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Summary Report for the Workshop on Issues Associated with Dermal Exposure and Uptake

U.S. Environmental Protection Agency
Bethesda, MD
December 10-11, 1998

Risk Assessment Forum
U.S. Environmental Protection Agency
Washington, DC 20460

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This report was prepared by Eastern Research Group, Inc. (ERG), an EPA contractor (Contract No. 68-C9-8148, Work Assignment No. 99-01) as a general record of discussion held during the Workshop on Issues Associated with Dermal Exposure and Uptake (December 10–11, 1998). As requested by EPA, this report captures the main points and highlights of the meeting. It is not a complete record of all details discussed, nor does it embellish, interpret, or enlarge upon matters that were incomplete or unclear. Statements represent the individual views of each workshop participant; none of the statements represent analyses by or positions of the Risk Assessment Forum or the EPA.

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FOREWORD

In January 1992, the EPA Office of Health and Environmental Assessment (now the National Center for Environmental Assessment) completed an interim report entitled *Dermal Exposure Assessment: Principles and Application*. This report provided guidance for conducting dermal exposure and risk assessments. The conclusions of this report were summarized at the January 1992 National Superfund Risk Assessors Conference. During this meeting, Regional risk assessors requested that a workgroup be formed to prepare an interim dermal risk assessment guidance for the Superfund program. The purpose of this guidance would be to promote consistency in the procedures used by the EPA Regions to assess risks from dermal exposure at Superfund sites. In August 1992, a draft Superfund Dermal Guidance was circulated for review and comment.

In 1995, a workgroup convened to address issues related to the August 1992 Superfund Dermal Guidance and to redraft the document. The revised guidance was peer-reviewed in February 1998. Several issues related to dermal exposure and risk assessment were raised during the peer review. The workgroup addressed some of these issues in a revised draft of the guidance. Other issues raised during the peer review were broader in scope.

To address these broader issues, the EPA Risk Assessment Forum sponsored a workshop held on December 10–11, 1998, in Bethesda, Maryland. At this workshop, 20 peer consultants discussed issues in four categories:

- Dermal exposure to contaminants in water.
- Dermal exposure to contaminants in soil.
- Adjustment of toxicity factors to reflect absorbed dose.
- Risk characterization and uncertainty analysis for dermal assessments.

In addressing these issues, the consultants were asked to consider:

- What is known today that can be applied to addressing the issue or providing additional guidance on the topic?
- What short-term studies could be conducted to address the issue or provide additional guidance?
- What longer-term research may be needed to address the issue or provide additional guidance?

This report summarizes the discussions at the workshop.

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CHAIRPERSON'S SUMMARY

A workshop on Issues Associated with Dermal Exposure and Uptake was held to provide a forum for discussion of generic technical issues raised during the February 1998 peer review of the Superfund Dermal Guidance (SDG). The peer consultants who participated in the workshop focused on four key areas of concern: estimating dermal absorption from water, estimating dermal absorption from soil, the use of oral-dermal toxicity adjustment factors, and dermal risk characterization/uncertainty. In each of these areas, the consultants attempted to identify and categorize three kinds of issues: (a) those which should be addressed in the finalization of the current SDG, (b) those which should be given immediate attention by the agency before any future dermal guidance is prepared, and (c) those which should serve as the basis for an ongoing research program to improve the accuracy and breadth of applicability of dermal risk assessment methodologies. Overall, the peer consultants felt that the SDG document was generally well written and provided a reasonable and justifiable basis for conducting dermal risk assessments, given the current state of the art for the prediction of dermal absorption.

Specifically with respect to dermal exposure from water, the consultants endorsed the use in the SDG of the predictive equation for skin permeability (K_p) of a chemical based on its octanol-water partition coefficient (K_{ow}) and molecular weight (MW). However, the consultants felt that the SDG should be revised to better document the derivation and implications of the 95% confidence intervals and "effective predictive domain" (EPD) for the estimation of K_p. The consultants strongly recommended that the agency give immediate attention to considering alternative bases for regressions to estimate K_p, including the use of molar volume rather than MW, as well as the use of molecular sub-structures, although it was recognized that these alternatives could not be considered in the timeframe for publication of the current SDG document. In addition, there was concern that the fact that the SDG gives preference to predicted, rather than experimental, values for K_p could serve to discourage the collection of experimental data on K_p for additional chemicals. Therefore, the agency should attempt to encourage the collection of such data in the future by the development of standard protocols defining acceptable experimental determinations of K_p to replace the predicted values.

With regard to dermal exposure from soil, the use in the SDG of default soil absorption fractions (Abs), which can be replaced with site-specific experimental data, was endorsed by the consultants. There was general agreement that much more experimental data is needed to improve this area of dermal risk assessment in the future. For this purpose, the agency should develop standard protocols defining acceptable *in vitro* and *in vivo* methods for measuring dermal absorption from soil. Factors that need to be considered include properties of the soil, chemical composition/aging, and duration/nature of dermal contact. Additional data is also needed on soil adherence and dermal transfer from surfaces (e.g., concrete).

It was the opinion of the consultants that the "toxicity factor" methodology for oral-to-dermal extrapolation described in the SDG is acceptable, but that the discussion in the SDG should be greatly expanded prior to publication to clarify the assumptions and limitations involved. In particular, while the method described in the SDG is acceptable as a default, the guideline should

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give preference to more desirable methods for route-to-route extrapolation, as discussed in a previous EPA workshop (Gerrity and Henry, 1990). The oral bioavailability associated with the critical toxicity study, which serves as the basis for the toxicity factor in the SDG, should be clearly distinguished from the human oral bioavailability used in oral exposure assessment.

The consultants felt that the discussion of risk characterization and uncertainty in the SDG was generally adequate. It is recommended that some attempt be made to categorize the importance of the various uncertainties listed in the document in at least a qualitative way (e.g., low, medium, high). For the future, more quantitative sensitivity and uncertainty analysis should be attempted.

The most consistent recommendation of the consultants was the need for the establishment of a (funded) standing agency dermal working group. The functions of this working group would include: (1) review of new experimental data on K_ps or Abs to determine acceptability as a replacement for the predicted/default values, (2) maintenance of a depository (preferably a worldwide web site) for reviewed experimental values of K_p, Abs, etc., (3) development of standard protocols, (4) fostering of exchange of information and standardization of dermal risk assessment across agency programs as well as with other agencies, and (5) continuing evaluation of progress in the science of dermal absorption and the potential for its incorporation in agency guidelines.

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1. INTRODUCTION

1.1 Workshop Purpose

The Workshop on Issues Associated with Dermal Exposure and Uptake was held on December 10 and 11, 1998, in Bethesda, Maryland, to discuss issues associated with estimating dermal exposure and uptake of environmental contaminants. The workshop discussions focused on generic technical issues raised during the February 1998 peer review of the *Risk Assessment Guidance for Superfund, Supplemental Guidance, Dermal Risk Assessment* (hereafter known as the Superfund Dermal Guidance). These issues are detailed in the charge to the peer consultants, which is included as Appendix A of this report. Although the discussion topics detailed in the charge were derived from the review of a proposed Superfund model, they are generically applicable to the estimation of chemical uptake within many U.S. Environmental Protection Agency (EPA) programs. Therefore, discussion of these issues at the workshop was intentionally broader than the originating context of the Superfund Dermal Guidance.

1.2 Workshop Participants

The peer consultants for the workshop consisted of 20 experts in dermal exposure and uptake from industry, academia, consulting, and state and Federal government agencies. Their expertise covered a broad range of exposure and risk assessment topics including chemical principals, dermal bioavailability, toxicity adjustments, and quantitative modeling. Over forty observers also attended the workshop, including six members of EPA's Dermal Workgroup who had authored the Superfund Dermal Guidance. The peer consultants and observers are listed in Appendixes B and C, respectively.

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1.3 Workshop Agenda

The workshop agenda is provided in Appendix D. The workshop began with welcoming remarks, presentations on EPA's Risk Assessment Forum and current dermal guidance, and a review of the charge to the peer consultants. This was followed with a series of four discussion sessions on issues associated with:

- Dermal exposure to contaminants in water.
- Dermal exposure to contaminants in soil.
- Adjustment of toxicity factors to reflect absorbed dose.
- Risk characterization and uncertainty analysis for dermal assessments.

Each of these sessions began with a brief presentation, given by a member of the EPA Dermal Workgroup, on background information relevant to that particular topic. The peer consultants then divided into three breakout groups. (Breakout group chairs and members are listed in Section 2.4.) For about an hour, the breakout groups separately discussed the specific issue questions listed in the charge (Appendix A). Then all consultants reconvened in a plenary session, during which each breakout group chair presented the key points from his or her breakout group discussion and the consultants then discussed the issue further as a group. Finally, observers were given an opportunity to comment. On the last afternoon of the workshop, after the four issue areas had been discussed, the peer consultants held a plenary discussion of dermal exposure issues and ideas for future workgroup activities.

1.4 Workshop Summary

This report summarizes the workshop presentations and discussions:

- Section 2 of this report summarizes the opening presentations, which provided background information and context for the workshop discussions.

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- Sections 3 through 6 summarize the presentations and discussions in each of the four issue areas. (The overheads used by the chairperson and EPA presenters are provided in Appendix E. Overheads used by the breakout group chairs in presenting the breakout group discussions can be found in Appendix F.)

- Section 7 of this report summarizes the final plenary discussion on dermal exposure issues. (The overheads developed during this discussion are included in Appendix F.) Following the workshop, two of the consultants submitted post-meeting comments. These are included in Appendix G.

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2. SUMMARY OF OPENING REMARKS

2.1 Welcome

Jan Connery of Eastern Research Group, Inc. (ERG) opened the workshop by welcoming participants and observers. She emphasized that the workshop was a peer consultation meeting rather than a peer review meeting. While the Superfund Dermal Guidance would serve as a resource for deliberations, it was not being peer-reviewed at the workshop. Ms. Connery stressed to the peer consultants that the scope of their discussions in the four topic areas should extend beyond Superfund to address issues generally applicable to estimating chemical uptake.

2.2 EPA Risk Assessment Forum's Role

Steve Knott, Exposure Science Coordinator for EPA's Risk Assessment Forum (RAF), provided background on the RAF and its role in sponsoring this workshop. The RAF was established in 1984 in response to recommendations made by the National Research Council for improving risk assessment practices in the Federal government. The mission of the Forum is to promote agreement within the Agency on difficult risk assessment issues and to make sure that this agreement is incorporated into Agency guidance. To do that, EPA assembles senior scientists from the EPA program offices to participate in a formal process to study and report on issues from an Agency-wide scientific perspective. Currently, 34 EPA senior scientists representing the following offices are involved in the Risk Assessment Forum:

- Office of Prevention, Pesticides and Toxic Substances
- Office of Solid Waste and Emergency Response
- Office of Air Quality Planning and Standards
- Office of Water
- Office of Research and Development
- Regions 1, 2, 5, 6, 7, and 10

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Mr. Knott explained that the projects these scientists take on are selected based on two criteria:

- They should involve controversial or cutting-edge issues.
- They should impact the risk assessment practices of the Agency as a whole, affecting a multitude of Agency programs.

Mr. Knott then discussed the RAF's involvement with dermal uptake issues. In February 1998, the Superfund Dermal Guidance was externally peer-reviewed. Two members of the Dermal Workgroup, which considered the recommendations and comments of those peer reviewers, were also RAF members—Kim Hoang and David Bennett. They recognized immediately that some of the issues raised could be of concern in other dermal exposure initiatives within the Agency, so they referred these issues to the RAF; this led to today's workshop. Specific issues and topics of interest to the Agency that can be addressed in the workshop include:

- Aggregate exposure to pesticides
- Risks to children
- Dermal uptake of contaminants in drinking water
- Research planning

2.3 Background on the Current Dermal Guidance

Mark Johnson from EPA Region 5 and Mark Maddaloni from EPA Region 2 provided background information and context concerning EPA's current dermal guidance. Mr. Johnson outlined some crucial dermal issues that EPA thinks will help define and refine Agency guidance documents. By refining its guidance documents, EPA hopes to aid risk assessors in performing dermal pathway exposure assessments. Discussions during the workshop, and the resulting guidance, will hopefully be extremely valuable to EPA—not only to the Superfund risk assessment process, but also to a diverse group of other Agency programs.

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Mr. Johnson focused his overview on two topics: (1) the evolution of the Superfund Dermal Guidance; and (2) how EPA plans to use this workshop's deliberations, and the information gained from them, to refine its dermal exposure assessment methodology.

Beginning with the evolution of the Superfund Dermal Guidance, Mr. Johnson identified significant dates and events associated with EPA dermal risk assessment:

- 1983: National Academy of Sciences (NAS) recommendations for risk assessment methodology.
- 1989: *Risk Assessment Guidance for Superfund* (RAGS).
- 1992: *Dermal Exposure Assessment: Principles and Applications* (DEA)—EPA's Office of Research and Development (ORD).
- 1992: *Superfund Interim Dermal Risk Assessment Guidance*.
- 1995: Dermal Workgroup formed to update and finalize Superfund Guidance.
- June, 1997: Internal Peer Review of draft Superfund Guidance.
- January, 1998: External Peer Review of draft Superfund Guidance.
- August, 1998: Draft revised based on peer review comments.
- October, 1998: Discussion issues for this workshop were identified.

In 1983, NAS made recommendations for a risk assessment methodology that consisted of four stages: hazard identification, toxicity assessment, exposure assessment, and risk characterization. After adopting the NAS risk assessment paradigm, EPA's Superfund program developed the Risk Assessment Guidance for Superfund (RAGS) in 1989. Superfund illustrated the need for EPA to define a consistent risk assessment methodology (including dermal exposure guidance) for the dermal pathway. Superfund is a very decentralized program within EPA and its risk assessment management decisions, methodologies, and practices vary greatly. Regional Offices perform most Superfund risk assessments and dictate how to address each site. There are thousands of sites and

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thousands of risk assessors, all of whom would benefit from EPA guidance and consistent methodology for performing risk assessments.

RAGS was the Agency's first attempt to combine all of the elements of risk assessment into a guidance document. RAGS provided guidance and a consistent approach to risk assessments for the EPA, as well as for the states, independent consultants, and others who performed assessments. For example, the document provided quantitative recommendations for how to estimate an absorbed dermal dose from water and soil. For some values (such as the chemical-specific dermal permeability coefficient ($_{Kp}$) for the estimated absorbed dose from water, and the chemical-specific absorbed fraction from soil [ABS] and soil adherence factor [AF] for the estimated absorbed dose from soil), RAGS suggests consulting the open literature. However, RAGS provides no guidance for doing this. Information is needed on the hundreds of chemicals that EPA characterizes at a Superfund site. Also, review and evaluation of the literature is needed to develop recommendations for the dermal pathway.

For ABS and AF, RAGS suggests using conservative estimates when information is not available. Because the Superfund program is highly decentralized, guidance to use conservative estimates leads to various levels of aggressive approaches, such as assigning a single absorption fraction to a whole class of chemicals. This has led to some degree of inconsistency across the Regions.

In 1992, ORD developed the DEA, which provides the scientific basis for quantitative evaluation of the dermal pathway. This document refined many of the parameters that were described qualitatively in RAGS.

Following development of the ORD document, Superfund developed the draft *Superfund Interim Dermal Risk Assessment Guidance*, which distilled the key elements of the more technical ORD document into practical guidance for Regional and state staff and their consultants. That draft guidance was widely used.

