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WASHINGTON, D.C. 20460

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OFFICE OF THE ADMINISTRATOR  
SCIENCE ADVISORY BOARD

February 15, 1993

Honorable Carol M. Browner  
Administrator  
U.S. Environmental Protection Agency  
401 M Street, S.W.  
Washington, D.C. 20460

Subject: Science Advisory Board's review of the Office of Research and Development's draft report *Dermal Exposure Assessment: Principles and Applications* (EPA/600/8-91/011B, January 1992)

Dear Ms. Browner:

Agency exposure assessors (particularly those dealing with contaminated waste sites) face a difficult task in dealing with exposures via skin contact with toxicants in air, water, and soil. To provide these assessors with an understanding of the principles of dermal exposure assessment and with the procedures for applying these principles to human situations, the EPA's Office of Research and Development developed the draft document referenced above, which summarized the current state of knowledge on dermal exposure to air, water, and soil; presented methods and models for estimating dermal absorption resulting from contact via these media; summarized available chemical specific experimental data describing dermal absorption properties; and established procedures for evaluating experimental data for application to exposure assessments.

The Environmental Health Committee (EHC) was asked to assess the general validity of the information in the document, and the way in which that information is applied to dermal exposure assessment. Additionally, the Committee was asked to consider more specific issues addressing (a) skin composition and dermal absorption processes; (b) skin models for evaluation of dermal absorbed dose; and (c) the applicability of measured absorption constants for chemicals in air, water, and soil.



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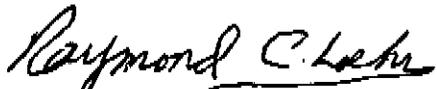
The EHC met in Washington, DC on August 17-18, 1992 to carry out its review. The Committee found the draft dermal exposure assessment document to be one of the better documents it has reviewed, and commends the Agency on the document's quality and general rigor. There are areas, however, in which improvements can still be made.

There should be unequivocal guidance as to when to use experimental data, rather than values estimated from models, and when there is a preference for using *in vitro*, rather than *in vivo* data. The Committee finds that *in vivo* data are more realistic, although they may be more difficult to derive and less likely to survive quality assurance scrutiny. In general, more weight should be given to experimentally-derived values than to those estimated from models. There are exceptions, however, and the document's weight-of-evidence table (if it was revised to serve this purpose) could be a valuable aid in making the decision to accept or reject experimental values.

The Committee would like to see further examination of model performance before the models are widely applied. Although the models appear to fit many compounds well, there is an important subset of compounds where the fit is poor, however, and the report glosses over the differences between expected and estimated values too readily. The document needs to clearly state the limitations of the models. Additional data should be sought to both strengthen and expand the models. The Committee also feels that it is important to have the model validation and estimation efforts undergo a rigorous statistical analysis. Full validation of the model will require also input of toxicologists with expertise in skin absorption and metabolism and analytical chemists, in order to deal with the important issues of metabolic activation/detoxification by the skin itself.

Finally, although a model to estimate the dermally absorbed dose per-event is useful, it would be best if the model could use measured, rather than predicted, dermal permeability values when possible. When measured data of good quality are available, they should have precedence over model estimates.

We appreciate the opportunity to review this document, and look forward to your response to the issues we have raised.



Dr. Raymond C. Loehr, Chair  
Science Advisory Board



Dr. Gary Carlson, Acting Chair  
Environmental Health Committee

 **EPA AN SAB REPORT:  
DERMAL EXPOSURE  
ASSESSMENT**

**REVIEW OF THE OFFICE OF  
RESEARCH AND  
DEVELOPMENT'S DRAFT  
REPORT *DERMAL EXPOSURE  
ASSESSMENT: PRINCIPLES  
AND APPLICATIONS*  
(EPA/600/8-91/011B, JANUARY  
1992) BY THE  
ENVIRONMENTAL HEALTH  
COMMITTEE**

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## **ABSTRACT**

The Environmental Health Committee (EHC) met in Washington, DC on August 17-18, 1992 to review the EPA draft report *Dermal Exposure Assessment: Principles and Applications* (EPA/600/8-91/011B, January 1992). The Committee addressed the scientific support for document's general guidance on dermal exposure assessment and considered specific issues relating to skin composition and dermal absorption processes; skin models for evaluation of dermal absorbed dose; and the applicability of measured absorption constants for chemicals in air, water, and soil.

