BIOAVAILABILITY OF DIOXINS AND DIOXIN-LIKE COMPOUNDS IN SOIL

Peer Review Report

Prepared by:

U.S. Environmental Protection Agency, Office of Solid Waste and Emergency Response, Office of Superfund Remediation and Technology Innovation

With contributions from:

Environmental Management Support, Inc.

May 4, 2011

TABLE OF CONTENTS

LIST OF APPENDICES iii

EXECUTIVE SUMMARY iv

1.0 INTRODUCTION 1

1.1 Background 1

2.0 PEER REVIEW PROCESS 2

2.1 Peer Review Charge 2

2.2 Summary of Finding 3

3.0 RESULTS 4

4.0 REFERENCES 4

LIST OF APPENDICES

Appendix A – Peer Review Comments A-1
Appendix B – Peer Review Materials..... B-2

EXECUTIVE SUMMARY

The Peer Review Panel (herein referred to as Panel) reviewed the report titled *Bioavailability of Dioxins in Soil and Soil-Like Materials* (herein referred to as Report) to address 16 charge questions regarding the information contained in the document.
The Report presents a summary of the published literature and analysis of the available data regarding relative bioavailability (RBA) of polychlorinated dibenzo-p-dioxins (PCDD) and polychlorinated dibenzofuran congeners (PCDF) in soil[1].

The external peer review resulted in an editorial revision of the Report. Peer Review findings are summarized below in Section 2.2 Summary of Findings and Section 3.0 Results. The revised final Report may be found at
http://www.epa.gov/superfund/health/contaminants/dioxin/dioxinsoil.html

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

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(ies) 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 PEER REVIEW PROCESS

2.1 Peer Review Charges

The Report qualifies as a technical document and is eligible for an independent peer review of the content. EPA retained Environmental Management Support, Inc. (EMS) to conduct an independent peer review of the Report. EMS conducted the review of the technical document in accordance with the EPA's Science Policy Council Peer Review Handbook (third edition, June 2006). Management of the review consisted of the following general activities:

- Identified areas of expertise necessary for a scientifically rigorous review.
- Identified a list of candidate expert peer reviewers.
- Evaluated the expertise of each of the candidate expert peer reviewers.
- Created a short list of candidate expert peer reviewers.
- Determined the interest and availability of the short list of candidate expert peer reviewers.
- Determined for each of the remaining list of candidate peer reviewers any potential conflict of interest or lack of impartiality, or the appearance of any potential conflict of interest or lack of impartiality; excluding candidates with either.
- Finalized a team of three expert peer reviewers.
- Developed charge questions in conjunction with EPA for the conduct of the peer review.
- Initiated the review.
- Coordinated the peer reviewers to finalize their written reviews.

This peer review was conducted as a letter review. Each of the reviewers was provided with a copy of the Report and charge questions. A copy of all the materials provided to the expert peer reviewers is included in this document.

In seeking candidates to serve as expert peer reviewers, as well as selecting the final team of reviewers, an effort was made to include individuals with expertise in one or more of the areas identified by EPA:

- Exposure and Risk Assessment
- Human Health Toxicity
- Pharmacokinetics
- Bioavailability
- Dioxin and Dioxin-Like Compounds in soil.

The final team of expert reviewers consisted of the following individuals:

- Dr. Michael DeVito, National Toxicology Program, National Institute of Environmental Health Science;
- Dr. Michael Honeycutt, Texas Commission on Environmental Quality; and
- Dr. Stephen Roberts, University of Florida.

Each of the reviewers was allowed four to six weeks to complete the review. Upon receipt of the letter reviews, each one was reviewed and formatted for EPA's review. A brief summary of the findings from the reviews are included below. Each of the final reviews is included as an attachment to this document.

2.2 Summary of Findings

- Each of the reviewers agreed that the RBA of dioxin in soils is less than 100%.
  Two of the three reviewers agreed that there were insufficient data to support a nationally-applicable value for RBA for use in risk assessments. The reviewer who did not agree recommended assigning a national RBA value less than 100% as a compromise due to the lack of data from a statistically balanced study on dioxins RBA in soil, but did not provide a scientifically defensible basis for doing so.
- Two of the three reviewers agreed that the current literature does not support a preferred animal model for use as an animal bioassay. The reviewer who disagreed preferred the swine model for an animal bioassay.
- None of the reviewers cited additional critical studies that could be included in the Report's analysis.
- The reviewers identified critical points of clarification that would be required to calculate a nationally applicable RBA. The reviewers focused on multiple doses in soil, animal

model disparities and soil characteristics that would influence the bioavailability of dioxin when ingested.

- The reviewers agreed that while the animal models presented in the Report (rat and swine) are appropriate and commonly used in bioavailability studies, the limited data available for species comparison and conflicting results on the degree of bioavailability suggest they do not produce equivalent results.
- There was consensus that congener chlorine content will influence the RBA of the congeners.
- The reviewers agreed that additional studies are required to establish a standard animal protocol to be used to determine a site-specific RBA for dioxin.

3.0 RESULTS

The external peer review resulted in an editorial revision of the initial Report. The peer reviewers' comments did not recommend revising the Report's scientific content or change its conclusions.

The revised final Report may be found at http://www.epa.gov/superfund/health/contaminants/dioxin/dioxinsoil.html.

The following sections include the peer review questions and comments (Appendix A) as well as the original peer review materials (Appendix B).

4.0 REFERENCES

USEPA 2006, Science Policy Council Peer Review Handbook, Third Edition, June 2006, http://www.epa.gov/peerreview

Appendix A – Peer Review Comments

CHARGE QUESTIONS to REVIEWERS

for Peer Review of Draft Report, "*Bioavailability of Dioxins In Soil and Soil-Like Materials: Literature Review and Data Analysis* " July 2010.

Michael DeVito, PhD

Section 1 General Charge Questions

1.1. Is the draft document *Bioavailability of Dioxins in Soil and Soil-like Materials: Literature Review and Data Analysis* clearly written and logical?

The draft document was clearly written and presents a logical argument

1.2. Are the objectives of the literature review clearly stated?

Yes

1.3 Has EPA objectively and clearly presented the rationale for its conclusions relevant to estimating the relative bioavailability (RBA) of TCDD or other PCDD/Fs in soil?

Yes

1.4 Do you agree with EPA's major conclusions regarding RBA of TCDD or other PCDD/Fs in soil? EPA's major conclusions are as follows:

a) RBA in soil is less than 100%

I agree

b) data currently available are not sufficient to estimate a nationally-applicable value for RBA for use in risk assessment (i.e., as an alternative to 100% or site-specific values)

I disagree. Since EPA concludes that RBA in soil is less than 100%, then using 100% is inappropriate. Based on the studies presented, the highest RBA of the soils tested is approximately 50%. One alternative to using the RBA of 100% is to assign an RBA of 75%. This is higher than all other soils tested, but may be a reasonable compromise due to the lack of data from a statistically balanced study on dioxins RBA in soil.

c) data currently available are not sufficient to determine the preferred animal species for use as an animal bioassay for predicting soil RBA in humans

I agree

d) site-specific data are recommended to develop site-specific cleanup levels.

I agree

If you disagree with any of the above conclusions, please comment on deficiencies in the conclusions or alternative conclusions that could be derived from the data.

1.5. Are you aware of other critical studies that would make a substantial impact on EPA's conclusions regarding RBA of TCDD and/or other PCDD/Fs?

Other than site specific data presented in this report, I am not aware of any other studies.

Section 2 Transparency and Clarity in the Selection of Key Data Sets for Relative Bioavailability Analysis

2.1. Is EPA's approach for selecting key studies and data sets from the key studies scientifically justified and clearly described?

Yes

2.2. Are the chosen data sets adequate for estimating RBA values for each tested soil in each of the studies?

I would be a little concerned with studies using only one dose level because of the dose dependent disposition of dioxins. While they can identify soils that are not 100% bioavailable, using a single dose level may tend to underestimate the bioavailability of a particular soil

2.3. Are the data relied upon for the estimation of RBA for each tested soil in each of the studies, applied in a scientifically sound manner?

Yes

2.4. Please comment on deficiencies, substantial inadequacies of the selected studies and data sets, and provide suggestions for existing or future studies that could inform the assessment of soil RBA.

One of the major assumptions used in these bioavailability studies is that of first order pharmacokinetics of TCDD and related congeners. Recent studies demonstrate that TCDD induces its own elimination and that there are dose dependent distribution of this chemical due to the induction of CYP1A2 and binding of dioxins to CYP1A2. Since this contrasts the assumption of first order elimination, single dose studies or other studies that do not take into account the dose dependency of the distribution and elimination would produce inaccurate estimates of the bioavailability of these chemicals. Most of the studies included in this report used only a single dose level of TCDD or related. While these studies clearly demonstrate that the dioxins in soil are not 100% bioavailable, they may underestimate the true bioavailability of dioxins from the soil.

Section 3 Use of Animal Bioassays to Estimate Relative Bioavailability

3.1. Are the animal models presented in this report appropriate for estimating RBA of TCDD and other PCDD/Fs in soil? Please also comment on the criteria EPA has used to evaluate the animal models:

The animals examined in this report are appropriate models to compare the relative bioavailability. The key point is the relative bioavailability and not actual bioavailability. Any of the experimental models used can provide useful information on the relative bioavailability. The use of some of the models to predict actual bioavailability would present some challenges.

a) similarities of physiology and anatomy of the animal model and human gastrointestinal tract

This is the an important parameter to consider when choosing an animal model

b) similarity of distribution of absorbed PCDD/Fs in adipose tissue relative to liver

This parameter has little impact on the cross species extrapolation of RBA, but would have an important influence on the estimate of the RBA in a particular species. As long as this is accounted for in the experimental design, then it should have little influence in the cross species extrapolation of the RBA.

c) Ah receptor binding, CYP450 induction, and clearance of PCDD/Fs

This parameter has little impact on the cross species extrapolation of RBA. As long as the dose dependent induction and clearance of dioxins is considered in the experimental design, then these parameters should have little impact on extrapolating the RBA to humans.

3.2. What is your opinion of the observation that the effect of chlorine number on RBA is different in swine and rats?

a) in swine, RBA appears to increase with increasing chlorination
b) in rats, RBA appears to decrease with increasing chlorination

I am a little hesitant to make these statements due to the limited data available. For example, in the swine data presented in Figure 1it looks as if tow data points really drive this relationship. The first point is the bioavailability value from W107 SW for TCDD. This is based on two data points one of which overlaps with the BU08 SW data and on that is approximately 10 fold lower. The second point is from BU08 SW for the heptachlorinated dioxins and this is approximately double that of the WI07 SW data. If you took these two points out, there probably would not be a significant relationship between chlorine content and bioavailability.

For rats, EPA uses the Budinsky and Finley studies. I do not agree with lumping these data together. These data sets are too variable to make sense. For example, they are using different soil types, congener patterns and concentrations of dioxins. These differences in the studies most likely are the cause of the large variability in the RBA estimates for the penta and hexa dioxins.

I think the data is not of sufficient quality to make broad statements on the bioavailability differences between species and congeners.

Please comment on how this observation conforms or conflicts with information regarding bioavailability provided by the National Academy of Science (NAS, 2006), World Health Organization (Van den Berg et al. 2006), and U.S. EPA (2003). Note that the swine studies (Budinsky et al., 2008; Wittseipe et al., 2007) included in EPA's recent literature review post-date these earlier reports

As described above I am quantitatively less certain that the chlorine effect is due to chlorine.

