabawassee River not attributable to Dow that may pose risk downstream of Midland. The Chippewa and upstream Tittabawassee Rivers differs from the Pine River, in its lack of point sources of contaminants, and

thus reflects a less impacted environment. These reference sites provide valuable insight to conditions upstream of Dow and enable assessment of risk potentially attributable to releases from Dow.

16. Scheduling of MSU studies and ENTRIX ERA.

***MDEQ Original Comment:** Many of the MSU studies in the floodplain are not scheduled to be completed until 2008. However, the BERA (which will include results from these studies) will be issued in late 2006. How will the ENTRIX risk assessors accommodate this temporal mis-match? Will they use data from incomplete studies or only use those components of studies that are complete? How will they address the possibility that the final years of particular studies may produce results at variance with the earlier years?*

ENTRIX Response: The development of the BERA report is predicated on the approval of this work plan. When the first draft of the BERA is produced it will include an evaluation of all data that are available at that time. This BERA will provide the risk managers with the basis to begin formulation of a decision framework. Results of the MSU studies and other data that become available at later dates can be used by risk managers to refine decisions.

Citations

- Augsburger, T.P., Di Giulio, R.T., Tillitt, D.E. 2005. Embryotoxicity of 2,3,7,8-TCDD to the Wood Duck (*Aix sponsa*). SETAC North America 26th Annual Meeting, PR092 Poster.
- Galbraith Environmental Services. 2003. Tittabawassee River Aquatic Ecological Risk Assessment: Polychlorinated Dibenzo-*p*-dioxins, Polychlorinated Dibenzofurnas.
- Galbraith Environmental Services. 2004. Tittabawassee River Floodplain Screening-Level Ecological Risk Assessment – Polychlorinated Dibenzo-*p*-Dioxins, Polychlorinated Dibenzofurans.
- Hecker, M., Murphy, M.B., Giesy, J.P., Hopkins, W.A., 2006. Induction of Cytochrome P4501A in African Brown House Snake (*Lamprophis fuliginosus*) Primary Hepatocytes. Environ. Toxicol. Chem. 25, 496-502.
- US EPA. 1993. Wildlife Exposure Factors Handbook Volumes I and II. PEA/600/R93/187b. Washington, D.C.
- US EPA. 1997. Ecological Risk Assessment Guidance for Superfund: Process for Designing and Conducting Ecological Risk Assessments Interim Final. EPA 540-R-97-006. Washington, D.C.
- US EPA. 1998. Guidelines for Ecological Risk Assessment. Risk Assessment Forum. EPA/630/R-95/002F, Washington, D.C.
- Walker, M.K., Spitsbergen, J.M., Olson, J.R., Peterson, R.E. 1991. 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) Toxicity during Early Life Stage Development of Lake Trout, (*Salvelinus namaycush*). Can.J.Fish Aquat. Sci. 48, 875-883.
- West, C.W., Ankley, G.T., Nichols, J.W., Elonen, G.E., Nessa, D.E., 1997. Toxicity and Bioaccumulation of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin in Long-Term Tests with the Freshwater Benthic Invertebrates *Chironomus tentans* and *Lumbriculus variegatus*. Environ. Toxicol. Chem. 16, 1287-1294.

November 22, 2006

**Memo re: Responses to the Michigan Department of Environmental Quality's
April 13, 2006 Notice of Deficiencies relevant to the Ecological Risk
Assessment work plans**

In this memo, we provide a disposition of comments including responses and/or clarifications regarding each of the topics relevant to the Ecological Risk Assessment (ERA) work plans that were raised in Attachments 2 and 3 of the Michigan Department of Environmental Quality (MDEQ) April 13, 2006 Notice of Deficiency (NOD).

Comments are numbered as in the MDEQ NOD. Comments and MDEQ responses are presented in italicized and indented font while ENTRIX responses follow in arial font as demonstrated in the following example.

