The Dow Chemical Company
Midland, MI 48674

October 15, 2007

George Bruchmann, Chief
Waste and Hazardous Materials Division
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Constitution Hall
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Subject: Submittal of Direct Contact Criteria Report for Midland Soils

The Dow Chemical Company (Dow) is submitting the Midland Soils Direct Contact Report as required under the license.

Please let Dow know if you have any questions regarding the information contained in this report.

"I certify under penalty of law that this document and all attachments were prepared under my direction or supervision according to a system designed to assure that qualified personnel properly gather and evaluate the information submitted. Based on my inquiry of the person or persons who manage the system, or those persons directly responsible for gathering the information, the information submitted is, to the best of my knowledge and belief, true, accurate, and complete. I am aware that there are significant penalties for submitting false information, including the possibility of fine and imprisonment for knowing violations."

Sincerely,

Ben Baker
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Enclosure(s)

Direct Contact Criteria Report

Midland Area Soils
Midland, Michigan

Submitted by:

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Date: October 15, 2007

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Executive Summary

As required by the Michigan Department of Environmental Quality ("MDEQ"), the purpose of this Report is to investigate and discuss the calculation of a site-specific residential soil direct contact criterion ("DCC") for 2,3,7,8-tetrachlorodibenzo-p-dioxin ("TCDD") for soil in the City of Midland, Michigan. This Report considers and includes a discussion of the impact of both cancer and non-cancer risk calculations. While it is anticipated that many aspects of this Report may have applicability beyond Midland, additional analysis would need to take into account new studies or advances improving the understanding of the toxicity of dioxin and dioxin like compounds as well as site specific information related to the potential for exposure. Finally, although this Report discusses numeric cleanup criteria, this Report should not be read to preclude the future development and use of non-numeric criteria, remedies and risk management strategies designed to address the potential for exposure to contaminated media.

According to Michigan law, all cleanup criteria, including site-specific criteria, must be based on the "best available information," including the "most scientifically credible and relevant data available." Determining what constitutes the "best available information" or the best scientific approach to take, however, is not always straightforward when applied in the context of the regulatory process related to the development of cleanup criteria. There are often various theories, studies, data, or methods that can be considered in the process of developing criteria; each with their own strengths and weaknesses. The goal of this Report, then, is not to propose and defend *one* definitive site-specific DCC, but, instead, to make a good faith investigation, and present a detailed discussion, of a broad range of possible criteria, based on the most scientifically credible and best information currently available. This Report and the analysis herein can serve as the basis for future discussions between Dow and the MDEQ, before particular issues and points related to dioxin risk assessment relevant to the development of site specific criteria are posed to an Independent Science Advisory Panel ("ISAP").

Dioxin risk assessment in the regulatory arena is complicated by the fact that the U.S. Environmental Protection Agency ("U.S. EPA") has not completed its assessment of the risk posed by dioxin and dioxin like compounds (EPA's "Reassessment"). Most recently, U. S. EPA

has not yet responded to the July, 2006, comments from the National Academy of Sciences ("NAS") on EPA's latest draft of its dioxin Reassessment.

The MDEQ's currently-promulgated DCC for TCDD is 0.09 parts per billion ("ppb") (or 90 parts per trillion ("ppt")). (In contrast, the U.S. EPA currently uses the significantly higher value of 1 ppb as its recommended cleanup level for TCDD in residential soils). MDEQ calculated its TCDD DCC of 90 ppt in 1995. It later proposed as regulatory criteria of 150 ppt, but then adopted in 2002, without the opportunity for public comment, the current 90 ppt, and did so without following the normal rules for the promulgation of criterion (instead MDEQ noted at the time that the criterion was not updated per the usual process, given that national efforts to reassess dioxin risks (i.e. EPA's Reassessment) were not yet complete). Since that time, MDEQ has updated some of the default values used in the direct contact criterion calculation. These up-to-date values are discussed and reflected in this Report (including previously agreed to changes to the "dermal absorption efficiency factor" ("AEd") and the "age adjusted dermal factor" ("DF")). Further, MDEQ's current DCC for TCDD is a "generic" criteria based on generic assumptions meant to be applicable state-wide. This Report incorporates "site-specific" information from studies conducted in Midland in order to better reflect actual site-specific conditions (including adjustments to the "ingestion absorption efficiency factor" ("AEi") based on Dow's site-specific bioavailability studies).

There have also been significant advances in the scientific community's general understanding of dioxin and dioxin-like compounds since 1995. In 2006, the National Toxicology Program ("NTP") completed its dioxin toxicity and carcinogenesis study on female rats, which is generally recognized as the current state-of-the-art study. The NTP study provides the most extensive information of its kind to date and is discussed and relied upon throughout this Report.

The NAS made a number of important recommendations to U.S. EPA in the NAS's critical evaluation of U.S. EPA's Reassessment, which have been incorporated into this Report. In particular, the NAS recommended, among other things, that scientists should assess TCDD cancer risks using a nonlinear (threshold) model, and that risks posed by TCDD would be better characterized using probabilistic methods of calculation. Regarding the first recommendation,

nonlinear models, unlike linear models, take into account the fact that there may be a minimum dose or level of exposure for some chemicals below which no adverse impacts occur (e.g., no tumor forms). There is strong scientific evidence that TCDD is such a chemical. Regarding the latter recommendation, probabilistic methods of calculation use ranges of values for each variable to better reflect the range of variability and uncertainty of the real world (e.g., people weigh different amounts at different ages) – in contrast to traditional "deterministic" calculations that choose one value to approximate the range (e.g., adults weigh, on average, 70 kilograms). Accordingly, this Report calculates a non-linear DCC for TCDD (in contrast to the linear approach used by the MDEQ), and has calculated all of the variables used in the applicable algorithms both deterministically *and* probabilistically.

A number of other recent studies have been reviewed and relied upon in this Report and are discussed at length. Perhaps most significantly, the University of Michigan recently issued its initial report summarizing the findings of its human exposure and biomonitoring study specifically designed to gauge exposure to dioxin in the Midland area through a number of potential exposure pathways, including contact with soil. Unlike MDEQ's current DCC and the calculations in this Report, which attempt to predict blood dioxin levels associated with certain levels of dioxin in soil, the University of Michigan actually measured blood dioxin levels of local residents. This "top-down" approach to assessing dioxin exposures is a valuable and seldom available complement to the "bottom-up" approach of a traditional exposure analysis, and serves as an important check on any calculation. Overall, the University's study results show that the current algorithm defaults used to predict exposure significantly overstate the risk of exposure.

Taking into consideration the above, this Report includes both deterministic and probabilistic calculations for the following potential risks: cancer (linear calculation), cancer (nonlinear calculation), and non-cancer (nonlinear calculation). Depending on what variables are selected for adjustment in each equation, numerous results are possible. For the sake of transparency, step-by-step calculations and results for all deterministic calculations are shown on the spreadsheets attached as **Appendix A** and additional probabilistic results are discussed later in this Report. The full range of alternative deterministic soil criteria developed for this Report are provided in the attached spreadsheets, the following table highlights some results (all values expressed to two significant figures):

TCDD Residential Direct Contact Criterion	**MDEQ**	**U.S. EPA**	**This Report, based on the best available information**					
	Cancer (linear)		Cancer (linear), adjusting only SF, AEi, AEd, and DF	Cancer (linear), adjusting SF, averaging time, EFi, IF, AEi, AEd, and DF	Cancer (linear)	Cancer (nonlinear)		Non-Cancer
Deterministic Calculation	0.090 ppb	1.0 ppb*	0.89 ppb	2.3 ppb	19 ppb	250 ppb		15 ppb
Probabilistic Calculation Range (1 % - 99%)	NA	NA	NA	NA	27 – 11,000 ppb	150 – 200,000 ppb		19 – 14,000 ppb

* EPA has used 1 ppb; it is unclear how this number was calculated.

1. Introduction

As required by the Michigan Department of Environmental Quality ("MDEQ"), the purpose of this Report is to investigate and discuss the calculation of a site-specific residential soil direct contact criterion ("DCC") for 2,3,7,8-tetrachlorodibenzo-p-dioxin ("TCDD"). Both cancer and non-cancer risks are discussed and assessed. This Report is in furtherance of section XI.B.3 of The Dow Chemical Company's Part 111 Hazardous Waste Management Facility Operating License ("License"), which, consistent with Michigan law, authorizes Dow to propose site-specific cleanup criteria for purposes of implementing the ongoing corrective action effort. This Report is part of the broader Human Health Risk Assessment being conducted for the Midland Area Soils under the proposed Midland Area Soils Remedial Investigation Work Plan.

Michigan law requires that all cleanup criteria be calculated based on the "best available information." The Michigan Department of Environmental Quality ("MDEQ") promulgated the current criterion in 2002 (but noted, in "footnote O" of the Part 201 rules, that the criterion was not updated per the usual process, given that national efforts to reassess dioxin risks were not yet complete). Since that time, MDEQ has updated some of the default values used in the direct contact criterion calculation. These changes are reflected in this Report. There have also been significant advances in the scientific community's understanding of dioxin and dioxin-like compounds in the past few years, both generally and in the Midland area. In 2006, the National Toxicology Program completed its dioxin toxicity and carcinogenesis study on female rats, which is generally recognized as the most thorough study of its kind to date, and the National Academy of Sciences completed its critical evaluation of the U.S. Environmental Protection Agency's own dioxin reassessment efforts. Also in 2006, the University of Michigan issued its initial report summarizing the findings of its human exposure and biomonitoring study designed to gauge exposure to dioxin in the Midland area through a number of potential exposure pathways, including contact with soil.

This Report incorporates the scientific advances and recommendations made in these and other third party studies, as well as studies conducted by The Dow Chemical Company ("Dow") specific to conditions in and around Midland.

This Report attempts to be as comprehensive as possible given the limited time provided. However, Dow may submit supplements to this Report as its assessment continues. Further, for the sake of brevity, some details and analysis upon which the calculations have been based have been left out of this Report. Dow is willing and prepared to provide additional detail and discuss the additional detail and analysis as would be useful to MDEQ. In this regard, Dow invites questions from the MDEQ and looks forward to meetings with the MDEQ to discuss the calculations in more detail and to prepare the charge questions for the ISAP.

2. Background

2.1 Legal

2.1.1 Applicable Michigan Law and License Provisions

Dow's License was issued under Michigan's hazardous waste management law, known as "Part 111" of Michigan's Natural Resources and Environmental Protection Act ("NREPA" aka "Act 451"). Like its federal counterpart, the Resource Conservation and Recovery Act ("RCRA"), Part 111 contains comparatively few legal requirements to guide corrective action activities. Therefore, the MDEQ and the U.S. EPA have agreed that, in Michigan, at least some of the processes and cleanup criteria promulgated pursuant to Michigan's environmental remediation law, known as "Part 201" of NREPA, may be used to meet Part 111 corrective action requirements:

> Region V . . . has determined that the MDEQ's use of Part 201 clean-up standards and related processes . . . are an acceptable way of achieving the objectives of the authorized Part 111 [corrective action] program.

Memorandum of Understanding between U.S. EPA and MDEQ (November 2000).

Under Part 201, cleanup criteria are either calculated using generic assumptions for use state-wide ("generic" criteria) or are calculated for a specific site ("site-specific" criteria). *See e.g.*,

M.C.L.A. § 324.20120a(1) and (2).[1] Because generic criteria rely on generic assumptions, such criteria may not accurately reflect conditions at a particular site or the best available information, and may be an overly conservative assessment of risk. In such a case, site-specific criteria based on actual site conditions and up-to-date science may be more appropriate.

Accordingly, Dow's License looks to the cleanup processes and cleanup criteria promulgated pursuant to Part 201, including the potential use of site-specific criteria developed using probabilistic risk assessment ("PRA") methods:

> The licensee has the option to propose steps to develop site-specific cleanup criteria, including proposed use of probabilistic risk assessment methods. Site-specific criteria may be developed as allowed pursuant to Part 111 of Act 451, which adopts environmental protection standards developed under Part 201 of Act 451 and the associated administrative rules, provided they are not less stringent than allowed pursuant to the provisions of RCRA. The licensee may include a description of the proposed steps to develop site-specific criteria in the SOW. A prerequisite to MDEQ approval of site-specific criteria would be implementation of associated requirements of Part 201 of Act 451 and the applicable administrative rules.

License Part XI.B.3(b)(iv). The approved Scope of Work for the Midland Area Soils Remedial Investigation ("SOW") similarly allows Dow to perform a probabilistic risk assessment and generate site-specific criteria as part of the human health risk assessment, and, in this regard, refers to collaborative PRA working sessions with MDEQ to assist in the process. The Framework for an Agreement between the State of Michigan and the Dow Chemical Company (January 2005) ("Framework Agreement") also contemplates the development and use of site-specific cleanup criteria, again using PRA methods, in the section entitled "Best Available Data and Science."[2]

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[1] In a June 25, 2007 letter to U.S. EPA, Mr. Bruchmann of the MDEQ correctly noted that "under state law, the MDEQ is obligated to allow Dow the prerogative to pursue the site-specific approach."

[2] "DEQ will assist in and consider on the merits the results of the ongoing bioavailability study in developing potential area wide and site-specific cleanup criteria for dioxins. If Dow demonstrates that the use of probabilistic risk assessment improves the analysis and characterization of variability and uncertainties regarding exposure and risks, DEQ will consider the results of Dow's proposed use of probabilistic risk assessment in developing potential area wide and site-specific cleanup criteria for dioxins in accordance with applicable law. These activities will proceed pursuant to an agreed-upon schedule." Framework Agreement Section III.B.4

2.1.2 Best Available Information

According to the Part 201 rules, all cleanup criteria, including site-specific criteria, must be based on the "best available information." Mich. Admin. Code R. 299.5706(1). "Best available information" means the "most scientifically credible and relevant data available about a particular hazardous substance," including "the peer reviewed scientific literature" and "information sources recognized by the risk assessment community . . . ." Mich. Admin. Code R. 299.5701(c). The primary goal of this Report is to propose site-specific residential direct contact criteria for Midland Study Area soils that accurately reflect site-specific conditions in Midland and that take into account the "best available information," including recent advances in the understanding of dioxin.

2.1.3 Applicable Algorithms and Variables

Current and future residents[3] in Midland may be exposed to dioxins and furans through incidental contact with soil on their property. This pathway includes incidental ingestion of soil as well as dermal contact with soil.

Under Part 201, both generic and site-specific cleanup criteria are calculated through the use of a series of algorithms provided in the Part 201 rules. For site-specific criteria, most of the algorithm variables may be changed as "appropriate" to the calculation. *See generally* Mich. Admin. Code R. 299.5706a(9). Therefore, the rules provide for significant flexibility to calculate criteria appropriate to the site based on the best available information. Not all variables need be site-specific, however; a mix of site-specific and default values may be used. This is consistent with U.S. EPA risk assessment policy, which recognizes the added value of appropriate site-specific data:

> Due to the uniqueness of individual waste sites, site-specific information plays an important role in risk assessments and management decisions on a regional level. In general, EPA considers site- and chemical-specific information in risk

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[3] Exposure risks for industrial and commercial workers are typically less. Such exposures and the corollary commercial and industrial site-specific criteria will be discussed in a future report.

assessments when it is available and appropriate, then uses default assumptions when data gaps exist.

Risk Assessment Principles & Practices, U.S. EPA, Office of the Science Advisor, EPA/100/B-04/001, p. 99 (EPA, 2004).

Rule 720 sets forth the algorithms for both cancer and non-cancer residential soil direct contact criteria, and provides certain generic default values, as shown below. Part 201 sets the cancer target risk level ("TRL") at 1 additional cancer above the background cancer rate per 100,000 individuals (10^{-5}); and the non-cancer hazard quotient at 1.[4] M.C.L.A. § 324.20120a(4). (These target risk values are not subject to change without a statutory amendment).

FOR CARCINOGENS:[5]

$$DCC = \frac{TR \times AT \times CF}{SF \times [(EF_i \times IF \times AE_i) + (EF_d \times DF \times AE_d)]}$$

			Default
DCC	(Direct contact criterion)	=	chemical-specific, µg/kg or ppb
TR	(Target risk level)	=	10^{-5}
AT	(Averaging time)	=	25,550 days (70 years x 365 Days/year)
CF	(Conversion factor)	=	1E+9 µg/kg
SF	(Oral cancer slope factor)	=	chemical-specific $(mg/kg\text{-}day)^{-1}$
EF_i	(Ingestion exposure frequency)	=	350 days/year
IF	(Age-adjusted soil ingestion factor)	=	114 mg-year/kg-day
AE_i	(ingestion absorption efficiency)	=	chemical-specific or default specified at R 299.5720(3)
EF_d	(Dermal exposure frequency)	=	245 days/year
DF	(Age-adjusted soil dermal factor)	=	353 mg-year/kg-day
AE_d	(Dermal absorption efficiency)	=	chemical-specific or default specified at R 299.5720(3)

[4] The target hazard quotient is the ratio of the chronic daily dose of a hazardous substance (reasonable maximum exposure) divided by the chronic reference dose for that substance; or, put another way, the ratio of the assumed exposure level and the reference or safe dose. *See* MDEQ RRD, *Operational Memorandum No. 1, Technical Support Document – Attachment 6,* p. 2 (April 2005); MDEQ RRD, *Operational Memorandum No. 1, Technical Support Document – Attachment 3,* p. 4 (December 10, 2004).

[5] It should be pointed out that although labeled as "For Carcinogens," this equation applies equally to any endpoint for which a threshold cannot be identified. Like wise, the equation labeled "For Non-Carcinogens" applies as well to any compound for which a threshold can be identified or reasonably assumed based on the weight of evidence. This would include some carcinogens, which might cause an increase in cancer through a threshold mechanism.

FOR NON-CARCINOGENS:

$$DCC = \frac{THQ \times RfD \times AT \times CF \times RSC}{[(EF_i \times IF \times AE_i) + (EF_d \times DF \times AE_d)]}$$

THQ	(Target hazard quotient)	=	1
RfD	(Oral reference dose)	=	chemical-specific mg/kg/day
AT	(Averaging time)	=	10,950 days (30 years x 365 days/year)
CF	(Conversion factor)	=	1E+9 μg/kg
RSC	(Relative source contribution)	=	1
EF_i	(Ingestion exposure frequency)	=	350 days/year
IF	(Age-adjusted soil ingestion factor)	=	114 mg-year/kg-day
AE_i	(Ingestion absorption efficiency)	=	chemical-specific or R. 299.5720(3) default
EF_d	(Dermal absorption frequency)	=	245 days/year
DF	(Age-adjusted soil dermal factor)	=	353 mg-year/kg-day
AE_d	(Dermal absorption efficiency)	=	chemical-specific or R. 299.5720(3) default

Mich. Admin. Code R. 299.5720(1).

The Midland Soils Study Area is impacted primarily by polychlorinated dibenzo-p-dioxins and to a lesser extent by dioxin-like polychlorinated dibenzo-p-furans ("PCCD/Fs"). Michigan law requires that all such compounds "be considered as 1 hazardous substance, expressed as an equivalent concentration of [TCDD], based upon the relative potency and concentration of the congeners present at the facility." Mich. Admin. Code R. 299.5734(1). Accordingly, this Report focuses on developing direct contact criteria for TCDD expressed as a toxic equivalent concentration or "TEQ." For now, other dioxins and furans substituted with chlorine at the 2,3,7 and 8 positions will be assessed, as required, by comparison to the TCDD criterion by applying toxic equivalency factor ("TEFs") to derive a TEQ.

TCDD-specific values for some algorithm variables are listed in Rule 752 Table 4:

Oral Reference Dose (RfD)	Oral Slope Factor (SF)	Initial Threshold Screening Level (ITSL)	Inhalation Unit Risk Factor (IURF)	Occupational Short Term Exposure Level (STEL)	Relative Source Contribution For Drinking Water (RSC)	Ingestion Absorp-tion Efficiency (AEI)	Dermal Absorp-tion Efficiency (AEd)	Relative Source Contri-bution For Soil (RSC)	Log Octanol-Water Partition Co-efficient (Log Kow)
mg/kg-day	(mg/kg-day)	ug/m^3	$(ug/m^3)^{-1}$	ug/m^3	unitless	unitless	unitless	unitless	
NA	NA	NA	NA	NA	0.2	0.5	0.03	0.2	7.04

Soil Organic Carbon-Water Partition Coeffi-cients (Koc)	Soil Koc For Ionizing Organic Com-pounds	Soil-Water Distribu-tion Coeffi-cients	Henry's Law Constant At 25°C (HLC)	Air Diffu-sivity (D, or D_a or D^{air})	Water Diffusiv-ity (D_w)	Lower Explosive Limit in Air (LEL)	Flash Point (FP)	Water Solubility (S)	Physi-cal State Identi-fier	Molecular Weight (MW)
L/kg	L/kg	L/kg	atm-m^3/mol.	cm^2/s	cm^2/s	unitless	^{0}F	ug/L		g/mol
8.33E+6	NR	NR	9.20E-6	0.047	8.0E-6	NA	NA	0.019	Solid	322

Generally, site-specific criteria "shall use the toxicological and chemical-physical data in table 4 of R 299.5752 . . . ." Mich. Admin. Code R. 299.5706a(9). However, for TCDD, several of the variables, including the oral slope factor ("SF") and the reference dose ("RfD"), are listed as "NA" (not available). Therefore, there are no restrictions as to any particular value for these variables, but instead, values based on the "best available information" may be proposed.

The rules also expressly provide that the following Table 4 parameters may be changed if different data would be "more appropriate" for a "specific facility":

i) relative source contribution for drinking water,
ii) ingestion absorption efficiency,
iii) dermal absorption efficiency,
iv) relative source contribution for soil,
v) soil k_{oc} for ionizing organic compounds, and
vi) soil-water distribution coefficients for inorganic compounds.

Mich. Admin. Code R. 299.5706a(9)(a). Finally, Table 4 only covers the toxicological and chemical-physical portion of the algorithm inputs. With the exception of the TRL and hazard quotient, which are set by statute, the other variables in the algorithms are subject to adjustment: "site-specific assumptions may be substituted for the default assumptions specified in . . . R 299.5720 . . . if appropriate." Mich. Admin. Code R. 299.5706a(9). Therefore, the Part 201 rules provide for significant flexibility to adjust the algorithm inputs in order to calculate site-specific criteria based on the "best available information" and site-specific conditions.

Section 3 of this Report lists and discusses the variables that are proposed for adjustment in order to calculate site-specific criteria for the Midland Study Area using the Part 201 algorithms.

2.1.4 Current Michigan Generic Residential Soil Direct Contact Criterion.

The currently promulgated generic residential soil direct contact criterion for TCDD in Michigan is 90 parts per trillion (ppt) (or 0.09 parts per billion (ppb)) based on cancer risk. Mich. Admin. Code R. 299.5746 Table 2. This Report incorporates new scientific findings unavailable when the MDEQ calculated this criterion, including the ongoing evaluation of the toxicity of dioxin and dioxin like compounds, updates to MDEQ exposure variables, and site-specific information on exposure.

Typically, when MDEQ promulgates new cleanup criteria into law, it calculates the criteria using the algorithms set forth in administrative rules 714 to 726 (including rule 720, discussed above) and the toxicological and chemical/physical data found in rule 752 Table 4 at the time. However, according to Rule 750 "footnote O" of Table 2, the generic criteria for 2,3,7,8-TCDD:

> are not calculated according to the algorithms presented in R [714] to [726]. The generic cleanup criteria are being held at the values that the department has used since August 1998,[6] in recognition of the fact that national efforts to reassess risks posed by dioxin are not yet complete. Until these studies are complete, it is premature to select a revised slope factor and/or reference dose for calculation of generic cleanup criteria.[7]

Mich. Admin. Code R. 299.5750(1)(O). *See also* Mich. Admin. Code R. 299.5706a(7) ("except as provided in . . . [footnote O] the toxicological and physical-chemical input values used by the department . . . are shown in table 4 of R. 299.5752"). In short, MDEQ singled out TCDD for special treatment, inconsistent with the normal process. In so doing, the 0.09 ppb criterion was not updated when the TCDD criteria were promulgated in December of 2002, but instead was

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[6] It is Dow's understanding that the current generic direct contact cleanup criteria were first developed in 1995. *See Michigan Department of Environmental Quality, Dioxin Contamination in the Midland Area,* pp. 1 – 2 (July 2, 2004).

[7] Footnote O expressly only applies to MDEQ's "calculation of *generic* cleanup criteria" (emphasis added), and therefore does not restrict the development of *site-specific* criteria.

held at its 1995 value that was just guidance and not a regulatory criterion. Footnote O and the 90 ppt criterion were also not included in any Part 201 rules package made available to the public before promulgation. Therefore, Dow and the public never had an opportunity to review MDEQ's calculations or comment on the 0.09 ppb criterion before it was adopted as a rule. Dow's attorneys explained in detail the problems with the 0.09 ppb criteria, both in terms of compliance with Michigan law as well as the major technical problems, by letter dated June 4, 2004, to Steve Chester from Margaret Coughlin of Dickinson Wright, a copy of which is attached. The legal deficiencies of MDEQ's promulgation of the 0.09 ppb standard after the close of the public comment period were confirmed by the June 2, 2004, deposition testimony of Andrew Hogarth.

