September 29, 1995

EPA-SAB-EC-95-021

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 Draft Dioxin Exposure and Health Effects Reassessment Documents

Dear Ms. Browner:

Dioxins are a group of anthropogenic chemical compounds created as unintended by-products through a number of activities including: combustion, certain types of chemical manufacture, chlorine bleaching of pulp and paper, and other industrial processes. Dioxins are produced in very small quantities compared to other pollutants; however, because this family of compounds are thought to be highly toxic, they have been treated as significant environmental pollutants since the early 1970's.

In 1988, EPA released two documents addressing risks from dioxins (*A Cancer Risk-specific Dose Estimate for 2,3,7,8-TCDD.* and *Estimating Exposure to 2,3,7,8-TCDD*) and requested that the Science Advisory Board (SAB) review them. The SAB report (SAB, 1989), released in November 1989, although not agreeing with several of the conclusions in the two documents, concluded that "both documents were carefully constructed and well written." The SAB report concluded with a recommendation to "...follow up on this excellent start..." by developing and validating new models for human exposure and for cancer and non-cancer risk endpoints, and to pursue active research programs resolve questions and incorporate new data. The Agency initiated a significant effort addressing dioxin exposure and risk, and on September 13, 1994, released for public review and comment (59 FR 46980) a 2,400 page draft reassessment of the toxicity of, and human exposure to, dioxin.

In December, 1994, the EPA Office of Research and Development (ORD)

requested that the SAB review the reassessment document, and submitted a draft Charge addressing some 40 issues. The SAB Executive Committee approved the creation of an *ad hoc* Dioxin Reassessment Review Committee (DRRC) and appointed Drs. Morton Lippmann and Joan Daisey as Co-Chairs. The DRRC was developed by building on the SAB's Environmental Health and Indoor Air Quality/Total Human Exposure Committees, and adding (following an extensive review and recruitment process) additional Consultants to fill gaps in needed expertise and to add depth in key scientific areas. In addition to the Co-Chairs, 37 scientists were appointed to the Dioxin Reassessment Review Committee.

A final Charge for the review, encompassing 43 specific questions was adopted after discussions involving ORD and SAB staff, and the Co-Chairs (the detailed Charge is provided in section 2.2 of the enclosed report). The DDRC subsequently met on May 15-16, 1995 in Herndon, Virginia to hear briefings by EPA staff, comments by Members of the public, and to discuss the relevant issues of the Charge. Following the public meeting, the Committee's report was developed through a series of mail reviews of successive drafts. It was approved by the SAB Executive Committee on September 21, 1995.

The enclosed report provides a detailed discussion of each of the specific issues raised by the Charge, and addresses some additional related questions which arose during the course of the review. The following comments provide a synthesis and overall perspective on the Committee's findings.

First, via-a-vis the Exposure Assessment draft document, the Committee wishes to commend those responsible for doing a very credible and thorough job assembling, integrating, and analyzing a very large body of data on dioxin source emissions, environmental levels, exposures, and human body burdens, all within the framework of human exposure assessment. The detailed recommendations of the DRRC largely address refinements, corrections and clarifications, not substantive revisions.

The exposure reassessment identifies the major known sources of dioxins and provides a reasonable estimate of total emissions. The Committee recommends that new information on emissions from the incineration of medical waste (and other sources) be incorporated if appropriate, and that the estimates of uncertainties in the emissions inventory be improved for several emissions categories. The Committee also recommends adding an explicit statement to the final document noting that the fractional contributions of various types of emissions sources to total emissions cannot be assumed to be identical to the fractional contributions of those sources to human

exposures. The Committee agrees with the EPA position that current levels of dioxin-like compounds in the environment derive primarily from anthropogenic sources and, based on available data, that the air-to-plant-to-animal pathway is most probably the primary way in which the food chain is impacted and humans are exposed. EPA should, however, take note of other potentially important exposure pathways, e.g., point source-to-water/sediments-to-fish, and cigarette smoking. There is also a very large gap in our understanding of the potential atmospheric transformation of vapor-phase dioxin-like compounds and of the air-to-plant transfer coefficients of these compounds.

The document's estimate of average dioxin exposure is reasonable, but has substantial uncertainties because of limited data; it thus cannot provide an estimate of the complete distribution of exposures for the U.S. population. The Committee recommends that these points be noted clearly and explicitly in the Summary volume for the benefit of policy makers and the public. The Committee commends and fully supports EPA's on-going efforts to develop better data on concentrations of dioxins in food and in human tissue and regards these as very high priority research needs.

The Committee supports EPA's use of Toxic Equivalencies (TEQ) for exposure analysis, but also recommends that EPA carefully review the draft Exposure Assessment document and ensure that the congener-specific data are used in all instances (such as transport, transformation, and deposition processes) in which differences in the physical and chemical properties of the congeners are likely to be important.

The Health Assessment draft document, in its first seven (of nine) chapters, provides a comprehensive review of the scientific literature on the biological mechanisms involved in the uptake of dioxin and related compounds, the binding of these agents to receptor sites, their metabolism and retention in tissues, and to biological response at the cellular, organ, organ system, and whole body levels. The Committee commends the EPA staff for this considerable accomplishment, and has made a number of comments and suggestions for relatively minor changes that should sharpen and clarify the content of the initial seven chapters. The Committee's most significant recommendations concerning these seven chapters center on the Agency's use of Toxic Equivalency Factors (TEF) to address the a broad range of dioxin-like compounds having the common property of binding to the Ah receptor, and producing related responses in cells and whole animals. The use of the TEFs as a basis for developing an overall index of public health risk is clearly justifiable, but its practical application depends on the reliability of the TEFs and the availability of representative and reliable exposure data. The Committee calls for clarifications in the specifications for TEFs of the various dioxin-like compounds for various health outcomes of concern,

including the development of separate TEFs for the major compound classes, i.e., 2,3,7,8-TCDD, other dibenzodioxins and furans, and coplanar PCBs. The Committee is confident that final versions of Chapters One through Seven will not need further review by the SAB.

Chapter Eight, on modeling, must integrate both human and laboratory animal data, and is critical to the reassessment's overall success. The human data typically derives from accidents and industrial exposures, and are subject to many confounding factors. Animal studies often involve high-to low-dose extrapolations as well as cross-species extrapolation. Both types of such data are inadequate, by themselves, for estimating the human health risks of chronic, low-dose environmental exposures to dioxin and related compounds. Although this chapter reflects a great deal of effort, several Members of the Committee found the exposition of important points to be unclear. Chapter Eight is also weakened by its reliance on the standard EPA default assumption of a linear non-threshold model for carcinogenic risk. The Committee suggests that EPA consider, in future revisions, alternative models, allowing for minimal response at low environmental levels of exposure, and which would be consistent with the body of available physiological (and, with the opportunities now arising, (pharma-cokinetic) modeling, epidemiological, and bioassay data.

Almost all the Members of the Committee concur with EPA's judgment that dioxin, under some conditions of exposure, is likely to increase human cancer incidence. The conclusion with respect to dioxin-like compounds is less firm. In the case of dioxin, virtually all of the Committee believes that the animal studies would be categorized as "sufficient" and the studies of humans as "limited," providing for an overall categorization of B_1, which would be expressed verbally as "Probably Carcinogenic to humans with limited supporting information from human studies." The Committee (on the basis of similar effects) would support the same designation for dioxin-like materials. PBBs and PCBs would receive ratings of B_1 and B_2, respectively.

Chapter Nine, on risk assessment, was not as thoroughly peer-reviewed before submission to the SAB as were the earlier chapters, and needs to be revised considerably to reflect the changes being made in Chapters 1-8 and to deal with the areas of weakness discussed below. The revised chapter would greatly benefit from an external peer review by an appropriate group. More specifically, the Committee identified, and wishes to emphasize to the Agency, particular areas of both strength and weakness in Chapter 9.

Three major strengths are apparent. First, by focusing serious attention on various non-cancer effects (both human health and ecological effects), the Agency has dispelled any mis-impression that EPA's risk assessment process is overly preoccupied with carcinogenic effects. Second, by evaluating an entire class of compounds, rather than a single compound, the Agency has responded to criticism that its risk assessment process can only address issues on a chemical-by-chemical basis. Third, a useful comparative perspective is provided in the draft conclusions where the Agency highlights the fact that the margin of safety (between background exposures and levels of exposure where effects have been observed in test animals) for dioxin-like compounds is smaller than the EPA usually sees for many other compounds.

Three major weaknesses were also noted. First, the presentation of scientific findings portrayed in the draft document's conclusions is not balanced *vis-a-vis* the possible risks posed by exposure to dioxin, with a tendency to overstate the possibility for danger. Second, important uncertainties associated with the Agency's conclusions are not fully identified and subjected to feasible analyses. Finally, the characterization of non-cancer risk is not performed in a manner which can facilitate meaningful analysis of the incremental benefits of risk management alternatives.

This letter can only highlight the major points of a detailed and extensive review by 39 SAB Members and Consultants of a 2000+ page document. Perforce, the letter cannot convey the many lesser, but important, findings and suggestions in the Committee's report. Also, it is important to note that although there is a broad consensus on most issues, not every Member/Consultant on the Committee agreed fully with every finding; such instances are noted in the report itself.

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

Dr. Genevieve Matanoski, Chair
Science Advisory Board

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Dioxin Reassesment Review
Committee

Dr. Joan Daisey, Co-Chair
Dioxin Reassessment Review
Committee

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U.S. ENVIRONMENTAL PROTECTION AGENCY
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1. EXECUTIVE SUMMARY

1.1 Exposure Document

The EPA and its staff have done a very credible and thorough job, and are commended for assembling, integrating, and analyzing a very large body of data on dioxin source emissions, environmental levels, exposures, and human body burdens, within the framework of human exposure assessment. In general, the data and analyses have been clearly presented, and uncertainties and limitations in the extant data described. Consequently, the recommendations of the Committee largely address refinements, corrections, and clarifications, not substantive revisions.

The reassessment identifies the major known sources of dioxins and provides a reasonable estimate of total emissions. The Committee recommends that the new information on emissions from incineration of medical waste and other sources be incorporated if appropriate. The Committee also recommends adding an explicit statement to the final document noting that the fractional contributions of various types of emissions sources to total emissions cannot be assumed to be identical to the fractional contributions of those sources to human exposures

At present, it is difficult to evaluate the relative contributions of local and more distant sources to the levels of dioxin in food. When better data become available from on-going EPA measurements of dioxin concentrations in food, the Committee suggests that the Agency consider using a Geographical Information System (GIS) for analysis of these data. With such a system, the geographic distributions of dioxin emissions sources and dioxin levels in food could be mapped and quantitative questions asked (and tested statistically) regarding the probable influences of local and more distant sources.

In the Exposure document, total estimated dioxin-like emissions for the U.S. have been directly compared to an estimate of the total amount of dioxin deposited to the surface of the U.S., based on available measured deposition factors. However, a scientifically-valid mass balance comparison would require estimating deposition of the emitted dioxins using atmospheric dispersion and deposition modeling and then comparing this estimate to the estimate obtained from measured and representative deposition data. The Committee concurs with EPA's position (Volume II, p. 3-166) that it is not scientifically valid to infer, based on the simple mass balance comparison, that there are missing sources of dioxins. The Committee also recommends that this section of the document be modified substantially so that the simple direct mass balance comparison is not provided, and that the scientific problems with this procedure, which are given, be modified appropriately to reflect this revision.

The Committee agrees with the EPA position that current levels of dioxin-like compounds in the environment are derived primarily from anthropogenic sources, and, based on available data, that the air-to-plant-to-animal pathway is most probably the primary way in which the food chain is impacted and humans are exposed. EPA should, however, take note of other potentially important exposure pathways, e.g., point source-to-water-to-fish, and cigarette smoking. There is also a very large gap in our understanding of the potential atmospheric transformation of vapor-phase dioxin-like compounds and of the air to plant transfer coefficients of these compounds.

The document's estimate of average dioxin exposure is reasonable, but has substantial uncertainties due to limited data, and cannot provide an estimate of the complete distribution of exposures for the U.S. population. In addition, although the body burden data are clearly not adequate for rigorous time-trend analysis, there is some evidence that exposure may be decreasing in the U.S. The Committee recommends that these points be noted clearly and explicitly in the Summary volume for the benefit of policy makers and the public. The Committee commends and fully supports EPA's efforts to develop better data on concentrations of dioxins in food and in human tissue and regards these as very high priority research needs.

The reassessment document indicated that it is possible that dioxins from historic reservoir sources might be re-introduced through various exposure pathways. The Committee agrees that the potential contributions from reservoirs might indeed be important and that these sources should be evaluated more thoroughly.

The Exposure document defines a "background" exposure based on existing monitoring data obtained from sites removed from known contaminant sources (or from food representative of the general supply). The Committee has two concerns with the "background exposures" as so defined. The first is that this term be used consistently throughout the document. The second concern is that the comparison of estimated exposures from a single planned facility to this "background" might not be adequate if the region already had a higher level of exposure than the "background" due to the presence of multiple existing sources. The Committee recommends that a "baseline" exposure assessment also be made for the local area or region for comparison to the "background," and that the Agency consider providing guidance for performing "baseline" exposure assessments, as well as assessments of the exposure increment from a proposed facility.

Finally, although the Committee supports EPA's use of Toxic Equivalences (TEQs) for exposure analysis, it also recommends that EPA carefully review the draft Exposure Assessment report and ensure that the congener-specific data are used in all instances (such as transport, transformation, and deposition processes) in which

differences in the physical and chemical properties of the congeners are likely to be important. The Committee has noted several such cases in this report.

1.2 Health Document

The document, in the first seven chapters, provides a comprehensive review of the scientific literature on the biological mechanisms involved in the uptake of dioxin and related compounds; the binding of these substances to receptor sites and their metabolism and retention in tissues; and cellular, organic, and whole body responses. **The Committee commends the EPA staff for this considerable accomplishment, and has made a number of comments and suggestions for relatively minor changes, corrections, and citations to additional literature that should sharpen and clarify the content of the initial seven chapters**. The Committee's most significant recommendations concerning these seven chapters center on the Agency's use of Toxic Equivalency Factors (TEF) to address the broad range of dioxin-like compounds having the common property of binding to the Ah receptor and producing related responses in cells and whole animals. **The use of the TEFs as a basis for developing an overall index of public health risk is clearly justifiable, but its practical application depends on the reliability of the TEFs and the availability of representative and reliable exposure data.** The Committee calls for clarifications in the specifications for TEFs of the various dioxin-like compounds for various health outcomes of concern, including the development of separate TEFs for the major compound classes, i.e., 2,3,7,8-TCDD, other dibenzodioxins and furans, and coplanar PCBs. **The Committee is confident that final versions of Chapters One through Seven will not need further review by the SAB.**

The eighth chapter on modeling is critical to the reassessment's overall success. The modeling must deal with both human and laboratory animal data. The human data are usually based on accidents and industrial exposures and are subject to confounding factors such as exposures to other toxicants, differences in population distributions of age, sex, ethnic background. diet, etc. Animal studies often involve high-to low-dose extrapolations as well as cross-species extrapolation. Both types of such data are inadequate, by themselves, for estimating the human health risks of chronic, low-dose environmental exposures to dioxin and related compounds. **Although the modeling chapter reflects a great deal of effort, several Members of the Committee found the exposition of important points to be unclear. Chapter Eight is also weakened**

by its reliance on the standard EPA default assumption of a linear non-threshold model for carcinogenic risk. The Committee suggests that EPA consider, in future revisions, alternative risk models, allowing for minimal response at low environmental levels of exposure, and which would be consistent with the body of available physiological (and, with the opportunities now arising, pharmaco-kinetic) modeling of factors such as deposition, tissue dose, and excretion, as well as the epidemiological, and bioassay data.

Vis-a-vis cancer, the Committee notes that all of the evidence available argues strongly that TCDD exerts its carcinogenic effect primarily through its effectiveness as a promoting agent stimulating cell replication in a reversible manner, and inhibiting apoptosis, both mechanisms presumably mediated through the Ah receptor and associated transduction mechanisms. **TCDD is thus not a complete carcinogen, and, to avoid confusion should not be designated as such in the EPA document. Almost all Members of the Committee do concur with EPA's judgment that 2,3,7,8-TCDD, under some conditions of exposure, is likely to increase human cancer incidence.[2] The conclusion with respect to dioxin-like compounds is less firm**. The Committee notes that the assignment of the dioxins, the PCBs, or PBBs to one of a mutually exclusive and collectively exhaustive set of carcinogenicity categories grossly oversimplifies the state of the science in most instances, excepting those compounds for which there is an abundance of uniformly consistent evidence, but that EPA must make such an assignment. Under the 1986 EPA cancer guidelines, levels of carcinogenic evidence, with mutually exclusive descriptive terms are provided. These choices include Group A -- human carcinogen; B_1 --probable human carcinogen on the basis of limited information from human studies as well as animal studies; Group B_2 -- probable human carcinogen on the basis of animal studies only; Group C -- possible human carcinogen; Group D -- not classifiable; and Group E -- evidence of non-carcinogenicity for humans. **In the case of dioxin, virtually all of the Committee believe that the animal studies would be categorized as "sufficient" and the studies of humans as "limited," providing for an overall categorization of B_1, which would be expressed verbally as "Probably Carcinogenic to humans with**

[2] One Member contends that no epidemiological study has produced evidence that is widely accepted by the scientific community, including the International Agency for Research on Cancer, as being convincing for the human carcinogenicity of dioxin.

limited supporting information from human studies." The Committee (on the basis of similar effects) would support the same designation for dioxin-like materials. PBBs and PCBs would receive ratings of B_1 and B_2, respectively.

Chapter nine, on risk assessment, was not as thoroughly peer-reviewed as were the preceding chapters. It needs to be revised considerably to reflect the changes being made in Chapters 1-8 and the areas of weakness discussed below. The chapter would greatly benefit from an external peer review by a group including some scientists active in dioxin research and individuals with outstanding credentials and experience in basic research and quantitative modeling of receptor-mediated processes. The review group should also include other scientists with broad toxicological, epidemiological, and public health experience to place the risks of dioxin and related compounds in perspective; and, as observers, risk managers who have to contend with concerns of the larger public in addressing regulatory options.[3]

More specifically, the Committee identified, and wishes to emphasize to the Agency, particular areas of both strength and weakness in Chapter 9.

