FINAL REPORT

BIOAVAILABILITY OF DIOXINS AND DIOXIN-LIKE COMPOUNDS IN SOIL

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ABBREVIATIONS AND ACRONYMS

ABA	absolute bioavailability
AhR	aryl hydrocarbon receptor
β	beta regression coefficient (i.e., regression slope)
bw	body weight
CI	confidence interval
CR	cancer risk
CSF	cancer slope factor
CYP450	cytochrome P450
GC/MS	gas chromatography/mass spectrometry
HpCD	heptachloro-p-dibenzodioxin
HpCF	heptachlorodibenzofuran
HxCD	hexachloro-p-dibenzodioxin
kg	kilogram
MAX	maximum
MED	median
MIN	minimum
mL	milliliter
NA	not available
ND	no data
ng	nanogram
NR	not reported
OCDD	octochloro-p-dibenzodioxin
OCDF	octochlorodibenzofuran
PCB	polychlorinated biphenyl
PCDD	polychlorinated dibenzo-p-dioxin
PCDF	polychlorinated dibenzofuran
PeCD	pentachloro-p-dibenzodioxin
pg	picogram
PeCF	pentachlorodibenzofuran
ppb	part per billion
ppm	part per million
ppt	part per trillion
RAGS	Risk Assessment Guidance for Superfund
RBA	relative bioavailability
RfD	reference dose
RM	reference material
SD	standard deviation
SE	standard error
TCDD	tetrachloro-p-dibenzodioxin
TCDF	tetrachlorodibenzofuran
TEF	toxic equivalence factor
TEQ	toxic equivalent
TM	test material
µm	micron
USEPA	U.S. Environmental Protection Agency
WHO	World Health Organization
2,4,5-T	2,4,5-trichlorophenoxyacetic acid

EXECUTIVE SUMMARY

The Risk Assessment Guidance for Superfund (RAGS) Part A (USEPA 1989) discusses making adjustments to Superfund site-specific risk assessments when the medium of exposure in an exposure assessment differs from the medium of exposure assumed by the toxicity value (cancer slope factor, reference dose value, etc.) based upon site-specific bioavailability data. An important consideration in assessing risks from exposures to dioxin in soil is whether an adjustment is needed in the application of the oral cancer slope factor (CSF) and/or oral chronic reference dose (RfD) for 2,3,7,8-tetrachloro-dibenzo-p-dioxin (TCDD). This adjustment would account for differences in the bioavailability of TCDD (and toxicologically related polychlorinated dibenzo-p-dioxins [PCDD] and polychlorinated dibenzofuran congeners [PCDF]) in soil and in the test medium used in the critical study(s) on which the CSF and/or RfD were based (e.g., dietary exposure vs. exposure to soil). An adjustment would be considered appropriate if evidence were sufficient to indicate that the relative bioavailability (RBA) of the PCDD/F mixture in soil was less than 100%. This report presents a summary of the published literature and analysis of the available data regarding RBA of PCDD/F in soil[1].

Objectives

The principal objectives of this literature review and data analysis are as follows:

1. Identify and summarize published literature potentially relevant to estimating RBA of PCDD/Fs in soil. Select studies that meet predetermined quality considerations.

2. Evaluate data contained in this literature to determine if they are adequate and sufficient to conclude that RBA for PCDD/Fs RBA in soil is less than 100%.

3. Use these data, if adequate and sufficient, to calculate a quantitative central tendency and upper bound estimate of RBA that can be applied when developing site-specific cleanup levels for dioxin in soil.

[1] Soil defined in this report include but not limited to studies utilizing media such as sediments and other materials

Results

Published literature potentially relevant to estimating RBA of PCDD/F in soil was identified, reviewed, and summarized. A total of nine studies were identified. Pertinent data from six of these studies were extracted and used to derive estimate(s) of RBA. Relative bioavailability estimates for all test materials were less than 100%.

The six studies were selected based on the quality and relevance of information provided in each study (Bonaccorsi et al. 1984; Budinsky et al. 2008; Finley et al. 2009; Lucier et al. 1986; Shu et al. 1988; Wittsiepe et al. 2007). All selected studies provided RBA estimates in test materials consisting of soil contaminated with dioxins *in situ.* Studies of spiked soil materials were not included in this analysis based on information suggesting that aging of contaminated soil may decrease the bioavailability of dioxins in soil (Poiger and Schlatter 1980; Ruby et al. 2002; Umbreit et al. 1986). Studies that administered dose levels of dioxins that were clearly toxic were likewise not included in this analysis (McConnell et al. 1984; Umbreit et al. 1986; Wendling et al. 1989).

The six studies selected for further analysis provided RBA estimates for 15 test materials (soil from recognized dioxin impacted sites) based on assays in the following experimental models:

- Swine: three test materials (Budinsky et al. 2008; Wittsiepe et al. 2007);
- Rats: 11 test materials (Budinsky et al. 2008; Finley et al. 2009; Lucier et al. 1986; Shu et al. 1988); and
- Rabbit: one test material (Bonaccorsi et al. 1984).

Only two of the 15 test materials were assayed in both swine and rats (Budinsky et al. 2008). Three of the six studies estimated RBA for multiple congeners with varying chlorination in eight different test materials (Budinsky et al. 2008; Finley et al. 2009; Wittsiepe et al. 2007). The remaining studies estimated RBA for 2,3,7,8-TCDD only.

Collectively, analyses of published RBA estimates for PCDD/F in soil support the following conclusions:

1. RBA for PCDD/F mixtures in soils assayed in swine and rats are less than 100%, as compared to a lipid or organic solvent vehicle as the reference material (e.g., corn oil).

2. RBA varies with congener chlorination. The direction of the relationship (i.e., positive or negative slope) is not the same when estimated based on data from swine or rat assays (Budinsky et al. 2008; Finley et al. 2009; Wittsiepe et al. 2007). Data from swine assays indicate an increase in RBA with increasing chlorine content (Budinsky et al. 2008; Wittsiepe et al. 2007), whereas data from rat assays indicate a decrease in RBA with increasing chlorination (Budinsky et al. 2008; Finley et al. 2009). These differences suggest substantially different RBA estimates may be obtained depending on the animal model used.

   The National Academy of Sciences (NAS 2006), the World Health Organization (Van den Berg et al. 2006), other international committees and organizations, the U.S. Environmental Protection Agency (USEPA 2003), and other state agencies (e.g., WASDE 2007) have recognized that soil will influence the bioavailability of mixtures of PCDD/Fs and have concluded that greater chlorinated congeners tend to be less bioavailable than the less chlorinated congeners. However, observations and analyses reported here suggest that the effect of chlorination on the RBA of dioxins in soil may be different for different animal models, as shown in the recently reported swine assays.

3. The dependence of RBAs on congener chlorination suggests soil RBA will depend on the congener composition of the soil (as well as the bioassay used to estimate RBA). Additionally, congeners with different levels of chlorination result in different composite RBA averages for soil when calculated based on total congener mass or 2,3,7,8-TCDD toxicity equivalents (TEQ). For example, based on the swine RBA assays, octachloro-p-dibenzodioxins (OCDD; eight chlorines substituted on eight available positions on the carbons of the benzene rings on either side of the central diheterabenzene, or "Cl8") and

octachlorodibenzofurans (OCDFs, Cl8) will have a higher RBA than lower chlorine content congeners. Therefore, for soil highly enriched with OCDDs and OCDFs (i.e., higher RBA and lower toxic equivalence factor [TEF]), the RBA based on total congener mass will be higher than the RBA based on total TEQ. If, on the other hand, the soil RBA is based on rat RBA assays, high enrichment of OCDDs and OCDFs would result in higher TEQ RBAs compared to RBAs for total congener mass.

4. The influence of abiotic constituents, compound aging, and other associated soil factors on RBA of dioxin in soil has not been evaluated systematically. Bioavailability appears to decrease with aging based on comparisons of laboratory-spiked soil and soil contaminated *in situ* (Poiger and Schlatter 1980; Umbreit et al. 1986) and is lower when administered as a mixture of activated carbon compared to an aqueous suspension (Poiger and Schlatter 1980). The latter observation suggests that organic carbon content may contribute to a decrease in dioxin bioavailability from soil.

5. Although, RBA for dioxins in the soils evaluated in these studies is less than 100%, estimating a representative range or upper bound value for RBA from these data is problematic because of the limited number of estimates, the confounding effects of congener chlorination on RBA, differences in the estimates based on swine and rat assays, and uncertainty with the RBA estimates due to potential differences in elimination kinetics between test and reference materials.

   In the swine assays, the total congener mass RBAs average 38% and range up to 50%; the total TEQ RBAs average 28% and range up to 33%. A statistically robust description of the distribution of the RBA values cannot be estimated from these swine studies, as they consist only of three test materials. In the rat studies, the total congener mass RBAs average 29% and range up to 68%; the total TEQ RBAs average 41% and range up to 64%. While the rat studies offer a larger data set for analysis, these data are still considered insufficient for representing the variability in RBA at U.S. sites having a range of soil characteristics and congener mixes. Also, the uncertainty regarding the extrapolation of RBA estimates in rodents to humans is considered too large. A

contributing factor to this uncertainty is a lack of mechanistic understanding of the differences in RBA estimates obtained from swine and rats.

Swine and rats also differ in the distribution of absorbed PCDD/Fs. Similar to humans, swine accumulate higher levels in adipose tissue relative to liver, whereas, the distribution in rats tends to show the opposite trend (Budinsky et al. 2008; Thoma et al. 1989, 1990). Moreover, using rat liver dioxin burden as a biomarker may have other implications related to species differences in binding to the aryl hydrocarbon receptor (AhR) and induction of cytochrome P450 (CYP450), the major route of metabolic clearance of PCDD/Fs (Budinsky et al. 2008; Connor and Aylward 2006; Finley et al. 2009; Flaveny et al. 2010).

While it is not the objective of this report to evaluate a preferred model, swine have been extensively used to predict RBA of arsenic and lead in humans based on the similarities between the physiology and anatomy of the swine and human gastrointestinal tracts (USEPA 2007). A comprehensive evaluation is necessary before determining whether one or more animal models are appropriate for characterizing RBA of PCDD/Fs in soil.

Conclusions

1. Currently available information suggests that RBA of dioxin in soils can be expected to be less than 100%.

2. Available estimates of soil dioxin RBA are not adequate and sufficient to estimate a value for RBA for use in risk assessment as an alternative to 100% or site-specific values.

3. A preferred animal model or bioassay protocol has not been established for predicting soil RBA in humans.

1.0 INTRODUCTION

1.1 Background

The Risk Assessment Guidance for Superfund (RAGS) Part A (USEPA 1989) discusses making adjustments to Superfund site-specific risk assessments when the medium of exposure in an exposure assessment differs from the medium of exposure assumed by the toxicity value (cancer slope factor, reference dose value, etc.) based upon site-specific bioavailability data. An important consideration in assessing risks from exposures to dioxin in soil is whether an adjustment is needed in the application of the cancer slope factor (CSF) and/or chronic reference dose (RfD) for 2,3,7,8-tetrachloro-dibenzo-p-dioxin (TCDD). This adjustment would account for differences in the bioavailability of TCDD (and toxicologically related polychlorinated dibenzo-p-dioxins [PCDD] and polychlorinated dibenzofuran congeners [PCDF]) in soil and in the test medium used in the critical study(s) on which the CSF and/or RfD were based (e.g., dietary exposure vs. exposure to soil). An adjustment may be considered appropriate if evidence were sufficient to indicate that the relative bioavailability (RBA) of the PCDD/F mixture in soil was less than 100%. This report presents a review of the published literature and analysis of the available data regarding RBA of PCDD/F in soil.

The principal objectives of this literature review and data analysis are as follows:

1. Identify and summarize published literature potentially relevant to estimating RBA of PCDD/Fs in soil. Select studies that meet predetermined quality considerations.

2. Evaluate data contained in this literature to evaluate whether they are adequate and sufficient to conclude that RBA for PCDD/Fs RBA in soil is less than 100%.

3. Consider use of these data, if adequate and sufficient, to recommend a quantitative central tendency and upper bound estimate of RBA when developing site-specific cleanup levels for dioxin in soil.

2.0 METHODS

2.1 Literature Search Strategy

The following approach was used to identify literature pertinent to the topic of bioavailability of PCDD/F in soil:

a. Literature published before 1998 was identified from the text and bibliography of the current (1998) *ATSDR Toxicological Profile for Chlorinated Dibenzo-p-Dioxins*.

b. Literature published subsequent to 1998 was identified based on results of a dioxin literature evaluation conducted in 2008 (for the period 1998–2008).

c. Literature published subsequent to 2008 was identified from a *de novo* bibliographic search (e.g., MEDLINE/TOXLINE) conducted for the period 2008–present. The search focused on relevant literature (e.g., absorption, bioavailability).

d. As pertinent literature from the above searches was identified and retrieved, the references in these reports were tree-searched to identify additional pertinent literature.

A preliminary description of the search results (prepared before initiation of literature retrieval) was developed and is included in Appendix A of this report.

2.2 Data Analyses

Relative bioavailability values were calculated, if not reported, based on reported group mean estimates for administered dose and liver PCDD/F levels. The general form of the calculations used to estimate RBA is given in Equations 1 and 2:

$$RBA = \frac{ABA_{TM}}{ABA_{RM}} \quad \text{Eq. (1)}$$

$$ABA = AF = \frac{ID}{ED} \cdot \frac{1}{(1-EF)} \quad \text{Eq. (2)}$$

where ABA_{TM} and ABA_{RM} are *absolute bioavailability* for the *test material* (e.g., soil) and *reference material* (e.g., dioxin in corn oil), respectively; *AF* is the absorbed fraction of the dose; *ID* and *ED* are the *internal dose* and *external dose*, respectively, of the test or reference material; and *EF* is the fraction of the absorbed dose eliminated by metabolism and excretion. In most studies, the internal dose metric (*ID*) was liver PCDD/F burden; however, the sum of liver and adipose burdens were also used in some studies (Budinsky et al. 2008; Wittsiepe et al. 2007). Although the elimination fraction (*EF*) appears in the expression for absolute bioavailability (*ABA* in Equation 2), it does not need to be considered in the calculation of RBA (Equation 1), as long as elimination kinetics are similar for the PCDD/F absorbed from the test material and reference materials (i.e., $EF_{TM} = EF_{RM}$). However, if EF_{RM} were to exceed EF_{TM}, the *ID/ED* ratio will underestimate RBA. The validity of the assumption of equal elimination kinetics of the test and reference materials is an important issue in the estimation of RBA for PCDD/F congeners, because the metabolic elimination of PCDD/Fs is dose-dependent. Dose-dependency derives from the induction of cytochrome P450 (CYP450), which is the primary mechanism for metabolic elimination of PCDD/Fs. This issue is addressed further in the data analysis sections of this report.

In most studies considered in this report, elimination fractions were not estimated. As a result, reported estimates for the ratio *ID/ED* would be expected to underestimate absolute bioavailability to varying degrees depending on the elimination kinetics of the specific PCDD/F

congeners considered. In this analysis, the *ID/ED* ratios for the test and reference materials were used in the calculation of RBA; no attempt was made to estimate absolute bioavailability.

For multiple congener studies, RBA was calculated based on congener mass as well as 2,3,7,8-TCDD (*TCDD*) toxic equivalents (TEQ), where the toxic equivalency factor (TEF) values were assigned to each congener based on Van den Berg et al. (2006). Only the group's means for dose and tissue levels were reported; therefore, mean congener mass and TEQ RBAs were calculated as weighted congener means, with weights assigned based on congener or TEQ dose (Equations 3 and 4):

$$Mass - weighted\ RBA = \sum MassDose_i \cdot RBA_i \qquad \text{Eq. (3)}$$

$$TEQ - weighted\ RBA = \sum TEQDose_i \cdot RBA_i \qquad \text{Eq. (4)}$$

where $MassDose_i$ and $TEQDose_i$ are the mass and TEQ dose for congener *i*, respectively, and RBA_i is the calculated or reported RBA for congener *i*.

Congener and TEQ doses (per kg body weight per day; kg bw/day) were either reported or calculated based on reported data on congener concentrations in the test soil, soil doses, and reported body weights of the test animals. The midpoint of the range was used in the dose calculation if body weight was reported as a range.

All data analyses were conducted using either Microsoft Excel 2007 (Microsoft) or STATGRAPHICS Centurion XV (v 15.2.06, StatPoint, Inc.).

3.0 RESULTS

3.1 General Features of RBA Studies

Nine studies providing RBA estimates of PCDD/F in soil were identified in the literature review. A tabular summary of each study is provided in Table 1 and more detailed summaries follow in Section 3.2. The studies include estimates based on assays in swine (Budinsky et al. 2008; Wittsiepe et al. 2007), rats (Budinsky et al. 2008; Finley et al. 2009; Lucier et al. 1986; Shu et al. 1988), rabbits (Bonaccorsi et al. 1984), and guinea pigs (Umbreit et al. 1986; Wendling et al. 1989). Three of the studies estimated RBA for multiple congeners (Budinsky et al. 2008; Finley et al. 2009; Wittsiepe et al. 2007); the remaining studies estimated RBA for 2,3,7,8-TCDD only. The soil test materials examined in these studies included samples collected from various environments that had been contaminated with dioxins *in situ*, largely from anthropogenic sources, as well as test materials prepared by introducing dioxins into test soil in the laboratory (*spiked* soil).