Format:

1. Title of Comment

Trustee or Public Comment

MDEQ Response to Comment

ENTRIX Response to comment

NOD Attachment 2: Comments from the Natural Resource Damage Assessment Trustees

4. Geographic Extent of Investigations – River Corridors

Trustees' Comment: *For many types of biological sampling and evaluation, year-to-year variability in levels of contamination, productivity, and other physiological endpoints is known to be significant. At this point, the Trustees believe that the entire Saginaw River and likely at least the inner part of Saginaw Bay will need to be included in the assessment in addition to the Tittabawassee River. Thus, biological sampling and evaluation that is conducted in the Tittabawassee River corridor and reference areas also should be conducted simultaneously in at least the Saginaw River corridor so that the extent of any impacts that might be observed can be determined under as similar conditions (and observers) as possible. The links between any impacts and sources of contaminants will need to be evaluated, so co-located soils, sediments, and dietary items should be collected for analysis simultaneously with the biological samples. These samples should be analyzed for PCDD/F [polychlorinated dibenzo-p-dioxins and furans] congeners as well as other compounds that could contribute to the observed impacts in order to elucidate source contributions.*

MDEQ Response to Comment: *With respect to concurrent biologic sampling and evaluation along the Saginaw River and Bay, the MDEQ agrees that this is necessary information for the NRDA and this is an area where additional data collection could be conducted as part of the remedial investigation to support the NRDA data needs. Dow is not required by its operating license to begin these types of evaluations until 2007. However, this is an area where Dow could choose to begin collecting additional data concurrently with work being conducted on the Tittabawassee River to support the NRDA process and to begin addressing Saginaw River and Bay remedial investigation needs. Note that this would require the development and prior approval of work plans by the Trustees and the MDEQ.*

ENTRIX Response to comment: *Dow and the Trustees have agreed that a downstream expansion of the geographic scope of the ERA would be beneficial. Dow has provided Michigan State University with funding to collect additional samples on the Shiawassee National Wildlife Refuge as well as two sites on the Saginaw River Downstream of the confluence of the Tittabawassee and Shiawassee Rivers, Veterans Memorial Park and the Dow Lighthouse Property. The sampling scheme builds on and complements the current Tittabawassee River ecological food web studies to provide insight into conditions on the Saginaw River. For additional information, see the June 7, 2006 memo from Ben Baker, DOW, to George Bruchmann, MDEQ.*

5. Geographic Extent of Investigations – Midland Area

Trustees' Comment: *Section 6 (Ecological Risk Assessment) of Dow's RIWP for the Midland Area states that habitats, receptors and pathways present in the Midland*

area will be evaluated in the RI and that the results of the ecological risk assessment (ERA) being performed for the Tittabawassee River and floodplain will be applied to those identified receptors and pathways. The source of the PCDD/Fs in the Midland Area is aerial deposition whereas the source of the PCDD/Fs in the river corridor is release and re-releases in the aquatic environment. Because of this, the patterns of congeners to which biota are exposed are different in the two areas. The modeled risk from different patterns of congeners can be addressed with the use of toxic equivalency factors (TEFs), to the extent that the TEFs are accurate and the assumption of additivity is met, but results from field assessments and bioassays may not be directly transferable from the river corridor to the Midland area.

MDEQ Response to Comment: *The MDEQ agrees with this comment which is applicable to the Midland RIWP. The Midland RIWP must be revised to address this comment. [12/1/06]*

ENTRIX Response to comment: The trustees raise two questions with regard to the application of the Tittabawassee River ERA results to a Midland area ERA: 1) the mode of deposition and patterns of congeners present in Midland area soils are different than those present in the Tittabawassee River and its floodplain; 2) due to different congener patterns, relationships between receptor TEQs and population health in the Tittabawassee River floodplain may not be transferable to the Midland area.

In response to the former concern, the floodplain investigation includes extensive sampling and congener-specific analysis of soil, food-web samples at multiple trophic levels, and receptor tissue. This will provide data to calculate both congener specific diet/soil and receptor/soil bioaccumulation factors that can be applied to the assessment of Midland Area receptor risk. From these congener specific bioaccumulation factors and measured soil concentrations, receptor TEQs in the Midland area will be estimated using 2005 WHO TEFs and then compared to appropriate toxic reference values. The trustees are correct in pointing out that the modeled risk is subject to the uncertainty associated with the accuracy of current TEFs and the assumption of additivity.