Three major strengths are apparent. **First, by focusing serious attention on various non-cancer effects, the Agency has dispelled any mis-impression that EPA's risk assessment process is overly preoccupied with carcinogenic effects. Second, by evaluating an entire group of compound classes (with a common attribute), rather than a single compound, the Agency responds to the generally-mistaken criticism that its risk assessment process can only address issues on a chemical-by-chemical basis. Third, a useful comparative perspective is provided in the draft conclusions where the Agency highlights the fact that the margin of safety (between background exposures and levels of exposure where effects have been observed in test animals) for dioxin-like compounds is smaller than that EPA usually accepts for many other compounds.**

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[3] One Member of the Committee disagrees with the suggested composition of the peer review group, specifically the inclusion of public health experts and risk managers. He believes that the presence of such participants would divert the focus of the review from science to other issues. These comments apply also to the proposals for peer review which appear in sections 4.1.3 and 5.2 of this report.

Three major weaknesses were also noted. **First, almost all of the Members of the Committee conclude that the presentation of scientific findings portrayed in the draft document's conclusions is not balanced *vis-a-vis* the possible risks posed by exposure to dioxin,** with a tendency to overstate the possibility for danger.[4] **Second, important uncertainties associated with the Agency's conclusions are not fully identified and are not subjected to feasible analyses. Finally, the characterization of non-cancer risk is not performed in a manner that can facilitate meaningful analysis of the incremental benefits of risk management alternatives.**

[4] However, several Members of the Committee do not agree with this statement and regard the EPA presentation as appropriately conservative within the context of public health protection.

2. INTRODUCTION

2.1 Background

Dioxins are a group of anthropogenic chemical compounds created as unintended by-products through a number of activities including: combustion, certain types of chemical manufacture, chlorine bleaching of pulp and paper, and other industrial processes. For the purpose of this review, the terms "dioxin" and "dioxin-like compounds" are used to refer to the family of dioxins, furans, and dioxin-like PCBs, and comprises 2,3,7,8-TCDD and other 2,3,7,8-substituted dioxins, 2,3,7,8-substituted furans, and those PCB congeners with at least four chlorine atoms which can assume a planar conformation and have dioxin-like activity, including the non ortho, mono ortho, and a few di ortho PCB congeners. Dioxins are produced in very small quantities (the emissions estimates in Table II-3 of Volume 1 of the Exposure Assessment sum to about 25 pounds or 11.3 kilograms annually) compared to other pollutants ; however, because they are thought to be highly toxic, they have been treated as significant environmental pollutants since the early 1970's.

In 1988, EPA released two documents addressing risks from dioxins (*A Cancer Risk-Specific Dose Estimate for 2,3,7,8-TCDD* and *Estimating Exposure to 2,3,7,8-TCDD*) and requested that the Science Advisory Board (SAB) review them. The SAB report (SAB, 1989), released in November 1989, although not agreeing with several of the conclusions in the two documents, concluded that “both documents were carefully constructed and well written.” The SAB report concluded a recommendation to “..follow up on this excellent start.” by developing and validating new models for human exposure and for cancer and non-cancer risk endpoints, and to pursue active research programs to resolve questions and incorporate new data.

The Agency initiated a significant effort addressing dioxin risk, and on September 13, 1994, released for public review and comment a 2,400 page draft reassessment of the toxicity of and exposure to dioxin (see 59 FR 46980). The development of this "public review draft" involved outside scientists as principal authors of several chapters, several public meetings to take comment on the Agency's plans and progress, and the publication of earlier drafts for public comment and review. The draft reassessment broadened its focus beyond 2,3,7,8-TCDD to include other dioxins, furans, and coplanar PCBs on the basis of equivalence of response in terms of Ah-receptor binding. Such receptor binding was considered an essential, if not sole determinant. The document was based on information currently available to EPA regarding the toxicity, sources, pathways of release to the environment, and the levels of these

compounds in the environment. It recognized that these compounds vary in potency and used toxicity equivalents based on experimental data to develop overall risk estimates.

In December, 1994, the EPA Office of Research and Development (ORD) requested that the SAB review the reassessment document, and submitted a draft Charge addressing some 40 issues. Following discussions involving ORD and SAB staff, and the Co-Chairs appointed by the SAB Executive Committee to lead the review, a final Charge with 43 issues (see Section 2.2 following) was adopted.

The SAB Dioxin Reassessment Review Committee (DRRC) was developed by building on the SAB's Environmental Health and Indoor Air Quality/Total Human Exposure Committees, and adding (following an extensive review and recruitment process) additional Consultants to fill gaps in needed expertise and to add depth in key scientific areas. In addition to the Co-Chairs, 37 scientists were appointed to the Committee. The DDRC met on May 15-16, 1995 in Herndon, Virginia to hear briefings by EPA staff and comments by Members of the public, and to discuss the relevant issues of the Charge. Following the public meeting, the present report was developed through a series of mail reviews of successive drafts, continuing until consensus was reached, or statements of both majority and minority viewpoints were incorporated.

2.2 Charge

Sections 2.2.1 and 2.2.2 following display the detailed Charge for the review. The Charge consists of background material supplied by EPA Office of Research and Development (ORD) staff, and the specific questions agreed upon following discussions between the Committee Co-Chairs, SAB staff, and ORD staff. The questions are displayed in *italic text* to differentiate them from the background material.

2.2.1 Exposure Document Charge

Overall Scientific Foundations of the Reassessment Document

(Question 1) Overarching the specific issues addressed below and not withstanding any specific finding of the Committee(s), do the available data and the analyses of these data, as presented in the draft, adequately support the major conclusions of the reassessment documents?

The exposure document was developed by EPA's Exposure Assessment Group with contract support from Versar, Inc. The effort began in 1992 and has included several internal review cycles and one external review. The primary objectives of the exposure reassessment document are to:

a) identify the sources that release dioxin-like compounds to the environment;
b) summarize data on the levels of these compounds in food and environmental media;
c) summarize data on human body burdens;
d) estimate background exposure levels; and
e) provide procedures for estimating human exposure as a result of site-specific releases

The key findings of the exposure document include the following: The principal pathway by which people are exposed to dioxin-like compounds is through the diet, with the consumption of animal products contributing over 90% of the average daily intake. It is hypothesized that the principal mechanism by which dioxin-like compounds enter the terrestrial food chain is via atmospheric transport and deposition. Current levels of these compounds in the environment are principally caused by anthropogenic activities. The EPA reassessment document is based on an extensive literature review which is complete through 1993 and includes a number of 1994 references. Over 1000 references were used.

EPA is seeking comment from the SAB in each of the above five areas, as well as posing this general question: *(Question 2) Are currently available models and approaches for estimating and apportioning the impacts of various sources adequate for this purpose -- i.e., addressing the specific issue areas enumerated below? Have the best extant approaches been employed?*

SOURCES:

1. An inventory of CDD/F (chlorinated dibenzo-dioxins and furans) emissions to land, air, and water is presented in the document. In general, the inventory is based on procedures and supporting data comparable to similar inventories conducted by a number of European countries. A qualitative uncertainty classification (low, medium, or high) was given to each estimate, and a range of uncertainty around each estimate was assumed. *(Question 3) Does the Committee recommend any changes to this inventory?*

2. The document concludes that the contribution of historical sources ("reservoirs") to current exposures is unknown. *(Question 4) Can the Committee suggest new ways or identify new data to evaluate further the importance of these sources?*

3. It is unknown whether local or distant sources contribute most to food levels at a particular location. *(Question 5) Can the Committee suggest new ways or identify new data to evaluate further this issue?*

4. A number of investigators from other countries have evaluated the possible existence of unknown sources by comparing estimates of emissions to estimates of deposition. Such an analysis is provided for the U.S. in this document. It concludes that too much uncertainty exists in both the emission and deposition estimates to make any firm judgments regarding unknown sources by comparison of these two estimates. *(Question 6) Does the Committee agree with this position?*

FOOD AND MEDIA LEVELS:

1. The uncertainty in the estimates of CDD/F levels in U.S. is difficult to characterize. The document highlights the limited number of samples used to derive averages and presents standard deviations (where possible to derive). Also, an analysis is presented showing the impact of deriving averages assuming nondetects equal zero versus assuming nondetects equal half of the detection limit. Finally, comparisons are made to European studies. *(Question 7) Has this uncertainty, due both to the possible varied quality of the data and the limited number of samples, been adequately emphasized and characterized?*

2. Some reviewers have suggested that the current U.S. food data should not be used to make preliminary estimates of background levels, even with the caveats. (*Question 8) Does the Committee agree with the document's approach?*

3. The document proposes the hypothesis that the air-to-plant-to-animal pathway is the primary way that the food chain is impacted. *(Question 9) Does the Committee concur with the rationale used to develop this hypothesis? Can the Committee offer further elaborations on the mechanisms which result in food chain impacts?*

4. The document concludes that environmental levels appear to be primarily a product of anthropogenic activities. This is based on trends seen in sediment data, which show a rise in the concentration of dioxin-like compounds beginning in the first half of the 20th Century. Only low levels have been found in ancient tissue remains. *(Question*

10) Does the Committee agree with the conclusion that environmental levels are primarily a product of human activities in the 20th Century?

HUMAN BODY BURDENS:

Human body burden data are presented from several studies. Although some of these studies are quite large (e.g., NHATS (National Human Adipose Tissue Survey) collected samples from over 800 individuals), they may not be statistically representative of the entire U. S. population. *(Question 11) Is this an important source of uncertainty for projecting background body burdens?*

BACKGROUND EXPOSURES:

Background exposures are estimated in two ways: a) using levels in food and standard consumption estimates; and b) by back-calculating from body burden data. *(Question 12) The Committee is asked to comment on the appropriateness of these calculations.*

SITE-SPECIFIC ASSESSMENT PROCEDURES:

1. The food chain and other fate models used in this document are relatively simple, steady-state approaches. They generally use partitioning techniques to model media transfers without consideration of the mass of the compartments. Accordingly, mass balance violations are theoretically possible. The general issues associated with these models can be grouped into three areas:

(Question 13) Is the steady-state assumption valid? Using steady state models is felt to be justified based on the assumption that the release rates of dioxin-like compounds are relatively constant and tendencies for these compounds to persist in the environment. The additional benefit of such models is that they tend to be less data intensive, and information was found for all parameters for the dioxin-like compounds. Does the Committee generally agree with the use of simple, steady state approaches for modeling the fate-and-transport of dioxin-like compounds? Does the Committee have comments on specific models or model parameters?

(Question 14) Is the lack of an explicit mass-balance derivation of the models an important concern? The current models have the advantage of being relatively easy to use. For example, bioaccumulation factors, which are multiplied by media concentra-

tion to estimate tissue concentrations (plants, animals), tend to be simple to use. Limited testing suggests that mass balance violations are unlikely as long as reasonable parameter values are used. Also, the general recommendation is included to conduct mass balance checks after modeling. Is this sufficient or are more complex approaches needed?

(Question 15) Have the models been sufficiently validated? Most aspects of these models were not derived on the basis of theory. Rather, they generally use approaches and parameter values that were derived from field or laboratory observations. Chapter 7 of Volume III details several exercises that are meant to address the validity of the models used in these procedures. Some of these exercises are the description and application of alternate modeling approaches compared with the approaches selected for the assessment. Additionally comparisons were made of model predictions to field measurements for the effluent discharge model, air-to-beef food chain model, and others. Although model validation is generally an ongoing concern, can the Committee make any statements as to the extent and merit of the validation exercises presented in Chapter 7? Can they make suggestions about further exercises which could be done? Can the Committee make statements as to the proper use of these models in light of the validation work presented in Chapter 7?

2. In addition to the general issues discussed above, three more specific fate model issues were highlighted:

(Question 16) Does significant photolysis occur during atmospheric transport of dioxin-like compounds? If so, how does the toxic equivalency (TEQ) of the mixture change? Some evidence exists that rapid photolysis can occur when these compounds are present in a vapor phase. Testing, however, has not been conducted under true atmospheric conditions. The degradation products have not been identified. The possibility exists that higher chlorinated dioxins and furans will yield more toxic lower chlorinated dioxins and furans. Given the lack of tests and unknowns about changes in TEQs, the document recommends assuming no degradation during atmospheric transport.

(Question 17) Have the air-to-plant transfer coefficients been appropriately estimated? These transfer factors are critical components of the dioxin food chain model. The document concludes that transfers of dioxins in the vapor phase dominate above ground vegetative concentrations, particularly feeds of livestock. The transfer coefficients were derived from laboratory studies on the transfer of 2,3,7,8-TCDD vapors onto grass leaves and other vegetation. Questions remain, however, regarding

extrapolation to other congeners, extrapolation to other vegetation, effects of photolysis, wash-off rates of deposited contaminants, etc.

(Question 18) Has the vapor/particle partitioning been appropriately estimated? The document reviews adsorption theory and provides a procedure to estimate the degree that dioxin-like compounds partition between the vapor and particle phases in the ambient air. The controlling factors are: molecular weight, chemical-specific vapor pressure, ambient temperature, and concentration of total suspended particulate. Does the Committee recommend any changes to this approach?

3. The procedures presented in Volume III are specifically designed for assessing the incremental impacts from specific sources. Two aspects of such assessments were not addressed in detail:

The general advice provided on considering background exposures when evaluating the impacts from a specific site is that incremental impacts can be compared to national background estimates for media concentrations and exposures (as presented in Volume II). No additional details or suggestions are provided. (Question 19) *Does the Committee agree with this approach*? *Does the Committee have any specific recommendations?*

The general advice provided on evaluating impacts from multiple sources of release is that point sources can be modeled individually and impacts summed at points of interest, but no additional details or suggestions are provided. *(Question 20) Does the Committee agree with this approach, or would the Panel recommend that multiple sources be more explicitly discussed in Volume III? And if so, does the Panel have any specific recommendations for such inclusions?*

2.2.2 Health Document Charge

Chlorinated dibenzo-*p*-dioxins and related compounds (commonly known simply as dioxins) are contaminants present in a variety of environmental media. These compounds are extremely potent in producing a variety of effects in experimental animals based on traditional toxicology studies at levels hundreds or thousands of times lower than most other chemicals of environmental interest. In addition, human studies demonstrate that exposure to dioxin and related compounds is associated with subtle biochemical and biological changes whose clinical significance is as yet unknown, and with chloracne, a serious skin condition associated with high level exposure to these and similar organic chemicals. Laboratory studies suggest the

probability that exposure to dioxin-like compounds may be associated with other serious health effects including cancer. Human data, while often limited in their ability to answer questions of hazard and risk, are generally consistent with the observations in animals. Whether the adverse effects noted above are expressed in humans, or are detectable in human population studies, is dependent on the dose absorbed and the intrinsic sensitivity of humans to these compounds. Recent laboratory studies have provided new insights into the mechanisms involved in the impact of dioxins on various cells and tissues and, ultimately, on toxicity. Dioxins have been demonstrated to be potent modulators of cellular growth and differentiation, particularly in epithelial tissues. These data, together with the collective body of information from animal and human studies, when coupled with assumptions and inferences regarding extrapolation from experimental animals to humans and from high doses to low doses, allow a characterization of dioxin hazards.

EPA is seeking comment from the SAB in the following areas of the Health Assessment document:

OVERALL SCIENTIFIC FOUNDATIONS OF THE REASSESSMENT DOCUMENTS

(Question 1) Overarching the specific issues addressed below and not withstanding any specific finding of the Committee(s), do the available data and the analyses of these data, as presented in this draft, adequately support the major conclusions of the reassessment documents?

DISPOSITION AND PHARMACOKINETICS:

The disposition and pharmacokinetics of 2,3,7,8-TCDD and related compounds have been investigated in several species and under various exposure conditions. These data and models derived from them are critical in understanding the sequelae of human exposure. Data related to disposition and pharmacokinetics of dioxin and related compounds and efforts to develop models to further understand tissue dosimetry are described in detail in Chapter 1 of the Health Assessment document:

An understanding of the relationship between exposure and dose is an important aspect of an adequate characterization of risk. The data base relating to this issue is extensive for 2,3,7,8-TCDD but is lacking for many of the related compounds. *(Question 2) Does the document adequately characterize the strengths and weaknesses of the data base and draw appropriate inferences for this group of compounds?*

The evaluation of available data and the development of physiologically based models has led to a better understanding of the disposition and pharmacokinetics of dioxin and related compounds than for most other environmental chemicals. *(Question 3) Has this understanding been well integrated into other aspects of the assessment such as route of exposure, toxicity equivalence, dose to the fetus, etc?*

This assessment relies extensively on estimates of body burden that are a function of the uptake, distribution, metabolism, and excretion of this complex mixture of structurally related compounds. Estimates of half-life in the body facilitate the understanding of bioaccumulation as a function of intake over a life-time, and of the impact of incremental exposures on blood or tissue levels both over the short and long term. *(Question 4) Have these issues been adequately dealt with in the health assessment document?*

Body burden data allow some estimation of historical body burdens to complement effects analysis in human populations presumed to have high exposures in earlier decades. *(Question 5) Has the magnitude, implications and uncertainty of these back extrapolations been adequately described?*

MECHANISMS OF DIOXIN ACTION:

Knowledge of the mechanisms of dioxin action may facilitate the risk assessment process by imposing bounds upon the assumptions and models used to describe possible responses to exposure to dioxin. In this document, the relatively extensive database on dioxin action has been reviewed, with emphasis on the contribution of the specific cellular receptor for dioxin and related compounds (the Ah receptor) to the mechanism(s) of action. Other reviews referenced in Chapter 2 provide additional background on the subject. Discussion in this chapter focusses on aspects of our understanding of mechanism(s) of dioxin action that are particularly important in understanding and characterizing dioxin risk including:

the similarities at the biochemical level between humans and other animals with regard to receptor structure and function;

the relationship of receptor binding to toxic effects; and

the role that the purported mechanism(s) of action might contribute to the diversity of biological responses seen in animals and, to some extent, in humans.