The Committee commended the Agency on the document's quality and general rigor, but also noted areas in which improvements were possible. The EHC recommended that the document state more clearly when experimental data, rather than values estimated from models, should be used for assessment, and stated its preference for *in vivo* data, and for experimentally-derived data when available.

The Committee would like to see further examination of model performance before the models are widely applied. Although the models appear to fit many compounds well, there is an important subset of compounds where the fit is poor, however. The document needs to clearly state the limitations of the models. Additional data should be sought to both expand and strengthen the models. The Committee also feels that it is important to have the model validation and estimation efforts undergo a rigorous statistical analysis. Full validation of the model will require also the input of toxicologists with expertise in skin absorption and metabolism and analytical chemists, in order to deal with the important issues of metabolic activation\detoxification by the skin itself.

Finally, although a model to estimate the dermally absorbed dose per-event is useful, it would be best if the model could use measured, rather than predicted, dermal permeability values when possible. When measured absorption data of good quality are available, they should have precedence over model estimates.

**KEYWORDS:** cutaneous exposure; dermal exposure; dermal absorption; dermal adsorption; dermal permeability; skin absorption; skin models.

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**U.S. ENVIRONMENTAL PROTECTION AGENCY  
SCIENCE ADVISORY BOARD  
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**Dermal Exposure Assessment Review  
August 17-18, 1992**

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## 1. EXECUTIVE SUMMARY

The Environmental Health Committee met in Washington, DC on August 17-18, 1992 to review the draft report *Dermal Exposure Assessment: Principles and Applications* (EPA/600/8-91/011B, January 1992), prepared by the Office of Health and Environmental Assessment of EPA's Office of Research and Development. The Committee was asked to address the scientific underpinnings of the general guidance on dermal exposure assessment<sup>1</sup> provided in the review document, as well as to consider specific issues relating to (a) skin composition and dermal absorption processes; (b) skin models for evaluation of dermal absorbed dose; and (c) the applicability of measured absorption constants for chemicals in air, water, and soil.

The Committee found the draft dermal exposure assessment document to be one of the better documents presented for review, and commends the Agency on the document's quality and general rigor. There are areas, however, in which improvements can still be made.

The document should state more clearly when experimental data, rather than values estimated from models, should be used. It is also unclear whether there is preference for *in vitro* or *in vivo* data. The Committee finds that *in vivo* data are more realistic although they may be more difficult to derive and less likely to survive quality assurance scrutiny. It is the opinion of the Committee that, in general, more weight should be given to experimentally-derived values than to those estimated from models. There are exceptions, however, and the document's weight-of-evidence table (if it was revised to serve this purpose) could be a valuable aid in making the decision to accept or reject experimental values.

The Committee would like to see further examination of model performance before the models are widely applied. Although the models appear to fit many compounds well, there is an important subset of compounds where the fit is poor, however, and the report glosses over the differences between expected and estimated values too readily. The document needs to clearly state the limitations of the models. Additional data should be sought to both expand and strengthen the models. The Committee also

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<sup>1</sup> The term "Dermal Exposure" is used by EPA to describe any contact with the skin by any medium containing chemicals, and quantified as the amount on the skin and available for adsorption and possible absorption. Although the use of "cutaneous exposure" and "dermal exposure" and/or "dermal absorption" might be somewhat more precise, this report follows Agency practice in using the broader meaning.

feels that it is important to have the model validation and estimation efforts undergo a rigorous statistical analysis. Full validation of the model will require also the input of toxicologists with expertise in skin absorption and metabolism and analytical chemists, in order to deal with the important issues of metabolic activation\detoxification by the skin itself.

Finally, although a model to estimate the dermally absorbed dose per-event is useful, it would be best if the model could use measured, rather than predicted, dermal permeability values when possible. When measured data of good quality are available, they should have precedence over model estimates.