Their latter concern pertains to the transferability of relationships between TEQs and population health assessments from the Tittabawassee River floodplain ERA to the Midland area. Although differences in congener patterns between the two sites adds to uncertainty, application of the World Health Organization TEFs is the best available scientific approach and standard practice in the evaluation of risk from dioxin like compounds. All known sources of uncertainty including those presented here will be discussed in the risk assessment evaluation.

6. Ecological Receptors

***Trustees' Comment:** The Baseline Ecological Risk Assessment Work Plan (BERA WP) lists the ecological receptors that will be the focus of both the BERA and the continuing field impact studies being conducted by Michigan State University (MSU). This list appropriately includes some species known to be sensitive to PCDD/Fs (e.g., mink), some expected to be highly exposed because of their position in the food web (e.g., great horned owl, great blue heron) and some because they represent specific feeding guilds. Some appear to have been selected because they are abundant and easy to work with in the field (e.g., tree swallow, house wren). These species may be representatives of species that are generally more tolerant to stressors than other species. The Trustees will need to consider the entire range of species that could have been or are being injured, so the species being studied will likely need to be placed in the context of a wider range of sensitivities and exposures.*

Additional species could be assessed now in order to reduce uncertainty in the Trustee's assessments in the future. The MSU team collected eggs from the wood duck boxes placed along the Tittabawassee River both upstream and downstream of Midland. Since preliminary data from the Trustee's study indicates that hooded mergansers use wood duck boxes and are more highly exposed than wood ducks, hooded merganser eggs collected by the MSU team should be analyzed (e.g., 10 eggs, each from a different box, both from the upstream and downstream portions of the river). The Trustees disagree with Entrix's conclusion that the American woodcock is not a resident on the site based on field observations. Woodcocks are known to breed on the Shiawassee NWR, though they are difficult to find unless trained observers are specifically searching for them. Exposure to woodcocks should be evaluated because of their close association with floodplain soils and their earthworm-dominated diet. A mammalian tertiary consumer like the red fox or coyote should be included in the BERA. Entrix has argued against their inclusion based on habitat (red fox) and foraging range (coyote), but the Trustees believe that sufficient habitat for red fox exists that they should be evaluated and protected and that an evaluation of the home range size for coyotes can be included in the BERA.

***MDEQ Response to Comment:** The MDEQ agrees with these comments which are applicable to the TR RIWP ecological risk assessment as well as the NRDA. The TR RIWP must be modified to specifically address these comments and to include the subject species in the BERA [12/1/06]*

ENTRIX Response to comment: Existing trustee data and newly acquired MSU data for wood ducks and hooded mergansers will be included in the ERA using the multiple lines of evidence approach outlined in the BERA Work Plan. Population health measurements will also be determined for two piscivorous birds (king fisher

and great blue heron) that have been observed to have greater site usage and thus, greater exposure to site conditions.

A mammalian top predator will be included as a receptor of concern. The coyote has been selected as the most suitable species for evaluation because of its greater potential for exposure via dietary items and documented presence in the Tittabawassee River floodplain.

A theoretical dietary exposure for woodcock will be calculated from the dietary items that are already being collected. Other currently selected receptors, including the American robin and short-tailed shrew, have much greater site usage and may be more representative of the exposure of animals that consume soil dwelling insects and worms at this site. In addition, evaluation of woodcock exposure will be limited to one line of evidence (dietary) whereas there will be multiple lines of evidence (dietary, tissue, and reproductive) and hence less uncertainty involved in the evaluation of American robin and short-tailed shrew.