Although footnote O states that the 0.09 ppb criterion was not calculated according to the Rule 720 algorithm, it appears that the MDEQ's 1995 calculation did use the same algorithm as set forth in Rule 720, along with the following values:

EQUATION FOR CARCINOGENS:

$$DCC = \frac{TR \times AT \times CF}{SF \times [(EF_i \times IF \times AE_i) + (EF_d \times DF \times AE_d)]}$$

			Default	Value used
DCC	(Direct contact criterion)	=	chemical-specific, µg/kg or ppb	
TR	(Target risk level)	=	10^{-5}	10^{-5}
AT	(Averaging time)	=	25,550 days (70 years x 365 Days/year)	25,550 days
CF	(Conversion factor)	=	1E+9 ug/kg	1E+9 µg/kg
SF	(Oral cancer slope factor)	=	chemical-specific $(mg/kg\text{-}day)^{-1}$	75,000 $(mg/kg\text{-}day)^{-1}$
EF_i	(Ingestion exposure frequency)	=	350 days/year	350 days/year
IF	(Age-adjusted soil ingestion factor)	=	114 mg-year/kg-day	114 mg-year/kg-day*
AE_i	(ingestion absorption efficiency)	=	chemical-specific or default specified at R 299.5720(3)	50%
EF_d	(Dermal exposure frequency)	=	245 days/year	245 days/year
DF	(Age-adjusted soil dermal factor)	=	353 mg-year/kg-day	2442 mg-yr/kg-day
AE_d	(Dermal absorption efficiency)	=	chemical-specific or default specified at R 299.5720(3)	3%

A number of these values do not reflect the best available information or current science. The age-adjusted dermal-absorbed-dose or "**dermal factor**" ("DF") of **2442 mg-yr/kg-day** of soil used by MDEQ was the default value prior to the rules being promulgated in 2002. *See MDEQ Interim Environmental Response Division Operational Memorandum No. 8, Revision 4* (June 5,

1995). Since that time, MDEQ has adopted and promulgated an updated DF of **353 mg-yr/kg-day**, which it has subsequently used for the calculation of all other direct contact criteria. The change is due to MDEQ's adoption of lower soil adherence factors ("AFs") for the DF calculation, from an AF of 1.0 mg/cm^2 for both adults and children to new values of 0.2 mg/cm^2 for children and 0.07mg/cm^2 for adults, a lower dermal absorption efficiency factor, and increases in exposed skin surface area for adults and children. *See* Table 2-1. *See also MDEQ RRD Operational Memo. No. 1* (April 2005). MDEQ has agreed that the new DF default value may be used for site-specific calculations.

The **dermal absorption efficiency factor** (AEd) represents the fraction of the contaminant that is assumed to penetrate the skin after contact. For this variable, MDEQ used **3%** (0.03) in its 1995 calculation. However, MDEQ has advised Dow that MDEQ intends to revise the AEd for dioxin from its current value (3%) to a new value of 1.75% (0.0175), reflecting a central tendency value and the best information currently available. Specifically, MDEQ's recommended value represents the approximate midpoint of two values (0.95% and 2.5%) from an EPA study of dermal absorption in rats cited in EPA's *Dermal Absorption Assessment* guidance (EPA, 1992). MDEQ has agreed that the new value (**1.75%**) may be used for purposes of calculating site-specific criteria.[8]

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[8] Although for purposes of this Report Dow has adopted these new default values, it should be understood that it is Dow's position that these new defaults still overstate the exposure potential and additional evaluation would likely result in development of more realistic values. For instance, U.S. EPA's Reassessment and its *Dermal Exposure Assessment* (U.S. EPA, 1992) cite additional studies of dermal absorption of TCDD across rat skin. Poiger and Schlatter (1980) concluded that approximately 2 percent of the administered dose of TCDD in a soil/water paste was found in the liver of the rats. Shu *et al*. (1988) found that after 24 hours of contact with rat skin, the degree of dermal uptake from contaminated soil was approximately 1 percent of the administered dose. A limitation of these studies is the extrapolation of experimental results in the rat to absorption across human skin. Rodent skin is about ten times more permeable than human skin, and the duration of exposure in these experiments is typically longer than the exposure duration in human exposure scenarios. U.S. EPA also notes in its Reassessment that *in vitro* permeation of TCDD across human skin was significantly lower than in mouse skin, and also cites one study of 1,2,3,7,8-PeCDF in monkeys that concluded that less than one percent of the administered dose was absorbed after six hours. A distribution for dermal absorption efficiency could be developed based on the studies cited above and on any further studies of dioxin and furan absorption from soil identified in the literature.

Likewise, soil adherence is also best described as a range of values. It depends on the area of skin exposed, the type of activity engaged in, and the soil characteristics. The derivation of a representative range of adherence factors for use in developing the Midland direct contact criteria could be done using raw data obtained from researchers who have evaluated this aspect of exposure. Prof. John Kissel's web site (http://depts.washington.edu/jkspage/index.html) has this data available for use by other parties and would form the basis for any additional analysis undertaken.

Table 2-1 Changes to direct contact criteria variables for TCDD

Variable	Variable name	Variable units	Previous value	New value
DF	**dermal factor**	**mg-yr/kg-day**	**2442**	**353**
SA_{child}	child surface area	cm^2/d	1820	2670
SA_{adult}	adult surface area	cm^2/d	5000	5800
$A_{F\text{-}child}$	child soil adherence factor	mg/cm^2	1.0	0.2
$A_{F\text{-}adult}$	adult soil adherence factor	mg/cm^2	1.0	0.07
A_d	**dermal absorption efficiency**	—	**0.03**	**0.0175**

There have also been a number of other scientific advances since 1995, including the completion of the National Toxicology Program's dioxin toxicity and carcinogenesis study on female rats, which is generally recognized as the most thorough study of its kind to date, and the National Academy of Sciences' evaluation of the U.S. EPA's own dioxin reassessment efforts. See section 2.3. In particular, these advances, and others, support adjustments to the oral cancer slope factor previously used by MDEQ (75,000 $(mg/kg\text{-}day)^{-1}$), as discussed more fully in section 3.

Exposed skin surface area will also vary with temperature and behavior (or age) and is likely lower in cooler months than warmer months and these variations could be better accounted for by a range as opposed to a single value. For instance, the fraction of skin surface area exposed may be hands only at 45°F, increasing linearly to hands, lower legs, forearms, and face for adults and children at 70°F+ in residential and recreational scenarios, where the temperature is based on the maximum daily temperature. Surface area fractions corresponding to particular body parts could be taken from the Exposure Factors Handbook (U.S. EPA, 1997a), and weather records obtained for MBS International Airport (WBAN 726379 14845). 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. To obtain surface area estimates for any revision to this default, the age variation of height from the NHANES 2003-2004 examination could be used, along with the covariance of weight and height obtained from these U.S. population data. The distributions of weights and heights at any age are indistinguishable from lognormal based on a preliminary analysis of the NHANES data (Burmaster, 1998; Burmaster and Crouch, 1997a). Median weights and heights, and the standard deviations of their logarithms, would 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 acts as a surrogate for body surface area using standard correlations between surface area, body weight, and height (Burmaster, 1998; U.S. EPA, 1997a).

The approach taken to exposed fractions of various body parts is similar to that used in the U.S. 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 could be augmented by other relevant data. The methodology to be adopted for estimation of average soil adherence is one recommended in U.S. EPA (1997a). Measured values for soil accumulation on all the appendages are summed.

2.1.5 Current U.S. EPA Cleanup Levels for TCDD

In comparison to Michigan's current value of 0.09 ppb, the U.S. EPA uses a significantly higher level of 1 ppb (1000 ppt) as its recommended cleanup level for residential soils, and a range of 5 ppb to 20 ppb (5000 ppt to 20,000 ppt) for commercial/industrial sites (where exposures are expected to be less). U.S. EPA, *Approach for Addressing Dioxin in Soil at CERCLA and RCRA Sites*, OSWER Directive 9200.4-26, (April 13, 1998). These defaults have been used at a number of sites in the United States. *See e.g.,* Rockwell International, Michigan (2002 Record of Decision ("ROD")); Selma Treating Company, California (2003 ROD); Brunswick Wood Preserving, Georgia (2002 ROD); Centredale Manor Restoration Project, Rhode Island (2005 Interim Final Baseline Human Health Risk Assessment).

2.2 Agreement between Dow and MDEQ

On December 20, 2006, Dow met with MDEQ and other State representatives to discuss some of the legal issues related to Dow's development and use of site-specific cleanup criteria.[9] The meeting resulted in agreement on a number of issues:

- Dow and the State agreed that the "best available information" should be used whenever possible to develop site-specific cleanup criteria.

- Both parties agreed that the regulations clearly allow changes to site-specific exposure assumptions and certain chemical-physical properties, as set forth in Rule 706a(9) and (9)(a), if such changes are based on site-specific circumstances or information peculiar to the site. For example, the parties agreed that Dow's site-specific bioavailability studies could form the basis of changes to the Ingestion Absorption Efficiency (AE_i) variable.[10]

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[9] *See* Letter from Mr. Peter C. Wright, The Dow Chemical Company to Ms. Kathleen L. Cavanaugh, Assistant Attorney General, State of Michigan, and Ms. Lynelle Marolf, MDEQ (February 1, 2007). This letter was reviewed and approved by the State.

[10] It is Dow's understanding that MDEQ is still assessing its position on whether "site-specific" criterion may only be based on information that is truly unique to the site (i.e., *not* of general, national, or worldwide

- The State noted that it intends to revise the default dermal absorption efficiency factor (AE_d) for dioxin from the current value of 3% to a new value of 1.75%, reflecting the best available information for dioxin. The parties agreed that Dow could begin relying on this updated value now, in contemplation of the upcoming change.

- The parties agreed that Dow may use the currently-promulgated age adjusted dermal factor (DF) of 353 mg-yr/kg-day when calculating site-specific criteria, in place of the prior value of 2442 mg-yr/kg-day.

At the December 20 meeting, Dow and the State were not able to agree on whether a rule change would be needed to adjust the cancer slope factor previously used by MDEQ (75,000 (mg/kg-day) $^{-1}$). Because the cancer slope factor for dioxin is currently listed as "NA" or "not available" in the administrative rules (the SF of 75,000 (mg/kg-day) $^{-1}$ does not appear anywhere in the rules), a new cancer slope factor may be calculated and used, based on the best available information. It is also the case that "footnote O," which, by its terms only applies to "generic criteria," does not limit or restrict the development of appropriate site-specific criteria. Although this issue has not yet been fully resolved, both Dow and the State agreed that if the parties arrive at a new and different cancer slope factor as the "best available information," the legal situation will be reassessed and appropriate action taken, including, if deemed necessary by the State, a rule amendment.

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applicability). It is Dow's position that it should be able to use *any* improvements or developments in information or science to make site-specific adjustments, even if the information or science might apply to other sites as well. This interpretation appears to be the most consistent with the overarching requirement of Part 201 to use the "best available information."

2.3 Recent Scientific Developments

2.3.1 National Academy of Sciences

In December of 2003, U.S. EPA released its most recent draft reassessment of dioxin risks, entitled *Exposure and Human Health Reassessment of 2,3,7,8-Tetrachlorodibenzo-p-Dioxin (TCDD) and Related Compounds* (EPA, 2003) (aka the "Reassessment"). In the summer of 2004, EPA asked the National Research Council of the National Academies of Science ("NAS") to create an expert committee to review the draft Reassessment. The committee, composed of eighteen national and international scientists from academia and government, conducted an exhaustive review of EPA's Reassessment and published its report in 2006, entitled *Health Risks from Dioxin and Related Compounds, Evaluation of the EPA Reassessment* (NAS, 2006). The NAS committee was critical of a number of aspects of the Reassessment, and made several specific findings and recommendations, including: a) EPA should assess cancer risks and develop the cancer slope using nonlinear (threshold) models, incorporating, in particular, the findings of the National Toxicology Program's new animal bioassay data (see below), b) EPA should use probabilistic methods to better characterize uncertainty and variability, and c) the committee urged the EPA to complete the derivation of toxicity values. It is uncertain when U.S. EPA will act on the committee's findings on the Reassessment. Thus, in the absence of U.S. EPA's response to the NAS, this Report investigates and incorporates, to the extent possible, the NAS committee's recommendations in order to ensure that the direct contact criterion to be applied is based on the best available information.

2.3.2 National Toxicological Program

Substantial new information has become available since the development of MDEQ's cancer slope value for TCDD, which was derived based on a 30 year old Dow study (Kociba *et al.*, 1978). In particular, subsequent to the MDEQ derivation of their slope factor, the National Toxicology Program published a state-of-the-art cancer bioassay for TCDD in 2006. *Toxicology and Carcinogenesis, Studies of 2,3,7,8-Tetrachlorodibenzo-p-Dioxin (TCDD) in Female Harlan Sprague-Dawley Rats* (NTP, 2006). The National Toxicology Program ("NTP") is an

interagency program within the U.S. Department of Health and Human Services. Established in 1978, the NTP is charged with coordinating and strengthening toxicological science and providing information about toxic substances to regulatory agencies and the public. The NTP study exposed groups of female rats to TCDD and dioxin-like compounds ("DLCs") for a period of up to two years via corn oil gavage. Tissues from more than forty rat body sites were then examined for each animal. The study's findings were subject to review by a subcommittee of independent university and industry scientists. The NAS review noted the superiority of the NTP data set:

> The committee points out that data from NTP released after EPA generated the 2003 Reassessment provide the most extensive information collected to date about TCDD carcinogenicity in test animals, and the committee found the NTP results to be compelling. NAS, 2006, p. 16.
>
> In 2003, when EPA's Reassessment was issued, the most recent NTP bioassay results (NTP 2004) were not yet published. Because this study represents an extensive data set developed using state-of-the-art methodology, EPA should integrate this information into its analysis. NAS, 2006, p. 128.

This Report uses the extensive data generated by the NTP, which represents the best information currently available, as the primary basis for calculating a cancer slope for TCDD.

2.3.3 University of Michigan Dioxin Exposure Study

Lacking actual site-specific and blood serum biomonitoring data, the algorithms discussed above in section 2.1.3 incorporate default exposure values that attempt to predict how much dioxin will actually be absorbed, through dermal contact or incidental ingestion, into the blood stream of an individual exposed to a certain amount of contamination in soil. Therefore, the algorithms attempt to predict exposure and dioxin levels in humans, but do not actually measure it. In this case, however, PCCD/F levels have been directly measured in blood serum by the University of Michigan in its extensive Dioxin Exposure Study ("UMDES").[11] The results show that the Part 201 algorithms and default variables overstate actual exposure by a factor of almost twenty. Put

[11] See http://www.sph.umich.edu/dioxin/.

another way, real blood levels are about 20 times lower than what is predicted by applying the Part 201 defaults. Accordingly, this Report incorporates pertinent information from the UMDES to adjust the default variables in order to better predict actual exposure.

The UMDES report was issued in August of 2006, but additional analyses are still ongoing. This human exposure and biomonitoring study measured and compared PCCD/Fs and PCBs in blood serum, soil, and household dust in Midland and environs and compared the results to control areas (Jackson and Calhoun Counties). 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 exposure.

The UMDES study team went through a substantial effort to design and execute the UMDES to ensure that the samples would be representative of the underlying population and to ensure that valid inferences could be drawn.[12] Cooperation and response rates were higher than expected (overall response rate 74.3%). The study design and its preliminary results were reviewed by an independent Scientific Advisory Board consisting of Linda Birnbaum, PhD, DABT (Diplomat 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 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);

[12] *See* http://www.sph.umich.edu/dioxin/protocol.html.

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 areas 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. The University obtained interview data from 1,324 persons and blood sample data from 946 of the interviewees, including 251 from the control area. Persons whose blood was sampled had to meet strict medical eligibility criteria. The University also analyzed almost two thousand soil samples[13] and over seven hundred dust samples from the residences of study participants. In the end, the UMDES provided a complete set of interview, blood serum, and soil and dust sample data for 731 persons.

The University is conducting an ongoing statistical analyses of the sampling results to evaluate potential associations between dioxin and dioxin-like congeners found in blood serum and soil concentrations, dust concentrations, food consumption, and other demographic characteristics, personal characteristics, or residence locations. Of particular relevance for this Report:

- Although the UMDES noted some differences in blood serum levels between exposed and local control populations for certain of the parameters measured, these differences were small and similar to that found in the general U.S. population. The primary

[13] The University obtained 766 samples from the surface soil (0–1 inch) around house perimeters; 449 samples for the 1–6 inch stratum around house perimeters; 484 samples from 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.

determinants of elevated blood levels were age, sex, and body mass. Because of the long life of some dioxins and furans in the body, these findings may represent exposures occurring primarily in the past.

- Individuals residing on soil with 1000 ppt TCDD (TEQ) showed very little effect on their blood levels (about 0.5 ppt), suggesting that soil exposure is largely inconsequential and makes a negligible contribution to the overall exposure of individuals. Similar findings were found when the correlations between blood levels and higher soil concentrations (90^{th} percentile) for various congeners were compared.

- There was no correlation between levels of dioxins and furans in house dust and dioxin and furan blood levels of residents.

- Specific chemical markers of historic releases (e.g., 2,3,4,7,8-PeCDF) that were found at elevated levels in soil, dust, and local biota were largely not found to be elevated in the blood of local residents, again suggesting exposure was not occurring or is inconsequential.

The UMDES data can be used to examine the validity and applicability of the various exposure and bioavailability parameters used in the Part 201 algorithms. Calculations relying on generic Part 201 exposure assumptions predict significant increases in blood dioxin levels for residents living in contaminated areas. However, the UMDES found no such increase in actuality. For example, using a simple one-compartment model, a 7.5 year half-life, a 17 year residence time, the Part 201 regulatory assumptions for adult exposure (including frequency, soil ingestion rates, dermal contact surface area and adherence rate, and bioavailability), and a contamination level of 1000 ppt dioxin, the Part 201 algorithms predict a dioxin (TEQ) increase of 9.9 ppt in blood serum. According to the UMDES, actual blood serum level increases, however, are only 0.5 ppt. Therefore, the Part 201 model over estimates exposure by almost twenty fold.[14]

[14] Specifically, the increment of serum lipid concentration of dioxins predicted to result from the default contact assumptions used by MDEQ was estimated by assuming simple first-order kinetics for dioxins. The adult exposure parameters for direct contact with soil (oral and dermal pathways) from MDEQ are presented in the table below, along with the calculated absorbed daily dose according to the direct contact criterion algorithms assuming 1000 ppt in soil (note that only the adult exposure parameters were used in this simulation).

Accordingly, the UMDES study provides input on specific exposure factors as well as a separate, parallel, "top-down" approach to assessing dioxin exposures that can complement the "bottom-

Parameter	Value	Units
MDEQ Adult soil ingestion assumptions		
d/f concentration	1000	ppt
(unit conversion)	1000	pg/gm
(unit conversion)	1	pg/mg
ingestion rate	100	mg/day
d/f ingestion rate	100	pg/day
body weight	70	kg
Bioavailability	0.5	
soil freq (345 d/365 d)	0.958904	
Oral absorbed dose	**0.68**	**pg/kg/day**
MDEQ Adult dermal contact assumptions		
d/f concentration	1000	Ppt
(unit conversion)	1000	pg/gm
(unit conversion)	1	pg/mg
soil adherence	0.07	mg/cm2
skin surf area	5800.00	cm2
dermal abs	0.03	
dermal freq	0.67	
Dermal absorbed dose	**0.116795**	**pg/kg-d**
Summed daily absorbed dose:	**0.80**	**pg/kg/d**

The estimated daily absorbed dose was entered as the dose rate into the standard equation for first order accumulation to estimate the increment in serum lipid concentration associated with a given duration of the estimated daily dose rate.

$C(t) = \frac{D}{Vk}\left(1 - e^{-kt}\right)$ Variables are defined and assumed values are presented in the following table.

Symbol	Parameter	Value	Units
C	Serum lipid TEQ increment	Calculated	ng/kg lipid (ppt lipid)
V	Volume of distribution (lipid – assumed to be 25% of 70 kg BW)	17.5	kg
k	Elimination rate (corresponds to half-life of 7.5 yrs)	0.09242	yr^{-1}
D	Yearly dose (365 d * 0.8 pg/kg/d * 70 kg)	20.44	ng/yr
t	Years of residence on soil as an adult – average for UMDES study	17	Yr
Predicted serum increment using Equation 1		10	ng/kg lipid

This predicted increment of serum TEQ based on the MDEQ exposure assumptions can be compared with the estimated serum TEQ increment found by the UMDES researchers to be associated with residence on properties with soils contaminated at 1000 ppt. As reported during the July 2007 CAP meeting, the UMDES study found an association between an average of 17 years of residence on soil at 1000 ppt of approximately 0.5 ppt TEQ serum lipid increase.

up" approach of a traditional exposure analysis. The value of looking at both approaches is that they complement one another, inform one another, and constitute checks on one another in that the various pathways and scenarios of the traditional approach should not add up to more total exposure than is actually measured. This Report makes appropriate adjustments to the default exposure variables in order to better predict actual exposure and the true risk posed by dioxin contamination.

2.4 Probabilistic Risk Assessment

This Report has assessed the variables discussed in section 3, below, probabilistically. A "probabilistic risk assessment" uses ranges of values or "distributions" for toxicity and exposure inputs, where appropriate.[15] A traditional deterministic risk assessment, on the other hand, uses a single estimate for each algorithm input or variable. In a deterministic assessment, in order to be protective, a conservative or worst-case estimate is often chosen, or "uncertainty factors" are applied, which can lead to overly conservative calculations. PRAs more accurately take variability and uncertainty into account. While a deterministic risk assessment calculates a single end point or value, a PRA results in a range of end points, or a "probability distribution" – a measure of risk with associated probabilities of occurrence.

As noted above, the Part 201 rules require that the "best available information" be used in developing cleanup criteria, including site-specific criteria. Probabilistic distributions may constitute the "best available information" for certain variables, because they more accurately depict variability and uncertainty. This position is supported by the National Academy of Sciences' review of EPA's Dioxin Reassessment, where the NAS recommended the use of "probabilistic models to the extent possible" as a "key finding." *Health Risks from Dioxin and Related Compounds, Evaluation of the EPA Reassessment,* p. 19 (NAS, 2006). According to the NAS:

> The risk estimates can be most fully characterized by performing probabilistic analyses when possible and by presenting the range of possible risk estimates

[15] For example, for exposure parameters, distributions can take into account variability in body weight, lifespan, diet and other inputs. In regard to toxicity, probabilistic methods can take into account the uncertainty inherent in the assumptions used in toxicity studies as well as differing results found from one study to the next.

> rather than by reporting the single point estimates. Risk characterization should provide useful information to risk managers to help them understand the variability and uncertainty in the risk estimates.

Id. p, 39.

Both MDEQ and U.S. EPA have recognized the benefits of probabilistic methods. In March of 2004, U.S. EPA's Office of the Science Advisor expressly recommended the use of probabilistic methods for expressing both exposure and toxicity values for risk assessment purposes:

> Probabilistic risk assessment incorporating the entire process, including the toxicity part of the risk assessment and not only the exposure component, would be particularly useful. In addition, probabilistic analysis may avoid some potential problems of apparent overestimation of risk estimates from multiplying [uncertainty factors] in a deterministic risk assessment.

Risk Assessment Principles & Practices, U.S. EPA, Office of the Science Advisor, EPA/100/B-04/001, p. 40-41 (U.S. EPA, 2004). The following documents also set forth general guidelines for using probabilistic methods: *Guiding Principles for Monte Carlo Analysis,* U.S. EPA, EPA/630/R-97/001 (U.S. EPA, 1997); *Risk Assessment Guidance for Superfund: Volume III – Part A, Process for Conducting Probabilistic Risk Assessment,* U.S. EPA (U.S. EPA, 2001). These documents have been consulted and relied upon in the preparation of this Report.

For the initial probabilistic assessment, a "single-dimensional" Monte Carlo analysis was adopted for the sake of simplicity in what in many ways is already a very complex assessment. In a single-dimensional Monte Carlo assessment, uncertainty and variability are combined together in the parameter assumptions and distribution of result. A more sophisticated treatment involving a two-dimensional Monte Carlo assessment, in which uncertainty and variability are treated separately, will be considered for possible future versions of this report, pending review, discussion, and acceptance by MDEQ and the Independent Science Advisory Panel (ISAP). All Monte Carlo simulations presented in this report were performed using Crystal Ball (Decisioneering Inc., Version 7) for Microsoft Excel, with 10,000 iterations used in each of the simulations.

2.5 Toxic Equivalency Factors

As noted above, the Part 201 regulations require that all dioxin-like compounds be considered as an equivalent concentration of TCDD. *See* Mich. Admin. Code R. 299.5734(1). Accordingly, "toxic equivalency factors" or "TEFs" are used in Michigan to assess dioxin-like compounds other than TCDD. A TEF is an estimate of the relative toxicity of dioxin-like compounds to TCDD, which is generally considered the most toxic dioxin. *See* Mich. Admin. Code R. 323.1205(s). TEFs are used to assess the risk posed by dioxin-like compounds and mixtures of compounds that sometimes lack their own toxicity data, such as many furans. When such compounds are sampled in the environment, the results are converted using the TEFs into 2,3,7,8-TCDD equivalent concentrations. These converted concentrations are then added together to determine the "toxic equivalence concentration" ("TEQ") of the compounds, *see* Mich. Admin. Code R. 299.9108(c), which is then compared to the cleanup criteria for TCDD.

While the use of TEFs and TEQs are recognized as legitimate and useful in many contexts, they have limitations for use in risk assessments as is explained below.. The National Academy of Sciences, while describing the TEF method as "a reasonable, scientifically justifiable" method of estimating dioxin congener toxicity, discussed at length the uncertainty and variability inherent in assigning TEF values. *Health Risks from Dioxin and Related Compounds, Evaluation of the EPA Reassessment,* p. 60, 54 – 59 (NAS, 2006). Midland Soils have been impacted by a mixture of PCCD/Fs that has a very different congener profile than what has been found in and along the Tittabawassee River. Therefore, any bias or errors in the TEFs for the congeners in question will have a like-effect on the TEQs and final risk assessment.

Uncertainty and bias can arise for many reasons: problems extrapolating from animal studies to humans for different congeners; issues regarding whether particular congeners behave similarly to TCDD in the human body for all effects;[16] differences in half-life between the compounds;

[16] For instance, if a cleanup criterion is developed for TCDD based on developmental effects on a fetus, then an assumption must be made that the dioxin-like compounds are similarly available to a fetus, or adjustments to the TEF must be made. For example, studies show that certain furans are only $1/10^{th}$ as available to a fetus as TCDD. *Disposition of Polychlorinated dibenzo-p-dioxins, Dibenzofurans, and Non-Ortho Polychlorinated Biphenyls in Pregnant Long Evans Rans and the Transfer to Offspring,* Chen, C.Y., J.T. Hamm, J.R. Hass, and L.S. Birnbaum (2001).

and questions extrapolating from one type of exposure (e.g., food intake) to another (e.g., dermal).[17] In the end, because the TEF approach is an *indirect* means of assessing toxicity, there is a greater chance for error and bias, or overly conservative results.