3.3. What is your opinion about the potential implications of a chlorine effect on RBA for predicting RBA in humans from animal bioassays (e.g., selection of appropriate animal

model, estimation of composite RBA for a soil material containing a mix of congeners, variability in congener composition of soils)?

I am much less certain of the chlorine effect than presented by EPA. I think the variability in bioavailability between congeners may be equally due to soil type or concentration of the congener administered. Therefore I believe that the potential implications are minor, particularly since EPA is recommending using 100% bioavailability unless there is site specific data.

3.4. EPA concludes that collection of site-specific data for estimating soil RBA is recommended for the purpose of developing site-specific clean-up levels. Please comment on the following:

a) importance of obtaining site-specific RBA data

This is a critical and appropriate conclusion

b) acceptance of an animal model for predicting RBA in humans
c) preferred animal model(s) and standard experimental protocol that would be acceptable for determining the site-specific RBA
d) need for additional studies in rodent, swine, primate, or other species for establishing a standard animal model protocol

Comments b, c and d are intertwined and I will respond to all three at once. Clearly there is limited data on the species differences in oral bioavailability between swine, rodents and primates for dioxins and further research is needed to better determine the magnitude of these differences and which species is best for this approach. The EPA make a reasonable conclusion that swine would be a better model than rodents for actual bioavailability. However, I am less certain this applies to relative bioavailability. AT this point I would take site specific data on either swine or rodents, provided the dose dependent pharmacokinetics was taken into account.

3.5. EPA has described two approaches to estimate RBA for congener mixtures for use in site risk assessment:

a) calculate the average RBA based on congener mass concentration in soil and congener RBA (*mass weighted RBA*)
b) calculate the average RBA based on congener TEQ concentration and congener RBA (*TEQ weighted RBA*)

What is your opinion on the relative merits and deficiencies in either approach, or on alternative approaches to estimating RBA for use in risk assessment?

I would prefer to calculate the average RBA based on congener mass concentration in the soil and congener RBA, then apply the TEF methodology on the bioavailable chemical. If there is a chlorine effect on RBA, then the concentration of the chemicals must be treated separately in the bioavailability estimates prior to TEQ evaluations.

Section 4 Uncertainties Identified in the Estimation of a Dioxin Soil RBA

4.1 Has EPA clearly described the major uncertainties attending its conclusions?

Yes

4.2 What is your opinion on the level of uncertainty in EPA's conclusions regarding RBA?

I think EPA provides a sound conclusion in that the use of 100% bioavailability is reasonable for all soil types that do not have site-specific data on bioavailability. The EPA has provided a clear description of the uncertainty and data limitations.

CHARGE QUESTIONS to REVIEWERS

for Peer Review of Draft Report, "*Bioavailability of Dioxins In Soil and Soil-Like Materials: Literature Review and Data Analysis* " July 2010.

Stephen M. Roberts, PhD

Section 1 General Charge Questions

1.1. Is the draft document *Bioavailability of Dioxins in Soil and Soil-like Materials: Literature Review and Data Analysis* clearly written and logical?

Yes, the draft document is clearly written and well organized. The points made are logical, for the most part, although a few may need to be reconsidered and others clarified (as discussed in response to some of the charge questions below). The Executive Summary faithfully captures the most important information from the main body of the report. The use of appendices for more detailed information is appropriate.

1.2. Are the objectives of the literature review clearly stated?

Yes, the objectives are quite clear.

1.3 Has EPA objectively and clearly presented the rationale for its conclusions relevant to estimating the relative bioavailability (RBA) of TCDD or other PCDD/Fs in soil?

The rationale for each of the conclusions is clearly explained.

1.4 Do you agree with EPA's major conclusions regarding RBA of TCDD or other PCDD/Fs in soil? EPA's major conclusions are as follows:

e) RBA in soil is less than 100%

I agree with the intent of this conclusion, although it could perhaps be better stated. The conclusion is worded as if RBA is a single value, when the report shows that it is a series of values for different congeners, and there is variability associated with each (e.g., from the influence of soil conditions).

Also, the conclusion may be stated too decisively given the limited number of soil samples for which RBA data are available. Something like, "Studies to date suggest that RBAs for dioxin mixtures are consistently less than 100%" or "RBAs measured in bioavailability studies were all less than 100%" might be easier to defend as not overreaching the data.

f) data currently available are not sufficient to estimate a nationally-applicable value for RBA for use in risk assessment (i.e., as an alternative to 100% or site-specific values)

I strongly agree. The number and types of contaminated soil samples examined to date are just too few to adequately capture the range of potential RBAs among dioxin-contaminated sites nationally.

g) data currently available are not sufficient to determine the preferred animal species for use as an animal bioassay for predicting soil RBA in humans

I agree. The report discusses considerations in determining the appropriate animal model, but concludes appropriately that we don't have enough information at present to make a confident choice.

h) site-specific data are recommended to develop site-specific cleanup levels.

I agree. There is plenty of evidence, as summarized in this report and elsewhere, that site-specific conditions such as the specific congeners present and soil conditions can affect substantially the RBA(s). Without site-specific data, determining the appropriate RBA to calculate site-specific cleanup levels would be strictly guesswork.

If you disagree with any of the above conclusions, please comment on deficiencies in the conclusions or alternative conclusions that could be derived from the data.

1.5. Are you aware of other critical studies that would make a substantial impact on EPA's conclusions regarding RBA of TCDD and/or other PCDD/Fs?

I think that the critical studies have been captured in the report. I am not aware of any other studies that would alter the conclusions of the report.

Section 2 Transparency and Clarity in the Selection of Key Data Sets for Relative Bioavailability Analysis

2.1. Is EPA's approach for selecting key studies and data sets from the key studies scientifically justified and clearly described?

The approach for selecting key studies is scientifically justified, and the most relevant studies were chosen to be the focus of the analysis. The clarity of the process could be improved, however. Specifically, there seems to be a disconnect between the literature survey presented in Appendix A and the review of studies in Section 3. The literature search product in Appendix A is broadly inclusive of a variety of types of studies that might provide inference on the bioavailability of dioxin from soil. The main body of the report focuses [appropriately in my opinion] on studies providing RBA estimates in animal models, with little mention of other studies. The problem is that there is no link between the two. If the RBA studies are the exclusive focus of the analysis, what was the point of finding and listing other types of studies in the literature survey? If the

other types of studies have something to offer, then why is there no discussion of their contribution to the analysis? Additional discussion, however brief, of the thinking involved in narrowing the focus to the nine studies presented in Section 3 would be useful.

2.2. Are the chosen data sets adequate for estimating RBA values for each tested soil in each of the studies?

Yes. Although some have limitations, all were adequate for providing an RBA estimate for the tested soils.

2.3. Are the data relied upon for the estimation of RBA for each tested soil in each of the studies, applied in a scientifically sound manner?

Yes, although there is a lack of transparency regarding the RBA values calculated for the report from some of the studies. In discussing specific studies in Section 3.2, RBAs are presented for some indicating that they were "calculated for this report" – apparently meaning that they were derived by the EPA using data presented in the published study. There is no description of how the data were interpreted and used to calculate these RBAs, making it difficult to assess their scientific basis.

2.4. Please comment on deficiencies, substantial inadequacies of the selected studies and data sets, and provide suggestions for existing or future studies that could inform the assessment of soil RBA.

A number of assumptions are needed in order to calculate RBA using the standard approach, including: 1) the doses are all in the linear pharmacokinetic range such that concentrations in the body are proportional to the absorbed dose; 2) Other than fraction of dose absorbed, the pharmacokinetics of the test and reference doses are the same; and 3) the method of assessing the absorbed dose is reasonably complete, or at least the test and reference doses are subject to the same type and degree of error. The

challenge for estimating the RBA for dioxin congeners is trying to insure that these assumptions are met, particularly the second two. The selected studies accomplished this to varying extents – the more recent studies (e.g., Budinsky et al.) seemed particularly aware of the need to address these points.

One study aspect that arguably deserves more discussion is the extent to which the reference dose in the study reflects absorption under the conditions in which the toxicity value was obtained. Admittedly, this is complicated somewhat by the use of different data sets to generate various estimates of TCDD cancer potency, e.g., rodent bioassays versus epi studies. However, the absorption of the reference dose is half of the RBA calculation, and the various methods of administering the reference dose (i.e., in corn oil versus food) in the RBA studies are not necessarily equivalent.

As discussed in response to 3.2, studies are needed to explain differences between rats and swine in terms of the effects of chlorination on absorption, and to determine to the extent possible the best animal model for assessment of the RBAs for dioxin in soil. There is also a need to greatly expand the suite of dioxin contaminated soils from which RBA information is obtained. This will facilitate predictive model development.

Section 3 Use of Animal Bioassays to Estimate Relative Bioavailability

3.1. Are the animal models presented in this report appropriate for estimating RBA of TCDD and other PCDD/Fs in soil? Please also comment on the criteria EPA has used to evaluate the animal models:

d) similarities of physiology and anatomy of the animal model and human gastrointestinal tract
e) similarity of distribution of absorbed PCDD/Fs in adipose tissue relative to liver
f) Ah receptor binding, CYP450 induction, and clearance of PCDD/Fs

Both animal models presented in this report (rat and swine) are commonly used in bioavailability studies and are appropriate for consideration. If the rat and swine gave essentially the same results, an argument could be made for the rat based simply upon cost. The limited data available for species comparison suggest that they do not produce equivalent results, however, making it important to determine which is the better predictor of RBA in humans. As the report points out, the anatomy and physiology of the swine digestive tract is more similar to humans, which is a point in favor of the swine. The report also states that the distribution of absorbed PCDD/Fs is primarily to the adipose tissue in swine and humans, but the liver in rats. This is important presumably because the greater the fraction of absorbed dose distributing to the liver, the greater the opportunity for confounding effects on RBA estimation due to changes/differences in metabolism and liver protein binding (see below). This point should perhaps be reconsidered, or at least examined more closely. The study of Budinsky et al. found distribution of most congeners was primarily to adipose tissue rather than liver in swine, but the opposite was found in the swine study of Wittsiepe et al., where distribution was primarily to the liver. [This is not mentioned in the report.] The difference may be due to the way congener concentrations in the tissues were expressed (per g tissue in the Budinsky et al. report and per g lipid in the Wittsiepe et al. paper), but it is difficult to tell without further analysis. Unfortunately, there are only two swine studies and they measured tissue concentrations in two different ways; this isn't a lot of information with which to make generalizations about species differences in dioxin congener disposition.

On the matter of Ah receptor binding, CYP450 induction, and clearance of PCDD/Fs, these are all confounding factors that affect RBA estimation. The report seems to suggest that these are more of an issue for the rat than the swine, but it is not clear why they don't apply to the swine as well. On page 31, there is discussion of AhR affinity and the difference in affinity for TCDD between mouse and human AhR. This is all well and good, but the issue here is rat versus swine versus human. This

comparison is not well developed in the report with respect to AhR binding, CYP450 induction, or clearance of PCDD/Fs. With the information presented, it is hard to conclude that one model is different from the other with respect to binding and clearance by the liver.