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The Dermal Workgroup was formed in 1995 to update and finalize the draft guidance. The revised document was internally peer-reviewed at EPA in 1997 and externally peer-reviewed in early 1998. The Workgroup revised the document based on the peer reviewer comments. In addition, the peer reviewers raised a number of issues that EPA felt would best be addressed by a separate peer consultation meeting. Many of these issues are captured in the charge for this workshop (Appendix A).

Mr. Johnson pointed out that dermal risk assessments support many decisions. At Superfund sites, for example, the dermal risk assessment may play a role in triggering cleanup and in defining cleanup goals. EPA staff and many states rely on this type of guidance. EPA therefore would like to increase the consistency and reduce the uncertainties of dermal risk assessment. While uncertainty was to be specifically addressed as part of the fourth discussion topic at this workshop, it also wove through the first three issue areas; Mr. Johnson expected that it might arise throughout the discussions. Mr. Johnson emphasized that the Agency would like to reduce the uncertainties in dermal risk assessment and he hoped that the workshop would help contribute to that goal.

2.4 Charge to the Peer Consultants

Harvey Clewell of ICF Kaiser International, who served as the workshop chair, reviewed the charge for the workshop. He suggested that, in approaching the meeting agenda, the peer consultants adopt a mental framework of "Today, Tomorrow, and Future":

- "Today" includes issues and problems that could be immediately addressed or fixed in the EPA document.
- "Tomorrow" includes issues that research has not yet fully addressed. Some of these issues were touched upon in the EPA document, but more work needs to be done before this information should be formally presented in a document. It seems possible for these information gaps to be filled in the near future.
- "Future" includes long-term needs and data gaps that should be addressed to improve dermal risk assessment. It is unlikely that these issues can be addressed in

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the near future, but they will eventually need to be examined in order to fully understand dermal exposure assessment issues.

Mr. Clewell said that the topics to be featured in the "Next Steps" discussion at the end of the workshop would be determined by the needs, interests, and desires of the peer consultants. Therefore, he asked the consultants think about what they would like to see happen in the future.

Mr. Clewell divided the consultants into three breakout groups as follows:

Group 1	Group 2	Group 3
Annette Bunge*	Gary Diamond*	John Kissel*
Clay Frederick	Kurt Enslein	Jim Bruckner
Clint Skinner	Paul Chrostowski	Rosalind Schoof
Gerhard Raabe	Philip Leber	Deborah Edwards
Jim Knack	Stephen Di Zio	Bob Bronaugh
Val Schaeffer	Robert Duff	Lawrence Sirinek
Ron Brown		

* Chairs

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3. DERMAL EXPOSURE TO CONTAMINANTS IN WATER

3.1 Presentation

Kim Hoang from ORD presented background information for the first discussion topic: dermal exposure to contaminants in water. (Dr. Hoang's overheads are included in Appendix E.)

In the current approach for organic chemicals, the skin permeability (K_p) is estimated as a function of a chemical's octanol/water partition coefficient (K_{ow}) and its molecular weight (MW). The relationship between K_p and these factors is based on a regression analysis of measured skin permeabilities. For metals and inorganic chemicals, the Superfund Dermal Guidance recommends using default K_p values. In the absence of measured values, a default of 0.001 cm/hr is recommended.

Dr. Hoang listed the methodologies in the ORD DEA that *will not* be changed, and then listed those that *will* be changed. Methodologies that will not be changed include:

- Use of a two-compartment membrane model to represent the skin.
- Approximations of exact solutions.
- Use of the Dermal Absorbed Dose per event (DA_{event}) (estimated from K_p) for event time (t_{event}) < time to reach steady state (t*), DA_{event} proportional to $\sqrt{t_{event}}$.
- Use of DA_{event} (estimated from K_p or $K_{p,max}$) for $t_{event} > t^*$, DA_{event} proportional to $\sqrt{t_{event}}$.
- Use of K_p correlation as a function of K_{ow} and MW.

EPA believes that these methodologies are scientifically sound and do not need further review. However, EPA would appreciate input on other methodologies in the guidance document that do need further development and improved scientific focus, including for example:

- Improving K_p correlation for organics:

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— Using Flynn's database as the ORD DEA does.

— Taking out three *in vivo* data points (xylene, toluene, styrene).

— Using two predictors: Log K_{ow} and MW.

— Calculating 95% confidence intervals (CIs) for both Flynn's data and the 200 chemical predictions.

Establishing a 95% CI for predicted K_p of existing chemicals in the ORD DEA.

Establishing an effective predictive domain (EPD) for predicted K_p.

— Statistical analysis of collinear data.

— From the original experimental data set, allow the determination of an EPD for extrapolation of unknown K_p.

Determining $K_{p,max}$ for chemicals outside of EPD.

Determining K_p for inorganics and default values.

Reassessing other default exposure assumptions.

Dr. Hoang noted that the dermal modeling approach used to derive a correlation equation was based on the experimental Flynn database. The Flynn database includes estimated values for over 200 chemicals. These estimated values are derived with uncertainty bounds (95% confidence level) to extrapolate data from known experimental values. She explained that the 95% confidence level provides some idea about the range of K_p with which risk assessors are faced. This allows site risk assessors to know the magnitude of uncertainty in their dermal risk assessment exposure dose estimates. Outside the EPD, however, the estimates are not valid. Knowing the magnitude of uncertainty should help risk assessors to (at least qualitatively) improve their dermal assessments. Currently, dermal risk assessors have no reliable data set to assist them in deciding which K_{ow} to use.

Dr. Hoang showed overheads that graphically depicted the EPD of ORD DEA predictions compared to Flynn's database, bounded by the 95% CIs (see Appendix E). Virtually all DEA-

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identified chemicals fell within the predicted EPD box of the Flynn database. Dr. Hoang showed a list of chemicals with high and low K_{ow} values that fell outside the EPD. She remarked that xylene, toluene, and styrene should be removed from the data set. This is because these three data points were collected using *in vivo* methodologies, which are not readily comparable to all other chemical data points derived from *in vitro* studies.

Dr. Hoang said she would welcome any suggested improvements to the current approach. The current methodologies use two predictor units (Log K_{ow} and MW) that are not interchangeable. There are no real guidelines for risk assessors concerning this dermal exposure issue. Dr. Hoang also discussed the default K_ps for inorganics, as well as other default exposure values such as the recommended dermal exposure values for central tendency and RME residential scenarios for water contact. Many of these default values may not accurately represent real-life scenarios. Depending on the nature of the contaminant in site-specific conditions, some chemicals may have a range of K_ps. For these chemicals, using default values may over- or underestimate dermal exposure dose estimates.

Comments would be particularly welcome on any of the following topics:

For organic chemicals:

- The database used to derive the correlation equation.
- The correlation equation (predictors K_{ow} and MW) used to estimate the K_p and the 95% CI.
- The statistical analysis used to establish the EPD for the K_p correlation equation.
- The use of $K_{p,max}$.
- The use of estimated K_p versus experimental data.

For inorganic chemicals:

- The approach recommended for metals and inorganic chemicals.
- The other exposure default values.

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- # Using the model instead of a chemical-specific study—which one is better? Why? (i.e., benefits, disadvantages of each).

The goal of the EPA Dermal Workgroup is to develop, for use at risk assessment sites, one correlation for all K_p estimates of various chemicals. The process of developing this correlation basically focuses on estimating absorption of a chemical into the skin. It does not include inhalation exposure, nor has it yet looked at the chemical volatilization process. Dr. Hoang said that this methodology essentially extends the previously used membrane model to create another physiological model. She looked forward to hearing how the breakout groups discussed the specific K_p issues listed in the charge (Appendix A). She hoped that the discussions would touch upon current thinking about the experimental versus estimated K_p values.

3.2 Discussion

Following Dr. Hoang's presentation, the peer consultants divided into three breakout groups to discuss dermal exposure to contaminants in water. Based on the charge (Appendix A), the breakout groups focused their discussion on the following six topic areas:

1. Comment on the correlation equation used to estimate the skin permeability coefficient (K_p) for organic chemicals. Is the approach used to estimate the K_p values and their 95% confidence intervals plausible? Include in the discussion consideration of the database analyzed to generate the correlation equation.

2. Comment on the statistical analysis used to establish the Effective Predictive Domain for the K_p correlation equation (i.e. the range of K_{ow} and MW where the predictive power of the regression equation would be valid). Evaluate the new methodology for calculating $K_{p,max}$ for chemicals outside of the Effective Predictive Domain.

3. Comment on the use of K_p and $K_{p,max}$ in the dermal absorption model (specifically the use of K_p for all t_{event} (exposure time)$<t^*$ (time to reach steady state absorption), and the use of K_p or $K_{p,max}$ when $t_{event}>t^*$).

4. Comment on the use of predicted K_p or $K_{p,max}$ vs. Chemical specific experimental values. Consider the criteria used to select studies to develop the regression model (see Appendix A of the Superfund Dermal Guidance). Should these and other criteria be used to judge chemical specific experimental values? What are the minimum criteria that

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should be satisfied before chemical specific experimental values can be used in lieu of model predictions?

5. Comment on the approach recommended for metals and inorganic chemicals. Is the default K_p (0.001 cm/hr), that was previously recommended in the 1992 Interim Guidance for Dermal Exposure Assessment, still scientifically sound and defensible?

6. Comment on the other default exposure assumptions (see Table 3.2) recommended to estimate the DA_{event} (e.g., t_{event} = 10 minutes for exposure in a shower). Are these events scientifically sound and defensible?

Following the breakout discussions, the consultants reconvened in a plenary session. The breakout group chairs summarized the discussions as follows. (Copies of the overheads used by the chairs in making their presentations are included in Appendix F.)

Group 1

Chair: Annette Bunge, Colorado School of Mines

Discussion Area 1

Group 1 determined that the correlation equation used to estimate the K_p for organic chemicals is probably sufficiently accurate, but that molar volume may be a better approach. Some members of Group 1 felt uncomfortable using a 95% CI because it assumes an unknown error structure. The database used to generate equations should include more relevant chemicals, particularly high and low Log K_{ow} chemicals. Procedures for collecting K_{ow} data should be standardized. Group 1 noted that Superfund is interested in many high production persistent chemicals. Discussions emphasized the need to increase data generation, specifically focusing on persistent chemicals in water. Group 1 discussed the importance of these persistent water-borne contaminants via the dermal pathway for Superfund and outside Superfund.

Discussion Areas 2, 3, and 4

Commenting on the statistical analysis used to establish the EPD for the K_p correlation equation, Group 1 decided that it was sufficiently accurate, but that risk assessors should not extrapolate outside the EPD. Experimental K_p values are not a problem if they contain only small errors and

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standard deviations. Group 1 felt that concern was warranted when there was only a single K_p study, or when there were several experimental K_ps with high variation. Group 1 also felt that there should be a domain based on the properties of data in the database. The methodology for calculating $K_{p,max}$ for chemicals outside of the EPD was sufficiently accurate in the dermal absorption model, but Group 1 felt that some questions still need to be answered in this area. Group 1 was uncomfortable with the use of K_p and $K_{p,max}$ in the dermal absorption model because they felt this method ignored data. Group 1 suggested that the "consensus" experimental values (e.g., the average) could be reported as an alternative. Group 1, however, came to no definite conclusions regarding the use of K_p and $K_{p,max}$ in the dermal absorption model. They did not decide what criteria should be used to judge chemical-specific experimental values, or what minimum requirements should be satisfied before chemical-specific experimental values can be used in lieu of model predictions.

Discussion Areas 5 and 6

As for the approach recommended for metals and inorganic chemicals, Group 1 felt that the default K_p (0.001 cm/hr) was sufficiently accurate, but noted that this default value did not account for chemical speciation. Group 1 discussed whether methyl mercury should be treated as an organic chemical rather than a metal. They also discussed the differences in dermal exposure from vapor mercury and water mercury. Group 1 asked why arsenic was not included in the metals list. When discussing shower default exposure assumptions, Group 1 expressed no great concerns or significant comments.

Discussion Areas 4, 5, and 6

Group 1 suggested that the document contain a description of the issues it does not address; some of these issues, though not relevant to Superfund, may be important on the broader scale. For example, pesticide absorption from pesticide formulation is not treated in the document. (Pesticide absorption is not a pathway of concern at most Superfund sites, but it is of concern in other EPA programs.)

Group 2

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Chair: Gary Diamond, Syracuse Research Corporation

Discussion Area 1

Group 2 expressed many ideas similar to those of Group 1. Group 2 expressed a concern that the predictive model used to estimate K_p for organic chemicals may be wrong. Group 2 recommended several ways to improve the K_p estimation. First, they suggested that researchers analyze and include information from the Vecchia database into their model. Group 2 also suggested that the model include substructural parameters in the correlation analysis, explore other K_{ow} predictive models, explore nonlinear models for relating K_{ow} and K_p, and use molar volume in place of molecular weight in the prediction algorithm. Group 2 discussed the need to consider variable dependency in the prediction algorithm (MW-K_{ow}, molar volume-K_{ow}) and to consider modeling transformed data (e.g., Log). They emphasized the need for scientific review of K_{ow} values to create a high quality database of K_p values. Group 2 suggested including information from the "Star List" into this data review. An attempt should be made to identify any other available data which could be incorporated into the model.

Group 2 stressed the need for the dermal guidance document to explore experimental K_{ow} values, including how the predictive model may be wrong. Group 2 also said that the document needs to clarify the derivation of the 95% upper confidence level. The document needs to explicitly state this information.

Discussion Area 2

Group 2 said that the document needs to clarify how it is defining "outliers of EPD" before they can comment on the statistical analysis used to establish the EPD. Moreover, the EPD approach needs to be clarified in the document to minimize confusion and disagreement about the EPD approach. Group 2 felt that EPA needs an approach for how to replace the predicted $K_{p,max}$ with experimental values, noting that the predictive approach yields highly conservative values of K_p.

Discussion Area 3

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Regarding exposure duration, Group 2 said that the document currently has no basis for distinguishing between exposure time and the time it takes to reach steady-state absorption. Exposure duration needs to be raised as an important uncertainty that is explicitly stated in the document.

Discussion Area 4

Group 2 felt that the use of a predicted model value (instead of chemical-specific experimental values) might not reward new data collection because researchers might see the model's value and assume that it is well established and needs no further verification. If EPA "forced" everyone to use its data, they might be discouraging people from going out and collecting new data because potential sponsors of research (i.e., industry) will conclude that EPA will not accept the use of new experimental data in site risk assessments. Therefore, Group 2 felt that EPA should make an effort to assure researchers that future data can and will be incorporated into this model and that verification of this model is greatly needed. Group 2 felt that EPA needs to reward data collection, or at least the idea of data collection.

Group 2 believed that use of a predictive model will contribute to consistency among different users at a diversity of sites. Group 2 stressed a need for criteria for evaluating experimental values. Currently there is no basis for deciding when to use experimental data and when to use estimated values. The group briefly discussed what criteria might be used to determine when to use experimental values, but no criteria were forwarded to the peer review panel for discussion.

Discussion Area 5

Group 2 recommended better documentation and explanation of how the workgroup derived chemical-specific K_p values. Group 2 felt that the workgroup's methodology should consider both ionized and non-ionized states of inorganics and whether or not they are using a value arrived at via *in vivo* or *in vitro* studies. The workgroup should consider the speciation of metals in its methodology. Group 2 asked how EPA deals with the ionization issue and felt that the document should explain the workgroup's approach, including the use of models and an explicitly stated assumption about relevant solution chemistry parameters (e.g., pH, ligand concentrations, etc.)