The World Health Organization ("WHO") similarly noted the problems associated with applying the current TEF and TEQ approaches to different matrices:

> Concurrent with the development of the TEF and TEQ approach has been its application to environmental matrices such as soil, sediment, industrial wastes, soot, fly-ash from municipal incinerators, waste water effluents, etc. As such, the TEQ approach has been and continues to be used to give a single value to complex environmental matrices, usually without taking into consideration whether this is actually a risk-based number. The expert panel emphasized that correct application of the present TEF scheme . . . . and TEQ methodology in human risk assessment is only intended for estimating exposure to dioxin-like chemicals from consumption of food products and breast milk, etc. This limitation is derived from the fact that those REP studies that have been considered most relevant for the determination of TEFs are largely based on oral intake studies, often through the diet.

Accordingly, the WHO noted that current TEF/TEQ values "do not have any toxicological implications or direct use in risk assessment . . . ." and emphasized that matrix specific variables such as fate, transport, and bioavailability should be taken into account before setting the relevant TEQ. *The 2005 World Health Organization Re-evaluation of Human and Mammalian Toxic Equivalency Factors for Dioxins and Dioxin-like Compounds,* p. 28, 29 (2005)(internal citations omitted).

This is strong support for analyzing a default TEF/TEQ based on site-specific information or new science, or for developing site-specific and congener specific cleanup criteria for dioxin-like compounds of concern when possible and practicable. Dow acknowledges that developing congener-specific cleanup criteria would appear to require an amendment to the Part 201 administrative rules, but such an amendment may be necessary for the rules to comport with the "best science."

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[17] *See e.g., The 2005 World Health Organization Re-evaluation of Human and Mammalian Toxic Equivalency Factors for Dioxins and Dioxin-like Compounds,* p. 28 – 29 (WHO, 2005).

3. Proposed Direct Contact Criteria for Consideration

Part 201 generally divides cleanup criteria calculations into two categories: carcinogenic and non-carcinogenic. If a substance poses both carcinogenic and non-carcinogenic risks "cleanup criteria shall be derived under this section for the most sensitive effect." M.C.L.A. § 324.20120a(4). Accordingly, this Report analyzes both carcinogenic and non-carcinogenic risks. Because the exposure variables and assumptions used in both the cancer and non-cancer equations are largely the same, this Report discusses exposure variables first. Cancer and non-cancer toxicity variables are then discussed separately.

3.1 Exposure Variables

This section provides a discussion of both deterministic and probabilistic calculations for the exposure variables used in the DCC algorithms.

3.1.1 Ingestion Exposure Frequency (Adults and Children) - EF_i

The EFi represents the number of days per year that a resident is exposed to, and therefore may ingest, soil (or dust) at their home.

This Report proposes an EF_i of **245 days per year** for its deterministic calculation. The Part 201 default is 350 days per year. Thus the MDEQ default exposure frequency of 350 days per year for ingestion differs markedly from the MDEQ default exposure frequency for the dermal pathway, of 245 days per year. In the evaluation of the dermal pathway, MDEQ accounts for the fact that during some of the year outdoor soil is not accessible either due to frost or snow cover. In this way, the residential EF_d takes into account the U.S. EPA's recommendation to consider local weather conditions (e.g., rain, snow cover, frozen soil, etc.). In MDEQ regulations for the dermal pathway it is assumed that Michigan winters last four months (120 days) making soil unavailable for contact during that time. In the ingestion pathway, however, MDEQ assumes that during those days of the year when outdoor contact with soil is not occurring, ingestion occurs through contact with indoor dust. In contrast, however, the extensive site-specific data provided by the UMDES evaluation did not identify a material relationship between TEQ in

blood and indoor dust TEQ concentrations.[18] Consequently, there is strong site-specific support to apply the 245 exposure frequency estimate for *both* dermal and ingestion pathways.

A lower exposure frequency makes sense for other reasons as well. The implicit assumption in the algorithm (plausible only for the highest-end exposures) is that anybody who can possibly come into contact with soil will come into contact with it. In most instances, however, being outdoors does not necessarily equate to being in contact with soil.

For the probabilistic assessment, climatology data for Midland, Michigan from the National Climatic Data Center were used to estimate an exposure frequency distribution (NCDC, 2007). Based upon data for 1996-2006, and the number of days/year above freezing with no precipitation (<0.01"), a normal distribution was defined for exposure frequency with a **mean of 209.8 days/year** and a **standard deviation of 19.4 days/year** (CV of 0.093). The 90% confidence interval (172-248 days/year) included the default value of 245 days/year. Use of these data for exposure frequency are considered conservative since they do not consider behavior patterns for outdoor activities which would serve to decrease the exposure frequency for contact with soil.

3.1.2 Dermal Exposure Frequency - EF_d

The EFd represents the number of days per year that a resident is exposed to, and therefore may touch, soil (or dust) at their home.

The inputs for the dermal exposure frequency are identical to that developed for the ingestion exposure frequency. In this case, the default value of **245 days** per year is retained for deterministic estimates, and is used as the upper end of the distribution range for probabilistic estimates. The **normal distribution (209.8, 19.4 days per year)** forms the basis for the probabilistic treatment of the site-specific direct contact criteria using the same rationale as discussed in the section above. Once again, the UMDES results suggest that these values

[18] See Section 2.3.3, above.

maintain conservatism and likely over-estimate the potential frequency of direct soil contact (dermal or oral).

3.1.3 Age-Adjusted Soil Ingestion Factor – IF

The IF is used to approximate the rate of soil ingested by an individual, first as a child and later as an adult.

The age-adjusted soil ingestion factor is calculated using the following equation provided in the Part 201 rules:

$$IF = \frac{IR_{child}\ ED_{child}}{BW_{child}} + \frac{IR_{adult}\ ED_{adult}}{BW_{adult}}$$

Mich. Admin. Code R. 299.5720. These variables are discussed below.

3.1.4 Body Weight for Adults and Children - BW_{adult} BW_{child}

BW refers to the body weight of an exposed individual, and is broken down into child and adult body weights.

For the deterministic assessment, default values of **15 kg** for 0-6 years and **70 kg** for 6-30 years were used.

For the probabilistic assessment, age-specific average body weights were calculated based upon exposure duration, assuming children born at the site. As a result, the ages that each individual are exposed are determined by the duration of exposure. For example, if the duration of exposure is 5 years, then the ages of exposure are 0 to 5 years. For consistency with the age-adjusted calculation used in setting the DCC, the average body weights for the age periods from 0-6 years and >6 years were calculated separately. Twenty-five lognormal distributions were defined for each age group body weight based upon the arithmetic means and standard deviations presented in columns 5 and 6 of **Table 3.1**. In each iteration of the simulation, the cumulative average body weights (column 3 of **Table 3.1**) were recalculated for both age periods based upon the

body weight values drawn from the lognormal distributions defined for each age group. Correlation coefficients of 0.95 were assumed for body weights from one age group to the next to best represent transitions in body weight from one age group to the next (i.e., avoiding drawing a 99th percentile value for age group 0-1 years along with a 1st percentile value for age group 1-2 years), while permitting at least some variation from one age group to the next. This assumption is consistent with the known variation in patterns of growth across children (Johnson, 1998).

A "lookup()" function was used in Microsoft Excel to ensure that the appropriate cumulative body weight values were incorporated into the age-adjusted calculation based upon the exposure duration value drawn for each iteration of the simulation. For example, if an exposure duration of 15 years is drawn in an iteration, the recalculated cumulative average body weights for 0-6 years and 6-15 years would be used in the age-adjusted calculation for that iteration.

This approach will tend to be more conservative than the deterministic approach since the body weights used in the >6 year category will be less than the 70 kg assumption used in the deterministic approach. However, this assumption is more consistent with the fact that the population being simulated is composed largely of children and young adults.

[Intentionally left blank.]

Table 3.1. Age-Specific Body Weights for Males and Females Combined

	Cumulative		Specific[1]		
Age Period	**Age Group (years)**	**Average Body Weight (kg)[2]**	**Age Group (yr)**	**Age Group Mean**	**Age Group SD**
0-6 years	0-1	11.3	0-1	11.3	1.65
	0-2	12.3	1-2	13.3	1.6
	0-3	13.3	2-3	15.3	2.05
	0-4	14.3	3-4	17.4	2.45
	0-5	15.4	4-5	19.7	3.15
	0-6	16.6	5-6	22.6	4.0
>6 years	6-7	24.9	6-7	24.9	4.45
	6-8	26.5	7-8	28.1	5.95
	6-9	28.2	8-9	31.5	7.35
	6-10	30.2	9-10	36.3	7.85
	6-11	32.4	10-11	41.1	10.5
	6-12	34.5	11-12	45.3	10.1
	6-13	36.8	12-13	50.4	12.05
	6-14	39.2	13-14	56	11.05
	6-15	41.3	14-15	58.1	10.4
	6-16	43.4	15-16	62.6	11.25
	6-17	45.2	16-17	63.2	11.45
	6-18	46.9	17-18	65.1	11.9
	6-19	48.4	18-19	66	11.3
	6-25	54.3	19-25	67.2	12.3
	6-35	60.2	25-35	71.5	14.35
	6-45	63.8	35-45	74	14.3
	6-55	66.0	45-55	74.5	14.45
	6-65	67.2	55-65	73.4	13.75
	6->65	67.7	>65	70.7	13.3

[1] Age specific body weights taken from Tables 7-2 and 7-3 of U.S. EPA's Exposure Factors Handbook (U.S. EPA, 1997). SD values estimated by averaging the values for both sexes.

[2] Calculated as the time-weighted arithmetic mean of the age group specific values in column 5 of this table.

Johnson FE., 1998. Population Variation in Growth Patterns, Section 2.5 in *Cambridge Encyclopedia of Human Growth and Development*, Cambridge University Press, Cambridge, UK.

3.1.5 Exposure Duration (Adults) – ED_{adult}

The ED is the assumed total length of time that someone's exposure will last, based on the length of their residency.

The exposure duration of 24 years for adults used by MDEQ[19] and EPA (1997, 2004) corresponds to an upper end estimate (approximately the 95th percentile) for duration of residence at the same address, with durations weighted according to the national age distribution in the late 1980s and national moving rates appropriate to that era. The default **24-year duration** is used for the DCC deterministic calculations.

For the probabilistic calculation, the following analysis was used. The deterministic value is based on data approximately three decades old. More recent moving rate information (as recent as 2005) is available from the U.S. Census Bureau Current Population Survey (see http://www.census.gov/population/www/socdemo/migrate.html). This up-to-date information may be analyzed using the same procedure as Johnson and Capel (1992) to estimate the duration of residence. Since moves are sometimes only short distances, and may be to other areas of Midland, this Report makes a conservative estimate by using the Midwest moving rate out of the original county of residence (2000-2005, both sexes combined)[20] to estimate the probability of remaining in Midland as a function of age (**Figure 3-1** and **Table 3-1**).

Table 3-2 was calculated using a replication of the methodology of Johnson and Capel (1992), with a minor modification for more realism.[21] For completeness, it is assumed that no children under age 1 move from Midland.

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[19] The Exposure Factors Handbook, cited as the source by MDEQ, relies on analyses by Israeli and Nelson (1992) and Johnson and Capel (1992), both of which obtain practically identical results using slightly different methodologies and data sources. The underlying assumptions are very similar.

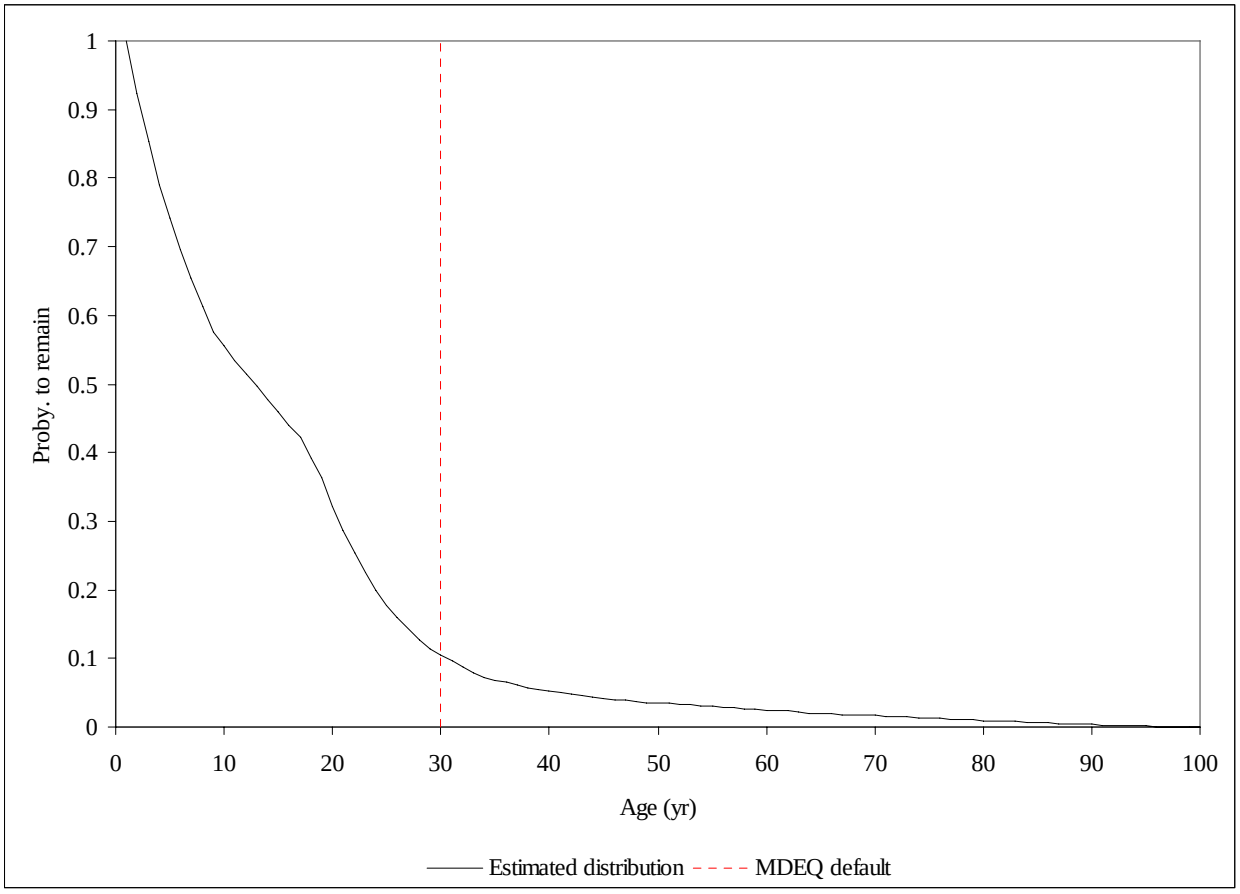
[20] See the Current Population Survey at http://www.census.gov/population/www/socdemo/migrate/cps2005-5yr.html, and http://www.census.gov/population/socdemo/migration/cps2005-5yr/tab01-3.xls, and for probabilities for deaths by single year for 2003: (http://www.cdc.gov/nchs/data/nvsr/nvsr54/nvsr54_14.pdf).

[21] The calculation is done in units of 1 year; instead of adding 1 year to the difference between integer final and starting ages, as in Johnson and Capel, 1992, the starting age is decremented and final age is incremented by a uniform random [0,1] value in order to interpolate between single years, and the difference between these adjusted values is used.

Table 3-2 Calculated probability of not remaining in Midland county – 1 year intervals.

Duration	Probability	Duration	Probability	Duration	Probability	Duration	Probability
0	0						
1	0.075813	26	0.857152	51	0.966603	76	0.988049
2	0.145763	27	0.872086	52	0.967462	77	0.988761
3	0.210362	28	0.885456	53	0.968305	78	0.989469
4	0.258714	29	0.895371	54	0.96952	79	0.990172
5	0.304084	30	0.90443	55	0.970698	80	0.990884
6	0.346666	31	0.912707	56	0.971855	81	0.99159
7	0.386638	32	0.920272	57	0.972963	82	0.992285
8	0.424162	33	0.927185	58	0.97406	83	0.992999
9	0.445228	34	0.931277	59	0.974909	84	0.993634
10	0.46554	35	0.935147	60	0.975756	85	0.994258
11	0.485099	36	0.938806	61	0.976941	86	0.994867
12	0.503956	37	0.942265	62	0.978101	87	0.995455
13	0.52214	38	0.945534	63	0.979218	88	0.996019
14	0.541443	39	0.947878	64	0.979964	89	0.996552
15	0.560004	40	0.95013	65	0.980702	90	0.997051
16	0.577895	41	0.952295	66	0.981437	91	0.997511
17	0.608167	42	0.954374	67	0.982172	92	0.997931
18	0.636342	43	0.956368	68	0.982904	93	0.998307
19	0.677658	44	0.957985	69	0.98349	94	0.998638
20	0.71429	45	0.959549	70	0.984091	95	0.998925
21	0.746761	46	0.961069	71	0.984694	96	0.999168
22	0.775546	47	0.96254	72	0.985315	97	0.99937
23	0.801053	48	0.963964	73	0.985944	98	0.999534
24	0.821853	49	0.964855	74	0.986637	99	0.999664
25	0.840472	50	0.965735	75	0.98734	100	1

Figure 3-1 Estimated probability of remaining in Midland as a function of age for those initially 1 year old (Note: the 30 year default corresponds to 6 years as a child and 24 years as an adult).



For adults (everyone over age 6), the distribution of probabilities to remain residing in Midland County is obtained from these by normalizing to the probability to remain at age 6 (this is a duration of 5 years in **Table 3-2**).

The assumption that exposure to soil is ongoing and at the same concentration following a move within the same county likely overestimates exposure and risk. This is because moves within the same county are more frequent than moves out of the county. As indicated in the 2005 Midwest census data and in data for Midland county,[22] more than half of all moves are within the same county. Although it is assumed here that concentrations will remain the same for someone moving within Midland County, TEQ concentrations are elevated within a relatively small part of the county and thus moves within the county are likely on average to result in moving to an

[22] http://www.census.gov/acs/www/Products/Profiles/Single/2003/ACS/Narrative/380/NP38000US6960.htm

area with lower concentrations. These in-county moves are not accounted for in this duration estimate thus representing a potential overestimate in exposure duration.

The probabilistic evaluation of the DCC used **a custom PDF based on the data in Table 3-1 above** by loading these data (calculated probability of not remaining in Midland county – 1 year interval) into Crystal Ball (the software program used to carry out the probabilistic calculations in this Report).

3.1.6 Exposure Duration (Child) – ED_{child}

The default **6 year** exposure duration used by MDEQ and EPA (1997, 2004) is applied in the deterministic calculation of the DCC.

The probabilistic evaluation of the DCC used **a custom PDF based on the data in Table 3-1 above** generated by loading these data into Crystal Ball (Calculated probability of not remaining in Midland county – 1 year interval).

3.1.7 Soil Ingestion Rate (Child) IR_{child}

The soil ingestion rate describes the amount of soil potentially ingested by an individual.

Drs. E.J. Calabrese and E.J. Stanek III at the University of Massachusetts are currently investigating children's soil ingestion rates (the "UMass Soil Ingestion Project"). These investigators are recognized as the international experts on soil ingestion. A general summary of the protocol for these investigations is provided in the proposed Midland HHRA Work Plan Appendix E, Attachment E-3. Once completed, alternate soil ingestion rates (probabilistic and deterministic) for children and adults will be proposed for use in the risk assessment and may be proposed for updates to the DCC as well.

Because the results of that investigation are not yet available, this Report uses the child soil ingestion rate distribution published by Stanek *et al*. (2001) shown in **Figure 3-2**. The ingestion rate is plotted on the X axis (with a logarithmic scale), and the probability in the form

of a z-score (the inverse normal of the probability) on the Y axis.[23] This has been fitted[24] by a distribution curve consisting of a mixture of two lognormal distributions with no upper bound on the ingestion rate. The fitted cumulative probability distribution is given by

$$\mathrm{P}(d) = \alpha\Phi\left(\frac{\ln(d/m_1)}{s_1}\right) + (1-\alpha)\Phi\left(\frac{\ln(d/m_2)}{s_2}\right)$$

where (1)

$$\begin{aligned} \alpha &= 0.8606 \\ m_1 &= 28.599 \quad \text{mg/d} \\ s_1 &= 0.7462 \\ m_2 &= 1.438 \quad \text{mg/d} \\ s_2 &= 0.6937 \end{aligned}$$

where $\Phi(\bullet)$ is the standard cumulative normal distribution.

[Intentionally left blank.]

[23] These scales have been chosen to provide a graphical display that adequately shows the distribution without unreasonably squashing any parts of it.

[24] The fitting procedure was approximate, to accurately fit the upper part of the curve and give reasonable values for the bottom end. The SD given by Stanek *et al*. for each percentile with a positive value was treated as giving an independent estimate for the CV at that percentile, and the maximum likelihood estimation then used. All negative values were treated as positive, but unknown, by ignoring them except insofar as they affect the percentiles.

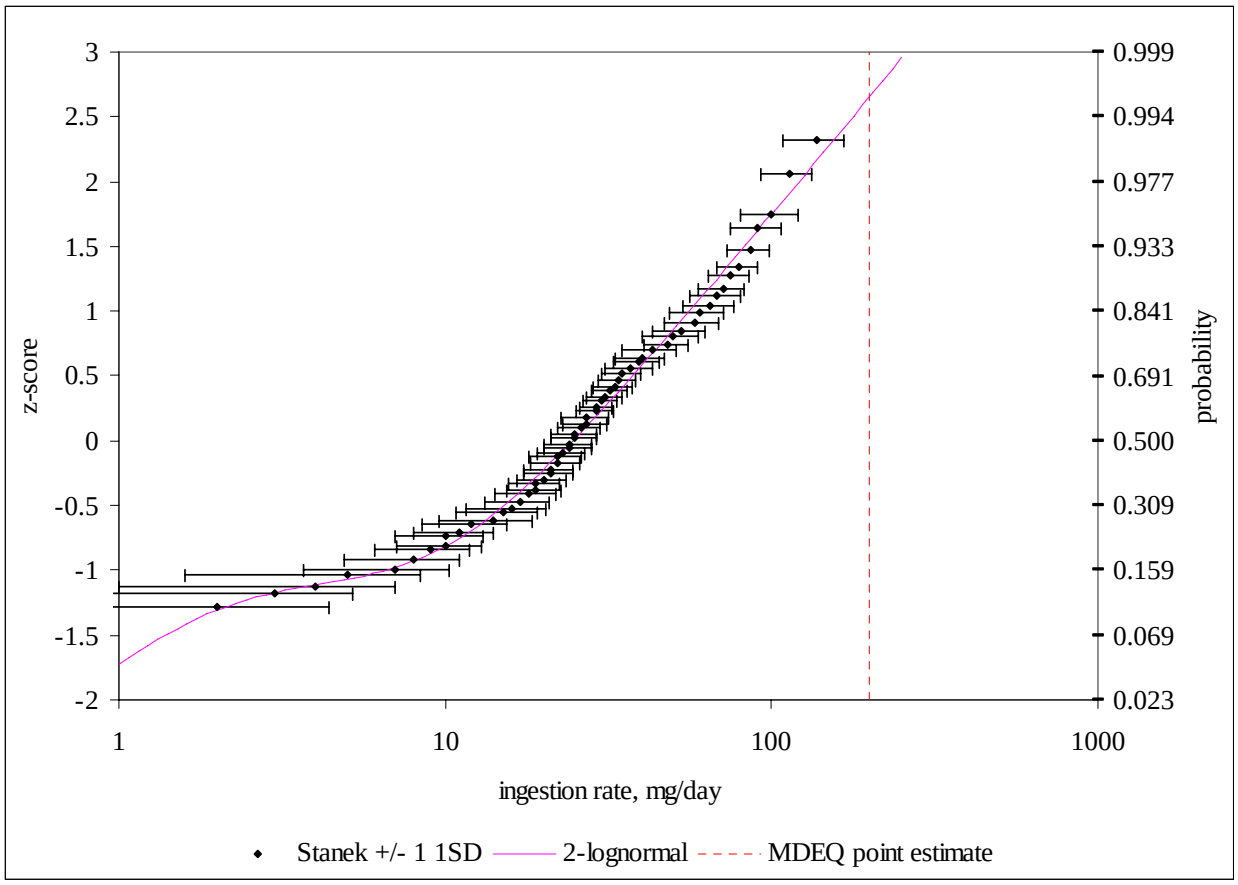


Figure 3-2 Child soil ingestion rate estimates (Stanek et al., 2001) and fitted distribution.

The median estimate for the fitted distribution is 24.5 mg/day, the mean is 32.8 mg/day, and the 95th percentile is 92.2 mg/day. The SD of this distribution is 28.1 mg/day, so the CV is 0.86 and is treated as a variability distribution. For the purposes of this evaluation, these measurements are treated as long term averages.

For the deterministic evaluation, this Report applies the 95th percentile value of **92.2 mg/day**.

For the probabilistic calculations, this Report uses **a custom distribution based on the two lognormal distributions described above.**

3.1.8 Soil Ingestion Rate (Adult) IR_{adult}

The soil ingestion rate for adults applied in the deterministic calculation is **46.1 mg/day**, based on an assumption that adults ingest half the amount of soil that children do (this assumption is consistent with the process used by EPA and MDEQ).

In considering the adult soil ingestion rate for the probabilistic calculation, the best available information is provided by Stanek et al. (1997). Their best mean estimate is 10 mg/day with a SD of 94 mg/day (this estimate is provided as an uncertainty estimate in the introductory text of the paper only). The distribution given in the text appears to be for individual days, rather than the desired long-term average, so this variable may need further analysis. For the probabilistic assessment, the soil ingestion rate was calculated as one half of the value drawn from the child soil ingestion rate for each iteration of the simulation, which maintains the relative relationship between adult and child rates assumed for the deterministic assessment. By linking the adult ingestion rate directly to the child ingestion rate, a perfect correlation is artificially assumed (*i.e.*, drawing a high child ingestion rate in an iteration results in a high adult ingestion rate as well), even though these may be independent (or at least less dependent). This practice may be viewed as conservative since it serves to overweight the probability in the tails of the resulting DCC distribution.