3.2. What is your opinion of the observation that the effect of chlorine number on RBA is different in swine and rats?

c) in swine, RBA appears to increase with increasing chlorination
d) in rats, RBA appears to decrease with increasing chlorination

Please comment on how this observation conforms or conflicts with information regarding bioavailability provided by the National Academy of Science (NAS, 2006), World Health Organization (Van den Berg et al. 2006), and U.S. EPA (2003). Note that the swine studies (Budinsky et al., 2008; Wittsiepe et al., 2007) included in EPA's recent literature review post-date these earlier reports.

As the report points out, previous conclusions by the NAS, WHO, and EPA regarding the relationship between chlorine content and RBA were based upon rat data only, and were not informed by the more recent swine studies. The observation here that the relationship between chlorine number and RBA is fundamentally different between the rat and swine raises the issue of determining the most appropriate animal model to a high level. Until this difference between species can be explained and an animal model with stronger scientific justification identified, progress in developing RBA values for site evaluation will be stalled.

3.3. What is your opinion about the potential implications of a chlorine effect on RBA for predicting RBA in humans from animal bioassays (e.g., selection of appropriate animal model, estimation of composite RBA for a soil material containing a mix of congeners, variability in congener composition of soils)?

Although the direction of the effect isn't clear, there seems to be consensus among studies examining RBAs of specific congeners that the extent of chlorination matters. Consequently, it is logical to propose that different RBAs for different congeners, or groups of congeners, be used to construct an overall RBA for a soil sample based upon congener content. There is, however, a missing dimension mentioned in the report that has not yet been explored, which is the influence of soil properties (e.g., organic carbon content) on the congener-specific RBAs. There is ample evidence to suggest that soil properties can affect the RBA (as cited in the report), but far too little data to establish quantitative relationships between soil properties and congener-specific RBAs. Developing those relationships will be a substantial undertaking.

3.4. EPA concludes that collection of site-specific data for estimating soil RBA is recommended for the purpose of developing site-specific clean-up levels. Please comment on the following:

e) importance of obtaining site-specific RBA data
f) acceptance of an animal model for predicting RBA in humans
g) preferred animal model(s) and standard experimental protocol that would be acceptable for determining the site-specific RBA
h) need for additional studies in rodent, swine, primate, or other species for establishing a standard animal model protocol

The report concludes that the RBA for dioxin is less than 100%, but too few soil samples have been evaluated to determine an alternative, upper bound RBA value to use as a national default. I agree with these conclusions. So the choice currently for calculation of site cleanup levels is to either use a default RBA of 100% or develop site-specific RBA data. This is basically a business decision, i.e., whether the refinement in cleanup levels afforded by incorporating site-specific RBA data is worth the cost of obtaining those data. If soil cleanup numbers are going to be adjusted based upon site-specific RBA considerations, collection of site-specific data will be required [obviously]. Models to predict site-specific dioxin RBAs based upon key site characteristics await development of a body of research in which those characteristics are identified and their relationships

with RBA quantified. It is difficult to predict how long it will take to develop that body of research.

Until predictive models can be developed, site-specific dioxin RBA information will have to be obtained empirically, i.e., through a study to estimate the dioxin RBA for soils at a given site. There is some literature on *in vitro* extraction methods to estimate dioxin bioavailability by measuring bioaccessibility, but acceptance of *in vitro* models for regulatory purposes usually requires an extensive evaluation of performance with a battery of soil samples for which RBA is known (e.g., as has been conducted for lead in soil and is underway for arsenic). An adequate suite of soils for conducting this type of evaluation for dioxin does not yet exist. This leaves, in the near term, *in vivo* studies using animal models as the only reliable means of developing defensible, site-specific RBA estimates.

Animal models are well accepted as providing useful information for predicting bioavailability in humans. The question is which animal model is best suited for studying comparative absorption of dioxin congeners from soil. This report raises that question, but does not provide a clear answer. I agree that based upon anatomical and physiological considerations, swine are more attractive than rats as a model. However, additional studies are urgently needed to resolve the animal model issue, and to establish a standard animal protocol. These studies could include limited experiments in higher order species such as primates in order to help establish relevance of the models to humans.

3.5. EPA has described two approaches to estimate RBA for congener mixtures for use in site risk assessment:

c) calculate the average RBA based on congener mass concentration in soil and congener RBA (*mass weighted RBA*)
d) calculate the average RBA based on congener TEQ concentration and congener RBA (*TEQ weighted RBA*)

What is your opinion on the relative merits and deficiencies in either approach, or on alternative approaches to estimating RBA for use in risk assessment?

The contribution of each congener toward risk is a function of both its RBA and TEQ. The TEQ weighted RBA handles this in a somewhat more transparent manner, in my opinion.

Section 4 Uncertainties Identified in the Estimation of a Dioxin Soil RBA

4.1 Has EPA clearly described the major uncertainties attending its conclusions?

The major uncertainties associated with its conclusions are clearly articulated. Discussion of the uncertainties and limitations in the current body of literature on estimation of dioxin RBA from soil is a major strength of this report.

4.2 What is your opinion on the level of uncertainty in EPA's conclusions regarding RBA?

The conclusions of the report highlight the uncertainties that exist in trying to estimate dioxin RBA from soil. These uncertainties have not been overstated, and the conclusions are sound, in my opinion.

CHARGE QUESTIONS to REVIEWERS

for Peer Review of Draft Report, "*Bioavailability of Dioxins In Soil and Soil-Like Materials: Literature Review and Data Analysis* " July 2010.

Michael E. Honeycutt, PhD**Section 1 General Charge Questions**

1.1. Is the draft document *Bioavailability of Dioxins in Soil and Soil-like Materials: Literature Review and Data Analysis* clearly written and logical?

Overall, yes. The document is generally well-written and easy to follow. I have some suggested edits.

- Page vii, line 174 – Don't start sentence with acronym; spell out
- Page vii - lines 187 through 195 refer to 13 test materials, but the bulleted text adds up to 15 test materials.
- Page vii, line 227 – "octachloro" is misspelled
- Page vii, line 230 – "octachlorodibenzofurans" is misspelled
- Page 12, line 343 – Don't start sentence with acronym; spell out
- Page 13, line 376 – "groups means" should be either "group means" or "groups' means"?
- Page 15, line 415 – "dose" should be added after "single"
- Page 16, line 445 – a semicolon should replace the period after "control"
- Page 17, line 483 – the comma after "27%" should be deleted
- Page 18, line 513 – a period is needed after "Appendix B"
- Section 3.2.4 should include soil concentrations. All the other study descriptions include soil concentrations.
- In section 3.2.7, you might include a short description of the soil decontamination process.
- Page 22, line 626 – octachloro is misspelled.

- Page 23, line 661 – delete one comma after “materials”
- Page 23, line 661 – Run on sentence. End sentence after “included” and capitalize “Most”
- Page 23, line 666 – Delete sentence starting with “Relative bioavailability….” It is already defined and this study uses the same definition of relative bioavailability.
- Page 23, line 669 – Don’t start sentence with acronym; spell out.
- Page 24, lines 670 and 671 – Don’t start sentence with acronym; spell out.
- Page 25 – Lines 686 and 694 refer to 13 test materials, but the bulleted text adds up to 15 test materials.
- Page 26, line 719 – “12.1” should be “12.2”
- Page 25, line 722 – “R^2=0.32” should be “R^2=0.34”
- Page 27, line 759 – “, respectively.” should be added after “26.6%”
- Page 28, line 770 – add “several” before “reasons”?
- Page 28, line 776 and Page 31, line 861 refer to Connor and Aylward (2006) and Flaveny et al. (2010) with no context. The context of the references are explained later in bullet 3 of section 4.2. It would be helpful to either add context the first two times the references are mention or add “(explained later)”.
- Page 28, line 787 – “18.3” should be “-18.3”
- Page 28, line 790 – “-13.9” should be “-13.07” and “R^2=0.37” should be “R^2=0.35”
- Page 28 - lines 791 and 793 mention seven test materials in Table 3, but Table 3 only contains five test materials
- Page 29, line 821 – “(TM2)” should be “(TM1)”
- Page 30, line 833 – delete “it” from after “doses”
- Page 30, line 853 – Run on sentence. End sentence after “PCCD/Fs” or change comma to semicolon.
- Page 30, line 857 – delete comma after “estimates”
- Page 31, line 867 – add a comma after “review”
- Page 31, line 868 – add “does” after “AhR”
- Page 34, line 967 – “more” should be “less”
- Page 34, line 975 – octachloro is misspelled
- Page 35, line 995 – delete “, however,”
- Page 35, line 1005 – add “do” either in front of or behind “rodent models”
- Page 38, line 1081 – don’t begin sentence with acronym
- Page 38, line 1084 – delete the comma after “reports”
- Page 39, line 1123 – delete the comma after “problematic”
- Tables 2 and 3 – add units; (%) after descriptors in left-hand column

1.2. Are the objectives of the literature review clearly stated?

Yes.

1.3 Has EPA objectively and clearly presented the rationale for its conclusions relevant to estimating the relative bioavailability (RBA) of TCDD or other PCDD/Fs in soil?

Yes. Clearly, dioxins and furans are less than 100% bioavailable, but data are not adequate to derive a nationally-applicable RBA. I absolutely agree with the conclusions.

1.4 Do you agree with EPA's major conclusions regarding RBA of TCDD or other PCDD/Fs in soil? EPA's major conclusions are as follows:

i) RBA in soil is less than 100%

Yes. I absolutely agree with this statement.

j) data currently available are not sufficient to estimate a nationally-applicable value for RBA for use in risk assessment (i.e., as an alternative to 100% or site-specific values)

Yes. I absolutely agree.

k) data currently available are not sufficient to determine the preferred animal species for use as an animal bioassay for predicting soil RBA in humans

I disagree with this statement. Swine are the preferred animal model. The fact that rats yield different results does not mean that swine are not the preferred animal model. Species differences are the norm, not the exception, in toxicology.

l) site-specific data are recommended to develop site-specific cleanup levels.

I agree with this statement. EPA should develop guidance on developing site-specific data.

If you disagree with any of the above conclusions, please comment on deficiencies in the conclusions or alternative conclusions that could be derived from the data.

1.5. Are you aware of other critical studies that would make a substantial impact on EPA's conclusions regarding RBA of TCDD and/or other PCDD/Fs?

No. Interestingly, Kimbrough et al (2010) published a similar review in Regulatory Toxicology and Pharmacology 57:43-54. The Kimbrough review is substantively very similar to the current EPA review, though the Kimbrough review did not attempt to determine a nationwide RBA.

Section 2 Transparency and Clarity in the Selection of Key Data Sets for Relative Bioavailability Analysis

2.1. Is EPA's approach for selecting key studies and data sets from the key studies scientifically justified and clearly described?

Yes.

2.2. Are the chosen data sets adequate for estimating RBA values for each tested soil in each of the studies?

Yes.

2.3. Are the data relied upon for the estimation of RBA for each tested soil in each of the studies, applied in a scientifically sound manner?

Yes.

2.4. Please comment on deficiencies, substantial inadequacies of the selected studies and data sets, and provide suggestions for existing or future studies that could inform the assessment of soil RBA.

The studies selected for review in this document are scientifically sound. Future studies should focus on soil characteristics that influence RBA.

Section 3 Use of Animal Bioassays to Estimate Relative Bioavailability

3.1. Are the animal models presented in this report appropriate for estimating RBA of TCDD and other PCDD/Fs in soil?

Yes.