## **2. INTRODUCTION**

### **2.1 Background**

EPA is faced with many situations in which humans are exposed to toxicants through skin contact with air, water, or soil. Exposure assessors dealing with contaminated waste sites in particular face a difficult task in dealing with exposures through one or all of media noted above. To provide these assessors with an understanding of the principles of dermal exposure assessment and the procedures for applying these principles to human situations, the EPA's Office of Research and Development developed a draft document (*Dermal Exposure Assessment: Principles and Applications*) which summarized the current state of knowledge on dermal exposure to air, water, and soil; presented methods and models for estimating dermal absorption resulting from contact via these media; summarized available chemical specific experimental data describing dermal absorption properties; and established procedures for evaluating experimental data for application to exposure assessments.

### **2.2 Charge**

The Environmental Health Committee was asked to assess the general validity of the information in the review document, and the way in which that information is applied to dermal exposure assessment. Additionally, the Committee was asked to consider the following more specific issues:

- a) Skin composition vs. dermal absorption processes (Chapters 2,3)

In the draft document, the two layers of the skin which are considered to be the main barriers to absorption are the stratum corneum and the viable epidermis. The stratum corneum is composed of hydrophilic and lipophilic pathways. On the other hand, the viable epidermis acts as if it was a thickened watery medium. Diffusion through this living strata is thought to be roughly one-tenth as facile as in bulk water. For lipophilic molecules, the stratum corneum could act as a reservoir, and therefore the viable epidermis presents a hydrophilic barrier to these molecules. These assumptions provide the basis for the approaches presented in the document. The Committee is asked to comment on these assumptions.

b) *Skin model for evaluation of dermal absorbed dose (Chapters 4, 5, 6, 7)*

The classical steady-state model based on Fick's first law was applied to inorganics in water and all chemicals from air (Chapters 4, 5, 7). This model assumes that the stratum corneum provides the limiting barrier to dermal absorption, and that steady-state absorption is established at the onset of exposure and remains constant during the entire exposure period (Chapter 4). For chemicals from soil, the mass absorbed is a function of the soil concentration, the adherence factor and the absorption fraction (Chapter 6, Equation 6.18). Please comment on these approaches. The Committee is asked to comment on these assumptions.

For organics in water (Chapter 4, 5), the stratum corneum could act as a reservoir, and the viable epidermis could act as the limiting barrier to absorption. A two-compartment model was recommended (Cleek and Bunge, 1992) (Chapter 4, Equations 4.35-4.48), which accounted for the contribution of these pathways in dermal absorption of organic molecules as a function of the physicochemical properties of these molecules (molecular weight and oil/water partition coefficient) and duration of exposure (which measures the reservoir effect - lag time - of the stratum corneum). For this model, estimation of the lag time is required. This lag time is defined in terms of the diffusion coefficient and the thickness of the barrier membrane (Chapter 5, Equation 5.14). The latter can be estimated from experimental measurements, and the former can be obtained from a correlation predicting permeability coefficients as a function of molecular weight and oil/water partition coefficient (Chapter 5, Equations 5.11, 5.13). This correlation is theoretically derived, and the coefficients of the dependent variables are empirically determined from experimental data of permeability constants of organic chemicals in water measured from *in vitro* absorption studies through human skin (Chapter 5, Equation 5.11). Unlike the steady-state approach used for other situations, experimental data for permeability coefficients of organics in water are not used directly in the estimation of the absorbed dose; instead new data on permeability coefficients can be used to improve upon the correlation. This approach provides a more conservative estimate of dermal absorption of organic chemicals than the steady-state assumption, and accounts for the length of exposure as compared to the lag time of the chemicals in the skin.

In light of the current information, is the steady-state assumption adequate for inorganics in water and in air? Is the 2-compartment model appropriate for organics in

water, and is it necessary to extend this model to organics in air? Should we attempt to develop a comparable model for soil absorption?