3.1.9 Ingestion Absorption Efficiency - AE_i

The AEi represents the fraction of the intake (i.e., contaminants ingested) that passes through the exchange boundary (e.g., the gastrointestinal tract) into the blood stream. This fraction can change depending on the medium of exposure; for example, soil versus vegetable oils used in animal studies.

To evaluate the potential for oral absorption (i.e., absorption following ingestion) of PCDD/Fs particularly from Midland soils, Dow sponsored a bioavailability study (Exponent 2005) and follow-up studies (Exponent and Summit 2006) that evaluated the potential oral absorption of dioxin in Midland soil relative to oral absorption potential in dioxin studies used to evaluate toxicity. Data from these studies, in correlation with a review of site-specific soil characteristics,

provide the best information currently available to define this variable, and is supported by multiple lines of evidence. The methods and results of the initial and follow-up study are attached as Appendix E-3 to the proposed Midland HHRA Work Plan. Attached as Appendix E-1 to the HHRA is a Technical Memorandum, updated per MDEQ's recent comments, summarizing the evaluation of bioavailability and the weight-of-evidence justification for the selection of an alternate relative bioavailability estimate.[25] Data applied here are briefly summarized in Table 3-3.

Table 3-3. TEQ-weighted overall RBA and absolute bioavailability estimates

	Midland Soil	
	RBA	Absolute Bioavailability[a]
Rat – Pilot	0.37	0.30
Rat - Follow-up	NR	NR
Swine (ND=1/2 DL)	0.23	0.19
Swine (ND=DL)	0.29	0.23
In vitro bioaccessibility estimate:	0.17	

Note: DL - detection limit
ND - not detected
NR - not repeated in the follow-up study

[a] Absolute bioavailability estimated assuming 80 percent bioavailability from corn oil vehicle as follows: absolute bioavailability = relative bioavailability × 0.8 bioavailability in corn oil vehicle.

For the deterministic calculation, this Report uses a value of **25% (0.25)** to replace the 50% (0.5) value previously used by MDEQ. This is the mid-point in a range of values developed from the swine used in the bioavailability studies and is drawn from data in Exponent (2005) as discussed in Appendix E-1 and Appendix E-3 of the proposed Midland HHRA Work Plan. Swine data were selected as the basis because swine are recognized to be a better model than rats for the human gastrointestinal system.

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Data in the Exponent (2005) study as summarized in Table 3-3 show the TEQ-weighted bioavailability for swine reported assuming that undetected data are present at one half of the detection limit (i.e., ND= 1/2DL) and assuming that undetected data are present at the full detection limit. This was done to provide a range of estimates incorporating uncertainties related

[25] U.S. EPA specifically recognizes the appropriateness of using site-specific studies to adjust bioavailability. U.S. EPA, Office of the Science Advisor, *Risk Assessment Principles & Practices*, EPA/100/B-04/001, p. 110 (EPA, 2004).

to undetected samples. The value derived, assuming that undetected data are present at ½ the detection limit, was 23% with a CV of approximately 0.23. Using, instead, an ND equal to the DL gives an estimated relative bioavailability of 29%, a factor 1.26 higher. It is highly unlikely that all the non-detects would be at their respective detection limits, but treating the value obtained using ND = DL as having as much as a 1 in 20 chance introduces an uncertainty that can be represented by an additional CV of 0.14. Adding this to the estimated value of 0.23 gives a CV of 0.27. Accordingly, the bioavailability is treated as a mean value of 23% with an uncertainty of 0.27. For the probabilistic calculation, this Report assumes a lognormal distribution and uses a value of **23%** with a **SD of 0.06**.

3.1.10 Age-Adjusted Soil Dermal Factor - DF

The DF is used to approximate the rate of soil contacted by an individual, first as a child and later as an adult.

The age-adjusted dermal-absorbed-dose or "dermal factor" ("DF") of 2442 mg-yr/kg-day previously used by MDEQ was the default value prior to the rules being promulgated in 2002. *See MDEQ Interim Environmental Response Division Operational Memorandum No. 8, Revision 4* (June 5, 1995). Since that time, MDEQ has adopted and promulgated an updated DF of 353 mg-yr/kg-day, which it has subsequently used for the calculation of all other direct contact criteria. The change is primarily due to MDEQ's adoption of lower soil adherence factors ("AFs") for the DF calculation, from an AF of 1.0 mg/cm^2 for both adults and children to new values of 0.2 mg/cm^2 for children and 0.07mg/cm^2 for adults. *See MDEQ RRD Operational Memo. No. 1* (April 2005). This change is consistent with the recommendations of EPA in its dermal risk assessment guidance (U.S. EPA, 2004). MDEQ agreed that the new DF default value of 353 mg-yr/kg-day could be used for site-specific calculations.

For the deterministic and probabilistic calculations, the DF is calculated using the algorithm provided in the Part 201 rules:

$$DF = \frac{SA_{child} \times EF \times AF_{child} \times ED_{child}}{BW_{child}} + \frac{SA_{adult} \times EF \times AF_{adult} \times ED_{adult}}{BW_{adult}}$$

Body weight (BW) and exposure duration (ED) are discussed above. The EF (event frequency) has been kept at its default of 1. The other variables are discussed below.

3.1.11 Adherence Factor (Adults) - AF_{adult}

The AF represents the amount of soil that adheres to the skin, as both a child and an adult. EPA has summarized the research on the range of adherence factors measured in adults and children engaged in various activities that involve soil contacting skin.

The Part 201 default value of **0.07 mg/cm^2** is the "50th percentile" estimate for gardeners (Exhibit C-2 of EPA, 2004a) and is used for the deterministic input variable. For the probabilistic evaluation, this Report assumes a lognormal distribution and applies the "50th percentile" and "95th percentile" values provided by EPA; it is assumed that they are estimates of long-term averages. Values for a number of activities resulting in high dermal contact with soil, including, landscaper/rockery, Gardeners, and Irrigation installers, were averaged to obtain an intimate soil contact category, then mixed with estimates for Groundskeepers (70% vs 30%) to obtain estimated nominal 50th and 95th percentiles of a variability distribution. The resulting lognormal distribution has a mean of **0.04 mg/cm^2** and a **SD of 0.05**.

3.1.12 Adherence Factor (Children) – AF_{child}

The **0.2 mg/cm**^{2} adherence factor for children currently used by MDEQ was based on the "95th percentile" weighted factor for children at a day-care center, or the "50th percentile" factor for children playing in wet soil, and is used here in deterministic calculations.

Dr. John Kissel's laboratory at the University of Washington is one of the primary sources of data regarding soil adherence, and is recognized as a key source of standard exposure factors compilations by U.S. EPA's Exposure Factor's Handbook and RAGS Dermal Guidance (2004). In considering the adherence factor for the probabilistic assessment, we examined the Kissel *et*

al. raw data (all from Kissel *et al.*, http://depts.washington.edu/jkspage/). Within the raw data, there are data on 42 children who were either playing in the greenhouse (wet or dry soil) or were in the daycare groups.[26] Considering the data for the 42 children, the distributions of loading on any body part (hands, arms, legs, faces, and feet) are pretty well lognormal, and the logarithms are reasonably correlated (correlation coefficients [r values] up to around 0.5). Either face or feet measurements are missing in every case. The following steps were taken to evaluate the data for the measurements from the 42 children:

(a) Fit linear models in the logarithm of loading rates to predict the missing measurement (face or feet) from hands, arms, and legs (correlation coefficient achieved is about 0.77);

(b) Use predicted missing value and estimate weighted loading, using as weights the fractions of total body surface areas given in EPA (2004a) for hands, arms, legs, faces, and feet;

(c) Assume each measurement corresponds to a long-term average (this probably results in an overestimate of variability).

The resultant lognormal distribution has an (arithmetic) mean of **0.14 mg/cm^2** and **SD of 0.27**. Further evaluation and development of soil adherence factors would reduce the uncertainty for this variable.

3.1.13 Skin Surface Area for Adults and Children – SA_{adult} and SA_{child}

The SA describes the skin surface area exposed to dermal contact. For deterministic calculations, this Report uses the current Part 201 skin surface area defaults for adults and children, **5800 cm^2** and **2670 cm^2**, respectively.

Because body weights and skin surface areas are highly correlated (*i.e.*, large skin surface areas correspond to individuals with large body weights), the probabilistic calculations for skin surface area used the following approach. Total child and adult skin surface areas were calculated from body weight using the following equation (Costeff, 1966):

$$SA = (4*BWc+7)/(BWc+90)*10000$$

[26] The latter were under age 7, the ages of those playing in the greenhouse are not provided on Kissel's web site (http://depts.washington.edu/jkspage/). The paper has been requested.

The fraction of total skin surface area was assumed to be a uniform distribution with a minimum value of zero and a maximum value that results in a skin surface area that corresponds to the default values used by MDEQ to calculate the generic direct contact criteria for TCDD (0. 0.418 for children and 0.35 for adults). For the probabilistic calculation, the total skin surface area was calculated from body weight using the formula listed above (since skin surface area is a function of body weight) and the fraction of skin exposed was treated as a uniform distribution **from zero to 0.32 for adults and zero to 0.42 for children.**

3.1.14 Dermal Absorption Efficiency - AE_d

The dermal absorption efficiency factor represents the fraction of the contaminant that is assumed to penetrate the skin after contact. For this variable, MDEQ used 3% (0.03) in its 1995 calculation. However, MDEQ has advised that it intends to revise the AE_d for dioxin from its current value (3%) to a new value of 1.75% (0.0175), reflecting the best information currently available. Specifically, MDEQ's recommended value represents the midpoint of two values (0.95% and 2.5%) from an EPA study of dermal absorption in rats cited in EPA's Dermal Absorption Assessment document (U.S. EPA, 1992), p. 6-29. The EPA study calculated adjusted dermal absorption efficiency values for TCDD across human skin of 0.95% and 2.5% for low organic content soil similar to typical Michigan soil. MDEQ has agreed that the new value of **1.75%** could be used for purposes of calculating site-specific criteria, and this Report does so for its deterministic calculations.

This 1.75 percent estimate is near the mid-point of the range described in EPA (1992b) for TCDD. That study used data from three studies: Poiger and Schlatter (1980), Shu *et al*. (1988), and U.S. EPA (1991a). Repeating EPA's analysis (not taking account of experimental uncertainties, and not correcting for organic carbon), and assuming a lognormal distribution, gives an estimate with a **mean of 1.2%** and a **SD of 0.019** for probabilistic purposes.

3.1.15 Averaging Time

In the determinsitic calculations based on a linear (non-threshold) cancer model, the default value of 70 years (25,550 days) was replaced with 75 years (27,375 days) to be consistent with the average lifetime provided by the US EPA Exposure Factors Handbook (1999). For the non-linear (threshold) cancer model and non-cancer RfD, the averaging time was the same as the default exposure duration (30 years or 10,950 days). For the probabilistic inputs, the averaging time for linear (non-threshold) cancer model retained the value of 75 years (27,375 days) while the non-linear (threshold) cancer model and non-cancer RfD was equal to the exposure duration.

3.1.16 Uncertainties Related to Approach

3.1.16.1 Modeling Longitudinal Variation in Exposures to Soil

As discussed above in this Report, Michigan Administrative Rule 720 sets forth algorithms for determining cancer and non-cancer residential soil direct contact criteria. Both of these algorithms use a similar approach to characterizing chronic exposure. This approach is designed to allow the algorithms to produce conservative upper bound estimates of exposure. As discussed by Price et al. 1996, however, this type of algorithm is an impediment to modeling variation in exposure across individuals. The problem is that the algorithms exclude consideration of day-to-day and longer-term variations in the factors that determine individuals' chronic (30 year) and lifetime average exposures.

Modeling how these "longitudinal" changes in the exposure factors affect individuals' short and long term exposures is called "longitudinal exposure modeling." Such modeling has been used by EPA to estimate pesticide exposures (EPA, 2001a), chronic arsenic exposure from treated wood (Zartarian et al. 2006), exposures from chemicals in fish (EPA, 2000), and is discussed in the RAGS guidance on PRA (EPA, 2001b). Other published exposure assessments that use this approach include Wilson et al. 2001, 2002; Price et al. 1996, 2001, 2005.

In this assessment, both the probabilistic and deterministic exposure assessments place a focus on children, consistent with EPA requirements. As children grow, their behaviors, surface areas, and body weights radically change. These longitudinal changes affect the doses children receive

at different ages. As a result, the accuracy of resulting estimates depend on our ability to take longitudinal changes into consideration when modeling chronic exposures across individuals who are exposed as children and then as young adults.

The most accurate way to model individuals' exposures to dioxins in soil is to separately model the doses received from the soil on each day of the individuals' lives. For example, the model would take the data on the number of days a child goes out of doors and develop models of daily behavior. On days when the child goes outside, doses from dermal contact will be determined. On days when the child did not, the dermal dose would be set at zero. The doses on a day when contact occurs are determined using the standard equations for determining dermal and ingestion doses. The body weight and surface area are determined based on the child's age. The daily dose on the i^{th} day (TD_i) is given by:

$$TD_i = (\text{Ingestion Dose}_i + \text{Dermal Dose}_i)/ BW_i$$

Repeating this process for every day of the portion of the individual's life when they live at their original home (exposure duration) and summing the doses gives the Total Lifetime Dose:

$$\text{Total Lifetime Dose} = \sum_{Duration} TD_i$$

The cancer DCC is then given by

$$DCC = \frac{TRxATxCF}{SF \times \text{Total Lifetime Dose}}$$

The non cancer DCC is developed in a similar fashion.

Modeling longitudinal variation allows a better consideration of data on a number of exposure factors. Many of the factors in the dose equation have significant longitudinal variation over individual's lives. The number of days that a child spends out of doors can be expected to vary from year to year because of changes in the child's interests (indoor versus out door activities), in family schedules (day care versus raised at home), in weather (some years have more dry warm days than others), and in the residence itself (construction of swing set in the back yard). As a result of such changes, a child at one age may be outside 250 days and in the following year

only 50 days. Dermal contact rates will also vary from day to day because of different choices in clothing and because of differences in outdoor activities. Finally, as discussed by Thompson (2004), soil ingestion rates are taken from studies with a short duration (a few days or few weeks). Children with high ingestion rates over these short periods of time will not necessarily have the same high ingestion rates over months or years.

The net effect of considering the longitudinal changes in these factors is that the variation of lifetime and 30 year average exposures will be much smaller then the distribution predicted by a probabilistic approach constrained to use the Rule 720 algorithms. The reason for this is that probabilistic models based on the algorithms assume that some individuals will interact with the soil 200+ days a year every year for 40+ years. While it is plausible that in any one year an individual may interact with the soil on more than 200 days it is not plausible that they will do so every year for 40+ years. Further, the assessment requires that the person have the same interaction with soil (same amount of soil consumed and the same dermal contact rate) for 200+ days for each of the first six years of the individual's life. This consistency in interaction is implausible since during these six years the individual changes radically from a newborn, to an infant, to a toddler, to a school age child. Thus, the exposure assumptions for individuals in the upper tail of the probabilistic version of the Rule 720 algorithms reflect collections of extreme events that simply do not occur in real life.

The impact of this over estimation of doses in the upper tail is that the proposed criteria are greater than the soil level actually needed to achieve the risk target of 1 in 100,000, or to keep individuals' total doses below the RfD. While this Report was drafted with the consideration of these limitations, the requirement to use the Rule 720 algorithms has prevented performing more technically sound and plausible probabilistic assessments.

3.1.16.2 Separation of Uncertainty and Variation

The current approach used in the probabilistic analysis mixes the uncertainty in the toxicity values (RfD and Slope Factor) and variation in exposure related factors (duration, soil intake, days out of doors, and body weight). As discussed by EPA (2001b), the preferred approach to

assessing risk is to separate uncertainty and variation, and modeling the uncertainty in the variation of soil levels that correspond to the risk target. Such an approach would allow the selection of a DCC that explicitly addresses the uncertainty in the data and the variation in exposures.

The impact of such a revision is unclear and may or may not change the final clean up criterion; however, such an analysis would allow the optimum use of the available data. As discussed by Price et al, (2005) and demonstrated by Zartarian et al, 2006, joint modeling of longitudinal exposures, inter-individual variability, and uncertainty can be performed in a single analysis

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3.2 Toxicity Variables

3.2.1 Cancer Slope Factor ("CSF")

This Report proposes to replace the cancer slope factor of 75,000 $(mg/kg\text{-}day)^{-1}$ previously used by MDEQ. The Part 201 rules define "cancer slope factor" as:

> a plausible upper-bound estimate of the probability of a response per unit dose of a hazardous substance over a lifetime. the [sic] cancer slope factor is used to estimate an upper bound probability of an individual developing cancer as a result of a lifetime exposure to a particular level of a potential carcinogen.

Mich. Admin. Code R. 299.5701(d). Rule 738, Mich. Admin. Code R. 299.5738, sets forth a number of requirements for calculating a cancer slope factor under Part 201. The changes proposed by this Report are consistent with these requirements and reflect the current state of science, including the NAS's recommendations, as well as changes that MDEQ has already adopted in other portions of their rules.

For instance, the "species scaling" factor used by MDEQ to calculate the 75,000 $(mg/kg\text{-}day)^{-1}$ slope factor is no longer the scaling factor used by MDEQ. The "species scaling" factor is a value meant to account for differences in mass between test species (e.g. rats) and humans. The 75,000 $(mg/kg\text{-}day)^{-1}$ slope factor was calculated using a species scaling factor of 2/3. *See* Linda D. Larsen, MDEQ ERD, *Technical Support Document Part 201 Cleanup Criteria for 2,3,7,8-*

Tetrachlorodibenzo-p-dioxin and Related Compounds, p. 3 (May 19, 1999) ("*Technical Support*"). However, at the time MDEQ promulgated footnote O and its 90 ppt direct contact criterion for dioxin, MDEQ also adopted a presumption in favor of a new species scaling factor of 3/4:

> It shall be assumed that scaling daily administered doses by body mass raised to the 3/4 power achieves equivalence in lifetime carcinogenic risk in different mammalian species. To derive a human slope factor from animal data, the default procedure shall be to multiply the animal slope factor by the ratio of human to animal body weights raised to the 1/4 power.

Mich. Admin. Code R. 299.5738(5). Accordingly, calculations in this Report use the up-to-date species scaling factor of 3/4 as required by the Part 201 rules.

Other changes to the cancer slope calculation are also appropriate to reflect the best available scientific information.

The foundation for MDEQ's cancer slope factor is a 30-year old Dow study (Kociba et al., 1978) that investigated the effect of TCDD on rats for a period of two years. The Kociba study has been the subject of considerable debate and reevaluation. It has been the primary source of cancer slope factors developed between regulatory agencies, both internationally and nationally, over the past decades although the study itself does not provide a CSF nor was such an application intended or envisioned when the study was carried out. The different choices in dose estimates and dose-response modeling made by these agencies has resulted in CSF estimates ranging over two orders of magnitude, which accounts for widely differing estimates of risk when applied. Substantial new information and scientific guidance has become available since MDEQ calculated its cancer slope for TCDD, including the recently published NTP cancer bioassays, which provide state-of-the-art cancer bioassay information for determining TCDD cancer potency values. The NAS also provided numerous and extensive recommendations to the EPA directed at increasing the scientific content of EPA's own risk characterizations for dioxin and dioxin-like compounds. The NAS review was critical of EPA's efforts, suggested major revisions of the document, and urged EPA to consider the recent NTP studies that were not yet

available when EPA completed its reassessment. This Report takes into consideration both the NTP and NAS findings and recommendations.

Specifically, MDEQ's 1995 cancer slope factor of 75,000 $(mg/kg\text{-}day)^{-1}$ is based on a linear multistage model[27] that does not incorporate a threshold dose value. MDEQ ERD, *Draft Deliberative Process Toxicological Assessment and Part 201 Cleanup Criteria for 2,3,7,8-Tetrachlorodibenzo-p-dioxin and Related Compounds,* p. 4 (April 25, 2002). One of the challenges to interpreting study data is that nearly all relevant risk studies reflect doses much higher than those that would actually be encountered in the environment. Consequently, analysts must extrapolate well below the doses used in the studies to real world exposure levels. MDEQ's slope factor assumes that the dose-response relationship is fixed and linear and that there is no exposure point below which no adverse cancerous effect is expected to occur.[28] However, the National Academy of Sciences concluded that the linear approach used by U.S. EPA "lacked adequate scientific support," and urged EPA to take the opposite approach, favoring a non-linear model that includes a threshold dose:

> although it is not possible to scientifically prove the absence of linearity at low doses, the scientific evidence, based largely on mode of action, is adequate to favor the use of a nonlinear model that would include a threshold response over the use of the default linear assumption.

and

> The committee unanimously agrees that the current weight of evidence on TCDD . . . favors the use of nonlinear methods for extrapolation below the point of departure (POD) of mathematically modeled human or animal data.

NAS, pp. 4, 85 and 135 (NAS, 2006).

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[27] The Part 201 rules define "linearized multistage model" as "a dose-response model which assumes that there are a number of distinct biological stages or changes that must occur for a normal cell to be transformed into a tumor and which assumes the dose-response relationship to be linear at low doses." Mich. Admin. Code R. 299.5703(b).

[28] Taken to its logical conclusion, this approach would mean that virtually every person on earth would develop cancer from dioxin since it is present at background levels worldwide. This obviously does not occur.

Calculations in this Report, as discussed below, incorporate a non-linear model and a threshold dose, consistent with these recommendations. This is also consistent with Michigan law, which expressly authorizes the use of non-linear models and dose thresholds when adequately supported by data.[29]

3.2.1.1 Review of Previous Assessments of the Carcinogenic Potential of TCDD

Several regulatory agencies and publications have derived linear estimates of cancer potency for TCDD, as summarized below.

- U.S. EPA (1997, HEAST) – In a Health Effects Assessment Document, U.S. EPA (1984) derived a cancer potency factor of 156,000 $(mg/kg\text{-}day)^{-1}$ for TCDD based upon liver and lung tumors observed in female rats (Kociba et al., 1978). However, this potency factor was assessed in terms of administered dose, which is not appropriate for persistent chemicals. Furthermore, as noted above, the NTP has completed a more recent and comprehensive cancer bioassay.

- MDEQ (1998) – In 1998, MDEQ relied upon a cancer potency factor of 75,000 $(mg/kg\text{-}day)^{-1}$, which was based upon a re-evaluation of the rat tumor pathology data of Kociba et al. (1978). However, like the U.S. EPA value, this potency factor was assessed in terms of administered dose, which does not accurately characterize the potential risks from persistent chemicals. Furthermore, the NTP has completed a more recent and comprehensive cancer bioassay.

- U.S. EPA Reassessment – In their Reassessment for TCDD, EPA derived cancer potency factors of 1,000,000 $(mg/kg\text{-}day)^{-1}$ based upon a consideration of rodent and epidemiology data. Although the rodent-based potency estimate was assessed in terms of body burden, many aspects of the assessment were roundly criticized by the NAS. Major criticisms of EPA's Reassessment included: (1) the linear approach (assumes no threshold for effect) used by U.S. EPA is a matter of policy; not science; (2) U.S. EPA should use probabilistic risk assessment methods (allowing the full range of scientific findings to be used), non-linear methods & internal dosimetry to more accurately

[29] Rule 738 requires the use of a linear multistage model if and when "animal bioassay data are used *and* a non-threshold mechanism of carcinogenicity is assumed . . . ." Mich. Admin. Code R. 299.5738(3)(emphasis added). Therefore, a non-linear model may be used whenever a threshold mechanism will be employed. Even when no threshold will be used, it appears that the agency still has discretion to use non-linear models when appropriate, given that this subsection ends: "[o]ther models, including modifications or variations of the linearized multistage model that are more appropriate to the available data may be used where scientifically justified." Mich. Admin. Code R. 299.5738(3). Dose thresholds may be used on a case-by-case basis "if biological data adequately demonstrate the existence of a threshold on a hazardous substance-specific basis" and/or "if human epidemiologic data, animal bioassay data, or other biological data indicate that a chemical causes cancer via a threshold mechanism . . . ." Mich. Admin. Code R. 299.5738(1).

describe dioxin cancer risk; (3) EPA should use all of the most current data in its risk estimates, in particular, the NTP animal cancer studies on dioxin; and (4) U.S. EPA did not explain the uncertainty and variability in their risk estimates.

- OEHHA (2007) – Draft cancer potency values of 26,000 and 391,000 $(mg/kg\text{-}day)^{-1}$ were derived by the California Office of Environmental Health Hazard Assessment ("OEHHA"), based upon multiple tumors sites observed in female rats in the NTP study using applied dose and adipose equivalency approaches, respectively. The value of 26,000 $(mg/kg\text{-}day)^{-1}$ based on applied dose was adopted by OEHHA in deriving the draft public health goal (PHG) of 0.001 ng/L for TCDD.

Other published values for TCDD include the following:

- Crouch et al. (2005) – A probability density function for the cancer potency factor of TCDD was derived by combining the results of ten cancer bioassays. A threshold term was introduced to the multistage model to estimate cancer potency. The resulting estimate (assessed in terms of allometrically-scaled administered dose) had a median and upper confidence value of 7,000 and 52,900 $(mg/kg\text{-}day)^{-1}$, respectively. Using body burden as an internal dose measure, three bioassays were used to derive a MLE of 0.13 (ng/kg)-1 and an upper bound of 55 $(ng/kg)^{-1}$.

- Gray et al. (2005) – The authors assessed TCDD potency with respect to combined liver tumors (adenoma, cholangiocarcinomas) in terms of rat body burden. BMD10 values of 430 and 439 ng/kg were derived using the Hill and multistage models, respectively. Upper and lower confidence limits were not derived, and human equivalent doses were not determined.

- Maruyama and Aoki (2006) – The authors assessed TCDD potency with respect to liver tumors in terms of rat liver burden. Physiologically Based Pharmaco Kinetic ("PBPK") models for the rat (Andersen et al. 1993) and human (Maruyama et al. 2002,2003) were used to estimate internal dose. The authors reported a range of cancer slope factors of 780 – 9,000 $(mg/kg\text{-}day)^{-1}$.