In all of the studies, the reference material was a lipid (e.g., corn oil) or organic solvent (e.g., acetone) that was spiked with an appropriate level and mixture of congeners to represent the congener profile in the test soil. Test soil and reference materials were administered to animals in repeated doses (Bonaccorsi et al. 1984; Budinsky et al. 2008; Wittsiepe et al. 2007) or as a single dose (Lucier et al. 1986; McConnell et al. 1984; Shu et al. 1988; Umbreit et al. 1986; Wendling et al. 1989). Test and reference materials were mixed with food (Bonaccorsi et al. 1984; Budinsky et al. 2008, Finley et al. 2009) or administered (in most rodent studies) as an aqueous or lipid vehicle suspension, respectively, by gavage (Bonaccorsi et al. 1984; Lucier et al. 1986; McConnell et al. 1984; Shu et al. 1988; Umbreit et al. 1986; Wendling et al. 1989).

3.2 Summary of Studies

Studies included in this assessment are described below in alphabetical order and are summarized in Table 1.

3.2.1 Bonaccorsi et al. (1984) Rabbit Study

Bonaccorsi et al. (1984) estimated RBA of 2,3,7,8-TCDD in soil taken from a contaminated area at Seveso, Italy. The soil was sieved to 200/300 mesh and analyzed by gas chromatography/ mass spectrometry (GC/MS). The soil had a mean TCDD content of 81±8 ppb. TCDD-free soil sieved identically was spiked in the laboratory by adding 20 or 40 ppb TCDD in acetone. Reference test materials consisted of 20 and 40 ppb TCDD in acetone:vegetable oil (v:v, 1:6) and 20 and 40 ppb TCDD in alcohol:water (v:v, 1:1). Soil and reference materials were administered as a gavage dose with the soil dose suspended in 10 mL water. Groups of male albino rabbits (2.6±0.3 kg at sacrifice) were administered daily gavage doses for 7 days at the following TCDD dose levels: 20 ng TCDD/day in acetone:oil (5 rabbits), 20 ng TCDD/day as lab-contaminated soil (7 rabbits), 40 ng TCDD/day in alcohol or acetone:oil (16 rabbits), 40 ng TCDD/day as lab-contaminated soil (13 rabbits), 80 ng TCDD/day in alcohol (5 rabbits), 80 ng TCDD/day as lab-contaminated soil (10 rabbits), 80 ng TCDD/day in Seveso soil (7 rabbits), and 160 ng TCDD/day in Seveso soil. Animals were killed on the eighth day and livers extracted and analyzed for TCDD content by GC/MS. TCDD uptake by the liver was similar among the 20 ng TCDD/day dose groups (TCDD:acetone group and TCDD lab-contaminated soil). At the 40 ng TCDD/day dose level, liver uptake of TCDD from lab-contaminated soil was 29% less (99% CI 0–53) than the TCDD:solvent control. At the 80 ng TCDD/day dose level, liver uptake of TCDD from lab-contaminated soil was 44% less (99% CI 19–68) than the TCDD:solvent control; uptake of TCDD from the Seveso soil sample was 68% less (99% CI 40–95) than the TCDD:solvent control. Based on reported doses and liver levels in animals that received 80 ng TCDD/day in Seveso soil in solvent, the RBA for Seveso soil was approximately 32% (calculated for this report).

3.2.2 Budinsky et al. (2008) Swine and Rat Studies

Budinsky et al. (2008) estimated RBA of PCDD and PCDF congeners in soil from two sites in Michigan. The soil samples were sieved (<250 µm). An urban site impacted by past incineration practices served as one source of soil and reflected a PCDD-dominated TEQ of 264 ppt comprised mainly of 2,3,7,8-TCDD and 1,2,3,7,8-pentachloro-p-dibenzodioxin (PeCD). A floodplain site of historic (late 1800s to early 1900s) chloralkali production was the source for the other soil and reflected a PCDF-dominated TEQ of 651 ppt. The TEQ concentrations were based on 2005 World Health Organization (WHO) TEQs (Van den Berg et al. 2006). Information regarding the contributions of specific congeners to the total TEQs is presented in Appendix B. The reference material was a mixture of the five PCDD/F congeners that contributed to the five highest mass congener fractions in each soil sample, in corn oil:acetone (99:1, v/v), and at a target concentration similar to that measured in the corresponding soil sample.

Swine (*Sus scrofa*, 6-weeks old, 5 per group) received 10 g soil per day (split into morning and afternoon doses) for 30 days. Soil samples were placed in moistened feed (1 g soil/10 g feed) and administered following a 2-hour fast. The reference material (PCDD/F in corn oil:acetone) was administered in a gelatin capsule placed in moistened feed with two doses each day for 30 days. The daily dosage of PCDD/F was 122 pg TEQ/kg bw/day for the urban soil and 313 pg TEQ/kg bw/day for the floodplain soil.

Sprague-Dawley rats (females, 6-weeks old, 10 per group) were administered soil as a 5% w/w soil-feed mixture for a period of 30 days. Food consumption was monitored to estimate daily dose. The reference material of PCDD/F in corn oil:acetone was administered by gavage for 30 days. The daily dosage of PCDD/F was 577 pg TEQ/kg bw/day for the urban soil and 2100 pg TEQ/kg bw/day for the floodplain soil.

Relative bioavailability in swine and rats was estimated from measurements of PCDD/F content of liver and adipose tissue. Adipose tissue mass as a percent of body weight of rats was estimated from published allometric relationships. Adipose mass of swine was estimated based

on direct measurements of adipose in three swine. Mean TEQ RBA based on swine assays were 23% for the urban soil and 27% for the floodplain soil. The corresponding estimates based on rat assays were 37% for the urban soil and 66% for the flood plain soil.

3.2.3 Finley et al. (2009) Rat Study

Finley et al. (2009) estimated RBA of PCDD and PCDF congeners in five soil samples collected from different locations at an operating industrial facility in the U.S. The samples were sieved to <250 µm particle size and analyzed for PCDD/F content using isotope dilution GC/MS according to USEPA Method 1613, revision B. PCDFs were the dominant contributors to the TEQ concentration in the soil samples; TEQ concentrations of the measured PCDD congeners ranged from 0.014–1.39 ppb (approximately 2.4–3.7% of the total soil TEQ). Information regarding the contributions of specific congeners to the total TEQs is presented in Appendix B. Sprague-Dawley rats (female, 15 weeks of age, 5 per group) received a single gavage dose of test soil (approximately 4 mL/kg bw of aqueous suspension) or reference material (4 mL/kg bw in corn oil). The congener profiles (i.e., concentration ratios) of the reference materials were based on the mean fractional contribution of each congener to the total TEQ concentration of the soil samples used in the study. The concentrations selected for each congener in the reference formulation was intended to reflect systemic exposures comparable to those of the soil-treated rats. The rationale for this approach was to estimate RBA at similar internal doses (i.e., liver levels) for the soil and reference materials, which would result in the same level of hepatic enzyme induction (i.e., similar metabolic clearance rates). The highest reference dose was intended to yield approximately 30% of the maximum dose administered to the soil-treated rats based on the expectation of incomplete absorption of PCDD/Fs from soil. Two lower reference concentrations (5- and 25-fold lower than the highest concentration) were included to account for the wide range of total TEQ concentrations in the different soil samples.

Relative bioavailability for selected PCDD/F congeners or for total TEQ were calculated by dividing the fraction of the administered dose in the liver of soil-treated rats by the mean fraction of the administered dose in the liver of the corresponding reference rats. TEQ RBA estimates in

the 5 different soil samples ranged from 17 to 50%. Information regarding the contributions of specific congeners to the TEQ-weighted RBA estimates is presented in Appendix B.

3.2.4 Lucier et al. (1986) Rat Study

Lucier et al. (1986) estimated RBA of 2,3,7,8-TCDD in a soil sample collected from a location in southwest Missouri known as the Minker site, a dumpsite for TCDD-contaminated soil. The soil contained TCDD at 880 ppb and was passed through a 60-gauge sieve before assay. The soil amount necessary to yield doses based on body weight were calculated using the TCDD concentrations given above and body weight (200 g). Groups of six female Sprague-Dawley rats (approximate weight of 200 g) were administered single doses of soil by oral gavage (dosing volume 2 mL in distilled water) at doses ranging from 0.015 µg TCDD/kg bw (0.004 g soil) to 5.5 µg TCDD/kg bw (1.25 g soil). Other groups of rats administered TCDD (in corn oil; dose volume 0.2 mL/kg bw) by gavage at doses of 1 or 5 µg/kg bw served as reference groups. No symptoms of acute toxicity were observed. Animals were sacrificed six days following treatment and livers were analyzed for TCDD content. For rats administered soil at a dose of 5.5 µg TCDD/kg bw, the mean TCDD liver concentration was 20.3±12.9 (standard deviation [SD]) µg/kg liver, compared to a mean TCDD liver concentration of 40.8±6.3 µg/kg liver for the reference group dosed at 5.0 µg TCDD/kg bw. At lower doses (1 µg TCDD/kg bw), mean TCDD liver concentrations were 1.8±0.3 and 7.6±2.5 g/kg liver for the soil-treated, and reference groups, respectively. Based on these results, RBAs for 1 and 5 µg TCDD/kg bw doses were estimated in this analysis to be 22 and 45%, respectively (calculated for this report).

3.2.5 McConnell et al. (1984) Guinea Pig Study

McConnell et al. (1984) assessed the bioavailability of TCDD in soil samples from the Minker/Stout and Times Beach sites in Missouri. Soil TCDD concentrations (soil sifted by 60-gauge mesh) in the Minker/Stout and Times Beach samples were 880 and 770 ppb, respectively. Based on these levels, test materials were administered to groups of 6 male Hartley guinea pigs (2.5-weeks old) by gavage in amounts that delivered TCDD doses of approximately 1, 3, or 10 µg/kg bw (in 5 mL distilled water). Reference animals (6/group) were administered reference

material consisting of pure TCDD in corn oil at 0, 1, or 3 µg/kg bw. The study authors noted that a reported LD_{50} for TCDD in guinea pigs is 2 µg/kg. An additional control group was administered 3.6 g of uncontaminated soil (no TCDD, PCDFs, or PCBs detected), at a dose equal to the highest administered dose of contaminated soil. The animals were observed for 30 days after dosing. At death or terminal sacrifice, livers were extracted and analyzed for TCDD. The 5 surviving guinea pigs administered 1 µg TCDD/kg bw in corn oil had a mean TCDD liver content of 1.6±0.2 (standard error [SE]) ppb. TCDD was not detected in livers of guinea pigs administered 1.3 µg TCDD/kg bw of Times Beach soil or 1.1 µg TCDD/kg bw of Minker/Stout soil. Higher TCDD doses (i.e., 3–3.8 µg TCDD/kg bw) were lethal to all animals administered TCDD in corn oil and to some of the animals administered TCDD in contaminated soil. Given the serious toxicity/lethality observed at the higher doses, estimates of RBA may not be reliable and are of questionable relevance to healthy animals. Based on liver concentrations of animals that survived or died before the 30-day observation period concluded, RBA estimates are approximately 8% for animals administered 3.8 µg TCDD/kg bw in the Times Beach soil, and 11% for animals administered 3.3 µg TCDD/kg bw in the Minker/Stout soil (calculated for this report). The study of McConnell et al. (1984) includes results of the rat study described in Lucier et al. (1986).

3.2.6 Shu et al. (1988) Rat Study

Shu et al. (1988) estimated bioavailability of 2,3,7,8-TCDD in soil collected from areas of Times Beach, Missouri, that was contaminated in the early to mid-1970s by spraying with a mixture of TCDD-contaminated oil. Soil samples were sieved through a 40-mesh before use. Measured TCDD concentrations in 3 soil samples were 1.9, 28.6, and 723 ppb. Uncontaminated soil from one area of Times Beach, verified for the absence of TCDD, was used to dilute the TCDD-contaminated soil to provide a range of TCDD doses in the test soil (3.2–1450 ppt). Test materials were administered as an aqueous suspension (0.25 g soil/mL), as a single gavage dose (8 mL/kg bw) to groups of 4 male Sprague-Dawley rats (180–250 g body weight). Reference groups were administered TCDD in corn oil (dose range: 2.0–1180 ng TCDD/kg bw; dose volume: 4 mL/kg bw). Animals were killed 24 hours post dose and livers were analyzed for TCDD. A plot of TCDD dose (ng TCDD/kg bw) versus percentage of TCDD concentration in

liver showed that hepatic TCDD levels increased with increasing dose for TCDD administered in both soil and corn oil and that the slopes for soil-based and corn oil-based hepatic levels were similar. These data support the validity of using the relative recoveries of TCDD in the liver for estimating oral bioavailability. Table 1 of Shu et al. (1988) presents values for the absolute bioavailability for TCDD (mean 42±4%, range: 37–49%). These absolute bioavailability values were calculated by adjusting the TCDD dose fraction in liver following dosing with corn oil by an estimate of the unabsorbed fraction of TCDD when it is administered to rats in corn oil (30%, Piper et al. 1973). For this report, RBA values were recalculated as the reported absolute bioavailability times 1.3. The resulting mean RBA was 56±6% (SD, n=6, range: 48–64%).

3.2.7 Umbreit et al. (1986) Guinea Pig Study

Umbreit et al. (1986) assessed the bioavailability of 2,3,7,8-TCDD in soil samples collected at a 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) manufacturing site in Newark, New Jersey. Soil analysis revealed more than 50 PCDD/Fs. TCDD concentration in the soil was approximately 2200 ppb. Experimental groups in the study included PCDD/F-contaminated soil, decontaminated (undisclosed decontamination technique) soil from the same site as a negative control, TCDD in a suspension of corn oil and acetone (9:1), corn oil as the reference material, and decontaminated soil that was recontaminated with TCDD 1 hour before use to serve as a positive control. The materials were administered to groups of guinea pigs (4/sex/group) as single gavage doses and animals were observed for up to 60 days after dosing. Reported TCDD doses were 3, 6, and 12 µg TCDD/kg bw for test material and 6 µg TCDD/kg bw for both the recontaminated soil and the corn oil solvent control. In animals treated with recontaminated soil and TCDD in corn oil, mortality was >50%, with deaths occurring within 31 days after dosing. No animals died in groups administered corn oil alone, decontaminated soil, or TCDD-contaminated soil. Liver TCDD content was determined at terminal sacrifice or at time of death if the animals died before the observation period ended. A TCDD level of 18 µg/kg liver was reported for composite liver samples from 6 of the guinea pigs administered recontaminated soil. A TCDD level of 90 ng/kg liver was reported for composite liver samples from 4 of the guinea pigs administered recontaminated soil at a dose of 12 µg TCDD/kg bw. TCDD was not detected in livers from the five guinea pigs that were analyzed following administration of decontaminated soil.

In a similarly-designed study, TCDD toxicity and liver uptake were assessed for a soil taken from a salvage site in close proximity to the 2,4,5-T manufacturing site. Residue from stills used at the manufacturing plant was dumped at this site before recycling of metal from the spent stills. Groups of guinea pigs (2/sex/group) were administered contaminated soil (reported TCDD dose of 320 µg/kg bw), decontaminated soil, or TCDD in corn oil (6 µg/kg bw). Three of the animals administered TCDD in corn oil died within 21 days after dosing. There were no deaths among the guinea pigs receiving contaminated or decontaminated soil. A TCDD level of 230 ng/kg

liver was reported for composite liver samples from 4 of the guinea pigs administered contaminated soil.

Liver TCDD levels were not reported for animals that received TCDD in corn oil, precluding calculation of soil RBA values. However, comparison of the liver TCDD concentrations following dosing with the site soil with those that were observed following dosing with the recontaminated soil indicates that soil contaminated *in situ* had a substantially lower bioavailability. RBA was less than 1% for the soil from the manufacturing site and approximately 24% for the soil for the metal yard (calculated for this report).

3.2.8 Wendling et al. (1989) Guinea Pig Study

Wendling et al. (1989) assessed the bioavailability of TCDD in soil samples from Times Beach, Missouri and from a 2,4,5-T manufacturing site in Newark, New Jersey. The Times Beach soil was contaminated primarily with 2,3,7,8-TCDD (510 ppb) with minor contributions from heptachloro-p-dibenzodioxin (HpCD) (7.3 ppb) and octachloro-p-dibenzodioxin (OCDD) (12 ppb). The Newark soil contained a mixture of congeners that included 2,3,7,8-TCDD (1400 ppb), PeCD (21 ppb), hexachloro-p-dibenzodioxin (HxCD) (140 ppb), HpCD (3500 ppb), and OCDD (5400 ppb). Guinea pigs received gavage doses of soil (3–10 µg TCDD/kg bw) or TCDD in 10% gum acacia. Liver PCDD congener concentrations were determined seven days after the dose (the time of first death attributed to TCDD). Mean liver concentration in animals that received 6 µg TCDD/kg bw in gum acacia was 56 ng/g liver. In animals that received 3 or 10 µg TCDD/kg bw in Times Beach soil, mean liver concentrations were 1.9 and 28 ng/g liver, respectively. Mean liver concentrations in animals that received 5 or 10 µg TCDD/kg in Newark soil were 94 and 1.5 ng/g liver, respectively. Based on these data, RBA of TCDD in soil (relative to the gum acacia reference) was approximately 30% for the Times Beach soil and 1.6% for the Newark soil (calculated for this report).