*c) Applicability of measured absorption constants*

For all chemicals in water (Chapter 5), a scoring system (Chapter 5, Table 5-1) was developed to assess the applicability of the experimental data to actual exposure scenarios. For inorganics in water, based on the observation that no measured permeability coefficient exceeds  $10^{-3}$  cm/hr (Chapter 5, Table 5-3), a conservative default value of  $10^{-3}$  cm/hr was adopted for all inorganics in water for which no experimental data exist (from the expert panel in the April, 1991 EPA Peer Review Workshop). For organics, a correlation was used to predict permeability coefficient as a function of molecular weight and  $\log K_{ow}$  (Chapter 5, Equation 5.8). Please comment on the scoring system for the experimental data, and the choice of the default value for inorganics as well as the correlation for organics.

For all chemicals in air (Chapter 7), some experimental data are available, and a regression equation is presented which correlates the permeability coefficient to fat/air partition coefficients for organic molecules from data in rats (Chapter 7, Equation 7.2). How much more work should be put in this area?

For all chemicals in soil (Chapter 6), useful experimental data of absorption constants exist for only three chemicals (Chapter 6, Table 6-3). Several approaches are discussed for estimating the values for other chemicals, but no recommendation was selected. Please evaluate these approaches in terms of their potential usefulness in addressing actual exposure scenarios, and if possible rank them on their order of priority for further development. Since the absorption fraction is actually dependent on the applied dose as well as exposure time, there has also been discussion about developing a permeability coefficient-based model to evaluate the absorbed dose. Please comment on this possibility and on the pros and cons of the various approaches.

### 3. DETAILED FINDINGS

#### 3.1 Skin Composition and Dermal Absorption Processes

Certain specific assumptions about the skin's functioning as a barrier between the environment and the body's internal biochemistry provide the basis for the approaches presented in the draft document under review. The two layers of the skin (the stratum corneum and the viable epidermis) are considered to be the main barriers to absorption. It is posited that the stratum corneum provides hydrophilic and lipophilic pathways, but the viable epidermis acts as if it was a thickened watery medium, with diffusion through this living strata estimated to be roughly one-tenth as facile as in bulk water. For lipophilic molecules, the stratum corneum could act as a reservoir, and therefore the viable epidermis would present a hydrophilic barrier to these molecules. The validity of this assumption is the first issue presented in the Charge to the Committee.

The Committee agrees that the stratum corneum provides both hydrophilic and lipophilic pathways for entry of toxicants into the viable epidermis. The stratum corneum is an effective barrier for large polar compounds but is an ineffective barrier for non-polar compounds which are metabolized in the avascular viable epidermis. Polycyclic aromatic hydrocarbons (PAHs) and N-heterocyclic hydrocarbons are examples of such compounds, and it is well established that there is aryl hydrocarbon hydroxylase (AHH) activity in the viable epidermis. If the viable epidermis has the necessary P-450 enzymes to oxidize non-polar compounds to more polar metabolites, the absorption from the stratum corneum will be increased. When a one- $\mu$ mole dose of dibenz (c,g) carbazole (DBC) was applied to the shaved skin of female ICR Mice, 97% entered the systemic circulation in 12 hours (John Meier, unpublished data). The metabolites and the parent compound both appear in the blood stream. For compounds metabolized in the skin, the Committee therefore suggests that the viable epidermis does **not necessarily** present a hydrophilic barrier. This finding is really part of a larger concern of the Committee on the importance of considering metabolic activation/detoxification by the skin itself.

There are many confounding factors which complicate attempts to assess the skin's functioning as semi-permeable barrier. Research has shown that:

- a. an increase in temperature, *in vitro*, increased uptake and decreased evaporation - high humidity increased the penetration of water soluble compounds but had no effect on lipophilic compounds (Hawkins and Reifenrath, 1984)
- b. at a pH of 5.4 the uptake of zinc oxide (*in vitro*) was about 21 times greater than at pH 7.4 (Agren, 1990)
- c. some studies use solvents (hexane in this case) which only extract the parent compound from tissues - the metabolites and conjugated moieties also represent the parent compound crossing the epidermis (Shu et al., 1988)
- d. lipophilic compounds are stored in fatty tissues, thus affecting measured blood levels
- e. increased activity such as exercise/work will increase blood flow and increase absorption of toxicants - most of the *in vivo* data are from studies performed on animals in the resting state (restricted movement, occluded, anesthetized).