(Question 6) Has the Health Assessment provided a useful summary and balanced perspective on these issues? Is the advance in knowledge of details of early cellular events in response to dioxin exposure clearly distinguished from our paucity of knowledge of the direct impact of these events on toxicity?

TOXIC EFFECTS OF DIOXIN:

General Issues

It is clear from the evaluation of the toxicologic literature that dioxin and related compounds have the ability to produce a wide spectrum of responses in animals and, presumably, in humans, if the dose is high enough. Relatively few chronic effects related to exposure to dioxin-like compounds have been observed in humans. The epidemiologic data are limited due to a number of possible factors: the absence of many, specific individual measurements of dioxin exposure for the general population; a limited number of cross-sectional and prospective studies of more highly exposed populations; the limited ability of epidemiologic studies to detect significant differences between exposed and relatively unexposed populations when the outcomes are relatively rare, the exposures are low, and the population under study is small; and the difficulty in quantifying the impact of all potentially confounding exposures. Evaluation of hazard and risk for dioxin and related compounds must rely on a weight-of-the-evidence approach in which all available data (animal and human) are examined together. This process often requires extrapolation of effects across various animal species, as well as to humans.

The reliability of using animal data to estimate human hazard and risk has often been questioned for this class of compounds. The document takes the position that, although human data are limited, evidence suggests that animal models are appropriate for estimating human risk if all available data are considered. *(Question 7) Does the Committee agree?*

For purposes of the current assessment, unless there are data to identify a particular species as being representative of humans for a particular effect, average humans can be reasonably assumed to be of average sensitivity for various effects, recognizing that individuals in the population might vary widely in their sensitivity to individual effects. *(Question 8) Is this a reasonable position to take given the available data? Is the rationale for this assumption clearly stated?*

Chloracne

Chloracne is the only clearly adverse health effect which is known to occur in dioxin exposed humans. Recognition of chloracne has been associated with high level exposure to these compounds, and as such, may represent a biomarker of exposure. *(Question 9) Does the Committee agree with the position stated in the Health Assessment that, because of the wide variability of the chloracnegenic response in humans and its varied persistence, the absence of chloracne is not a reliable indicator of low exposure to dioxin and related compounds?*

Cancer

While the data base from epidemiologic studies remains controversial, it is the view of this reassessment that this body of evidence supports the laboratory data indicating that TCDD probably increases cancer mortality of several types. The Peer Panel that met in September, 1993, to review an earlier draft of the cancer epidemiology chapter suggested that the epidemiology data alone were still not adequate to implicate dioxin and related compounds as "known" human carcinogens but that the results from the human studies were largely consistent with observations from laboratory studies of dioxin-induced cancer and, therefore, should not be dismissed or ignored. Other scientists, including those who attended the Peer Panel meeting, felt either more or less strongly about the weight of the evidence from epidemiology studies, representing the range of opinion that still exists on the interpretation of the cancer epidemiology studies. *(Question 10) Does the Health Assessment document adequately reflect those views? Have uncertainties in the epidemiology data base been well characterized? Would the Committee care to add its view to those already stated in the document?*

An extensive data base on the carcinogenicity of dioxin and related compounds in laboratory studies exists and is described in detail in Chapter 6. There is adequate evidence that 2,3,7,8-TCDD is a carcinogen in laboratory animals. Few attempts have been made to demonstrate the carcinogenicity of other dioxin-like compounds. Other than a mixture of two isomers of hexachlorodibenzodioxin (HCDDs) which produced liver tumors in both sexes of rats and mice (NTP, 1980), the more highly chlorinated CDDs and CDFs have not been studied in long-term animal cancer bioassays. However, it is generally recognized that these compounds bioaccumulate and exhibit toxicities similar to TCDD and are, therefore, also likely to be carcinogens (SAB, 1989). *(Question 11) Does the Committee have any additional comments on extending the*

inference of carcinogenicity of 2,3,7,8-TCDD to the broader class of dioxin-like compounds as defined in the assessment document?

The Health Assessment document describes dioxin and related compounds as complete carcinogens, based on their ability to produce tumors in all animals tested in the absence of exogenous initiating agents. At the same time, it recognizes that these compounds can be described operationally as potent promoters of carcinogenicity without traditionally defined genotoxic activity. *(Question 12) Has the document adequately characterized the carcinogenic activity of these compounds so as to distinguish between these descriptors?*

The EPA's 1985 classification of 2,3,7,8-TCDD as a "probable" human carcinogen under the Agency's risk assessment guidance for carcinogens was based exclusively on the adequacy of the animal carcinogenicity database. The current assessment characterizes 2,3,7,8-TCDD and related compounds as likely to be human carcinogens under some conditions of exposure, and re-affirms the classification of "probable" carcinogens but with greater confidence than in 1985. Increased confidence is based on the total weight of the evidence based on unequivocal animal evidence, limited human evidence and mechanistic evidence supporting biological plausibility. *(Question 13) Does the Committee agree with this characterization of the cancer hazard of dioxin and related compounds? Given efforts underway to revise the Agency's Cancer Guidelines, should this class of compounds be assigned an alphanumeric classification according to the 1986 Guidelines? (A? B_1? B_2?)*

Developmental Toxicity

Since developmental toxicity following exposure to TCDD-like congeners occurs in fish, birds, and mammals, it is likely to occur at some level in humans. It is not currently possible to state exactly how or at what levels humans in the population will respond with adverse impacts on development or reproductive function. Data analyzed in Chapter 5 and Chapter 7 suggest, however, that adverse effects may be occurring at levels lower than originally thought to represent a "no observed adverse effect level (NOAEL)" in animals. Traditional toxicology studies had led to the conclusion that the NOAEL was in the range of intake values of 1 ng TEQ/kg/day. *(Question 14) Does the Committee agree that current data would suggest that the NOAEL in animals should be lower?*

Immunotoxicity

Evidence has accumulated to demonstrate that the immune system is a target for toxicity of TCDD and structurally related compounds. The evidence has derived from numerous studies in various animal species. Animal studies suggest that some immunotoxic responses may be evoked at very low levels of dioxin exposure. Epidemiological studies also provide conflicting evidence for the immunotoxicity of these compounds in humans. Few changes in the immune system in humans associated with dioxin body burdens have been detected when exposed humans have been studied. Both direct and indirect (e.g., hormonally mediated) impacts on the immune system have been hypothesized to be the basis of dioxin immunotoxicity. *(Question 15) Has the significance of the human data been adequately characterized? Are the clinical methods which have been applied to immune function in humans exposed to dioxin sufficiently sensitive to detect immunotoxicity? Does the Health Assessment provide sufficient discussion of the strengths and weaknesses of the animal data on immune function to support its conclusions regarding the potential for immunotoxicity in humans exposed at or near background levels?*

Other Effects

A number of other effects of dioxin and related compounds have been discussed in some detail throughout the chapters in this assessment. While they serve to illustrate the wide range of effects produced by this class of compounds, some may be specific to the species in which they are measured and may have limited relevance to the human situation. On the other hand, they may be indicative of the fundamental level at which dioxin produces its biological impact and may represent a continuum of response expected from these fundamental changes. While all may not be adverse effects (some may be adaptive and of neutral consequence), several effects have been noted in human studies or in primates and have been given special mention. *(Question 16) Are there other important effects that should be highlighted?*

DOSE-RESPONSE:

Development of biologically-based dose response models for dioxin and related compounds as a part of this reassessment has led to considerable and valuable insights regarding both mechanisms of dioxin action and dose response relationships for dioxin effects. These are described in some detail in Chapter 8. These efforts have provided additional perspectives on traditional methods such as the linearized multistage (LMS) procedure for estimating cancer potency or the uncertainty factor ap-

proach for estimating levels below which non-cancer effects are not likely to occur. These methods have also provided a biologically based rationale for what had been primarily statistical approaches. The development of models like those in Chapter 8 allows for an iterative process of data development, hypothesis testing, and model development. These efforts have resulted in incorporation of more of the available biological data into models to predict human risk at low increments of exposure. *(Question 17) Does the Committee agree with the approaches to dose-response that have been used in the Health Assessment? Given the evolving nature of this effort should collaborative efforts to refine these techniques continue as a high priority?*

The U.S. EPA has frequently defined a reference dose (RfD) for toxic chemicals to represent a scientific estimate of the dose below which no appreciable risk of non-cancer effects is likely to occur following chronic exposures. In the case of dioxin and related compounds, calculation of an RfD based on human and animal data and including standard uncertainty factors to account for species differences and sensitive sub-populations would result in reference intake levels on the order of 10-100 times below the current estimates of daily intake in the general population. For most compounds where RfDs are applied, the compounds are not persistent, background exposures are generally low, and are not taken into account. Dioxin and related compounds present an excellent example of a case where background levels in the general population are likely to have significance for evaluation of the relative impact of incremental exposures associated with a specific source. Since RfDs refer to the total chronic dose level, the Health Assessment document takes the position that the use of the RfD in evaluating incremental exposures in the face of a background intake exceeding the RfD would be inappropriate. *(Question 18) Does the Committee agree? Is the rationale for this position clear?*

Observations described in this assessment suggest a continuum of response to exposure to dioxin-like chemicals. By a continuum of response, we suggest that as dose increases the probability of occurrence of individual effects increases and the severity of collective effects increases. This continuum provides a basis for inferring a relationship between some early events which are not necessarily considered to be adverse effects with later events which are adverse effects. Considerable uncertainty remains in inferring how these events are related, although we know more about how dioxin-like compounds may elicit effects than we know about the mechanisms of action for most chemicals. This inference may be the most contentious of all and it is likely that a wide range of opinion will be provided by the scientific community regarding the relationship of these mechanistic observations and prediction of potential for adverse

effects in exposed humans. *(Question 19) Does the Health Assessment document provide a balanced perspective regarding the uncertainties embodied in this inference?*

TOXICITY EQUIVALENCE FACTORS (TEFs):

The EPA and the international scientific community have agreed that the use of toxicity factors (TEFs) to predict relative toxicities of mixtures of this class of compounds has an empirical basis, is theoretically sound, and, in the absence of more complete data sets on the toxicity of individual members of this class, is a useful procedure. This is not to say that the use of TEFs is a certain procedure. Since 1986 when the first Agency-wide consensus on the use of TEFs was published, additional refinements to the data bases and to the use of TEFs have occurred. Published revisions in accord with international agreement appeared in 1989. In the course of this reassessment, critical data were collected and agreement was reached regarding the contribution of dioxin-like PCBs to overall TEQs. Additional validation of the TEQ concept in predicting effects of this class of compounds on wildlife species lends further support to the use of this approach. This relatively simple, additive approach does not take into account interactions between dioxin-like compounds and other chemical exposures. *(Question 20) Does the Committee agree with the EPA's use of TEFs in the Health Assessment document? Have the uncertainties and the assumptions intrinsic to the use of TEFs been clearly described? Should EPA consider presenting the assessment results in an alternative manner?*

LABORATORY ANIMALS/ HUMAN RESPONSE:

Based on our knowledge of the biochemical and biological similarities between laboratory animals and humans, our understanding of some of the fundamental impacts of this class of compounds on biological systems, and comparable responses from animal and human studies both in vitro and in vivo, EPA has made the decision to use laboratory animal data to contribute to weight-of- the-evidence conclusions on human hazard and risk. *(Question 21) Does the Committee agree that this decision is reasonable?*

Humans do not appear to be an unusual responder for dioxin effects; that is, humans do not, on average, appear to be either refractory to or exquisitely sensitive to the effects of dioxin-like compounds. While positive human data are preferable for ascribing hazard or risk, the lack of adequate human data to demonstrate causality for many suspected dioxin effects is assumed not to negate the findings from laboratory animal and in vitro studies. Although some scientists may disagree, in our estimation,

the database on dioxin and related compounds regarding a wide range of responses across animal species is one of the most comprehensive among all environmental chemicals. The fundamental understanding of mechanisms of dioxin action provides a unifying theory for the mechanisms for observed effects in laboratory animals and humans, and for using a weight-of-the-evidence approach considering all relevant data to infer the human health impacts of dioxin and related compounds. *(Question 22) Have the strengths and weaknesses of this position been well articulated?*

OVERALL CONCLUSIONS:

The final chapter of the Health Assessment document integrates information on exposure and effects relating to the impact of dioxin and related compounds on human health. It also contains overall conclusions on this issue. As such, it represents a risk characterization. *(Question 23) Does this chapter adequately characterize the data-base, assumptions, and uncertainties relating to the potential health effects of dioxin and related compounds? Does it provide the information in enough of a public health context to be understandable to decision-makers?*

3. DETAILED FINDINGS--EXPOSURE DOCUMENT

3.1 Sources

3.1.1 Estimating and Apportioning Sources (Charge Question 2)

The approach for estimating and apportioning the relative contributions of various types of sources is to multiply average emission factors for each source type by the mass flow (i.e., the amount of combustion) in each category to estimate the total emissions of dioxin and dioxin-like compounds[5] to the environment for each source category, then sum the totals and examine the relative contributions of each type of source.

It should not be assumed that the fractional contributions of various types of combustion sources to total emissions are identical or similar to their contributions to human exposures for the population in general. This distinction should be explicitly stated. It is quite possible that the major sources of dioxin in food may not be those that represent the largest fractions of total emissions in the U.S. The geographic locations of sources relative to the farms from which much of the beef, pork, milk, and fish come, is important to consider. That is, the farm lands which produce much of our food may not be necessarily located near the major sources of dioxin and related compounds.

Total estimated dioxin-like emissions for the U.S. have been compared to an estimate of the total amount of dioxin that is deposited to the surface of the U.S. based on available deposition factors. The ranges of the two estimates overlap, giving some suggestion of a mass balance for the U.S. as a whole. Although such mass balance comparisons have been published in the literature, there is a significant scientific problem with doing this very simple comparison on a continental or regional scale without doing atmospheric dispersion and deposition modeling of the emissions. Specifically, the atmospheric lifetime of the accumulation mode particles (0.1 to about 2-3 μm), in which much of the dioxins and dioxin-like compounds are found, is on the order of many days. Thus, a large proportion of the particles with dioxin-like compounds that are emitted in the eastern U.S. are likely to be deposited in the Atlantic Ocean, Canada, Europe, or even the Arctic, depending upon source locations and weather patterns. Given the long atmospheric half-life of the particulate dioxin-like

[5] For the source estimation, only dioxins and furans were included.

compounds, a global or hemispheric mass balance would be necessary. In order to do a scientifically acceptable mass balance comparison of emissions and deposition for the U.S., deposition of emitted dioxins must be estimated using atmospheric dispersion and deposition modeling, and the deposition estimates from the emissions then compared to measured deposition data. In addition, more representative measured deposition data would be needed.

The Committee recommends that this section of the report be modified so that this simple direct mass balance comparison is not provided, and the scientific reason for not doing so be explained. The Committee agrees with EPA's statement (Volume II, p. 3-166) that it is thus not scientifically valid to infer from such a comparison that there are any missing sources of dioxins.

3.1.2 Source Inventory (Charge Question 3)

The dioxin emission inventory has identified the major known sources and has, in general, made a reasonable estimate of the total emissions from each source category. However, some revisions should be made.

The incineration of medical waste was estimated to be the largest source of dioxin emissions. After this estimate was made, new information became available that indicates that current emissions from medical waste incineration might be significantly lower than initially estimated by EPA. The EPA should review these (and any other) new data that becomes available, and revise the estimates as appropriate. The emission estimates for industrial and residential wood combustion should also be reviewed and revised, as well as the estimates for dioxin emissions from the combustion of diesel fuel.

The Agency should assess the time-frame for the emission inventory. Also, EPA needs to evaluate more thoroughly the emissions data and define more carefully the width of the uncertainty range based upon engineering assessments and data availability.

Due to the uncertainties in dioxin emissions data, and the variability in emissions, there is significant uncertainty in the emission estimates. The EPA has estimated an uncertainty range of either a factor of five or a factor of ten for each dioxin source category, based primarily on the uncertainty in the estimated emission factors. The Committee thinks that the uncertainty in emissions has been underestimated in some

cases. In addition, uncertainty classifications should attempt to build upon the classification systems already used in existing EPA emissions factors databases.

There appear to be some sources identified in international inventories or by commentors which were not considered or were not assessed in the EPA Reassessment Document. Some discussion of these sources is important to the completeness of the report even if they are later determined to be negligible sources of CDD/CDF emissions.

3.1.3 Dioxin Reservoirs (Charge Question 4)

The reassessment document indicated that in addition to exposures from sources that are currently emitting CDD/CDF, it is possible that CDD/CDF from historic reservoir sources are being re-introduced to exposure media. The assessment conducted on this issue (section 3.7 of the EPA document) was a simple evaluation of the relative importance of one year's emissions from currently emitting sources to those from preexisting reservoirs. This simple assessment, based upon an assumption of first-order dissipation rates and an assumed half-life of dioxin in the reservoir, indicated the large potential size of the CDD/CDF reservoirs relative to annual deposition rates. Given that heretofore, the presence of CDD/CDF in subsurface lake and ocean sediments had generally been considered to be innocuous deposits, no attempt was made to quantify further the contribution of the reservoirs to human exposure.

The Committee concluded that the potential contributions from reservoirs might indeed be important and should be evaluated. It is important to be able to evaluate the relative contributions of reservoirs and currently emitting sources, particularly in light of the fact that emitting sources appear to be in decline. Thus the relative contribution of these reservoir sources may become even more important. A limiting case which may be particularly informative is an assessment of exposure in the absence of currently emitting sources. Some of the reservoirs, such as sediments, may act as a relatively minor continuous source from surface biological processes, but become much more significant during major storm events, cleanup, or navigational dredging. Other reservoirs may be relatively active and their continuing contribution to exposure should be assessed in order to account for all sources of exposure.

The Committee suggests a technique to evaluate the potential importance of reservoir material to exposure. EPA could evaluate the plausibility of different reservoir materials re-entering exposure scenarios through the use of engineering estimates and limited case analysis. Although this analysis would not be quantitative since the actual

extent of reservoirs materials is not fully known, the analysis would provide some assessment of the importance of particular reservoirs and exposure scenarios.

3.1.4 Local/Distant Contributions to Dioxin Levels in Food (Charge Question 5)

The question of the relative contribution of local and distant sources to food levels at a site is a difficult one to answer experimentally and would probably require extensive studies at many sites. Furthermore, the answer could well be different in different parts of the U.S.