The Newark soil contained a mixture of PCDD congeners allowing comparison of liver concentrations of each congener per unit of congener dose. Based on these data, congener

RBAs, relative to TCDD, were reported as: 1,2,3,7,8-PeCD, 130%; 2,3,6,78-HxCD, 60%; 1,2,3,4,6,7,8-HpCD, 40%; and OCDD, 16% (e.g., $RBA_{OCDD}/RBA_{TCDD} * 100 = 16\%$).

3.2.9 Wittsiepe et al. (2007) Swine Study

Wittsiepe et al. (2007) assessed RBA of PCDD/Fs in soil (30.6% sand, 36.5% silt, 32.9% clay, 6.8% organic carbon) collected from land that had been treated with sludge from the port of Hamburg, Germany. Soil particles >1 mm in size were removed by sieving. PCDD/F was present in soil at 5.3 µg TEQ/kg soil (ppb). The congener pattern showed increasing concentrations with grade of chlorination and was dominated by PCDF congeners.

The study used two groups of four Goettingen mini-pigs (age 56–78 days at the beginning of the experiment) that were hand-fed test material in pellets (small amounts of feed, milk powder, and water) once per day for 28 days. Test material consisted of either 0.5 g PCDD/F-contaminated soil/kg bw/day (resulting in daily uptake of 2.63 ng TEQ/kg bw/day) or solvent-extracted PCDD/Fs (hexane-acetone, 50/50) from the same soil that was used for soil test material. The solvent-extracted material served as the reference material and was administered at a dose of 1.58 mg TEQ/kg bw/day. Animals were killed on study day 29 and adipose, liver, muscle, brain, and blood were extracted and analyzed for PCDD/F content using GC/MS. To assess whether or not PCDD/Fs in the tissues of the soil-treated and solvent-treated mini-pigs originated from the feeding of the test materials, a group of untreated mini-pigs was included. Most PCDD/F congeners were not detectable in tissues from these controls, although a few congeners were detected in trace amounts. Liver and adipose tissue contained the highest concentrations of PCDD/Fs in the soil- and solvent-treated mini-pigs. Bioavailability in selected tissues was calculated as the ratio of the mass of a PCDD/F congener in the tissue to the administered mass of the same congener from soil or solvent. Bioavailability and relative bioavailability data were generated for specific congeners, grouped PCDDs, grouped PCDFs, and grouped PCDD/Fs for liver, adipose tissue, and all examined tissues combined. Relative bioavailability for PCDDs was 26.4% (liver), 27.3% (adipose tissue), and 23.2% (total tissues). Relative bioavailability for PCDFs was 35.7% (liver), 23.9% (adipose tissue), and 32.0% (total tissue). RBAs for PCDD/Fs were 31.9% (liver), 25.2% (adipose tissue), and 28.4% (total tissues).

4.0 DISCUSSION

A subset of the nine reviewed studies was selected for further analyses of RBA for dioxins in soil. Six studies were selected based on the quality and relevance of information provided in each study (Bonaccorsi et al. 1984; Budinsky et al. 2008; Finley et al. 2009; Lucier et al. 1986; Shu et al. 1988; Wittsiepe et al. 2007). All selected studies provided RBA estimates for PCDD/Fs in test materials consisting of soil contaminated with dioxins *in situ*; studies of spiked soil materials were not included in this analysis, based on information suggesting that aging of contaminated soil may decrease the bioavailability of dioxins in soil (Poiger and Schlatter 1980; Ruby et al. 2002; Umbreit et al. 1986). Studies that administered dose levels of dioxins that were clearly toxic were not included in this analysis (guinea pig studies by McConnell et al. 1984; Umbreit et al. 1986; Wendling et al. 1989).

The six studies selected for further analysis provided RBA estimates for 13 different test materials based on assays in the following experimental models:

- Swine: 3 test materials (Budinsky et al. 2008; Wittsiepe et al. 2007);
- Rats: 11 test materials (Budinsky et al. 2008; Finley et al. 2009; Lucier et al. 1986; Shu et al. 1988); and
- Rabbit: 1 test material (Bonaccorsi et al. 1984).

Only 2 of the 13 test materials were assayed in both swine and rats (Budinsky et al. 2008). Three studies estimated RBA for multiple dioxin (and furan) congeners with varying levels of chlorination (Budinsky et al. 2008; Finley et al. 2009; Wittsiepe et al. 2007). The remaining studies estimated RBAs for 2,3,7,8-TCDD only. All RBA estimates have been tabulated in Appendix B.

The following sections analyze the multiple congener RBA estimates for swine and rats (Section 4.1), compare the composite averages estimated from the swine and rat studies (Section 4.2), analyze the influence of dose on RBA estimates for 2,3,7,8-TCDD (Section 4.3), and discuss potential implications of these findings for site-specific risk assessment (Section 4.4).

4.1 Analysis for Multiple Congener RBA Estimates

As noted above, three of the six studies selected for further analysis estimated RBA for multiple dioxin (and furan) congeners with varying levels of chlorination (Budinsky et al. 2008; Finley et al. 2009; Wittsiepe et al. 2007). These three studies demonstrate a pronounced influence of chlorine content of each homologue on RBA and distinctly different relationships for RBA estimates measured in swine and rats (discussion follows).

4.1.1 Multiple Congener RBA Estimates in Swine

Relative bioavailability estimates for multiple congeners were reported for three test materials based on assays conducted in swine (Budinsky et al. 2008; Wittsiepe et al. 2007). Relative bioavailability estimates for all three test materials assayed in swine are plotted against chlorine content of each congener (mole chlorine/mole congener) in Figure 1. Increasing chlorine content was associated with increasing RBA for the combined data set (β=5.2 RBA per mole Cl/mole congener, R^2=0.34, p=0.0013). Table 2 presents summary statistics for RBA estimates in swine. The regression coefficients (β) for RBA as a function of congener chlorination for each test material assayed in swine were positive and significant ($p<0.05$ with β values ranging from 4.7 to 12.2).

Mass fractions of congeners in soils also varied with chlorine content. This resulted in a tendency for higher administered doses to have higher chlorinated congeners, although the correlation was relatively weak (r=0.48). However, in a multiple regression analysis in which both chlorine content and congener dose were included in the regression (discussed in more detail in Section 4.3), dose was not a significant predictor of RBA.

Two approaches are presented in Table 2 for calculating the composite RBA for the congener mixture:

Congener mass-weighted mean. In this approach, individual RBA estimates for each congener are weighted by the mass fraction of each congener in the administered soil dose. This also corresponds to the mass fraction in each soil sample. Mass-weighted estimates were 48.9, 27.0, and 36.6%.

TEQ-weighted mean. In this approach, individual congener RBAs are weighted for their contributions to 2,3,7,8-TCDD TEQ as described by Van den Berg et al. (2006). The resulting TEQ-weighted estimates are 23.0, 26.6, and 32.9%.

The differences between the mass-weighted and TEQ-weighted composite RBA estimates can be attributed in part to the significant association between RBA and congener chlorine content. If the RBAs for all congeners were identical, the mass-weighted and RBA-weighted relative bioavailability estimates would also be identical. The observation that RBA varies with congener chlorine content has important implications for the estimation of soil dioxin RBA. Soil having different homologue compositions can be expected to have different RBAs, and the RBA for the total dioxin mass in a given soil may differ from the RBA for the total TEQ.

Table 2 also presents summary statistics on the unweighted RBA estimates (i.e., mean RBAs of all congeners in each test material, without weighting the congener-specific RBAs for congener mass or TEQ mass in the soil). The computed values are not particularly useful to estimate the composite RBA since they do not account for variations in congener mass or TEQ. However, they do provide information on the range of values for the individual congeners. The mean RBA values for the three test materials were 33.8, 30.2, and 28.4%, with the range extending to 55%.

Summary statistics for the combined sample of three test materials assayed in swine are provided in the bottom rows of Table 2. The mean and SD RBA estimates were 37.5±11.0% for the mass-weighted average and 27.5±5.1% for the TEQ-weighted average with median values of 36.6% and 26.6%, respectively. Higher values for the mass-weighted estimate reflect the combined effects of a greater contribution of the more chlorinated homologues in the soil samples and higher RBA values for these homologues in the swine assays.

At this time, these data are not considered adequate or sufficient to establish a nationally-applicable upper bound estimate of RBA for dioxin in soil. The test materials that have been evaluated in swine consist of an urban soil and floodplain soil/sediment in Michigan (Budinsky et al. 2008) and soil treated with sludge near Hamburg, Germany (Wittsiepe et al. 2007). Two of the test materials are dominated by PCDFs, with one sample containing less than 1% TCDD-TEQ. These soils do not represent the range of PCDD/F-contaminated waste nor soil conditions in the U.S.

While it is not an objective of this report to evaluate a preferred animal model, there are several potential strengths with using swine for estimating RBA of dioxins in soil. As demonstrated for lead bioavailabililty, similarities between the physiology and anatomy of juvenile swine and human gastrointestinal tracts make swine a suitable model for predicting RBA in humans (USEPA 2007). However, it is important to note that juvenile swine are appropriate for estimating lead bioavailability because the primary concern is exposure to young children, as compared to PCDD/Fs where all life stages are of interest. Swine and rats also differ in the distribution of absorbed PCDD/Fs. Similar to humans, swine accumulate higher levels in adipose tissue relative to the liver, whereas, the distribution in rats tends to show the opposite trend (Budinsky et al. 2008; Thoma et al. 1989, 1990). A comprehensive evaluation is necessary before determining whether one or more animal models are appropriate for characterizing RBA of PCDD/Fs in soil.

4.1.2 Multiple Congener RBA Estimates in Rats

An analysis similar to that described above for the swine assays was applied to the multiple congener RBA estimates for seven test materials assayed in rats in the studies reported by Budinsky et al. (2008) and Finley et al. (2009). Summary statistics for RBA estimates in rats, including the regression statistics for the relationship between RBA and congener chlorination, are presented in Table 3. In contrast to the results obtained from swine assays, increasing congener chlorine content was significantly associated with lower RBA estimates in rats for each test material assayed ($p<0.05$ with β values ranging from -4.2 to 18.3). The combined RBA estimates for the seven test materials assayed in rats are plotted against chlorine content of each

congener in Figure 2. Although the correlation coefficient for the association was relatively weak in the combined data (β = -13.07, R^2=0.35, $p<0.0001$), a negative association was significant ($p<0.05$), for each of the seven test materials assayed in rats (see Table 3).

Composite average RBA estimates for the five test materials assayed in rats are also presented in Table 3. The congener mass-weighted estimates ranged from 10.8–68.3%; the mean and SD were 28.6±19.3% and the median was 25.1%. The TEQ-weighted estimates ranged from 16.7–64.4%; the mean and SD were 40.6±14.8% and median was 37.7%. The lower values for the mass-weighted estimates reflect the combined effect of higher contribution of the more chlorinated congeners in the soil samples and lower RBA values for these congeners in the rat assays. The composite RBA estimates varied approximately 5- to 7-fold. The source of variability in the composite RBA estimates cannot be explained with currently available data. In Finley et al. (2009), total organic carbon content of the five soil test materials evaluated was less than 1% and was stated by the authors to have "varied little" between test materials (data not reported). The mass distribution of congeners was also similar in the test materials. Other soil characteristics that may have contributed to the wide range of RBA estimates were not identified in the study (nor was this the intent of the study).

While the rat studies offer a larger data set for analysis, these data are still considered insufficient for representing the variability in RBA at U.S. sites having a range of soil characteristics and congener mixes. Also, the uncertainty regarding the extrapolation of RBA estimates in rodents to humans is considered too large. A contributing factor to this uncertainty is a lack of mechanistic understanding of the differences in RBA estimates obtained from swine and rats.

4.2 Comparison of Swine and Rat RBA Estimates

The mean composite RBA estimates for swine (n=3; see Table 2) and rats (n=7, see Table 3) are not statistically different (mass weighted: p=0.48; TEQ-weighted: p=0.18; unpaired *t*). Direct comparison of RBA estimates for identical soil samples assayed in both swine and rats are available for only two test materials (Budinsky et al. 2008). RBA estimates for these two test materials are shown in Tables 2 and 3 and are summarized together in Table 4. As shown in

Table 4, there are marked differences in the RBA estimates for swine and rats. The mass-weighted estimate for test material 1 (TM1) is higher in swine, compared to rats, and the estimate for test material 2 (TM2) is lower in swine; compared to rats; however, TEQ-weighted estimates for both materials are lower in swine compared to the estimates in rats (40 and 60%, respectively). However, the number of comparisons is too small (i.e., two test materials) for meaningful statistical comparisons.

Potential contributing factors to the marked differences between the RBA for swine and rats include physiological differences between swine and rats (e.g., gastrointestinal pH, gastric and small intestinal transit times) and/or differences between the assay protocols (e.g., dose levels, multiple dosing vs. single dose; dosing in food vs. gavage dosing). As noted previously, congener dose was not a significantly influential variable for RBA in swine or rats over the dose ranges for the three studies. Furthermore, whether the dosing regimen was a single gavage dose or multiple doses does not appear to be an important factor based on results reported in Budinsky et al. (2008). In that study, test material and reference materials were administered in multiple doses over a period of 30 days in both rats and swine, and RBA was estimated using the same liver and adipose tissue dioxin burden biomarkers. Even with these similar dosing protocols, the chlorine-RBA regression coefficients were positive in the swine assays for two test materials and negative for the rat assays for the identical test materials.

The above results suggest species differences are contributing factors to differences in the RBA estimates for swine and rats. Although speculative at this point, possible explanations could include the following:

1. *Gastrointestinal transit times*. Gastrointestinal transit times could limit the absorption of materials that are more slowly released from the soil matrix; a limitation that could be more pronounced in rats that have faster transit times than swine (Rivest et al. 2000; Tuleu et al. 1999). In all of the studies, reference materials were administered in a corn oil vehicle and, as noted in Budinsky et al. (2008), differences in absorption of dioxin congeners from the corn oil vehicle may contribute to the observed differences in RBA estimates based on the swine and rat assays.

2. *Distribution of absorbed dioxin*. Swine and rats also differ in the distribution of absorbed PCDD/Fs, swine accumulate higher levels in adipose tissue relative to liver, whereas, the distribution in rats tends to show an opposite trend (Budinsky et al. 2008; Thoma et al. 1989, 1990). A larger fraction of the absorbed dose delivered to the liver in rats could contribute to a stronger dose-dependence of metabolic clearance in the rat compared to swine. This has potential implications on the RBA estimates if liver doses achieved with the reference and test materials are not sufficiently similar to ensure similar metabolic clearances following dosing with each material.

3. *AhR affinity and dose-response*. Substantial species-specific differences in response to TCDD are well documented in the literature. The biological response to exposure to TCDD in a given species is determined by pharmacokinetic factors, as well as by the structure and behavior of the AhR at the cellular/molecular level. While a detailed review of TCDD receptor binding studies is outside the scope of this review, mouse AhR binds TCDD with an approximately 10-fold higher relative affinity than human AhR does (Flaveny et al. 2009; Ramadoss and Perdew 2004). Also, interspecies data on the most sensitive and best understood response to binding of TCDD and related compounds to the AhR (enzyme induction) are consistent with higher receptor binding affinity in rodents compared to humans and support the hypothesis that TCDD is a less potent inducer in humans than in rodents (Connor and Aylward 2006).

Given the current uncertainty in our understanding of the mechanisms underlying the differences in observed RBA estimate obtained from swine and rat bioassays, additional studies are needed to develop a preferred animal model and bioassay protocol for estimating dioxin RBA in soil.

4.3 Influence of Dose on RBA Estimates for 2,3,7,8-TCDD

As noted in the discussion of the multiple congener studies, congener dose did not appear to be a major influential variable in determining congener RBA over the range of doses examined in these studies. A larger set of estimates are available for 2,3,7,8-TCDD over a wider range of dose. Five studies provide RBA estimates for 2,3,7,8-TCDD in six test materials (Bonaccorsi et al. 1984; Budinsky et al. 2008; Lucier et al. 1986; Shu et al. 1988; Wittsiepe et al. 2007), two of which were tested at multiple doses of 2,3,7,8-TCDD in rats (Lucier et al. 1986; Shu et al. 1988). The individual RBA estimates are plotted against dioxin dose (pg/kg bw/day) in Figure 3. The estimates based on assays of three test materials in swine appear to exhibit a trend of increasing RBA with increasing dose; however, no consistent trend is evident from the rat studies (R^2=0.12, p=0.40). The mean value for the data set is 41±19% (SD, n=12) and the range is 2–64%. Shu et al. (1988) estimated RBAs for 6 doses of 2,3,7,8-TCDD in soil from Times Beach (solid triangles in Figure 3) and a dose trend is not evident in these data (R^2=0.36, p=0.21). Studies that provide RBA estimates only for 2,3,7,8-TCDD (Bonaccorsi et al. 1984; Lucier et al. 1986; Shu et al. 1988) have limited utility for estimating RBA values for use in risk assessment, because these studies do not provide RBA estimates for the PCDD/F mixture in the soils tested.