For the reasons listed above, validation of the model will require a joint effort, and the Committee recommends that toxicologists with expertise in skin absorption and metabolism and an analytical chemist select the studies.

The lack of data regarding how the model will handle mixtures is an important omission. The Committee realizes, however, that the EPA is aware of, and attempting to deal with, the thorny issue of exposure to complex mixtures in a much broader context. Revisions of the draft document should include a statement that the model does not deal with the absorption of complex mixtures. Such a caveat will have to suffice until such time as the state-of-the-art advances. The Committee also noted, in passing, that the document does not deal explicitly with the immunological functions of the skin.

### 3.2 Skin Models for Evaluation of the Dermal Absorbed Dose

The approach proposed by EPA is based on a classical steady-state model which assumes that the stratum corneum provides the limiting barrier to dermal absorption, and that steady-state absorption is established at the onset of exposure and remains constant during the entire exposure period. For soil-borne chemicals, the mass absorbed is assumed to be a function of the agent's concentration, the adherence factor, and the absorption fraction. For agents in water, a two-step model is proposed (see discussion below).

There are two major issues to be addressed, in addition to providing guidance for the calculation of dermal exposure. First, the document should clearly identify the data gaps and types of data needed to confirm and refine the equations. Second, although the exposure determination process, the document should encourage development of indicated data for the purpose of improving the model.

In each analysis it should be acknowledged that the ultimate objective is not only a simple model but a model that accurately predicts human exposures. Therefore efforts to assure that *in vitro/in vivo* correlations are strong for the environmental contaminants in the instant exposure scenario are of paramount importance.

In recognition of the limited human data available on only a relatively small number of environmental agents, the exposure evaluation must recognize and utilize well conducted studies of the compounds of specific interest, in preference to model-derived calculations. If data are not available in the literature or are not generated by the potentially regulated industry, then the model must be invoked, using 100% absorption as a default position. Although the complexities of these studies (particularly human *in vivo* studies) are numerous, they should provide a more accurate exposure assessment and will simultaneously generate data for refinement of the current model (which is based primarily on *in vitro* data) by expansion by the number of *in vitro* tests and utilization of *in vivo* test systems.

With regard to the utilization of the two step model and its possible extension beyond the organics in water exposure route, there are both theoretical and practical considerations. First, efforts should be made to confirm the applicability of the model to the data available.

Examining the data provided in Table 5.4 of the draft document, a simple cross-tabulation of  $\log K_{ow}$  (partition coefficient between octanol and water) values vs. molecular weight (MW) shows that two chemicals, i.e., digitoxin and sucrose, are clear outliers, and should not be used in the predictive model, as they would unduly influence the characteristics of the model, and give a false impression of the range of its applicability. It is not clear as to why these two very different substances are outliers, and a further examination of the data might be of value in furthering out understanding of the underlying processes involved.

The regression equation estimating  $K_p$  (the permeability coefficient), recalculated on the basis of the remaining 91 chemicals, is:

$$\log K_p = -2.75 + 0.776 \log K_{ow} - 0.00677 \text{ MW}$$

The resulting adjusted  $R^2$  (coefficient of determination, a measure of the percent of total variance accounted for by the predictive estimators) for this equation is 0.67, i.e., not materially different from that of equation 5.8.

The contribution of each of the variables to the  $R^2$  is about equal. A plot of the residuals shows that there is considerable correlation between the residuals and  $\log K_p$ . This indicates that there is at least one missing explanatory variable which, if it (they) was (were) included in the equation, would materially improve the explanatory power, and therefore predictive power, of the equation. This is another way of saying that the fact that the  $R^2$  is not nearer unity is not only due to the noise in the data but to a clearly identifiable extent, the incompleteness of the model.

Three other compounds appear to be outliers: ethyl benzene, styrene and toluene. However, their removal from the equation does not significantly affect its performance.