***Trustees' Comment:** The BERA does not include assessment of fully aquatic species. The Trustees will need to consider injuries to fish and benthic invertebrates in our assessment process, and the risk to these groups of biota should be assessed in the BERA to test the assumption that protecting mink will protect the aquatic food web.*

***MDEQ Response to Comment:** The MDEQ agrees with these comments which are applicable to the TR RIWP ecological risk assessment as well as the NRDA. The TR RIWP must be modified to specifically address these comments and to include the subject species in the BERA. [12/1/06]*

ENTRIX Response to comment: Section 3.3.2 of the BERA Work Plan addresses species that were not selected as receptors of concern. *“Terrestrial and aquatic invertebrates will be collected in order to estimate COPEC exposures to organisms that feed on them. However, since such invertebrate organisms lack a functional AhR-mediated pathway, they are not expected to be directly affected by COPECs, such as PCDDs and PCDFs. Thus, the main reason for exclusion of terrestrial and aquatic invertebrates as ROCs is their lack of sensitivity to PCDDs and PCDFs.”* Insensitivity of invertebrates to dioxin is well documented (West et al. 1997) and fish are less sensitive to dioxin than birds and mammals (Hecker et al. 2006).

The work plan focuses resources on wildlife with the greatest potential risk and thus the most likely potential risk drivers in the evaluation of the Tittabawassee River and floodplain. Given our current knowledge of the site this is most likely piscivorous wildlife rather than invertebrates or fish. Avian and mammalian piscivores were also

selected as assessment endpoints in the previous Tittabawassee River Aquatic Ecological Risk Assessment provided by MDEQ and authored by Galbraith Environmental Sciences “because these endpoints represent protection of the ecological receptors that are likely to be most vulnerable to PCDDs and PCDFs within the assessment area, they are likely to be protective of the other, less vulnerable, exposed ecological resources.” In this prior study, risks to fish or aquatic invertebrates were not considered.

There is existing evidence indicating that COPECs, such as PCDDs and PCDFs, are not adversely affecting the health of the Tittabawassee River fisheries, including harvest data from DNR creel surveys and the fact that walleye eggs spawned in the Tittabawassee River are being used to stock other fisheries in the DNR fish hatchery program. Eggs and larval fish are considered much more sensitive to dioxin than adult fish (Walker et al. 1991), and the highly successful propagation of walleye from Tittabawassee River stocks suggest that risk to fish is unlikely.

***Trustees’ Comment:** The Trustees request split samples from a subset of the ecological sampling being performed in support of the BERA. We would be happy to discuss this in more detail with the relevant parties.*

***MDEQ Response to Comment:** The MDEQ agrees with this comment. A mechanism must be developed as part of the BERA to address splitting of samples with the Trustees and/or the MDEQ. [12/1/06]*

ENTRIX Response to comment: Michigan State University has previously offered to make splits of samples available to interested parties. These splits can be obtained by contacting Matthew Zwiernik at 517-749-5243 or Zwiernik@msu.edu.

***Trustees’ Comment:** The Trustees understand the difficulties in selecting and obtaining access to suitable reference areas for ecological field studies, but we have some concerns with the reference sites identified in the RIWP and being used by MSU. The soils and sediments in the reference areas need to be fully characterized and RIWP includes very few (two?) sampling points in the reference areas. The use of the Pine River as a reference area is confounded by the presence of point sources of other contaminants (e.g., PBB, DDT/DDE, petroleum hydrocarbons) upstream and the uncertainty in the gradient of those contaminants as the Pine River flows into the Tittabawassee, through the impounded area of the Dow dam, and then downstream of Midland.*

***MDEQ Response to Comment:** The MDEQ agrees with these comments which are applicable to the TR RIWP ecological risk assessment as well as the NRDA. The TR*

RIWP must be modified to specifically address these comments and to include the subject species in the BERA. [12/1/06]

ENTRIX Response to comment: Intense sampling of food-web dietary items has occurred at one site on the Pine river and one site on the Tittabawassee River upstream of Dow. To date, the MSU field team has collected many more than their targeted 2 sediment and soil samples at each reference location. A minimum of 10 samples have been collected for each type at each location. In addition, top-level receptors such as mink and great horned owl that integrate exposure to chemicals over time and space are being sampled throughout the Pine, Chippewa, and upper Tittabawassee Rivers. Rather than extensive characterization of soils and sediments throughout these reference locations, chemical residues in the tissue of top-level receptors will indicate the presence or absence of bioaccumulative compounds.