4.4 Implications for Risk Assessment

The observation that congeners do not have the same RBA may have important implications for the application of RBA values in dioxin risk assessment. Currently, dioxin risk typically is estimated based on assigning TEFs to estimates of average daily intake for chlorinated dibenzodioxin and dibenzofuran congeners with TEF reflecting the relative toxic potency of each congener, relative to 2,3,7,8-TCDD (Equation 5).

$$TEQ = \sum C_i \cdot TEF_i \qquad \text{Eq. (5)}$$

where *TEQ* is the 2,3,7,8-TCDD Toxic Equivalent, C_i is the concentration of congener *i*, and TEF_i is the TEF of congener *i*. The TEQ value is used in the appropriate equation for average

daily intake (ADI_{TEQ}), which is then used in the appropriate risk equation (e.g., Equations 6 and 7):

$$HQ = \frac{ADI_{TEQ}}{RfD_{2,3,7,8-TCDD}} \quad \text{Eq. (6)}$$

$$CR = CSF_{2,3,7,8-TCDD} \cdot ADI_{TEQ} \quad \text{Eq. (7)}$$

where *HQ* is the hazard quotient, *RfD* is the reference dose, *CR* is the cancer risk, and *CSF* is the cancer slope factor.

For a dioxin mixture in soil, the RBA adjustment could be applied to the calculation of the TEQ (Equation 8) or to the calculation of the hazard quotient or cancer risk (Equations 9 and 10):

$$TEQ = \sum C_i \cdot TEF_i \cdot RBA_i \quad \text{Eq. (8)}$$

where RBA_i is the soil RBA for congener *i*.

$$HQ = \frac{ADI_{TEQ} \cdot RBA_{TEQ}}{RfD_{2,3,7,8-TCDD}} \quad \text{Eq. (9)}$$

$$CR = CSF_{2,3,7,8-TCDD} \cdot ADI_{TEQ} \cdot RBA_{TEQ} \quad \text{Eq. (10)}$$

where RBA_{TEQ} is the RBA for total TEQ in the soil.

The RBA estimates used in the calculation of TEQ (Equation 8) generally may be those for the individual congeners and the sum of the products $C_i \times RBA_i$ generally may be the congener mass-weighted RBA for the soil. The RBA estimate used in the calculation of the hazard quotient or cancer risk (Equations 9 and 10) generally may be the RBA for total TEQ in the soil. The latter generally may be a function of the individual congener RBAs, the congener composition of the soil, and the congener TEFs.

One limitation of using the RBA for total TEQ is that soil that has similar or identical characteristics (e.g., total organic carbon and/or particle size), but different congener composition could have different RBAs for total TEQ. On the other hand, using RBA values for specific congeners normally should be relatively constant for soil having identical characteristics. On this basis, a reasonable approach to developing site-specific soil cleanup levels may be to determine RBA values for specific congeners and apply them in risk assessments in a computation similar to Equation 8.

4.5 Uncertainties in RBA Estimates

Several important uncertainties may influence any risk assessment applications of the RBA estimates provided in this report.

The RBA estimates considered in this analysis do not represent a statistical sample of soil in any particular geographic region that is representative of all soil in the U.S. and may or may not adequately represent the variability expected over a wider range of soil types and compositions.

Significant differences are evident between RBA estimates for test materials assayed in swine and rats. This includes large differences in the average RBA values for the same test material assayed in swine and rats (Budinsky et al. 2008), as well as regression coefficients for the effect of congener chlorine content on RBA that are in opposite directions. Explanations for these differences are not apparent from the data and are probably due to species differences and less likely from differences in assay protocols. No studies that compared RBA in humans to RBA estimated from animal models were retrieved in the literature search.

The estimates of RBA based on both the swine and rat assays show significant association between chlorine content of dioxin congeners and the relative bioavailability in animal models. Because of this correlation, average RBA for a given soil, based on either congener mass or total TEQ, can be expected to vary with the congener composition of the soil. Given this source of variability, the recommended approach for risk assessment generally would be to derive congener-specific RBA estimates. The currently available data provide RBA estimates for

chlorine content classes of congeners. Estimates have large coefficients of variation that introduce relatively large uncertainty into the estimates for most chlorination classes.

Relative bioavailability estimates made in this analysis assume that elimination kinetics of PCDD/F absorbed from soil are the same or very similar to PCDD/F absorbed from the reference vehicle (e.g., corn oil). If the elimination kinetics are not the same, RBAs calculated in the cited reports and in this analysis, will not reflect the actual differences in the absorption fractions for the soil and reference materials. For example, if the rate of elimination of the PCDD/F absorbed from the reference material was greater than from the soil material, RBA estimates would be biased low (i.e., the *ID/ED* ratios for reference and test material will yield an underestimate of the true RBA).

This problem becomes important if the absorbed doses from the reference and soil materials are sufficiently different to result in different levels of enzyme induction and, thereby, different elimination kinetics. This was the outcome of rat studies, but not in the swine studies, reported in Budinsky et al. (2008); enzyme induction (as measured by liver P4501A activity) was higher in rats that received the dose in test material compared to soil. If these differences resulted in faster elimination of absorbed PCDD/F in animals that received the reference material, then the RBAs calculated for these test materials may have been underestimated in the rats. The magnitude due to the underestimation cannot be estimated from data reported in Budinsky et al. (2008). In the Finley et al. (2009) rat study, doses in soil and reference materials were adjusted with the intention of yielding approximately the same liver concentrations of PCDD/F. For two of the test materials (TM 2 and TM 3), induction was significantly greater following the test material dose compared to the reference dose. If these differences resulted in faster elimination of absorbed PCDD/F in animals that received the test material, then the RBAs calculated for these test materials may have been overestimated. Here again, the magnitude of the overestimate cannot be estimated from the data reported in Finley et al. (2009).

All RBA estimates considered in this analysis were made relative to a lipid or organic solvent vehicle as the reference material (e.g., corn oil). The direct relevance of this type of vehicle to

the exposures that formed the bases for the cancer slope factor and/or RfD need to be considered in evaluating their applicability to cancer and non-cancer risk assessment.

Given the above uncertainties, currently available data do not support the general, national application of RBA estimates from this report to risk assessment. However, available data suggest that RBA values less than 100% can be expected at sites. On this basis, EPA recommends the development of site-specific protocols to outline the collection of site-specific data for the purpose of informing decisions at specific sites concerning dioxin-contaminated soil.

5.0 SUMMARY AND CONCLUSIONS

5.1 Summary of Findings

Collectively, analyses of published RBA estimates for PCDD/F in soil supports the following conclusions:

1. RBA for PCDD/F mixtures in soils assayed in swine and rats is less than 100%, as compared to a lipid or organic solvent vehicle as the reference material (e.g., corn oil).

2. RBA varies with congener chlorination. The direction of the relationship (i.e., positive or negative slope) is not the same when estimated based on data from swine or rat assays. Data from swine assays indicates an increase in RBA with increasing chlorine content (Budinsky et al. 2008; Wittsiepe et al. 2007), whereas, data from rat assays indicates a decrease in RBA with increasing chlorination (Budinsky et al. 2008; Finley et al. 2009). These differences suggest substantially different RBA estimates may be obtained depending on the animal model used.

   The National Academy of Sciences (NAS 2006), the World Health Organization (Van den Berg et al. 2006), other international committees and organizations, the U.S. Environmental Protection Agency (USEPA 2003), and other state agencies (e.g., WASDE 2007) have recognized that soil will influence the bioavailability of mixtures of dioxins/furans and have concluded have concluded that greater chlorinated congeners tend to be less bioavailable than the less chlorinated congeners. However, observations and analyses reported here suggest that the effect of chlorination on the RBA of dioxins in soil may be different for different animal models, as shown in the recently reported swine assays.

3. The dependence of RBAs on congener chlorination suggests soil RBA will depend on the congener composition of the soil (as well as the bioassay used to estimate RBA). Congeners with different levels of chlorination result in different composite RBA

averages for soil when calculated based on total congener mass or 2,3,7,8-TCDD TEQ. For example, based on the swine RBA assays, octachloro-p-dibenzodioxins (OCDD; 8 chlorines substituted on 8 available positions on the carbons of the benzene rings on either side of the central diheterabenzene, or "Cl8") and octachlorodibenzofurans (OCDFs, Cl8) will have a higher RBA than lower chlorine content congeners. Thus, for soil highly enriched with OCDDs and OCDFs (i.e., higher RBA and lower TEF), the RBA based on total congener mass will be higher than the RBA based on total TEQ. If, on the other hand, the soil RBA is based on rat RBA assays, high enrichment of OCDDs and OCDFs would result in higher TEQ RBAs compared to RBAs for total congener mass.

4. The influence of abiotic constituents, compound aging, and other associated soil factors on soil RBA has not been evaluated systematically. Bioavailability appears to decrease with aging based on comparisons of laboratory spiked soil and soil contaminated *in situ* (Poiger and Schlatter 1980; Umbreit et al. 1986) and is lower when administered as a mixture of activated carbon compared to an aqueous suspension (Poiger and Schlatter 1980). The latter observation suggests that organic carbon content influences dioxin bioavailability from soil.

5. Although RBA for dioxins in soils evaluated in these studies is less than 100%, estimating a representative range or upper bound value for RBA from these data is problematic because of the limited number of estimates, the effect of congener chlorination on RBA, and differences in the estimates based on swine and rat assays.

   In the swine studies, the total congener mass RBAs average 38% and range up to 50%; the total TEQ RBAs average 28% and range up to 33%. A statistically robust description of the distribution of the RBA values cannot be estimated from these swine studies, as they consist only of three test materials. In the rat studies, the total congener mass RBAs average 29% and range up to 68%; the total TEQ RBAs average 41% and range up to 64%. While the rat studies offer a larger data set for analysis, these data are still considered insufficient for representing the variability in RBA at U.S. sites having a

range of soil characteristics and congener mixes. Also, the uncertainty regarding the extrapolation of RBA estimates in rodents to humans is considered too large. A contributing factor to this uncertainty is a lack of mechanistic understanding of the differences in RBA estimates obtained from swine and rats.

Swine and rats also differ in the distribution of absorbed PCDD/Fs. Similar to humans, swine accumulate higher levels in adipose tissue relative to the liver, whereas the distribution in rats tends to show the opposite trend (Budinsky et al. 2008; Thoma et al. 1989, 1990). Moreover, using rat liver dioxin burden as a biomarker may have other implications related to species differences in binding to the AhR and induction of CYP450, the major route of metabolic clearance of PCDD/Fs (Budinsky et al. 2008; Connor and Aylward 2006; Finley et al. 2009; Flaveny et al. 2010).

While it is not the objective of this report to evaluate a preferred animal model, swine have been extensively used to predict RBA of arsenic and lead in humans based on the similarities between the physiology and anatomy of the swine and human gastrointestinal tracts (USEPA 2007). A comprehensive evaluation is necessary before determining whether one or more species are appropriate for characterizing RBA of PCDD/Fs in soil.

A similar analysis of RBA data was reported by the State of Washington Department of Ecology (WASDE 2007). The date of this analysis preceded the publication of the Finley et al. (2009) rat study and the Budinsky et al. (2008) swine and rat studies. It should be noted that all other studies reported in WASDE (2007) are also reviewed in this report, although, not all studies were included in the analyses presented in this report. In particular, studies conducted in guinea pigs were not included in the analyses for this report because these studies administered TCDD doses at or above the LD_{50} for guinea pigs. In addition, analyses in the current report were restricted to studies that evaluated soil contaminated with PCDD/F *in situ* (not soils spiked in the laboratory).

Based on analysis of the available at the time congener-specific analyses, WASDE (2007) concluded that the weighted gastrointestinal absorption for most mixtures will fall

within the range of 0.4 to 0.6, with the most likely value being 0.5. WASDE (2007) selected a value of 40% for a default RBA to be used in risk assessments, calculated by dividing 30% absolute bioavailability (value used to characterize absorption of soil-bound dioxins and furans) by 80% (value used to characterize absolute bioavailability of dioxin/furan in the toxicological studies used to calculate the cancer slope factor). The basis for the estimate of 30% for the absolute bioavailability is not clearly articulated. As previously discussed (see Section 2.2), none of the studies cited in this analysis or in WASDE (2007) provided data amenable to estimating absolute bioavailability.

Although the Wittsiepe et al. (2007) swine study is cited in WASDE (2007), it is discussed only in the context of reported values of absolute bioavailability, and uncertainties associated with the Wittsiepe evaluation was not explained in WASDE . As noted previously (see Section 2.2), the method used to estimate absolute bioavailability in the Wittsiepe et al. (2007) study (and in all studies considered in this analysis) would have underestimated the absorption fraction by an amount related to the elimination fraction, which was not reported. For this reason, no attempt was made to estimate absolute bioavailability from the Wittsiepe et al. (2007) study or any other studies for the current analysis.

5.2 Conclusions

Collectively, at this time these results support the conclusion that the RBA for dioxin in the soils evaluated in these studies is less than, and likely to be substantially less than 100%, as compared to a lipid or organic solvent vehicle as the reference material (e.g., corn oil). However, estimating a representative range or upper bound value for RBA from these data is problematic because of the limited number of estimates, the effect of congener chlorination on RBA, differences in the estimates based on swine and rat assays, and uncertainty with the RBA estimates due to potential differences in elimination kinetics between test and reference materials. Thus, while substantial progress has been made in the science of estimating RBA of dioxins in soils, EPA considers the currently available data to be inadequate for estimating a nationally applicable value for RBA for use in developing soil cleanup levels for dioxin. Furthermore, EPA considers the currently available data to be insufficient for determining a preferred animal model, or bioassay protocol for predicting soil RBA in humans.

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Table 1. Summary of RBA Studies of Dioxins in Soil

Reference	Test Material	Species/Number	Methods	RBA
Bonaccorsi et al. 1984	Source: Seveso, Italy soil (200–400 mesh) TCDD Concentration: 81 ng/g (ppb)	Rabbit (Albino, male, 2.6±0.3 kg), 5–16/group	ID Metric: liver TCDD concentration TM Dose: 0.02 to 0.08 µg TCDD/day; 7 days TM Dosing: aqueous suspension, oral gavage, single dose RM Dosing: oral gavage in 50% ethanol, single dose	32%
Budinsky et al. 2008	Source: TM1: urban soil, Michigan (sieved to <250 µm) PCDD/F: 264 pg TEQ/g (ppt) Source: TM1: floodplain soil, Michigan (sieved to <250 µm) PCDD/F: 651 pg TEQ/g	Swine (*Sus scrofa*, sex and weight not given), 5/group	ID Metric: liver plus adipose PCDD/F content TM Dose: 122, 313 pg TEQ/kg-bw/day TM Dosing: 5 g soil placed in moistened feed, twice/day, 30 days RM Dosing: corn oil/acetone (99:1 v:v) in gelatin capsule, placed in moistened feed, twice/day, 30 days	23% (urban) 27% (flood plain) (TEQ-weighted)
Budinsky et al. 2008	Source: urban soil, Michigan (sieved to <250 µm) PCDD/F: 264 pg TEQ/g (ppt) Source: floodplain soil, Michigan (sieved to <250 µm) PCDD/F: 651 pg TEQ/g (ppt)	Rat (Sprague-Dawley, female, 250 g), 10/group	ID Metric: liver plus adipose PCDD/F content TM Dose: 577, 2100 pg TEQ/kg bw/day TM Dosing: 5% w/w soil-feed mixture, 30 days RM Dosing: corn oil/acetone (99:1, v:v), oral gavage, 30 days	37% (urban) 66% (flood plain) (TEQ-weighted)
Finley et al. 2009	Source: Operating U.S. industrial facility (sieved to <250 µm) PCDD/F Concentrations: TM1: 15.0 ng TEQ/g soil TM2: 45.0 ng TEQ/g soil TM3: 36.8 ng TEQ/g soil TM4: 2.8 ng TEQ/g soil TM5: 0.53 ng TEQ/g soil (ppb)	Rat (Sprague-Dawley, female, 251–321 g), 6/group	ID Metric: liver PCDD/F content TM Dosing: aqueous suspension, oral gavage, single dose TM Dose: TM1: 30,000 pg TEQ/kg bw/day TM2: 90,200 pg TEQ/kg bw/day TM3: 590 pg TEQ/kg bw/day TM4: 560 pg TEQ/kg bw/day TM5: 290 pg TEQ/kg bw/day RM Dosing: corn oil, oral gavage, single dose	TM1: 16.7% TM2: 48.4% TM3: 37.7% TM4: 46.5% TM5: 33.3% (TEQ Weighted)