In the future, better data and new or revised models may make such activities more feasible, and lead to a full understanding of the movement of contaminants from emission sources to food pathways.

When better quality data are available, the Agency should consider using geographic information systems (GIS) for their analysis. With such systems, the geographic distributions of dioxin emissions and food (beef, pork, chicken, milk) could be mapped and compared. Although not quantitative, this examination is likely to produce some insights and testable hypotheses. Once the more current measurements of dioxins in food become available, these can also be mapped and quantitative questions can be asked and tested statistically regarding the probable influences of local, regional, and distant sources

3.1.5 Uncertainty in Deposition Estimates (Charge Question 6)

Various research groups have tried to balance the input of dioxins *into* the atmosphere with their output *from* the atmosphere. The input calculations are based on source inventories, done on a national, region, and international scale. The output estimates are based on calculations and measurements of fluxes from the atmosphere. Most of these data (summarized in Volume II, pages 3-4, 3-5, and 3-166 to 3-168) indicate a large discrepancy between deposition from the atmosphere and inputs into the atmosphere. This discrepancy indicates that 10-50 times **more** dioxins are being deposited from the atmosphere than are being emitted into the atmosphere. However, the simple mass balance comparison of the estimates of emissions and deposition fails to take into account the atmospheric lifetimes of accumulation mode particles and their long range transport in the atmosphere. Thus a certain (unknown) fraction of the dioxins emitted within the continental United States are certainly transported by the atmosphere and deposited beyond the borders. In addition, dioxin deposition can not

be expected to be geographically uniform; in consequence, this very simple mass balance comparison cannot be used to infer unknown sources.

There is another technical problem with this comparison. These deposition rate estimates are based on direct measurements of wet and dry deposition by several research groups. However, these measurements have been converted to TEQ values in order to compare them to emission estimates. This conversion is justified by the overall strategy of the dioxin reassessment; however, it is strictly correct only when the ratios of the various congeners is the same in the various samples. **To be technically rigorous, the deposition calculations and emission estimates should be based on individual congeners and isomers, perhaps focusing on a few of the most abundant compounds.**

The Committee, however, agrees with EPA that there is much value in an evaluation of the mass balance comparison of emissions and deposition. Such a comparison (which we are pleased to learn from EPA staff is now underway by the Agency), however, must involve modeled estimates of dispersion, transport, and finally deposition from sources within a given region. The modeled emissions-based estimate of deposition could then be compared to measured deposition for the region.

Improved measurements of deposition fluxes for the U.S. is a fruitful area for investigation. Most published studies have taken samples in highly industrialized and urbanized regions of the world. It is risky to extrapolate these measurements to the entire United States. A strategy in which deposition fluxes are calculated from geographically diverse samples taken throughout the United States could lead to a more accurate and precise estimate of the total deposition rate to the United States.

3.2 Food and Media Levels

3.2.1 Problems in Estimating CDD/F Levels (Charge Question 7)

A very limited number of samples are available to make the preliminary estimates of CDD/CDF in air, water, soil, and food products. Such estimates are appropriate and useful, and EPA has tried to provide some idea of the uncertainties and variability in the
data. However, there are some refinements and additions that can and should be made in revising the report.

a) The reported sample analyses were performed at different laboratories, using different methods of analysis, and the samples were not all collected and analyzed in the same time period. Thus, there are some underlying sources of uncertainty and variability which are not adequately represented by using simple statistics (mean, standard deviation). For example, if environmental levels are declining, as indicated by sediment samples, the samples may have a time variability which the reader might not
recognize. Some cautions on these aspects of uncertainties should be added to the report.

b) It is recommended that the reported data be examined with respect to the number of significant figures used and that these be reduced as appropriate. For example, the daily intake should not be reported as 119 pg/day TEQ, but as being on the order of 100. By handling the results this way, it becomes clear that there are not really significant differences between the estimates for the U.S. and other countries given the uncertainties in the estimates.

c) Although the reassessment document makes no unwarranted claims about the accuracy of the food data for exposure assessment, it is important that policy makers be fully aware of the limitations of the use of the results in the policy arena. For example, the Committee does not believe that these data are appropriate for trends analysis of body burdens or for geographical or demographic trends in exposure. Nor are the currently available data sufficient to characterize the variability of exposures in the U.S. population. In the summary volume, it would be very helpful to policy makers to explicitly point out these kinds of limitations and to note that the exposure estimate is only an estimate of the central tendency of exposures within the U.S.

In the future, as better measured data become available, the data analyses should include use of probability techniques, not just simple statistics.

3.2.2 Use of U.S. Food Data (Charge Question 8)

U.S. food data for the estimation of background exposure to dioxin-like compounds is presently inadequate, but the EPA is commended for its major effort to obtain new data, on which the Committee was briefed, but did not specifically

review. Shortcomings aside, the available information from the U.S. along with that from other countries indicates a central trend or mean for background food exposure of about 100 pg per day. A very recent food study effort by EPA (with contributions from the U.S. Department of Agriculture and the Food and Drug Administration) has generated significant data on the TEQ content of beef (Winters *et al.*, 1994). The new value is considerably (3 to 4 times) lower than that used in the document. This would suggest that the overall daily intake of PCDD/PCDF may be less than 100 pg. Additional data gathering is now in progress for milk samples, and is planned for pork, poultry, eggs, and vegetable oils.

Current information on the variation or distribution of this value within the U.S. is imprecise, however. The sampling part of the EPA program is quite strong as it is statistically planned, and the distribution within the U.S. is being studied, as well as production within various regions. From this initial undertaking, it appears that sources of food for much of the U.S. are widely distributed geographically, and that exposure is national in scope with only limited regional differences.

The Committee was of the opinion that, in the cases where analyses showed non-detectable numbers (ND), the best estimate of the true value, with currently available information and methodology, was to use one-half the limit of detection. The effect of using this approach on measures of central tendency of a distribution depends, however, on the actual detection limit (which is a function of sample properties and analytical procedures) and the proportion of values in the distribution at or below the detection limit. For example, if the detection limit is relatively high, and a large proportion of the values in the distribution are at or below the limit of detection, then using one-half the detection limit will probably overestimate measures of central tendency. The Committee suggests that EPA explore alternative statistical approaches to handling ND values in the future, particularly the well-established maximum likelihood method. This approach requires only that the parametric form of the underlying distribution be known.

The food study program underway by EPA shows a good detection limit for TCDD (0.05 ppt on a fat basis or about 0.01 ppt on a whole weight basis) but significantly higher values (0.5 ppt fat or 2.5 ppt whole weight) for the penta-, hexa-, and hepta-congeners. For example the food data of Schecter *et al.* (1993) have been criticized for its lack of controlled sampling but the detection limits of the analytical method are lower than those of EPA. In order to minimize the variation in estimation of the PCDD/PCDF content of foods by this uncertainty in detectability, EPA should try to improve their analytical detection limits for the penta-, and hexa- congeners (those for the hepta- and

octa- are not as important since they contribute less to the TEQ). In this activity, there is a tradeoff between reliability of analytical levels and the detection limit. In general, the closer one approaches the detection limit of a method, the less certain one becomes of the value, and the further one is removed from the detection limit, (usually) greater confidence is given to the analytical value. The Committee believes that EPA, in measuring PCDD/PCDF concentrations in foods, should take the necessary steps to obtain detection limits on the samples as low as technically feasible. Such an approach will minimize the uncertainty engendered by using one-half of the detection limit for ND results. The Committee considers that EPA is putting (correctly) more weight on the latter. It is also desirable that EPA report data on both a whole-weight and fat basis to compare to other studies.

A number of public comments related to a paper presented at Dioxin 93 (Welge *et al.,* 1993) showing that the PCDD/F content of blood was the same for vegetarians and non-vegetarians. The Committee is of the opinion that the above study is inconclusive. The individuals classified as vegetarians followed such a diet between 5 and 10 years (median values). Classification as a vegetarian was based on non-consumption of both meat and fish. The diet was not verified by any means, and the study did not address consumption of milk, dairy products, and eggs -- all known food sources of PCDD/PCDFs.

3.2.3 Air/Plant/Animal Pathway and Other Food Chain Impacts (Charge Question 9)

Given the existing data, it is probably premature to conclude that the air-to-plant-to-animal pathway[6] is the primary way the entire food chain is impacted. Nonetheless, this is a reasonable hypothesis, one that is consistent both with the extant data and existing models. Based on the analysis of the existing and very limited food measurement data, EPA has focused on the air-to-plant-to-animal exposure pathway. It is important that EPA not lose sight of other potentially significant exposure pathways such as emissions from point sources- to-water-to-fish and possible exposures from cigarette smoking.

In terms of concentrations, existing data suggest that fish have a higher average concentration than any other food, although the ingestion rate is lower. In terms of

[6] After deposition on plants, particles are washed into the soil by precipitation and plants die and decay into soil, so that ultimately the deposited dioxins accumulate in the soil; consequently, for grazing animals, this pathway includes intake of dioxin via ingestion of both plants and soil.

human exposure, foodfish (especially freshwater fish from the larger waterbodies) are likely to be exposed to additional point sources of PCDDs/Fs such as publicly operated treatment works, as well as to air emissions. For this human exposure scenario, such sources may be of equal or greater importance than the air emissions. Given that some populations eat larger quantities of fish (e.g., anglers, Native Americans, etc.), the water-fish pathway deserves additional discussion as an important exposure pathway.

The weaknesses in the conclusion that the air-plant-food pathway is dominant are carefully examined in Volume III, Chapter 7. One major conclusion about beef concentrations is that the "Total TEQ concentrations compare favorably with observed total TEQ at 0.48 ppt and predicted TEQ at 0.36 ppt." One concern is using TEQs to support this conclusion. This comparison, using the sum of 17 values, each of which is multiplied by a factor ranging from 1 to 0.0001, is misleading. The total TEQ concentrations between predicted and observed differ by a factor of 4 (8.15 to 2.13) and ratios of observed to calculated values for individual congeners varies from 0.13 to 22, roughly two orders-of-magnitude. Here, and throughout the document, the EPA must move away from the TEQ comparison and begin to assess by individual congener comparisons. When this is done, the strength of a number of EPA's conclusions about exposure and consequent human risk decreases. Another way to compare these results is to note that 9 out of the 17 or about 53 percent of the congener values differ by a factor of 5 or more.

The same type of analyses are carried out for the air-to-hay pathway calculations. Unfortunately, there are only observed (other than non-detect) values for five congeners to make the comparison. For those five values, the observed concentrations are greater than the modeled ones. The analysis concludes that, "Given the range of the detection limit, 0.31-6.4 ppt for the hay sampling, the model's predictions of grass concentrations are generally consistent with observations, with the exception of the OCDD and OCDF concentrations." Two of the five comparisons are OCDD and OCDF, and the lack of data for the other comparisons cannot verify the model or conclusions.

The fairly good agreement in TEQs, the sum of the total concentrations, and the fact that most of the individual congener comparisons agree within an order-of-magnitude, all support the conclusion that the air-plant-animal pathway is the major input to the food chain. As noted above, this is a worthwhile hypothesis and may well be true; but given the lack of data and the number of assumptions needed, it can not be proved at this time. The document should state this fact explicitly and might also note that no good alternatives are available.

3.2.4 Smoking--An Additional Potential Exposure Pathway[7]

There is an additional exposure pathway that should be considered. Cigarette smoking **may** account for a very significant fraction of dioxin exposures for some of the population (25% of adults). Smoking has not been considered in the reassessment document; although the Committee does not consider this omission to be a major flaw, smoking should be considered in future revisions. There are now three papers in the literature that report that dioxin is present in mainstream cigarette smoke. Muto & Takizawa (1989) estimated that a pack-a-day smoker has a daily intake of about 4.3 pg of polychlorinated dibenzo-dioxins per kg of body weight. Lofroth and Zebuhr's (1992) measurements of mainstream smoke imply an intake of 18 pg TEQ per day per person for a pack-a-day smoker. This is about 13% of the daily median intake estimated from other sources in the EPA exposure assessment. There is also a paper by Ball *et al*. (1990) which reports dioxin emissions for mainstream smoke that are about an order-of-magnitude lower than those reported in the other two publications. Although differences of an order-of-magnitude in dioxin measurements are common, there is reason to suspect that they may have had substantial losses in their sampling apparatus. Beck *et al.* (1994) found no differences in PCDD/PCDF content of human breast milk between smokers and non-smokers. Nonetheless, given that the exposures are actually distributions, and that some members of the population are heavy smokers, this source should be considered. The Agency should also consider possible contributions to exposure from environmental tobacco smoke (ETS). It would be useful to know if any good data on the dioxin content (or lack of dioxin content) in sidestream smoke exist.

3.2.5 Anthropogenic vs. Natural Sources of Dioxin (Charge Question 10)

The background for this question is the observation in the late 1970s that dioxins are produced by the combustion of many common materials, including municipal solid waste. This led some scientists to suggest that dioxins had been with us since "the advent of fire" and that dioxins could be produced by natural combustion (for example, by forest fires). At that time, there were some suggestions that observed levels of dioxins were primarily the result of coal combustion or perhaps of wood burned in small stoves. This speculation was largely refuted by sediment core studies, both in the United States (primarily in the Great Lakes) and in Europe, which indicated that

[7] This discussion does not relate to a specific question in the Charge. The issue of smoking as a possible exposure pathway arose during the preparation of this report.

environmental dioxin levels increased significantly beginning about 1935-40 (see Volume II, pages 3-92 to 3-94). Since the advent of fire clearly predated this time, it can be concluded that dioxins were largely anthropogenic and associated with events taking place around 1935-40. What were these events? Coal combustion could be ruled out because the consumption of coal in the United States was essentially constant from the turn of the century until about 1970; this record did not agree with the sediment core data. The explanation is likely to be the introduction of chlorinated organic compounds (polyvinyl chloride and chlorinated pesticides are but two examples) in the 1935-40 time-frame. Other sources such as leaded gasoline (which commonly contained ethylene dichloride and ethylene dibromide), diesel emissions, and PCBs are also possibly significant contributors. Although the details of dioxin formation are not yet quantitatively understood, the introduction of these chlorinated products into wastes that were combusted appears to be the most likely cause of the increased dioxin deposition measured in sediments.

These sediment core data are now numerous. Several such studies have been published for lakes from throughout the world, and these studies have not been challenged in the scientific literature. Therefore, it is very clear that dioxins are a Twentieth Century phenomenon closely correlated with the production of chlorinated compounds. The Committee concurs strongly with the conclusion that “environmental levels of dioxins are primarily a product of human activities in the twentieth century.” The draft document could make this point even more persuasively by citing all of the sediment core studies that have been published, even though some of them have been for lakes outside of the U.S.

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Incidentally, there is an undercurrent of opinion (which has also been expressed in the public comments received about the draft reassessment) which says that "forest fires are possibly the major source of dioxin in the environment.” The Committee concludes that this contention is not correct. Many of the sediment core studies in the scientific literature span times during which forests in the lake's watershed were burned by natural causes. There was no elevation of dioxins in the sediment record at the time of these forest fires. A recent study by Buckland *et al*. (1994) found no difference in soil dioxin levels in Australian conservation areas before and after brush fires. Consequently, the Committee concludes that environmental levels of dioxins are primarily a product of human activities in the Twentieth Century.

There is one other feature of these sediment core data that warrants comment. Most of the sediment records show a decrease in dioxin deposition starting around 1970; in other words, dioxin deposition from the atmosphere to lake sediments was at

its highest around 1970. This decrease seems to be continuing, and it may well be attributable to decreased emissions from large-scale combustion systems; regulations for such systems are not thought to have had major impacts prior to the early 1980s; consequently, the origin of the decline is still unclear.

Beyond the sediment core studies, the history of dioxin emissions has been addressed by two studies (Ligon *et al.*, 1989; Schecter, 1988) of mummified human tissue (see Volume II, pages 3-149 to 3-150). These results suggest that dioxins were present only at very low levels in humans at the time these individuals were mummified (about 2800 years ago in the Ligon study, and 400 years ago in the Schecter report). The presence of these compounds in modern humans at much higher concentrations is well known; therefore, these ancient tissue analyses support the concept that dioxins have not been with us since "the advent of fire," but are a more recent addition to our environment. However, unlike sediment core studies, these tissue measurements, in addition to being limited to only two samples, do not tell us when dioxins became an important part of the environment.

3.3 Human Body Burdens

3.3.1 Uncertainty in Estimating Human Body Burdens (Charge Question 11)

Body burden data are presented in Chapter 5, pages 5-18 to 5-27 of the exposure reassessment document. These data provide one index of exposure to dioxins; the data on body burden are also used to estimate exposures using a pharmacokinetic model that back calculates the dose needed to achieve the observed adipose tissue levels (assuming steady state exposure/dose). The principal U.S. data come from the National Human Adipose Tissue Survey (NHATS). Table 5-8 presented mean adipose tissue data for a number of congeners for 865 samples collected in 1987 and analyzed as 48 composites, each containing an average of 18 specimens. Analyses are reported as showing increasing levels with increasing age and as being lower in 1987 in comparison with previous findings from 1982. Except for one congener there was no variation by region and no variation for any congener by race and sex. Additional data are provided from U.S. reports by Patterson (1994) and Schecter (1991). Data from Germany and elsewhere are also cited. The report assumes a level of 2,3,7,8 -TCDD in adipose tissue of 5.0 to 6.7 ppt for the purpose of estimating typical exposure.

The Committee believes that reliable nationally representative body burden data are not available. The reassessment acknowledges that the NHATS data, the most extensive available, cannot be considered as representative, and the smaller data sets are even less likely to estimate average exposure accurately. Because the exposure histories of the individuals included in the NHATS studies are unknown, the average could be biased upwards by occupational exposures or residential exposures from smoking. However, there would be little impact on the mean unless exposure markedly increased levels, given the sample size of 885 samples in NHATS. The Committee anticipates that only a small proportion of the population would be heavily contaminated. On the other hand, the possibility remains that selection of the samples may have been weighted towards more exposed persons. The reassessment document does not attempt to estimate the potential for such bias nor its consequences.