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Discussion Area 6

Regarding other default exposure assumptions, Group 2 felt that the workgroup needs to generate a loss term for dermal factors (i.e., loss to air, exfoliation, etc.) and default exposure assumptions. These factors should be generated on a chemical-specific basis. Group 2 felt that it would be useful to explore probabilistic approaches for representing the other factors in the dose algorithms. Group 2 members felt that it was possible, albeit unlikely, for shower default absorption values to exceed drinking water exposure default values for volatile organic compounds (VOCs). They felt that this was not a likely scenario for non-VOCs.

Other Issues

After discussing all issue topics, Group 2 discussed *in vitro* correlation, specifically the Potts and Guy equation. They also discussed the EPD ($K_{p,max}$), short-term versus long-term exposure events (2.4 $\hat{o}_{lag}$), and criteria for predicted K_p values versus measured values.

Group 3

Chair: John Kissel, University of Washington

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Discussion Areas 1–4

Group 3 grouped the first four issues together in their discussion. Several consultants said that they would like to see the document clearly explain the workgroup's approach to dermal risk assessment as it relates to maximum contaminant levels, and uncertainties involved in this approach. Adding a discussion about maximum contaminant levels might put the dermal risk assessment document in perspective, and help prevent risk assessors from using this information in ways unintended by the workgroup. Group 3 determined that EPA guidance for dermal risk assessment should encourage (or at least not actively discourage) data collection. The EPA dermal risk assessment methodology needs to contain a standard protocol if site-specific experimentation is to be conducted. Group 3 emphasized that talking about models in the absence of site-specific validation is short-sighted. EPA needs to seek validation via experimentation. EPA also needs to seek consistency, and their guidance document should point out where consistent and inconsistent topics exist in the area of dermal risk assessment.

Discussion Area 5

Group 3 criticized the default assumption value of 10^{-3} for inorganics. They raised questions about mercury and concluded that the EPA workgroup needs more investigation and information on mercury before they release the document. The default value for other metals seemed very conservative.

Discussion Area 6

Group 3 questioned whether a 10-minute default shower duration was adequate.

Additional Comments

Group 3 suggested that EPA needs to use residential versus recreational variables in Figure 1.1 of the document. Group 3 also expressed concern that maximum contaminant concentrations must be used. Finally, Group 3 suggested that the workgroup consider improving the clarity of the document's writing.

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General Discussion

Dr. Clewell summarized the three groups' discussions, saying that the groups apparently agreed that the correlation equation used to estimate K_p for organic chemicals and the use of the predicted K_p values were appropriate, but that they could be improved. The success of such methodologies varies by contaminant. The three groups grudgingly accepted the EPD domain for the K_p correlation model and the use of K_p and $K_{p,max}$ in the dermal absorption model. Some peer consultants felt the model should address lag times and distinguish between short-term versus long-term exposure events. Other criteria to be considered when generating dermal data include factors such as time to steady state, donor vehicle, receptor vehicle, temperature, pH, *in vivo* versus *in vitro*, pore effects, and metabolism.

Peer consultants said that they would like to see EPA demonstrate an *in vivo/in vitro* correlation. Several peer consultants noted that the higher molecular density compounds, such as halogenated hydrocarbons, may be the most problematic compounds to model.

Peer consultants recognized that, for *in vivo* systems, species differences come up, as well as individual factors like age, health, and skin region. Other differences arise between *in vivo* and *in vitro* systems as well. For example, dead human skin has low glucose levels compared to live skin cells. In addition, metabolism in the skin must be considered.

The workgroup model currently does not include metabolism or chemical metabolic factors into its calculations. Subsets of chemicals influenced by metabolic factors, however, have been identified (e.g., metabolism for organophosphate pesticides). For such chemicals, evidence shows that pore effects and metabolism in the skin are significant. One consultant suggested that EPA look at chemicals in the body, where they go after they enter the body, and how they are metabolized by various parts of the body. Currently, there is a complete data break between how much of a chemical is absorbed and what happens to the chemical once it enters the body. Peer consultants agreed that there may be different criteria, depending on the nature of the chemical, as to what might be worth considering in the experimental design. It is probably going to be necessary to set

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criteria that are chemical-class-specific, but this does not prevent the workgroup from coming up with protocols.

Peer consultants noted that the EPA workgroup probably needs to create different criteria depending on the nature of the chemical. They briefly discussed tissue issues (e.g., split versus full, *in vivo* versus *in vitro*), and noted that some comparative studies have already been conducted and data are already available. Currently, some data exist on the effect of different kinds of skin tissue preparations that can be helpful in ascertaining whether the skin preparation is going to significantly impact the experiment. For example, the temperature effects on uptake and the pH effects on uptake are already well documented.

Annette Bunge suggested that EPA try not to use anything in the system that would alter the skin permeability more than contact with water would. For example, when conducting dermal experiments, try not to include surfactants; use only water so that additional variables and potentially confounding factors can be eliminated. Peer consultants agreed that a Volpo "no barrier" receptor vehicle would be a good standard receptor vehicle for these experiments because Volpo does not affect skin permeability.

Mr. Clewell asked if peer consultants were generally comfortable with the conclusion that a 10-minute shower may lead to more chemical exposure than a full day's drinking water. No peer consultants strongly disagreed with this, although several said that it was highly improbable. One peer consultant noted that inhalation in a shower is an extremely important pathway. More empirical demonstrations have been done to demonstrate the significance of inhalation exposure than have been done for dermal exposure. Current information on completed dermal pathway exposure in a shower consists of only one data set for one chemical (work done by Jo and coworkers). Researchers have no idea how important the dermal pathway is for non-VOC chemicals. Peer consultants agreed that EPA needs to gather more shower data, especially for nonvolatile organic contaminant compounds.

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Val Schaeffer suggested consulting the Organization for Economic Cooperation and Development (OECD) for information on *in vitro* guidelines and related dermal exposure issues. He said that OECD is currently developing standardized methods to assess dermal exposure and that this workgroup should be aware of OECD progress. OECD's standardized methods involve many criteria this workgroup has addressed. Dr. Schaeffer suggested that there may already be an *in vitro* method being considered and harmonized by OECD. The OECD project sounds like it has initiated the process to select the criteria needed for data acceptance of *in vitro* studies.

Clay Frederick clarified that there are two types of data collection. The first is obtaining water partition coefficients, K_{ow} from available literature and experimental data. These coefficients are values based on physical and chemical properties. They should be reproducible values, assuming researchers use the same protocol. The second type of data collection, for K_p, is more problematic and justifies modeling extrapolations of existing data.

This brought the group to discuss criteria/credibility issues. Dr. Schaeffer said that standard criteria methods for dermal studies are being developed right now. Dr. Frederick emphasized, however, that it would be worthwhile to support the creation of the criteria. Other peer consultants agreed that this should be emphasized.

Dr. Bunge commented on the correction of model guidelines. She said that EPA could do the same thing for molar volume measurements that it has done for molecular weight in the model. Dr. Bunge said that chemicals with larger MW for their size (e.g., halogenated hydrocarbons) tend to be outliers of the current EPA correlation for estimating permeability coefficients. Based on the small number of chemicals that have been analyzed and modeled using both molecular weight and molar volume, participants felt that this issue belonged in the "Tomorrow" category.

Dr. Frederick said that he would like to see this workgroup establish a dermal database/website on EPA's website similar to EPA's Integrated Risk Information System (IRIS). This website could be updated regularly with the most recent available scientific information for reference by risk assessors and other interested parties. Several other peer consultants endorsed this idea of a

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central reference point and information clearinghouse to help ensure that risk assessor all use the same data sets, and to provide consistency throughout EPA's dermal risk assessment methodologies. This website could be set up similarly to EPA's Right-to-Know initiatives. A dermal website could potentially have a very strong influence on enhancing the quality of experimental data, improving data compatibility between studies, and strengthening risk assessments involving dermal pathway exposure. Dr. Frederick felt that this database/website might be fairly simple to start up and could fall into the "Today" category. Other peer consultants felt that this project was likely to be fairly labor-intensive and would better fall in the "Tomorrow" category.

Observer Comment

Leonard Kieffer, EPA

Leonard Kieffer commented on the OECD *in vitro* guideline, saying that OECD is probably not as far along as Dr. Schaeffer suggested. Canada and the U.S. are currently in major disagreement with the rest of the OECD. Some work is being done or will be started that tries to correlate *in vivo* and *in vitro* studies to achieve better guidelines. Mr. Kieffer recommended that this workgroup put the *in vitro* guideline initiative in the "Future" category.

Brail Berattum, BASF Corporation

Brail Berattum had one generic comment applicable to the entire meeting. The Chemical Manufacturers' Association (CMA) is currently funding a research program with $25 million per year for dermal funding. This funding is spread among ten broad areas. One of the areas is exposure assessment, led by Mike Jajak from Rohm and Haas Company. In the Exposure Assessment Group, one of the key issues is exposure parameters specific to the dermal pathway. The Exposure Assessment Group met the week of December 14, 1998, and reviewed the CMA requests for proposals for these broad-scale dermal issues, including identifying a methodology and nonchemical-specific criteria for dermal exposure. Mr. Berattum volunteered to serve as a liaison between CMA and peer consultants, EPA, and other parties interested in this funding.

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4. DERMAL EXPOSURE TO CONTAMINANTS IN SOIL

4.1 Presentation

Mr. Johnson from EPA Region 5 presented background information concerning the second discussion topic: dermal exposure to contaminants in soil. (Mr. Johnson's overheads are included in Appendix E.)

Mr. Johnson began by saying that the Dermal Workgroup's recommendations for estimating dermal exposure and uptake of chemical contaminants in soil are the same as those presented in the Superfund Dermal Guidance. This approach estimates an absorbed systemic dose for dermal contact with soil based on limited data. In the absence of measurements, a default absorption fraction of 10% is recommended for semivolatile organic compounds (SVOCs). For inorganic chemicals, a default of 1% is recommended.

Estimates of soil-to-skin adherence must be used with estimates of absorption fraction from soil to calculate the Dermal Absorbed Dose per event (DA_{event}). Recommendations on the use of soil-to-skin adherence factors (AFs) also are presented in the Superfund Dermal Guidance. Soil-to-skin AFs vary by activity and soil moisture content. Mr. Johnson briefly discussed the two methods used to evaluate dermal absorption from soil:

- Fraction absorbed (percent of applied dose absorbed into blood)
- Flux model (rate of migration of chemical in skin)

Mr. Johnson raised the question about whether or not the fraction-absorbed approach was the most appropriate at this time. He reviewed the calculation the workgroup used to estimate an absorbed dose per exposure event (see overhead in Appendix E) and suggested that the consultants think about how the monolayer theory impacts the dermal absorption fraction value. Mr. Johnson also showed the consultants an overhead of activity-specific surface-area-weighted AFs, noting that an adjustment for K_{ow} was not yet included in the estimates.

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Mr. Johnson also showed an overhead of recommended dermal absorption factors from soil for a variety of inorganic compounds. Recommended dermal absorption factors, however, were only available for a handful of chemicals and chemical families. For these chemicals, the dermal absorption factors were average numbers based on small data sets with very limited (if any) statistical rigor. Chemicals for which experimental data are unavailable include most metals and SVOCs. The generic defaults for screening the metals and SVOCs were 0.001 and 0.1, respectively. Mr. Johnson hoped that the peer consultants would have a chance to discuss the appropriateness of these screening values.

Mr. Johnson listed the soil AFs that can influence absorbed systemic doses for dermal contact with soil:

- Soil properties influence skin adherence (e.g., moisture content, particle size, soil type).
- Soil adherence varies across different body parts.
- Soil adherence varies with exposure activity.

The workgroup evaluated several exposure scenarios for the dermal pathway, including residential child, residential adult, commercial/industrial worker, and recreational. Mr. Johnson listed numerous activities that fell into these four categories of exposure scenarios. A full list of these activities is included in Appendix E, and includes such possibly exposed groups as children playing, gardeners, farmers, and soccer players.

Mr. Johnson described the workgroup's method for weighting soil AFs for a variety of body parts into one estimate of exposure for the whole body. An overhead depicted body part-weighted averages using several shaded boxes enclosed in one large rectangle. The rectangle represented the potentially exposed body, with each shaded box representing a specific body part (e.g., leg, arm, face). The shade intensity of each shaded box represented a chemical's loading density; an unshaded box indicated an unexposed or unevaluated body part. Using these methods, the workgroup obtains a body part-weighted average AFs for the entire body that is easily

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incorporated into dermal risk assessment calculations. Such a body part-weighted average is convenient because the exposed average can be used as a surrogate estimate of other exposed areas lacking quantitative data.

To conclude his presentation, Mr. Johnson showed an overhead of estimated activity-specific surface-area-weighted soil AFs. These weighted soil AFs were based on exposure to face, forearms, hands, lower legs, and/or feet. The soil AFs also accounted for activities and exposure scenarios. Weighted soil AFs were reported for the 50th and 95th percentiles. Mr. Johnson felt that the 95th percentile represented a reasonable maximum exposure estimate. Dr. Clewell raised the issue of how to adjust the soil AF to account for site-specific conditions. For example, the soil AF could factor soil particle size into the model.

4.2 Discussion

Following Mr. Johnson's presentation, the peer consultants divided into the three breakout groups to discuss dermal exposure to contaminants in soil. Based on the charge (Appendix A), the breakout groups focused their discussion on the following five topic areas:

1. Discuss the current absorption fraction approach as applied to the dermal absorption of chemical contaminants from soil. Consider such factors as the duration of soil contact, the soil particle size, and the level of soil moisture and whether these factors should be used to adjust the absorption estimate. Overall, is the proposed methodology scientifically sound and defensible?

2. Comment on the soil absorption values presented in Table 3.4 of the Superfund Dermal Guidance. Are these estimates supported by the available data? Are they scientifically sound and defensible?

3. Comment on the proposed default absorption fraction of 10% for organic compounds in soil. Is the rationale for selecting this default clear and transparent? Is the estimate scientifically sound and defensible? Is there enough supporting evidence to allow this estimate to be characterized as representative of the average?

4. Comment on the proposed default absorption fraction of 1% for inorganic chemicals in soil. Is the rationale for selecting this default clear and transparent? Is the estimate

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scientifically sound and defensible? Is there enough supporting evidence to allow this estimate to be characterized as representative of the average?

5. Comment on the proposed approach to calculate a total body soil-to-skin AF based on the surface area weighted AFs for each body part. Is this a scientifically sound approach? Could other methodologies be recommended?

Following the breakout discussions, the consultants reconvened in a plenary session. The breakout group chairs summarized the discussions as follows. (Copies of the overheads used by the chairs in making their presentations are included in Appendix F.)

Group 1

Chair: Annette Bunge, Colorado School of Mines

Discussion Area 1

Group 1 felt that the workgroup's dermal absorption fraction approach may be the best available approach given current theoretical limitations and data limitations. They noted that the data assumed 24 hours of exposure and that not all data in the literature are included. Group 1 raised the issue of how new data should be included into the table. The group suggested that all data listed in the table should include and adjust for monolayer cover factors (and be noted as such). Monolayer cover or less represents what realistically occurs. Group 1 expressed concern that the experiments currently do not account for numerous factors that affect dermal absorption, including the effects of exposure time, mechanisms of transfer from soil to skin, and soil transfer to the skin. Specifically, these variables include sweating, direct contact, vapor pressure (even for nonvolatiles), and turnover versus no turnover.