Table 1. Summary of RBA Studies of Dioxins in Soil

Reference	Test Material	Species/Number	Methods	RBA
Lucier et al. 1986	Source: Minker/Stout site, Missouri (sieved 60 gauge) TCDD: 880 ng/g (ppb)	Rat (Sprague-Dawley, female), 6/group	ID Metric: liver TCDD concentration TM Dose: 1.1, 5.5 µg TCDD/kg-bw TM Dosing: aqueous suspension, oral gavage, single dose RM Dosing: corn oil, oral gavage, single dose	22% (1.1 µg/kg) 45% (5.5 mg/kg)
McConnell et al. 1984	Source: Times Beach site, Missouri (sieved 60 gauge) TCDD: 770 ng/g (ppb) Source: Minker/Stout, Missouri (sieved 60 gauge) TCDD: 880 ng/g (ppb)	Guinea pig (Hartley, male, 2.5 weeks old), 6/group	ID Metric: liver TCDD concentration TM Dosing: aqueous suspension, oral gavage, single dose TM Dose: 1–10 µg TCDD/kg bw/day RM Dosing: corn oil, oral gavage, single dose	8% (Times Beach, 3.8 µg/kg, 20% lethality) 11% (Minker Stout, 3.3 µg/kg, 33% lethality)
Shu et al. 1988	Source: Times Beach soil, Missouri (sieved through 40 mesh screen) TCDD: 1.9 to 723 ng/g (ppb)	Rat (Sprague-Dawley derived, 180 to 250 g), 4/group	ID Metric: liver TCDD concentration TM Dosing: aqueous suspension, oral gavage, single dose TM Dose: 3.2, 7.0, 40, 37, 175,1450 ng TCDD/kg RM Dosing: corn oil, oral gavage, single dose	44% (3.2 ng/kg) 49% (7 ng/kg) 38% (40 ng/kg) 43% (37 ng/kg) 45% (175 ng/kg) 37% (1450 ng/kg)
Umbreit et al. 1986	Source: Manufacturing plant in Newark, NJ TCDD: ~2,300 ng/g (ppb) Source: Salvage yard contaminated with chemical stills, Newark NJ TCDD: NR	Guinea pig (males and females; strain, weight and age not given, 8/group)	ID Metric: liver TCDD concentration TM Dose: 3, 6, 12 µg TCDD/kg TM Dosing: aqueous suspension, oral gavage, single dose RM Dosing: corn oil/acetone (9:1, v:v), oral gavage, single dose	<1% (manufacturing site, 12 µg/kg, relative to spiked soil) 24% (salvage yard, 0.32 µg/kg, relative to spiked soil)
Wendling et al. 1989	Source: Times Beach, Michigan TCDD: 510 ng/g (ppb) Source: Newark, NJ TCDD: 1,400 ng/g (ppb)	Guinea pig (200 g), 2/group	ID Metric: liver TCDD concentration TM Dosing: 10% gum acacia, oral gavage, single dose TM Dose: 3–10 µg TCDD/kg RM Dosing: 10% gum acacia, oral gavage, single dose	7%, 30% (Times Beach, 3 or 10 µg/kg) 2.0, 1.6% (Newark, 5 or 10 µg/kg)

Table 1. Summary of RBA Studies of Dioxins in Soil

Reference	Test Material	Species/Number	Methods	RBA
Wittsiepe et al. 2007	Source: Surface soil near Hamburg, Germany PCDD/F: 5.3 ng TEQ/g (ppb)	Swine (Goettingen mini-pig, males and females, 6975 g), 4/group	ID Metric: PCDD/F content of tissues (adipose, blood, brain, liver, muscle) TM Dosing: 0.5 g soil/kg bw/day placed in moistened feed TM Dose: 2.3 ng TEQ/kg bw/day, 28 days RM Dosing: hexane/acetone (1:1, v:v), placed in moistened feed, 28 days	28.4±9.9 (SD) (total congener)

ID, internal dose; NR, not reported; PCDD/F, polychlorinated dibenzo-p-dioxin/dibenzo furan; ppb, parts per billion; pg, picogram; ppt, parts per trillion; RM, reference material; SD, standard deviation; TCDD, tetrachloro-p-dibenzodioxin; TEQ, toxic equivalent; TM, test material; µm, micron

Table 2. Summary Statistics for Multiple Congener RBA Estimates in Swine

Individual Study Statistics	BU08 TM1	BU08 TM2	WI07
Congener mass-weighted mean	48.9 %	27.0 %	36.6 %
TEQ-weighted mean	23.0 %	26.6 %	32.9 %
Unweighted congener mean	33.8 %	30.2 %	28.4 %
Unweighted congener SD	16.5 %	6.1 %	9.9 %
Unweighted congener MIN	18.0 %	22.0 %	2.0 %
Unweighted congener MAX	55.0 %	37.0 %	42.2 %
Chlorine-RBA regression coefficient	12.2	7.1	4.7
Chlorine-RBA regression R^2	0.94	0.95	0.31

TM Summary Statistics	Mean	SD	MIN	MED	MAX
Congener mass-weighted[a]	37.5 %	11.0 %	27.0 %	36.6 %	48.9 %
TEQ-weighted[b]	27.5 %	5.1 %	23.0 %	26.6 %	32.9 %
Unweighted congener	30.8 %	2.7 %	28.4 %	30.2 %	33.8 %

Based on data for urban soil (TM1) and flood plan soil (TM2) reported in Budinsky et al. 2008 (BU08); and data for one soil test material reported in Wittsiepe et al. 2007 (WI07).

[a] Weighted average, where weights are congener dose (pg/kg bw/day).
[b] Weighted average, where weights are TEQ dose (pg/kg bw/day), based on Van den Berg et al. (2006) TEF assignments.

MAX, maximum; MED, median; MIN, minimum; RBA, relative bioavailability; SD, standard deviation; TEQ, toxic equivalent; TM, test material

Table 3. Summary Statistics for Multiple Congener RBA Estimates in Rats

Individual Study Statistics	BU08 TM1	BU08 TM2	FO09 TM1	FI09 TM2	FI09 TM3	FI09 TM4	FI09 TM5
Congener mass-weighted mean	34.9 %	68.3 %	10.8 %	25.1 %	17.0 %	28.4%	15.7%
TEQ-weighted mean	37.2 %	64.4 %[a]	16.7 %	48.4 %	37.7 %	46.5%	33.3%
Unweighted congener mean	39.2 %	62.4 %	17.3 %	50.5 %	39.3 %	50.9%	35.8%
Unweighted congener SD	5.2 %	15.0 %	7.3 %	25.7 %	22.1 %	22.9%	18.1%
Unweighted congener MIN	34.0 %	52.0 %	5.0 %	16.0 %	13.0 %	19.0%	13.0%
Unweighted congener MAX	47.0 %	89.0 %	27.0 %	100 %	79.0 %	82.0%	61.0%
Chlorine-RBA regression coefficient	-4.2	-17.5	-18.3	-13.5	-15.8	-4.2	-17.5
Chlorine-RBA regression R^2	0.40	0.55	0.68	0.42	0.82	0.40	0.55

TM Summary Statistics	MEAN	SD	MIN	MED	MAX
Congener mass-weighted[b]	28.6 %	19.3 %	10.8 %	25.1 %	68.3 %
TEQ-weighted[c]	40.6 %	14.8 %	16.7 %	37.7 %	64.4 %
Unweighted congener	42.2 %	14.3 %	17.3 %	39.3 %	62.4 %

Based on data for urban soil (TM1) and flood plan soil (TM2) reported in Budinsky et al. 2008 (BU08); and data for sample 1–5 (TM1–TM5) reported in Finley et al. 2009 (FI09).

[a] Budinsky et al. (2008, see Table 6) reported 66%; the reason for the difference is not apparent.
[b] Weighted average, where weights are congener dose (pg/kg bw/day).
[c] Weighted average, where weights are TEQ dose (pg/kg bw/day), based on Van den Berg et al. (2006) TEF assignments.

MAX, maximum; MED, median; MIN, minimum; RBA, relative bioavailability; SD, standard deviation; TEF, toxic equivalence factor; TEQ, toxic equivalent; TM, test material

Table 4. Comparison of RBA Estimates for Swine and Rats in Identical Test Materials

	Swine RBA (%)	Rat RBA (%)	Swine/Rat Ratio
TM1 (mass-weighted)	48.9	34.9	1.4
TM1 (TEQ-weighted)	23.0	37.2	0.6
TM2 (mass-weighted)	27.0	68.3	0.4
TM2 (TEQ-weighted)	26.6	64.4	0.4

Based on data from Budinsky et al. (2008).

RBA, relative bioavailability; TEQ, toxic equivalent; TM, test material

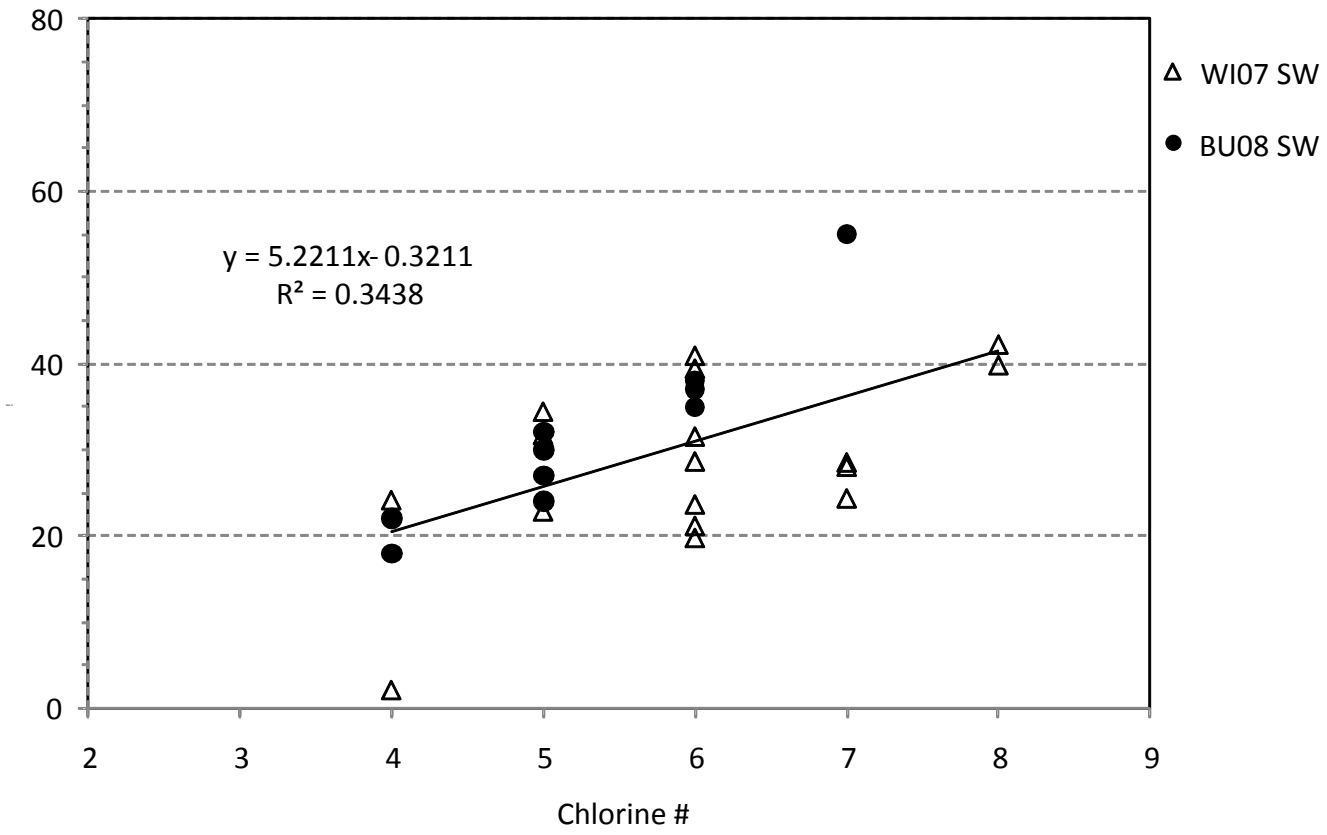

Figure 1. Relationship between congener chlorine content (mole chlorine/mole congener) and RBA based on swine assays of three test materials (Budinsky et al. 2008, BU08; Wittsiepe et al. 2007, WI07). The regression equation is for the combined data from both studies; regression coefficients for the individual studies are provided in Table 1.

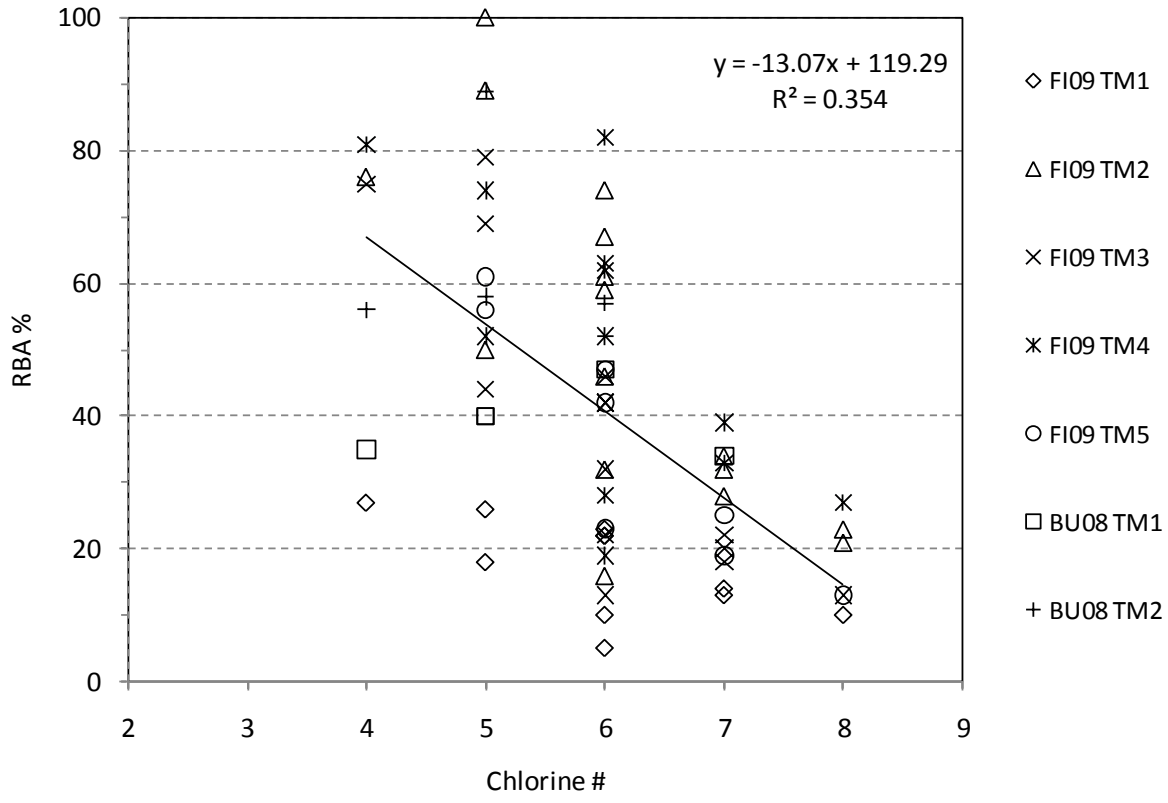

Figure 2. Relationship between congener chlorine content (mole chlorine/mole congener) and RBA based on rat assays of seven test materials (Budinsky et al. 2008, BU08; Finley et al. 2009, FI09). The regression equation is for the combined data from both studies; regression coefficients for the individual studies are provided in Table 2.

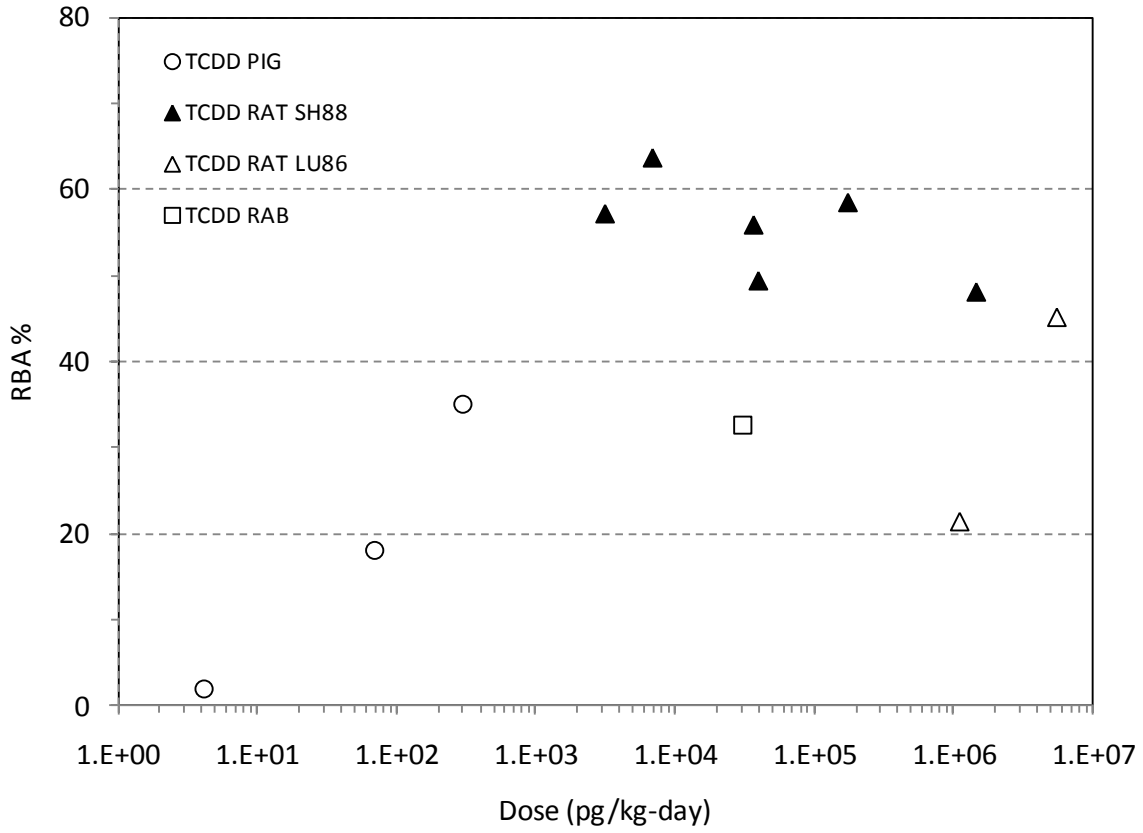

Figure 3. Relationship between 2,3,7,8-TCDD dose (pg/kg bw/day) and RBA based on swine, rat, and rabbit assays of six test materials (Bonaccorsi et al. 1984; Budinsky et al. 2008; Lucier et al. 1986; Shu et al. 1988; Wittsiepe et al. 2007).