Please also comment on the criteria EPA has used to evaluate the animal models:

g) similarities of physiology and anatomy of the animal model and human gastrointestinal tract

This is one of the most important factors. Differences in anatomy and physiology will have a significant downstream effect on subsequent absorption and distribution, which in turn will have a significant downstream effect on cellular, intracellular, metabolic, and elimination processes.

h) similarity of distribution of absorbed PCDD/Fs in adipose tissue relative to liver

This factor is just as, or perhaps nearly as, important as similarities in physiology and anatomy. Differences in distribution will lead to differences in cellular, intracellular, metabolic, and elimination processes.

i) Ah receptor binding, CYP450 induction, and clearance of PCDD/Fs

The upstream factors of species differences in absorption and distribution make these the least important factors.

3.2. What is your opinion of the observation that the effect of chlorine number on RBA is different in swine and rats?

e) in swine, RBA appears to increase with increasing chlorination

This makes perfect sense. This same phenomenon occurs in aquatic species.

f) in rats, RBA appears to decrease with increasing chlorination

This illustrates why rats are not a good animal model for humans and why swine are.

Please comment on how this observation conforms or conflicts with information regarding bioavailability provided by the National Academy of Science (NAS, 2006), World Health Organization (Van den Berg et al. 2006), and U.S. EPA (2003). Note that the swine studies (Budinsky et al., 2008; Wittseipe et al., 2007) included in EPA's recent literature review post-date these earlier reports.

Neither NAS, 2006, USEPA, 2003, nor Van den Bert, et al, 2006 appear to directly address the issue of differences in RBA among species as it pertains to risk assessment. Nevertheless, the present document does not conflict with the above references.

3.3. What is your opinion about the potential implications of a chlorine effect on RBA for predicting RBA in humans from animal bioassays (e.g., selection of appropriate animal model, estimation of composite RBA for a soil material containing a mix of congeners, variability in congener composition of soils)?

The effect of chlorination on RBA can be dealt with. Using the appropriate animal model (swine) for both the native soil and the appropriate solvent will control for the effect of degree of chlorination.

3.4. EPA concludes that collection of site-specific data for estimating soil RBA is recommended for the purpose of developing site-specific clean-up levels. Please comment on the following:

i) importance of obtaining site-specific RBA data

With EPA proposed new dioxin toxicity factors and PRGs, obtaining site-specific data will be very important since background levels of dioxins will likely be unacceptably high. Obtaining site-specific RBA data will be very important in delineating extent of contamination at a remediation site, as well as in deciding a remedy.

j) acceptance of an animal model for predicting RBA in humans

Swine is the best animal model for humans. A swine study is more expensive, but it is also more appropriate.

k) preferred animal model(s) and standard experimental protocol that would be acceptable for determining the site-specific RBA

Swine is the best animal model. I am not aware of a standard experimental protocol that is acceptable to EPA. EPA should develop one.

l) need for additional studies in rodent, swine, primate, or other species for establishing a standard animal model protocol.

Studies could be conducted better define an appropriate swine RBA study (dosing method, dose rate, study length, etc.).

3.5. EPA has described two approaches to estimate RBA for congener mixtures for use in site risk assessment:

e) calculate the average RBA based on congener mass concentration in soil and congener RBA (*mass weighted RBA*)
f) calculate the average RBA based on congener TEQ concentration and congener RBA (*TEQ weighted RBA*)

What is your opinion on the relative merits and deficiencies in either approach, or on alternative approaches to estimating RBA for use in risk assessment?

Van den Bert, et al, 2006 recommend the mass-weighted RBA approach as “preferable”. I have no strong opinion one way or the other.

Section 4 Uncertainties Identified in the Estimation of a Dioxin Soil RBA

4.1 Has EPA clearly described the major uncertainties attending its conclusions?

Yes. I can't think of anything else that should be addressed.

4.2 What is your opinion on the level of uncertainty in EPA's conclusions regarding RBA?

EPA elucidated the appropriate level of uncertainty in the document.

Appendix B – Peer Review Materials

DRAFT REPORT: BIOAVAILABILITY OF DIOXINS IN SOIL AND SOIL-LIKE MATERIALS

July 2010

External Peer Review Statement of Work

Background and Overview

Environmental Management Support, Inc. (EMS), under contract EP-W-07-037 with the Environmental Protection Agency's (EPA) Office of Solid Waste and Emergency Response, has been asked to obtain external, independent reviews of the draft report, *Bioavailability of Dioxins in Soil and Soil-Like Materials*.

The purpose of this peer review is to identify any technical problems, omissions, or inconsistencies in the draft report, and to obtain expert opinion as to the usefulness and appropriateness of report for its stated objectives. Your comments and recommendations will be used to revise the draft report so that the final version reflects sound technical information and guidance.

General Instructions

Your responsibilities are as follows:

- Review and execute the Peer Review Conflict of Interest Certification, and return it to EMS as soon as possible (a digital signature or scanned signature is acceptable).
- Keep track of the number of hours you spend on this peer review (and report them when you submit your invoice).
- Review the draft report in light of the charge questions at the end of this SOW and your personal experience and expertise.
- Please tie your comments as much as possible to the product, page, section, and line number(s) so we will be able to consider your comment in context.
- If you mention any additional references in your comments, please provide an electronic copy of those references, if possible, a full citation, or Internet address of where they reside.

E-mail your comments to EMS's Peer Review Manager (Diane Dopkin, diane.dopkin@emsus.com, 301-589-5318 ext. 38), on or before August 10, 2010. You may submit either a narrative sequence of comments tied to the document line number or else an annotated pdf copy of the report (using the Text Edits and Insert Comments modes), plus your specific responses to the charge questions below and any additional comments by e-mail.

We suggest you consider a number of points, covered below, but we rely on your expertise and experience to cover any aspect of report.

CHARGE QUESTIONS TO REVIEWERS

Section 1 General Charge Questions

1.1. Is the draft document *Bioavailability of Dioxins in Soils and Soil-like Materials* clearly written and logical?

1.2. Were the stated objectives clearly worded? Has EPA presented its rationale for assigning a relative bioavailability (default gastrointestinal absorption fraction) value objectively and clearly?

1.3. Are you aware of other critical studies that would make a substantial impact on the conclusions formed for assigning a default relative bioavailability (RBA) value for tetrachloro-p-dibenzodioxin (TCDD) and/or other polychlorinated dibenzodioxins and dibenzofurans (PCDD/Fs)?

Section 2 Transparency and Clarity in the Selection of Key Data Sets for Relative Bioavailability Analysis

2.1.a Is EPA's approach for selecting data sets from the key animal bioassays identified for RBA scientifically justified and clearly described?

2.1.b Is the document transparent in the rationale for selecting the data sets used to assign a bioavailability factor?

2.2. Are the primary studies scientifically justified and clearly described?

2.3.a Are the data relied upon for the estimation of relative bioavailability applied in a scientifically sound manner?

2.3.b If not, please identify and provide a rationale for alternative approaches.

2.4.a Are the chosen data sets adequate for the determination of a default RBA estimate?

2.4.b If not, please comment on vagaries, substantial inadequacies, and suggestions for existing or future studies that will meet your experiment criteria.

Section 3 The Use of Swine or/and Rodent Data to Estimate a Relative Bioavailability Factor

3.1 Swine and monkey models were used by EPA to establish RBA and 95% upper control limit (UCL) of arsenic in soil. Murine models were not considered. Monkey studies of dioxin RBA were not identified. Using precedent as the basis for selecting an appropriate animal model for estimating dioxin RBA in soil, is it appropriate to exclude murine RBA data *a priori*? Please comment.

3.2 Murine models use liver dioxin levels as a surrogate for intestinal absorption fraction. After accepting the following premises: a.) mouse aryl hydrocarbon receptor (AhR) binds TCDD with a 10-fold greater affinity than humans; b.) rat liver enzymes are induced at body burden levels an order of magnitude less than humans; and c) for chlorinated compounds like PCBs, bioaccumulation increases as degree of chlorination increases, please comment on the following question.

3.2.a Can TCDD in the rat liver be considered a reliable index for estimating oral bioavailability?

3.3 The observation that congeners do not have the same RBA values as TCDD has important implications for the application of RBA values in dioxin risk assessment. A critical contention for using swine data and excluding murine data is the response to increasing chlorination of dioxin congeners/homologues, where RBA increases in the swine model and decreases in the rat model. The marked difference for the relationship between congener chlorine content and RBA based on swine and rat assays present a conundrum and no data have been developed to explain the observations.

3.3.a Please comment.

3.3.b Can swine and rat data be combined reliably to estimate a unified dioxin soil RBA.

3.3.c What criteria did you use to provide a positive or negative response?

3.4.a Given that swine and rat dioxin soil RBA data are divergent with respect to chlorination of congeners, will it be possible to use one species or the other or both to assign congener specific RBA values?

3.4.b Does the stated preference for swine studies to determine RBA for humans have scientific merit?

3.5. EPA guidance recommends that even in cases where sufficient data exist to support default medium-specific absorption factors for a chemical, site-specific data collection may also be important. Please comment on:

3.5.a the future consideration for the importance of obtaining site-specific RBA data.

3.5.b the acceptance of animal model dioxin soil RBA as a surrogate for human RBA.

3.5.c the importance of securing funding for additional swine experiments and monkey studies for dioxin soil RBA determinations, and

3.5.d an animal model that would be acceptable for determining the site-specific value.

Section 4. Uncertainties Identified in the Estimation of a Dioxin Soil RBA

4.1 Please comment on whether EPA has clearly described the major qualitative uncertainties.

4.2 About 70 data sets were incorporated into the estimate of arsenic RBA; this review, for estimate, relied on six that were selected for the quality and relevance of information provided in each study. In most circumstances, substantial uncertainty would validate the decision to combine RBA estimates from both swine and murine studies.

Given the restricted data set in both species used to calculate RBA would you opine that uncertainty is acceptable to posit a value using swine data alone?