An examination of the correlation between  $\log K_{ow}$  and MW (after removing the outlier compounds sucrose and digitoxin discussed earlier) shows it to be 0.44. While it is not possible (within the scope of this review) to precisely define the extent to which this correlation limits the applicability of the equation, at the very least it can only be used within the boundaries of a polygon with the following ( $\log K_{ow}$ , MW) limits: (-1.4, 30), (1.8, 520), (5.3, 480), (3.5, 100). All other regions of the space are forbidden. For example, it would not be allowable to apply the equation to a compound for which  $\log$

$K_{ow} = -1.0$  and  $MW = 300$ . There is little point in determining the exact limits at this time,<sup>2</sup> as the equation needs to be refined through the inclusion of additional parameters, as discussed below, before that endeavor is worthwhile.

It is difficult, however, to make serious suggestions as to what the additional parameters may be without knowing a great deal more about the sources of the data in Flynn's 1990 collection. Perhaps indicator variables identifying the sources and/or types of data could be considered. Because of the substantial residual correlation it is more likely that one or more additional physicochemical parameter(s) may be indicated. One may want to consider aspect ratio, i.e., some function of area and volume in place of molecular weight. In the absence of a mechanism-derived parameter one could also consider molecular connectivity or kappa indices. The Committee is reasonably confident that some parameter can be found to improve the fit of the equation.

Quite separately from the equation itself, one wonders whether there are not more data in the literature than the 97 data points in the Flynn paper. The Committee recommends strongly that, before any predictive equation is published, the literature be thoroughly searched to identify any further experimental  $K_p$  values. Even an additional 20 data points would be worthwhile, particularly if some of the additional points provide data outside of the polygon specified above.

The Committee is also concerned that the physio-chemical model does not take into account metals or ionic compounds, substances of obvious concern in environmental toxicology.

As noted above, a special consideration is that the bioavailability of the compound from the soil should be verified and quantified before the dose to the skin is estimated. The section on vapor/skin exposure and the models to be used in that situation offer a similar issue in that there may be no environmental exposure situation (excluding occupational where respiratory protection may be used and other principles and documentation may apply) where the vapor/skin exposure route would be determinative for exposure/risk assessment or would be a major contributor to risk assessment. If not, then it may not be necessary to calculate exposure and a default or *de minimis* assumption may be used rather than attempting to define exposure from limited data.

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<sup>2</sup>The procedure for determining exact limits is described in Mandel, 1985.

(Further detail will be provided in the sections on the specific areas of water, soil, and vapor exposures.)

There are several additional issues which indirectly impact the questions posed and the document. In addition to the previously discussed issues the text (perhaps in a concluding section) should clarify the logic for using different models in different (e.g., water, soil) exposure situations, since the draft is to be a guidance document. Also, the issue of different exposure assessments for children should be discussed, as well as situations in which the skin may not be intact.

The Committee recommends an opening summary or introduction clearly stating the limitations of the data and consequent restriction of the utilization of the models to be proposed. This revision would make the document easier to read. As the document is now organized, the reader becomes aware of the limitations only after wading through a great deal of complex material. In addition in the initial section and in the document the preference for measured data should be stated. More recognition should be given to human exposure as the ultimate target and the *in vitro/in vivo* correlations that lead to that result.

Given these additions and revisions, including the caveats about limitations of the model, the Committee believes the document to be informative and useful. It is appropriate to use the non-steady state, two step model for organics in water and to use the steady state models for soil and vapor. When better data are available the two step model may then be appropriate for all chemical exposure assessments.

### **3.3 Applicability of Measured Absorption Constants**

Chapter 6 of the dermal exposure assessment guide discusses several approaches for estimating absorption values for soil-borne chemicals, but no recommendation is offered. The Committee was asked to evaluate these approaches re their potential usefulness in addressing actual exposure scenarios.

Exposure to contaminants via exposure to soil presents a much more complex evaluation problem than the other two exposure vehicles considered. As noted earlier in this report, not only would mixtures present a more difficult problem, but the matrix itself is certain to present the dominant variable. This is certainly proving to be the case when considering the absorption of TCDD (tetracholorodibenzenyl-p-dioxin) and lead.