Appendix A – Literature Search Product:

Bioavailability of Dioxins in Soil

LITERATURE SEARCH PRODUCT:

BIOAVAILABILITY OF DIOXINS IN SOIL

Prepared for:

Bioavailability Subcommittee of the Technical Review Workgroup
Office of Solid Waste and Emergency Response
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INTRODUCTION

Search Strategy

The following strategy was used to identify literature pertinent to the topic of bioavailability of dioxin in soil:

1. Literature published before 1998 was identified from the text and bibliography of the current (1998) ATSDR Toxicological Profile for Chlorinated Dibenzo-p-Dioxins.

2. Literature published subsequent to 1998 was identified based on results of a dioxin literature evaluation conducted in 2008 (for the period 1998–2008).

3. Literature published subsequent to 2008 was identified from a *de novo* bibliographic search (e.g., MEDLINE/TOXLINE) conducted for the period 2008–present. The search strategy focused on relevant literature (e.g., absorption, bioavailability).

Literature Search Product Organization

The literature search product is organized by topic, with subsections organized by species where appropriate, as follows:

- 1.0 Bioavailability and Pharmacokinetics Studies in Humans
  - 1.1 Soil
  - 1.2 Other Media
- 2.0 Bioavailability and Pharmacokinetics Studies in Animals
  - 2.1 Soil (organized by species)
  - 2.2 Other Media (organized by species)
- 3.0 Toxicity Studies of Dioxin in Soil in Animals (organized by species)
- 4.0 *In Vitro* Bioaccessibility
- 5.0 PBPK Modeling

6.0 Risk Assessments

7.0 Reviews

Considerations

General considerations in identifying pertinent studies:

1. Studies and information that may yield useful quantitative information about absolute or relative bioavailability (ABA or RBA, respectively) of dioxins may include (in order of decreasing value and certainty regarding RBA estimates):

    a. Studies in which bioavailability (e.g., dioxin concentrations in serum or tissue lipid) of dioxins were directly compared in animals exposed to dioxins in food or soil (e.g., analogous to swine RBA studies for lead or arsenic).

    b. Comparisons of results of separate studies in which bioavailability of dioxins were measured in animals exposed to dioxins in food or soil. These studies could include toxicity studies in which serum and/or tissue samples were assayed for dioxin levels using comparable methods.

    c. Pharmacokinetic modeling studies in which bioavailability of dioxins in food and/or soil may have been estimated based on fitting bioavailability parameter values to observations (e.g., dioxin concentrations in serum or tissue lipid).

    d. Studies in which toxic potency (e.g., ED_{50}) were compared in animals administered dioxins in food or soil.

2. Currently, dioxin risk is estimated based on assigning TEF to estimates of average daily intake for dioxin congeners, where the TEF values reflect relative toxic potency of each congener, relative to 2,4,7,8-TCDD (Equation 1).

$$TEQ = \sum C_i \cdot TEF_i \quad \text{Eq. (1)}$$

where *TEQ* is the 2,3,7,8-TCDD Toxicity Equivalent, C_i is the concentration of congener *i*, and TEF_i is the TEF of congener *i*. The TEQ value is used in the appropriate equation for average daily intake (ADI_{TEQ}), which is then used in the appropriate risk equation (e.g., Equations 2 and 3):

$$HQ = \frac{ADI_{TEQ}}{RfD_{2,4,7,8-TCDD}} \quad \text{Eq. (2)}$$

$$CR = CSF_{2,4,7,8-TCDD} \cdot ADI_{TEQ} \quad \text{Eq. (3)}$$

where *HQ* is the hazard quotient, *RFD* is the reference dose, *CR* is the cancer risk, and *CSF* is the cancer slope factor.

3. The TEF values for individual congeners reflect, to varying degrees, contributions of bioavailability and toxicokinetics to toxic potency (i.e., to the extent that the derivation of the TEF is informed by results of *in vivo* and/or ingestion bioassays).

4. The TEF methodology introduces several complexities into the adjustment of soil dioxin risk to account for RBA of dioxins in soil.

    a. Ideally, estimates of soil RBA for each congener would be needed to account for congener-specific RBA (e.g., Equation 4):

$$TEQ = \sum C_i \cdot TEF_i \cdot RBA_i \quad \text{Eq. (4)}$$

    where RBA_i is the soil RBA for congener *i*.

    b. A less desirable approach would be to apply an estimate of the soil RBA for 2,3,7,8-TCDD to all congeners. This would introduce uncertainty into the risk estimate to the extent that RBA varies across congeners (e.g., Equations 5 and 6):

$$HQ = \frac{ADI_{TEQ} \cdot RBA_{2,4,7,8-TCDD}}{RfD_{2,4,7,8-TCDD}}$$ Eq. (5)

$$CR = CSF_{2,4,7,8-TCDD} \cdot ADI_{TEQ} \cdot RBA_{2,4,7,8-TCDD}$$ Eq. (6)

LITERATURE SEARCH PRODUCT
BIOAVAILABILITY OF DIOXINS IN SOIL

1.0 Bioavailability and Pharmacokinetics Studies in Humans

1.1 Soil

No literature identified.

1.2 Other Media

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2.0 Bioavailability and Pharmacokinetics Studies in Animals

2.1 Soil

<u>Rats</u>

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Guinea Pigs

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Swine

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Cows

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2.2 Other Media

Rats

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Appendix B – RBA Data

	Study	Study Code	Species	Test Material	TM Code	Congener		Cl #	Dose	+/-	SD	Unit	RBA	+/-	SD	Test Material Dosing Protocol	Reference Material Dosing Protocol	Bioavailability Metric	Test Material Vehicle	Reference Vehicle
1	Wittsiepe et al. 2007	WI07	Swine	Sludge-treated soil	1	2,3,7,8-TCDD	D	4	4.13	#NA		pg/kg-day	2.0	#NA		28-day repeated dosing in doughball	28-day repeated dosing in spiked doughball	adipose+blood+brain+liver+muscle burden	Dougball	Hexane/acetone
2	Wittsiepe et al. 2007	WI07	Swine	Sludge-treated soil	1	1,2,3,7,8-PeCDD	D	5	17.8	#NA		pg/kg-day	31.7	#NA		28-day repeated dosing in doughball	28-day repeated dosing in spiked doughball	adipose+blood+brain+liver+muscle burden	Dougball	Hexane/acetone
3	Wittsiepe et al. 2007	WI07	Swine	Sludge-treated soil	1	1,2,3,4,7,8-HxCDD	D	6	25.1	#NA		pg/kg-day	23.6	#NA		28-day repeated dosing in doughball	28-day repeated dosing in spiked doughball	adipose+blood+brain+liver+muscle burden	Dougball	Hexane/acetone
4	Wittsiepe et al. 2007	WI07	Swine	Sludge-treated soil	1	1,2,3,6,7,8-HxCDD	D	6	51.8	#NA		pg/kg-day	21.1	#NA		28-day repeated dosing in doughball	28-day repeated dosing in spiked doughball	adipose+blood+brain+liver+muscle burden	Dougball	Hexane/acetone
5	Wittsiepe et al. 2007	WI07	Swine	Sludge-treated soil	1	1,2,3,7,8,9-HxCDD	D	6	43.7	#NA		pg/kg-day	19.7	#NA		28-day repeated dosing in doughball	28-day repeated dosing in spiked doughball	adipose+blood+brain+liver+muscle burden	Dougball	Hexane/acetone
6	Wittsiepe et al. 2007	WI07	Swine	Sludge-treated soil	1	1,2,3,4,6,7,8-HpCDD	D	7	291	#NA		pg/kg-day	24.3	#NA		28-day repeated dosing in doughball	28-day repeated dosing in spiked doughball	adipose+blood+brain+liver+muscle burden	Dougball	Hexane/acetone
7	Wittsiepe et al. 2007	WI07	Swine	Sludge-treated soil	1	OCDD	D	8	348	#NA		pg/kg-day	39.8	#NA		28-day repeated dosing in doughball	28-day repeated dosing in spiked doughball	adipose+blood+brain+liver+muscle burden	Dougball	Hexane/acetone
8	Wittsiepe et al. 2007	WI07	Swine	Sludge-treated soil	1	2,3,7,8-TCDF	F	4	162	#NA		pg/kg-day	24.1	#NA		28-day repeated dosing in doughball	28-day repeated dosing in spiked doughball	adipose+blood+brain+liver+muscle burden	Dougball	Hexane/acetone
9	Wittsiepe et al. 2007	WI07	Swine	Sludge-treated soil	1	1,2,3,7,8-PeCDF	F	5	413	#NA		pg/kg-day	22.8	#NA		28-day repeated dosing in doughball	28-day repeated dosing in spiked doughball	adipose+blood+brain+liver+muscle burden	Dougball	Hexane/acetone

	Study	Study Code	Species	Test Material	TM Code	Congener		Cl #	Dose	+/-	SD	Unit	RBA	+/-	SD	Test Material Dosing Protocol	Reference Material Dosing Protocol	Bioavailability Metric	Test Material Vehicle	Reference Vehicle
10	Wittsiepe et al. 2007	WI07	Swine	Sludge-treated soil	1	2,3,4,7,8-PeCDF	F	5	202	#NA		pg/kg-day	34.4	#NA		28-day repeated dosing in doughball	28-day repeated dosing in spiked doughball	adipose+blood +brain+liver+ muscle burden	Dougball	Hexane/ acetone
11	Wittsiepe et al. 2007	WI07	Swine	Sludge-treated soil	1	1,2,3,4,7,8-HxCDF	F	6	971	#NA		pg/kg-day	40.9	#NA		28-day repeated dosing in doughball	28-day repeated dosing in spiked doughball	adipose+blood +brain+liver+ muscle burden	Dougball	Hexane/ acetone
12	Wittsiepe et al. 2007	WI07	Swine	Sludge-treated soil	1	1,2,3,6,7,8-HxCDF	F	6	736	#NA		pg/kg-day	31.5	#NA		28-day repeated dosing in doughball	28-day repeated dosing in spiked doughball	adipose+blood +brain+liver+ muscle burden	Dougball	Hexane/ acetone
13	Wittsiepe et al. 2007	WI07	Swine	Sludge-treated soil	1	2,3,4,6,7,8-HxCDF	F	6	146	#NA		pg/kg-day	39.4	#NA		28-day repeated dosing in doughball	28-day repeated dosing in spiked doughball	adipose+blood +brain+liver+ muscle burden	Dougball	Hexane/ acetone
14	Wittsiepe et al. 2007	WI07	Swine	Sludge-treated soil	1	1,2,3,7,8,9-HxCDF	F	6	146	#NA		pg/kg-day	28.6	#NA		28-day repeated dosing in doughball	28-day repeated dosing in spiked doughball	adipose+blood +brain+liver+ muscle burden	Dougball	Hexane/ acetone
15	Wittsiepe et al. 2007	WI07	Swine	Sludge-treated soil	1	1,2,3,4,6,7,8-HpCDF	F	7	3559	#NA		pg/kg-day	28.5	#NA		28-day repeated dosing in doughball	28-day repeated dosing in spiked doughball	adipose+blood +brain+liver+ muscle burden	Dougball	Hexane/ acetone
16	Wittsiepe et al. 2007	WI07	Swine	Sludge-treated soil	1	1,2,3,4,7,8,9-HpCDF	F	7	1375	#NA		pg/kg-day	28.0	#NA		28-day repeated dosing in doughball	28-day repeated dosing in spiked doughball	adipose+blood +brain+liver+ muscle burden	Dougball	Hexane/ acetone
17	Wittsiepe et al. 2007	WI07	Swine	Sludge-treated soil	1	OCDF	F	8	9706	#NA		pg/kg-day	42.2	#NA		28-day repeated dosing in doughball	28-day repeated dosing in spiked doughball	Liver + adipose burden	Dougball	Hexane/ acetone
18	Budinsky et al. 2008	BU08	Swine	Urban soil	1	2,3,7,8-TCDD	D	4	70	2.0	SD	pg/kg-day	18	8	SD	30-day repeated dosing in doughball	30-day repeated dosing in spiked doughball	Liver + adipose burden (ND=1/2 DL)	Dougball	Corn oil/ acetone (99:1)

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19	Budinsky et al. 2008	BU08	Swine	Urban soil	1	1,2,3,7,8-PeCDD	D	5	36	1.0	SD	pg/kg-day	24	10	SD	30-day repeated dosing in doughball	30-day repeated dosing in spiked doughball	Liver + adipose burden (ND=1/2 DL)	Dougball	Corn oil/ acetone (99:1)
20	Budinsky et al. 2008	BU08	Swine	Urban soil	1	1,2,3,6,7,8-HxCDD	D	6	39	1.0	SD	pg/kg-day	38	21	SD	30-day repeated dosing in doughball	30-day repeated dosing in spiked doughball	Liver + adipose burden (ND=1/2 DL)	Dougball	Corn oil/ acetone (99:1)
21	Budinsky et al. 2008	BU08	Swine	Urban soil	1	1,2,3,4,6,7, 8-HpCDD	D	7	621	21	SD	pg/kg-day	55	13	SD	30-day repeated dosing in doughball	30-day repeated dosing in spiked doughball	Liver + adipose burden (ND=1/2 DL)	Dougball	Corn oil/ acetone (99:1)
22	Budinsky et al. 2008	BU08	Swine	Urban soil	1	2,3,4,7,8-PeCDF	F	5	19	1.0	SD	pg/kg-day	32	9	SD	30-day repeated dosing in doughball	30-day repeated dosing in spiked doughball	Liver + adipose burden (ND=1/2 DL)	Dougball	Corn oil/ acetone (99:1)
23	Budinsky et al. 2008	BU08	Swine	Flood-plain soil	2	2,3,7,8-TCDF	F	4	1120	45	SD	pg/kg-day	22	4	SD	30-day repeated dosing in doughball	30-day repeated dosing in spiked doughball	Liver + adipose burden (ND=1/2 DL)	Dougball	Corn oil/ acetone (99:1)
24	Budinsky et al. 2008	BU08	Swine	Flood-plain soil	2	1,2,3,7,8-PeCDF	F	5	561	23	SD	pg/kg-day	30	13	SD	30-day repeated dosing in doughball	30-day repeated dosing in spiked doughball	Liver + adipose burden (ND=1/2 DL)	Dougball	Corn oil/ acetone (99:1)
25	Budinsky et al. 2008	BU08	Swine	Flood-plain soil	2	2,3,4,7,8-PeCDF	F	5	460	18	SD	pg/kg-day	27	2	SD	30-day repeated dosing in doughball	30-day repeated dosing in spiked doughball	Liver + adipose burden (ND=1/2 DL)	Dougball	Corn oil/ acetone (99:1)
26	Budinsky et al. 2008	BU08	Swine	Flood-plain soil	2	1,2,3,4,7,8-HxCDF	F	6	375	15	SD	pg/kg-day	35	2	SD	30-day repeated dosing in doughball	30-day repeated dosing in spiked doughball	Liver + adipose burden (ND=1/2 DL)	Dougball	Corn oil/ acetone (99:1)
27	Budinsky et al. 2008	BU08	Swine	Flood-plain soil	2	1,2,3,6,7,8-HxCDF	F	6	85	3.0	SD	pg/kg-day	37	2	SD	30-day repeated dosing in doughball	30-day repeated dosing in spiked doughball	Liver + adipose burden (ND=1/2 DL)	Dougball	Corn oil/ acetone (99:1)