Discussion Area 2

Group 1 said that the workgroup's accepted default values for soil absorption were not completely scientifically defensible because numerous factors were not incorporated into the table's data. For example, the table did not account for:

- Properties of applied soil (e.g., organic carbon, moisture content)

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- Particle size distribution
- Amount of applied soil relative to amount required for monolayer coverage
- Where monolayer coverage occurred (i.e., adjustment to monolayer)
- Contamination procedure
- Default chemical groups

Group 1 recommended that the workgroup create chemical default values based on groups or categories of chemicals. These chemical groups could be defined by chemical vapor pressures or by chemical ability to transfer from the soil. Group 1 recognized that understanding mechanisms of transfer in order to group chemicals may require more experimental data.

Discussion Area 3

Group 1 felt that the rationale for the default absorption fraction of 10% for organic compounds was not clear and transparent. Moreover, they did not believe that the 10% default value was scientifically supportable because the data are weak.

Discussion Area 4

Group 1 said that no clear rationale existed for the default absorption fraction of 1% for inorganic compounds. They felt that there was not enough supportable evidence for the 1% default assumption.

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Discussion Area 5

Group 1 had no comment on the workgroup's proposed approach to calculate a total body soil-to-skin AF based on the surface-area-weighted AFs for each body part.

General Discussion

Group 1 summarized their conclusion by saying that researchers need to gather and generate more data on dermal exposure to contaminants in soil. Group 1 suggested that part of the dermal workgroup charge should be to create standardized procedures so that people can really start gathering more data that can be integrated with wide-ranging applications.

Group 2

Chair: Gary Diamond, Syracuse Research Corporation

Discussion Area 1

Group 2 said that more experimental data are needed on dermal exposure to contaminants in soil to fully assess the adequacy of the workgroup's approach. Specifically, Group 2 would like to see more experimental data generated on kinetics, of adsorption and absorption of chemicals from soil. There may need to be a time adjustment to the absorption factor to account for rate effects. An exploration of the modeling of adsorption and a screening approach to estimate adsorption (e.g., solvent extraction assays) would be useful. Group 2 recommended creating guidelines for experimental data collection. They would like to see a standard soil characterization for experimental data that would provide specific guidelines about soil particle size, loading, and aging factors. Current experimental data appear biased toward large particle sizes and unaged soil. Group 2 also felt it was important to create guidelines for *in vivo* experiment preparation and protocol.

Discussion Area 2

Group 2 identified numerous chemical-specific problems with the soil absorption values cited in Table 3-4 . They did not elaborate on these chemical-specific issues, but said that available data

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are limited and more data are necessary for a variety of contaminants in order to make these soil absorption values scientifically sound and defensible.

Discussion Area 3

Group 2 felt that the proposed default absorption fraction of 10% for organic compounds in soil is adequate ("better than nothing") given the limited data set. They recognized that the data set is limited and that this 10% may not be the best value, but that it appears to be the best given available data limitations. Group 2 emphasized, however, that the document does not adequately explain the basis and empirical support for the 10% default value. Current empirical support for this default value is not overwhelming: existing data are biased and limited. Group 2 emphasized the need for more experimental data on absorption fraction. They suggested that the workgroup may want to present these default values to risk assessors as a distribution or range of values reflecting uncertainity, rather than as a point estimate.

Group 2 also suggested that experimental data for soil extraction using a solvent might be a basis for departing from the use of these default values. Therefore, the document might want to include a discussion about when and how these default values should be used for screening or baseline risk assessments. Group 2 said that the document should explicitly state the limitations of using these default values for screening purposes.

Discussion Area 4

Group 2 expressed little confidence in the proposed default absorption fraction of 1% for inorganic compounds in soil, primarily because the 1% value is based on only two studies (arsenic, cadmium). Group 2 said that they need more data in order to reach agreement on inorganic default values. They asked the workgroup to clearly explain the basis and rationale for the cadmium value, specifically why cadmium was set apart from other inorganic compounds. Group 2 suggested that the workgroup may want to present these default values to risk assessors as a distribution or range of values rather than as a point estimate.

Discussion Area 5

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Group 2 felt that the proposed approach to calculate a total body soil-to-skin AF based on the surface-area-weighted AFs for each body part was "a great leap forward." Group 2 endorsed the general concept, but for the most part felt uncomfortable with using percentages in these calculations. Instead of percentages, they would prefer to do more analysis of underlying probabilities to determine central tendencies and the underlying confidence level of such estimates. Group 2 suggested that the workgroup explore various statistical approaches for estimating the central tendencies and reasonable maximum exposure (RME) values.

Group 3

Chair: John Kissel, University of Washington

Discussion Area 1

Group 3 said that, for the short term, the workgroup's dermal absorption fraction approach appears acceptable, but that the current approach is limited because it relies entirely on experimental data for absorption at 24 hours. This constraint may be problematic when the workgroup tries to increase the complexity of their approach to consider the actual duration of exposure events. For the long term, Group 3 would like to expand the data set to incorporate experimental data of all kinds, including data for less than 24 hours. This will require further experimental research and data collection.

Group 3 said that current default numbers for soil contact rates appear to be consistent with the empirical observations of one of the group's members. These current default values appear approximately right even though they appear to have been derived at least in part on inaccurate assumptions. Therefore, Group 3 recommended that the workgroup not change the individual parameters in their current absorption fraction approach for soil unless they plan on addressing and overhauling their entire approach. Due to the magnitude of such an initiative, which would have to incorporate factors such as time-dependent absorption kinetics and soil characteristics (e.g., particle size, aging, moisture content), Group 3 recommended that this project be placed in the "Future" category.

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Discussion Area 2

According to Group 3, the table's soil absorption values were biased and heavily dominated by *in vivo* (e.g., Wester et al.) data. Such dependence on *in vivo* data may not be scientifically sound and defensible, because these studies:

- **#** Used particle sizes that were too large.
- **#** Involved a pattern of contact that may or may not better correspond to real exposures than *in vitro* methods.
- **#** Did not age the contaminant on the soil

Discussion Area 3

Group 3 said that the proposed default absorption fraction of 10% for organic compounds in soil is "good enough." They recognized that data to verify this default assumption are limited and that more data are needed.

Discussion Area 4

Group 3 said that the proposed default absorption fraction of 1% for inorganic compounds in soil seems conservative. Group 3 recognized that extremely limited data are available for inorganic compounds, but that this default assumption probably overestimates exposure. They raised the issue that not all metals are well absorbed into the body orally either, and asked how the workgroup might account for gastrointestinal absorption adjustments when performing route-to-route extrapolation.

Discussion Area 5

The general concept and proposed approach for the total body soil-to-skin AF received Group 3's support. Group 3 said that the approach was generally good, but that they would like to see the model account for site-specific conditions. Briefly, Group 3 discussed hand-loading and other variables that may need to be addressed in the model so that exposures are not unnecessarily over- or underestimated.

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General Discussion

Jim Bruckner raised the issue of factors influencing the dermal availability of chemicals in soil. It was noted that absorbed doses are altered by the solubility of a chemical (e.g., for different compounds of the same metal). The expert consultants also discussed how the dermal model should account for sweating, the rate of transfer, soil dust adherence to skin, and contaminant transfer in skin. Additionally, higher contamination levels generally exist in fine-particle soils than in coarser material. Therefore, site-specific conditions are likely to influence dermal absorption. Mr. Clewell raised the example of arsenic inhalation, saying that the composition of a chemical in the environment significantly affects the chemical's absorption into the body. Therefore, the state of a chemical and other site-specific issues are relevant factors that should be incorporated into the ABS values for dermal contact with soil. Dr. Leber suggested using total body adherence factor (TBAF) extraction methodology to determine chemical availability. Most peer consultants endorsed using TBAF methodologies, and agreed that if a chemical is not available to the solvent then it will not be available to the skin.

Observer Comment

No observers commented on this topic.

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5. ADJUSTMENT OF TOXICITY FACTORS TO REFLECT ABSORBED DOSE

5.1 Presentation

Mark Maddaloni from EPA Region 2 began the toxicity adjustment discussion by presenting an equation: risk = dose x toxicity. He emphasized that in this equation, the units need to be harmonious. Typically, dose and toxicity are represented as administered doses and experimental data on dermal doses are not available. Therefore, the question arises of how to adjust toxicity values derived from oral dosing studies to correspond to dermal exposures. The methodologies described in the Superfund Dermal Guidance recommended that "adjustment of oral toxicity values should be considered when characterizing the risk associated with the dermal exposure route." The Superfund Dermal Guidance also provided a summary of some gastrointestinal absorption efficiencies and a table of recommendations pertaining to whether adjustment of the oral toxicity factor might be necessary. The apparent solution to this dilemma is to adjust the toxicity factor to reflect the actual absorbed dose in a given scenario.

Adjusting toxicity factors to reflect actual absorbed doses can be done using the following equation: $Dose_{abs} = dose_{adm} \times Fraction_{abs}$. The workgroup endeavored to incorporate this adjustment into their dermal guidance document. Using this equation, complete chemical absorption (. 100%) (i.e., the absorbed dose equals the administered dose) requires no toxicity adjustment. Poor chemical absorption, however, means that the absorbed dose is relatively small compared to the administered dose, thereby requiring a change in toxicity factor to accurately represent internal dose.

To accurately incorporate toxicity adjustments into risk assessment guidance, the workgroup must address two issues that may be problematic due to limited available data. First, the workgroup must obtain absorption estimations from critical studies; second, the workgroup must practically apply toxicity adjustments for risk assessments.

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Mr. Maddaloni defined a "critical study" as one that defines reference dose concentrations, and therefore is the basis for deriving a toxicity factor. A critical study is essentially a toxicity assessment based on a dose/response relationship that rarely accounts for bioavailability determinations. Critical study results can vary depending on host characteristics and study regimen (i.e., how the dose was administered). Most critical studies contain minimal, if any, information about absorbed dose. Rather than redoing critical studies to obtain needed experimental data, the workgroup performed an extensive literature review of chemical-specific bioavailability studies. They focused their literature search on bioavailability studies that most closely mimicked the methodologies and variables of critical studies, specifically similar host characteristics (e.g., species, age, sex) and dosing regimens (e.g., route, vehicle, dosage). From this information, the workgroup compiled a table of various compounds, their oral absorption (bioavailability), and whether or not a toxicity factor adjustment was necessary. This table can be found in the Superfund Dermal Guidance document.

As for the practical application of toxicity adjustments for risk assessments, the workgroup recognized that, theoretically, a toxicity adjustment would be necessary whenever absorption in a critical study was less than 100%. Because, however, critical studies have limited precision and vary in their results and approaches, Mr. Maddaloni said, adjusting for toxicity factors when analyzing chemicals with high absorption dose rates (e.g., 95%) may result in "toxicological hair splitting." A high degree of uncertainty is often involved in assessing chemical bioavailability. Therefore, using toxicity adjustments for high-absorption rate chemicals could imply a false level of accuracy and precision regarding absorbed doses. For these reasons and other practical purposes, the workgroup proposed a "50% rule": toxicity adjustments should only be applied when absorption in a critical study was less than 50%. Mr. Maddaloni asked the expert consultants to comment on the proposed 50% rule and its implications on policy decisions for managing uncertainty.

After Mr. Maddaloni concluded his presentation, Mr. Clewell asked the consultants also to think about toxicity factors in the context of:

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Metabolic effects.

Organic versus inorganic issues.

Overestimating versus underestimating risks.

5.2 Discussion

Following Mr. Maddaloni's presentation, the peer consultants divided into three breakout groups to discuss the adjustment of toxicity factors to reflect absorbed doses. Based on the charge (Appendix A), the breakout groups focused their discussion on the following two topic areas:

1. In cases where the critical study, which forms the basis of the toxicity factor, hasn't provided adequate information on oral absorption, the Superfund Dermal Guidance attempts to identify appropriate bioavailability studies in the peer reviewed literature. Such studies are reflected based on their resemblance to the critical study in terms of dosing regimen (e.g., route, vehicle, and dosage) and host characteristics (e.g., species, age, and sex), in order to provide sufficient information on the oral absorption of the chemical in question. Comment on the factors considered in the selection of appropriate bioavailability studies. Should other factors be considered? Also, comment on the studies summarized in Table 4.1. Are the estimates of gastrointestinal absorption the best available?

2. The information in Table 4.1 in Chapter 4 is then used to determine if an adjustment in the toxicity factor is necessary to account for the difference in the estimated dose between the oral and dermal routes. The Superfund Dermal Guidance recommends making quantitative adjustments to toxicity factors only when there is evidence to indicate that the oral absorption in the critical study was significantly less than complete. An oral absorption fraction of 50% is recommended as the cut-off for this purpose. This avoids making minor adjustments for chemicals that exhibit relatively efficient absorption (80-90%). Further, the 50% cut-off is intended to reflect the inherent variability associated with measuring bioavailability. Comment on the approach for deciding when to make adjustments to the oral toxicity factor. Are these recommendations scientifically sound and defensible? Is the rationale for selecting a 50% cut-off clear and transparent? Is the cut-off estimate scientifically sound and defensible?

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Following the breakout discussions, the consultants reconvened in a plenary session. The breakout group chairs summarized the discussions as follows. (Copies of the overheads used by the chairs in making their presentations are included in Appendix F.)

Group 1

Chair: Annette Bunge, Colorado School of Mines

Discussion Area 1

Group 1 did not enthusiastically support the workgroup's approach of adjusting toxicity values using selected bioavailability studies. Group 1 suggested that it might be better to use gastrointestinal absorption factors for estimating oral bioavailability and creating a dermal reference dose. Given current data constraints, gastrointestinal absorption factors might prove more scientifically feasible for inorganic compounds. For organic compounds, Group 1 suggested, a reference dose based on experimental dermal data would be most preferable. In the absence of such data, the workgroup should consider adjusting its toxicity factors based on inhalation- or intravenous-pathway studies, provided that these data are available.

Discussion Area 2

Group 1 was not enthusiastic about the workgroup's 50% cut-off value, but they admitted that 50% was acceptable. The group said that the document's discussion of absorption factors should consider and note first-pass metabolic transformations. In some instances, when metabolic transformation factors are accounted for, dermal contact can be more toxic than oral ingestion for the same dose (i.e., inactivation). In other instances, oral ingestion is more toxic than dermal contact for the same dose (i.e., activation). The only way to assess such route-to-route extrapolations is to consider metabolic transformations. Group 1 recommended to the workgroup that they address this issue by including language in the document that says it is appropriate to use a gastrointestinal absorption factor for chemicals with efficient absorption rates (e.g., 80–100%), except for those chemicals with known or expected or possible first-pass metabolic effects.

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When discussing route-to-route extrapolations, Group 1 said that the effective absorbed dose rate (i.e., timing of exposure) must be taken into account by the workgroup. Specifically, the workgroup should address whether or not the toxicity factor was derived from short- or long-term ingestion studies, and whether or not these toxicity factors are being applied to short- or long-term dermal exposure periods. The workgroup could address such issues by identifying ingestion study methodologies (e.g., short- or long-term gavage, feeding, or drinking studies) and dermal exposure scenarios (e.g., short- or long-term shower, pica behavior, or occupational exposure). Group 1 acknowledged that it is difficult to relate toxicity for one dosing procedure to another. Single administered doses (e.g., injection) cannot often successfully be compared to divided administered doses (e.g., feeding studies) because they fail to consider chemical concentrations per unit period of time. Therefore, dermal risk assessment is not only a matter of determining exposure time, but also relating this exposure to the time-frame and dose administration periods involved in the critical study.