Especially for soil, simple *in vitro* models seem rather remote from exposure assessment aims. Fick's law, often used to introduce dermal toxicology, represents an approximation to an approximation to an approximation. As embodied in equation 6.2 and following, it does not seem to be very useful as a guide. A defect, not due to the document but to the way research is typically conducted, is that only pieces of such models are investigated. For clarity in the document, incidentally, the components of equation 6.2 (and others) should be more clearly described.

Perhaps the most important lack in this section is the kind of information indicating how soil matrix influences exposure. It would appear that the assumption was made that all materials found in the environment in soil or other media were readily available for skin penetration. Studies performed on materials of concern, such as dioxin and lead, indicate that there are significant differences in bioavailability depending upon soil types. In addition to these studies, there are vast amounts of data on human exposure and subsequent absorption available from industrial and military sources, a supposition supported by comments at the Committee's meeting. For example, controlled studies with pesticides have been conducted on humans. These pesticides (malathion, lindane, and a carbamate (Abate)) were mixed with pyrax powder.<sup>3</sup> Cholinesterase levels in the blood were measured, and with the exception of one of the materials, there were no indications of skin penetration even when the materials were applied over a 28-day period (Steinberg *et al.*, 1971, 1972). While these studies lack the elegance of studies being conducted twenty years later, had the two ounces of 1-2% pesticide powder applied to the total body surface and to the clothing of the individuals, penetrated the skin as described by the model, there would most certainly been a decrease in blood cholinesterase. Although the Committee realizes that such matrix effects complicate the model considerably, they are important from the standpoint of "real-life exposure" situations.

The Committee recommends that the Office of Research and Development's Exposure Assessment Group explore the availability of such data, some of which apparently are available in the open literature, and some of which are available in EPA files without conflicting with proprietary interests. Risk management initiatives will be based on dermal availability if this is a critical mode of exposure.

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<sup>3</sup>Pyrax is a clay used for several purposes including the production of powders.

For chemicals in air (Chapter 7), some experimental data are available, and a regression equation is presented which correlates the permeability coefficient to fat/air partition coefficients for organic molecules from data in rats (Equation 7.2). The Agency is seeking guidance on how much more work should be committed to this area.

In general, this chapter is clearly written although some of the introductory material is redundant with that in earlier chapters. It provides valuable equations for the person who is working in the field and needs to calculate vapor pressure or to convert ppm to mg/m<sup>3</sup>. The decision tree shown in Figure 7-1 is particularly useful.

The heart of the chapter is the regression equation for predicting the dermal permeability coefficient of chemical vapors based on a model developed by McDougal et al. (1990). Such models can be quite useful in predicting the activities of chemicals in the absence of experimental knowledge on a particular compound. However, the limitations of the model must be recognized and discussed more explicitly.

The only limits to the model discussed in Chapter 7 are that compounds with unknown permeability coefficients must have fat/air partition coefficients within the range of the compounds from which the model was derived. Obviously, such a model is also limited by the number and type of vapors used to derive the model. Only eight vapors were studied. As with chemicals in other physical states, discussed elsewhere, one would expect that factors other than the fat/air partition coefficient would influence permeability, such as metabolism of the compound or the ability of the vapor to damage the skin barrier, particularly those chemicals which may remove lipid. Such limitations should be discussed. In answer to the question posed in the charge, additional work should be done to determine if the model is valid for a more extensive list of vapors and to determine what properties of chemicals influence the fit to the model. It is important to know not only what chemicals do not fit the model but why they don't fit so that the model can evolve and be improved. In fact, the simple correlation presented looks so useful, it is imperative to determine whether the correlation is that simple or is a result of the particular data set used. Chemicals that are known to be metabolized in the skin and chemicals that damage the skin should be included in the studies.

The Committee also believes that additional data are available dealing with absorbed doses of gases and vapors. A great many studies have been done in humans by the military. While some of the data are not readily available, other results

do appear in the published literature. Such data, while perhaps limited in the number of chemicals examined, could be very useful in testing the validity of the model.

