Derivation of Soil Cleanup Levels for 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) Toxic Equivalence ($TEQ_{D/F}$) in Soil Through Deterministic and Probabilistic Risk Assessment of Exposure and Toxicity

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ABSTRACT

Aerial deposition from historical emissions from Dow Chemical operations in Midland, Michigan has resulted in residential soil polychlorinated dibenzo-*p*-dioxins and furans (PCDD/Fs) as 2,3,7,8-tetrachloro-dibenzo-*p*-dioxin (TCDD) toxic equivalence ($TEQ_{D/F}$) concentrations that are generally less than EPA's 1 ppb TEQ cleanup level (U.S. EPA 1998) within the city of Midland. In some cases, soil concentrations of $TEQ_{D/F}$ are greater than the 0.090 ppb default Michigan Department of Environmental Quality (MDEQ) direct contact criteria (DCC) (MDEQ 2005, CH2M Hill 2007). While risk assessments at contaminated sites are extensively used for guiding critical and resource intensive decisions, detailed risk assessments that rigorously integrate key exposure and toxicity terms are less frequently conducted. This poster represents such an effort, deriving DCC for PCDD/Fs in residential soil using site-specific information and deterministic and probabilistic methods. In addition, TCDD and $TEQ_{D/F}$ risk assessment has been the subject of extensive scientific and regulatory debate including in-depth comments provided by two EPA Science Advisory Boards (SABs) and by the National Academy of Sciences (NAS) on the proposed EPA Draft Dioxin Risk Assessment. This risk assessment presents toxicity values seeking to address the NAS recommendations. Deterministic DCC estimates derived with site-specific exposure variables and toxicity values based on key NAS recommendations ranged from 19 to 250 ppb through application of linear and nonlinear means, respectively, to estimate cancer risks. A wide range of possible DCC estimates were calculated using Monte Carlo methods, with the 1 ppb cleanup value traditionally used by EPA falling below the first percentile of calculated DCC estimates.

EXPOSURE ASSESSMENT

Deterministic and probabilistic methods were used to estimate a range of DCC (Table 1 and Equations 1–4).

- The probabilistic approach used a 1-dimensional Monte Carlo assessment, with variability and uncertainty treated in a combined manner.

Considerable site-specific exposure inputs were applied:

- **Ingestion absorption efficiency (AE_i)** estimate of the relative oral bioavailability of 23% for PCDDs/Fs from soil compared to that in corn oil (Ruby et al. 2002; Budinsky et al. 2008) of was derived based on data for swine (Table 2)
  - TCDD and TEQD/F soil oral relative bioavailability estimates from other locations are less than 50% in all but two studies (Lucier et al. 1986, McConnell et al. 1984, Wendling et al. 1989, Bonacorsi et al. 1984, Umbreit et al. 1986, Wittsieppe et al. 2007), i.e., data in rat investigations from Budinsky et al. (2008) in Midland and data from a rat study reported by Shu et al. (1988)
  - Swine bioavailability data were selected as a better model than rats for the human gastrointestinal system (U.S. EPA 2006; Casteel et al. 2006; Krishnan et al. 1994; Eklund et al. 2004; Weis and LaVelle 1991) and are the preferred model for human nutrition (Miller and Ullrey 1987; Book and Bustad 1974).
- **Exposure duration (ED)** was estimated from the probability of not remaining in Midland calculated for one year intervals from ages 0 to 100 (Johnson and Capel 1992) and U.S. Census data on moving and death rates of Midland Country residents (U.S. Census Bureau 2007a,b; Arias 2007) (Figure 1 and Table 1).
- **Soil and Dust Ingestion Factor (IR_{child}/IR_{adult})** Soil ingestion rate data for children from Stanek et al. (2001) were plotted on the x-axis (with a logarithmic scale), and the probability in the form of a normal ordinate (the inverse normal of the probability) on the y-axis (Figure 2)
  - Data were fitted by a distribution curve consisting of a mixture of two lognormal distributions with no upper bound on the ingestion rate
  - The standard deviation given by Stanek et al. (2001) for each percentile with a positive value was treated as giving an independent estimate for the coefficient of variance at that percentile, and maximum likelihood estimation then used
  - Soil ingestion rates for adults were derived assuming adults ingest half as much soil as children, consistent with typical default factors and also consistent with the limited data available for adult soil ingestion (Stanek et al. 1997) (Table 1).