Lastly, Group 1 felt that the document needs to describe Table 4.1's toxicity factor data better. Specifically, the workgroup should discuss the derivations and limitations of such toxicity factor data. Without such qualification of the table data, Group 1 anticipates that risk assessors may be tempted to misuse the data. Group 1 suggested that the document include the derivation of the reference dose from the critical study, since the reference dose value is the basis for recommending adjustment for using dermal absorption fractions.

Group 2

Chair: Gary Diamond, Syracuse Research Corporation

Discussion Area 1

Group 2 felt that the document needs to state explicitly that the values for absorption factors shown in Table 4.1 apply to the species and study design on which the RfD was based, and that these absorption factors may not be applicable to humans (see Appendix G). Some Group 2 members felt that if better human data were available, they should be included in the table. All Group 2 members agreed that the table should include toxicity factors; the table should specify whether

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their values are applicable to reference doses or cancer slope factors. Group 2 also noted that values in the table indicate a level of precision that may not be realistic (e.g., ±0.1%). They also said that the default assumption value of 50% ("other organics") may not apply to larger-molecular-weight chemicals (e.g., petroleum hydrocarbons). One member of Group 2 suggested that if EPA had better biomarkers of exposure, then the Agency would not need to compile such a data table. Another consultant pointed out that the cadmium and nickel values in Table 4.1 do not reflect the best available data on cadmium and nickel absorption fractions. This may have resulted from the need to select estimates that best reflect the experimental design of the study on which the RfD or cancer slope factor was based. The group also discussed how the workgroup might best extrapolate oral-to-dermal exposures using Haber's assumption. Group 2 felt that the document needs to consider dose-rate differences in the various studies and exposure scenarios.

Discussion Area 2

Group 2 discussed the "50% rule" recommended cut-off value for toxicity factor adjustments. Most Group 2 members endorsed the 50% rule, although there was some concern about how to assess data to determine if 50% is met. Group 2 said that EPA needs to create an oral absorption guidance document similar to the Agency's dermal guidance document. This document should guide researchers and risk assessors on how to evaluate the quality and usefulness of dermal data. This, in turn, will facilitate the incorporation of this data into risk assessment decisions.

Group 3

Chair: John Kissel, University of Washington

Discussion Area 1

Many of Group 3's responses reaffirmed points made by Group 1. Group 3 felt that all the incorporated information in the table was appropriate, but noted that the document text did not explicitly state the factors considered in the selection of the appropriate bioavailability studies. Group 3 suggested that the workgroup include information about the selected studies and their resemblance to a critical study in terms of dosing regimen (e.g., route, vehicle, and dosage) and host characteristics (e.g., species, age, and sex). Group 3 recommended that the workgroup

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rework the document so that it explicitly states the importance of considering dosing regimens, host characteristics, measures of bio-availability, and the potential for first-pass activation/inactivation; all these factors are highly relevant to making route-to-route extrapolations.

Discussion Area 2

Group 3 said that the workgroup's current approach for deciding when to make adjustments to the oral toxicity factor, using an oral absorption fraction of 50%, may lead to a false sense of confidence. Risk assessors may see this information, which is often based on very little experimental data and contains a high degree of uncertainty, and believe that the toxicity factor and oral absorption fractions are more precise measurements than they really are. This could unwittingly lead risk assessors to misuse such information. Therefore, Group 3 felt that the document should include additional language describing relevant uncertainties regarding the adjustment of toxicity factors.

The 50% cut-off for adjusting a chemical's oral toxicity factor was not very popular with Group 3. They suggested that 80% may be a more reasonable cut-off point.

Group 3 was concerned that the workgroup's entire approach to bioavailability might not be applicable to most chemicals. They emphasized that researchers cannot assess route-to-route extrapolations if they do not have chemical-specific information, and currently much of these data do not exist. Therefore, the document text needs to qualitatively address these uncertainties about availability. Addressing these unknowns and uncertainty issues regarding toxicity factors will help to put the dermal guidance in perspective, helping risk assessors to recognize any potential imprecision in the data.

Group 3 felt that acknowledging these uncertainties is especially important when it comes to adjusting the toxicity factors of environmental levels of contaminants. The workgroup also felt that acknowledging skin metabolic factors is important. Currently, numerous gaps exist in data on the importance of skin metabolism of chemicals. For example, no one knows what happens with the

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release of the metabolites (i.e., what happens to metabolites in the skin). The impact of metabolites may be small, or it may be significant, but researchers currently have no understanding of these processes due to limited data.

General Discussion

Mr. Clewell briefly reviewed the three groups' discussions. He began by mentioning the expert consultants' desire that the document more thoroughly discuss and put into perspective the studies and information about bioavailability. Mr. Clewell recapped the general acceptance of using a 50% cut-off level for toxicity factor adjustment. He then asked the consultants to try to distinguish "Today" versus "Tomorrow" issues regarding the adjustment of toxicity factors to reflect an absorbed dose.

Dr. Bunge and other experts agreed that the "Today" category should include descriptive text for Table 4.1 that clearly and completely shows what assumptions the workgroup used to derive the table's toxicity factor values. Specifically, the document should clearly state which critical studies were used, and how they were administered, so that people will not use the table's values for purposes other than those originally intended by the workgroup.

One expert said that EPA's approach effectively removes toxicology from risk assessment in an attempt to simplify the process. In the "Tomorrow" category, the experts hope that the workgroup will be able to better incorporate toxicology (e.g., metabolism, human versus animal factors) and epidemiology into their toxicity adjustment and dermal risk assessment processes.

Dr. Frederick felt that assessing toxicity factors using data from human studies is a practical way to address oral bioavailability and metabolic effects. Dr. Frederick also emphasized the practicality of the 50% cut-off value, saying that it is appealing because it will enable researchers to effectively ignore toxicity adjustments for organic chemicals and only assign toxicity factor adjustments to the inorganic compounds.

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Mr. Clewell emphasized that to a large extent, many of the consultants' concerns can be addressed just as EPA addressed local toxicity issues—by explicitly acknowledging the need to consider the possibility of route-specific metabolism. Many of the constraints for route-to-route extrapolation are also evident in traditional dosimetry approaches that inherently incorporate uncertainty into their species and route extrapolation assumptions. There was general agreement that more data are needed for the oral-to-dermal extrapolation. Several expert consultants strongly recommended that the workgroup add text to the document that explicitly describes when to use the toxicity values in this dermal guidance document table and when to use other (e.g., human) default values. This will help put the default values into their proper perspective, so that people do not think that the dermal guidance document has 100%-accurate answers.

The expert consultants discussed other shortcomings of the toxicity adjustment approach, specifically that it does not account for exposure times, first-pass metabolic effects, and site-specific conditions of environmental availability. The consultants recognized that incorporating all of these theoretical ideas, into a "nice" table or text discussion, would be complex. They felt, however, that even if EPA is not sure how to resolve these issues, that the workgroup must at least identify these data gaps: these unknowns are crucial to the overall dermal guidance approach. Gary Diamond said that the EPA might be able to achieve this goal simply by creating a fuller presentation of its species-specific and human absorption fraction estimates. Dr. Diamond also suggested that the document should more explicitly state that its goal is to estimate bioavailability in the critical study.

All expert consultants agreed that the document needs to encourage data collection. They discussed Haber's law (concentration x time = constant) and its implications of exposure time versus bioavailability time. In general, for prolonged periods of exposure time, toxicity approaches zero. However, the consultants agreed that a chemical's bioavailability may further prolong exposure, thereby confounding results. Further difficulties arise when guidance is used in multi-pathway assessment (e.g., when risk assessors are adding systemic dose received via the dermal route to other routes of exposure to achieve a total dose of one or more chemicals in the body). In these cases, risk assessors are not necessarily relying on a prolonged low-level dermal

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exposure as that which is producing the critical toxic endpoint; such exposure usually adds to the effects of exposures by other routes.

Observer Comment

No observers commented on this topic.

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6. RISK CHARACTERIZATION AND UNCERTAINTY

6.1 Presentation

EPA's 1997 Policy for Use of Probabilistic Analysis in Risk Assessment and 1995 Policy for Risk Characterization call for greater clarity, transparency, reasonableness, and consistency in Agency risk assessments. To address these objectives, all major uncertainties and an evaluation of their influence on the outcome of the risk assessment should be discussed in a risk characterization. The expert consultants discussed many of the major uncertainties identified in the Superfund Dermal Guidance.

To begin their discussions about risk characterization and uncertainty in dermal risk assessment, Anne-Marie Burke outlined the four steps of the risk assessment process: hazard identification, exposure assessment, dose-response assessment, and risk characterization. Ms. Burke discussed EPA's policy for risk characterization, as defined in 1995, as striving to achieve "greater clarity, transparency, reasonableness and consistency in Agency risk assessments." Essentially, EPA's goal was to identify clearly where conclusions were based on science, where conclusions were based on science policy, where default assumptions were used, and how these default assumptions impacted the risk assessment process. To achieve these measures, EPA decided to:

- Discuss their assumptions and uncertainties and how they potentially influence the outcome of risk assessment.
- Present several types of risk information.
  - range of exposures (high-end, central tendency risk)
  - sensitive subgroups
- Assist and improve communication between risk assessors and risk managers.

Ms. Burke reminded the expert consultants of the charge questions. She also asked the consultants to consider whether current data are robust enough to develop standard assumptions for dermal

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risk characterization, and if so, what these standard assumptions might be. Then Ms. Burke gave a brief overview of the elements of the four-step risk assessment process.

Hazard identification involves identifying a subset of chemicals detected which are most likely to result in adverse health effects. During hazard identification, risk assessors consider information about occurrence and distribution of chemicals in the environment; fate, mobility, and persistence in the environment; chemical concentrations; and toxicity based on animal and/or human studies. For the dermal-water pathway, EPA retains a chemical in risk assessment if the dermal pathway contributes at least 10% of the dose from the oral route. For the dermal-soil pathway, EPA retains a chemical in risk assessment if it has a high dermal absorption value (i.e., is readily bioavailable).

As defined in EPA's risk assessment process, *exposure assessment* determines the conditions under which individuals could be exposed to contaminants and the doses exposed people could receive. Ms. Burke reviewed the exposure assessment equations for dermal-water and dermal-soil pathways.

Ms. Burke then addressed uncertainties associated with the exposure assessment step of dermal risk assessment. Major uncertainties identified by EPA for the dermal-water pathway include:

- Model for DA_{event}
  - $K_p \pm K_{ow}$
- Concentration term for water
- Exposure time

Ms. Burke talked about EPA's kinetics of absorption uncertainty assumptions. She stressed that the Agency needs a more formal process to address uncertainties involved in the dermal risk assessment process.

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Major uncertainties identified by EPA for the dermal-soil pathway include:

- AF
- Concentration term for soil
- Dermal-soil absorption values
- Model for DA_{event}
- Frequency
- Surface area
- Default absorption values for classes of chemicals

Ms. Burke restated the conclusion, drawn from prior consultant discussions, that most experts at the meeting accepted the 10% default value for organic compounds in soil. The expert consultants were not, however, very confident in the 1% default value for inorganic compounds in soil.

Dose-response assessment (the third step of the risk assessment process) involves evaluating toxicity information and characterizing the relationship between the dose of the contaminant received with the incidence of adverse health effects in the exposed population. Dose-response assessments develop chemical-specific reference doses and slope factors. Ms. Burke noted that the same approach for these assessments is used for dermal-water and dermal-soil pathways. Uncertainties associated with the dose-response step of dermal risk assessment include:

- The lack of reference doses and cancer slope factors specific for the dermal pathway.
- The lack of dermal slope factor for cPAHs (most slope factor information is derived from direct dermal application).

For *risk characterization*, the fourth stage of the dermal risk assessment process, Ms. Burke reviewed the equations for cancer endpoints (excess cancer risk) and noncancer endpoints (hazard quotient). She pointed out several assumptions and uncertainties regarding risk characterization,

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including the lack of information on gastrointestinal absorption and the lack of information about toxicity at the skin surface.

Ms. Burke concluded her presentation by asking the expert consultants to consider whether or not it seems reasonable that the dermal pathway can drive the risk assessment process in certain circumstances.

6.2 Discussion

Following Ms. Burke's presentation, the peer consultants divided into three breakout groups to discuss risk characterization and uncertainty issues. Based on the charge (Appendix A), the breakout groups focused their discussion on the following four topic areas:

1. Have the factors which make the most significant contribution to uncertainty been identified in this guidance? Is the discussion of the uncertainties complete?

2. How should these uncertainties be characterized in a dermal risk assessment in order to effectively communicate the results to risk managers and the public?

3. Using the default assumptions in this guidance, the estimated risks associated with dermal exposure are often greater than the risks for the ingestion or inhalation routes, particularly for contaminants in soil. How does the magnitude of the uncertainty for estimating dermal risks compare to the uncertainty for these other routes of exposure? How should this information be used to characterize the uncertainty for the dermal route?

4. How can the magnitude of the uncertainties be reduced in order to improve the overall quality of risk assessment?

Following the breakout discussions, the consultants reconvened in a plenary session. The breakout group chairs summarized the discussions as follows. (Copies of the overheads used by the chairs in making their presentations are included in Appendix F.)

Group 1

Chair: Annette Bunge, Colorado School of Mines

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Discussion Area 1

Group 1 emphasized that more data, especially soil data, are needed to reduce uncertainties in the dermal guidance document. Group 1 said that a 10% default value for organic compounds in soil was a threshold starting place, but that much more research is needed. The group mentioned studies on 4-cyanophenol, as evidence that absorption from soils can exceed the 10% default. Group 1 felt that the guidance document identified all important uncertainties, but recommended that the document discuss some uncertainties in greater detail. Group 1 also suggested that the ionization of chemicals in water not necessarily be regarded as an uncertainty in the context of this dermal guidance document. They also raised questions about the impact of pH factors on the dermal risk assessment process.

Discussion Area 2

Addressing the characterization of uncertainty, Group 1 suggested that the workgroup consider labeling uncertainty with a numerical order of magnitude value (e.g., 2-, 10-, 100-fold). Representing uncertainty with order of magnitude values may help to put the relative importance of various factors into perspective. In other words, it will be easier for risk assessors to determine which uncertainties are more likely to be more significant and which are likely to be less significant in the dermal risk assessment process. Group 1 recommended that the workgroup consider categorizing uncertainties by:

- Exposed dose
- Absorbed dose
- K_p, t_{exp}, Absorption Factor
- Dermal to oral (species) extrapolation

Discussion Area 3

Group 1 said that it may sometimes be possible for dermal risks to exceed oral or inhalation exposure risks, but more research needs to be done to identify chemicals and/or chemical classes for which this makes sense. Some consultants in Group 1 suggested that dermal risks may

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outweigh other exposure pathway risks for high-molecular-weight chemicals such as hydrocarbons.

Discussion Area 4

Group 1 felt that the magnitude of uncertainties can be reduced by more data collection. Specifically, Group 1 would like to see more dermal data generated for chemicals in soil and for high-molecular-weight chemicals in water.

Group 2

Chair: Gary Diamond, Syracuse Research Corporation

Discussion Area 1

Group 2 felt that variables that could be represented as reflecting variability include: shower time, surface area, and absorption fractions. Available data are not adequate to support distributions of K_ps for individual chemicals.