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28	Budinsky et al. 2008	BU08	Rat	Urban soil	1	2,3,7,8-TCDD	D	4	302	17	SD	pg/kg-day	35	4	SD	30-day repeated exposure in feed	30-day gavage in corn oil/acetone (99:1)	Liver + adipose burden (ND=1/2 DL)	Feed	Corn oil/ acetone (99:1)
29	Budinsky et al. 2008	BU08	Rat	Urban soil	1	1,2,3,7,8-PeCDD	D	5	172	10	SD	pg/kg-day	40	3	SD	30-day repeated exposure in feed	30-day gavage in corn oil/acetone (99:1)	Liver + adipose burden (ND=1/2 DL)	Feed	Corn oil/ acetone (99:1)
30	Budinsky et al. 2008	BU08	Rat	Urban soil	1	1,2,3,6,7,8-HxCDD	D	6	247	14	SD	pg/kg-day	47	3	SD	30-day repeated exposure in feed	30-day gavage in corn oil/acetone (99:1)	Liver + adipose burden (ND=1/2 DL)	Feed	Corn oil/ acetone (99:1)
31	Budinsky et al. 2008	BU08	Rat	Urban soil	1	1,2,3,4,6,7,8-HpCDD	D	7	4820	270	SD	pg/kg-day	34	2	SD	30-day repeated exposure in feed	30-day gavage in corn oil/acetone (99:1)	Liver + adipose burden (ND=1/2 DL)	Feed	Corn oil/ acetone (99:1)
32	Budinsky et al. 2008	BU08	Rat	Urban soil	1	2,3,4,7,8-PeCDF	F	5	100	6.0	SD	pg/kg-day	40	2	SD	30-day repeated exposure in feed	30-day gavage in corn oil/acetone (99:1)	Liver + adipose burden (ND=1/2 DL)	Feed	Corn oil/ acetone (99:1)
33	Budinsky et al. 2008	BU08	Rat	Flood-plain soil	2	2,3,7,8-TCDF	F	4	6430	370	SD	pg/kg-day	89	12	SD	30-day repeated exposure in feed	30-day gavage in corn oil/acetone (99:1)	Liver + adipose burden (ND=1/2 DL)	Feed	Corn oil/ acetone (99:1)
34	Budinsky et al. 2008	BU08	Rat	Flood-plain soil	2	1,2,3,7,8-PeCDF	F	5	3920	230	SD	pg/kg-day	58	5	SD	30-day repeated exposure in feed	30-day gavage in corn oil/acetone (99:1)	Liver + adipose burden (ND=1/2 DL)	Feed	Corn oil/ acetone (99:1)
35	Budinsky et al. 2008	BU08	Rat	Flood-plain soil	2	2,3,4,7,8-PeCDF	F	5	3370	200	SD	pg/kg-day	52	3	SD	30-day repeated exposure in feed	30-day gavage in corn oil/acetone (99:1)	Liver + adipose burden (ND=1/2 DL)	Feed	Corn oil/ acetone (99:1)
36	Budinsky et al. 2008	BU08	Rat	Flood-plain soil	2	1,2,3,4,7,8-HxCDF	F	6	2630	150	SD	pg/kg-day	57	3	SD	30-day repeated exposure in feed	30-day gavage in corn oil/acetone (99:1)	Liver + adipose burden (ND=1/2 DL)	Feed	Corn oil/ acetone (99:1)

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37	Budinsky et al. 2008	BU08	Rat	Flood-plain soil	2	1,2,3,6,7,8-HxCDF	F	6	649	38	SD	pg/kg-day	56	4	SD	30-day repeated exposure in feed	30-day gavage in corn oil/acetone (99:1)	Liver + adipose burden (ND=1/2 DL)	Feed	Corn oil/ acetone (99:1)
38	Finley et al. 2009	FI09	Rat	Surface soil 1	1	2,3,7,8-TCDD	D	4	32.8	#NA		pg/kg-day	#NA	#NA		Single gavage dose, aqueous suspension	Single gavage dose in corn oil, 3 dose levels	Liver burden	Aqueous suspension	Corn oil
39	Finley et al. 2009	FI09	Rat	Surface soil 1	1	1,2,3,7,8-PeCDD	D	5	350	#NA		pg/kg-day	#NA	#NA		Single gavage dose, aqueous suspension	Single gavage dose in corn oil, 3 dose levels	Liver burden	Aqueous suspension	Corn oil
40	Finley et al. 2009	FI09	Rat	Surface soil 1	1	1,2,3,4,7,8-HxCDD	D	6	330	#NA		pg/kg	#NA	#NA		Single gavage dose, aqueous suspension	Single gavage dose in corn oil, 3 dose levels	Liver burden	Aqueous suspension	Corn oil
41	Finley et al. 2009	FI09	Rat	Surface soil 1	1	1,2,3,6,7,8-HxCDD	D	6	1070	#NA		pg/kg	22	5	SD	Single gavage dose, aqueous suspension	Single gavage dose in corn oil, 3 dose levels	Liver burden	Aqueous suspension	Corn oil
42	Finley et al. 2009	FI09	Rat	Surface soil 1	1	1,2,3,7,8,9-HxCDD	D	6	1184	#NA		pg/kg	#NA	#NA		Single gavage dose, aqueous suspension	Single gavage dose in corn oil, 3 dose levels	Liver burden	Aqueous suspension	Corn oil
43	Finley et al. 2009	FI09	Rat	Surface soil 1	1	1,2,3,4,6,7,8-HpCDD	D	7	756	#NA		pg/kg	#NA	#NA		Single gavage dose, aqueous suspension	Single gavage dose in corn oil, 3 dose levels	Liver burden	Aqueous suspension	Corn oil
44	Finley et al. 2009	FI09	Rat	Surface soil 1	1	OCDD	D	8	20200	#NA		pg/kg	#NA	#NA		Single gavage dose, aqueous suspension	Single gavage dose in corn oil, 3 dose levels	Liver burden	Aqueous suspension	Corn oil
45	Finley et al. 2009	FI09	Rat	Surface soil 1	1	2,3,7,8-TCDF	F	4	2560	#NA		pg/kg	27	5	SD	Single gavage dose, aqueous suspension	Single gavage dose in corn oil, 3 dose levels	Liver burden	Aqueous suspension	Corn oil

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46	Finley et al. 2009	FI09	Rat	Surface soil 1	1	1,2,3,7,8-PeCDF	F	5	22000	#NA		pg/kg	26	6	SD	Single gavage dose, aqueous suspension	Single gavage dose in corn oil, 3 dose levels	Liver burden	Aqueous suspension	Corn oil
47	Finley et al. 2009	FI09	Rat	Surface soil 1	1	2,3,4,7,8-PeCDF	F	5	11260	#NA		pg/kg	18	4	SD	Single gavage dose, aqueous suspension	Single gavage dose in corn oil, 3 dose levels	Liver burden	Aqueous suspension	Corn oil
48	Finley et al. 2009	FI09	Rat	Surface soil 1	1	1,2,3,4,7,8-HxCDF	F	6	66400	#NA		pg/kg	23	5	SD	Single gavage dose, aqueous suspension	Single gavage dose in corn oil, 3 dose levels	Liver burden	Aqueous suspension	Corn oil
49	Finley et al. 2009	FI09	Rat	Surface soil 1	1	1,2,3,6,7,8-HxCDF	F	6	57000	#NA		pg/kg	22	5	SD	Single gavage dose, aqueous suspension	Single gavage dose in corn oil, 3 dose levels	Liver burden	Aqueous suspension	Corn oil
50	Finley et al. 2009	FI09	Rat	Surface soil 1	1	1,2,3,7,8,9-HxCDF	F	6	27200	#NA		pg/kg	5	1	SD	Single gavage dose, aqueous suspension	Single gavage dose in corn oil, 3 dose levels	Liver burden	Aqueous suspension	Corn oil
51	Finley et al. 2009	FI09	Rat	Surface soil 1	1	2,3,4,6,7,8-HxCDF	F	6	24600	#NA		pg/kg	10	2	SD	Single gavage dose, aqueous suspension	Single gavage dose in corn oil, 3 dose levels	Liver burden	Aqueous suspension	Corn oil
52	Finley et al. 2009	FI09	Rat	Surface soil 1	1	1,2,3,4,6,7,8-HpCDF	F	7	458000	#NA		pg/kg	13	3	SD	Single gavage dose, aqueous suspension	Single gavage dose in corn oil, 3 dose levels	Liver burden	Aqueous suspension	Corn oil
53	Finley et al. 2009	FI09	Rat	Surface soil 1	1	1,2,3,4,7,8,9-HpCDF	F	7	166600	#NA		pg/kg	14	3	SD	Single gavage dose, aqueous suspension	Single gavage dose in corn oil, 3 dose levels	Liver burden	Aqueous suspension	Corn oil
54	Finley et al. 2009	FI09	Rat	Surface soil 1	1	OCDF	F	8	4140000	#NA		pg/kg	10	3	SD	Single gavage dose, aqueous suspension	Single gavage dose in corn oil, 3 dose levels	Liver burden	Aqueous suspension	Corn oil

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55	Finley et al. 2009	FI09	Rat	Surface soil 2	2	2,3,7,8-TCDD	D	4	346	#NA		pg/kg	#NA	#NA		Single gavage dose, aqueous suspension	Single gavage dose in corn oil, 3 dose levels	Liver burden	Aqueous suspension	Corn oil
56	Finley et al. 2009	FI09	Rat	Surface soil 2	2	1,2,3,7,8-PeCDD	D	5	1480	#NA		pg/kg	100	10	SD	Single gavage dose, aqueous suspension	Single gavage dose in corn oil, 3 dose levels	Liver burden	Aqueous suspension	Corn oil
57	Finley et al. 2009	FI09	Rat	Surface soil 2	2	1,2,3,4,7,8-HxCDD	D	6	1258	#NA		pg/kg	74	6	SD	Single gavage dose, aqueous suspension	Single gavage dose in corn oil, 3 dose levels	Liver burden	Aqueous suspension	Corn oil
58	Finley et al. 2009	FI09	Rat	Surface soil 2	2	1,2,3,6,7,8-HxCDD	D	6	2900	#NA		pg/kg	67	6	SD	Single gavage dose, aqueous suspension	Single gavage dose in corn oil, 3 dose levels	Liver burden	Aqueous suspension	Corn oil
59	Finley et al. 2009	FI09	Rat	Surface soil 2	2	1,2,3,7,8,9-HxCDD	D	6	3120	#NA		pg/kg	46	4	SD	Single gavage dose, aqueous suspension	Single gavage dose in corn oil, 3 dose levels	Liver burden	Aqueous suspension	Corn oil
60	Finley et al. 2009	FI09	Rat	Surface soil 2	2	1,2,3,4,6,7,8-HpCDD	D	7	2120	#NA		pg/kg	32	4	SD	Single gavage dose, aqueous suspension	Single gavage dose in corn oil, 3 dose levels	Liver burden	Aqueous suspension	Corn oil
61	Finley et al. 2009	FI09	Rat	Surface soil 2	2	OCDD	D	8	60400	#NA		pg/kg	23	3	SD	Single gavage dose, aqueous suspension	Single gavage dose in corn oil, 3 dose levels	Liver burden	Aqueous suspension	Corn oil
62	Finley et al. 2009	FI09	Rat	Surface soil 2	2	2,3,7,8-TCDF	F	4	28600	#NA		pg/kg	76	9	SD	Single gavage dose, aqueous suspension	Single gavage dose in corn oil, 3 dose levels	Liver burden	Aqueous suspension	Corn oil
63	Finley et al. 2009	FI09	Rat	Surface soil 2	2	1,2,3,7,8-PeCDF	F	5	80600	#NA		pg/kg	89	9	SD	Single gavage dose, aqueous suspension	Single gavage dose in corn oil, 3 dose levels	Liver burden	Aqueous suspension	Corn oil

	Study	Study Code	Species	Test Material	TM Code	Congener		Cl #	Dose	+/-	SD	Unit	RBA	+/-	SD	Test Material Dosing Protocol	Reference Material Dosing Protocol	Bioavailability Metric	Test Material Vehicle	Reference Vehicle
64	Finley et al. 2009	FI09	Rat	Surface soil 2	2	2,3,4,7,8-PeCDF	F	5	47200	#NA		pg/kg	50	4	SD	Single gavage dose, aqueous suspension	Single gavage dose in corn oil, 3 dose levels	Liver burden	Aqueous suspension	Corn oil
65	Finley et al. 2009	FI09	Rat	Surface soil 2	2	1,2,3,4,7,8-HxCDF	F	6	198000	#NA		pg/kg	61	6	SD	Single gavage dose, aqueous suspension	Single gavage dose in corn oil, 3 dose levels	Liver burden	Aqueous suspension	Corn oil
66	Finley et al. 2009	FI09	Rat	Surface soil 2	2	1,2,3,6,7,8-HxCDF	F	6	168600	#NA		pg/kg	59	5	SD	Single gavage dose, aqueous suspension	Single gavage dose in corn oil, 3 dose levels	Liver burden	Aqueous suspension	Corn oil
67	Finley et al. 2009	FI09	Rat	Surface soil 2	2	1,2,3,7,8,9-HxCDF	F	6	80000	#NA		pg/kg	16	2	SD	Single gavage dose, aqueous suspension	Single gavage dose in corn oil, 3 dose levels	Liver burden	Aqueous suspension	Corn oil
68	Finley et al. 2009	FI09	Rat	Surface soil 2	2	2,3,4,6,7,8-HxCDF	F	6	76800	#NA		pg/kg	32	3	SD	Single gavage dose, aqueous suspension	Single gavage dose in corn oil, 3 dose levels	Liver burden	Aqueous suspension	Corn oil
69	Finley et al. 2009	FI09	Rat	Surface soil 2	2	1,2,3,4,6,7,8-HpCDF	F	7	994000	#NA		pg/kg	28	3	SD	Single gavage dose, aqueous suspension	Single gavage dose in corn oil, 3 dose levels	Liver burden	Aqueous suspension	Corn oil
70	Finley et al. 2009	FI09	Rat	Surface soil 2	2	1,2,3,4,7,8,9-HpCDF	F	7	394000	#NA		pg/kg	34	3	SD	Single gavage dose, aqueous suspension	Single gavage dose in corn oil, 3 dose levels	Liver burden	Aqueous suspension	Corn oil
71	Finley et al. 2009	FI09	Rat	Surface soil 2	2	OCDF	F	8	6500000	#NA		pg/kg	21	3	SD	Single gavage dose, aqueous suspension	Single gavage dose in corn oil, 3 dose levels	Liver burden	Aqueous suspension	Corn oil
72	Finley et al. 2009	FI09	Rat	Surface soil 3	3	2,3,7,8-TCDD	D	4	418	#NA		pg/kg	#NA	#NA		Single gavage dose, aqueous suspension	Single gavage dose in corn oil, 3 dose levels	Liver burden	Aqueous suspension	Corn oil

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73	Finley et al. 2009	FI09	Rat	Surface soil 3	3	1,2,3,7,8-PeCDD	D	5	1446	#NA		pg/kg	79	12	SD	Single gavage dose, aqueous suspension	Single gavage dose in corn oil, 3 dose levels	Liver burden	Aqueous suspension	Corn oil
74	Finley et al. 2009	FI09	Rat	Surface soil 3	3	1,2,3,4,7,8-HxCDD	D	6	1116	#NA		pg/kg	52	10	SD	Single gavage dose, aqueous suspension	Single gavage dose in corn oil, 3 dose levels	Liver burden	Aqueous suspension	Corn oil
75	Finley et al. 2009	FI09	Rat	Surface soil 3	3	1,2,3,6,7,8-HxCDD	D	6	2760	#NA		pg/kg	46	7	SD	Single gavage dose, aqueous suspension	Single gavage dose in corn oil, 3 dose levels	Liver burden	Aqueous suspension	Corn oil
76	Finley et al. 2009	FI09	Rat	Surface soil 3	3	1,2,3,7,8,9-HxCDD	D	6	3000	#NA		pg/kg	32	5	SD	Single gavage dose, aqueous suspension	Single gavage dose in corn oil, 3 dose levels	Liver burden	Aqueous suspension	Corn oil
77	Finley et al. 2009	FI09	Rat	Surface soil 3	3	1,2,3,4,6,7,8-HpCDD	D	7	1824	#NA		pg/kg	20	4	SD	Single gavage dose, aqueous suspension	Single gavage dose in corn oil, 3 dose levels	Liver burden	Aqueous suspension	Corn oil
78	Finley et al. 2009	FI09	Rat	Surface soil 3	3	OCDD	D	8	47400	#NA		pg/kg	#NA	#NA		Single gavage dose, aqueous suspension	Single gavage dose in corn oil, 3 dose levels	Liver burden	Aqueous suspension	Corn oil
79	Finley et al. 2009	FI09	Rat	Surface soil 3	3	2,3,7,8-TCDF	F	4	36800	#NA		pg/kg	75	7	SD	Single gavage dose, aqueous suspension	Single gavage dose in corn oil, 3 dose levels	Liver burden	Aqueous suspension	Corn oil
80	Finley et al. 2009	FI09	Rat	Surface soil 3	3	1,2,3,7,8-PeCDF	F	5	75200	#NA		pg/kg	69	8	SD	Single gavage dose, aqueous suspension	Single gavage dose in corn oil, 3 dose levels	Liver burden	Aqueous suspension	Corn oil
81	Finley et al. 2009	FI09	Rat	Surface soil 3	3	2,3,4,7,8-PeCDF	F	5	43600	#NA		pg/kg	44	6	SD	Single gavage dose, aqueous suspension	Single gavage dose in corn oil, 3 dose levels	Liver burden	Aqueous suspension	Corn oil