3.2.1.2 TCDD's Mode of Action and Weight of Evidence Supporting a Threshold-Based Cancer Potency Factor

The U.S. EPA provides a framework and guidelines for selecting the appropriate method for conducting dose-response analysis for carcinogens (U.S. EPA, 2005). Specifically, the guidelines describe how a choice between linear and non-linear dose-response extrapolations is made. The choice is largely based on weight of evidence supporting a mode of action (MOA) involving a) direct genotoxicity or b) processes other than genotoxicity. The U.S. EPA guidelines call for assembling a MOA to facilitate this weight of evidence analysis and the choice of a dose-response method (U.S. EPA, 2005). Guidelines for assembling a MOA, referred to as the Human

Relevance Framework, were initially published by the World Health Organization's International Programme on Chemical Safety (Sonich-Mullin et al., 2001; Boobis et al., 2006). They were later endorsed by an International Life Sciences Committee (Meek et al., 2003) before being adopted by the U.S. EPA.

A number of individual scientists (Byrd et al., 1998; Popp et al., 2006) as well as scientific organizations have, through extensive review, concluded that cancer risk assessment for TCDD should be made based on a threshold approach. Specifically, the National Academy of Sciences (NAS), in their report on the U.S. EPA's Draft Dioxin Reassessment made the following recommendations:

> 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. However, the committee recognizes that it is not scientifically possible to exclude totally a linear response at doses below the POD, so it recommends that EPA provide risk estimates using both approaches and describing their scientific strengths and weaknesses to inform risk managers of the importance of choosing a linear vs. nonlinear method of extrapolation. To the extent that EPA favors using default assumptions for regulating dioxin as thought it were a linear carcinogen, such a conclusion should be made as part of risk management. EPA should strictly adhere to the distinction between risk assessment, which is a scientific activity, and risk management, which takes into account other factors.

NAS, p. 190. The NAS also stated the following in support of a threshold (non-linear) approach:

> The committee concludes that EPA did not support its decision adequately to rely solely on this default linear model and recommends that EPA add a scientifically rigorous evaluation of a nonlinear model, that is consistent with receptor-mediated responses and the recent NTP cancer bioassay studies . . . . the available data support the use of a nonlinear model, which is consistent with receptor-mediated responses and a potential threshold, with subsequent calculations and interpretation of MOEs.

NAS, p. 124. The NAS panel was comprised of recognized experts in cancer biology, the molecular biology and cell signaling aspects of the aryl hydrocarbon receptor (AHR) through which TCDD and many other chemicals act. Their conclusions reflect the predominate view

among experts, and are best understood when viewed in the context of a mode of action for TCDD induced hepatocarcinogenesis.

The purpose of this section is to provide a concise summary of the most plausible MOA for TCDD induced hepatocarcinogenesis, outline the evidence supporting the underlying key events, and conclude, based on published U.S. EPA guidance, whether the cancer risk assessment for TCDD should be based on a linear or non-linear low-dose extrapolation. The analysis presented here is not intended to follow the full human relevance framework (Sonich-Mullen et al., 2001; Meek et al., 2003). Instead, the analysis focuses on the first three steps of the framework, presentation of a plausible mode of action, and description of the key events and the nature of the dose-response relationships for the key events. The remaining steps are addressed indirectly through citations to primary literature that summarize the strength of the association between key events and tumor formation and the biological plausibility of the key events being associated with tumor development.

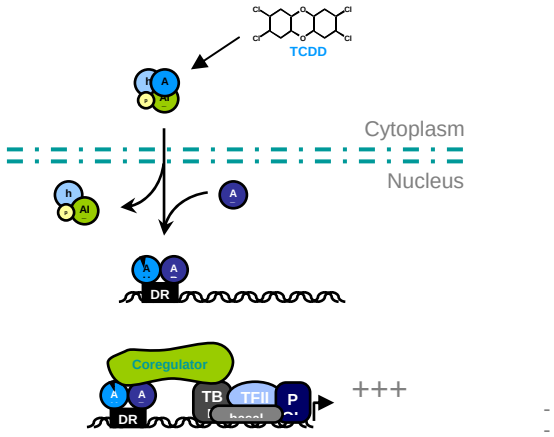
The mode of action section is followed by a weight-of-the-evidence ("WOE") section. Inclusion of the WOE elements is necessary for a comprehensive understanding of the multiple lines of scientific evidence that compliment the MOA data and further support a threshold cancer potency factor for TCDD. These WOE elements include human responsiveness to AHR activation, the normal biology of the AHR, the issue of AHR ligand mixtures, and the epidemiological evidence of highly exposed populations.

3.2.1.2.1 Mode of Action for TCDD Induced Hepatocarcinogenesis

TCDD is postulated to cause the development of hepatic tumors in rats, as observed in chronic bioassays through the following series of events: Systemic exposure leading to concentrations of TCDD in hepatocytes and other cells of the liver sufficient to cause binding to the AH Receptor and sufficient occupancy to initiate signaling through the AH receptor/ARNT network, affecting regulation of apoptosis and/or cell proliferation rates. The outcome is the establishment of conditions in the liver which promote the clonal expansion of spontaneously initiated cells into altered hepatic foci, some few of which acquire additional mutations and become hepatocellular

carcinomas/adenomas or cholangiocarcinomas/adenomas. These series of events can be described as comprising two key events: AH receptor binding/signaling and affects on apoptosis/cell proliferation leading to promotion. The evidence supporting these key events is discussed below.

Key Event 1: AH Receptor Binding/Signaling. The initial key event is binding of TCDD to the AHR receptor with subsequent alteration in AHR activity (Mills and Andersen, 1993). Since discovery of the AHR (Poland et al., 1976), the overwhelming scientific evidence has identified the AHR receptor as the pivotal component for dioxin-induced effects (Mimura and Fujii-Kuriyama, 2003; Okey, 2007). The AHR receptor- and protein-protein interactions involved with TCDD's effects are shown in the following figure.



TCDD binds to and activates the AHR in the cell cytoplasm, inducing transformation and translocation to the nucleus where the AHR forms a heterodimer with ARNT that then binds to DRE regulatory element in regulated genes, recruits coregulators which in turn recruits and stabilizes the transcriptosome in the gene promoter resulting in gene transcription.

AHR activation includes: 1) binding of the ligand [,i.e., TCDD] to the AHR receptor, 2) disassociation of chaperone proteins (p23, Hsp90, and XAP2), 3) translocation of the AHR-ligand complex to the nucleus via the nuclear translocation signal domain involving calpain activation, 4) binding of AHR-dioxin complex to ARNT, 5) binding of the ARNT-AHR-ligand complex to the Dioxin Response Element, 6) remodeling of chromatin by deactylases and the binding of co-activators or co-repressors, 7) a role for AHR repressor protein (AHRR) that

competes with AHR for ARNT, and 8) degradation of the AHR complex by a ubiquitin pathway (Suzuki and Nohara, 2007; Schnekenburger et al., 2007; Ramadoss and Perdew, 2005; Ramadoss et al., 2004; Narvaez et al., 2005; Dale and Eltom, 2006; Hankinson, 2005; Teh et al., 2006; Ma, 2007; Pollenz and Buggy 2006; Pollenz, 2007). Additional AHR-related pathways have been reported that are independent of dioxin-response element-dependent gene expression (Aintobi et al., 2007; Hoffer et al., 1996). Each receptor and protein-to-protein interaction accumulates according to the laws of mass-action to induce a biological effect, provided sufficient dioxin or AHR ligands are present (the dose-response criteria). AHR-mediated effects, like all other receptor-mediated effects, exhibit threshold phenomenon (Limbird, 2005; Limbird and Taylor, 1998; Poland, 1997; Byrd et al., 1998).

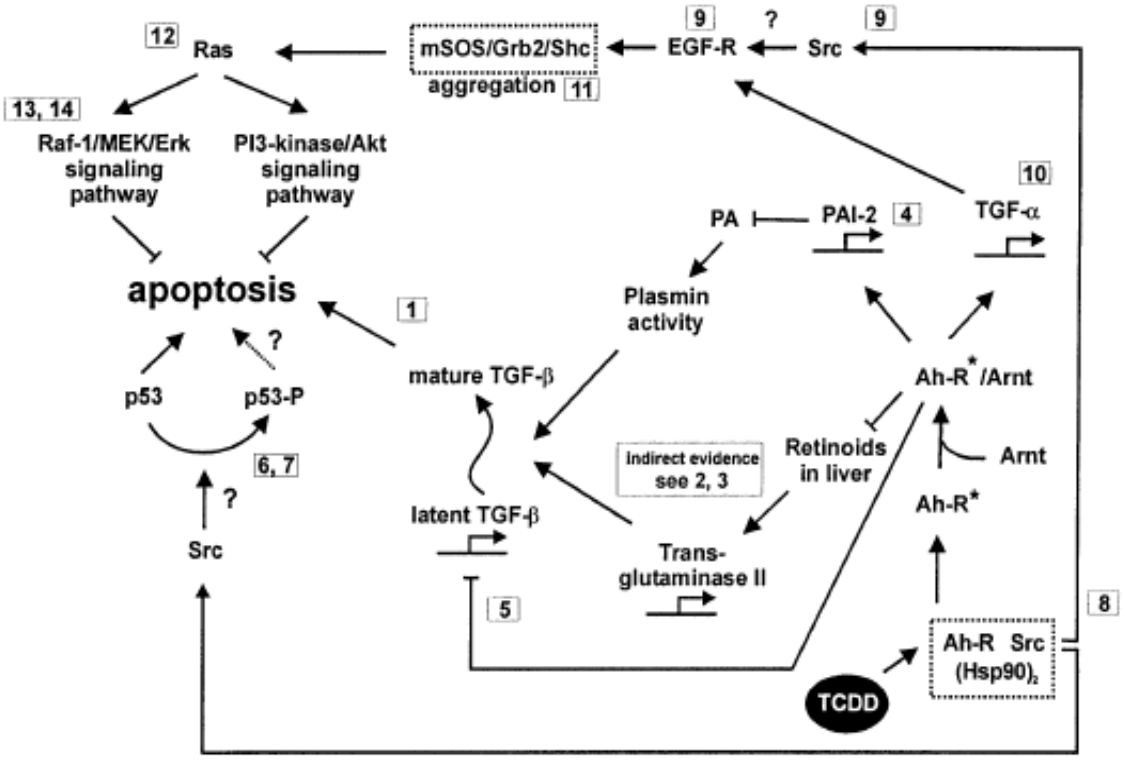
Key Event 2: Tumor Promotion. TCDD has been consistently and conclusively shown to be a tumor promoter in liver and skin models of multistage carcinogenesis (Schwarz et al., 2000; Waern et al., 1991; Worner and Schrenk, 1996; Teeguarden et al., 1999; Moolgavkar et al., 1996; Poland et al., 1982; Hebert et al., 1990; Richards et al., 2004). In addition to this direct evidence of a mode of action driven by promotion, experimental evidence has ruled out the alternative mode of action, one driven by direct mutagenicity: TCDD is not mutagenic (Shu et al., 1987; Randerath et al., 1988; Turteltaub et al., 1990). The National Toxicology Program recently concluded: "In summary, no mutagenic activity was detected with TCDD in a variety of *in-vitro* and *in-vivo* short term tests" (NTP, 2006). There is then overwhelming direct evidence of a tumor promotion based MOA and none supporting a role for TCDD acting as a direct mutagenic compound.

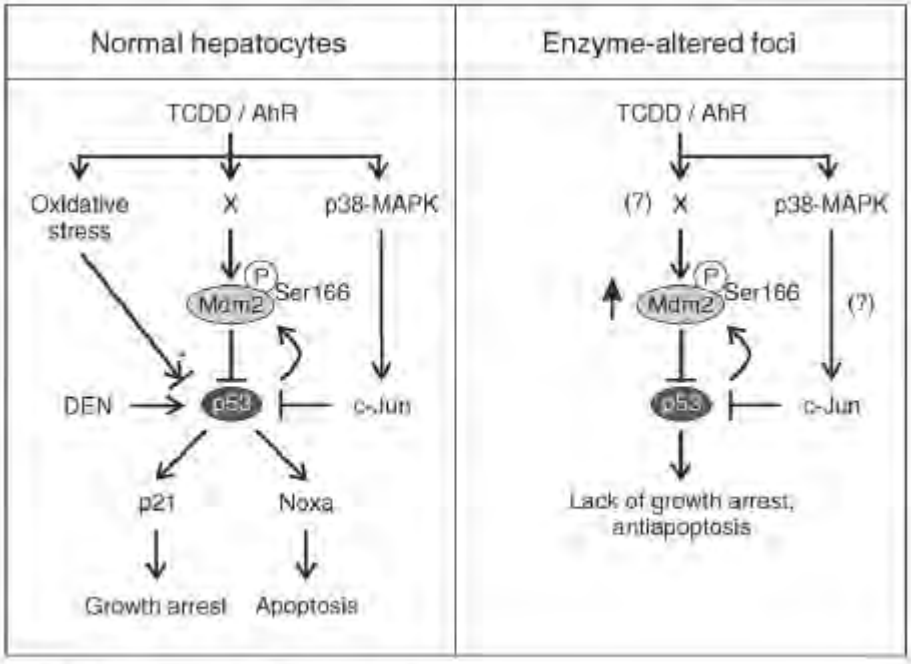
Activation of the AHR pathway(s) (**Key Event 1**) appears necessary for TCDD's promoter properties since animals with less responsive AHR pathways are less sensitive to TCDD's promotional effects (Beebe et al., 1995). It is of note that indole-3-carbinol (I3C), a dioxin-like, naturally occurring compound that can activate AHR pathways, is a tumor promoter and yet its' beneficial effects on tumor prevention are being seriously addressed in two clinical trials in which I3C is given to cancer patients to prevent cancer (National Cancer Institute; NTC00100958; NTC00033345). On one hand, an AHR ligand with demonstrated promotional properties is actively tested for its therapeutic effects, recognizing any potential to promote

cancer as being a threshold phenomenon that can be managed. On the other hand, TCDD is treated as a one-hit, linear carcinogen even though it possesses the same mode of promoting action as I3C. This highlights the inconsistency between U.S. EPA's linear approach to cancer risk assessment and the threshold approach adopted by the National Institutes of Health (NIH), scientific and medical community for receptor-mediated promoters.

Tumor promotion is the result of agent induced disruption in the balance between normal programmed cell death (apoptosis) and cell division rates that leads to a net growth advantage for populations of initiated cells (Goldsworthy et al., 1996). There is evidence that TCDD inhibits apoptosis in initiated or damaged cells and that this key event has been recognized for over 10 years (Stinchcombe et al., 1995; Woerner and Schrenk, 1996 and 1998; Park and Matsumura, 2006; Luebeck et al., 2000; Schrenk et al., 2004; Schwarz et al., 1995). A recent examination of numerous rodent liver carcinogens for which gene array data were available, found that 27 of the 37 signature genes associated with rodent liver tumors were either proliferative- or antiapoptotic-related genes (Fielden et al., 2007.) The following figures from Schwarz et al. (2000) and Bock and Kohle (2006) identify some of the cell signaling and regulatory pathways through which TCDD can inhibit apoptosis. The point of these two figures is that there are emerging mechanistic data that show how cell signaling changes induced by TCDD lead to inhibition of apoptosis. Again, the two key events, inhibition of apoptosis and induced cell proliferation (discussed below) affect the cell cycle in a manner that promotes the development of initiated cells within foci to develop into adenomas and carcinomas.

[Intentionally left blank.]





* TCDD decreases DEN-induced p53

Involvement of a p53 role in normal apoptosis appears to be an important mechanistic feature of TCDD-induced AHR activation (Paajarvi et al.2005). The cell signaling changes caused by TCDD that inhibit apoptosis are complex and yet to be fully elucidated. However, it should be noted that low doses of TCDD actually inhibit the formation of spontaneously generated precancerous liver foci (Teeguarden et al., 1999).

TCDD's ability to induce cell proliferation may also contribute to it tumor promoting effects (Schwarz et al., 1995; Whysner and Williams, 1996; Buchmann et al., 1994). This key event is similar to inhibition of apoptosis with respect to temporality. The most recent evidence for TCDD-induced proliferation comes from the NTP (2006) cancer bioassay of TCDD. Clear evidence of increased cell proliferation was seen by 31 weeks into the study and at the higher dosages. Earlier studies include a two-week administration study in which proliferation was only observed in the periportal regions of the liver whereas overall hepatic proliferation did not increase (Fox et al., 1993). Cell proliferation increases were observed in other initiation promotion studies after 90 days (Maronpot et al., 1993) or after 30 to 60 weeks of TCDD administration followed by reversal of proliferation once TCDD was stopped (Walker et al., 1998). Good experimental work provides mechanistic information further supporting the plausibility of increased cell proliferation with respect to TCDD's promotional MOA (Tian et al., 2002; Patel et al., 2006).

There is a considerable body of literature describing elements of the AHR pathways and processes they regulate, which are informative regarding the specifics of the mechanism by which TCDD causes tumor promotion (Knerr and Schrenk, 2006; Puga et al., 2002; Puga et al., 2000; Marlowe and Puga, 2005; Puga et al., 2007; Bock and Kohle, 2006). These are summarized here because they bring considerable weight to the proposal that promotion is driven by TCDD activated AHR modulation/disruption of normal cellular pathways and processes that control apoptosis and cell proliferation. The following cell-cycle related changes have been reported for TCDD: stimulation of mitogenic inflammatory and immune responses associated with cell stress pathways involving prostaglandin and prostacyclin changes, (Matsumura et al., 2007; Vogel et al., 2007; Pande et al., 2005), changes in signaling pathways including plasminogen activator inhibitor type 2 (Gohl et al., 1996), cyclin-dependent kinase inhibitors

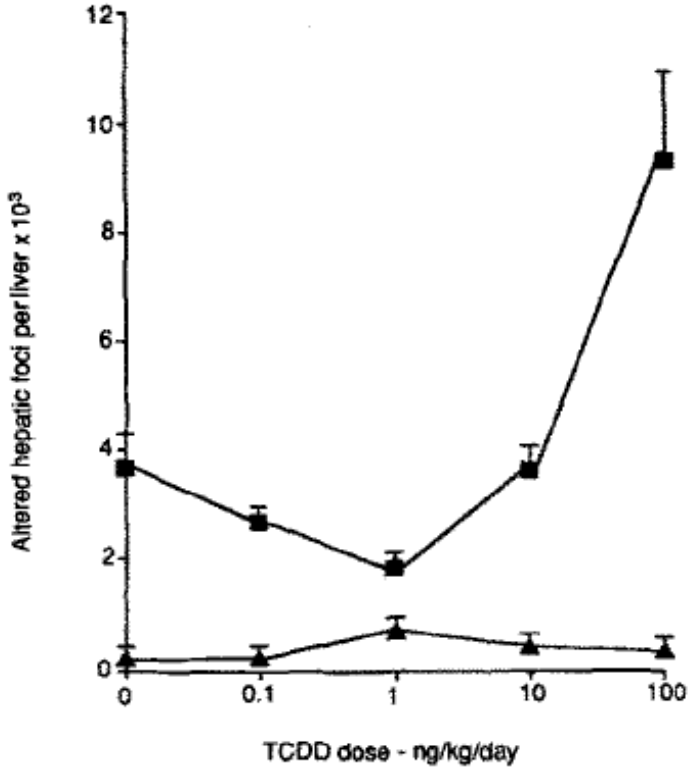
(Crawford et al., 2003), activation of Gpr15, B94, Sahh and Siah2 (Rivera et al., 2007), modulation of c-Src and ERK-2 (Kitamura et al., 2006; Dunlap et al., 2002) and alteration in Tsc-22 (Iida et al., 2007), alterations in retinoid pathways unique to rats (Toyoshiba et al., 2004; Kelley e al., 2000; Schmidt et al., 2003), and induction of reactive oxygen occurring through different mechanisms (Badawi et al., 2000; Graham et al., 1988). TCDD also induces a gene battery, including Nrf2, that serves to attenuate any oxidative stress induced by TCDD (Kohle and Bock, 2006). In summary, the cell-signaling system that controls cell biology is incredibly complex (Kohn, 1999) and new exploratory gene array studies (Ovando et al., 2006;) will add to the growing mechanistic information supporting TCDD's major key events of apoptosis inhibition and increased cell proliferative response.

3.2.1.2.2 Dose-Response

The National Academy of Sciences concluded that the weight of evidence favors the use of nonlinear approaches to low-dose extrapolation of TCDD effects for cancer risk assessment. The preponderance of evidence supports the non-linearity in the dose response for each of the key events identified as being necessary for TCDD's carcinogenic effects in the rodent liver.

While AHR binding, indeed binding to receptor systems in general, is recognized as being a linearly related to free concentrations of ligand at low concentrations, receptor occupancy is known to be non-linear across a wide range of doses (Limbird, 2005; Poland, 1997; Byrd et al., 1998). Furthermore, while receptor binding/occupancy is linear low-dose, processes downstream of receptor binding including cell signaling, changes in gene expression and modulation of highly regulated biological processes such as apoptosis and cell proliferation (see previous figure), are not necessarily so. The high degree of regulation of these processes, shown in the figures above, illustrate the multiple control points, feedback loops, and redundancies that ultimately reflect excessive activation that lead to TCDD-induced promotion. All together, these complex, myriad numbers of cell-signaling interactions culminate in non-linear biological responses.

Tumor promotion in general has long been believed to operate through non-linear threshold processes. Practical thresholds have been observed for both the induction of liver tumors by TCDD (Kociba, the 1982 NTP study) and the induction of their presumed precursor lesions, altered hepatic foci. The following figure shows the dose-response for induction of altered hepatic foci showing a clear non-linear relationship between administered dose and the incidence of these lesions. The square boxes are the TCDD-treated groups and the triangles are controls. U-shaped dose response curves have also been observed for Phenobarbital (discussed in Teeguarden et al., 1998), another classic tumor promoter. TCDD has also been shown to inhibit spontaneous development of pre-neoplastic lesions (Teeguarden et al., 1999) resulting in U-shaped dose-response curves as described by Andersen and Barton (1998).



In the NTP 2006 cancer bioassay the relationship between the dose of TCDD, and liver tumors, shows a threshold: "Differences in the shapes of the dose-response curves for several neoplasms were noted between the studies, with the NTP study showing non-linearity for all neoplasms." (Walker et al., 2006). Thresholds for increases in proliferation, a process implicated in the mechanism of promotion for TCDD, were reported after 90 days in an initiation-promotion assay

(Maronpot et al., 1993). The reported dose-response relationships for TCDD exhibit threshold phenomenon consistent with TCDD's receptor-based mechanism and it promotional mode of action.

In conclusion, TCDD has been conclusively shown to be a tumor promoter and has been proven to be non mutagenic (Shu et al., 1987; Randerath et al., 1988; Turteltaub et al., 1990), thereby justifying a threshold basis for cancer risk assessment (Schwarz et al., 2000; Waern et al., 1991; Worner and Schrenk, 1996; Teeguarden et al., 1999; Moolgavkar et al., 1996; Poland et al., 1982; Hebert et al., 1990). This conclusion is consistent with U.S. EPA's cancer risk assessment guidelines. Most importantly, the preponderance of evidence summarized here supports the non-linearity of dose-response patterns for the main key events and those biochemical processes underlying them.

3.2.1.2.3 Weight of Evidence

While the mode of action is an important component of the overall weight-of-evidence justifying a threshold approach to cancer risk assessment, there are other lines-of-evidence that must be considered. These include:

- The AHR is necessary for normal development and physiology; a linear approach assumes that the normal background activity of the AHR is pathological. This assumption is not supported by the evidence that a low-level of activated AHR is necessary for normal development and other biological processes. Hence, the linear approach to dioxin cancer risk assessment is scientifically invalid.
- Humans are less sensitive to dioxin than rats from which the cancer data are derived and used in derivation of a cancer potency factor.
- Dioxins exist in a mixture and this mixture can have antagonistic effects.
- Epidemiological studies do not show an increase risk of cancer. Exposures associated with these negative epidemiological findings are much greater than current background exposures subject to this risk assessment.
- The major route of exposure to dioxins is via food. Food levels have declined significantly over the last 30 years and background concentrations of dioxin in our bodies due to the food supply will continue to decline.

3.2.1.2.4 Physiological Role of the AHR

The AHR plays an important role in normal development and biology (Barouki et al., 2007; Puga et al., 2005). For example, AHR knockout mice (mice lacking an AHR) exhibit notable liver developmental abnormalities and pathology (Schmidt et al., 1996; Lahvis et al., 2000), abnormal vitamin A metabolism (Andreola et al., 1997), immune system impairment (Gonzalez et al., 1995), reproductive defects (Abbott et al., 1999; Baba et al., 2005; Fujii-Kuriyama et al., 2007), and increased risk of certain cancers (i.e., low levels of activated AHR prevents cancer) (Hirabayashi et al., 2007). At the same time, TCDD activation of the AHR in animals with an intact AHR exerts an inhibitory influence on certain tumors including spontaneously occurring breast and uterine cancers in rats (Kociba et al., 1978) and prostate cancer (Fritz et al., 2006). TCDD inhibits *c-fos*, a uterine oncogene in rats (Astroff et al., 1991) and it induces favorable molecular changes related to breast cancer (Gillesby et al., 1997; Hsu et al., 2007). The AHR may serve an important role in preventing and/or modulating atherosclerosis (Ichihara et al., 2007; McMillan and Bradfield, 2007). Gonzalez et al. (1995) concluded: "Thus, AHR may protect the liver from endogenously-generated toxins or it may be directly involved in liver cell differentiation or apoptosis. . . . The AHR is clearly required for normal development and physiological activity in the mouse." In view of the 1000-fold greater naturally occurring TEQ in human blood (i.e., TEQ activity from natural sources, not dioxins), it is assumed that the AHR has a biological role in normal human physiology (Connor et al., 2006; Schecter et al., 1999). A linear approach to cancer risk assessment holds that this basal low-level AHR activity required for normal development and physiology is pathological. This assumption is biologically implausible as it is contrary to the AHR's normal biological role that requires the presence of a constant low-level of activated AHR.

Humans are fundamentally less sensitive than rats to TCDD. This difference in sensitivity may have several biological explanations, but one of these is that the human Ah receptor possesses a key mutation that renders it 10-fold less receptive to binding the TCDD molecule (see numerous citations as reviewed in Connor and Aylward, 2006). This is similar to the AHR mutation conferring relative TCDD insensitivity to the DBA mouse. This fundamental shift in sensitivity is reflected in data regarding enzyme induction (the most sensitive direct biological response to

dioxin exposure in every tested species) in response to exposure to TCDD and other dioxin-like compounds in animals and humans.