Reference sites were selected on the main tributaries of the Tittabawassee River, upstream of the Dow facility. These sites were selected as the most relevant reference sites for evaluating contaminants and ecology prior to any impacts of Dow. As the trustees state, the Pine River drainage does contain point sources of PBBs and DDT and its metabolites, however, this drainage does serve as reference to conditions present upstream of Dow. It also allows for the evaluation of potential loading of contaminants to the Tittabawassee River not attributable to Dow that may pose risk downstream of Midland. The Chippewa and upstream Tittabawassee Rivers differ from the Pine River, in their lack of point sources of contaminants, and thus reflect a less impacted environment. These reference sites provide valuable insight to conditions upstream of Dow and enable assessment of risk potentially attributable to releases from Dow.

Attachment 3 Public comments

5. Comments on the Dow Chemical Company's Proposed SLERA and BERA

(b) Neglect of American Woodcock and Hooded Mergansers

***Public Comment:** Though we recognize that not all bird species can be studied in any ecological study, it would seem imperative, given the levels of dioxin/furans in earthworms, to study a bird species whose diet is heavily dependent on earthworms, such as the Woodcock. Similarly, initial sampling has already disclosed high levels of dioxin/furans in Hooded Mergansers eggs. It would follow that both of these species should be included in any wildlife study, and we would like to know why they were excluded?*

***MDEQ Response to Comment:** Please refer to the MDEQ's response to Trustee's comment 6 in Attachment 2 of this NOD, which also addresses the above comments. [12/1/06].*

ENTRIX Response to comment: Please refer to ENTRIX response to Attachment 2, comment 6 "Ecological Receptors".

(c) Gap in Predatory Mammals

***Public Comment:** What is the biological uptake of local toxics is the question of most magnitude in this and any ecological investigation involving toxics in the soil and sediment. For that reason, it baffles us as to why those animals feeding highest on the food chain were neglected in the proposed study. We speak of red fox and coyote. It is our understanding that the habitat in the Tittabawassee River floodplain is excellent for both species, and would expect their inclusion in any ecological study. Why were they not proposed? Similarly, it is our understanding that the existing habitat is excellent for river otters. Why have they not been included in the study? If the consultants' response is that river otters have not been found, given historical evidence of their presence, and their exclusive diet of fish, what conclusions can be made?*

***MDEQ Response to Comment:** Please refer to the MDEQ's response to the Trustees' Comment 6 in Attachment 2 of this NOD, which also addresses the above comments. With respect to the inclusion of river otters, the MDEQ will defer to the expertise of the Michigan Department of Natural Resources and the U.S. Fish and Wildlife Service on this issue, which would best be addressed as part of the NRDA process. [12/1/06]*

ENTRIX Response to comment: Please refer to ENTRIX response to Attachment 2, comment 6 “Ecological Receptors”. Relative to otter, the ERA workplan is designed to utilize mink as a surrogate species for all piscivorous mammals, which is a reasonable approach given the relatedness of the two species and the availability of more laboratory toxicity data for mink than otter.

(d) Absence of Fish

Public Comment: We realize that fish are a part of the study in as much as they provide food for animals studied, particularly mink. However, it is a major deficiency of the proposal to leave out the uptake of toxics in fish. Fish, of course, are a clear part of the human food chain, and major recreational and tourist attraction. Knowledge of the uptake of dioxins/furans would provide important insight into the costs of the contamination.

MDEQ Response to Comment: The MDEQ concurs with this comment. Fish must be included in both the ecological and human health risk assessments, as well as for the NRDA purposes. The TR RIWP must be revised to specifically address and respond to this comment. [12/1/06]

ENTRIX Response to comment: Please refer to ENTRIX response to Attachment 2, comment 6 “Ecological Receptors”. Data have already been collected for whole fish by both MDEQ and MSU that can be utilized in the ERA. Fillet data for use in HHRA are not part of the BERA and will be addressed elsewhere.