According to Group 2, the dermal guidance document identified several tools for characterizing uncertainty:

- Conducting sensitivity analysis (ranking of importance)
- Identifying research needs
- Identifying what distributions are needed

Group 2 identified other uncertainties, including temperature effects, aging of skin, concentration terms, summing across pathways, different absorption dose rates, pathway-specific toxicologic targets, and K_p prediction uncertainty. Group 2 felt that the workgroup identified these uncertainties in the guidance and that the next step was to quantify these uncertainties to determine which factors are most important.

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Discussion Area 2

To effectively communicate uncertainty regarding dermal risk assessment, Group 2 recommended that the workgroup quantitatively identify the uncertainties by level of importance. Group 2 also raised the question of how the collection of site-specific data might reduce uncertainty, but did not draw specific conclusions or make recommendations regarding site-specific data collection. Group 2 recommended that the workgroup consider addressing uncertainty with an order of magnitude or range value, saying that sometimes a higher confidence can be achieved with a distribution than a point estimate.

Discussion Area 3

Group 2 said that if the dermal risk drives soil pathway risk assessments, then the model and default assumptions for estimating risks are probably flawed. Currently, data do not exist to support the conclusion that health effects at Superfund sites are associated with the dermal pathway. Group 2 suggested that it would be good to have a dermal reference dose for a select few problem chemicals (e.g., PAHs, organic chlorine pesticides). Such chemical-specific data could serve as benchmarks that may enable researchers and risk assessors to determine whether or not dermal pathway exposure is a problem.

Discussion Area 4

To improve the overall quality of dermal risk assessment and reduce uncertainty, Group 2 recommended that the workgroup focus on evaluating and validating models. The workgroup should more thoroughly evaluate the types of studies used to create the models. The workgroup might also consider comparing existing data using biomarkers of exposure (e.g., biological exposure index [BEI]) with estimated dermal doses. Group 2 suggested that the workgroup apply models for estimating K_ps and dermal doses to pharmaceuticals. For example, the workgroup could evaluate the K_ps predictive model and dermal dose model by conducting relatively simple nicotine or nitroglycerin human studies. Human studies such as these will enable the workgroup to compare their predicted dermal doses with *in vivo* estimated dermal doses, which will in turn help them to evaluate and validate their models. Group 2 felt that the current validation studies cited in the dermal guidance document are not adequate to support a confidence statement.

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The weakest part of the model's variable distributions was the lack of soil data. The group agreed that information gathering and generating should be a priority to improve the overall quality of dermal risk assessment. They said that the workgroup might want to approach data gathering with a probabilistic-distribution mind set. Even if these data are of poor quality, it is highly probable that researchers will obtain more information from scientifically unsound probability distributions than they would from scientifically unsound single-point estimates.

Group 3

Chair: John Kissel, University of Washington

Discussion Area 1

Overall, Group 3 felt that the dermal guidance document addressed most of the factors that significantly contribute to uncertainty. Group 3 distinguished between identifying the uncertainties and emphasizing the uncertainties in order to put dermal risk assessment uncertainties into perspective. The expert panelists felt that the document should emphasize some of the identified uncertainties over others. They suggested that the workgroup place particular emphasis on uncertainties regarding route-to-route extrapolations and dermal absorption of inorganics from soil. For example, the document should discuss route-to-route extrapolations and toxicity factor uncertainties in its introduction of Section 5.2.

Discussion Area 2

Group 3 suggested qualitatively ranking uncertainties based on Agency confidence levels, using "low," "medium," and "high" ratings of parameter confidence. The experts emphasized communicating "comparative" risk estimates to risk managers and the public.

Discussion Area 3

Group 3 said that the magnitude of uncertainty regarding dermal exposure is greater and more problematic than other exposure-route uncertainties. The two uncertainties highlighted by Group 3 were route-to-route extrapolations and exposure estimates for inorganics from soil. Group 3 suggested that the workgroup consider adding monolayer adjustment (with an appropriate

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explanation of how and when to use it) in the document text. Group 3 also felt that the dermal guidance needs more discussion and recommendations regarding sediments and sediment exposure. Group 3 discussed replenishment of contaminated soil on the skin, concluding that it was another uncertainty area that the workgroup might want to address.

Discussion Area 4

Group 3 felt that more data acquisition will lower the magnitude of dermal exposure uncertainties and improve the overall quality of risk assessments. Group 3 recommended creating standard protocols for dermal studies. Consultants in Group 3 also suggested that the workgroup search for opportunities to validate their assumptions and approaches used in the dermal models and guidance.

General Discussion

Mr. Clewell summarized the group's discussions about dermal risk characterization and uncertainty. He mentioned factors such as the oral toxicity factors, exclusion of skin toxicity, predicted K_ps versus experimental data, the lack of soil data, and other dermal data gaps and uncertainties. The expert consultants briefly discussed the benefits and costs of conducting *in vitro* versus *in vivo* experiments for dermal data generation. Mr. Clewell said that the most important variable in chemical availability appears to be chemical form (composition); the consultants agreed that chemical form and compound variations are more important than site-specific soil conditions.

The panelists discussed the implications of the fact that there are so many data gaps; they recognized that for many risk assessors, the level of uncertainty regarding dermal exposure to inorganics in soil is so high that pathway is often not included in the risk assessment process. For example, the State of New Jersey does not examine the dermal pathway as part of its risk assessment process, primarily because the State does not want to let dermal uncertainty drive risk management. Several expert consultants expressed concern about functionally ignoring dermal exposure. This concern generally focused on dermal exposure to organic chemicals.

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Dr. Frederick said that he is not overly concerned with dermal exposure to inorganic chemicals because the metal ions do not readily pass through soil into skin. Paul Chrostowski emphasized that all chemicals have an octanol/water partition coefficient, even those that do not readily pass through the skin. Several panelists said that they do not feel comfortable dismissing the dermal pathway for inorganics, even though they have doubts that such exposure is significant. Dr. Chrostowski and Rosalind Schoof summarized the conversation by saying that the object of this dermal guidance is to get good data, even if the values for exposure are very low. Therefore, the goal of the workgroup should be to encourage data generation. The consultants recognized that the impetus to research dermal exposure can be enhanced with Agency encouragement and support—for example, if EPA were to integrate new research into their dermal guidance document. Several consultants also recommended developing a protocol for site-specific data generation in order to facilitate and enhance the integration of dermal exposure pathway data and to reduce scientific uncertainty.

The expert consultants recommended that EPA keep the dermal guidance workgroup as a standing working group to provide technical information when needed.

Several panelists endorsed the concept of using the Internet to work toward consistency for the national point of view for dermal risk assessment guidance. An Internet webpage could be created to describe the workgroup. One panelists suggested routing the dermal workgroup webpage through the Risk Assessment Forum. Consultants strongly endorsed creating such Internet links for the dermal workgroup, including a dermal guidance database that would be regularly updated with the most recently available data (similar to EPA's IRIS website).

Observer Comment

Garrett Keating, of the Lawrence Livermore Lab, noted that the words "more data" appeared on nearly every overhead and asked what kind of data, specifically, is needed. Mr. Keating said that risk assessors need guidance in the dermal-soil pathway. Currently, virtually any dermal-soil protocol is considered equally acceptable. Regarding dermal-water exposure, there are

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potentially two kinds of data: steady-state data (the model needs improving) and validation data (the model needs testing). Mr. Keating asked the consultants to address these issues while the document is being developed. He also recommended that, as more *in vivo* data become available, EPA consider ways to incorporate the new information in the document.

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7. NEXT STEPS: PLENARY DISCUSSION ON DERMAL EXPOSURE ISSUES

Before concluding the two-day meeting, Mr. Clewell asked the expert consultants to prioritize the key points they want to convey to EPA, ranking them using three levels: "Today" (short-term), "Tomorrow" (medium-term), and "Future" (long-term).

"Today"

In the short term, the expert consultants would like to see the following points incorporated into and/or more fully addressed in the Superfund Dermal Guidance document:

- Clarify the derivation of the 95% CI for K_p calibration.
- Clarify the basis and derivation of EPD boundaries.
- Clarify the document's text, especially the discussions involving uncertainties.
- Address the fact that the document "underpredicts halogenated chemicals"—consider adjustment based on density.
- Insert the monolayer correction into the document (where appropriate).
- Insert an acknowledgment and citation of the reference (Gerrity and Henry, 1990) for the preferred route-to-route extrapolation.
- Perform sensitivity/uncertainty analysis and rank the uncertainties using qualitative/quantitative measurements (e.g., low, medium, high).
- Define, illustrate, and bound how to calculate lag time ($\hat{o}_l$).
- Define recreational exposure assumptions (including sediment and surface water recreational criteria).
- Establish the workgroup as a standing dermal workgroup (with funding).

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- Acknowledge in the document that there may be a loss of VOCs during shower scenarios because the water chemical concentrations lessen when the water contacts air.

- Add vehicle to toxicity factor table.

"Tomorrow"

In the early stages of the "tomorrow" medium-term period, meaning in the next couple of months, the consultants hope to see the workgroup:

- Perform a regression analysis for K_p using the Vecchia database.

- Perform the regression for K_p using K_{ow} and molar volume rather than K_{ow} and MW.

After this is done, the consultants recommend that the workgroup:

- Perform the regression for K_p using molecular substructures and compare with current method.

- Continue ranking uncertainties using sensitivity/uncertainty analysis of parameters.

- Establish a standard resource depository and clearinghouse (e.g., a website) for reviewed K_p values and other important dermal data to encourage consistency.

- Develop standard criteria for dermal-soil exposure protocols and K_p determinations that allow risk assessors to use chemical-specific experimental K_ps (and soil AFs) instead of predicted K_ps. Criteria should be developed for both retrospective and prospective use in evaluating and planning.

  — *in vivo* protocols

  — *in vitro* protocols

- Refine soil adherence estimates using Dr. Kissel's information.

- Address transfer factors, including dermal exposure estimates from contact with concrete, utility poles, and other surfaces.

- Incorporate pesticide deposition and absorption (neat vs. aqueous) issues.

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- Create an Agency Dermal Working Group (with funding) to address dermal issues spanning all EPA divisions.

- Transfer and integrate dermal data across EPA programs.

Future

Beginning in the next millennium and continuing far into the future, the consultants hope to see the workgroup and other dermal researchers:

- Generate more dermal data, especially for inorganics from soil. This data should include information about specific chemical forms and soil types.

- Collect data, for priority chemicals, on toxicity (portal-of-entry effects). When justified, derive dermal reference doses considering both systemic toxicity effects and portal-of-entry type effects.

- Focus on *in vitro* dermal-soil studies, then progress to *in vivo* studies: develop *in vitro* (and later *in vivo*) study protocols, then use the generated *in vitro* data to learn how dermal exposure is impacted by soil variability, chemical form, and other variables. Expert consultants noted that this may be difficult because broad generalizations may not be accurate and risk assessors may need site-specific data to properly assess dermal exposure issues.

- Use *in vitro* dermal studies to create and/or refine protocols that risk assessors and researchers should use in addressing various classes of chemicals (e.g., inorganics, SVOCs, pesticides, persistent chemicals). *In vitro* studies may also be used to develop screening tests for risk assessors. The panelists noted that the protocols and screening tests may vary by chemical class.

- Conduct human *in vivo* studies with internal biomarkers. For example, look at dermal exposure to benzopyrene or nicotine in order to correlate environmental exposure with measurable systemic exposure. This will help to compare modeled versus experimental data.

- Develop more complete mathematical models (pharmacokinetic and kinetic) for extrapolating to human from animal-study data. Use human studies with butoxyethanol or isopropanol for validation.

- Address how risk assessors can assess the influence of chemical mixtures in the dermal pathway.

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- Examine chemical disposition in different tissues and the ensuing effects of chemicals on various target tissues.

- More thoroughly research the effects of skin metabolism, skin reservoir effects, and chemical metabolism in skin.

After completing the “Today,” “Tomorrow,” and “Future” lists, Mr. Clewell adjourned the meeting by thanking the expert consultants, the EPA workgroup, and observers for their participation in the Risk Assessment Forum’s Workshop on Issues Associated with Dermal Exposure and Uptake.

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APPENDIX A

CHARGE TO PEER CONSULTANTS

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Workshop on Issues Associated with Dermal Exposure and Uptake

U.S. Environmental Protection Agency
Washington, D.C.
December 1998

Charge to Experts/Discussion Issues

This workshop is being held to discuss issues associated with estimating dermal exposure and uptake of environmental contaminants. The workshop discussions will focus on generic technical issues raised during the February 1998 peer review of the *Risk Assessment Guidance for Superfund, Supplemental Guidance, Dermal Risk Assessment* (hereafter known as the Superfund Dermal Guidance). Although the workshop issues were derived from the review of a proposed Superfund model, they are generically applicable to the estimation of chemical uptake within many U.S. Environmental Protection Agency (EPA) programs. Therefore, discussion of these issues at the workshop should not be limited to the context of the Superfund Dermal Guidance.

Background

In January 1992, the EPA Office of Health and Environmental Assessment (now the National Center for Environmental Assessment, NCEA) completed an interim report entitled *Dermal Exposure Assessment: Principles and Applications*. This report provides guidance for conducting dermal exposure and risk assessments. The conclusions of this report were summarized at the January 1992 National Superfund Risk Assessors Conference. During this meeting, Regional risk assessors requested that a workgroup be formed to prepare an interim dermal risk assessment guidance for the Superfund program. The purpose of this guidance would be to promote consistency in the procedures used by the EPA Regions to assess risks from dermal exposure at Superfund sites. In August 1992, a draft Superfund Dermal Guidance was circulated for review and comment.

In 1995, a workgroup convened to address issues related to the August 1992 Superfund Dermal Guidance and to redraft the document. The revised guidance was peer reviewed in February 1998. Several issues related to dermal exposure and risk assessment were raised during the peer review. The workgroup addressed some of these issues in a revised draft of the guidance. Other issues raised during the peer review were broader in scope. The EPA Risk Assessment Forum is organizing the present workshop to discuss some of these broader, more generic issues.

Discussion Issues

The generic technical issues identified during the February 1998 peer review of the Superfund Dermal Guidance can be organized into four categories: issues associated with dermal exposure to contaminants in water, issues associated with dermal exposure to contaminants in soil, issues associated with the adjustment of toxicity factors to reflect absorbed dose, and issues

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related to risk characterization and uncertainty analysis for dermal assessments. These issues will be the focal point for discussions during this workshop. For each category, workshop participants are referred to specific sections of the November 1998 draft of the Superfund Dermal Guidance for background and technical details.

The questions within each category are intended to help structure and guide the workshop discussions. In addressing these questions, workshop participants are asked to consider: what do we know today that can be applied to answering the question or providing additional guidance on the topic; what short term studies could be conducted to answer the question or provide additional guidance; and what longer term research may be needed to answer the question or provide additional guidance.

Dermal Exposure to Contaminants in Water

Proposed approaches for estimating dermal exposure and uptake of chemical contaminants in water are presented in Chapter 3 of the November 1998 draft Superfund Dermal Guidance. In the approach for organic chemicals, a skin permeability coefficient (K_p) is estimated as a function of a chemical's octanol/water partition coefficient (K_{ow}) and its molecular weight (MW). The relationship is based on a regression analysis of measured skin permeabilities. For metals and inorganic chemicals, the Superfund Dermal Guidance recommends using measured K_p values. In the absence of measured values, a default of 0.001 cm/hr is recommended.