Although the NHATS data may be sufficiently robust to provide a reasonable estimate of the mean, the range of tissue concentrations is not provided by these data because the samples were pooled for analysis. Further, because of the modest sample size, the data are not adequate for trends analysis and would have limited statistical power for any comparisons across groups, whether defined by race, sex, or geography . Thus, the findings of the analysis on these factors should be given little weight.

3.4 Background Exposures

3.4.1 Estimating Background Exposures via Food/Body Burden Data (Charge Question 12)

The Committee agrees that it is appropriate to use food data and food factor information to estimate exposure to the 2,3,7,8-TCDD. It is also appropriate to use body burden data on TCDD to estimate daily uptake from all sources (half-life of about 7.5 yr).

As noted earlier, the food analysis data are too limited to extrapolate the results to reflect the distribution for the entire U.S. population. Data obtained from different geographical areas, with a statistical emphasis on those foods that contain the bulk of the dioxins and furans, are needed before these data can be used to estimate uptake. The Committee also recommends that EPA evaluate cigarette smoking as a possible exposure pathway for dioxins (see discussion in section 3.2.4).

3.5 Site-Specific Assessment Procedures

3.5.1 Steady-State Assumptions and Modeling (Charge Question 13)

The Committee did not raise objections to or have comments on the validity of the steady-state approach or challenge the model selection. It was noted, however, that in future efforts it would be desirable to have some estimate of the importance of long-term accumulation in sinks such as sediments or soil.

There were also some concerns about the potential input of harbor dredging and storm events on re-suspended solids. Although these occurrences probably have minor impacts on the exposure of the total population, they might impact on certain sub-populations with high fish intakes. This comment is intended to point out the need for future work and to describe potential risks that may not be addressed in the present system of analysis.

3.5.2 Mass-Balance Issues (Charge Question 14)

On page 3-55 to 3-57 of the exposure reassessment document, where the use of the COMPDEP model is described, it is stated that the model should be run with no deposition for gas-phase contaminants, and with both wet and dry deposition included for particles. Given the nature of atmospheric dispersion models, this implies that, for gas-phase CDD/Fs, the plume disperses with full reflection at the ground surface, and for particles there is a loss at the ground surface based on the flux attributable to the wet and dry deposition. This reflects the state-of-the art in atmospheric dispersion modeling. Nevertheless, this approach ignores some significant mass balance and energy balance issues with regard to the dispersed CDD/F species. To understand these issues, the gas-phase CDD/Fs at the interface between air and the soil, at vegetative surfaces, or at surface water with which they come in contact, must be considered. This is especially true, since EPA believes that this is the predominant mechanism for the contamination of food. Even though these gas-phase contaminants are not expected to “deposit” physically onto these surfaces, a partitioning in response to the tendency of natural systems to maintain thermodynamic equilibrium is expected. Consider that in the atmosphere both the particles and pure gas phase provide comparable reservoirs for CDD/F congeners. Since the surface-to-air-volume ratio of the ground surface and vegetation surfaces are much larger relative to the atmosphere than the surface-to-volume ratio of air particles, how can the partitioning of CDD/F compounds at air/plant and air/soil interfaces be ignored? In an air/soil, air/plant, or air/water system, chemical thermodynamics is likely to favor a relatively large fraction of the chemical in the non-air compartment. Consequently, there is a fairly strong chemical potential likely to drive the chemicals from air into these other media, where

they are likely to be retained, transformed, and re-emitted, either in the gas phase or bound to particles.

These types of processes cannot be captured using the COMPDEP (Complex Deposition) model but instead require chemical potential models. At this time, we cannot ascertain the magnitude of any errors thus introduced to the output of the COMPDEP model, or their significance to the assessment. In order to explore the significance of the omissions of mass-balance in the COMPDEP model, there is a need also to develop a regional-scale chemical potential model and apply it individually to the CDD/F compounds. **It is important here to emphasize that these types of transport and transformation processes are compound- and congener- specific and therefore should not be estimated on a TEQ basis.** Until such extensions can be developed and applied, the use of COMPDEP remains the best alternative.

3.5.3 Model Validation Issues (Charge Question 15)

The Committee considered the comparisons of model-estimated versus measured environmental contaminant concentrations. It was noted that the narrative material in the reassessment document described seven such comparisons, and no generalizations about model function could be easily drawn. It appears that there has been no overstatement of model validity and that a considerable effort has been made to uncover all useful methods for validating the models with the existing data. It was noted by EPA that the validation exercise for the beef bioconcentration model algorithm was performed and that the results supported the model. There were no suggestions for alternative model use, but the review of the earlier SAB guidance on peer review and model validation (SAB, 1989) should be discussed in the document.

The Committee also discussed the distinction between model validity and model *system* validity. The existing system of analysis will not answer questions of long-term contaminant accumulation in sinks and would be difficult to adapt for use with multiple sources. The Committee suggests that if these other important questions are to be addressed, a different framework will have to be developed.

It is important to note that the above comments are not intended to suggest that the current framework is inappropriate, inaccurate, or in need of revision for its stated use as a data and methodology resource for risk assessment.

3.5.4 Photolysis and Atmospheric Transport (Charge Question 16)

The relative abundance of the various dioxin homologues and congeners differs between sources and the environment and environmental sinks. For example, most combustion sources generate a dioxin mixture with relatively high concentrations of tetrachloro- and pentachloro- dibenzofurans, whereas the environmental sinks are dominated by relatively high concentrations of octachlorodioxin. It has been suggested that the lesser chlorinated compounds are degraded between the source and the sink and that the mechanism for this degradation is photolysis (see Volume II, pages 2-30 to 2-35 of the exposure document). The significance of photolysis is a difficult question for the Committee (or the EPA) to answer because there are virtually no data on this subject. Photolysis is probably important, but all evidence on this point is qualitative and indirect.

During the atmospheric transport of dioxins, they can exist in one of two forms: either in the vapor-phase (in which the compounds are airborne as individual molecules) or in the particle-phase (in which the dioxins are sorbed onto atmospheric particles). Photolysis of dioxins in each of these two phases proceeds at different rates and by different mechanisms. Unfortunately, there are very few data on either of these mechanisms. Data on the photolysis of dioxins from the atmospheric particle-phase are limited to one study, which indicates that dioxins associated with fly-ash are stable when exposed to simulated atmospheric photolysis conditions. Of course, this is only one study which needs to be replicated.

Two mechanisms for the degradation of dioxins in the vapor phase are possible. The first is direct photolysis, in which the molecule of interest reacts with a photon. The very limited extant data indicate that 2,3,7,8-TCDD has a half-life of a few minutes under these conditions (Orth *et al.,* 1989). The second mechanism, which is probably the most important, is the reaction of dioxins with hydroxyl (OH) radicals. Most atmospheric chemists consider this to be the primary mechanism by which organic compounds are removed from the atmosphere. Thus, determining the rate constants for reactions of dioxins with OH has been of considerable interest. Unfortunately, experimental difficulties have precluded the direct measurement of these values. In the absence of experimental data, models (based on various substituant effects) have been used (Atkinson, 1987; Atkinson, 1991). These calculations indicate that the atmospheric lifetimes of dioxins and furans are in the range of 1 to 40 days. The tetrachloro- congeners are at the low end of that range, and the octachloro- congeners are at the high end. Reactions with OH are considerably slower than those induced by direct photolysis. (Incidentally, this work on OH reactions was not presented in the draft reassessment document, and it should be added.)

There are clearly insufficient data on which to base any firm conclusions about the general issue of atmospheric photolysis. It seems likely that important loss processes in the atmosphere are photolytic and that reactions with OH are important. However, rate constants for none of these reactions are known, and it is impossible to assess their significance.

Based on the modeled rate constants cited above, it is likely that the lower chlorinated compounds are degraded more rapidly than the higher chlorinated compounds. For example, the tetrachloro- dioxins are probably degraded more rapidly than the octachloro- dioxins. This estimate agrees with observations that the less chlorinated dioxins and furans are reduced in relative concentration between environmental sources and sinks. However, it should be emphasized that this is all mere speculation in the absence of any data on the relative rates of the pertinent reactions.

Photolysis may also be important in other parts of the environmental transport scenario for dioxins. Photolysis in water must be considered after deposition of these compounds from the atmosphere to lakes or oceans. Photolysis on soil and on plant surfaces must be considered as these compounds begin their movement into the human food supply. In all of these cases, data on photolytic reactions are very sparse. In addition, a knowledge of the products of these environmental transformations is not available. Is it possible that congeners with low TEFs are being transformed in the environment to congeners with higher TEFs? Clearly these are all areas in which additional research is needed.

3.5.5 Air-to-Plant Transfer (Charge Question 17)

As stated in the Charge, the question of the importance of air-to-plant transfer is too difficult to answer at this time with the available data. The air-to-plant transfer coefficients suggested by EPA are reasonable for 2,3,7,8-TCDD (given the available data), but there are insufficient data to support the assumptions for the transfer coefficients for the other PCDDs and PCDFs.

For EPA to understand the importance of the issue of air-to-plant transfer, the fundamental physical and chemical properties for most PCDDs and PCDFs need to be determined (and confirmed). Values for $K_{o/w}$ (the octanol/water partition coefficient) and vapor pressure, water solubility, and photolytic half-life should be near the top of the list of data gaps that need to be filled to answer this question.

It is not possible to work backward from concentrations of CDD/Fs in cows to estimate what was on the plant which the animals ingested, because of the significant contribution of soil ingestion by grazing cows to the total uptake. It is widely thought that some fraction of PCDD taken up by grazing animals will normally be associated with ingestion of contaminated soil. Ideally, a high quality field study of air concentrations of CDD/Fs and CDD/Fs versus the concentration in vegetation would be the basis for the air-to-plant transfer coefficient estimate. This type of study would probably be performed in several agricultural areas. Some Committee Members preferred this approach over laboratory studies because of the inability to replicate what happens in the outdoor environment.

3.5.6 Vapor/Particle Partitioning (Charge Question 18)

The EPA document presents three alternative approaches for the estimation of vapor/particle partitioning and discusses the limitations of each. It is important to note that actual measurements of vapor/particle partitioning in air are technically difficult. Lacking such data, the model proposed by Bidleman (1988) was selected by EPA for estimating partitioning as the best of the three approaches.

One approach considered was to derive partition estimates from stack sampling data. The inherent sampling artifacts (e.g., the use of heated filters to collect particles) introduced by current stack monitoring methods were recognized as the main limitation of this approach. A further limitation is the need for modeling the changes in vapor/particulate partitioning downwind from the source, as the plume components undergo dilution, condensation, and coagulation. Given the effects of these processes on vapor/particle partitioning of CDD/Fs, the model estimates would be quite unreliable and must be considered to be preliminary estimates.

Another approach consists of using current ambient monitoring data. The available data, however, are limited with respect to the particle size distribution and environmental condition represented. Furthermore, these data have been typically obtained with high-volume samplers such as the PS-1; particles are collected with a filter while the vapor-phase compounds not retained in the filter are captured by a sorbent trap located downstream from the filter. The main limitation of these data is that part of the particle-bound CDD/Fs collected by the filter may re-volatilize, particularly when large volumes of air are moved through the filter. Consequently, the fraction of the CDD/Fs collected by the sorbent trap may overestimate the vapor phase fraction actually found in the atmosphere. Nonetheless, these data could provide an upper bound estimate of vapor/particle partition.

The third approach, and the one selected (as noted above) for estimating vapor/particle partitioning (a choice which the Committee considers acceptable), is the model proposed by Bidleman (1988), which is largely based on fundamental properties of the CCD/Fs. Phase partitioning is assumed to be conserved between the source and downwind receptor. There are some limitations to this approach, such as the use of solid phase vapor pressures at 25° C, whereas ambient temperatures could vary significantly (the EPA document applies the model for 20° C). This could be the major reason why the calculated data in table 3-5, page 3-42 agree so poorly with the measured data. However, the model results appear to be in general agreement with the vapor/particle partition trend in the ambient data, that is, the tetra- and penta-substituted congeners tend to partition to the vapor phase, and hexa/hepta chlorinated compounds are mainly particle-bound. Since vapor/particle partition depends on ambient temperature, further evaluation of the results from the model could be performed by comparing ambient data obtained during the temperature extremes of winter and summer. The Committee recommends that EPA undertake such an effort.

3.5.7 Background Exposures and Site-Specific Evaluation (Charge Question 19)

The definition of "background" as applied in the current assessment is given on page 5-1 of Volume II as: "...background exposures estimated in this chapter are based on monitoring data obtained from sites removed from known contaminant sources (or food data representative of the general food supply.)" On the other hand, the site specific assessment is directed at estimating incremental exposure resulting from a specific source. There seems to be an implicit contradiction in these two statements, since the implications of an increment in exposure from the emissions of a given source are a function of existing conditions (i.e., the presence or absence of other similar or different sources). Depending on those specific sources, the "background" default assumptions of the six scenarios presented in Chapter 5 of Volume III may not be appropriate. Certainly the data on environmental concentrations of CDD/Fs presented in Volume II demonstrate that there is significant variability in levels even among sites which could be categorized in the same scenario.

The term "background" is also confusing because, in spite of the preferred definition stated above, it is used in the rest of the document to represent other concepts. For the purpose of site-specific assessments, the term "baseline conditions" appears to be more appropriate than "background." The Agency might then consider providing guidance for performing baseline exposure assessments for specific sites. Such guidance may include the following recommendations for the user:

a) use site-specific media concentrations rather than defaults whenever possible;

b) if these data are unavailable, use information from a comparable site in terms of the types and density of sources present, land-use conditions, and geographic/atmospheric characteristics;

c) when site-specific or comparable site data are not available, use regional data.

The Agency might consider including examples of how a site-specific baseline evaluation might be performed. Consideration of site-specific baseline conditions would obviously implicitly include the contributions from existing multiple sources.

3.5.8 Evaluation of Multiple Sources (Charge Question 20)

For the reasons discussed in detail in section 3.5.7 above, it may not be appropriate to utilize the national background exposure estimates presented in Volume II of the draft report as representing the site-specific background levels.

Where a site is impacted by multiple existing sources of dioxin-like compounds, it is appropriate to model the contribution of each individual existing source and then sum their emissions and depositions for the purpose of calculating a baseline quantification of total exposure for that site. Whenever possible, baseline calculations should be developed on a media-specific basis. This baseline exposure calculation may differ significantly from the national background levels discussed in Volume II. The dioxin ambient air/deposition map currently in development by EPA will hopefully provide information on regional deposition levels that can provide more localized background level information.

The SAB Indoor Air Quality/Total Human Exposure Committee has previously raised the concern in the context of its review of the EPA draft document *Addendum to the Methodology for Assessing Health Risks Associated with Indirect Exposure to Combustor Emissions* that a more regional approach be adopted for evaluation of exposure and health risks from indirect exposures to combustor emissions (SAB, 1994). Dioxin-like compounds were among the pollutants of concern with respect to these sources. **The Committee recommends that guidance be provided in Volume III to indicate that a regional, as well as site-specific, exposure assessment be undertaken in areas with multiple existing sources of dioxin-like compounds.**

Currently, the draft report provides little information for the reader regarding how to assess baseline exposures at a site with multiple existing sources of dioxin-like compounds. The inclusion of a case-study example would make the report more informative.

3.6 Overall Scientific Foundations of the Reassessment Document (ChargeQuestion 1)

The EPA staff has done a very credible and thorough job on a large and complex task. They are to be commended on the work that they have done to assemble, integrate, and analyze a very large body of data on source emissions, environmental levels, exposures, and human body burdens in the framework of human exposure assessment. In so doing, they have uncovered key data gaps and issues, developed some reasonable priorities for future efforts, and begun to implement research efforts to address information gaps. In general, the work has been clearly presented and the documents are well written. It should also be noted that, as a result of this integrated assessment, a number of industries are currently seeking to address gaps in emissions measurement data.

The EPA has done a good job of evaluating the sources of dioxins, based on available data, and significant sources of uncertainty have been qualitatively identified. In addition, this document provides the foundations for a quantitative treatment of uncertainties--a task that is, however, beyond the scope of the current reassessment document. Although there is great uncertainty in the levels of dioxins in some environmental samples, these levels are consistent with the emission inventory; that is, comparison of the emission inventory and environmental levels does not imply that there are significant unknown sources. There is also some evidence, i.e., decreases in concentrations of dioxins in surface sediments and human tissue samples, that indicates that emissions of dioxin are decreasing. Further environmental and human monitoring is, however, required to confirm this.

In assessing sources of dioxin-like compounds, the total estimated dioxin emissions for the U.S. have been compared to an estimate of the total amount of dioxin that is deposited to the surface of the U.S. based on available deposition factors. The difference between the two estimates has raised some concerns about possible “missing sources.” There is a serious scientific problem with trying to perform such a simplified mass balance on a continental or regional scale. That is, the atmospheric lifetime of accumulation mode particles (0.1 to about 2-3 μm) is of the order of many days. Thus, a large proportion of the particles with dioxin-like compounds that are

emitted in the eastern U.S., for example, are likely to be deposited in the Atlantic Ocean, Canada, Europe, or even the Arctic, depending upon source locations and weather patterns. Given the long atmospheric half-life of the particulate dioxin-like compounds, a global or hemispheric mass balance is necessary. A second, and perhaps even more serious concern, is that the mass balance calculations have been performed using only two data points for deposition in the U.S. (Bloomington, Indiana and Green Lake, New York). These locations are unlikely to be representative of average deposition in this country. **Given these problems, it is strongly recommended that the sections of the report in which the very simplified mass balance comparison of the emissions inventory and the deposition mass are compared be modified so that a direct comparison is not made and it is made clear that such a comparison is not scientifically valid. In addition, these findings also mean that the simple mass balance presented here cannot be used to infer "missing sources."**

The available scientific evidence strongly indicates that current levels of dioxin-like compounds in the environment are largely derived from anthropogenic sources (see section 3.2.5). There is also considerable scientific evidence that the principal mechanism by which dioxin-like compounds enter the terrestrial food chain is via atmospheric transport and deposition. However, there is a very large gap in our understanding of the potential atmospheric transformation of vapor-phase dioxin-like compounds; specifically, there are no experimental measurements of photodegradation or degradation via reaction with hydroxyl radicals. Environmental measurements of deposition of particulate and vapor-phase dioxin-like compounds to the surface are also extremely limited, although we understand that there are now some efforts to address this data gap.