Table 1. Residential direct contact criteria (DCC_c/DCC_n) for dioxins and furans as toxic equivalence ($TEQ_{D/F}$) in residential soil

					Probabalistic Evaluation: Exposure Factors			
		Parameter input	DEQ Values per August 31, 1998 MDEQ memorandum	Deterministic Evaluation: Exposure Factors[a]	Mean	Standard Deviation	Assumed Distribution	Citation and Notes
Equation 1: $DCC_c = \frac{TR \times AT_c \times 1 \times 10^{-9\ \mu g/kg}}{SF \times (EF_i \times IF \times AE_i + EF_d \times DF \times AE_d)}$ **Equation 2:** $DCC_n = \frac{THQ \times RfD \times AT_{nc} \times 1 \times 10^{-9\ \mu g/kg}}{EF_i \times IF \times AE_i + EF_d \times DF \times AE_d)}$	DCC_c/DCC_n	Direct Contact Criteria (DCC_c) Cancer or (DCC_n) noncancer (µg/kg $TEQ_{D/F}$)	0.09	2.2	Calculated (See Figures 3–5)			
	TR; THQ	Target cancer risk; target hazard quotient =1	1.0E-05	1.0E-05	1.0E-05	NA	Point	MDEQ (2001); U.S. EPA (1990)
	AT_c; AT_n	Averaging time (cancer), Noncancer= ED*365	25,550	27,375	27,375	NA	Point	U.S. EPA (1989)
		Conversion factor	1.00E+09	1.00E+09	1.00E+09	NA	Point	U.S. EPA (1989)
	SF	Cancer slope factor (mg/kg-day)$^{-1}$	75000	26000	1790	647	Lognormal	Deterministic MDEQ (2001 [Kociba et al. 1978]); OEHHA (2007 [NTP 2006]); PRA - NTP (2006) and Maruyama and Aoki (2006)
	EF_d	Dermal exposure frequency (days)	245	245	209.8	19.4	Normal	Midland climate data; U.S. EPA (1991)
Equation 3: $IF = \frac{IR_{child} \bullet ED_{child}}{BW_{child}} + \frac{IR_{adult} \bullet ED_{adult}}{BW_{adult}}$	IF	Age-adjusted ingestion factor	114	53	Calculated from parameters defined below			
	BW_{child}	Child 1–6 body weight (kg)	15	15	Age-specific arithmetic mean	Age-specific standard deviation	Normal	U.S. EPA (1997)
	BW_{adult}	Adult body weight (kg)	70	70	Age weighted arithmetic mean	Age-specific standard deviation	Normal	U.S. EPA (1997)
	ED_{child}	Exposure duration children ages 1–6	6	6	Custom distribution for residential tenure (first six years child)			U.S. Census Bureau (2007a,b); Arias (2007) (See also Figure 1)
	ED_{adult}	Exposure duration for adults (years)	24	24	Custom distribution for residential tenure			
	EF_i	Ingestion exposure frequency (days)	350	245	209.8	19.4	Normal	MDEQ (2001) default dermal
	IR_{child}	Soil ingestion rate 1–6 (mg-day)	200	92.2	32.8	0.86	Custom	Derived from Stanek et al. (2001) (see Figure 2 and Equation 5)
	IR_{adult}	Soil ingestion rate adult (mg-day)	100	46.2	Distribution 1/2 child rate		Calculated	
	AE_i	Ingestion absorption efficiency	0.5	0.25	0.23	0.06	Lognormal	Budinsky et al. (2008) and Tables 1,3
Equation 4: $DF = \frac{SA_{child} \bullet EF \bullet AF_{child} ED_{child}}{BW_{child}} + \frac{SA_{adult} \bullet EF \bullet AF_{adult} \bullet ED_{adult}}{BW_{adult}}$	DF	Age-adjusted dermal soil factor	2,442	353	Calculated from parameters defined below			
	SA_{child}	Skin surface area, 1-6 year olds (cm^2)	1,820	2,670	Calculated from BW	NA	Uniform 0-0.42 (fraction exposed)	Range assumed-upper limit corresponded to default
	AF_{child}	Soil adherance factor, 1-6 years (mg/cm^2)	1	0.2	0.14	0.27	Lognormal	Kissel (2009)
	SA_{adult}	Skin surface area, adult (cm^2)	5,000	5,800	Calculated from BW	NA	Uniform 0-0.42 for fraction exposed	Range assumed-upper limit corresponded to default
	AF_{adult}	Soil adherance factor, adult (mg/cm^2)	1	0.07	0.04	0.047	Lognormal	Kissel (2009)
	AE_d	Dermal absorption efficiency (unitless)	0.03	0.0175	0.012	0.019	Lognormal	Poiger and Schlatter (1980), Shu et al. (1988), U.S. EPA (1991)