Chapter 7 also extends discussions of dermal exposure of vapors into the risk assessment process. In the Committee's view, this seems out of line with the scope of the rest of the document and is not necessary.

An example using n-hexane vapor in a risk characterization is given. The maximum achievable concentration is calculated based on the vapor pressure of n-hexane. This is a valuable calculation for eliminating any compounds that have vapor pressures too low to present any hazard from vapor absorption. However, in the example given, the authors appear to use this calculation of maximum achievable concentration as an example of a vapor exposure to n-hexane, 6 hr/day for 5 days/week. It would be hard to imagine when a person might be exposed to such a high vapor concentration of hexane ( $610 \text{ g/m}^3$ ) and if they were, they would not last 6 hours before death due to central nervous system effects. This example needs to be rewritten using a reasonable, environmentally relevant, vapor concentration for n-hexane.

Four different values for the dermal permeability coefficient of benzene are given in Chapter 7 (all within an order of magnitude). Some discussion of the possible reasons for the variability should be given. The user of the document will need guidance for choosing among them. For risk assessments, such a range of values is not so bad and perhaps that should be stated.

The document proposes (page 7-26), that the irritant properties of a chemical toward the skin can be estimated from the irritant properties of the same chemicals toward the respiratory tract. The Committee recommends caution in making such estimations, because the properties of the epithelium lining the respiratory tract are quite different from the skin. Respiratory tract irritants should be considered as possible skin irritants, but the concentration causing the irritancy is likely to be quite different for the two sites.

The document also states (page 7-4) that the partition coefficient between the skin and blood is the "best" partition coefficient parameter. It is not at all clear what the authors mean by "best." Both the partition coefficient between the air and the skin and

the partition coefficient between the skin and the blood are important for consideration of potential exposure. The Committee recommends deletion of the sentence.

#### 4. CONCLUSIONS

The Committee commends the Agency (and the staff involved) on the quality and general rigor of the draft dermal exposure assessment document; it is our consensus that this is one of the better documents presented for our review. This praise notwithstanding, the Committee has identified areas in which improvements can still be made.

The document does not clearly state when experimental data are to be used and when values estimated from models are to be used. A decision tree flow chart or some other tool might be helpful in articulating guidance here. In general, more weight should be given to experimentally-derived values than to those estimated from models. There are exceptions, however, and here the weight-of-evidence table could be used in the decision to accept or reject experimental values. The current weight-of-evidence criteria are not sufficient and need to be revised for this purpose. Data quality is an important issue here, and it is not covered comprehensively in the current scoring system. Some of the second order criteria (e.g., number of animals, chemical concentrations) might be as important as the first order criteria for this purpose. The document is unclear whether there is preference for *in vitro* or *in vivo* data; superficially the current scoring system provides no guidance, and the text appears to prefer *in vivo* data. Some verbal comments of EPA participants at the review seemed to suggest that *in vitro* data are preferred; the Committee finds that *in vivo* data are more realistic although they may be more difficult to derive and less likely to survive quality assurance scrutiny.

The Committee would like to see further examination of model performance before the models are widely applied. The models appear to fit many compounds well; however, as indicated in detail above, there is an important subset of compounds where the fit is poor. More discussion and analysis of the types of compounds where the fit is poor are needed. The current report glosses over the differences between expected and estimated values too readily, and it was not comforting to hear at the meeting that some of the predictions were poor because they were compared with *in vivo* rather than *in vitro* data. Good quality data of the former type are of greater concern, and if the models predict the latter rather than the former, the models must undergo further development. The Committee also feels that it is important to have the model validation and estimation efforts undergo a rigorous statistical analysis. Full validation of the model will require also the input of toxicologists with expertise in skin absorption and

metabolism and analytical chemists, in order to deal with the important issues of metabolic activation\detoxification by the skin itself.

It clearly is useful to have a model to estimate the dermally absorbed dose per event. The same model concerns addressed above are also relevant here. In addition, the availability of a model that could use measured, rather than predicted, dermal permeability values would be very useful. When measured data of good quality are available, they should have precedence over model estimates.

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