The evidence that the principal pathway for human exposure to dioxin-like compounds is through the diet, with consumption of animal products accounting for the dominant or overwhelming fraction of exposure, is also quite robust. The associated air/plant/animal pathway hypothesis has considerable support, although it has not been proven unequivocally, particularly in view of the very limited available data. It is also important not to lose sight of other potentially significant dietary exposure pathways, such as emissions from point sources to water or sediment, and then to food. In addition, cigarette smoking should be evaluated as a potentially significant exposure source for smokers in the population (about 25% of U.S. adults are smokers). If the estimates of dioxin-like compounds in beef and pork presented in the report, based on very limited data, are found to be too high, then cigarette smoking (for which the dioxin

estimated are also based on very limited data) could account for a significant proportion of exposure for smokers.

Estimates of human exposures, based on currently available information from exposure analysis and analyses of human tissue samples, are consistent and are likely to provide a reasonable central estimate of the distribution of exposures for the population. Existing measurements of dioxin-like compounds in food, however, are very limited. Consequently, we lack data that would allow an estimate to be made of the distribution of exposures for the U.S. population.

The Committee found the term “background” somewhat confusing and suggests that “national average background exposure,” or some similar explicit term should be used in future drafts for greater clarity.

The Committee also believes that the very brief discussion and recommendations on multiple sources should be substantially expanded and that more detail should be provided. Of the two approaches suggested, it was felt that the better approach would be to model multiple sources in a region and then make comparisons of the potential exposure contributions of a new source to local exposures. The results might be termed "baseline," and considered along with national average background exposure, as well as with increments in exposure from a specific facility.

Understandably, the focus of the report is on site-specific models, which are needed for regulatory purposes, e.g., to answer questions such as “Is a proposed facility likely to result in a significant increase in exposure above background?” Ongoing work to refine, test, and validate these models can be considered a "microscopic" approach. It would, however, also be very useful to have a macroscopic approach, including more regional and global mass balances and multimedia modeling. That is, other types of models should be used to examine other issues. For example, the very similar levels of these compounds which have been found in food and humans in a number of countries, suggests that they probably are widely distributed via atmospheric transport processes throughout the Northern Hemisphere and that more global (or hemispheric) evaluations of mass balance should be undertaken.

4. DETAILED FINDINGS--HEALTH DOCUMENT

4.1 Disposition and Pharmacokinetics Issues

4.1.1 Strength of the database (Charge Question 2)

The Charge for this review (see section 2.2) states that "An understanding of the relationship between exposure and dose is an important aspect of an adequate characterization of risk." A specific concern is how the extant data are used to predict tissue dose levels of 2,3,7,8-TCDD in humans under low exposure conditions.

There is a an extensive animal data base relating exposure to tissue dose for 2,3,7,8-TCDD (although data are lacking for many of the related compounds), and there is a substantial (and generally solid) body of data on the absorption and distribution of 2,3,7,8-TCDD in animals (Birnbaum, 1985; Gasiewicz *et al.*, 1983; Neal *et al.*, 1982; Olson *et al.*, 1983; Van den Berg *et al.*, 1994). There are insufficient human data to support deposition and tissue dose modeling however, and this data gap severely restricts animal (largely rodent) to human extrapolation. Further, there are only a limited number of animal studies that reflect accurately likely environmental exposure scenarios for humans. For example, gastrointestinal absorption of 2,3,7,8-TCDD is influenced by the presence of other compounds, the nature of the matrix, and the very limited aqueous solubility of 2,3,7,8-TCDD. These and other factors relevant to the partitioning of 2,3,7,8-TCDD and gut absorption are of critical concern, given the fact that foodstuffs are considered by EPA to represent a major source of chronic low level human exposure to dioxins .

The pulmonary exposure data base is based on the pulmonary absorption of 2,3,7,8-TCDD from solution; absorption by this route is known to be high. The most likely non-dietary human exposure to 2,3,7,8-TCDD, however, would be through inhalation of particulate matter incorporating dioxin in a solid matrix (e.g., fly ash). Although data on pulmonary absorption from a solid matrix are available (Nessel *et al.*, 1990; Nessel *et al.*, 1992a; Nessel *et al.*, 1992b), these data are not addressed in the reassessment document.

Given the large data base, a more thorough analysis of the biological determinants of tissue absorption and deposition (particularly with low dose exposure) should be carried out. For example, mice show a different pattern of distribution to the skin than rats, with the former more accurately reflecting data

obtained in non-human primates (Brewster and Birnbaum, 1988; Gallo *et al.*, 1992; Rahman *et al.*, 1992).

The hepatic distribution patterns of 2,3,7,8-TCDD in animals appears to be dose-dependent and saturable. This is an area that needs further study, particularly with regard to potential interspecies differences and the development of valid human physiologically-based pharmacokinetic (P_BP_K) models.

In general, the reassessment document has drawn extensively from the existing animal data relating exposure/tissue dose and absorption/distribution, but did not characterize adequately the strengths and weaknesses of the data base. Further, the inferences drawn leave some issues unaddressed. A greater effort needs to be made to describe the long-term effects of the decrease of PCDD- and PCDF levels in the environment, and in turn, in human exposures. This description should provide an improved estimate of the mix of chemicals in the TEQ and their capacity to be both agonists and antagonists (or synergists) in the overall biological effects of 2,3,7,8-TCDD and 2,3,7,8-TCDD-like compounds, as well as those chlorinated compounds that are reviewed in the health assessment documents but are not 2,3,7,8-TCDD-like. In addition, to enhance further the value of the reassessment, a greater effort is needed to provide a better understanding of the consequences and possible interaction of employing both the receptor model for risk assessment and the utilization of the concept of TEQ. For example, what can be expected in this context with a range of halogenated chemicals that may interact in various ways as either agonists or antagonists? What can be expected from a mixture of such compounds, when considering both additive or non-additive effects, with constant or changing concentrations of those individual components which contribute to both response and the TEQ value?

In chapters I through 7, which mainly review the current research data, the document provides a generally balanced evaluation, and inferences from these chapters are appropriate except as noted above. However, Chapter 8 presents an incomplete review of the dose response model (Linear Multi-Stage [LMS] and modified LMS) approach, with no consideration of alternative models used by other agencies, nor discussion of the literature. This is reflected in the summary chapter. **Thus, the Committee recommends that EPA provide either additional discussion of alternative approaches and their implications for risk assessment in Chapter 8, or present a clear justification for choosing this particular dose-response approach over others. Chapter 9 should also be modified to reflect these additions.**

4.1.2 Disposition and Pharmacokinetics (Charge Question 3)

In addition to the specific questions asked about disposition and pharmacokinetics by the Charge, the introductory sentence leading into this issue must also be evaluated. This sentence states " The evaluation of available data and the development of physiologically-based models has led to a better understanding of the disposition and pharmacokinetics of dioxin and related compounds than for most other environmental chemicals." This sentence implies that these models are well-established and ready for incorporation into the current assessment. **It is the Committee's consensus, however, that there are several issues that should be addressed before these models can be used effectively in the risk assessment**. The following questions should be addressed in a revised assessment document:

a) Does the database to determine mechanism and models apply only to 2,3,7,8-TCDD or may it be extended to other related compounds? Currently the great majority of data on physiologically based kinetic models is derived from 2,3,7,8-TCDD research, but about 90% of estimated "risk" is from related compounds (as stated in the reassessment document, p. 9-81).

b) Do the models proposed extend to all dose ranges, particularly to low dose? The data used in current models were not generally derived from studies conducted at low dose levels. There is significant controversy as to the shape of the curve in the models proposed at the low dose levels.

c) Are all organs effectively addressed in the models? The models appear to focus on liver and fat concentrations in rodents; however, the target organs in the epidemiology studies for carcinogenesis are the gastrointestinal tract and others. It is not clear that the models effectively describe the exposure and metabolism of those possibly impacted tissues. Particular questions may exist with respect to the lung for carcinogen exposures that occur by the respiratory route (although this route is probably of minor significance for most of the population, it could be of concern for occupational exposures).

d) If models have primarily been determined from short-term or single-dose studies, do these results apply to chronic studies and/or longer term exposures? In particular, the chronic Kociba *et al.* (1978, 1979) studies, which included low exposure levels, did not necessarily fit one of the

models proposed, whereas the dose finding studies did. A question then exists concerning the model's efficacy for the real life-low exposure situation.

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e) Do the models apply across relevant mammalian species?

f) What is the relationship between "dose" as used in the dose-response models and tissue or body burden that the EPA uses in many comparisons between human and animal exposures and risks?

Lastly, the variability of the half-life of 2,3,7,8-TCDD in the human leads to questions about the precision of the models. The estimated half-life discussed varied from five to 11.3 years. The range given here may represent a difficult communication issue, and affects the precision of the model.

In the body of the health reassessment document, the issue of P_BP_K modeling is discussed in three chapters (1,8, and 9). However, there is little evidence of actual integration of any of these models into specific portions of the document. The concept of physiologic-based modeling is discussed separately in the risk assessment portions of the document, and is conceptually a part of the process. Scrutiny of the document (and oral discussions with the document's authors at the public meeting) however, yielded no evidence of use of a specific P_BP_K model in the risk assessment. Given the issues noted above, this is understandable and not considered to be a particular weakness by the Committee (however, opportunities do exist--see the discussion below), but future revisions of the document should be clear as to the degree to which such modeling has been incorporated into the assessment process.

Notwithstanding the lack of incorporation of these models into the current reassessment and the significant questions noted above, the database on dioxin could provide an opportunity to utilize state-of-the-art P_BP_K models. The Carrier-Brunet-Brodeur model (Carrier *et al.*,1995a; 1995b) (which was not yet published at the time the Health Reassessment was under development) , for example , incorporates non-linear elimination rates; as body burden declines, half-life increases. The applicability of this model and its implications should be discussed in any future revision of the reassessment document. **The opportunity to utilize the Ah receptor binding in modeling is significant, and these models should be more effectively incorporated into the risk assessment through revisions to Chapter 8.**

4.1.3 Incremental Exposures and Bioaccumulation (Charge Question 4)

The EPA reassessment document provides a large amount of animal and human data regarding bioaccumulation of 2,3,7,8-TCDD. However, it is readily apparent that a large gap exists in our knowledge regarding the pharmacokinetics of common, environmentally occurring congeners of 2,3,7,8-TCDD. If Toxicity Equivalency Factors (TEF) are going to be used to assess human toxicity, and if approximately 10% of the total exposure to dioxins is attributable to 2,3,7,8-TCDD, an accurate estimation of total potential for toxicity can be made only if information is available regarding distribution, metabolism, and half-lives of other major contributing components (See discussion in section 4.13). It is not possible to make a general estimate of toxicity if we know nothing of the pharmacokinetics of the majority of the dioxin-like compounds to which humans are exposed. The reassessment is silent on this issue, but data from autopsy evaluations have been published by Schecter (1991) and should be used (if possible) to extend our knowledge of the pharmacokinetics of these compounds.

Major shortcomings are evident in the data base and the relevant issues have not been dealt with adequately. For example, no attention has been given to reviewing the half-lives of many of the important compounds that constitute the TEQ. Data from studies concerning exposures of subsistence fishermen appear to be in conflict with the EPA estimation of body burden (Columbia River Intertribal Fish Commission, 1993; Dewailly *et al.*, 1994; Svensson *et al.*, 1991). These studies suggest that the reassessment's estimated body burdens may be as much as two orders-of-magnitude higher than actual levels; this difference may be related to errors introduced by not accounting for the various half-lives of the agents included in the TEQ.

4.1.4 Uncertainties in Back Extrapolations of Body Burden (Charge Question 5)

The Committee's primary concern with the topic of the body burden back extrapolation lies with EPA's treatment of uncertainty regarding the half life of dioxin, and the exposition of the methods for the back calculation in the health document.

As discussed at the public meeting, the Committee anticipates that future revisions of the reassessment document will incorporate the latest data set from the Ranch Hand study, which should narrow considerably the range of estimates for dioxin half-life, and so reduce the uncertainty (from that source) in the back extrapolation of

body burden. In addition, we expect that EPA will revise the discussion on the back calculation method to include material covered in Chapter 6 of the exposure document, but not currently addressed in the health document.

4.2 Mechanisms of Dioxin Action

4.2.1 Animal-to-Human Extrapolations of Receptor Structure/Function (Charge Question 6)

Mechanisms of dioxin action are discussed in various parts of the Health Assessment document. Overall, the presentations are very useful. Whether or not the document addresses all the relevant information and alternatives depends, however, on the section that is being read. Chapter 2 offers an unequivocal assessment that "...the Ah receptor *mediates* the biological effects of TCDD." Yet, when reading Chapters 3, 4 and 5 dealing with specific toxic events, it becomes clear that numerous fundamental uncertainties occur and mechanisms of action for the toxic events beyond receptor binding are largely unknown. In Chapter 9, however, there is a return to the acceptance presented in Chapter 2. This may indicate that the authors of Chapter 9 are willing to go along with the Ah receptor information as it exists today.

One major difficulty lies with the use of the term "mediator" and perhaps confusion about what constitutes a "mechanism of action." Other than what is described in the sections dealing with developmental toxicity (e.g., cleft palate, hydronephrosis), very little is known about the biological steps that finally lead to frank toxicity; the lack of information in immunotoxicity is particularly limiting. Much of what is purported to link the Ah receptor to specific toxic events is merely the demonstration of an *association* between the binding of TCDD to the receptor and an eventual appearance of an adverse effect some time later in some species (when the interspecies variation in doses that produce lethality can be over 8,000-fold, based on the data provided in Table 3-1, Volume 1, of the reassessment document). But the possible "downstream" events, if they exist, between Ah receptor binding and the final toxic manifestation are not well established. "Mechanism of action" should mean that at least some of the intermediate steps, after Ah receptor binding and leading to the pathologic processes involved, are known to some extent. The loose use of the term "mediator" implies that the *association* apparently observed is in reality the *initiator* of the process. In actual fact, the only mechanism of action involving the Ah receptor that has been worked out sufficiently well to be called the biological sequence that describes a "mechanism of action' is the induction of cytochrome P450. What is known about the induction

process is truly elegant. The rest of the *biological consequences* of TCDD exposure are yet to be described adequately and sequentially in mechanistic terms.

The document (Chapter 2) presents an excellent review of what is known about the Ah receptor and the multiple steps involved in TCDD-induced cytochrome P450 induction. Research findings during the last 10 or so years that have identified the structure and mode of action of the Ah receptor represent a major scientific achievement. How a planar polar compound such as TCDD binds with a cellular receptor, followed by translocation into the nucleus, where transcriptional activity of DNA is influenced, is very well understood. On the other hand, there is a large intellectual chasm between the elegant science describing the details of the TCDD receptor and its mechanism of initiating a cellular response, and the poorly understood manifestations of the toxic events associated with an alteration of the homeostasis of an animal. The linkage between Ah receptor action and specific cellular toxicity remains undefined. Several Members of the Committee noted that the possibility that the Ah receptor system may be a sensing pathway to protect the cell is not considered, nor are there other attempts to put forth scientifically testable hypotheses. In any future revisions, EPA should present more clearly the major deficiencies that exist in the current mechanism database and provide some discussion of any plausible alternative hypotheses.

Although the Ah receptor is likely involved in producing TCDD toxic effects of potential concern to humans, there are multiple levels of regulation of the receptor pathway. The induction of CYP1A1 does not serve as a good model for all receptor-mediated responses to dioxin, particularly those that result in altered patterns of growth and differentiation. The studies of Poland and Knutson (1982b) in hairless mice indicated that for responses such as epidermal hyperkeratinization and skin tumor promoting activity, the Ah receptor is necessary, *but not sufficient*. Two implications from these studies are: a) that toxicity is under multiple genetic control, and b) the most sensitive response in animal models is not necessarily the most valid predictor of toxicity in humans. Chloracne remains the most definitive response documented in humans and clearly occurs at high exposure levels. However, there are relatively few animal models for chloracne. Most of the “mechanistic data” support the involvement of the Ah receptor, but say little (in the context of toxicity), about how the activation of this protein alters normal physiologic function and/or development. Risk assessments based solely on Ah receptor activation or on the existing knowledge of CYP1A1 induction are unlikely to provide a biologically defensible prediction (quantitatively or qualitatively) of likely toxic outcomes in humans, particularly under low exposure scenarios.

Regarding the Ah receptor in humans, there is adequate evidence that, in overall function, the human Ah receptor mechanism essentially acts the same as the Ah receptor in rodents and in other laboratory species. The Ah receptor in humans, however, has an affinity for TCDD that is lower than the affinity in C57BL/6 mice or in most laboratory rat strains. There may be at least a 10-fold range of variation among the human population in the affinity with which the Ah receptor binds TCDD. Induction of CYP1A1 exhibits classical sigmoidal log-dose response curves in several human cell lines in culture.

The EPA document's phrase "...and the role that the purported mechanisms of action might contribute to the diversity of biological response seen in animals and, to some extent, in humans?" in this question can be better posed as "...how convincing is the evidence for the purported mechanisms that link receptor binding to toxic effects in humans?" Unfortunately, the evidence is quite mixed. There is only limited evidence for toxic effects in the Ranch Hand study (USAF, 1991; CDC, 1988a,b). Studies of the Seveso population (Bertazzi *et al.*, 1993; Bertazzi *et al.*, 1989; Mocarelli *et al.*, 1986) show significant excesses of multiple myeloma and hepatobilliary tract cancer in women, and lymphoreticulosarcoma in men in zone B, and soft tissue sarcoma in men in zone R. These lesions, however, were seen in the zones of lower, not higher, estimated exposure. Conversely, and further clouding the issue, these same studies also report decreases in breast[8] and other cancers in females (although the number of cases is very small and the decrease may be spurious). In the exposed chemical plant workers studied by the National Institute of Occupational Safety and Health (NIOSH) (Fingerhut *et al.*, 1991), there is no excess cancer of any kind in the less heavily exposed workers (i.e., those who were exposed for less than one year). Workers with over one year's exposure showed statistically significant increases in respiratory system cancer, but they were exposed to a wide variety of potentially carcinogenic agents in addition to dioxin. Given the possible confounding, and the somewhat equivocal links of dioxin to excess cancer in the group as a whole, it is difficult to document a dioxin-cancer relationship.[9] [10]

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[8] Some Committee Members suggest that this reduction may result from the anti-estrogenic effects of dioxin.