Lambert et al. (2006) measured CYP1A2 activity in Yucheng subjects. TEQ-related increases in CYP1A2 activity, as measured by caffeine metabolism, did not appear to be TEQ-related until blood concentrations of 300 to 400 ppt or greater were reached. These human CYP1A2 activity results vs. TEQ indicate that humans are less sensitive to TCDD-induced CYP1A2 induction than are Sprague Dawley female rats (Toyoshiba et al., 2004b). Thirteen Seveso subjects with blood TCDD concentrations ranging from 23.9 to 268 ppt did not exhibit induction of either CYP1A1 or 1A2 mRNA, which are the most sensitive markers of AHR activation (McHale et al., 2006). Abraham *et al*. (2002), in examining highly exposed humans, concluded that moderate TCDD exposure (up to a serum lipid TCDD concentration of 1000 ppt) does not cause CYP1A2 induction. This result explains why chemical workers with mean TCDD of 157 ppt and St Lawrence River fish eaters with a blood level of 300 ppt TEQ showed no CYP1A2 induction while CYP1A2 induction was observed in Taiwanese patients ingesting contaminated rice oil (with blood levels of 3000 to 6000 ppt TEQ). A study of Inuit women with blood levels of TEQ five to seven times that of controls found no increased CYP1A1 activity in placentas suggesting that such induction requires in excess of 125 to 175 ppt TEQ before it expresses itself (Pereg et al. 2002). Evidence showing human insensitivity to TCDD extends beyond simple enzyme induction. For example, two Austrian women, with extremely high body burden concentrations of TCDD, exhibited severe chloracne whereas their major clinical findings were normal (Geusau et al., 2001) and epidemiological studies of exposed workers exposed to relatively high levels of dioxin (TEQ) have no consistent evidence of adverse health effects associated with TEQ exposures (discussed further below).

The human AHR has significantly lower binding affinity with TCDD relative to other species and this is due to a highly conservative difference in the TCDD binding region of the human AHR. While sequencing of the human AHR has found a number of polymorphisms, none of the polymorphisms are found in the TCDD binding region and, therefore, the human AHR is very stable for lower binding to dioxins in the human population. Other polymorphisms found outside of the TCDD binding region have either no effect on AHR activity or, conversely, when two specific polymorphisms are found in the same AHR, the TCDD-induced AHR activity is

decreased (Wong et al., 2001) Guzelian et al., (2006) and Connor and Aylward (2006), provide further review on the relative unresponsiveness of humans to some of the more sensitive enzyme induction changes induced by TCDD and differences in AHR that are responsible. This species difference in sensitivity should be accounted for in that a rat-derived cancer potency factor should be adjusted with a species-specific uncertainty factor that accounts for the fact that humans are at least 10-fold less sensitive than rats to TCDD.

Dioxin exposures always occur as a mixture. Any dioxin cancer potency factor applied in human health risk assessment ignores the presence of other AHR ligands present in the mixture and their role in inhibiting or modulating the effects of TCDD. Humans are exposed to a great number of AHR ligands formed endogenously, ingested in the diet (naturally occurring AHR ligands) or from combustion/industrial sources such as TCDD (Connor et al., 2007; Schecter et al., 1999). Ligands for the AHR come from many different sources including herbs, fruits and vegetables, tea, and the breakdown of plant materials in the form of humic acid (Bittner et al., 2006: Jeuken et al., 2003). Humans have about a 1000-fold greater TEQ from natural sources than that attributable to dioxins, furans and PCBs (Connor et al., 2007; Schecter et al., 1999). Some of these naturally occurring dioxin-like compounds, or endodioxins, are fairly potent AHR ligands (Oberg et al., 2005) and are reported to inhibit or likely to protect against dioxin toxicity (Park et al., 2005; Hamada et al., 2006; Connor and Finley, 2003). A linear approach to dioxin cancer risk assessment grossly exaggerates the cancer risk since as it ignores the impact of these other AHR ligands. A threshold approach would yield less uncertainty and exaggeration with respect to the presence of other AHR ligands that could antagonize the cancer risk attributed to dioxins.

The international Agency for Research on Cancer classified TCDD as a known human carcinogen based on animal studies and mechanistic information. However, the epidemiology data was thought to be limited. Increased risk of all cancers combined, lung cancer, non-Hodgkin's lymphoma (NHL), and soft tissue sarcoma were seen in some studies but not all (IARC, 1997). While the epidemiology data has not shown consistent cancer findings, three studies have been used for human cancer risk assessment for dioxins because the populations were large, there was a long observation period, the exposures had been assessed by serum dioxin evaluations, and incidences of chloracne indicated the potential for high exposure

(Steenland et al., 2003; Ott et al., 1996; Flesch-Janys et al., 1995). These studies all report an increased risk of all cancers combined. Recently, an extensive dioxin serum evaluation of trichlorophenol was completed of workers in Midland, Michigan who had been studied previously for cancer (Collins et al., 2007a; Bodner et al., 2003). Eleven percent of these workers were found to have chloracne (Bond et al., 1990). This study is large, has a significant number of serum dioxin evaluations to assist in exposure estimation, has high exposure given the prevalence of chloracne, and has a long observation period. The most recent update of this study finds no consistent evidence that these chlorophenol workers have an increased risk of cancer collectively or in any type of cancer related to TCDD exposure (Collins et al., 2007b, c, and d). The lack of consistent findings across human studies on cancer risk from highly exposed workers evinced from serum dioxin evaluations indicates that TCDD at levels experienced in manufacturing operations may not be carcinogenic to humans.

The scientific evidence supporting TCDD's classification as a known human carcinogen has relevance to the development of a TCDD cancer potency factor. Since epidemiological evidence is inconclusive for its human carcinogenicity classification (IARC, 1997; Cole et al., 2004) the only justification for TCDD's human carcinogenicity classification is the assumption that the same mechanism for causing tumors in laboratory animals is relevant to humans. We now know there are differences in gene expression between rat and human liver cells with respect to TCDD and these differences are also seen when comparing TCDD to 2,3,7,8-TCDF and 2,3,4,7,8-PeCDF and that tissues respond differently to TCDD thereby challenging the assumption that TCDD contributes to any and all tumor types in humans (Gollapudi et al., 2007; Rowlands et al. 2007; Zhang et al., 2007). Gene expression differences create questions about the similarities between humans and rats as to whether or not humans really do respond similarly to TCDD. As previously discussed, for another rodent liver carcinogen, Phenobarbital, which has many mode of action similarities with TCDD, a scientific committee concluded that phenobarbital's ability to cause tumors in rodents was not relevant for human risk assessment (Holsapple et al., 2006). Since the scientific evidence is lacking for classifying TCDD as a known human carcinogen, this knowledge should be factored into development of TCDD's cancer potency factor.

3.2.1.2.5 Summary and Conclusions

A threshold, non-linear cancer potency factor for dioxins is supported by a large body of scientific evidence, by the criteria that have been established for judging the mode of action, and by the overall weight of evidence regarding the effects of dioxin and dioxin-like compounds in humans. This opinion was reflected in the recommendations the NAS made to the EPA concerning the draft Dioxin Reassessment. Other scientists have also published papers describing TCDD's mode of action (Teeguarden and Walker, 2003) or calling for a threshold approach to dioxin cancer risk assessment (Popp et al., 2006).

> A dose-response assessment for dioxin based on receptor binding would predict a nonlinear dose-response relationship with a threshold for tumor induction. A nonlinear relationship is more consistent with the available chronic animal bioassays and human epidemiology studies (Byrd et al., 1998).

For a similar carcinogenic mode of action involving Phenobarbital (PB), a recent analysis of the mode of action for rodent carcinogens (Holsapple et al., 2006) concluded:

> Additional PB responses that are key in the tumorigenic effect include increased cell proliferation, inhibition of apoptosis, hypertrophy, and development of altered hepatic foci. These effects are all CAR-dependent . . . . Hence, for those compounds for which there are robust data for a PB-like MOA it can be concluded that the carcinogenic response is not relevant to humans.

Even though one might argue that the rodent tumor response to TCDD, given that it follows a receptor-based mode of action similar to Phenobarbital, lacks relevance for humans, the data are more than adequate to justify a threshold-based cancer potency factor. On the other hand, a linear approach is not scientifically justified and is most consistent with a one-hit theory of carcinogenicity. A one-hit theory for cancer has no scientific foundation when one considers the complexities for tumor development (Hanahan and Weinberg) and the cumulative weight of evidence data for dioxins.

3.2.1.3 Methods

Nonlinear and linear estimates of cancer potency were derived for TCDD as described below.

3.2.1.3.1 Nonlinear Cancer Potency Estimates

For the nonlinear assessment, a cancer reference value was derived for TCDD using the following equation:

$$RfD = \frac{POD}{UF_a \times UF_h \times UF_s \times UF_l \times UF_d} \qquad Eq.\ 1$$

where,

RfD (Cancer)	=	Reference dose;
POD	=	NOAEL, LOAEL, benchmark dose (BMD);
UF_a	=	Uncertainty factor for interspecies variation;
UF_h	=	Uncertainty factor for human variation;
UF_s	=	Uncertainty factor for sub-chronic to chronic exposure duration extrapolation;
UF_l	=	Uncertainty factor for use of a LOAEL; and
UF_d	=	Uncertainty factor for database deficiencies.

For the deterministic assessment, a conservative estimate of the POD (*i.e.*, 95% lower confidence limit) was adopted along with point estimates for each of the uncertainty factors. For the probabilistic assessment, a probability density function was developed for the POD and each uncertainty factor. The uncertainty factors are discussed in more detail below.

3.2.1.3.2 Linear Cancer Potency Estimates

For linear estimates of cancer potency, cancer dose-response assessments have historically relied upon the 95% upper confidence limit on the linear term of the multistage model (q1*). Based upon U.S. EPA guidelines for carcinogen risk assessment (U.S. EPA, 2005a, b), nonlinear estimates of cancer potency can be estimated using a margin of exposure ("MOE") or RfD approach (see Eq. 1), while linear estimates of cancer are estimated from the point of departure using the following equation:

$$CSF = \frac{BMR}{POD} \qquad Eq.\ 2$$

Where,

BMR = benchmark response rate (*e.g.*, 10%, 5%, 1%); and
POD = point of departure (central tendency, upper and lower confidence limits)

For the deterministic assessment, a conservative estimate of the POD (*i.e.*, 95% lower confidence limit) was adopted. For the probabilistic assessment, a probability density function was developed for the POD.

3.2.1.4 Summary of Proposed Cancer Slope Factor

The process for deriving a cancer value for TCDD includes a number of decision points, which include:

1. Identification of the Critical Effect/Data Set(s)
2. Identification of a Dose Measure(s)
3. Identification of a Response Measure(s)
4. Selection of a Dose-Response Model(s)
5. Selection of Response Level(s) (Point of Departure)
6 Low-Dose Extrapolation
7. Presentation of Cancer Value

The assessment presented below relies upon the published dose-response assessment of Maruyama and Aoki (2006). The dose-response assessment of Maruyama and Aoki (2006) was selected as the basis for determining a cancer slope factor for TCDD for the following reasons:

- The assessment relies upon data from the cancer bioassay conducted by NTP (2006), which provided definitive dose-response information in a sensitive test species (female rat) and target tissue (liver).
- The dose-response data were assessed in terms of tissue dose (liver burden), rather than administered dose, which is inappropriate for persistent chemicals, or body burden, which may be inappropriate for interspecies extrapolation due to issues associated with differences in body composition and distribution between rats and humans.

- Physiologically-based pharmacokinetic (PBPK) models, a mathematical tool that has been embraced by regulatory agencies for use in risk assessment (U.S. EPA, 2006), were used by Maruyama and Aoki (2006) to account for pharmacokinetic differences between rats and humans.

Each of the decision points is summarized below.

3.2.1.4.1 Identification of the Critical Effect/Data Set

The NTP cancer bioassays serve as the definitive dose-response data set for TCDD based upon a consideration of the number of dose groups (five), number of animals tested per dose (53-54), and tissue time course data collected (liver, adipose), which permits the use of internal dose in the dose response assessment. Liver adenomas, as identified by Maruyama and Aoki. (2006), which appears to be a sensitive tumor site, was used to estimate the cancer potency of TCDD.

Table 3-2 Dose-Response Data for Liver Adenomas in Female Rats (NTP, 2006)

Applied dose (ng/kg BW)	Liver Dose 1 (ng/g tissue)[1]	Liver Dose 2 (ng/g tissue)[2]	Liver Adenomas	Number of animals
0	0	0	0	53
3	0.28	1.57	0	54
10	0.93	4.37	0	53
22	2.05	7.27	0	53
46	4.28	9.96	1	53
100	9.3	12.3	13	53

[1] Concentrations were calculated with a proportional expression and a concentration data in NTP study (Maruyama and Aoki, 2006).
[2] Concentrations were simulated with a rat PBPK model (Andersen et al., 1993) (Maruyama and Aoki, 2006).

Use of the NTP 2006 data may be viewed as conservative, since the test species (female rat) was selected on the basis of its sensitivity to the carcinogenic effects as identified in previous studies (Kociba *et al*., 1978). However, the assessment of Maruyama and Aoki (2006) does not consider additional liver tumors (cholangiocarcinomas), tumors at other tissue sites that were significantly increased (lung, oral mucosa, uterus), or equivocal tumor sites (pancreas, liver cholangioma, hepatocholangioma). Therefore, a critical assumption of this assessment is that risk assessment decisions based on a sensitive tumor type (liver adenoma) will also be protective of other tumor types. The potential impact of using alternative tumor sites is discussed in Section 3.2.1.4.8.

Although U. S. EPA also used epidemiology data to estimate the cancer potency for TCDD, a recently published analysis indicates that the dose-dependent elimination of TCDD makes backward extrapolation of past internal TCDD doses highly uncertain (Aylward et al., 2005). For this reason, the epidemiology data were not used to estimate the cancer potency for TCDD.

3.2.1.4.2 Identification of a Dose Measure

Maruyama and Aoki (2006) assessed the dose-response data in terms of internal dose using two estimates of liver burden (**Table 3-2**). For liver dose 1, concentrations were calculated with a proportional expression and concentration data in the NTP. For liver dose 2, concentrations were simulated with a rat PBPK model (Andersen *et al.*, 1993)(Maruyama and Aoki, 2006). Liver burden is considered to be a better predictor of liver response than body burden or administered dose. For this assessment, liver dose 1 was conservatively selected since the values are slightly lower than the corresponding values for liver dose 2, which will result in higher estimates of cancer potency. Liver burden is currently the only target tissue dose that can be estimated with a high degree of confidence in both rats and humans and for which the mode of action has been adequately studied.

3.2.1.4.3 Identification of a Response Measure

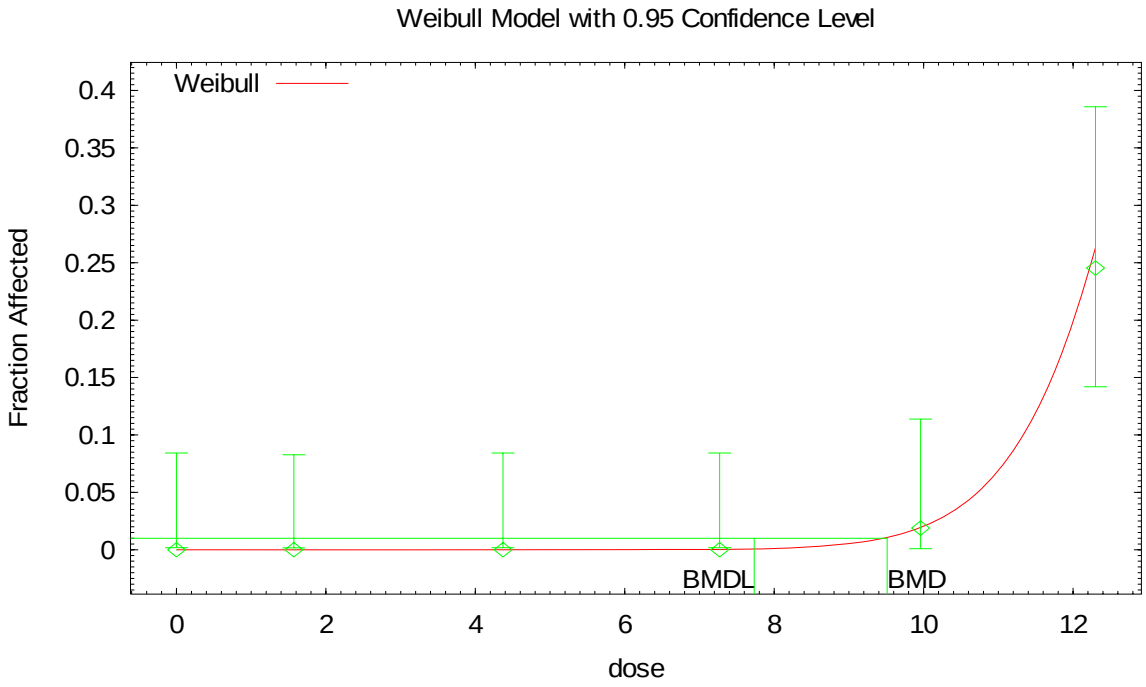
The dose-response data were assessed in terms of extra risk, which serves as the default response measure for tumor incidence data. The assessment of Maruyama and Aoki (2006) did not consider adjusting tumor incidence for mortality (*e.g.,* poly-3 adjustment). The potential impact of adjusting tumor incidence is discussed in Section 3.2.1.4.8.

3.2.1.4.4 Selection of a Dose-Response Model

Maruyama and Aoki (2006) examined several dose-response models (multistage, logistic, and Weibull). All three models provided acceptable fits to the data, as well as similar values for the point of departure. The Weibull model was selected since it provided a slightly better fit to the

data (p-value = 1.000, indicating a perfect fit to the data) (Maruyama and Aoki, 2006) (**Figure 3-3**). The authors did not present the Akaike information criteria (AIC), which can also be used to guide model selection. However, in a majority of cases, the p-value and AIC will indicate the same model as providing the best overall fit to the data. The impact of using alternative dose-response models is discussed in Section 3.2.1.4.8.

Figure 3-3. Fit of Weibull Model to Dose-Response Data for Liver Adenomas in Female Rats (NTP, 2006)



3.2.1.4.5 Selection of a Point of Departure

The point of departure is intended to serve as the dividing line between the dose "range of observation," where dose-response data are available, and the dose "range of extrapolation," where dose-response data are lacking and must be predicted. Maruyama and Aoki (2006) used the dose producing a 1% increase in extra risk (ED01) and its corresponding 95% lower confidence limit. Because the ED01 corresponds to the dose at which the dose-response relation becomes nonlinear, and because it falls well within the range of observation (there are three data points below the ED01), the use of a 1% response rate appears to be appropriate for this data set. The impact of using alternative points of departure is discussed in the uncertainty section below.

For the deterministic assessment, the LED01 values presented in the table below were used to determine a cancer value for TCDD.

Table 3-3. Points of Departure Based Upon Liver Adenomas in Female Rats (Maruyama and Aoki, 2006).

Point of Departure	Internal Dose (ng/g liver)	Human Equivalent Dose (ng/kg-day)[1]
ED01	3.73	6.3
LED01	1.97	3.3

[1]Human equivalent doses were not presented by the authors, but were instead estimated from the unit risk values presented by Maruyama and Aoki (2006).

For the probabilistic assessment, uncertainty in the point of departure was characterized as a lognormal distribution with a central tendency value equal to the ED01, and a 5th percentile equal to the LED01.

3.2.1.4.6 Low-Dose Extrapolation

A biologically-based dose-response model, which serves as the preferred basis for low-dose extrapolation (USEPA, 2005), is not available for TCDD. Methods for low dose extrapolation include linear and nonlinear methods, as described above. Because data for TCDD do not support a direct genotoxic mode of action, but instead support a role as a tumor promoter (see MOA summary above), a nonlinear method of low-dose extrapolation is the most appropriate for TCDD as recommended by the NAS (2006). A linear estimate of cancer potency is presented for the sake of comparison and to reflect the Part 201 approaches for assessing cancer risk. The difference in the derivation between the two approaches, linear (non-threshold) and non-linear (threshold), is in the method from which the values are derived. Because it assumes a threshold exists for the effects of dioxin, the non-linear extrapolation utilizes an approach identical to that used to derive a non-cancer reference dose (RfD) except that it has a cancer reference dose as its endpoint. In such an approach, the Cancer RfD would be used in the same algorithm as that used to set a non-cancer direct contact criteria. *See* Mich. Admin. Code R. 299.5720. The linear extrapolation uses a dose-response model (linearized multi-stage model) that results in an upperbound slope factor for doses well below the observed experimental results.

For the nonlinear assessment, the following uncertainty factor values were used:

- UF_a – The default value of 10 for UF_a is comprised of values of 3.16 (square root of 10) for toxicokinetic variation and 3.16 for toxicodynamics variation. For the deterministic assessment: (1) the toxicokinetic component of UF_a was set equal to 1.0, since a PBPK model was used to account for species differences (Maruyama and Aoki, 2006); and (2) for the toxicodynamic component, a value of 0.1 was conservatively adopted since there are numerous data that suggest humans are less sensitive than rats by at least a factor of 10 with respect to receptor binding and downstream events (Connor and Aylward, 2006; Guzelian *et al*., 2006). Lambert *et al.* (2006) showed the relationship between TEQ and CYP1A2 mediated caffeine metabolism that suggests a NOEL of between 3400 and 400 ng/kg equivalent to a TCDD body burden of 100 to 140 ng/kg since rats begin to display CYP induction around 2 ng/kg; this suggests an increased sensitivity of rats on the order of 50 fold or greater. Since U.S. EPA and the NAS agree that the Ah Receptor (AhR) binding leading to CYP induction is the critical event that initiates and precedes the cascade of events that result in TCDD's various toxic endpoints, this difference in sensitivity needs to be accounted for in the derivation of both cancer and non-cancer toxicity criteria. For the probabilistic assessment: (1) the UF of 1.0 was retained for the toxicokinetic component; and (2) the UF for the toxicodynamic component was allowed to range from 0.1 to 1.0 as a uniform distribution to include the more likely assumption that humans are less sensitive than rats.

- UF_h - The default value of 10 for UF_h is comprised of values of 3.16 (square root of 10) for toxicokinetic variation and 3.16 for toxicodynamics variation, which is intended to cover potentially sensitive subpopulations. For the deterministic assessment, a value of 3.16 was adopted for the toxicokinetic component to account for individual variation in TCDD half-life. For the toxicodynamic component, a conservative value of 3.16 was retained to account possible variation in sensitivity between individuals. Abraham *et al*. (2002) in examining highly exposed humans concluded that moderate TCDD exposure (up to a serum lipid TCDD concentration of 1000 ppt) does not cause CYP1A2 induction. This result explains why chemical workers with mean TCDD of 157 ppt and St Lawrence River fish eaters with a blood level of 300 ppt TEQ showed no CYP1A2 induction while Taiwanese patients ingesting contaminated rice oil (with blood levels of 3,000 to 6,000 ppt TEQ) did. By comparison, the US population average background is approximately 25 ppt TEQ and the UM DES study group falls between that level and approximately 33 ppt TEQ on average (UM DES, 2006). If applicable to humans, the inhibitory effects of TCDD on CYP1A2 induction *in vitro* would suggest that moderately increased doses would increase human caffeine metabolism while high doses would inhibit it due to saturation and inhibition of the enzyme by the excess TCDD. In fact, the opposite happens (Guzelian *et al*. 2006). The related CYP1A1 enzyme can be co-induced with CYP1A2, but unlike CYP1A2 is found in extrahepatic tissues. Tawainese women poisoned by contaminated rice oil (with a body burden thought to be as high as 10,000 ppt TEQ) were found to have placental CYP1A1 levels 100 times greater than controls (placentas were reported to contain 60 to 892 times the TEQ than controls) (Connor and

Aylward, 2006; Lucier *et al*. 1987; Schecter *et al*. 1996). A study of Inuit women with blood levels of TEQ five top seven times that of controls found no CYP1A1 induction in placentas suggesting that such induction requires in excess of 125 to 175 ppt TEQ before it expresses itself (pereg et al. 2002). Further, an examination of human polymorphisms of the AHR (Wong *et al*., 2001) found no differences in ligand binding by humans displaying two polymorphisms (V570I and P571S) and the normal genotype. However, *in vitro* expression experiments revealed these variants failed to support TCDD induction of CYP1A1 expression suggesting these variants may be less sensitive to the effects of TCDD and related compounds that act through the AHR. This suggests that sensitive human sub-populations may not exist for AHR binding and induction of CYP enzymes. For the probabilistic assessment, 1) the toxicodynamic component was defined as a uniform distribution ranging from 1.0 to 3.16 to account for the fact that AHR polymorphisms do not affect binding of the ligands to the receptor and 2) the toxicokinetic component was also defined as a uniform distribution ranging from 1.0 to 3.16.

- UF_s – Because the key study (NTP, 2006) included lifetime exposures, a value of 1.0 was adopted for both the deterministic and probabilistic assessments.

- UF_l – Although benchmark dose methods were used to estimate a point of departure, a value of 3 was adopted for UF_l to ensure that the resulting cancer value falls below the threshold for tumor formation for the deterministic assessment.. Inspection of **Figure 3-3**, indicates that doses 3-fold lower than the point of departure show no evidence of increased tumors in female rats. For the probabilistic assessment, this value was allowed to range from 1.0 to 10 because of uncertainty over the location of the threshold relative to the POD.

- UF_d – Because the toxicokinetics, carcinogenicity, and mode of action of TCDD have been well studied, a value of 1 is adopted for both the deterministic and probabilistic assessments.

A value of 30 (1 x 10 x 1 x 3 x 1) was adopted for the net uncertainty factor in the deterministic assessment of a cancer potency factor. For the probabilistic assessment, the net uncertainty factor was best characterized as a gamma distribution with a location of 0.21, scale of 9.55, and a shape of 1.35.