(e) Absence of Reptiles and Amphibians

Public Comment: There is no mention in the proposed ecological study of reptiles and amphibians. Turtles and frogs are presumably part of the food chain, and an entire family of species. Why are they neglected? Frogs, in particular, have been described internationally as the proverbial canary in the mine. The disappearance of frogs and the well-publicized frog mutations have focused much attention on the species. Why wouldn't Dow consider frogs to be a primary subject of any local ecological investigation?

MDEQ Response to Comment: The MDEQ concurs with this comment. Reptiles and amphibians must be included in both ecological and human health risk assessments, as well as for the NRDA purposes. Snapping turtle, in particular, is harvested for food from the Tittabawassee River and is important as a cultural food source. The TR RIWP must be revised to specifically address and respond to this comment. [12/1/06]

ENTRIX Response to comment: In the process of their field investigations the MSU research group has identified frogs as a key component of the great blue heron diet and has adequately sampled multiple frog species for inclusion in the food web investigation.

Frogs have not been included as receptors of concern in the ERA because frogs are relatively insensitive to dioxin-like compounds, likely due to low affinity of these compounds to the frog Ah-receptor (Lavine et al. 2005; Elskus 2005; Huang et al. 1998; Korfmacher et al. 1986; Beatty et al. 1976). Much less is known about the sensitivity of reptiles including snakes and turtles (Sparling et al. 2000). However, there are no studies indicating that they would be more sensitive than birds or mammals (see Hecker et al. 2006). The MDEQ response to comment regarding turtles raises issues of human health risk assessment that are not relevant to this BERA. The ERA work plan focuses resources on wildlife with the greatest potential risk and thus the most likely potential risk drivers in the evaluation of the Tittabawassee River and floodplain. Given our current knowledge of the site, this is most likely piscivorous wildlife rather than amphibians or reptiles.

Avian and mammalian piscivores were also selected as assessment endpoints in the previous Tittabawassee River Aquatic Ecological Risk Assessment provided by MDEQ and authored by Galbraith Environmental Sciences “because these endpoints represent protection of the ecological receptors that are likely to be most vulnerable to PCDDs and PCDFs within the assessment area, they are likely to be protective of the other, less vulnerable, exposed ecological resources.” In this prior study, risks to amphibians or reptiles were not considered.

(f) Failure to Propose Caged Mink Study

Public Comment: *In the 1960s, following the deaths and reproductive failures among ranch mink fed Great Lakes fish, Michigan State University biologist Richard Aulerich and Robert Ringer conducted a series of studies which found the mink were dying because they were highly sensitive to PCBs. Given the similarity of PCBs to dioxin/furan contamination in Tittabawassee River fish, it seems reasonable in any competent ecological study, to determine the effect of these fish on caged mink. Why is Dow proposing to dose the food given to the caged mink instead of feeding them fish from the Tittabawassee River?*

MDEQ Response to Comment: *The MDEQ concurs with this comment. Fish from the Tittabawassee River must be used to determine if adverse effects are occurring in*

mink. This can be done in conjunction with mink feeding studies that Dow is proposing to conduct to evaluate individual contaminants. The TR RIWP must be revised to specifically address and respond to this comment. [12/1/06]

ENTRIX Response to Comment: Discussions of a potential laboratory mink feeding study have included consideration of using Tittabawassee River dietary items as feed. If the decision is made to proceed with the study, the details will be established and consideration will be given to this concept. The collection of >20 mink directly from the Tittabawassee River gives insight to the exposure of and effects to mink that consumed diets of Tittabawassee River fish, small mammals, and other dietary items. Results from this study to date suggest that mink from the Tittabawassee River floodplain downstream of Dow are in good condition.