1. Comment on the correlation equation used to estimate the skin permeability coefficient (K_p) for organic chemicals. Is the approach used to estimate the K_p values and their 95% confidence intervals plausible? Include in the discussion consideration of the database analyzed to generate the correlation equation.

2. Comment on the statistical analysis used to establish the Effective Predictive Domain for the K_p correlation equation (i.e., the range of K_{ow} and MW where the predictive power of the regression equation would be valid). Evaluate the new methodology for calculating $K_{p,max}$ for chemicals outside of the Effective Predictive Domain.

3. Comment on the use of K_p and $K_{p,max}$ in the dermal absorption model (specifically the use of K_p for all t_{event} (exposure time) < t* (time to reach steady state absorption), and the use of K_p or $K_{p,max}$ when t_{event} > t*).
4. Comment on the use of predicted K_p or $K_{p,max}$ vs. chemical specific experimental values. Consider the criteria used to select studies to develop the regression model (see Appendix A of the Superfund Dermal Guidance). Should these and other criteria be used to judge chemical specific experimental values? What are the minimum criteria that should be satisfied before chemical specific experimental values can be used in lieu of model predictions?

5. Comment on the approach recommended for metals and inorganic chemicals. Is the default K_p (0.001 cm/hr), that was previously recommended in the 1992 Interim

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Guidance for Dermal Exposure Assessment, still scientifically sound and defensible?

6. Comment on the other default exposure assumptions (see Table 3.2) recommended to estimate the Dermal Absorbed Dose per event (DA_{event}) (e.g., t_{event} = 10 minutes for exposure in a shower). Are these defaults scientifically sound and defensible?

Dermal Exposure to Contaminants in Soil

Recommendations for estimating dermal exposure and uptake of chemical contaminants in soil are presented in Chapter 3 of the Superfund Dermal Guidance. The approach is very briefly summarized in this chapter and the reader is referred to Chapter 6 of the 1992 *Dermal Exposure Assessment: Principles and Applications* for details on the methodology. Table 3.4 in Chapter 3 lists recommended absorption fractions for two metals and eight organic compounds/classes of compounds. These estimates are based on data. Table 3.4 also lists two default absorption fractions to be used in the absence of measurements. For semivolatile organic compounds, a default absorption fraction of 10% is recommended. For inorganic chemicals, a default of 1% is recommended.

Estimates of soil-to-skin adherence must be used with estimates of absorption fraction from soil to calculate the Dermal Absorbed Dose per event (DA_{event}). Recommendations on the use of soil-to-skin adherence factors also are presented in Chapter 3 of the Superfund Dermal Guidance. Table 3.3 in Chapter 3 list some soil-to-skin adherence factors by activity and soil moisture content.

1. Discuss the current absorption fraction approach as applied to the dermal absorption of chemical contaminants from soil. Consider such factors as the duration of soil contact, the soil particle size, and the level of soil moisture and whether these factors should be used to adjust the absorption estimate. Overall, is the proposed methodology scientifically sound and defensible?

2. Comment on the soil absorption values presented in Table 3.4 of the Superfund Dermal Guidance. Are these estimates supported by the available data? Are they scientifically sound and defensible?

3. Comment on the proposed default absorption fraction of 10% for organic compounds in soil. Is the rationale for selecting this default clear and transparent? Is the estimate scientifically sound and defensible? Is their enough supporting evidence to allow this estimate to be characterized as representative of the average?

4. Comment on the proposed default absorption fraction of 1% for inorganic chemicals in soil. Is the rationale for selecting this default clear and transparent? Is the estimate scientifically sound and defensible? Is their enough supporting

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evidence to allow this estimate to be characterized as representative of the average?

5. Comment on the proposed approach to calculate a total body soil-to-skin adherence factor based on the surface area weighted adherence factors for each body part. Is this a scientifically sound approach? Could other methodologies be recommended?

Adjustment of Toxicity Factors to Reflect Absorbed Dose

Chapter 4 of the Superfund Dermal Guidance provides a discussion on adjusting toxicity values derived from oral dosing studies. The methodologies described in the Superfund Dermal Guidance attempt to estimate absorbed or internal dose following dermal exposure. However, many toxicity factors (such as the cancer slope factors and RfDs reported in IRIS) are derived from an administered oral dose. Therefore, it is recommended in Chapter 4 that "adjustment of oral toxicity values should be considered when characterizing the risk associated with the dermal exposure route." Table 4.1 in Chapter 4 provides a summary of some gastrointestinal absorption efficiencies that are available in the published literature. Also provided in the table are recommendations pertaining to whether adjustment of the oral toxicity factor would be necessary.

1. In cases where the critical study, which forms the basis of a toxicity factor, hasn't provided adequate information on oral absorption, the Superfund Dermal Guidance attempts to identify appropriate bioavailability studies in the peer reviewed literature. Such studies are selected based on their resemblance to the critical study in terms of dosing regimen (e.g., route, vehicle, and dosage) and host characteristics (e.g., species, age, and sex), in order to provide sufficient information on the oral absorption of the chemical in question. Comment on the factors considered in the selection of appropriate bioavailability studies. Should other factors be considered? Also, comment on the studies summarized in Table 4.1. Are the estimates of gastrointestinal absorption the best available?

2. The information in Table 4.1 in Chapter 4 is then used to determine if an adjustment in the toxicity factor is necessary to account for the difference in the estimated dose between the oral and dermal routes. The Superfund Dermal Guidance recommends making quantitative adjustments to toxicity factors only when there is evidence to indicate that the oral absorption in the critical study was significantly less than complete. An oral absorption fraction of 50% is recommended as the cut-off for this purpose. This avoids making minor adjustments for chemicals that exhibit relatively efficient absorption (80-90%). Further, the 50% cut-off is intended to reflect the inherent variability associated with measuring bioavailability. Comment on the approach for deciding when to make adjustments to the oral toxicity factor. Are these recommendations scientifically sound and defensible? Is the rationale for selecting a 50% cut-off clear and transparent? Is the cut-off estimate scientifically sound and defensible?

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Risk Characterization and Uncertainty

The EPA's 1997 Policy for Use of Probabilistic Analysis in Risk Assessment and 1995 Policy for Risk Characterization call for greater clarity, transparency, reasonableness, and consistency in Agency risk assessments. To address these objectives, all major uncertainties and an evaluation of their influence on the outcome of the risk assessment should be discussed in a risk characterization. Some of the major uncertainties in dermal risk assessments are identified in Chapter 5 of the Superfund Dermal Guidance. These include:

the reliance on adjusted oral toxicity factors to estimate toxicity from the dermal route of exposure;

the exclusion of toxic effects at the skin surface in the risk assessment;

the recommended use of permeability coefficients for water that are based on model predictions, rather than measured values;

the lack of quantitative information for the dermal absorption of chemicals in soil; and

variability and uncertainty in dermal exposure parameters for soil contact, such as skin surface area exposed, soil-to-skin adherence, and frequency of exposure.

1) Have the factors which make the most significant contribution to uncertainty been identified in this guidance? Is the discussion of the uncertainties complete?

2) How should these uncertainties be characterized in a dermal risk assessment in order to effectively communicate the results to risk managers and the public?

3) Using the default assumptions in this guidance, the estimated risks associated with dermal exposure are often greater than the risks for the ingestion or inhalation routes, particularly for contaminants in soil. How does the magnitude of the uncertainty for estimating dermal risks compare to the uncertainty for these other routes of exposure? How should this information be used to characterize the uncertainty for the dermal route?

4) How can the magnitude of these uncertainties be reduced in order to improve the overall quality of the risk assessment?

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APPENDIX B

LIST OF PEER CONSULTANTS

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Bethesda, MD
December 10-11, 1998

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APPENDIX C

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APPENDIX D

AGENDA

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Workshop on Issues Associated with Dermal Exposure and Uptake

Bethesda Ramada
Bethesda, MD
December 10-11, 1998

Agenda

Workshop Chair: **Harvey Clewell, ICF Kaiser, International**
Workshop Facilitator: **Jan Connery, Eastern Research Group, Inc.**

THURSDAY, DECEMBER 10, 1998

8:00AM **Registration/Check-In**

8:30AM **Welcome Remarks, Meeting Structure, Objectives, and Peer Consultant Introduction**
Harvey Clewell and Jan Connery

9:00AM **U.S. EPA Risk Assessment Forum's Role**
Steve Knott, U.S. Environmental Protection Agency (U.S. EPA), Risk Assessment Forum

9:10AM **Background on the Current Dermal Guidance**
Mark Johnson, U.S. EPA, Region V and Mark Maddaloni, U.S. EPA, Region II

9:40AM **Charge to the Peer Consultants**
Harvey Clewell

9:55AM **Presentation on Discussion Issue One:**
Dermal Exposure to Contaminants in Water
Kim Hoang, U.S. EPA, Office of Research and Development (ORD)/National Center for Environmental Assessment West (NCEA-W)

10:10AM BREAK

10:25AM **Breakout Group Discussion of Issue One**

11:25AM **Summary of Discussion Issue One**

12:10PM **Observer Comments**

12:20PM LUNCH

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THURSDAY, DECEMBER 10, 1998 ***(continued)***

1:20PM	**Presentation on Discussion Issue Two: Dermal Exposure to Contaminants in Soil** *Mark Johnson*
1:35PM	**Breakout Group Discussion of Issue Two**
2:35PM	**Summary of Discussion Issue Two**
3:20PM	**Observer Comments**
3:30PM	BREAK
3:45PM	**Presentation on Discussion Issue Three: Adjustment of Toxicity Factors to Reflect Absorbed Dose** *Mark Maddaloni*
4:00PM	**Breakout Group Discussion of Issue Three**
5:00PM	**Summary of Discussion Issue Three**
5:45PM	**Observer Comments**
6:00PM	ADJOURN

FRIDAY, DECEMBER 11, 1998

8:45AM	**Planning and Logistics** *Harvey Clewell*
9:00AM	**Presentation on Discussion Issue Four: Risk Characterization and Uncertainty** *Ann-Marie Burke, U.S. EPA, Region I*
9:25AM	**Breakout Group Discussion of Issue Four**
10:15AM	BREAK
10:30AM	**Summary of Discussion Issue Four**
11:15AM	**Observer**
11:30AM	LUNCH
12:30PM	**Next Steps: General Discussion on Dermal Exposure Issues**
2:30PM	**Workshop Summary** *Harvey Clewell*
3:00PM	ADJOURN

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APPENDIX F

BREAKOUT GROUP OVERHEADS

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BREAKOUT GROUP DISCUSSION OF ISSUE ONE:
DERMAL EXPOSURE TO CONTAMINANTS IN WATER

GROUP 1

1. Comment on correlation equation for K_p
   K_p equation? — OK, molar volume may be better
   95% CI? — uncomfortable with this—assumes an error structure that is unknown

   Database used to generate equation—
   More data generation
   — relevant chemicals
   — Log K_{ow} (high & low)
   — standardized procedures
   ± Superfund interests are persistent chemicals
   also included in high production chemicals

2. Statistical analysis of EPD—OK
   There should be a domain based on the properties of data in the database
   Extrapolation outside the EPD—No
   $K_{p,max}$? OK

3. K_p & $K_{p,max}$—OK?

4. $K_p/K_{p,max}$ vs. exp. values.
   ± uncomfortable with ignoring data
   ± options:
   report correlation value
   report "consensus" exp. values. Average (?)

5. Metals—OK, but could be improved. Some issues are:
   speciation is not considered
   methyl mercury—organic rather than metal?
   mercury vapor
   arsenic is missing in metals list

6. No significant comment

May want to state in the document dermal absorption issues of importance to EPA that are <u>not</u> treated. For example, pesticide absorption from pesticide formulation is not treated in document.

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GROUP 2

Issue 1: In Vitro Correlation

1. Database—analyze Vecchia

2. Include substructural parameters in corr. analysis—better r^2
   Explore other K_{ow} predictive models

3. Explore nonlinear models for relating K_{ow}-K_p

4. Use molar volume in place of MW (software avail.)

5. Consider variable dependency (MW-K_{ow}, molar volume-K_{ow})

5a. Consider data transformation in model (e.g., Log)

6. Need high quality database of K_{ow}s—reviewed
   e.g. "Star List"; other data experience

7. UCL_{95}—doc needs to show how UCL_{95} was derived

8. Need to explore experimental K_{ow}s, e.g., HPLC
   - Predictive model may be wrong
   - Need clarification of UCL_{95} A NOW

Issue 2: K_p EPD

1. Need clarification of "outliers of EPD"

2. Need approach for replacing predicted K_{pmax} w/ experimental
   - Predictive approach yields highly conservative values of K_p

Issue 3: EXP Duration

1. No basis for distinguishing t_c < or > t_{ss}
   This needs to be explicitly stated in doc.

Issue 4: Predicted vs. Experimental

1. Use of model might not reward new data collection

2. Use of model contributes to consistency

3. Need criteria for evaluating experimental values

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Issue 5: Inorganic

1. Better documentation of derivation of chemical-specific K_ps

9. Methodology needs to consider both ionized & non-ionized states of inorganics
   How did EPA deal w/ this issue
   Use models—water parameters

Issue 6: DEF EFs

1. Need loss term for C_w—Doc needs to address C_w term on chemical-specific basis

2. PRA

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GROUP 3

1.-4. Guidance should encourage (at least not discourage) data collection
- — need protocols if site specific experimentation is to be conducted
- ± Seek validation
- 1. Seek consistency across EPA groups

5. 10^{-3} for inorganics
- — Hg?
- — Others don't drive?

6. 10-minute shower
- — some doubt as to validity as screen (NHAPS?)
- — Fig. 1.1
  residential vs. recreational

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GENERAL DISCUSSION

C 1. In vitro correlation (Potts & Guy equation)

2. Effective predictive domain
   — $K_{p,max}$

3. Short-term vs. long-term exposure events
   — 2.4 $\hat{o}_{lag}$

C 4. Predicted K_p vs. measured
   — criteria

5. Metals/inorganics
   — default K_p

C 6. Exposure defaults
   — shower > D.W.
   — VOCs

Dermal data

Criteria:
- S.S.
- Donor vehicle "just H_2O"
- Receptor vehicle
  - "no barrier"
  - VOLPO
- T, pH
- In vivo vs. in vitro
  - receptor (high Log K_{ow})
  - pore effect (low K_{ow})
  - metab. (OPs)
- OECD

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BREAKOUT GROUP DISCUSSION OF ISSUE TWO:
DERMAL EXPOSURE TO CONTAMINANTS IN SOIL

GROUP 1

MORE DATA

1. Current Absorption Factor Approach vs. Rate Approach

   Given the theoretical limitations and data limitations maybe this is the best we can do now—

   — Note that data assume 24 hour exposure always
   — Not all data in the literature are included—
   — How should data be added—?
   — Data listed in table should be for less than monolayer coverage (and noted as such)

   Concerns
   a) time effect
   default values—b) mechanisms of transfer from soil to skin (expected vs. actual): sweating, direct contact, vapor pressure
   c) Soil transfer to skin; turn-over vs. no turn-over

2. Data used—
   — soil properties of applied soil (org. carbon, moisture)
   — particle size
   — amount of soil (cp. to monolayer)
   — adjustment to monolayer?
   — contamination procedure
   — default-chemical groups

3. 10% organic compound default?
   No, not clear

4. 10% for inorganic
   No, not clear

   ± Solvent extraction (cp. to max. conc. in solvent)

5. No comment

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GROUP 2

1. Need more experimental data:
   - kinetics
     - ± rate approach
     - ± time adjustment of absorption fraction

   - absorption fraction
   - screen based on extraction—modeling of adsorption

   Need guidance for experimental:
   - std. soils
   - — particle size]
   - — loading] current data biased towards:
   - — aging]
     - — large particle size
     - — unaged
   - expt. prep.
   - — in vitro
   - — in vivo est. of absorption

2. Table 3-4

   Numerous chemical-specific issues with values in table

3. 10% organic default ± ˆ "better than nothing"
   - — basis not clearly presented
   - — empirical support is not overwhelming
     - (need more data)
     - (existing data biased)
   - — Soil extraction (solvent) might be a basis for departing from default
     - — state limitations of use for screening

4. 1% organic default
   - — low confidence in default
     - — based on 2 studies
   - — need more data
   - — explanation of basis of value for cadmium

3. & 4. Present default as distribution
   - (e.g., range)

5. SA weighting—"A great leap forward"

   Estimates for multiple activities
   - — need to explore various statistical approaches for estimating CT & RME

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GROUP 3

1. ABS
   - short term yes
   - long term, move to ÎT … 24 hours (requires knowledge of ABS as f[t])
   - current implicit adult SCR - good, can't change parameters in isolation (contact duration)
   - particle size, aging—yes (LT), moisture - no

2. Table 3.4
   - dominated by Wester et al. data
     - particle size too big
     - in vivo contact?
     - aging

3. 10% org. default
   - OK

4. 1% metal default

   No GI adjustment?