DRAFT 7 REPORT

BIOAVAILABILITY OF DIOXINS IN SOIL AND SOIL-LIKE MATERIALS

Prepared for:

U.S. Environmental Protection Agency, Office of Superfund Remediation and Technology Innovation, Environmental Response Team – West
Las Vegas, NV 89119
Bill Albrecht, Work Assignment Manager, SERAS-067

Prepared by:

SRC, Inc.
Chemical, Biological, and Environmental Center
6502 Round Pond Road
North Syracuse, NY 13212

August 13, 2010

TABLE OF CONTENTS

LIST OF TABLES ix

LIST OF FIGURES ix

LIST OF APPENDICES ix

ABBREVIATIONS AND ACRONYMS x

EXECUTIVE SUMMARY xi

Objectives xi

Results xii

Conclusions xv

1.0 INTRODUCTION 16

1.1 Background 16

2.0 METHODS 17

2.1 Literature Search Strategy 17

2.2 Data Analyses 17

3.0 RESULTS 20

3.1 General Features of RBA Studies 20

3.2 Summary of Studies 20

3.2.1 Bonaccorsi et al. (1984) Rabbit Study 21

3.2.2 Budinsky et al. (2008) Swine and Rat Studies 21

3.2.3 Finley et al. (2009) Rat Study 23

3.2.4 Lucier et al. (1986) Rat Study 24

3.2.5 McConnell et al. (1984) Guinea Pig Study 24

3.2.6 Shu et al. (1988) Rat Study 25

3.2.7 Umbreit et al. (1986) Guinea Pig Study 26

3.3.8 Wendling et al. (1989) Guinea Pig Study 27

3.2.9 Wittsiepe et al. (2007) Swine Study 28

4.0 DISCUSSION 30

4.1 Analysis for Multiple Congener RBA Estimates 31

4.1.1 Multiple Congener RBA Estimates in Swine 31

4.1.2 Multiple Congener RBA Estimates in Rats 33

4.2 Comparison of Swine and Rat RBA Estimates 34

4.3 Influence of Dose on RBA Estimates for 2,3,7,8-TCDD 36

4.4 Implications for Risk Assessment 37

5.0 SUMMARY AND CONCLUSIONS 39

5.1 Summary of Findings 39

5.2 Uncertainties in RBA Estimates 42

5.3 Conclusions 44

6.0 REFERENCES 46

LIST OF TABLES

Table 1. Summary of RBA Studies of Dioxins in Soil 49
Table 2. Summary Statistics for Multiple Congener RBA Estimates in Swine..... 52
Table 3. Summary Statistics for Multiple Congener RBA Estimates in Rats 53
Table 4. Comparison of RBA Estimates for Swine and Rats in Identical Test Materials 54

LIST OF FIGURES

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) 55
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)..... 56
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). 57

LIST OF APPENDICES

Appendix A – Literature Search Product: Bioavailability of Dioxins in Soil A-1
Appendix B – RBA Data B-1

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	heptachlorodibenzofurn
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
PCDD	polychlorinated dibenzo-p-dioxin
PCDF	polychlorinated dibenzofuran
PeCD	pentachloro-p-dibenzodioxin
pg	picogram
PeCF	pentachlorodibenzofurn
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	tetrachlorodibenzofurn
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 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 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.

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.

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. RBA 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 13 test materials (soil from recognized dioxin impacted sites) 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 of the 6 studies estimated RBA for multiple congeners with varying chlorination in 8 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%.

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 PCCD/Fs and have concluded that higher chlorinated congeners tend to be less bioavailable than the more 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 toxicity equivalents (TEQ). For example, based on the swine RBA assays, octochloro-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 octochlorodibenzofurans (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, and differences in the estimates based on swine and rat assays.

   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. Nevertheless, were adequate data available from swine assays, reliance on swine RBA estimates, as opposed to rat RBA estimates, would be appealing for several reasons. Similarities between the physiology and anatomy of the swine and human gastrointestinal tracts make swine a preferable model for predicting RBA in humans than rodent models (USEPA 2007). Swine and rats also differ in the distribution of absorbed PCCD/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).

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.

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.

4. Until an applicable value for dioxin RBA can be established, collection of site-specific data on RBA is recommended to inform cleanup decisions.

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 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 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:

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

5. 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%.

6. 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.

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:

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

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

- 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).

- 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

RBA 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:

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

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

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 (2006). Only the groups 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 (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 PCCD/F was 122 pg TEQ/kg bw/day for the urban soil and 313 pg TEQ/kg bw/day for the flood plain 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 PCCD/F was 577 pg TEQ/kg bw/day for the urban soil and 2100 pg TEQ/kg bw/day for the flood plain soil.

RBA 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 was passed through a 60-gauge sieve before assay. 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, CDFs, 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 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).

3.3.8 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 octochloro-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%.

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 I-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. Relative bioavailability was calculated as the ratio of the bioavailability in soil to the bioavailability in 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. RBAs for

PCDDs were 26.4% (liver), 27.3% (adipose tissue), and 23.2% (total tissues). RBAs for PCDFs were 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

Data from a subset of the nine reviewed studies were selected for further analyses of RBA for dioxins in soil. Six studies were selected based 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 6 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 are 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 the 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

RBA estimates for multiple congeners were reported for three test materials based on assays conducted in swine (Budinsky et al. 2008; Wittsiepe et al. 2007). 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 12.1). RBA 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, $R^2=0.32$, $p=0.0013$). 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 RBA 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%. 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.

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. Nevertheless, were adequate data available from swine assays, reliance on swine RBA estimates, rather than on rat RBA estimates, would be appealing for reasons. Similarities between the physiology and anatomy of the swine and human gastrointestinal tracts make swine a preferable model for predicting RBA in humans than rodent models (USEPA 2007). Swine and rats also differ in the distribution of absorbed PCCD/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). Using rat liver dioxin burden as a biomarker may have other more important implications when Connor and Aylward (2006) and Flaveny et al. (2010) studies on AhR binding are considered.

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 ($\exists = -13.9$, $R^2=0.37$, $p<0.0001$), 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 seven 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 (TM2) 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 it 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 PCCD/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 (see Section 4 for further discussion of this issue). Using rat liver dioxin burden as a biomarker may have other important implications if Connor and Aylward (2006) and Flaveny et al. (2010) are considered.

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 physiological 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 (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 are consistent with higher binding affinity and support the hypothesis that the human AhR is less functional than the AhR of the more sensitive laboratory animals at a molecular level as explained comparing enzyme induction to TEQ/kg bw (Connor and Aylward 2006). Flaveny (2010) elegantly explains the substantial differences between the mouse and human AhR and structural factors related to lower human AhR affinity for TCDD.

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).

4.4 Implications for Risk Assessment

The observation that congeners do not have the same RBA has important implications for the application of RBA values in dioxin risk assessment. Currently, dioxin risk 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):

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

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

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):

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

where RBA_i is the soil RBA for congener i.

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

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

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

The RBA estimates used in the calculation of TEQ (Equation 8) would be those for the individual congeners and the sum of the products $C_i \times RBA_i$ would 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) would be the RBA for total TEQ in the soil. The latter would 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 would be expected to be relatively constant for soil having identical characteristics. On this basis, it would appear that the preferred approach to developing site-specific soil cleanup levels would be to determine RBA values for specific congeners and apply them in risk assessments in a computation similar to Equation 8.

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%.

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 that higher chlorinated congeners tend to be less bioavailable than the more 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, octochloro-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 octochlorodibenzofurans (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, however, 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. Nevertheless, were adequate data available from swine assays, reliance on swine RBA estimates, as opposed to rat RBA estimates, would be appealing for several reasons. Similarities between the physiology and anatomy of the swine and human gastrointestinal tracts make swine a preferable model for predicting RBA in humans than rodent models (USEPA 2007). Swine and rats also differ in the distribution of absorbed PCCD/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).

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.

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 gastrointestional 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. 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 Uncertainties in RBA Estimates

Several important uncertainties would apply to any risk assessment applications of the RBA estimates provided in this report.

1. 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. As a result, site-specific RBA assessments may be preferable to application of a range and upper bound value based on this limited data set.

2. 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.

3. Estimates of RBA based on both the swine and rat assays show significant association between chlorine content of dioxin congeners and RBA. 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 preferred approach for risk assessment 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.

4. RBA 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).

5. 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 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 encourages the collection of site-specific data for the purpose of informing decision making at specific sites.

5.3 Conclusions

Collectively, 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%. 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, and differences in the estimates based on swine and rat assays. 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 currently the available data to be insufficient for determining a preferred animal model, or bioassay protocol for predicting soil RBA in humans. Thus, until such time that a nationally-applicable value for dioxin RBA can be

established, collection of site-specific data is recommended to inform site-specific cleanup decisions.

6.0 REFERENCES

ATSDR (Agency for Toxic Substances and Disease Registry). 1998. Toxicological Profile for Chlorinated Dibenzo-p-Dioxins. Centers for Disease Control and Prevention, Agency for Toxic Substances and Disease Registry. Atlanta, GA. Available online from: http://www.atsdr.cdc.gov/ToxProfiles/tp.asp?id=366&tid=63.

Bonaccorsi A, diDomenico A, Fanelli R, Merlin F, Motta R, Vanzati R, Zapponi GA. 1984. The influence of soil particle adsorption on 2,3,7,8-tetrachlorodibenzo-p-dioxin biological uptake in the rabbit. Disease, metabolism, and reproduction in the toxic response to drugs and other chemicals. Arch Toxicol Suppl 7:431–434.

Budinsky RA, Rowlands JC, Casteel S, Fent G, Cushing CA, Newsted J, Giesy JP, Ruby MV, Aylward LL. 2008. A pilot study of oral bioavailability of dioxins and furans from contaminated soils: Impact of differential hepatic enzyme activity and species differences. Chemosphere 70(10):1774–1786.

Connor KT, Aylward LL 2006. Human response to dioxin: aryl hydrocarbon receptor (AhR) molecular structure, function, and dose-response data for enzyme induction indicate an impaired human AhR. J Toxicol Environ Health B Crit Rev. 9(2):147–171.

Finley B, Fehling K, Warmerdam J, Morinello EJ. 2009. Oral bioavailability of polychlorinated dibenzo-p-dioxins/dibenzofurans in industrial soils. Hum Ecol Risk Assess 15:1146–1167.

Flaveny CA, Murray IA, Perdrew GH. 2010. Differential gene regulation by the human and mouse aryl hydrocarbon receptor. Toxicol Sci 114(2):217–325.

Lucier GW, Rumbaugh RC, McCoy Z, Hass R, Harvan D, Albro P. 1986. Ingestion of soil contaminated with 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) alters hepatic enzyme activities in rats. Fundam Appl Toxicol 6:364–371

McConnell EE, Lucier GW, Rumbaugh RC, Albro PW, Harvan DJ, Hass JR, Harris MW. 1984. Dioxin in soil: Bioavailability after ingestion by rats and guinea pigs. Science 223:1077–1079.

NAS (National Academy of Science). 2006. Health Risks from Dioxin and Related Compounds: Evaluation of the EPA Reassessment. National Academy Press.

Piper WN, Rose JQ, Gehring PJ. 1973. Excretion and tissue distribution of 2,3,7,8-tetrachlorodibenzo-p-dioxin in the rat. Environ Health Perspect 5:241–244.

Poiger H, Schlatter C. 1980. Influence of solvents and adsorbents on dermal and intestinal absorption of TCDD. Food Cosmet Toxicol 18:477–481.

Ramadoss P, Perdew GH 2004. Use of 2-azido-3-[125I]iodo-7,8-dibromodibenzo-p-dioxin as a probe to determine the relative ligand affinity of human versus mouse aryl hydrocarbon receptor in cultured cells. Mol Pharmacol 66(1):129–136.

Rivest J, Bernier JF, Pomar C. 2000. A dynamic model of protein digestion in the small intestine of pigs. J Anim Sci 78:328–340.

Ruby MV, Fehling KA, Paustenbach DJ, Landenberger BD, Holsapple MP. 2002. Oral bioaccessibility of dioxins/furans at low concentrations (50-350 ppt toxicity equivalent) in soil. Environ Sci Technol 36(22):4905–4911.

Shu H, Paustenbach D, Murray FJ, Marple L, Brunck B, Rossi DD, Teitelbaum P. 1988. Bioavailability of soil-bound TCDD: Oral bioavailability in the rat. Fund Appl Toxicol 10:648–654.

Thoma H, Mucke W, Kretschmer E. 1989. Concentrations of PCDD and PCDF in human fat and liver samples. Chemosphere 18:491–498.

Thoma H, Mucke W, Kuert G. 1990. Concentrations of polychlorinated dibenzo-p-dioxin and dibenzofuran in human tissue and human liver. Chemosphere 20:433–442.