NA – not applicable

[a] Application of these exposure variables and a linear SF of 3,000 $(mg/kg\text{-}day)^{-1}$, or a non-linear SF of 0.011 ng/kg-day results in DCCc of 19 and 250 ug/kg, respectively.

Table 2. $TEQ_{D/F}$-weighted overall relative bioavailability (RBA) and absolute bioavailability estimates

	City of Midland Soil (values as %)	
	Relative Bioavailability	**Absolute Bioavailability[a]**
Rat – Pilot study	37	30
Rat – Follow-up study	Not Measured	Not Measured
Swine (ND=1/2 DL)	23	19
Swine (ND=DL)	29	23
In vitro bioaccessibility estimate:	17	Not Measured

Note: DL – detection limit
ND – not detected
Values (midpoint) applied in these DCC calculations.
[a] Absolute bioavailability estimated assuming 80 percent bioavailability from corn oil vehicle.

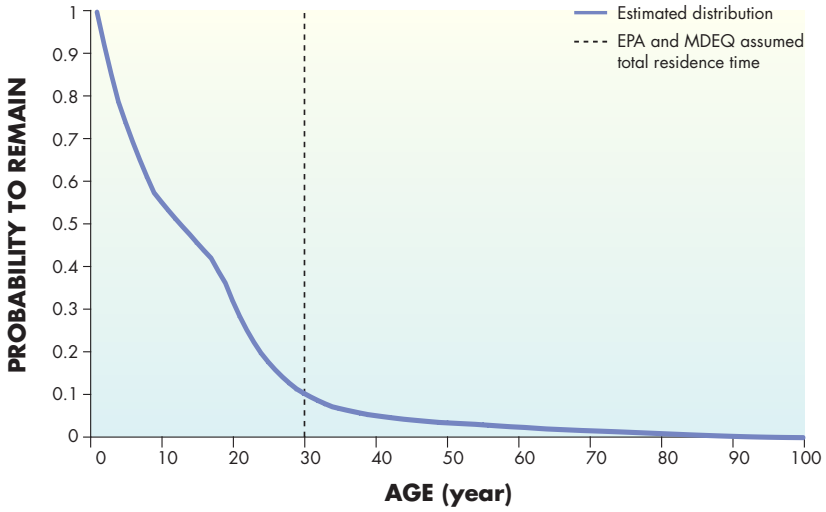

Figure 1. Estimated probability of remaining at residence (exposure duration) as a function of age for those initially 1 year old