(g) Inadequate Bio-Uptake Research

***Public Comment:** The Michigan State University bio-uptake study appears to be nothing more than a pilot study. With only four sites downriver from Dow and two upriver, the number seems completely inadequate from a scientific perspective. How can one extrapolate from a mere six sites? Moreover, the sites themselves appear to have been selected more for convenience than any scientific protocol. Given the dynamic and varied ecology of the floodplain, a grid and random selection process should have been used, with hundreds of samples taken along random locations throughout the twenty-four mile floodplain.*

***MDEQ Response to Comment:** Please refer to the MDEQ's response to Trustees' Comment 5 in Attachment 2 of this NOD, which also addresses the above comments. Also, see the comments that were previously provided to Dow and its contractors addressing the design of ecological risk assessment. [12/1/06]*

ENTRIX Response to comment: In designing any sampling strategy, tradeoffs have to be made between number of sites and the number of samples analyzed per site. In this study, relationships between contaminant concentrations in soil and dietary items were determined through intensive sampling of fewer sites with a greater priority given to factors that are critical for long-term wildlife studies, including presence of habitat, co-location of food web items, ability to access locations, and potential for elevated concentrations of COPECs. Biological sampling is often more restricted in relation to sediment or soil sampling due to the effort required to collect biological samples and the inherent destructiveness in such sampling. There is nothing unusual about such a sampling approach, as it is widely used by agencies and researchers to provide input to bioaccumulation models. The six locations

where extensive food-web sampling has been conducted are not intended to characterize conditions on the entire floodplain, but rather to establish site-specific congener-specific trophic-level relationships that can then be applied to predict receptor exposure based on the extensive soil and sediment concentration measurements taken in the floodplain during the remedial investigation.

Another consideration is that although the lower trophic levels such as invertebrates and small mammals were taken from within the sampling plots, the higher trophic level receptors were taken opportunistically at many locations along the river. These higher trophic level receptors that are the focus of this ecological risk assessment (e.g. mink and great horned owl), effectively integrate exposure from their entire home range, allowing us to relate exposure to large areas of the floodplain.

Citations

- Beatty, P.W., Holischer, M.A., Neal, R.A. 1976. Toxicity of 2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin in Larval and Adult Forms of *Rana catesbeiana*. Bull. Envir. Cont. Toxic. 16, 578-581.
- Elkus, A. 2005. The Implications of Low-Affinity AhR for TCDD Insensitivity in Frogs. Toxicol. Sci. 88, 1-3.
- Hecker, M., Murphy, M.B., Giesy, J.P., Hopkins, W.A., 2006. Induction of Cytochrome P4501A in African Brown House Snake (*Lamprophis fuliginosus*) Primary Hepatocytes. Environ. Toxicol. Chem. 25, 496-502.
- Huang, Y-W, Melancon, M.J., Jung, R.E., Karasov, W.H., 1998. Induction of Cytochrome P450-Associated Monooxygenases In Northern Leopard Frogs, *Rana pipiens*, by 3,3', 4,4', 5-Pentachlorobiphenyl. Environ. Toxicol. Chem. 17, 1564-1569.
- Korfmacher, W.A., Hansen, Jr., E.B., Rowland, K.L., 1986. Tissue Distribution of 2,3,7,8-TCDD in Bullfrogs Obtained from a 2,3,7,8-TCDD-Contaminated Area. Chemosphere 15, 121-126.
- Lavine, J.A., Rowatt, A.J., Klimova, T., Whittington, A.J., Dengler, E., Beck, C., Powell, W.H. 2005. Aryl Hydrocarbon Receptors in the Frog *Xenopus laevis*: Two AhR1 Paralogs Exhibit Low Affinity for 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD). Toxicol. Sci. 88, 60-72.
- Sparling, D.W. Linder, G., Bishop, C.A. editors. 2000. Exotoxicology of Amphibians and Reptiles. Pensacola, FL: Society of Environmental Toxicology and Chemistry. 904p.
- Walker, M.K., Spitsbergen, J.M., Olson, J.R., Peterson, R.E. 1991. 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) Toxicity during Early Life Stage Development of Lake Trout, (*Salvelinus namaycush*). Can. J. Fish Aquat. Sci. 48, 875-883.
- West, C.W., Ankley, G.T., Nichols, J.W., Elonen, G.E., Nessa, D.E., 1997. Toxicity and Bioaccumulation of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin in Long-Term Tests with the Freshwater Benthic Invertebrates *Chironomus tentans* and *Lumbriculus variegatus*. Environ. Toxicol. Chem. 16, 1287-1294.