Tuleu C, Andrieux C, Boy P, Chaumeil JC. 1999. Gastrointestinal transit of pellets in rats: Effect of size and density. Int J Pharm 180(1):123–131.

Umbreit TH, Hesse EJ, Gallo MA. 1986. Bioavailability of dioxin in soil from a 2,4,5-T manufacturing site. Science 232:497–499.

USEPA (U.S. Environmental Protection Agency). 1989. Risk Assessment Guidance for Superfund: Volume III - Part A, Process for Conducting Probabilistic Risk Assessment. Office of Emergency and Remedial Response, U.S. Environmental Protection Agency, Washington, DC.

USEPA (U.S. Environmental Protection Agency**)**. 2003. Exposure and Human Health Reassessment of 2,3,7,8-Tetrachlorodibenzo-p-Dioxin (TCDD) and Related Compounds. National Center for Environmental Assessment
Research and Development, U.S. Environmental Protection Agency, Washington, DC. December 2003, NAS Review Draft (available at www.epa.gov/ncea/dioxin).

USEPA (U.S. Environmental Protection Agency). 2007. Estimation of Relative Bioavailability of Lead in Soil And Soil-Like Materials Using *In Vivo* and *In Vitro* Methods. Office of Solid Waste and Emergency Response, U.S. Environmental Protection Agency, Washington, DC 20460. OSWER 9285.7-77.

Van den Berg M, Birnbaum LS, Denison M, De Vito M, Farland W, Feeley M, Fiedler H, Hakansson H, Hanberg A, Haws L, Rose M, Safe S, Schrenk D, Tohyama C, Tritscher A, Tuomisto J, Tysklind M, Walker N, Peterson RE. 2006. The 2005 World Health Organization re-

evaluation of human and mammalian toxic equivalency factors for dioxins and dioxin-like compounds. Toxicol Sci 93(2):223–241.

WASDE (Washington State, Department of Ecology). 2007. Relative Bioavailability Estimates for Dioxins/Furans in Soil. Discussion paper prepared for USEPA Science Advisory Board. March 2007.

Wendling T, Hileman F, Orth R, Umbreit T, Hesse, Gallo M. 1989. An analytical assessment of the bioavailability of dioxin contaminated soils to animals. Chemosphere 18:925–932.

Wittsiepe J, Erlenkamper B, Welge P, Hack A, Wilhelm M. 2007. Bioavailability of PCDD/F from contaminated soil in young Goettingen mini-pigs. Chemosphere 67(9):S355–S36.

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, pictogram; 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

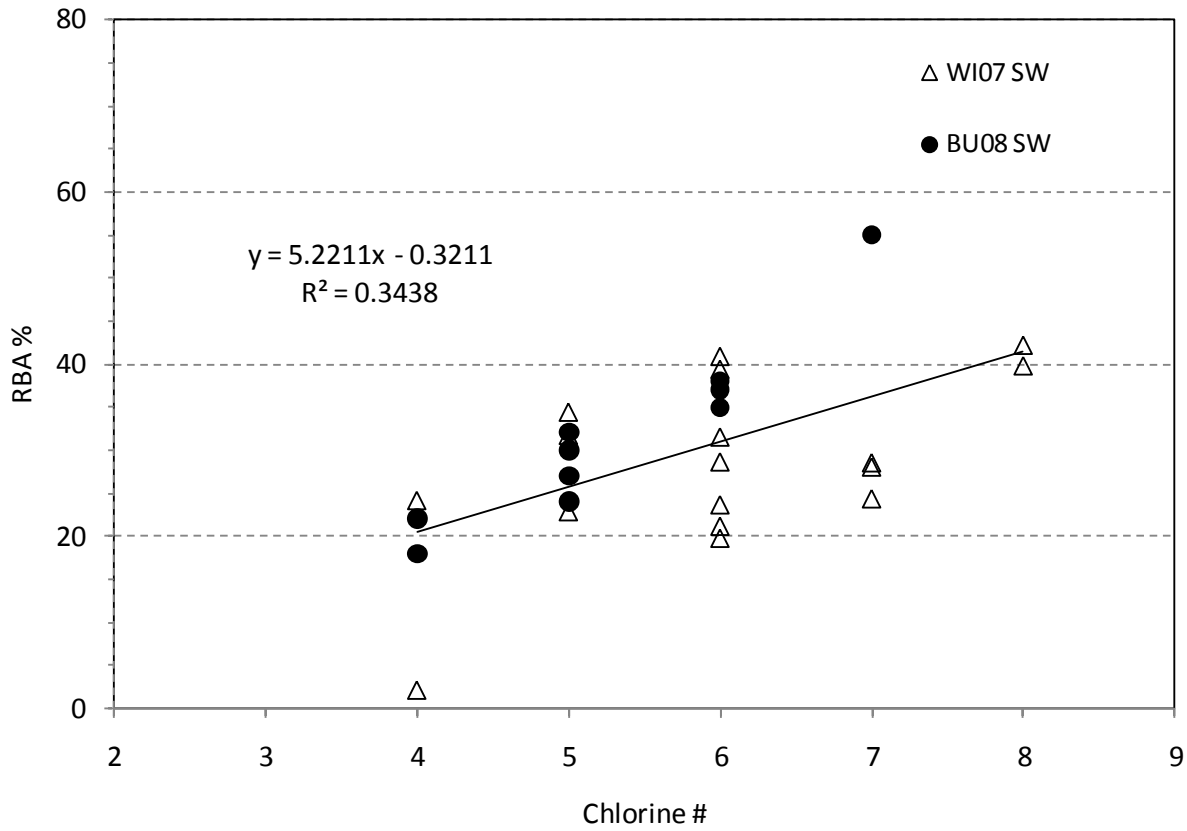

Figure 1. Relationship between congener chlorine content (mole chlorine/mole congener) and RBA based on swine assays of three test materials (Budinsky et al. 2008, BU08; Wittsiepe et al. 2007, WI07). The regression equation is for the combined data from both studies; regression coefficients for the individual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

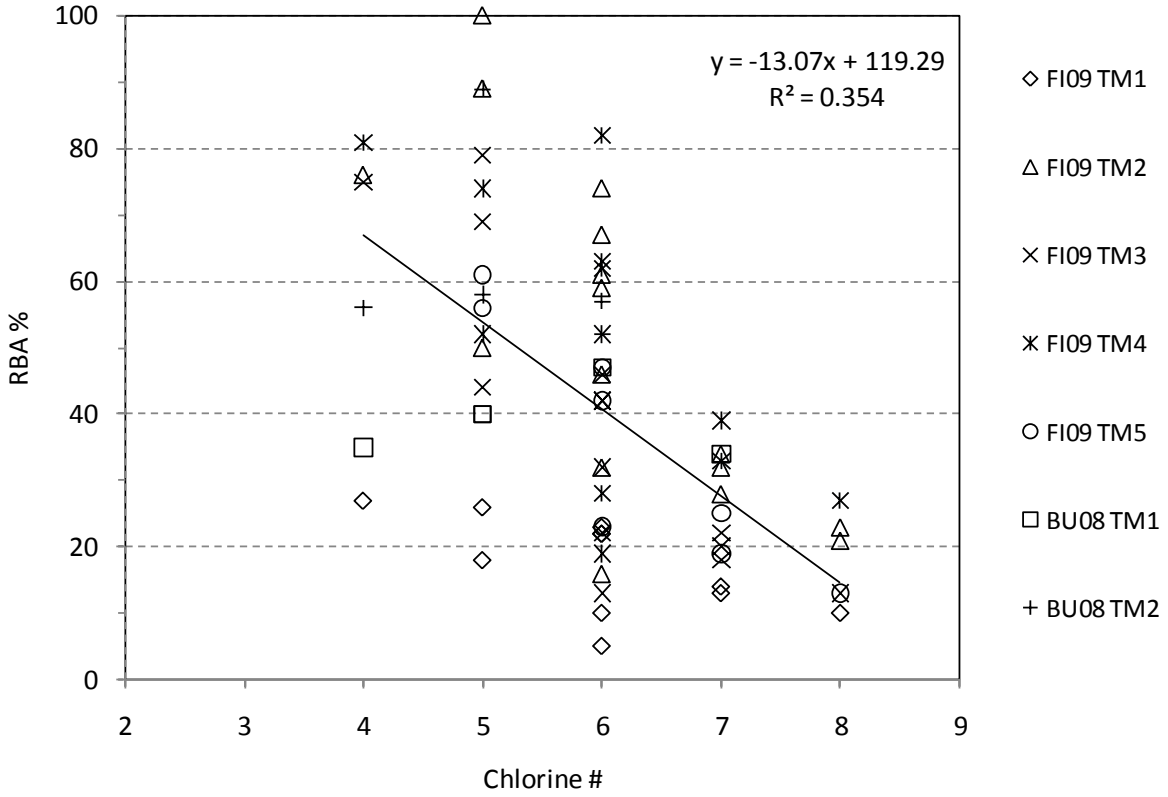

Figure 2. Relationship between congener chlorine content (mole chlorine/mole congener) and RBA based on rat assays of seven test materials (Budinsky et al. 2008, BU08; Finley et al. 2009, FI09). The regression equation is for the combined data from both studies; regression coefficients for the individual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

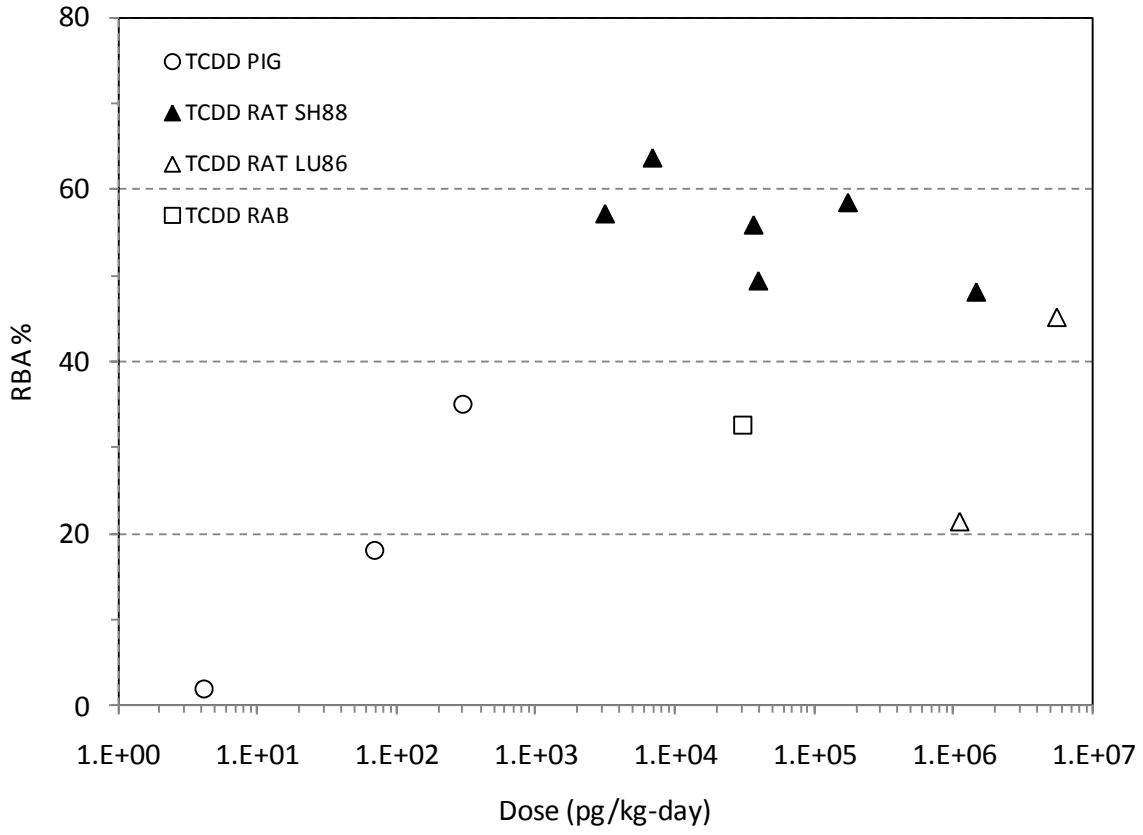

Figure 3. Relationship between 2,3,7,8-TCDD dose (pg/kg bw/day) and RBA based on swine, rat, and rabbit assays of six test materials (Bonaccorsi et al. 1984; Budinsky et al. 2008; Lucier et al. 1986; Shu et al. 1988; Wittsiepe et al. 2007).