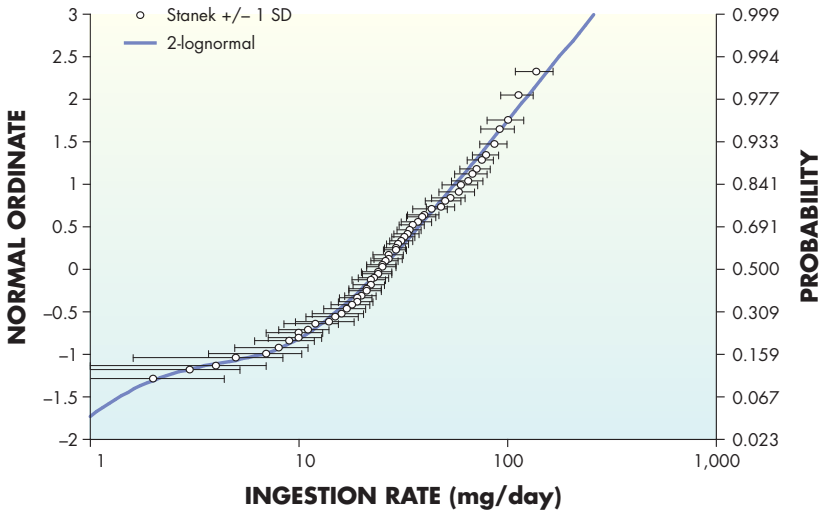

Figure 2. Child soil ingestion rate estimates (Stanek et al. 2001) and fitted distribution

TOXICITY ASSESSMENT

EPA's *Exposure and Human Health Reassessment of 2,3,7,8-Tetrachlorodibenzo-p-Dioxin (TCDD) and Related Compounds* (U.S. EPA 2003) (hereafter the "Reassessment") was the subject of an exhaustive review by an NAS committee (NAS 2006), which made several specific findings and recommendations to EPA, including:

- Use a nonlinear (threshold) dose-response modeling for cancer
- Incorporate the findings of the NTP 2006 cancer bioassay for 2,3,7,8-TCDD
- Use probabilistic methods to better characterize uncertainty and variability
- Derive noncancer toxicity values
- Improve the application of Toxic Equivalence Factor values.

EPA's response to the NAS recommendations is ongoing and thus this DCC estimate included derivation of toxicity values.

Cancer Endpoint

- A combination of a toxicokinetic model and data-derived uncertainty factors were used in deriving the cancer potency estimates for TCDD
- The NTP (2006) data for liver cancer adenoma were applied based on data analyses conducted by Maruyama and Aoki (2006)
- Human equivalent doses were estimated from the unit risk values presented by Maruyama and Aoki (2006) using a human physiologically-based pharmacokinetic (PBPK) model (Maruyama et al. 2002, 2003)
- A conservative point of departure (POD) was selected from those data (Table 3)
- The deterministic assessment applied the Maruyama and Aoki (2006) result from the Weibull model (*P*-value = 1.000 for fit with data)
- The probabilistic assessment applied the dose corresponding to a one percent increase in cancer incidence (ED01) selected because it corresponds to the dose at which the dose-response relationship begins to increase, and falls well within the range of observation

Noncancer Risks

This risk assessment relies primarily upon the World Health Organization's Joint Exposure Committee on Food Additive's (JECFA 2001) Tolerable Daily Intake value of 2.3 pg/kg-day, which was derived to address both cancer and noncancer effects.

- Except for the possibility of deriving a noncancer RfD from human data (Aylward et al. 2008), the Bell et al. (2007a,b,c) study provides considerable improvement over other published rat reproduction studies
- Initial analysis of the Bell et al. (2007a,b,c) reproductive/developmental studies for deriving noncancer toxicity values by these authors resulted in a noncancer toxicity value similar to the tolerable intake from JECFA (i.e., 2.1 pg/kg-day) applied here.