5. Total body AF
   - generally good
   - site specific?

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BREAKOUT GROUP DISCUSSION OF ISSUE THREE:
ADJUSTMENT OF TOXICITY FACTORS TO REFLECT ABSORBED DOSE

GROUP 1

1. GI Absorption Factors for estimating oral bioavailability ± dermal RfD

   OK for inorganics (more defensible)

2. For organics ±
   - dermal RfD best
   - IV or inhalation better

   Almost all absorbs—
   - but should consider oral 1st pass metabolic transformations
     - oral inactivation (dermal would be more toxic than oral)
     - oral activation (oral more toxic)

Recommend language saying OK to use GI Absorption Factor (-100%), except for chemicals with known or expected or possible 1st pass effects.

<u>Route-to-route extrapolation—absorbed dose rate</u>
ingestion
- gavage
- feeding
- drinking

dermal
- showering exposures ± shot time
- soil or occupational exposures ± long time

Ch. 4 needs to describe better what the data in Table 4.1 are & are not. Anticipate the temptation for misuse of the data—may want to include RfD from the critical study since the absorption fraction is tied to this.

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GROUP 2

RAGS:

oral6dermal

$$8HQ = \frac{I}{RfD @ AF9}$$

water6soil

$$9HQ = \frac{I @ RAF9}{RfD}$$

ˆ NEED <u>lower</u> & <u>upper</u> bounds & <u>CTE</u> (central tendency estimate)

$$HQ_{oral} = \frac{I_{oral}}{RfD_{oral}}$$

$$HQ_{dermal} = \frac{U_{dermal}}{?}$$

<u>Options</u>

1. $$HQ_{dermal} = \frac{U_{dermal}}{RfD @ AF_H}$$

2. $$HQ_{dermal} = \frac{U_{dermal}}{NOAEL_{sp} @ AF_{sp} @ UF}$$

<u>Option 1</u>

$$HQ_{dermal} = \frac{U_{dermal}}{NOAEL_{sp} @ AF_{sp} @ UF}$$

1. Revision of RfD prompts revision (review) of AF_{sp}
2. AF_{sp}/AF_H is (may) be a component of UF
3. AF_{sp} are tox. factor-specific (RfD, CSF)

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4. AF_{sp} ... AF_H

5. AF proliferation:
   — AF_{sp}, RfD (1998, 1999, 2005, etc.)
   — AF_{sp}, CSF (1998, 1999, 2005, etc.)
   — AF_H

<u>Option 2</u>

$$HQ_{der} = \frac{U_{der}}{RfD \cdot AF_H}$$

1. Consistent w/definition of RfD

2. Requires EPA to develop one set of AF values, i.e. AF_H

3. Update of AF_H is prompted by new AF data, not new RfD

4. AF_H can be assessed using "standard" approach:
   — weight of evidence
   — UFs—inter- & intraspecies
   — lower and upper bounds etc.

5. EPA has to develop AF_H values anyway to support extrapolations across chemical species and matrix (e.g., source ± soil)

6. Avoids "AF proliferation"

7. Prompts data collection on AF_H needed to support EXP-UPT-biokinetic modeling

<u>TABLE 4.1 VALUES:</u>

— Speciation of inorganics may not be comparable across routes

— Need to be clear that values are for oral ± dermal extrapolation and apply to the $NOAEL_{sp}$ and not necessarily to humans

— If better data for AF_H are available, should it be represented in table 4.1?

— Need to specify to which tox. factor the values in Table 4.1 apply (RfD or CSF)

— Values indicate level of precision that may not be realistic (e.g., 1.# %)

— "Other organics"—may not apply to TPH

— If we had better biomarkers of exposure, we wouldn't need Table 4.1

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— C_d & N_i values do not reflect best data on AF N_i & C_d

— Need to consider dose-rate differences
  — oral ± dermal (i.e., Haber's assumption)

MADD. RULE:

— OK

— How do you assess the data to determine if 50% criteria is met?

MISC.:

Need guidance on how to assess AF_{oral}
There is no "oral" guidance analogous to dermal

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GROUP 3

1. Route, vehicle, dosage
   species, age, sex
   noted in text ± should be added to table
   - + dosing regimen
   - + measure of availability
   - + 1st pass activation/inactivation (and dose)

2. Availability adjustment w/o PK adjustment

   ± danger of false confidence
   50% adjustment not popular (80%?)

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BREAKOUT GROUP DISCUSSION OF ISSUE FOUR:
RISK CHARACTERIZATION AND UNCERTAINTY

GROUP 1

MORE DATA—Especially from soil and, for chemicals with a large Log K_{ow}, from water

1. Have all of the factors been identified ± laundry list
   Yes—
   ± ionization of chemicals in water are not necessarily uncertain if pH is known or can be estimated

2. Characterization of uncertainty?
   Order of magnitude indications?
   2, 10, 100 fold?
   Relative importance—
   which uncertainties are more likely to be large/small

   May want to group uncertainties in:
   (1) exposed dose
   (2) absorbed dose
   K_p, t_{exp}, Abs. Factor
   (3) dermal to oral (species) extrapolation

3. Is it possible that dermal risks really could be larger than oral or inhalation?

   Yes, sometimes—
   Identify chemicals (classes) that this makes sense for?

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GROUP 2

Model variable distributions

- # Shower time—high conf. in variability est.
- # SA— " " "
- # ADH factor—when "Kissel is ready"
- # K_p "don't go there yet"
- # sometimes you have higher confidence in a distribution than a point estimate

UFs

- # sensitivity analysis
  - — ranking of importance
  - — ID research needs
  - — what distributions are needed
- # other UFs:
  - — temperature effects
  - — aging of skin
  - — conc. term
  - — summing across pathways
    - — different abs. dose rates
    - — pathway specific tox. targets
  - — K_p prediction uncertainity

U Communication

- # Quantify uncertainty—
  - ± Which factors are most important?
  - ± Can collection of data @ the site reduce uncertainty?

Dermal UNC Relative to Other Pathways

- # If dermal risk drives soil pathway risk:
  "Houston, we have a problem"
  - C No data supporting health effects at SF sites associated w/dermal pathway
- # It would be good to have dermal RfDs for a few problem chemicals (e.g., PAHs)
  - — Benchmarks—is the dermal pathway a problem?

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Reducing Uncertainty

Compare biomarkers of exposure (e.g., BEI) w/ estimated dermal dose

Apply models for estimated K_p & dermal dose to pharmaceuticals: nicotine, nitroglycerin
- — K_p model evaluation
- — dermal dose model evaluation

Compare predicted dermal dose w/in vivo estimated dermal dose

ˆ Model(s) evaluation/validation is needed
— validation studies cited are not adequate to support a confidence statement

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GROUP 3

How does this approach relate to MCLs
- — concern that MCLs might be used nonconservatively

1. ~ Yes? ID vs. emphasize
   - — route-to-route (but not PK, metabolism)
   - **±** dermal absorption of inorganics from soil

   - **#** section 5.2 intro
     - **±** no mention of route-to-route
   - **#** L, M, H ratings of parameter confidence
   - **#** check list with refs. of PDFs

2. Emphasize "comparative"

3. Dermal uncertainty vs. other routes

   clearly worse
   - **±** route-to-route
   - **±** inorganics from soil

   - **#** add monolayer adjustment
   - **#** sediments?
   - **#** replenishment? **±** ABS

4. **#** more data (standard protocols?)
   - **#** hunt for validation opportunities

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APPENDIX G

POST-MEETING COMMENTS

Note: Post-meeting comments were not required but were submitted by two of the peer consultants, Dr. Gary Diamond and Dr. Kurt Enslein.

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Comments on November 1998 Draft of RAGS Supplemental Guidance: Dermal Risk Assessment

by Dr. Gary Diamond

1. General

The document is very important and will be extremely useful to risk assessors. The Dermal Workgroup should be commended for their efforts to develop and bring this guidance document forward.

2. Table 3.1

The bases for the recommended values of K_p are not obvious from the document. It would be very useful to the reader if the derivation could be made available in a supplemental document or file. This would facilitate updates to the values should new data become available (i.e., the reader needs to know what data were considered in the derivations to identify "new" data). The 1992 ORD report cites Moore et al. (1980) as the basis for a K_p value of 4E-06 cm/hr (page 5-83). The 1998 guidance document cites 5E-07 cm/hr for lead acetate, presumably based on Moore et al. (1980), although this is not stated (Table 3.1). I attempted to derive this value from the Moore et al. (1980) and came up with values ranging between 3.5E-07 - 4.9E-07 cm/hr, depending on which time points were averaged.

3. Table 3.4

The value for the dermal absorption fraction of cadmium in soil is cited as 0.01, from Wester et al. (1992). However, Wester et al (1992) seems to support a values that range from 0.0002 - 0.0007.

4. Adjustment of Toxicity Factors

The oral pathway Hazard Quotient (HQ) is calculated as:

Eq. 1

$$HQ_{oral} = \frac{I_{oral}}{RfD_{oral}}$$

where I is intake and RfD is the oral dose that is not expected to produce an adverse effect in humans, given the associated uncertainties in our understanding of the toxicology of the chemical.

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In the calculation of the dermal pathway HQ, intake (I), is replaced with uptake (U), the "absorbed dermal dose". The issue at hand is the corresponding term that replaces the RfD:

Eq. 2

$$HQ_{dermal} = \frac{U_{dermal}}{?}$$

Two very different approaches are:

Eq. 3

$$HQ_{oral} = \frac{U_{dermal}}{RfD \cdot AF_H}$$

Eq. 4

$$HQ_{oral} = \frac{U_{dermal}}{NOAEL_{Sp} \cdot AF_{Sp} \cdot UF}$$

In Eq 3, the RfD, the "non-adverse intake in humans", is factored by an estimate of the oral absorption fraction in humans (AF_H). In Eq 4, the NOAEL estimate in the species (Sp) used in the "critical study" is factored by an estimate of the absorption fraction in that species (AF_{Sp}) (and for that experimental design).

These two approaches are conceptually very different and require different types of supporting data. The data needed to support Eq 3 are data that would support a best estimate of the oral absorption of the chemical in humans. The data needed to support Eq 4 are data needed to estimate the oral absorption of the chemical in the bioassay (or in exposure scenario, if the RfD was based on a human epidemiology study).

In my opinion, Eq 4 is problematic in the following ways:

A change in the "critical study" will require EPA to derive an AF_{Sp} for the new study design (species, route, dose, etc).

The "critical study" provides a quantitative launching point for the estimate of the NOAEL in the most sensitive human population (i.e., the RfD). This is usually achieved by applying uncertainty factors to a LOAEL or NOAEL observed in a bioassay or epidemiological study. These uncertainty factors account for uncertainties in our understanding of interspecies and intra(human)species variability in absorption. If we factor the $NOAEL_{Sp}$ with AF_{Sp}, we need to consider an adjustment to the UF applied to the $NOAEL_{sp}$.

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Values for AF_{Sp} are not only chemical-specific, but they must be toxicity factor specific. That is, if the oral toxicity and oral cancer bioassays are in different species (or are of different exposure designs), different AF_{Sp} values may be needed in the estimate of the dermal pathway HQ and cancer risk..

The values for AF_{Sp} recommended by EPA must not be confused with values for AF_H used to adjust the intake (I) in the estimate of HQs for exposure pathways not represented by the RfD (e.g., using an RfD for water soluble arsenic to estimate the HQ exposure to less soluble forms of arsenic in soil). I fear that the list of AF_{Sp}s in Table 4-1 of the dermal guidance will be erroneously interpreted as reasonable estimates of AF_H, they are not (at least this is true for the values presented for nickel and cadmium).

5. Table 4.1 and Supporting Documentation

Given the above comments on toxicity factor adjustments, some additional comments on Table 4.1 follow:

The table should identify the toxicity factor (e.g., RfD, CSF) to which the adjustment applies.

The document should provide a more complete evaluation of AF values for each chemical, and should note the subset of the data set that is being used to estimate AF_{sp}. For example. Elakhovskay (1972) is the basis for an estimate of AF_{sp} for nickel, presumably because it is the only long-term oral dosing study in which nickel absorption estimates could be derived (the estimate is based on urinary nickel measurements made during a 6-month daily gavage study). However, there are at least 10 other studies from which estimates of AF can be derived, seven of which are studies in human subjects or populations (Sunderman et al., 1989; Cronin et al., 1980; Christensen and Lagassoni, 1981; Gawdrodger et al., 1986; Menne et al., 1978; Spuit and Bongarrts, 1977; Horak and Sunderman, 1977; McNeely yet al., 1972; Ho and Furst, 1973; Jasim and Tjälve, 1986a,b; Tjälve and Stahl, 1984).

The table cites AF values for cadmium in food and water. However, there is really no basis for unique values in the two media (Diamond et al., 1994); and the same can be said for lead and cadmium (James et al., 1985; Maddaloni et al., 1998; Sunderman et al., 1989). Whether the metal is in food or water makes little difference. What does make a difference is <u>when</u> the metal is ingested with respect to the ingestion of food; thus, the absorption of the metal in water will be high if it is ingested after a fast that continues for several hours after the metal is ingested; absorption will be lower if the metal is ingested in water right before, during or after a meal. Presumably, the reason there are unique food and water AF values for cadmium in Table 4.1 is because there are unique food and water RfDs for cadmium on IRIS. The basis for the two RfDs is the assumption of higher absorption of cadmium when it is ingested in water than when it is ingested in food; the rationale

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for this assumption is similarly flawed, in my opinion. As an aside, there are four high quality studies of cadmium absorption in humans, in addition to the McLellan et al. (1978; the latter citation is listed as McLellan, 1978 in Table 4.1): Flanagan et al., 1978; Newton et al., 1984; Shaikh and Smith, 1980; Rahola et al., 1972).

A document that provides guidance on how to evaluate data on oral bioavailability/gastrointestinal absorption, of similar depth and quality as the dermal document, would be of great benefit to risk assessment.

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