3.2.1.4.7 Cancer Value Presentation

For the nonlinear assessment, dividing the LED01 value by a net uncertainty factor of 30 results in a deterministic cancer RfD value of 110 pg/kg-day. For the probabilistic assessment, the cancer RfD was best described as a lognormal distribution with a mean of 1,100 pg/kg-day and a standard deviation of 1,500 pg/kg-day.

For the linear assessment, dividing a response rate of 0.01 by the LED01 results in a cancer potency estimate of 3,000 $(mg/kg\text{-}day)^{-1}$. For the probabilistic assessment, the resulting cancer potency estimate was best characterized as a lognormal distribution with a mean of 1,790 $(mg/kg\text{-}day)^{-1}$ and a standard deviation of 648 $(mg/kg\text{-}day)^{-1}$.

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3.2.1.4.8 Uncertainty

The dose-response assessment presented above incorporated decisions made based upon the best available data and science at each decision point. The potential impact of alternative options at each decision point is discussed briefly below.

- *Critical Effect/Data Set* – Additional tumor sites were increased in female rats exposed to TCDD, including oral cavity, lung, uterus, and pancreas. However, it is difficult to combine tumors sites when each is evaluated in terms of tissue dose. OEHHA (2007) derived cancer potency estimates in terms of adipose dose for each of these tumor sites as well as for combined tumors, and determined that the potency estimate for all tumors combined was approximately 5-fold higher than based upon liver adenomas alone (as done by Maruyama and Aoki, 2006). On the other hand, cancer potency estimates based upon species other than the female rat are expected to be lower than those derived from the female rat data.

- *Dose Measure* – The assessment of Maruyama and Aoki (2006) included two estimates of rat liver dose, which were fairly similar at the high dose, but nearly a factor of 6 different at the low dose (**Table 3-2**). These differences resulted in an approximate four-fold difference in the resulting cancer values between use of liver doses 1 and 2. Potency estimates derived by U.S. EPA (2003) in terms of body burden and by OEHHA (2007) in terms of adipose burden were considerably higher than those derived by Maruyama in terms of liver burden.

- *Response Measure* - Because the liver tumor rate in control animals is zero, extra risk and added risk are equivalent, and therefore the selection of the measure of risk does not have an impact on the results. As stated above, Maruyama and Aoki (2006) did not adjust incidence for mortality. Use of poly-3 adjusted incidence for liver adenomas did not

have an appreciable impact (<5%) on the ED01 and LED01 values estimated by the Weibull model.

- *Dose-Response Model* – Maruyama and Aoki (2006) examined three dose-response models, all of which provided excellent fits to the data. In general, the estimates for the point of departure were in excellent agreement with one another (within 30%), and therefore the selection of the dose-response model has only a small impact on the results.

- *Point of Departure* – Consideration of alternative points of departure can have a significant impact on linear estimates of cancer potency when the data are highly nonlinear, as in this case. Use of the LED10 (10% response rate) from the Weibull model, which falls at the high end of the range of observation, results in a linear potency estimate that is approximately seven-fold higher than that estimated from LED01 (1% response rate). Conversely, use of the LED001 (0.1% response rate) from the Weibull model, which falls at the low end of the range of observation, results in a linear potency estimate that is approximately seven-fold lower than that estimated from the LED01.

3.2.2 Summary of Proposed Cancer Criterion

The results of a linear and non-linear cancer evaluation for TCDD, treated both deterministically and probabilistically, are summarized in the following table.

	Nonlinear		**Linear**	
	Deterministic	**Probabilistic**	**Deterministic**	**Probabilistic**
Point of Departure (units)	LED01 = 3.3 (ng/kg-day)	Lognormal (mean=6.3, 5th percentile=3.3) (ng/kg-day)	LED01 = 3.3 (ng/kg-day)	Lognormal (mean=6.3, 5th percentile=3.3) (ng/kg-day)
Uncertainty Factor	30	Gamma (location=0.21, scale = 9.55, shape = 1.35)	NA	
Cancer Value (units)	0.11 (ng/kg-day)	Lognormal (mean=1100, SD=1500) (pg/kg-day)	3,000 (mg/kg-day)$^{-1}$	Lognormal (mean=1,790, SD=648) (mg/kg-day)$^{-1}$

The following direct contact soil criteria were calculated using all of the cancer variable inputs and the exposure variables discussed earlier in this section. A spreadsheet showing step-by-step calculations and results is attached as **Appendix A**.

Deterministic Approach

Linear Extrapolation (No Threshold Model) = **19 ppb** (19 ug/kg)

Non-Linear Extrapolation (Threshold Model) = **250 ppb** (250 ug/kg)

Probabilistic Approach

The range of probabilistic results is summarized as follows:

				Percentile (ppb)*				
Basis	**Mean* (ppb)**	**SD* (ppb)**		**1st**	**5th**	**50th**	**95th**	**99th**
Linear Model	920	2600		**27**	54	300	3,500	11,000
Non-Linear Model	17,000	53,000		**150**	410	4,500	68,000	200,000

*Values expressed to two significant figures

3.2.3 Non-Cancer Calculations

The MDEQ's generic residential direct contact criterion of 90 ppt or 0.090 ppb for TCDD is currently based on assumed carcinogenic effects of TCDD and related compounds. MDEQ has not formally calculated or promulgated non-cancer based criteria for TCDD, nor has EPA. Although not expressly required by Dow's License or the Midland SOW, this Report has, consistent with Michigan law, evaluated non-cancer effects in order to gauge whether non-cancer effects are more sensitive, and therefore, should be applied. There are a number of non-cancer effects currently associated with TCDD, including hepatotoxicity (liver effects), immunotoxicity (immune system effects), and reproductive/developmental toxicity. Developmental toxicity is generally accepted as the most sensitive effect, and is therefore the driving non-cancer consideration.

In regard to non-carcinogenic calculations, Part 201 states:

> If the hazardous substance poses a risk of an adverse health effect other than cancer, cleanup criteria shall be derived using appropriate human health risk assessment methods for that adverse health effect and the generic set of exposure assumptions . . . for the appropriate category or subcategory. A hazard quotient of 1.0 shall be used to derive noncancer cleanup criteria.

M.C.L.A. § 324.20120a(4).

The Part 201 algorithm for non-cancer direct contact criteria is discussed in section 2, above.

3.2.3.1 Derivation of a Reference Dose for Non-Cancer Risks of TCDD

Based upon an evaluation of the best available information, a reference dose ("RfD") of 66 pg/kg-day (6.6E-09 mg/kg-day) was calculated for the deterministic portion of the DCC evaluation. The probabilistic assessment of the RfD is discussed below.

Part 201 defines the RfD as:

> a conservative estimate of the daily intake of the human population, including sensitive subgroups, that is likely to be without appreciable risk of deleterious effect during a lifetime. The reference dose is expressed in units of milligrams per kilogram body weight per day.

Mich. Admin. Code R. 299.5703(c).[30] The Part 201 rules also note that:

> The minimum data required to calculate a cleanup criterion for a noncarcinogen when the route of exposure is ingestion or dermal absorption shall be the reference dose that is determined on the basis of the best available information and considering the weight of evidence.[31]

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[30] Generally speaking, reference doses are typically based on "no observed adverse effect levels" ("NOAELs") or "lowest observed adverse effect levels" ("LOAELs") or other similar departure points – i.e., the dosage levels at which adverse effects begin to be noticed in test animals – multiplied or divided by adjustment factors, such as subjective modifying factors ("MFs") used to adjust for study quality, etc., and/or uncertainty factors ("UFs") used to account for sensitive human receptors, toxicodynamic factors, interspecies extrapolation, and similar adjustments. Such adjustments are usually made by orders of magnitude (i.e., x 10).

[31] "Weight of evidence" means an evaluation of the relevant scientific data conducted to determine the likelihood that a hazardous substance is a human carcinogen or causes noncancer adverse health effects, or both. The evaluation may include any of the following information in addition to toxicological bioassays:

(i) Structure-activity relationships.
(ii) Chemical-physical properties.

Mich. Admin. Code R. 299.5736(1). MDEQ has not promulgated a RfD for TCDD.[32] Rule 752 Table 4 lists the RfD for TCDD as "NA" or "not available." Mich. Admin. Code R. 299.5752 Table 4. In the end, there are few legal limitations placed on developing a RfD for TCDD, other than the requirement that the RfD be "determined on the basis of the best available information and considering the weight of evidence."

Reference values are typically derived using the following equation:

$$RfD = \frac{POD}{UF_a \times UF_h \times UF_s \times UF_l \times UF_d} \qquad Eq.\ 1$$

where,

RfD (non-cancer)	=	Reference dose;
POD	=	NOAEL, LOAEL, benchmark dose (BMD);
UFa	=	Uncertainty factor for interspecies variation;
UFh	=	Uncertainty factor for human variation;
UFs	=	Uncertainty factor for subchronic to chronic exposure duration extrapolation;
UFl	=	Uncertainty factor for use of a LOAEL; and
UFd	=	Uncertainty factor for database deficiencies.

This section provides a critical review of previous non-cancer dose-response assessments for TCDD, a discussion of possible candidate bases for an RfD, and a recommendation for the RfD to be used in deriving the non-cancer direct contact criteria for TCDD.

3.2.3.1.1 Review of Previous Non-Cancer Assessments

(iii) Short-term test findings.
(iv) Results of appropriate physiological, biological, and toxicological observations.
(v) Comparative metabolism and pharmacokinetic studies.

Mich. Admin. Code R. 299.5703(h).

[32] Nor did EPA calculate a RfD for TCDD in its Reassessment.

Several non-cancer toxicity criteria have been derived for TCDD (**Table 3-4**). Each of these criteria was derived based on observed effects (particularly, development of the male reproductive tract) in offspring exposed to TCDD while *in utero* and postnatally via lactation. Most of the criteria (except for that of OEHHA) were derived with the goal of maintaining adult maternal exposures below levels associated with effects in the offspring. Three of the criteria (Agency for Toxic Substances and Disease Registry ("ATSDR"), Great Lakes, and OEHHA), were derived on an intake basis. The WHO/UN Food and Agriculture Organization Joint Expert Committee on Food Additives (WHO/FAO JECFA) value was derived on the basis of maternal body burden, with a back-calculation of a human chronic dietary intake rate that would correspond to the tolerable maternal body burden over many years of exposure.

Table 3-4 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

OEHHA (2007)	1 pg/kg-day	Toth *et al.* (1979) Amyloidosis and dermatitis in mice	OEHHA adopted a fundamentally different approach than the other agencies. OEHHA derived their RfD from a LOAEL of 1 ng/kg-day for an endpoint, and was left in terms of administered dose (*i.e.*, no attempts to account for differences in toxicokinetics between humans and rodents). The LOAEL value was then divided by a default uncertainty factor of 1,000, which is considerably larger than that adopted by other agencies (9.6-100).

The developing offspring, exposed *in utero* and postnatally through lactation, were identified as the most sensitive receptors identified in laboratory studies of non-cancer effects of dioxin. This was explicitly recognized by all of the agencies (except OEHHA) that have derived non-cancer criteria for TCDD and related compounds. All of the current criteria (except OEHHA's) 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.[33]

Each of the current non-cancer criteria for TCDD and associated chemicals has shortcomings, including the following:

1. Rier *et al.* (2001) revealed data that demonstrates 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 to exclude the Bowman et al. (1989) and Schantz et al. (1992) data from their quantitative assessments.

2. The decreased sperm counts reported by Gray *et al.* (1997) on which the ECSCF and WHO/FAO JECFA values are based were not observed in a recent, large study conducted in rats following either acute or subchronic exposure to TCDD (Bell *et al*., 2007a,b).

3. 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

[33] 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. This is reflected in the pattern of body burdens noted in the general population, where children demonstrate lower body burdens than adults (see, for example, Link et al. 2005). Existing non-cancer criteria are directed explicitly to protect children through protecting them from elevated *in utero* and breast milk exposures by controlling the adult maternal body levels of these compounds.

environmental exposure situation. 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.

4. All of the available studies used TCDD alone. The non-cancer toxicity criteria for reproductive/developmental endpoints rely upon maternal exposure as a dose surrogate for fetal/neonatal exposure, under a simplifying assumption that fetal/neonatal exposure is proportionate to maternal exposure. Although this assumption may be valid for a single congener, difficulties arise when extrapolations are attempted across congeners, as is typical of the TEF approach (see Section 2.5). (Evaluation and use of TEFs for application to the site-specific DCC will be part of a separate submission).

5. The RfD derived by OEHHA relies upon an endpoint (amyloidosis and dermatitis in mice) not used by any other agency. The dose response assessment was conducted in terms of administered dose, and no attempts were made to account for toxicokinetic differences between mice and humans, despite available data and methods for doing so. Furthermore, the uncertainty factor used by OEHHA (1,000) is much larger than used by other agencies.

Because of these limitations, and because additional key studies have been recently published, this Report derives an alternative value below. The process for deriving an RfD for TCDD includes essentially the same decision points as used above for the cancer dose-response assessment.

3.2.3.1.2 Identification of the Critical Effect/Data Set

As noted above, the effects of TCDD on the development of the male reproductive tract due to *in utero* and postnatal exposures have been identified as the most sensitive non-cancer endpoint by regulatory agencies. Recently, a series of studies were conducted for the purposes of generating definitive dose-response data for this endpoint (Bell *et al*., 2007a,b,c), without the deficiencies noted above for previous studies. This series of studies is summarized below.

- *Acute Exposure* - Groups of 75 (control vehicle) or 55 (50, 200, or 1000 ng of TCDD/kg bodyweight) female Wistar(Han) rats were exposed to TCDD on gestational day (GD)15, then allowed to litter (Bell *et al*., 2007a). The high-dose group dams showed no sustained weight loss compared to control, but four animals had total litter loss. Pups in the high-dose group showed reduced body weight until postnatal day ("PND") 21, and pups in the medium dose group showed reduced body weight in the first week postpartum. Balano-preputial separation ("BPS") was significantly delayed in the high-dose group male offspring. There were no significant effects of treatment when the offspring were subjected to a functional

observational battery or mated with females to assess reproductive capability. The authors concluded that these data show that TCDD is a potent developmental toxin after exposure of the developing fetus but that acute developmental exposure to TCDD on GD15 caused no decrease in sperm counts.

- *Subchronic Exposure* - Five- to six-week-old rats were exposed to a control diet or a diet containing TCDD to attain an average dose of 2.4, 8, and 46 ng TCDD/kg/day for 12 weeks (Bell *et al*., 2007b). Offspring from the high-dose group showed an increase in total litter loss, and the number of animals alive on PND 4 in the high-dose group was ~26% less than control. The high and medium dose offspring showed decreased weights at various ages. BPS was significantly delayed in all three dose groups compared to control. The authors concluded that these data confirm that developmental exposure to TCDD shows no potent effect on adult sperm parameters or accessory sexual organs, but show that delay in BPS occurs after exposure to low doses of TCDD, and this is dependent upon whether TCDD is administered acutely or chronically.

A third publication was released that presented dosimetry information from both the acute and subchronic studies (Bell *et al*., 2007c). Because these studies provide response information under two different exposure regimens, these data can be used to determine an appropriate dose metric (i.e., average or peak exposure). Based upon a review of these two studies, delayed BPS appears to be the most sensitive endpoint. Rather than serving as a biomarker for endocrine modulation, the effects of TCDD on BPS noted in these two studies appear to be related to the effects of TCDD on body weight. The study authors reported a good correlation between BPS delay and body weight reduction on PND 4 (Bell *et al*., 2007c). Furthermore, delays in sexual maturation, including BPS, have been reported in rats in response to feed restriction and subsequent weight loss (Carney *et al.*, 2004). For this reason, the effects of TCDD on BPS are assumed to be secondary to the effects of the chemical on body weight. Dose-response data for the effects of TCDD on body weight on PND 4 are presented in the table below.

Table 3-5. Reduced Body Weight Gain in Rats Exposed to TCDD (Bell et al., 2007a,b,c)

			Body Weight PND 4(g)[1]		**Body Weight (% control)**	
Study	**Peak Maternal Body Burden During Gestation (ng/kg)**	**N**	**MEAN**	***SD***	**MEAN**	**SD**
Acute (PND 42)	0.04	97	8.81	1.07	1	0.121
	1.77	87	8.73	1.00	0.991	0.113
	6.57	91	8.34	0.93	0.946	0.106
	35.9	64	7.42	1.16	0.842	0.131
Subchronic (PND 44)	0.04	111	8.61	1.39	1	0.161

	9.54	110	7.93	1.18	0.921	0.137
	20.7	107	7.82	1.30	0.908	0.151
	97.0	78	7.54	1.20	0.876	0.139

[1] Body weight on PND 4 was correlated with BPS delay (Bell et al., 2007c).

3.2.3.1.3 Identification of a Dose Measure

Because sufficient data are not available to reliably estimate neonatal body burdens of TCDD due to fetal & lactational exposure to TCDD, the dose-response data for neonatal body weight loss were assessed in terms of peak maternal body burden as a surrogate dose for fetal/neonatal body burden.

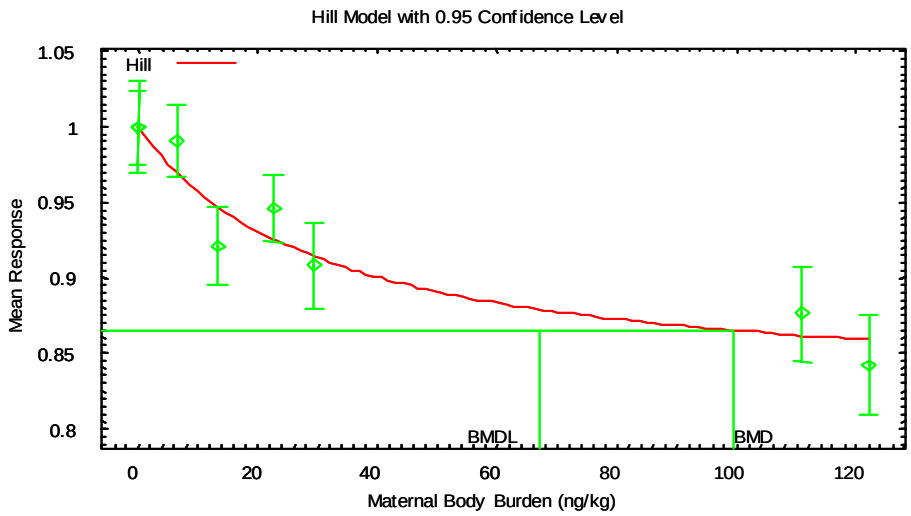
3.2.3.1.4 Identification of a Response Measure

The dose-response data for body weight are continuous data and were assessed in terms of severity of response relative to control response.

3.2.3.1.5 Selection of a Dose-Response Model

Of the continuous models in BMDS 1.4.1, the Hill model (with the intercept and n restricted to a value of 1) provided the best overall fit to the data (p-value=0.108; AIC=-2232; Figure 3-4).

Figure 3-4. Fit of the Hill Model to the Dose-Response Data for Reduced Body Weight in Male Rat Pups



3.2.3.1.6 Selection of Response Level(s) (Point of Departure)

Because the data are continuous (severity) rather than dichotomous (incidence), and because it is not known precisely what magnitude in body weight reduction is required to produce an effect on BPS, the dose producing a reduction in the mean response by 1 standard deviation (BMD SD) and its 95% lower confidence limit (BMD LSD) were selected as appropriate POD values. For the deterministic assessment, the BMD SD and BMD LSD were determined to be 99.4 and 67.0 ng/kg (maternal body burden), respectively. A first order assumption, identical to that used by JECFA (2001), was used to estimate the human equivalent dose based upon the following equation:

$$Dose\ (ng/kg\text{-}day) = (BB*ln(2)) / (f*t_{1/2})$$

Where,

BB = body burden (ng/kg);

f = fraction of dose absorbed (0.25 based upon the deterministic assumption for absorption from soil as summarized in Section 3.1.10); and

$t_{1/2}$ = TCDD halflife (2774 days; default value used by JECFA (2001))

Based upon this approach, the human equivalent doses corresponding to the ED and LED are 0.10 and 0.066 ng/kg-day, respectively. For the probabilistic assessment, uncertainty in the POD was assumed to be lognormally distributed with a mean equal to 0.10 ng/kg-day and a 5^{th} percentile of 0.066 ng/kg-day.

3.2.3.1.7 Uncertainty Factors

For deriving a non-cancer RfD for the developmental effects of dioxin, the following uncertainty factor values were used:

- UF_a – The default value of 10 for UF_a is comprised of values of 3.16 (square root of 10) for toxicokinetic variation and 3.16 for toxicodynamics variation. For the deterministic assessment: (1) the toxicokinetic component of UFa was set equal to 1.0, since a PBPK model was used to account for species differences (Maruyama and Aoki, 2006); and (2) for the toxicodynamic component, a value of 1.0 was conservatively adopted since there are numerous data that suggests humans are less sensitive than rats by at least a factor of 10 with respect to receptor binding and downstream events (Connor and Aylward, 2006; Guzelian *et al*. 2006). Lambert *et al* (2006) showed the relationship between TEQ and CYP1A2 mediated caffeine metabolism that suggests a NOEL of between 400 and 500 ng/kg equivalent to a TCDD body burden of 100 to 140 ng/kg since rats begin to display CYP induction around 2 ng/kg, this suggest a increased sensitivity of rats on the order of 50 fold or greater. Since US EPA and the NAS agree that the Ah Receptor (AhR) binding leading to CYP induction is the critical event that initiates and precedes the cascade of events that result in TCDD's various toxic endpoints, this difference in sensitivity needs to be accounted for in the derivation of both cancer and non-cancer toxicity criteria. For the probabilistic assessment: (1) the UF of 1.0 was retained for the toxicokinetic component; and (2) the UF for the toxicodynamic component was allowed to range from 0.1 to 1.0 as a uniform distribution to include the more likely assumption that humans are less sensitive than rats.

- UF_h - The default value of 10 for UF_h is comprised of values of 3.16 (square root of 10) for toxicokinetic variation and 3.16 for toxicodynamics variation, which is intended to cover potentially sensitive subpopulations. For the deterministic assessment a value of 3.16 was adopted for the toxicokinetic component to account for individual variation in TCDD half-life. For the toxicodynamic component, a conservative value of 3.16 was retained to account possible variation in sensitivity between individuals. Abraham *et al*. (2002) in examining highly exposed humans concluded that moderate TCDD exposure (up to a serum lipid TCDD concentration of 1000 ppt) does not cause CYP1A2 induction. This result explains why chemical workers with mean TCDD of 157 ppt and St Lawrence River fish eaters with a blood level of 300 ppt TEQ showed no CYP1A2 induction while

Taiwanese patients ingesting contaminated rice oil (with blood levels of 3,000 to 6,000 ppt TEQ) did. By comparison, the US population average background is approximately 25 ppt TEQ and the UM DES study group falls between that level and approximately 33 ppt TEQ on average (UM DES, 2006). If applicable to humans, the inhibitory effects of TCDD on CYP1A2 induction *in vitro* would suggest that moderately increased doses would increase human caffeine metabolism while high doses would inhibit it due to saturation and inhibition of the enzyme by the excess TCDD. In fact, the opposite happens (Guzelian *et al*. 2006). The related CYP1A1 enzyme can be co-induced with CYP1A2, but unlike CYP1A2 is found in extrahepatic tissues. Tawainese women poisoned by contaminated rice oil (with a body burden thought to be as high as 10,000 ppt TEQ) were found to have placental CYP1A1 levels 100 times greater than controls (placentas were reported to contain 60 to 892 times the TEQ than controls) (Connor and Aylward, 2006; Lucier *et al*. 1987; Schecter *et al*. 1996). A study of Inuit women with blood levels of TEQ five top seven times that of controls found no CYP1A1 induction in placentas suggesting that such indcutuion requires in excess of 125 to 175 ppt TEQ befor e it expresses itself (pereg et al. 2002). Further, an examination of human polymorphisms of the AhR (Wong *et al*., 2001) found no differences in ligand binding by humans displaying two polymorphisms (V570I and P571S) and the normal genotype. However, *in vitro* expression experiments revealed these variants failed to support TCDD induction of CYP1A1 expression suggesting these variants may be less sensitive to the effects of TCDD and related compounds that act throught the AhR. This suggests that sensitive human sub-populations may not exist for AhR binding and induction of CYP enzymes. For the probabilistic assessment, 1) the toxicodynamic component was defined as a uniform distribution ranging from 1.0 to 3.16 to account for the fact that AhR polymorphisms do not affect binding of the ligands to the receptor and 2) the toxicokinetic component was held fixed at 1.0.

- UF_s – Because the key study (Bell *et al.* 2007) covered the entire window of susceptibility for reproductive development, a value of 1.0 was adopted for both the deterministic and probabilistic assessments.

- UF_l – Because benchmark dose methods were used, and because reduced body weight was not accompanied by other adverse effects in rats and therefore an approximate 10% reduction in body weight is considered to be a minimally adverse, a value of 1 was adopted for UF_l.

- UF_d – Because the toxicokinetics, toxicity, and mode of action of TCDD have been well studied, a value of 1 is adopted for both the deterministic and probabilistic assessments.

For both the deterministic, a net uncertainty factor of 10 (1x10x1x1x1) is considered appropriate for deriving an RfD based on the increased sensitivity of animals to the effects of dioxin and related compounds and apparent lack of human differences and sensitive subpopulations when the biochemical events considered key to the expression of dioxin toxicity are taken into account. This net UF value is consistent with that used by JECFA (2001). For the probabilistic

assessment, the net uncertainty factor was best characterized as a gamma distribution with a location of 0.1, and scale of 1.2, and a shape of 1.9.

3.2.3.1.8 Presentation of the RfD Value

For the deterministic assessment, division of the BMD LSD value of 66 pg/kg-day by a net uncertainty factor of 10, yields an RfD value of 6.6 pg/kg-day. For the probabilistic assessment, the RfD distribution was best characterized as a lognormal distribution with a mean of 70 pg/kg-day and a standard deviation of 64 pg/kg-day.

3.2.4 Relative Source Contribution

Unlike the cancer algorithm provided by the Part 201 rules, the non-cancer algorithm contains a "relative source contribution" ("RSC") variable. This Report recommends a RSC of 1, which is the Part 201 default value for soil direct contact calculations.