Table 3. Basis for cancer slope factors derived from NTP (2006) liver adenoma results using linear and nonlinear approaches within deterministic and probabilistic methods

	Nonlinear (Reference dose [RfD])		Linear (Slope Factor)	
	Deterministic	**Probabilistic**	**Deterministic**	**Probabilistic**
Point of departure[a] (units)	LED01 = 3.3 (ng/kg-day)	Lognormal (mean=6.3; 5th percentile=3.3) (ng/kg-day)	LED01 = 3.3 (ng/kg-day)	ED01 = Lognormal (mean = 6.3; 5th percentile = 3.3) (ng/kg-day)
Uncertainty factor	30 (1×10×3×1) 1 (toxicokinetics); 10 within human population variability; 3 to remain below the tumor threshold; and 1 because study was chronic	Product of 4 uniform distributions	NA	NA
Cancer value (units)	0.11 (ng/kg-day)	Lognormal (mean=1,100; SD=1,500) (pg/kg-day)	3,000 $(mg/kg\text{-}day)^{-1}$	Lognormal (mean=1,790; SD=648) $(mg/kg\text{-}day)^{-1}$

NA – not applicable

[a] Expressed as human equivalent internal dose as derived by Maruyama and Aoki (2006) LED01= the approximate 95% lower confidence limit of the dose producing a 1% increase in excess risk. ED01= dose corresponding to a 1% increase in cancer incidence.

The Tridge, a 3-way bridge crossing the meeting of Chippewa and Tittabawassee rivers in downtown Midland, Michigan

Photo Source: Jake Novak (2006)

RESULTS AND DISCUSSION

Deterministic and probabilistic calculations were run using methods and inputs (Tables 1 and 3) described above for the following potential risks: cancer (assuming a linear dose-response), cancer (nonlinear calculation), and noncancer (nonlinear calculation) (Table 4 and Figures 3–5).

Table 4. Direct contact criteria (DCC) estimates for $TEQ_{D/F}$ in soil in ppb

	Estimates Based on Cancer Endpoint		Estimates Based on Noncancer Endpoint
	Low-Dose Linear	Nonlinear Threshold RfD	JECFA (2001) RfD
Deterministic calculation	19 ppb	250 ppb	5.3 ppb
Probabilistic calculation 50th percentile (5th to 95th)	300 (54–3,500)	4,500 (410–68,000)	16 (2.9–140)

- A wide range of possible DCC estimates were calculated using Monte Carlo methods, with the 1 ppb cleanup value traditionally used by EPA falling below the first percentile of calculated DCC estimates for both cancer and non-cancer endpoints (Figures 3–5)
- The impact of using a threshold cancer potency value results in residential DCC values at least an order of magnitude higher than use of a linear assumption (Figure 4)
- Using these soil concentration values in a forward Monte Carlo risk assessment yielded results corresponding to the 95th percentile values for their respective distributions indicating that, given the assumptions of this assessment, there is only a ~5% probability that the target risk/HQ is exceeded using the 5th percentile DCC values of 410 and 54 ppb (Figure 5)

Sensitivity Analysis

A sensitivity analysis was conducted for the purpose of identifying which parameter values have the largest effect on variance in the distributions (Crystal Ball for Microsoft Excel, Decisioneering Inc.; Version 7), (Figure 6).

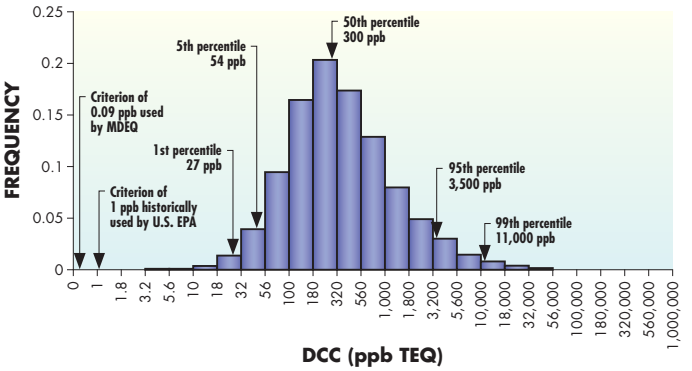

Figure 3. DCC estimates calculated probabilistically based on linear cancer slope factor