[9] Several Members of the Committee suggest that EPA has neglected other human exposure studies of interest, particularly the health effects seen in the Taiwan rice oil PCB poisoning episode (as reported in Rogan *et al.*, 1988; Wu *et al.*, 1984; Chang *et al.*, 1982a; Chang *et al.*, 1982b: and Chang *et al.*, 1981) which could reduce the reliance on animal-to-man extrapolation.

[10] Noting that cancer excesses were seen in the Fingerhut *et al.* (1990; 1991) studies only in workers with 20 or more years of latency, one Committee Member argues that the Bertazzi study should be discounted as uninformative. It was carried out only ten years after exposure, the levels of exposure to the people in the zones that are characterized as having excess cancers are far less than those of the workers studied by Fingerhut *et al.*, In this Member's opinion, both the reported excesses and deficits are more likely to result from chance than from any dioxin effect.

4.3 Toxic Effects of Dioxin

4.3.1 Animal Models for estimating Human Risk (Charge Question 7)

The Committee believes that the EPA reassessment document reviewed and summarized adequately the current knowledge base on the experimental disease(s) produced by TCDD and related compounds in animals.

The Committee agreed that, because there is a limited amount of human data, EPA will have to rely on the results of animal studies for some portion of its risk characterization. However, the Committee also finds that it is probably not appropriate for the Agency to single out the results of a given study (unless it is of a seminal nature) for decision making. The EPA would be better served to employ a weight-of-the-evidence approach, using the totality of the data.

The Committee noted that although there were many interspecies consistencies in response following exposure to the compounds in question, there were also many significant inconsistencies. The Committee questions whether some of the interspecies differences were “true” differences or were a reflection of the dose levels used in the different studies. A portion of the interspecies Inconsistencies may be attributed to the fact that some of the animal studies involved lethal exposure levels but that other studies did not. For example, some of the effects noted in animals (see Table 9-2 of the reassessment document), e.g. “wasting disease,” chloracne, testicular atrophy, hepatotoxicity, cardiovascular lesions, hypoglycemia, edema, and porphyria, were found primarily in animals that died. Many of these effects were **not** observed in cows, however, and none of the cattle studies involved lethal exposure levels. Therefore, the lack of interspecies comparability may indeed be a reflection of the dose levels used in particular species/studies.

Another apparent inconsistency which may be a reflection of study design is related to the carcinogenicity of TCDD. Although TCDD has not been reported to be carcinogenic in guinea pigs, rabbits, chickens, cows, or monkeys, none of the studies were of sufficient length to ascertain whether it is indeed carcinogenic or not in these species. Additionally, the lack of observed chloracne in a given species may be related to anatomical differences; many of the tested species have "fur” rather than true "hair”

follicles as are found in monkeys and humans. Also, a feather follicle (chicken) is anatomically quite different than a hair follicle. Some discussion of these points would be beneficial to readers of the reassessment document.

The Committee also suggests that the document discuss "primary" versus "secondary" effects of exposure. For example, some of the effects related to TCDD exposure (testicular atrophy, cardiovascular pathology, edema, and porphyria) may not be directly related to the compound, but may rather be a reflection of the “sick animal” syndrome. Comparative mechanistic and pharmacokinetic data would be needed before making a conclusion that a given effect is directly attributable to TCDD or related compounds. The degree of uncertainty in this regard needs to be discussed in the document and needs to be reflected by using “?” marks in Table 9-2.

The Committee believes that Table 9-2 is extremely important and is very likely to be used by the casual reader; consequently it should be made as accurate as possible. Members of the Committee have noted errors in the Table, and we suggest that the tabular material in the document be reviewed for accuracy.

In summary, the Committee finds that there is evidence of both inter-species consistency and inconsistency in the EPA document. These variances need to be addressed in an objective manner in the document, and discussed in conjunction with all the uncertainties inherent in the various endpoints. In addition, the Committee felt strongly that an examination of the totality of the animal data will be required in the final hazard characterization.

Finally, nearly all of the Members of the Committee take strong exception to the definitive sentence on page 9-78 (see also the Committee’s discussion of Charge Question 1, in section 2.2.2 of this report) of the EPA document, which states:

> *“The scientific community has identified and described a series of common biological steps that are necessary for most If not all of the observed effects of dioxin and related compounds in vertebrates, including humans. Binding of dioxin-like compounds to the cellular protein Ah receptor represents the first step in the series of events attributable to exposure to dioxin-like compounds, including biochemical, cellular, and tissue-level changes in normal biological processes. Binding to the Ah receptor appears to be necessary for all well studied effects of dioxin but is not sufficient, in and of Itself, to elicit these responses.”*

This pronouncement is too strong. **Virtually all the Committee believes that it is more accurate to state that binding of TCDD and related compounds to the Ah receptor is a marker of exposure, but has not yet been established to be "necessary" for the induction of several of the observed effects.** This degree of uncertainty needs to be stated in the document.

4.3.2 Variations in Human Sensitivity (Charge Question 8)

The issue of human sensitivity may be divided into two questions. First, are human sensitivities so distributed that a representative average can be assumed? Secondly, do humans on average yield a response which might be considered to be average relative to the spectrum of responses in animals?

Wide variations in response to dioxins are well documented in animal studies, with at least a three-fold order-of-magnitude being reported for some responses between animal species and even within a given animal species such as rats and mice, or between very young hamsters and adult hamsters. Responses of humans are known to vary by several orders-of-magnitude with respect to the exposure to many exogenous substances as drugs, where some individuals are known to be responders while others are considered non-responders. It is reasonable to assume, therefore, that responses of humans to TCDD and its congeners will vary widely. Furthermore, observations reported in human exposure studies as from Seveso, Italy (Bertazzi *et al.*, 1993; Bertazzi *et al.*, 1989; Mocarelli *et al.*, 1986) and the U.S. Air Force Ranch Hand Study
(USAF, 1991; CDC, 1988a,b) as well as other studies of occupational cohorts clearly indicate that wide variations in the frequency and severity of response occur.[11]

The Committee finds that there is no single animal model that could accurately predict human responses. EPA, in its revision, should identify clearly the limitations of existing animal models in terms of their ability to predict the various health outcomes that may occur in humans as a result of exposure to dioxin and dioxin-like compounds. Are humans expected to yield an average response relative to the spectrum of responses in animals? Humans could be as sensitive as the most sensitive mouse species, or insensitive as the least sensitive mouse species to TCDD. Based on the available human data, it is debatable whether the most sensitive species, or the most

[11] One Member of the Committee objects to this statement, citing findings in this review which assert that the only adverse human health effect tied to dioxin is chloracne. Given this latter finding, he does not accept that studies "clearly indicate that wide variations in the frequency and severity of response occur."

representative animal species, should be used when selecting an animal model to predict TCDD toxicity in humans. Ideally, if a high degree of confidence in the model existed, one should use the animal species that is most representative of humans. If no single model is appropriate, animal models should be selected that permit a conservative approach to be employed with respect to extrapolation to human subjects.

What is unclear with respect to the question regarding average sensitivity is what constitutes an *average response* in humans who exhibit an *average sensitivity*, and at what level of exposure, both acute and chronic, does this occur?

When considering toxicity to humans, one must always consider the most sensitive population. Can highly sensitive sub-populations be identified that are at greatest risk to dioxin exposure? Such sub-populations might include pregnant women, infants, and children or members of a population with an above average exposure as populations whose subsistence diet consists largely of fish.

Although variations in response are reported and presented in the document, the document (in the opinion of most of the Committee) does not (and perhaps cannot, given that dioxin-specific effects beyond chloracne--see the discussion below--are not established) concisely articulate that wide variations in human sensitivity to dioxin exposure occur and should be anticipated. The emphasis is heavily placed on low level exposures that might cause toxicity in some individuals.[12]

4.4 Chloracne as an Indicator of Exposure (Charge Question 9)

The Committee believes that the EPA document reflected adequately the current knowledge base on chloracne as it relates to the subject compounds. Chloracne is a clear indicator of exposure, but the absence of chloracne in an exposed subject is not an indicator of low exposure. In fact, the Committee's consensus is that chloracne is the **only** lesion of note clearly established as being related to TCDD exposure; in the absence of sufficient data on human tissue levels at peak development of chloracne, however, a dose-response relationship is difficult to

[12] Several Members have noted that they find the EPA emphasis on low-level exposures to be appropriate and consistent with prudent public health practice.

ascertain.[13] The Committee also noted that chloracne has also been found in people exposed to related compounds such as dibenzofurans and PCBs.

4.5 Cancer

4.5.1 Epidemiological Evidence (Charge Question 10)

When a difference between compared groups is observed, “causation” may still not be imputed. Similarly, when no difference is seen, it cannot be concluded that the study variable is not associated (noting, of course, that the presence of “association” does not impute causation) with some outcome or is not “causal.” Causation is not itself an experimental or epidemiological result but a *judgment* made about the results. In making such a judgment an epidemiologist takes into account the possibility that bias and chance may play a part, but *additionally* examines the observed association in terms of certain characteristics associated with "causal" relationships. These are sometimes referred to as the Hill criteria (for A. Bradford Hill, who first codified them). They are: a) strength of the association; b) consistency; c) specificity; d) relationship with time; e) biological gradient (dose-response relationship); f) biological plausibility; g) coherence of the evidence; h) observed change following some intervention; and i) analogous findings.

The reassessment document mentions three of the Hill criteria (gradient, consistency, and strength) but does not explicitly use them as a tool to organize its discussion of causality. The Committee does not regard this as a failing, since the Hill criteria are not so much “rules,” as viewpoints to aid in interpretation. The EPA response is that causation judgments were not explicitly part of Chapter 7, although the Committee notes conclusions of Chapter 7 were used as a partial basis for Chapter 9. **We find this acceptable, since the entire discussion is couched in terms of characteristics of causal associations.**

Understanding the operation of bias and chance is especially important in interpreting so called "negative studies" (studies where no differences are apparent, or where the differences are not “statistically significant”). Differences produced by real effects can easily be masked by poor exposure classifications (misclassification bias), Chance can appear as a possible explanation merely by virtue of a small population

[13] Several Members of the Committee believe that recent research findings published after the Committee’s public meeting (e.g. Kogevinas *et al.* 1995; Huisman *et al.*, 1995) establish some cancer and developmental effects in humans as outcomes of either CDD or TCDD exposures.

available for study (poor statistical power), and potential risks can be undetectable by observing the exposed population for too short a time (bias produced by failure to account for adequate latency), to name just a few factors complicating interpretation of such outcomes. On the other hand, factors that can produce spurious increases in exposed groups in environmental epidemiological studies are much less common, most forces operating to *lower* the observed risks, not raise them. **The reassessment document does a quite good job of taking these limitations into account, but could still benefit from additional discussion of the effects of confounding factors.** Specifically, EPA should incorporate in a revised Chapter 9 the means of addressing confounding factors discussed by Agency staff at the review meeting.

To summarize the above discussion, evaluating internal validity requires the assessment of the roles played by bias, chance and real effect. Each can operate, sometimes reinforcing other factors, sometimes offsetting other factors. There is often disagreement about studies among experts, stemming from differing weights each places on the influence of bias, chance and real effect. Such differences in science are common, both in and out of the regulatory process. The Assessment is explicit about the judgments it makes, allowing others to differ if they feel that other emphases are warranted. The Committee feels this is preferable to merely cataloging variant points of view.

An evaluation of internal validity helps a scientist in deciding how much to rely on the specific result of the experiment or study. It does *not* tell a scientist how much to extend that result to contexts or situations different than the one studied, i.e., how much to *generalize* the result. A separate evaluation for *external* validity is needed. The limits and extent of generalization are given by a study's external validity. In our context the question is whether a proposition developed in one context (e.g., a high dose occupational study like that of Fingerhut *et al.,* 1990) can be generalized to cover other contexts (e.g., environmental exposures). Unfortunately, there are no rules for how far to generalize, if at all. Each study must be evaluated in a specific context to determine the extent to which it can be generalized.

Cross-species generalization is not a problem for the epidemiological studies, but the question of generalizing to environmental doses remains. Interestingly, Chapter 7A of the Assessment (Epidemiological Data, Part A: Cancer Effects) does not comment on the applicability of the epidemiologic data to environmental exposures, satisfying itself with answering the question of whether TCDD and related compounds have the capacity to cause cancer in humans under *any* conditions. It answers in the affirmative, citing several studies of "sound design and adequate size" that have found

a risk of soft tissue sarcoma (STS) (p. 7-74). Association of STS with dioxin exposure was raised by Hardell and colleagues (Hardell *et al.*, 1979; Hardell, 1981a,b; Hardell and Eriksson, 1988; Hardell, 1993) and, according to the reassessment, has "stood up to extensive criticism and a great deal of subsequent research." (pp. 7-73, 7-74). The document also notes that the entirety of the association in these studies may be"real" and not "due to selection bias, differential exposure misclassification, confounding, or chance." Although there are differing opinions about the validity of the Swedish studies, most Members of the Committee find that the Assessment clearly discusses the direction and degree of influence of the various sources of bias in these studies.

The reassessment similarly discusses non-Hodgkin's Lymphoma (NHL) and, based upon a lack of a "minimally consistent picture of increased risks" fails to conclude at this time that dioxin exposure is related to NHL. This conclusion was arrived at by a clearly stated and scientifically defensible argument that is adequately supported.

The reassessment also states that the epidemiologic data suggest that lung cancer might also be related to dioxin exposure, and cites the findings of the NIOSH study (Fingerhut *et al*., 1991) which reported statistically significant increases in respiratory system cancer (for those with over one year's exposure and a 20 year latency period. Because of possible uncontrolled confounding by smoking, as well as by exposure to many other carcinogens in the workplace, the EPA document is more tentative on this judgment, but considers that residual confounding is insufficient to explain the observed increase in respiratory system cancer risk. Here the basis for the EPA's position is weaker, reflecting the current lack of data on the possible nature of a dioxin/cancer relationship in the presence of confounding by smoking and occupational exposure to chemicals. Although the Committee does not reject the EPA's position, neither can it reject the alternative explanations which some Members of the Committee think have more merit.

The document found insufficient data to make conclusions regarding stomach cancer, generally increased risk of all types of cancer, and sex differences in cancer risk. The Committee agrees.

In summary, almost all Members of the Committee found that the reassessment's judgments on the epidemiology data (subject to the caveats noted) to be generally defensible. The document took into account many of the concerns of the broad

scientific community and discussed them explicitly, but, of course, could not discuss all significant alternative viewpoints.[14]

The Committee does have some concerns about the ways and the extent to which uncertainties in the epidemiological data base were characterized. The reassessment document (p. 7-77) refers to "uncertainties associated with the epidemiologic evidence." Some of these uncertainties are the usual ones attendant upon a subject where much research remains to be done and many questions are still unanswered. The more important uncertainties are those connected with the epidemiologic method itself. Observing some unintended or "natural" experiment in the real world, which is the essence of observational studies like epidemiology, has the enormous advantage that it involves human beings living under conditions similar to ones of concern to regulators and public health officials. For epidemiology, the uncertainties are largely associated with the questions of internal validity extensively discussed in the Assessment itself (questions of bias, chance and real effect). The reassessment document did **not** discuss remaining questions of external validity, the most important of which are the high exposure to low exposure generalization. The EPA should comment on this issue in any future revision, as well as on the relationships between agricultural and forestry, and environmental exposure levels (as well as varying exposure routes and patterns and associated environmental conditions and chemicals in these situations) and the cancers observed at those exposure levels.[15]

4.5.2 Carcinogenicity of Dioxin-like Compounds (Charge Question 11)

TCDD is one member of a large family of halogenated polycyclic aromatic compounds. The EPA reassessment document describes such congeners and some of their metabolic and carcinogenic effects. A number of other studies have demonstrated the effectiveness of other dibenzodioxins and dibenzofurans, both individually and in mixtures, as promoting agents in the rat liver model (e.g. Nishizumi and Masuda, 1986; Waern *et al.*, 1991; Shrenk *et al.*, 1994). Although the data is as yet too sparse to make any extensive generalizations, it is reasonable to hypothesize that many of these congeners of TCDD will be effective promoting agents and thus carcinogenic at some dose.

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[14] Likewise, the Committee did not discuss in its public meeting, or address in this report, all the relevant epidemiological studies noted in the reassessment document or the extant literature.

[15] One Member of the Committee notes that the reported effects of low-level exposure to forestry and agricultural workers predicts overwhelming incidence of certain tumors in the far more highly exposed production workers. Those tumors are not in excess or are barely in excess (see above) in the production workers. At least, this absence of external validation casts doubt on the generalization of the forestry and agricultural studies. At worst, they indicate that those studies are flawed.

Another large class of closely related halogenated aromatic hydrocarbons are the polyhalogenated biphenyls. Many of the members of this class are promoting agents in the rat liver system (Sargent *et al.*, 1991; Jensen and Sleight, 1986; Luebeck *et al.*, 1991; Preston *et al.*, 1985) and in other organ systems as well (Anderson *et al.*, 1994). In addition many, but not all, polyhalogenated biphenyls interact specifically with the Ah receptor (Kafafi *et al.,* 1993) at K_D (the apparent equilibrium disassociation constant for ligand binding to the Ah receptor) levels that approach that of TCDD. However, the majority of the Committee concluded that the structure, metabolism, gene regulation and toxicities of this class, while overlapping with some of the characteristics of dibenzodioxins and dibenzofurans (Safe, 1990) are sufficiently different from those of the latter to argue that polyhalogenated biphenyls not be a part of this document.[16] They may be considered for future studies on assessments using this document as a model.

Since many dibenzodioxins and dibenzofurans occur as components of mixtures, there have been several studies of the carcinogenicity of such mixtures indicating additivity of their promoting activity (Schrenk *et al.*, 1994; Huff *et al.*, 1991). In some instances synergy of components of mixtures of biphenyls have been reported (Sargent *et al.*, 1991; 1992).