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82	Finley et al. 2009	FI09	Rat	Surface soil 3	3	1,2,3,4,7,8-HxCDF	F	6	158200	#NA		pg/kg	42	6	SD	Single gavage dose, aqueous suspension	Single gavage dose in corn oil, 3 dose levels	Liver burden	Aqueous suspension	Corn oil
83	Finley et al. 2009	FI09	Rat	Surface soil 3	3	1,2,3,6,7,8-HxCDF	F	6	128200	#NA		pg/kg	42	6	SD	Single gavage dose, aqueous suspension	Single gavage dose in corn oil, 3 dose levels	Liver burden	Aqueous suspension	Corn oil
84	Finley et al. 2009	FI09	Rat	Surface soil 3	3	1,2,3,7,8,9-HxCDF	F	6	60000	#NA		pg/kg	13	2	SD	Single gavage dose, aqueous suspension	Single gavage dose in corn oil, 3 dose levels	Liver burden	Aqueous suspension	Corn oil
85	Finley et al. 2009	FI09	Rat	Surface soil 3	3	2,3,4,6,7,8-HxCDF	F	6	61800	#NA		pg/kg	22	3	SD	Single gavage dose, aqueous suspension	Single gavage dose in corn oil, 3 dose levels	Liver burden	Aqueous suspension	Corn oil
86	Finley et al. 2009	FI09	Rat	Surface soil 3	3	1,2,3,4,6,7,8-HpCDF	F	7	680000	#NA		pg/kg	18	3	SD	Single gavage dose, aqueous suspension	Single gavage dose in corn oil, 3 dose levels	Liver burden	Aqueous suspension	Corn oil
87	Finley et al. 2009	FI09	Rat	Surface soil 3	3	1,2,3,4,7,8,9-HpCDF	F	7	294000	#NA		pg/kg	22	3	SD	Single gavage dose, aqueous suspension	Single gavage dose in corn oil, 3 dose levels	Liver burden	Aqueous suspension	Corn oil
88	Finley et al. 2009	FI09	Rat	Surface soil 3	3	OCDF	F	8	4160000	#NA		pg/kg	13	2	SD	Single gavage dose, aqueous suspension	Single gavage dose in corn oil, 3 dose levels	Liver burden	Aqueous suspension	Corn oil
89	Finley et al. 2009	FI09	Rat	Surface soil 4	4	2,3,7,8-TCDD	D	4	19.54	#NA		pg/kg	#NA	#NA		Single gavage dose, aqueous suspension	Single gavage dose in corn oil, 3 dose levels	Liver burden	Aqueous suspension	Corn oil
90	Finley et al. 2009	FI09	Rat	Surface soil 4	4	1,2,3,7,8-PeCDD	D	5	76.2	#NA		pg/kg	#NA	#NA		Single gavage dose, aqueous suspension	Single gavage dose in corn oil, 3 dose levels	Liver burden	Aqueous suspension	Corn oil

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91	Finley et al. 2009	FI09	Rat	Surface soil 4	4	1,2,3,4,7,8-HxCDD	D	6	66	#NA		pg/kg	#NA	#NA		Single gavage dose, aqueous suspension	Single gavage dose in corn oil, 3 dose levels	Liver burden	Aqueous suspension	Corn oil
92	Finley et al. 2009	FI09	Rat	Surface soil 4	4	1,2,3,6,7,8-HxCDD	D	6	226	#NA		pg/kg	82	#NA		Single gavage dose, aqueous suspension	Single gavage dose in corn oil, 3 dose levels	Liver burden	Aqueous suspension	Corn oil
93	Finley et al. 2009	FI09	Rat	Surface soil 4	4	1,2,3,7,8,9-HxCDD	D	6	260	#NA		pg/kg	#NA	#NA		Single gavage dose, aqueous suspension	Single gavage dose in corn oil, 3 dose levels	Liver burden	Aqueous suspension	Corn oil
94	Finley et al. 2009	FI09	Rat	Surface soil 4	4	1,2,3,4,6,7,8-HpCDD	D	7	151.4	#NA		pg/kg	#NA	#NA		Single gavage dose, aqueous suspension	Single gavage dose in corn oil, 3 dose levels	Liver burden	Aqueous suspension	Corn oil
95	Finley et al. 2009	FI09	Rat	Surface soil 4	4	OCDD	D	8	5380	#NA		pg/kg	#NA	#NA		Single gavage dose, aqueous suspension	Single gavage dose in corn oil, 3 dose levels	Liver burden	Aqueous suspension	Corn oil
96	Finley et al. 2009	FI09	Rat	Surface soil 4	4	2,3,7,8-TCDF	F	4	2060	#NA		pg/kg	81	10	SD	Single gavage dose, aqueous suspension	Single gavage dose in corn oil, 3 dose levels	Liver burden	Aqueous suspension	Corn oil
97	Finley et al. 2009	FI09	Rat	Surface soil 4	4	1,2,3,7,8-PeCDF	F	5	3860	#NA		pg/kg	74	9	SD	Single gavage dose, aqueous suspension	Single gavage dose in corn oil, 3 dose levels	Liver burden	Aqueous suspension	Corn oil
98	Finley et al. 2009	FI09	Rat	Surface soil 4	4	2,3,4,7,8-PeCDF	F	5	2080	#NA		pg/kg	52	8	SD	Single gavage dose, aqueous suspension	Single gavage dose in corn oil, 3 dose levels	Liver burden	Aqueous suspension	Corn oil
99	Finley et al. 2009	FI09	Rat	Surface soil 4	4	1,2,3,4,7,8-HxCDF	F	6	11340	#NA		pg/kg	63	8	SD	Single gavage dose, aqueous suspension	Single gavage dose in corn oil, 3 dose levels	Liver burden	Aqueous suspension	Corn oil

	Study	Study Code	Species	Test Material	TM Code	Congener		Cl #	Dose	+/-	SD	Unit	RBA	+/-	SD	Test Material Dosing Protocol	Reference Material Dosing Protocol	Bioavailability Metric	Test Material Vehicle	Reference Vehicle
100	Finley et al. 2009	FI09	Rat	Surface soil 4	4	1,2,3,6,7,8-HxCDF	F	6	9340	#NA		pg/kg	62	8	SD	Single gavage dose, aqueous suspension	Single gavage dose in corn oil, 3 dose levels	Liver burden	Aqueous suspension	Corn oil
101	Finley et al. 2009	FI09	Rat	Surface soil 4	4	1,2,3,7,8,9-HxCDF	F	6	4400	#NA		pg/kg	19	3	SD	Single gavage dose, aqueous suspension	Single gavage dose in corn oil, 3 dose levels	Liver burden	Aqueous suspension	Corn oil
102	Finley et al. 2009	FI09	Rat	Surface soil 4	4	2,3,4,6,7,8-HxCDF	F	6	4200	#NA		pg/kg	28	3	SD	Single gavage dose, aqueous suspension	Single gavage dose in corn oil, 3 dose levels	Liver burden	Aqueous suspension	Corn oil
103	Finley et al. 2009	FI09	Rat	Surface soil 4	4	1,2,3,4,6,7,8-HpCDF	F	7	90600	#NA		pg/kg	33	4	SD	Single gavage dose, aqueous suspension	Single gavage dose in corn oil, 3 dose levels	Liver burden	Aqueous suspension	Corn oil
104	Finley et al. 2009	FI09	Rat	Surface soil 4	4	1,2,3,4,7,8,9-HpCDF	F	7	27600	#NA		pg/kg	39	5	SD	Single gavage dose, aqueous suspension	Single gavage dose in corn oil, 3 dose levels	Liver burden	Aqueous suspension	Corn oil
105	Finley et al. 2009	FI09	Rat	Surface soil 4	4	OCDF	F	8	1253333	#NA		pg/kg	27	3	SD	Single gavage dose, aqueous suspension	Single gavage dose in corn oil, 3 dose levels	Liver burden	Aqueous suspension	Corn oil
106	Finley et al. 2009	FI09	Rat	Surface soil 5	5	2,3,7,8-TCDD	D	4	#NA	#NA		pg/kg	#NA	#NA		Single gavage dose, aqueous suspension	Single gavage dose in corn oil, 3 dose levels	Liver burden	Aqueous suspension	Corn oil
107	Finley et al. 2009	FI09	Rat	Surface soil 5	5	1,2,3,7,8-PeCDD	D	5	15.56	#NA		pg/kg	#NA	#NA		Single gavage dose, aqueous suspension	Single gavage dose in corn oil, 3 dose levels	Liver burden	Aqueous suspension	Corn oil
108	Finley et al. 2009	FI09	Rat	Surface soil 5	5	1,2,3,4,7,8-HxCDD	D	6	13.6	#NA		pg/kg	#NA	#NA		Single gavage dose, aqueous suspension	Single gavage dose in corn oil, 3 dose levels	Liver burden	Aqueous suspension	Corn oil

	Study	Study Code	Species	Test Material	TM Code	Congener		Cl #	Dose	+/-	SD	Unit	RBA	+/-	SD	Test Material Dosing Protocol	Reference Material Dosing Protocol	Bioavailability Metric	Test Material Vehicle	Reference Vehicle
109	Finley et al. 2009	FI09	Rat	Surface soil 5	5	1,2,3,6,7,8-HxCDD	D	6	40.6	#NA		pg/kg	#NA	#NA		Single gavage dose, aqueous suspension	Single gavage dose in corn oil, 3 dose levels	Liver burden	Aqueous suspension	Corn oil
110	Finley et al. 2009	FI09	Rat	Surface soil 5	5	1,2,3,7,8,9-HxCDD	D	6	44.8	#NA		pg/kg	#NA	#NA		Single gavage dose, aqueous suspension	Single gavage dose in corn oil, 3 dose levels	Liver burden	Aqueous suspension	Corn oil
111	Finley et al. 2009	FI09	Rat	Surface soil 5	5	1,2,3,4,6,7,8-HpCDD	D	7	23.6	#NA		pg/kg	#NA	#NA		Single gavage dose, aqueous suspension	Single gavage dose in corn oil, 3 dose levels	Liver burden	Aqueous suspension	Corn oil
112	Finley et al. 2009	FI09	Rat	Surface soil 5	5	OCDD	D	8	840	#NA		pg/kg	#NA	#NA		Single gavage dose, aqueous suspension	Single gavage dose in corn oil, 3 dose levels	Liver burden	Aqueous suspension	Corn oil
113	Finley et al. 2009	FI09	Rat	Surface soil 5	5	2,3,7,8-TCDF	F	4	338	#NA		pg/kg	#NA	#NA		Single gavage dose, aqueous suspension	Single gavage dose in corn oil, 3 dose levels	Liver burden	Aqueous suspension	Corn oil
114	Finley et al. 2009	FI09	Rat	Surface soil 5	5	1,2,3,7,8-PeCDF	F	5	847	#NA		pg/kg	61	18	SD	Single gavage dose, aqueous suspension	Single gavage dose in corn oil, 3 dose levels	Liver burden	Aqueous suspension	Corn oil
115	Finley et al. 2009	FI09	Rat	Surface soil 5	5	2,3,4,7,8-PeCDF	F	5	464	#NA		pg/kg	56	15	SD	Single gavage dose, aqueous suspension	Single gavage dose in corn oil, 3 dose levels	Liver burden	Aqueous suspension	Corn oil
116	Finley et al. 2009	FI09	Rat	Surface soil 5	5	1,2,3,4,7,8-HxCDF	F	6	2360	#NA		pg/kg	47	13	SD	Single gavage dose, aqueous suspension	Single gavage dose in corn oil, 3 dose levels	Liver burden	Aqueous suspension	Corn oil
117	Finley et al. 2009	FI09	Rat	Surface soil 5	5	1,2,3,6,7,8-HxCDF	F	6	2040	#NA		pg/kg	42	11	SD	Single gavage dose, aqueous suspension	Single gavage dose in corn oil, 3 dose levels	Liver burden	Aqueous suspension	Corn oil

	Study	Study Code	Species	Test Material	TM Code	Congener		Cl #	Dose	+/-	SD	Unit	RBA	+/-	SD	Test Material Dosing Protocol	Reference Material Dosing Protocol	Bioavailability Metric	Test Material Vehicle	Reference Vehicle
118	Finley et al. 2009	FI09	Rat	Surface soil 5	5	1,2,3,7,8,9-HxCDF	F	6	968	#NA		pg/kg	23	#NA		Single gavage dose, aqueous suspension	Single gavage dose in corn oil, 3 dose levels	Liver burden	Aqueous suspension	Corn oil
119	Finley et al. 2009	FI09	Rat	Surface soil 5	5	2,3,4,6,7,8-HxCDF	F	6	830	#NA		pg/kg	#NA	#NA		Single gavage dose, aqueous suspension	Single gavage dose in corn oil, 3 dose levels	Liver burden	Aqueous suspension	Corn oil
120	Finley et al. 2009	FI09	Rat	Surface soil 5	5	1,2,3,4,6,7,8-HpCDF	F	7	14460	#NA		pg/kg	19	7	SD	Single gavage dose, aqueous suspension	Single gavage dose in corn oil, 3 dose levels	Liver burden	Aqueous suspension	Corn oil
121	Finley et al. 2009	FI09	Rat	Surface soil 5	5	1,2,3,4,7,8,9-HpCDF	F	7	4680	#NA		pg/kg	25	8	SD	Single gavage dose, aqueous suspension	Single gavage dose in corn oil, 3 dose levels	Liver burden	Aqueous suspension	Corn oil
122	Finley et al. 2009	FI09	Rat	Surface soil 5	5	OCDF	F	8	105333	#NA		pg/kg	13	5	SD	Single gavage dose, aqueous suspension	Single gavage dose in corn oil, 3 dose levels	Liver burden	Aqueous suspension	Corn oil
123	Shu et al. 1988	SH88	Rat	Surface soil - Times Beach	1	2,3,7,8-TCDD	D	4	3200	#NA		pg/kg	57	#NA		Single gavage dose, aqueous suspension	Single gavage dose in corn oil	Liver burden	Aqueous suspension	Corn oil
124	Shu et al. 1988	SH88	Rat	Surface soil - Times Beach	1	2,3,7,8-TCDD	D	4	7000	#NA		pg/kg	64	#NA		Single gavage dose, aqueous suspension	Single gavage dose in corn oil	Liver burden	Aqueous suspension	Corn oil
125	Shu et al. 1988	SH88	Rat	Surface soil - Times Beach	1	2,3,7,8-TCDD	D	4	40000	#NA		pg/kg	49	#NA		Single gavage dose, aqueous suspension	Single gavage dose in corn oil	Liver burden	Aqueous suspension	Corn oil
126	Shu et al. 1988	SH88	Rat	Surface soil - Times Beach	1	2,3,7,8-TCDD	D	4	37000	#NA		pg/kg	56	#NA		Single gavage dose, aqueous suspension	Single gavage dose in corn oil	Liver burden	Aqueous suspension	Corn oil

	Study	Study Code	Species	Test Material	TM Code	Congener		Cl #	Dose	+/-	SD	Unit	RBA	+/-	SD	Test Material Dosing Protocol	Reference Material Dosing Protocol	Bioavailability Metric	Test Material Vehicle	Reference Vehicle
127	Shu et al. 1988	SH88	Rat	Surface soil - Times Beach	1	2,3,7,8-TCDD	D	4	175000	#NA		pg/kg	59	#NA		Single gavage dose, aqueous suspension	Single gavage dose in corn oil	Liver burden	Aqueous suspension	Corn oil
128	Shu et al. 1988	SH88	Rat	Surface soil - Times Beach	1	2,3,7,8-TCDD	D	4	1450000	#NA		pg/kg	48	#NA		Single gavage dose, aqueous suspension	Single gavage dose in corn oil	Liver burden	Aqueous suspension	Corn oil
129	Lucier et al. 1986	LU86	Rat	Surface soil - Minker MO	1	2,3,7,8-TCDD	D	4	1100000	#NA		pg/kg	22	#NA		Single gavage dose, aqueous suspension	Single gavage dose in corn oil	Liver concentration	Aqueous suspension	Corn oil
130	Lucier et al. 1986	LU86	Rat	Surface soil - Minker MO	1	2,3,7,8-TCDD	D	4	5500000	#NA		pg/kg	45	#NA		Single gavage dose, aqueous suspension	Single gavage dose in corn oil	Liver concentration	Aqueous suspension	Corn oil
131	Bonaccorsi et al. 1984	BO84	Rabbit	Surface soil - Sevaso	1	2,3,7,8-TCDD	D	4	30769	#NA		pg/kg-day	33	#NA		7-day gavage dose, aqueous suspension	7-day gavage dose, 50% ethanol	Liver concentration	Aqueous suspension	50% ethanol

HpCDD, heptachloro-p-dibenzodioxin; HpCDF, heptachloro-p-dibenzofuran; HxCDD, hexachloro-p-dibenzodioxin; HxCDF, hexachlorodibenzofuran; PeCDD, pentachloro-p-dibenzodioxin; PeCDF, pentachloro-p-dibenzofuran; TCDD, tetrachloro-p-dibenzodioxin; TCDF, tetrachlorodibenzofuran; OCDD, octochloro-p-dibenzodioxin