According to the Part 201 rules, the RSC is "that portion of a person's total daily intake of a noncarcinogenic hazardous substance that comes from the medium being addressed by the cleanup criterion." Mich. Admin. Code R. 299.5703(d). The RSC default value for soil direct contact is 1.0, meaning that the default assumption is that all material exposure comes from the soil in question. Mich. Admin. Code R. 299.5720. The RSC value is directly related to the calculated cleanup criteria; therefore, the lower the RSC, the lower the cleanup criteria.

As discussed in section 2, above, the Part 201 rules presume that any person developing site specific criteria "shall use" the toxicological and chemical-physical data found in Rule 752 Table 4, which includes soil RSCs. Mich. Admin. Code R. 299.5706a(9). For TCDD, the MDEQ departed from the default soil RSC of 1.0, and promulgated a factor of 0.2 instead. Mich. Admin. Code R. 299.5752 Table 4.

Moving from the default RSC of 1 to 0.2, was done without the legal authority to do so. In a 2000 MDEQ Interoffice Communication, MDEQ cites to the EPA study *Estimating Exposures to*

Dioxin-Like Compounds (EPA, 1994a) as well as a 1994 study by Schecter et al. and a 1999 report by Schaum et al., to conclude that "the average U.S. citizen is exposed to TCDD and related compounds in their daily diet." The MDEQ then makes note of the uncertainty inherent in the calculations, but, nevertheless, chooses a new RSC anyway:

> Given the uncertainty surrounding both the development of the oral RfD and the analysis of average dietary exposures, it is unlikely that use of an RSC more restrictive than 20% will provide significant public health or environmental benefit. Therefore, ERD supports the use of an RSC of 20% for development of Part 201 soil DCC for TCDD and related compounds protective of noncarcinogenic effects.

MDEQ, *Interoffice Communication, Relative Source Contribution Factor for Part 201, Environmental Remediation, of the Natural Resources and Environmental Protection Act, 1994 PA 451, as Amended (NREPA), Soil Direct Contact Criteria* (Feb. 10, 2000) (hereinafter "*2000 Communication*"). Significantly, the Communication does not provide any support for choosing 20% in particular, and also admits that going any lower would be "unlikely" to provide significant benefit. In a later document, the MDEQ implicitly admits that 0.2 is, at best, an approximation:

> However, the data are insufficient at this time to more precisely predict the levels at which these or other non-soil exposures may occur. It is therefore assumed that 80% of the average exposure to TCDD and related compounds occurs from a source other than exposure to contaminated soils. Therefore, Part 201 soil direct contact criteria for TCDD and related compounds protective of noncarcinogenic effects are calculated employing a 20% relative source contribution factor (RSC).

MDEQ, *Draft Deliberative Process, Toxicological Assessment and Part 201 Cleanup Criteria for 2,3,7,8-tetrachlorodibenzo-p-dioxin and Related Compounds* (April 25, 2002). It appears that this approximation was based on national food basket (grocery store) surveys, not Midland-specific information. Such approximations based on generalized data are fraught with uncertainty. For example, there is evidence that dioxin concentrations in food are decreasing, making an appropriate RSC difficult to pinpoint. *See WHO European Center for Environmental Health, Assessment of the Health Risks of Dioxins,* p.3 (May 25-29, 1998) (noting that countries that have implemented measures to reduce dioxin emissions have seen dietary intake levels reduce by a factor of two in just seven years). Other background sources of dioxin are also

declining. According to the NAS, "background concentrations of TCDD, other dioxins, and [dioxin like compounds] continue to decline. EPA's estimates of releases due to these compounds to air, water, and land from reasonably quantifiable sources in 2000 showed a decrease of 89% from its 1987 estimates." NAS, p. 2. Given the complexity, ubiquitous nature, and rapid change of these background exposures, it is difficult to calculate or scientifically justify a particular RSC.

For these reasons, Part 201 expressly creates a presumption in favor of an RSC of 1, and prohibits changes to the RSC based on generalized data. Section 20a of Part 201 states that for non-carcinogenic effects in soils, the default intake "shall be **assumed** to be 100% of the protective level" (i.e., an RSC of 1.0), "**unless** compound **and site-specific** data **are available** to demonstrate that a different source contribution is appropriate." M.C.L.A. § 324.20120a(4) (emphasis added). The provision specifically requires "site-specific" data, which, according to recent discussions with MDEQ, does not include generalized or nationwide data, but instead is limited to data specific to the site. Therefore, MDEQ changed from the default of 1 even though "site-specific" data were not "available" as required.

The use of a RSC lower than 1 also contradicts Part 201 generally. Using a lower-than-default RSC due to national food supply dietary exposures effectively makes a party liable for exposures that the party did not create, and in an exposure medium that the party does not and cannot control. . Moreover, from a practical point of view, when, as in this case, background exposures make up a large portion of the total exposure, there is little or nothing to be gained by remediating non-background sources.

In this regard, MDEQ decided not to include lead-based paint exposure considerations in its calculations for cleanup criteria for lead because paint exposures were so high: "it is clear that outdoor soil remediation programs cannot adequately mitigate total lead exposure and address the issue of deteriorating lead-based paint." *Michigan Department of Natural Resources, Justification Type B Cleanup Criteria for Lead* (Oct. 26, 1993). Similarly, food-based dioxin exposures cannot and should not be addressed through soil response action. Far from assuring "the protection of the public health, safety, and welfare, and the environment," as MDEQ is

charged with doing, M.C.L.A. § 324.20118(2)(a), requiring the larger national dioxin exposure in the food supply to be addressed through soil criteria would not be productive, fair, or legal.

A RSC less than 1.0 is contrary to the overall intent of the liability scheme set forth by Part 111 and Part 201.[34] From the standpoint of liability, a person is only responsible for contamination caused by releases from its facility, not other people's facilities or other unrelated sources of exposure. According to Part 111, an "owner or operator . . . of a facility . . . is subject to the corrective action requirements . . . for all releases of a contaminant from any waste management unit **at the facility** . . . ." M.C.L.A. § 324.11115a. *See also* Mich. Admin. Code R. 299.9629 ("Owners or operators . . . shall institute corrective action for all releases of a contaminant from any waste management units at the facility . . . ."). Similarly, when Part 201 was amended in 1995, the Legislature intentionally moved from a strict liability standard to a fault-based one, declaring "[t]hat liability for response activities to address environmental contamination should be imposed upon those persons **who are responsible for the environmental contamination**." M.C.L.A. § 324.20101(f). Accordingly, under Part 201, a person is only liable if it is "responsible for an activity causing a release." M.C.L.A. § 324.20126. . As a general rule under Part 201, owners and operators are not liable for "background" exposures. Part 201 allows the substitution of a "background concentration" for a generic cleanup criterion when the background concentration is higher, which lowers effective liability and ensures that parties are not held responsible for contamination outside their control. Mich. Admin. Code R. 299.5706a(5)(b) and R. 299.5707.[35]

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[34] Dow's corrective action liability is based on Part 111 and the obligations set forth in its Part 111 License. Dow has not admitted liability under Part 201; however, because Part 201 is being used to guide the corrective action process, Part 201's liability scheme is discussed.

[35] Similarly, under Part 201, if harm is divisible, then a liable party is only responsible for their portion of the harm:

> If 2 or more persons acting independently are liable under section 20126 and there is a reasonable basis for division of harm according to the contribution of each person, **each person is subject to liability under this part only for the portion of the total harm attributable to that person.**

M.C.L.A. § 324.20129(1). Although this section expressly only applies to situations where contamination is caused by two or more "liable" parties, the underlying intent certainly applies in this case: because there is a reasonable basis for the division of the harm between dietary exposures and the harm attributable to Dow, Dow should not be made liable for the whole.

Finally, the remedial processes under Part 201, which EPA and MDEQ have adopted to fulfill Part 111 corrective action requirements, are likewise limited. Response action is limited in its scope and is tied closely to the **site and the land use** in question, not cumulative background exposure:

> 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). *See also* M.C.L.A. § 324.20120a(14) ("actual site conditions"); Mich. Admin. Code R. 299.5528(3)(a) ("contamination at the facility"); R. 299.5532 ("address all releases of hazardous substances in all media at a facility"); R 299.5536 ("address all contamination at a facility"); Mich. Admin. Code R. 299.5734 (all dioxins shall be considered as 1 hazardous substance, expressed as an equivalent concentration of 2,3,7,8-TCDD, based upon relative potency and concentration of the congeners "present at the facility"). Use of a low RSC improperly moves the focus from addressing contamination at the facility to dealing with a worldwide condition.

Similarly, a responsible party need only address "relevant pathways" of exposure. A relevant pathway means "an exposure pathway that is reasonable and relevant because there is a reasonable potential for exposure to a hazardous substance to occur to a human or nonhuman receptor from a source or release." Mich. Admin. Code R. 299.5103(h). According to Part 201, the MDEQ "shall utilize **only** reasonable and relevant exposure pathways in determining the adequacy of a site specific criterion." M.C.L.A. § 324.20120a(2) (emphasis added). In this case, relevant "pathways" do not include grocery store sources of exposure. Therefore, use of a low RSC incorporates other exposure pathways that were not meant to be considered.

For these reasons, this Report uses the default RSC of 1 to calculate its proposed non-cancer criteria for the Midland area. The use of an RSC of 1 is consistent with the RSC for *all* substances under Part 201, except for the arbitrary number of 0.2 selected for TCDD in Table 4.

3.2.5 Summary of Proposed Non-Cancer Criteria

Using a RfD of 6.6 E-09 mg/kg-day and the exposure assumptions discussed in this section above, the Part 201 algorithm for threshold effects (the "non-cancer" algorithm), and treating it both deterministically and probabilistically, provides the following site-specific direct contact criteria:

Deterministic Approach

Based on an RfD of 6.6E-09 mg/kg-day and all of the exposure assumptions defined above, the DCC value for noncancer endpoints was determined to be 15.0 ppb (15 ug/kg). A spreadsheet showing step-by-step calculations and results is attached as **Appendix A**.

Probabilistic Approach

The range of probabilistic results is summarized as follows:

			Percentile (ppb)*				
Basis	**Mean (ppb)***	**SD (ppb)***	**1st**	**5th**	**50th**	**95th**	**99th**
Non-cancer (developmental toxicity)	1,100	2,900	**19**	42	360	4,400	14,000

*Values expressed to two significant figures.

3.3 Summary of Calculated Direct Contact Criteria

The deterministic treatment of the non-linear cancer model provides a DCC value (250 ppb) that is higher than the linear cancer model (19 ppb) as expected. The deterministic DCC value based upon noncancer endpoints (15 ppb) is essentially identical to that calculated for the linear cancer assessment when expressed to one significant figure (20 ppb). Examining these endpoints and models probabilistically, the range of DCC values (based upon the 1st and 99th percentiles of each resulting distribution) are as follows: 27-11,000 ppb (threshold cancer); 150-200,000 ppb (non-threshold cancer), and 19-14,000 ppb (non-cancer).

Following the empaneling of the ISAP (discussed below) the review of the ISAP and the then report of the ISAP, Dow will propose residential direct contact criteria to MDEQ, consistent with the human health risk assessment provisions of Dow's Remedial Investigation Work Plan (RIWP) for Midland. Before or following the ISAP process Dow may alternatively propose to MDEQ for approval a non-numeric approach to risk management in Midland that will be consistent with the Midland RIWP and Michigan law.

4. Independent Science Advisory Panel

Based on prior discussions with MDEQ and as addressed in the Midland RIWP, Dow anticipates that an independent organization will be selected by Dow and MDEQ to assist in the development and operation of the Independent Science Advisory Panel (ISAP) to review all or portions of this Report. The independent organization will be tasked to assemble a panel of outside individuals with specific areas of expertise. The independent organization will assist MDEQ and Dow in the development of a list of charge questions that address the major areas and issues associated with deriving and implementing a site-specific DCC for Midland Area residential soils.

The ISAP would be provided in advance with the final DCC report and supporting information along with the charge questions. After an appropriate review period, the ISAP would assemble in the Midland area and begin the process of review, questioning, debate, and decision. MDEQ and Dow would present the results of the DCC and issues related and respond to the panel's

questions and comments. Outside parties would have an opportunity to attend and observe and participate to some degree. Following the presentation and questions, the ISAP would discuss the matter and charge questions among themselves in an attempt to reach consensus and make recommendations to the sponsors. The ISAP could support the site-specific DCC as derived, support it with modifications, or reject it. MDEQ and Dow as the sponsors of the ISAP would have the opportunity to respond to the request for modifications or resubmit a revised DCC to another panel if necessary.

After the ISAP completes its work and issues its final report, Dow can take that work and use it to propose a residential direct contract criteria to MDEQ. MDEQ, in the course of reviewing Dow's proposed criterion, could also use the work of the ISAP in it administrative determination of the approval of site specific criterion for Midland Soils.

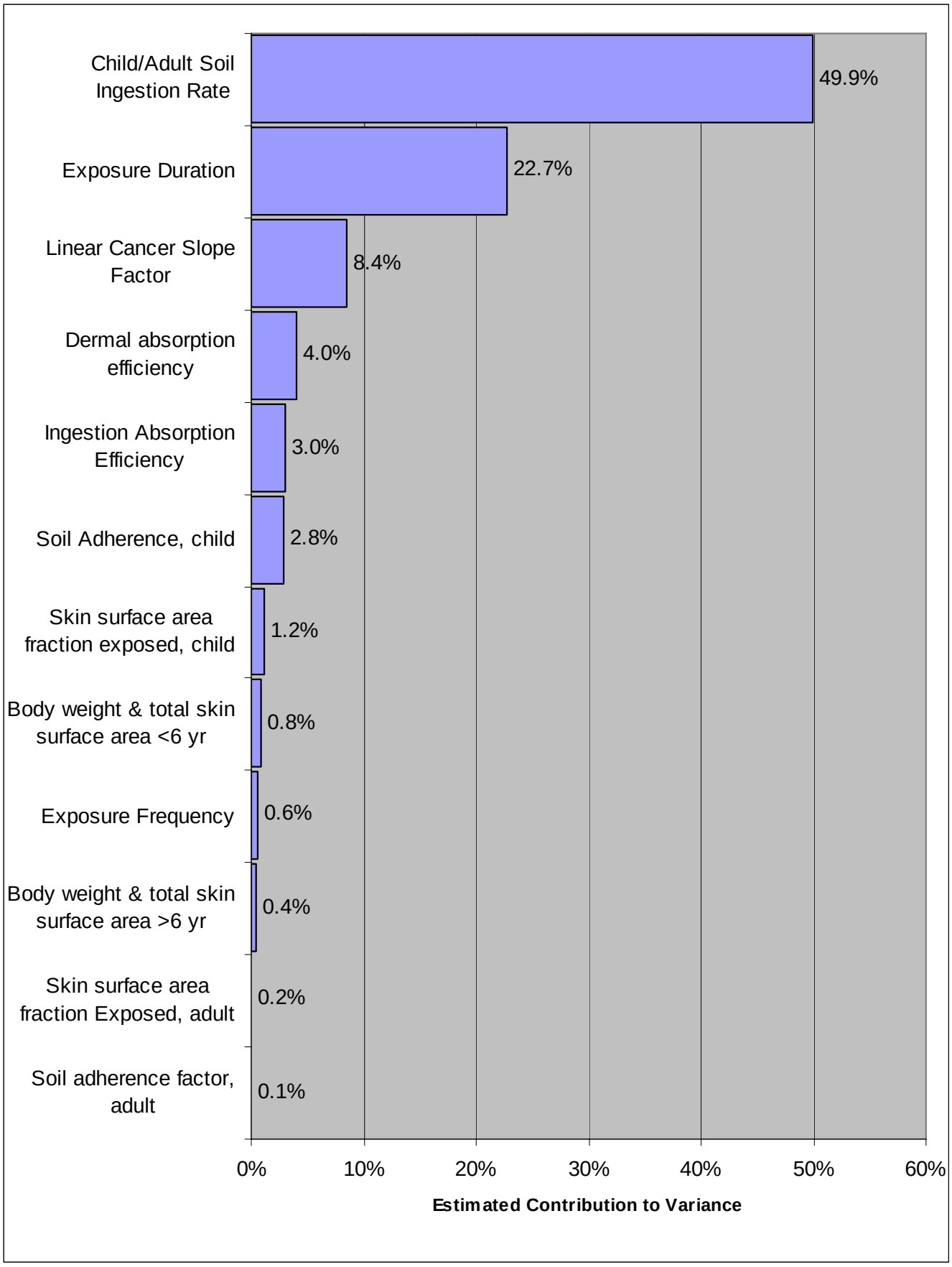
5. Sensitivity Analysis

A sensitivity analysis was conducted in Crystal Ball (Decisioneering Inc.; Version 7) for Microsoft Excel for the purpose of identifying which parameter values have the largest effect on variance in the DCC distributions. For the linear cancer assessment, the variation in soil ingestion rate for children and adult (49.9%), variation in exposure duration (22.7%), and the uncertainty in the cancer slope factor (8.4%) were the largest contributors to variance in the distribution of DCC values. See Figure below. The 8.4% of variation estimated for the cancer slope factor can be attributed to the uncertainty estimated in the point of departure. For the nonlinear cancer assessment, the uncertainty in the cancer RfD (47.4%), the variation in the soil ingestion rate for children and adult (34.5%), and the variation in the exposure duration (12.0%) were the largest contributors to variance in the distribution of DCC values (see Figure below). Within the 47.4% of variance estimated for the cancer RfD, the contributors to variance in the cancer RfD distribution were the uncertainty in the toxicodynamic portion of UFa (34.4%), UFl (33.4%), the uncertainty in the point of departure (12.0%), the uncertainty in the toxicokinetic portion of UFh (11.0%), and the uncertainty in the toxicodynamic portion of UFh (9.2%). For

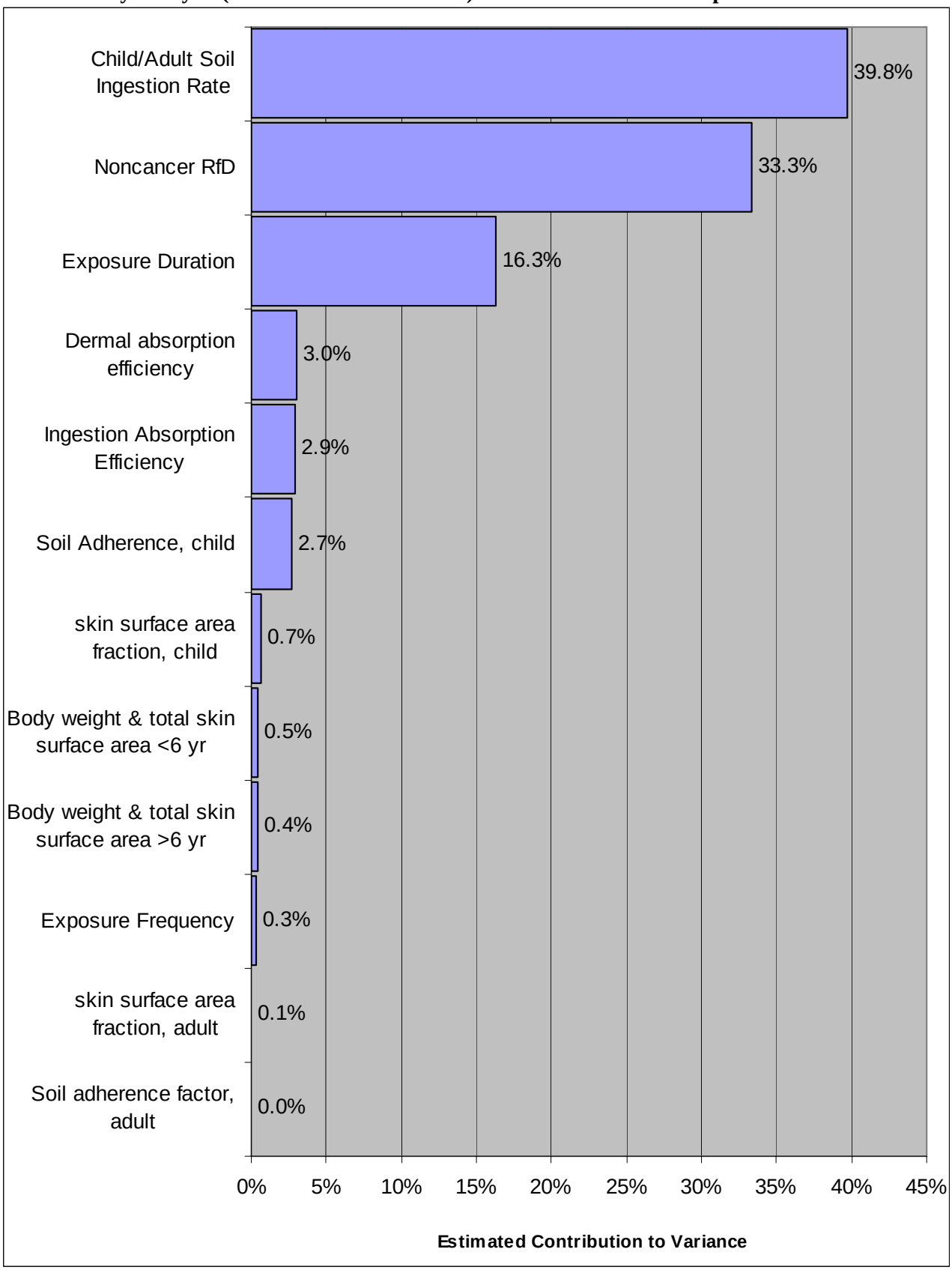
the noncancer assessment, the variation in the soil ingestion rate for children and adult (39.8%), the uncertainty in the noncancer RfD (33.3%), and the variation in exposure duration (16.3%) were the largest contributors to variance in the distribution of DCC values (see Figure below). Within the 33.3% of variance estimated for the noncancer RfD, the contributors to variance in the noncancer RfD distribution were the uncertainty in the toxicodynamic portion of UFa (56.9%), the uncertainty in the toxicodynamic portion of UFh (18.4%), the uncertainty in the toxicokinetic portion of UFh (16.8%), and the uncertainty in the point of departure (7.9%).

[Intentionally left blank.]

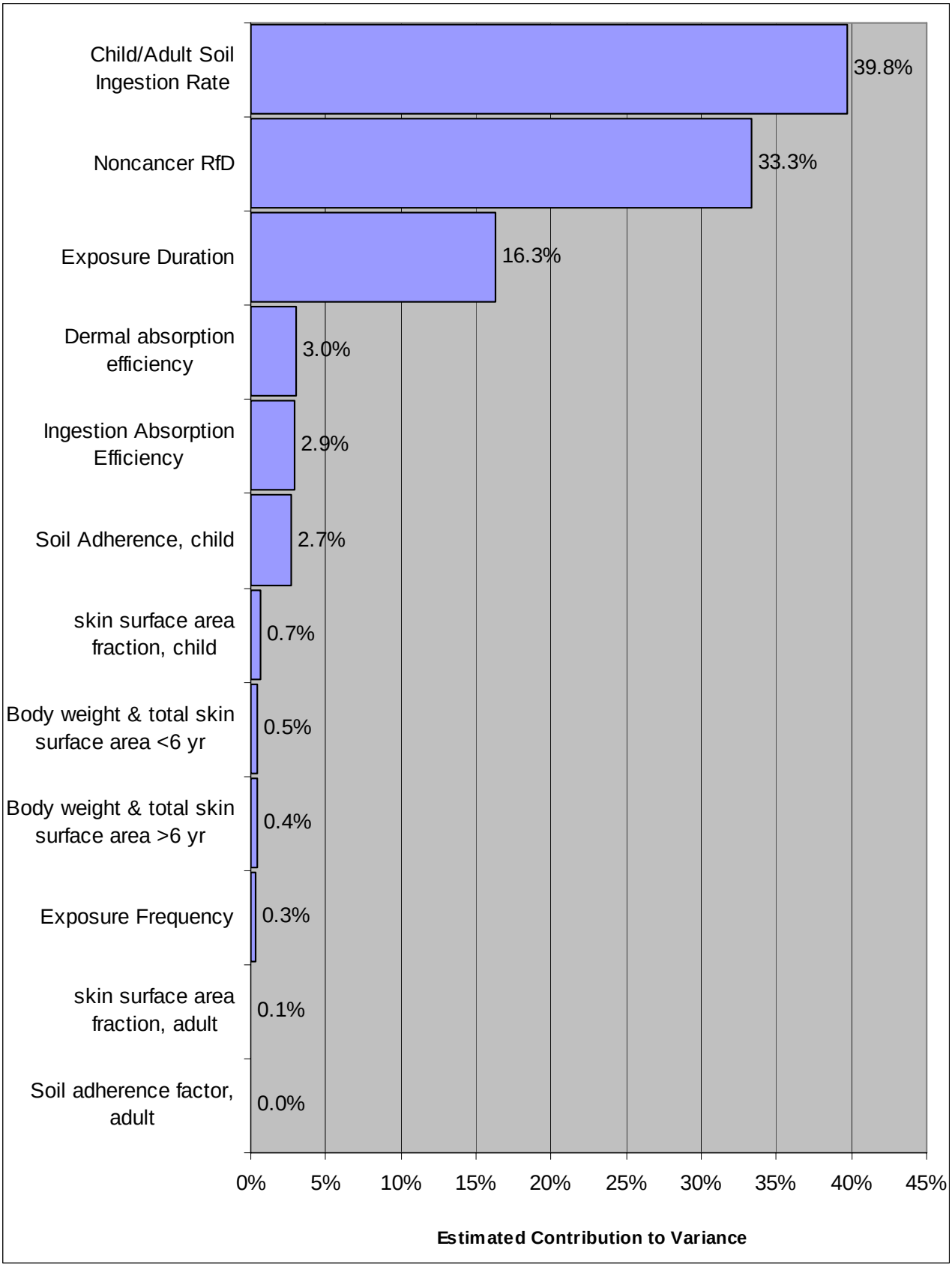
Sensitivity Analysis (Contribution to Variance) for DCC Values Based Upon Linear Cancer Assessment



Sensitivity Analysis (Contribution to Variance) for DCC Values Based Upon Nonlinear Cancer



Sensitivity Analysis (Contribution to Variance) for DCC Values Based Upon Noncancer Assessment



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