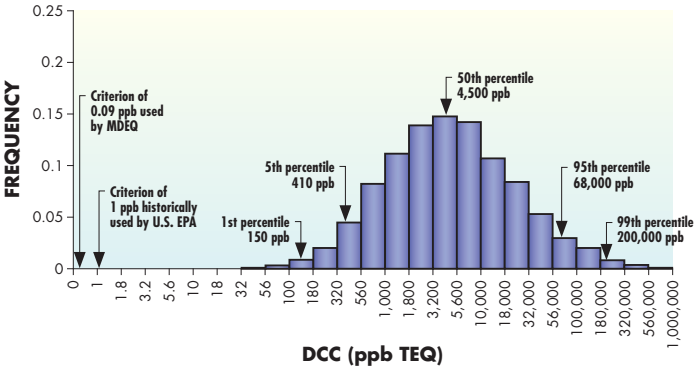

Figure 4. DCC estimates calculated probabilistically based on nonlinear cancer slope factor

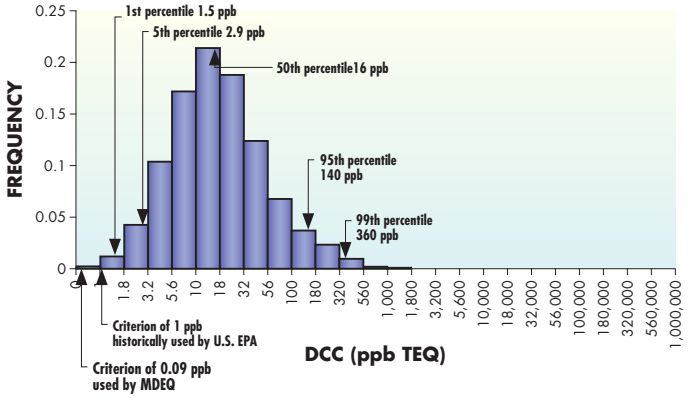

Figure 5. DCC estimates calculated probabilistically based on noncancer endpoints (JECFA value)

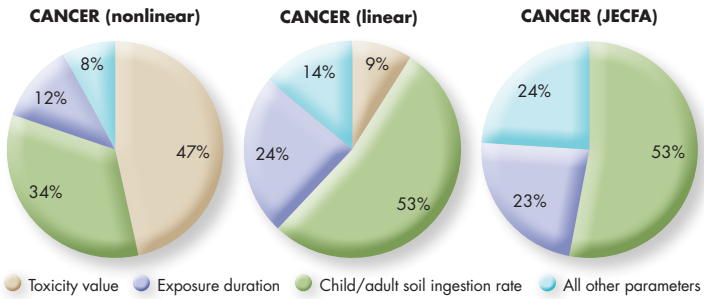

Figure 6. Sensitivity analysis

DISCUSSION

Consistent with the NAS (2008) review entitled Science and Decisions: Advancing Risk Assessment, this assessment applies the available scientific data to fully characterize the variability and uncertainty in the exposure and toxicity terms used to estimate risks associated with direct contact with $TEQ_{D/F}$ in soil.

- Considerable effort was directed at characterizing key exposure terms including soil ingestion and site-specific exposure duration (Figure 7)
- Site-specific oral bioavailability was also characterized and accounted for a lower, but important, amount of the variability in these analyses
- The toxicity assessment offered here addresses the ongoing data gap in the current EPA draft dioxin reassessment and applies the NTP (2006) cancer bioassay results for analysis of carcinogenicity as well as findings on the mode of action of PCDD/Fs for both cancer and noncancer effects
- The University of Michigan Dioxin Exposure Study (UMDES) investigation represents an unusually comprehensive analysis of environmental exposures and serum $TEQ_{D/F}$ for 1,324 people representative of those residing for at least 5 years in the Midland and the Tittabawassee River and Saginaw River floodplains (Hedgeman et al. 2008; Franzblau et al. 2008a,b, 2009a,b; Garabrant et al. 2008a,b; Demond et al. 2008)
  - Evaluation of the relationship between a residential soil $TEQ_{D/F}$ and serum $TEQ_{D/F}$ did not identify any correlation
  - The DCC estimates presented here are consistent with this UMDES finding.

The resulting range of calculated direct contact criteria provides risk managers with a full range of estimates to use in making management decisions.

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