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
U.S. Environmental Protection Agency
Washington, DC 20408

Prepared by:

Julie Klotzbach
SRC, Inc.
Chemical, Biological, and Environmental Center
6502 Round Pond Road
North Syracuse, NY 13212

January 5, 2010

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).

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

where *TEQ* is the 2,4,7,8-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):

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

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

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):

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

   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 2,4,7,8-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):

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

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

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

Abraham K, Hille A, Ende M, et al. 1994. Intake and fecal excretion of PCDDs, PCDFs, HCB and PCBs (138,153,180) in a breast-fed and a formula-fed infant. Chemosphere 29:2279–2286.

Abraham K, Knoll A, Ende M, et al. 1996. Intake, fecal excretion, and body burden of polychlorinated dibenzo-p-dioxins and dibenzofurans in breast-fed and formula-fed infants. Pediatr Res 40:671–679.

Dahl P, Lindstrom G, Wiberg K, et al. 1995. Absorption of polychlorinated biphenyls, dibenzo-p-dioxins and dibenzofurans by breast-fed infants. Chemosphere 30:2297–2306.

McLachlan MS. 1993. Digestive tract absorption of polychlorinated dibenzo-p-dioxins, dibenzofurans, and biphenyls in a nursing infant. Toxicol Appl Pharmacol 123:68–72.

Pluim HJ, Wever J, Koppe JG, et al. 1993. Intake and faecal excretion of chlorinated dioxins and dibenzofurans in breast-fed infants at different ages. Chemosphere 26:1947–1952.

Poiger H, Schlatter C. 1986. Pharmacokinetics of 2,3,7,8-TCDD in man. Chemosphere 15:1489–1494.

Rohde S, Moser GA, Papke O, et al. 1999. Clearance of PCDD/Fs via the gastrointestinal tract in occupationally exposed persons. Chemosphere 38(14):3397–3410.

Schlummer M, Moser GA, McLachlan MS. 1998. Digestive tract absorption of PCDD/Fs, PCBs, and HCB in humans: Mass balances and mechanistic considerations. Toxicol Appl Pharmacol 152(1):128–137.

2.0 Bioavailability and Pharmacokinetics Studies in Animals

2.1 Soil

<u>Rats</u>

Budinsky RA, Rowlands JC, Casteel S, et al. 2008. A pilot study of oral bioavailability of dioxins and furans from contaminated soils: Impact of differential hepatic enzyme activity and species differences. Chemosphere 70(10):1774–1786.

McConnell EE, Lucier GW, Rumbaugh RC, et al. 1984. Dioxin in soil: Bioavailability after ingestion by rats and guinea pigs. Science 223:1077–1079.

Guinea Pigs

McConnell EE, Lucier GW, Rumbaugh RC, et al. 1984. Dioxin in soil: Bioavailability after ingestion by rats and guinea pigs. Science 223:1077–1079.

Umbreit TH, Hesse EJ, Gallo MA. 1986a. Bioavailability of dioxin in soil from a 2,4,5-T manufacturing site. Science 232:497–499.

Swine

Budinsky RA, Rowlands JC, Casteel S, et al. 2008. A pilot study of oral bioavailability of dioxins and furans from contaminated soils: Impact of differential hepatic enzyme activity and species differences. Chemosphere 70(10):1774–1786.

Wittsiepe J, Erlenkamper B, Welge P, et al. 2007. Bioavailability of PCDD/F from contaminated soil in young Goettingen mini-pigs. Chemosphere 67(9):S355–S364.

Cows

Jones D, Safe E, Morcum E, et al. 1989. Bioavailability of grain and soil-borne tritiated 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) administered to lactating Holstein cows. Chemosphere 18:1257–1263.

Chickens

Petreas M, Ruble R, Visita P, et al. 1996. Bioaccumulation of PCDD/Fs from soil by foraging chickens. Organohalogen Compounds 29:51–54.

2.2 Other Media

Rats

Abraham K, Weberrub U, Wiesmuller T, et al. 1989a. Comparative studies on absorption and distribution in the liver and adipose tissue of PCDDs and PCDFs in rats and marmoset monkeys. Chemosphere 19:887–892.

Abraham K, Wiesmuller T, Brunner H, et al. 1989b. Absorption and tissue distribution of various polychlorinated dibenzo-p-dioxins and dibenzofurans (PCDDs and PCDFs) in the rat. Arch Toxicol 63:193–202.

Abraham K, Wiesmuller T, Brunner H, et al. 1989c. Elimination of various polychlorinated dibenzo-p-dioxins and dibenzofurans (PCDDs and PCDFs) in rat feces. Arch Toxicol 63:75–78.

Allen JR, Van Miller JP, Norback DH. 1975. Tissue distribution, excretion and biological effects of [14C]tetrachlorodibenzo-p-dioxin in rats. Food Cosmet Toxicol 13:501–505.

Birnbaum LS, Couture LA. 1988. Disposition of octachlorodibenzo-p-dioxin (OCDD) in male rats. Toxicol Appl Pharmacol 93:22–30.

Chen CY, Hamm JT, Hass JR, et al. 2001. Disposition of polychlorinated dibenzo-p-dioxins, dibenzofurans, and non-ortho polychlorinated biphenyls in pregnant Long Evans rats. Toxicol Appl Pharmacol 173(2):65–88.

Diliberto JJ, Jackson JA, Birnbaum LS. 1996. Comparison of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) disposition following pulmonary, oral, dermal and parenteral exposures to rats. Toxicol Appl Pharmacol 138:158–168.

Diliberto JJ, Kedderis LB, Jackson JA, et al. 1993. Effects of dose and routes of exposure on the disposition of 2,3,7,8-((3)H)tetrabromodibenzo-p-dioxin (TBDD) in the rat. Toxicol Appl Pharmacol 120(2):315–326.

Fries GF, Marrow GS. 1975. Retention and excretion of 2,3,7,8-tetrachlorodibenzo-p-dioxin by rats. J Agric Food Chem 23:265–269.

Hakk H, Larsen G, Feil V. 2001. Tissue distribution, excretion, and metabolism of 1,2,7,8-tetrachlorodibenzo-p-dioxin in the rat. Chemosphere 42(8):975–983.

Hebert CD, Birnbaum LS. 1987. The influence of aging on intestinal absorption of TCDD in rats. Toxicol Lett 37:47–55.

Hurst CH, DeVito MJ, Birnbaum LS. 2000. Tissue disposition of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) in maternal and developing Long-Evans rats. Toxicol Sci 57(2):275–283.

Huwe JK, Feil VJ, Larsen GL, et al. 1998. Metabolism and disposition of 1,4,7,8-tetrachlorodibenzo-p-dioxin in rats. Chemosphere 37(9-12):1885–1893. Erratum in: Chemosphere 38(8):1957–1958.

Kedderis LB, Diliberto JJ, Jackson JA, et al. 1992. Effects of dose and route of exposure on dioxin disposition. Chemosphere 25(1-2):7–10.

Krowke R, Chahoud I, Baumann-Wilschke I, et al. 1989. Pharmacokinetics and biological activity of 2,3,7,8-tetrachlorodibenzo-p-dioxin: 2. Pharmacokinetics in rats using a loading-dose/maintenance-dose regime with high doses. Arch Toxicol 63:356–360.

Lakshmanan MR, Campbell BS, Chirtel SJ, et al. 1986. Studies on the mechanism of absorption and distribution of 2,3,7,8-tetrachlorodibenzo-p-dioxin in the rat. J Pharmacol Exp Ther 239:673–677.

Li X, Weber LWD, Rozman KK. 1995. Toxicokientics of 2,3,7,8-tetrachlorodibenzo-p-dioxin in female Sprague-Dawley rats including placental and lactational transfer to fetuses and neonates. Fund Appl Toxicol 27:70–76.

Norback DH, Engblom JF, Allen JR. 1975. Tissue distribution and extraction of octachlorodibenzopara-dioxin in the rat. Toxicol Appl Pharmacol 32:330–338.

Piper WN, Rose RQ, Gehring PJ. 1973. Excretion and tissue distribution of 2,3,7,8-tetrachlorodibenzo-p-dioxin in the rat. Environ Health Perspect 5:241–244.

Poiger H, Schlatter C. 1980. Influence of solvents and adsorbents on dermal and intestinal absorption of TCDD. Food Cosmet Toxicol 18:477–481.

Rose JQ, Ramsey JC, Wentzler TH, et al. 1976. The fate of 2,3,7,8-tetrachlorodibenzo-p-dioxin following single and repeated oral doses to the rat. Toxicol Appl Pharmacol 36:209–226.

Van den Berg M, Olie K, Hutzinger O. 1983. Uptake and selection in rats of orally administered chlorinated dioxins and dibenzofurans from fly-ash and fly-ash extract. Chemosphere 12:537–544.

Van den Berg M, de Vroom E, van Greevenbroek M, et al. 1985. Bioavailability of PCDDs and PCDFs absorbed on fly ash in rat, guinea pig and Syrian golden hamster. Chemosphere 14:865–869.

Van den Berg M, Van Greevenbroek M, Olie K, et al. 1986. Bioavailability of polychlorinated dibenzo-p-dioxins and polychlorinated dibenzofurans on fly ash after semi-chronic oral ingestion by the rat. Chemosphere 15:509–518.

Van den Berg M, Sinke M, Wever H. 1987. Vehicle dependent bioavailability of polychlorinated dibenzo-p-dioxins (PCDDs) and dibenzofurans (PCDFs) in the rat. Chemosphere 16:1193–1203.

Wacker R, Poiger H, Schlatter C. 1986. Pharmacokinetics and metabolism of 1,2,3,7,8-pentachlorodibenzo-p-dioxin in the rat. Chemosphere 15:1473–1476.

Mice

Gasiewicz TA, Geiger LE, Rucci G, et al. 1983. Distribution, excretion, and metabolism of 2,3,7,8-tetrachlorodibenzo-p-dioxin in C57BL/6J, DBA/2J, and B6D2F1/J mice. Drug Metab Dispos 11:397–403.

Koshakji RP, Harbison RD, Bush MT. 1984. Studies on the metabolic fate of [14C]2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) in the mouse. Toxicol Appl Pharmacol 73:69–77.

Guinea Pigs

Gasiewicz TA, Neal RA. 1979. 2,3,7,8-Tetrachlorodibenzo-p-dioxin tissue distribution, excretion, and effects on clinical parameters in guinea pigs. Toxicol Appl Pharmacol 51:329–339.

Nolan RJ, Smith FA, Hefner JG. 1979. Elimination and tissue distribution of 2,3,7,8-tetrachlorodibenzo- p-dioxin (TCDD) in female guinea pigs following a single oral dose. Toxicol Appl Pharmacol 48:A162.

Olson JR. 1986. Metabolism and disposition of 2,3,7,8-tetrachlorodibenzo-p-dioxin in guinea pigs. Toxicol Appl Pharmacol 85:263–273.

Olson JR, Gasiewicz TA, Neal RA, et al. 1980. Tissue distribution excretion, and metabolism of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) in the Golden Syrian Hamster. Toxicol Appl Pharmacol 56:78–85.

Poiger H, Weber H, Schlatter CH. 1982. Special aspects of metabolism and kinetics of TCDD in dogs and rats: Assessment of toxicity of TCDD-metabolites(s) in guinea pigs. In: Hutzinger O, Frei RW, Merian E, et al., eds. Chlorinated dioxins and related compounds: Impact on the environment. New York, NY: Pergamon Press, 317–325.

Van den Berg M, de Vroom E, van Greevenbroek M, et al. 1985. Bioavailability of PCDDs and PCDFs absorbed on fly ash in rat, guinea pig and Syrian golden hamster. Chemosphere 14:865–869.

Hamsters

Van den Berg M, de Vroom E, van Greevenbroek M, et al. 1985. Bioavailability of PCDDs and PCDFs absorbed on fly ash in rat, guinea pig and Syrian golden hamster. Chemosphere 14:865–869.

Swine

Cavret S, Laurent C, Feidt C, et al. 2003. Intestinal absorption of ^{14}C from ^{14}C-phenanthrene, ^{14}C-benzo[a]pyrene and ^{14}C-tetrachlorodibenzo-para-dioxin. Reprod Nutr Dev 43(2):145–154.

Laurent C, Feidt C, Grova N, et al. 2002. Portal absorption of ^{14}C after ingestion of spiked milk with ^{14}C-phenanthrene, ^{14}C-benzo[a]pyrene or ^{14}C-TCDD in growing pigs. Chemosphere 48(8):843–848.

Cows

Feil VJ, Huwe JK, Zaylskie RG, et al. 2000. Chlorinated dibenzo-p-dioxin and dibenzofuran concentrations in beef animals from a feeding study. J Agric Food Chem 48:6163–6173.

Richter W, McLachlan MS. 2001. Uptake and transfer of PCDD/Fs by cattle fed naturally contaminated feedstuffs and feed contaminated as a result of sewage sludge application. 2. Nonlactating cows. J Agric Food Chem 49:5857–5865.

Slob W, Olling M, Derks JJGM, et al. 1995. Congener-specific bioavailability of PCDD/Fs and co-planar PCBs in cows: Laboratory and field measurements. Chemosphere 31:3827–3838.

Monkeys

Abraham K, Weberrub U, Wiesmuller T, et al. 1989a. Comparative studies on absorption and distribution in the liver and adipose tissue of PCDDs and PCDFs in rats and marmoset monkeys. Chemosphere 19:887–892.

3.0 Toxicity Studies of Dioxin in Soil in Animals

Rats

Lucier GW, Rumbaugh RC, McCoy Z, et al. 1986. Ingestion of soil contaminated with 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) alters hepatic enzyme activities in rats. Fundam Appl Toxicol 6:364–371.

Mice

Umbreit TH, Hesse EJ, Gallo MA. 1987. Reproductive toxicity in female mice of dioxin-contaminated soils from a 2,4,5-trichlorophenoxyacetic acid manufacturing site. Arch Environ Contam Toxicol 16:461–466.

Umbreit TH, Hesse EJ, Gallo MA. 1988. Reproductive studies of C57B/6 male mice treated with TCDD-contaminated soils from a 2,4,5-trichlorophenoxyacetic acid manufacturing site. Arch Environ Contam Toxicol 17:145–150.

Guinea Pigs

Umbreit TH, Patel D, Gallo MA. 1985. Acute toxicity of TCDD contaminated soil from an industrial site. Chemosphere 14:945–947.

Umbreit TH, Hesse EJ, Gallo MA. 1986. Comparative toxicity of TCDD contaminated soil from Times Beach, Missouri, and Newark, New Jersey. Chemosphere 15:2121–2124.

4.0 *In Vitro* Bioaccessibility

Cavret S, Laurent C, Feidt C, et al. 2003. Intestinal absorption of ^{14}C from ^{14}C-phenanthrene, ^{14}C-benzo[a]pyrene and ^{14}C-tetrachlorodibenzo-para-dioxin. Reprod Nutr Dev 43(2):145–154.

Ruby MV, Fehling KA, Paustenbach DJ, et al. 2002. Oral bioaccessibility of dioxins/furans at low concentrations (50-350 ppt toxicity equivalent) in soil. Environ Sci Technol 36(22):4905–4911.

5.0 PBPK Modeling

Carrier G, Brunet RC, Brodeur J. 1995. Modeling of the toxicokinetics of polychlorinated dibenzo-p-dioxins and dibenzofurans in mammalians, including humans. II. Kinetics of absorption and disposition of PCDD/Fs. Toxicol Appl Pharmacol 131:267–276.

Kerger BD, Leung HW, Scott PK, et al. 2007a. An adaptable internal dose model for risk assessment of dietary and soil dioxin exposures in young children. Toxicol Sci 100(1):224–237.

Kerger BD, Leung HW, Scott PK, et al. 2007b. Refinements on the age-dependent half-life model for estimating child body burdens of polychlorodibenzodioxins dibenzofurans. Chemosphere 67(9):S272–S278.

Leung H-W, Ku RH, Paustenbach DJ, et al. 1988. A physiologically based pharmacokinetic model for 2,3,7,8-tetrachlorodibenzo-p-dioxin in C57BL/6J and DBA/2J mice. Toxicol Letters 42:15–28.

Leung H-W, Paustenbach DJ, Murray FJ, et al. 1990. A physiological pharmacokinetic description of the tissue distribution and enzyme-inducing properties of 2,3,7,8-tetrachlorodibenzo-p-dioxin in the rat. Toxicol Appl Pharmacol 103:399–410.

Maruyama W, Yoshida K, Tanaka T, et al. 2002. Determination of tissue-blood partition coefficients for a physiological model for humans, and estimation of dioxin concentration in tissues. Chemosphere 46:975–985.

Wang X, Santostefano MJ, Evans MV, et al. 1997. Determination of parameters responsible for pharmacokinetic behavior of TCDD in female Sprague-Dawley rats. Toxicol Appl Pharmacol 147(1):151–168.

6.0 Risk Assessments

Ahlborg UG, Hanberg A. 1992. Toxicokinetics of PCDDs and PCDFs of importance to the development of human risk assessment. Toxic Substances Journal 12:197–211.

DeVito MJ, Birnbaum LS. 1995. The importance of pharmacokinetics in determining the relative potency of 2,3,7,8-tetrachlorodibenzo-p-dioxin and 2,3,7,8-tetrachlorodibenzofuran. Fundam Appl Toxicol 24:145–148.

Eschenroeder A, Jaeger RJ, Ospital JJ, et al. 1986. Health risk analysis of human exposures to soil amended with sewage sludge contaminated with polychlorinated dibenzodioxins and dibenzofurans. Vet Hum Toxicol 28:435–442.

Gough M. 1991. Human exposure from dioxin in soil-a meeting report. J Toxicol Environ Health 32:205–245.

Kimbrough RD, Falk H, Stehr P, et al. 1984. Health implications of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) contamination of residential soil. J Toxicol Environ Health 14:47–93.

Paustenbach DJ, Shu HP, Murray FJ. 1986. A critical examination of assumptions used in risk assessments of dioxin contaminated soil. Regul Toxicol Pharmacol 6:284–307.

Paustenbach DJ, Wenning RJ, Lau V, et al. 1992. Recent developments on the hazards posed by 2,3,7,8-tetrachlorodibenzo-p-dioxin in soil: Implications for setting risk-based cleanup levels at residential and industrial sites. J Toxicol Environ Health 36(2):103–150.

Paustenbach DJ, Fehling K, Scott P, et al. 2006. Identifying soil cleanup criteria for dioxins in urban residential soils: How have 20 years of research and risk assessment experience affected the analysis? J Toxicol Environ Health B Crit Rev 9(2):87–145.

Pohl H, DeRosa C, Holler J. 1995. Public health assessment for dioxins exposure from soil. Chemosphere 31(1):2437–2454.

7.0 Reviews

Gasiewicz TA, Olson RJ, Geiger LE, et al. 1983b. Absorption, distribution, and metabolism of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) in experimental animals. In: Tucker RE, Young AL, Gray AP, eds. Human and environmental risk of chlorinated dioxins and related compounds. New York, London: Plenum Press, 495–525.

Haws LC, Su SH, Harris M, et al. 2006. Development of a refined database of mammalian relative potency estimates for dioxin-like compounds. Toxicol Sci 89(1):4–30.

Hong B, Garabrant D, Hedgeman E, et al. 2009. Impact of WHO 2005 revised toxic equivalency factors for dioxins on the TEQs in serum, household dust and soil. Chemosphere 76(6):727–733.

Olson J. 1993. Health assessment for 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) and related compounds. Chapter 1. Disposition and pharmacokinetics. Govt Reports Announcements & Index (GRA&I), Issue 22. U.S. Environmental Protection Agency, Office of Health and Environmental Assessment: Washington, DC.

Van den Berg M, De Jongh J, Poiger H, et al. 1994. The toxicokinetics and metabolism of polychlorinated dibenzo-p-dioxins (PCDDs) and dibenzofurans (PCDFs) and their relevance to toxicity. Crit Rev Toxicol 24:1–74.

Van den Berg M, Birnbaum LS, Denison M, et al. 2006. The 2005 World Health Organization reevaluation of human and mammalian toxic equivalency factors for dioxins and dioxin-like compounds. Toxicol Sci 93(2):223–241.

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	Referenc 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

	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	Referenc Vehicle
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
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

	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	Referenc Vehicle
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)
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)

	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	Referenc Vehicle
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)
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)

	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	Referenc Vehicle
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)
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

	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	Referenc Vehicle
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
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

	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	Referenc Vehicle
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
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

	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	Referenc Vehicle
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
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

	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	Referenc Vehicle
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

	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	Referenc Vehicle
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

	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	Referenc Vehicle
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
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

	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	Referenc Vehicle
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
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

	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	Referenc Vehicle
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
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

	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	Referenc Vehicle
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
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

	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	Referenc Vehicle
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
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

	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	Referenc Vehicle
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
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

	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	Referenc Vehicle
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, hexachlorodibenzofurn; PeCDD, pentachloro-p-dibenzodioxin; PeCDF, pentachloro-p-dibenzofuran; TCDD, tetrachloro-p-dibenzodioxin; TCDF, tetrachlorodibenzofurn; OCDD, octochloro-p-dibenzodioxin

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)

	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
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)

	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
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)

	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
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

	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
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

	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
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

	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
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

	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
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

	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
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