Although the discovery and characterization of the Ah receptor were delineated using polycyclic hydrocarbons (halogenated or not) as ligands (Thorgeirsson and Nebert, 1977), it has been assumed that naturally occurring and/or endogenous ligands occur. Recent studies (Bjeldanes *et al.*, 1991) identified some naturally occurring indoles as effective ligands. However, the contribution of such agents to the "dioxin burden" as ligands of the Ah receptor is unknown. Clearly more studies in this area are needed.

In summary, dibenzodioxins and dibenzofurans which have been studied as congeners of TCDD, exhibit qualitatively similar toxicities, ligand reactivity with the Ah receptor, and show carcinogenic potential as promoting agents. However, the data in this field are too incomplete at this time to make generalizations in the direct application of findings with one member of the class, e.g., TCDD, to all others. Promoting activity of mixtures of this class can be additive and, in some cases, may be synergistic. The Committee (albeit with several Members taking exception) recommends that the polyhalogenated biphenyls, although having many similarities in their metabolic, toxic,

[16] Several Members disagree strongly with this finding and recommend the inclusion of polyhalogenated biphenyls in the assessment.

and carcinogenic effects to TCDD, should be considered in a separate class and not considered in depth in this document.

4.5.3 Carcinogenic Activities of Dioxin and Dioxin-Like Compounds (Charge Question 12)

The EPA reassessment document, in describing the experimental evidence, makes a clear distinction between studies that imply TCDD as a multi-site, complete carcinogen, as opposed to studies that emphasize the promoting properties of the agent. The principal animal assays that evaluated the carcinogenic potential of TCDD and some of its congeners are adequately reviewed. On occasion, however, emphasis is placed on the fact that TCDD is carcinogenic well below the maximum tolerated doses; what should also be noted is that quite often the response was statistically not significant (e.g., skin tumors in hamsters (Rao *et al.,* 1988) and liver tumors in mice (Sugar *et al*., 1979)).

In the document, the classification of TCDD as a complete carcinogen is done on an operational, not mechanistic basis. This is confusing since the classical definition of a complete carcinogen necessarily involves a consideration of the mechanism(s) whereby the agent effects its action. The term “complete carcinogen” has been reserved, until the advent of this and other recent documents on the carcinogenicity of TCDD (Huff *et al.,* 1994), for agents capable of inducing all stages of cancer development, initiation, promotion, and progression (Boyland, 1980; Pitot, 1990). TCDD, as documented in the reassessment (as well as from other sources), is incapable of initiating cells in multiple *in vitro* and *in vivo* studies, and has never been satisfactorily demonstrated to have progressor activity. It should not be classified as a complete carcinogen any more than phenobarbital, phorbol esters, uracil or galactosamine would be considered as complete carcinogens. Thus, if the term “complete carcinogen” is to be retained as a classification of the carcinogenic action of TCDD, a full definition of the term as used in the document must be given to prevent the confusion noted above. Furthermore, designation as a complete carcinogen implies in the minds of most readers direct mutational and clastogenic activity of the agent, which the evidence does not support for TCDD.

The reassessment document also describes a second set of studies in which TCDD was characterized as having promoting capabilities. TCDD is classified as an “... extraordinarily strong promoter of liver and skin tumors.” The following studies are referenced in the EPA document as support for this statement:

a) Liver studies:

1) Liver-tumor promotion by TCDD following initiating treatment with partial hepatectomy/DEN (Diethylnitrosamine)was first described in 1980 (Pitot *et al.,* 1980*)*. In female adult Charles River rats treated with a high dose of TCDD following partial hepatectomy, five out of seven eventually developed liver tumors vs. none out of four in controls. This was accompanied by an increase of enzyme-altered foci. No effects were seen in five animals treated with a low dose of TCDD. The findings are significant when a one-tailed Fisher's exact test is applied.

2) In another study with adult female rats, a single dose of DEN was used as initiator and TCDD as a promoting agent (Graham *et al,* 1988). This study also suffers from low statistical power, and tumor data, at 60 weeks, are only available for one (the highest) out of three TCDD doses studied (5/8 vs. 1/5 in controls). According to the authors, "The number of animals was not sufficient to determine whether the incidence in DEN initiated/TCDD-promoted rats was different from that seen in rats treated with DEN alone." (A significant effect was claimed when DEN/TCDD-treated animals were compared to animals that had not received DEN - clearly an inappropriate comparison).

3) A third study (referenced several times in the EPA document) was not published in the peer-reviewed literature (Clark *et al.,* 1991) and the complete data do not appear to have been published elsewhere. The report should be specific in this regard. Data on tumor incidence are only given for intact and for ovariectornized animals initiated with DEN and treated with TCDD; apparently only one TCDD dose was used. No control data (rats initiated with DEN and treated with solvent) are presented. When the available data on liver tumor incidence are analyzed by Fisher's Exact test, they do not support the assertion that ovariectomy would provide a "protective effect" against liver tumor development. However, analysis of the same data with an uncorrected chi-square test, which is more appropriate for such an application (D'Agostino *et al.*, 1988) results in highly significant support ($p<.01$) for the hypothesis of a mitigation of effect in ovariectomized rats.

4) Another study has become available in the open literature since preparation of the EPA reassessment document (Sills *et al.,* 1994). The group sizes of animals used in this particular study provide better statistical power (between 12 and 15 animals per group) than do the previous studies. Despite the larger numbers, the increased tumor incidence in initiated-TCDD treated female weanling rats (five out of 15 animals) is not sufficiently high to demonstrate a difference from the controls (1 out of 12 animals) at a conventional level of statistical significance.

It is interesting to note that, taken individually, two of the four studies on rat liver tumor promotion by TCDD cannot demonstrate a statistically significant effect, a point that should be addressed in the document. However, in all studies, there is evidence of a TCDD effect and, if the data from the four studies are pooled using appropriate statistical methodologies, the promoting effect of TCDD becomes highly significant.

Furthermore, there is a substantial data base wherein, although no direct data on tumor incidence or multiplicity are provided, convincing evidence is given that treatment of initiated animals with TCDD increases significantly, and in a dose-dependent manner, the presence of altered hepatic foci and other signs suggestive of a strong promoting potential (Sills *et al.,* 1994; Pitot *et al.,* 1987; Dragan *et al.,* 1992; Buchmann *et al.,* 1994; Flodstrom *et al.,* 1991; Waern *et al.,* 1991). A recent and extensive study on the topic (Dragan *et al.,* 1992) emphasizes the complexity of this particular endpoint. The EPA document describes several mechanistic studies and attempts are made to link the promoting activity of TCDD to such biochemical events as enzyme induction, internalization of EGFR, estrogen receptors, and similar endpoints. A recent study on inhibition of intercellular communication by TCDD might be added to this discussion (DeHaan *et al.,* 1994).

b) Skin studies

Promoting activity of TCDD was also shown in two skin studies:

1) In 1982, TCDD was described as promoting skin tumor development in hairless mice (Poland *et al.,* 1982a). The data presented in this paper fully support the assertion that TCDD is a skin tumor promoter.

2) A second experiment (Hebert *et al.,* 1990) claimed to confirm some of Poland's observations, but when read carefully actually did not quite do so. The table reporting the incidence of proliferative lesions does not

indicate statistically significant observations. If the data are analyzed, only the number of mice with papillomas in the lowest TCDD group is statistically higher than in controls. This is in contrast to the description of the data given by the authors: "With the exception of the lowest-dose TCDD group, all mice initiated with MNNG and treated with promoters had an increased number of papillomas and nodules" (p. 366). The document should be corrected. Significant skin tumor-promoting responses were seen with the congeners PCDF and HCDF, but there was a paradoxical dose-effect relationship throughout (e.g., lower doses produce higher responses), and this anomaly should also be pointed out.

One aspect of this particular study is incorrectly represented in the EPA document. On page 6-23 of the EPA document, line 4-8, it is stated:

> *Results (of the Hebert study) demonstrated that 2,3,4,7,8-CDF was 0.2 to 0.4 times as potent as TCDD and that 1,2,3,4,7,8-CDF was 0.08 to 0.16 times as potent as TCDD. These data suggest that the tumor-promoting potencies of structural analogues of TCDD, like the promotion of liver tumors, reflect relative binding properties of the Ah receptor.*

This statement is in contrast to what Hebert *et al*. (*op cit*.) said about the same data (p. 366): “The lack of a clear dose-response makes it impossible to compare the relative potencies of the three compounds as promoters or to comment on the validity of the TEF approach for promotion as an endpoint.”

The potency estimates of 0.2 to 0.4 or 0.08 to 0.16, attributed mistakenly in the EPA document to promoting activity, are derived from a comparison of the relative changes in body weight and organ/body weight ratios (*op cit*. p. 372). This error should be corrected in the revised document.

c) lung tumors

The claim that TCDD promotes lung tumors is based on one experiment in which it was found that in ovariectornized rats, treated with DEN and given TCDD, lung tumors developed (four in 39 rats), whereas none were found in 37 intact animals treated with DEN and TCDD (Clark *et al*., 1991). No data on animals treated with DEN alone are available. The study was not published in the open literature (which should be noted in the document). The effect is statistically significant however, when analyzed with the appropriate test (uncorrected Chi-square).

A second study on the promotion of lung tumors in mice by TCDD (Beebe *et al.,* 1995 reported that TCDD enhances tumor multiplicity in the lungs of mice treated with DMN. This study needs to be discussed within the larger context of the murine lung tumor model being a representative system for tumor promotion.

Although the EPA document provides a good over-all view on the studies done on liver and skin tumor promotion by TCDD, both a more critical analysis of the database and a more in-depth discussion of mechanisms underlying tumor promotion, should be added. Although some investigators believe that tumor promotion must result in neoplasms, the stage of promotion, in fact, only involves the development of preneoplastic lesions ranging from enzyme altered foci in rodent liver models to early papillomas in multistage epidermal carcinogenesis in the mouse. In model systems wherein the stage of promotion can be studied independent of the stage of progression, a number of characteristics of the stage and of the effects of promoting agents have been delineated (Yuspa and Poirier, 1988; Rahmsdorf and Herrlich, 1990; Pitot, 1993). Primary among these characteristics is the reversibility of the stage both at the level of gene expression and lesion growth. Promoting agents themselves typically exert their effects via receptor mechanisms and signal transduction. Promoting agents in various systems *in vitro* and *in vivo* inhibit programmed cell death and apoptosis (Schulte-Hermann *et al.,* 1991; Magnuson *et al.,* 1994; Wright *et al.,* 1994). **Although there are some other promoter hallmarks not yet established for TCDD, it conforms to all the characteristics of promoting agents noted above, and thus one is led to the conclusion that any carcinogenic effect of prolonged TCDD exposure is primarily, if not exclusively, the result of its action as a promoting agent.**

All of the evidence to date argues strongly that TCDD exerts its carcinogenic effect primarily through its effectiveness as a promoting agent, stimulating cell replication in a reversible manner and inhibiting apoptosis, both mechanisms presumably mediated through the Ah receptor and associated transduction mechanisms. TCDD is not a complete carcinogen and thus to avoid confusion should not be designated as such. Many structural congeners of TCDD appear to act in a similar manner to dioxin but there are as yet insufficient data to make any generalizations with respect to mechanisms of carcinogenesis or toxicity for all such structurally related chemicals.

Finally, EPA needs to consider to what extent data on female rat liver foci should be used in modeling the tumorigenic activity of TCDD, be it as a promoting agent or as an “incomplete” carcinogen. The ratio of foci to tumors is far from being 1:1. Many foci

may disappear when treatment is withdrawn; on the other hand, it is impossible that foci can grow to the size suggested by mathematical models, since one focus would occupy the entire liver, a fact pointed out in the document. Attempts to incorporate data into models and risk assessments will require a critical in-depth analysis of the biology of altered hepatocyte foci.

4.5.4 Characterization of Dioxin/Dioxin-like Compounds as Human Carcinogens (Charge Question 13)

Dioxin has been shown to produce malignancies in rats and mice of both sexes Although the epidemiological evidence linking dioxin exposure to the genesis of malignant neoplasms is limited, and does not offer compelling evidence of carcinogenicity to humans when taken by itself, this evidence is by no means inconsistent with such an effect. **Almost all Members of the Committee therefore concur with the judgment that 2,3,7,8-TCDD, under some conditions of exposure, is likely to increase human cancer incidence.[17] The conclusion with respect to dioxin-like compounds is less firm.** Since the information from animal studies is much less robust, and that from human studies often limited by uncertainties about exposure, the judgment depends wholly on the similarity between the chemical effects of dioxin and those of its congeners, the dibenzofurans and other related compounds. For the congeners and dibenzofurans, enough evidence indicating similarity of biologic action exists to adopt the presumption that they too are likely to be carcinogenic to humans under some conditions (although in nearly all instances the doses required to produce the same incidence would be higher than those for dioxin).

With respect to the polyhalogenated biphenyls which share only some of the physical characteristics and activities of dioxin, the degree of carcinogenicity has not been formally assessed in the present EPA document. However, at least one other authoritative body, the International Agency for Research on Cancer (IARC), has conducted such a formal assessment and judged both polychlorinated (IARC, 1974; 1978a; 1987a) and polybrominated (IARC, 1978b; 1986; 1987b) biphenyls to be probable human carcinogens, both on the basis of animal studies as conclusive as those for dioxin, and, in the case of PBBs, with limited evidence from human studies. The Committee did not dispute the IARC judgement that PCBs and PBBs as likely to cause human cancer under some conditions of exposure.

[17] Several Members contend that no epidemiological study has produced evidence that is widely accepted by the scientific community, including the IARC, as being convincing for the human carcinogenicity of dioxin.

The Committee agrees that assignment of the dioxins, the PCBs, or PBBs to one of a mutually exclusive and collectively exhaustive set of carcinogenicity categories considerably oversimplifies the state of the science in most instances, possibly excepting those compounds for which there is an abundance of uniformly consistent evidence. However, prudent regulators must act and cannot base their regulation on ambiguous or inconsistent detail. They must make every effort to treat dangers of similar magnitude evenhandedly, even when there are limited management options. Although the level of exposure and the potency of the agent are measured on a meaningful continuous scale and can be incorporated into decisions on the basis of unambiguous continua, the degree of uncertainty re the human carcinogenicity of a compound is not measured in this manner, but is usually considered as a categorical term. It is desirable that consistent criteria for this inevitable categorization are employed.

Under the proposed revisions to EPA's guidelines, there are essentially three alternative choices (unless "known to" is considered an alternative to "likely to"):

a) likely to cause cancer under some conditions
b) not likely to cause cancer
c) likelihood cannot be determined

In Chapter 9 of the reassessment document, the basis for a detailed multidimensional assessment is described and the various caveats are underlined, but a choice between these three alternatives (actually, between the first and the third--see below) is still required.

Under the 1986 EPA cancer guidelines, three more levels of carcinogenic evidence, with mutually exclusive descriptive terms are provided, giving regulators more alternative choices. These choices include Group A -- human carcinogen; B_1 -- probable human carcinogen on the basis of limited information from human studies as well as animal studies; Group B_2 -- probable human carcinogen on the basis of animal studies only; Group C -- possible human carcinogen; Group D -- not classifiable; and Group E -- evidence of non-carcinogenicity for humans.

In the case of dioxin, even if the additional alternatives were provided, virtually all of the Committee believes that the animal studies would be categorized as "sufficient" and the studies of humans as "limited," providing for an overall categorization of B_1, which would be expressed verbally as "Probably Carcinogenic to humans with limited

supporting information from human studies." PBBs and PCBs would receive ratings of B_1 and B_2, respectively.

There is some merit in the provision of a slightly more detailed set of alternatives, but the provision of Group E, as well as of the proposed revised scheme category of "not likely to cause cancer" may be ill-advised. Since all mechanisms of carcinogenesis are not completely understood, and all sets of study conditions (species, dosage, co-carcinogens, etc.) cannot be foreseen, it seems unwise to suggest that evidences of non-carcinogenicity could ever be universally generalizable, at least as worded (with no reservations). Were one to employ a restrictive phrase such as "under study conditions judged to replicate most recognized conditions of human exposure," the class would be more defensible, although one still would need to draw a difficult line based on the conditions of the negative studies.

4.6 Developmental Toxicity and Animal NOAELs (Charge Question 14)

The specific issue of animal No Observed Adverse Effect Levels (NOAEL), as it is framed in the Charge, is inconsistent with the question posed concerning the use of the Reference Dose (RfD) in evaluating incremental exposures (see health question 18), and on pages 9-69 ff of the reassessment document. The latter question derives from the argument that RfDs (which are based on NOAELs), are inappropriate for the current assessment because background levels may be significant. If that argument is sound, why should it not apply to animal models?

Furthermore, even if the effect level procedure could be defended for animals, is it the optimal metric? The basis for Charge question 18 is the reasoning that the proper evaluation of risk in this context is the increment per arbitrary unit of exposure, expressed as some measure of body burden. This is one instance in which dose-response modeling, as by Benchmark doses, may confer a substantial advantage. What is gained by using NOAELs and RfDs? In a somewhat analogous situation--the relationship between lead exposure (defined as blood lead level) and IQ--the risk is better expressed as 0.25 IQ points for each 1μg/dL than as an RfD. This would be a more appropriate model for TCDD because, as with lead, the location of a threshold for developmental outcomes is rather uncertain.

If, for consistency with traditional EPA practices, a NOAEL were to be extracted from the animal data, 1 ng/kg day^{-1} appears to lie in an ambiguous zone. Murray *et al.* (1979), in a multi-generation study, found that 10 ng per kg^{-1} per day^{-1} of TCDD lowered the body weights and food consumption of f1 and f2 rats and also affected postnatal survival. At 1 ng per kg^{-1} per day^{-1} both increases and decreases were noted among the

survival indices of f1 litters. A NOAEL of 1 ng per kg^{-1} per day^{-1} would be a reasonable figure if based on these data.

On the basis of other endpoints, however, it may not be as reasonable. Monkeys whose mothers were undergoing exposure to TCDD in food (Schantz *et al.*, 1989) were impaired, relative to controls, in a behavioral task called reversal learning. They also displayed differences from controls in social behaviors (Schantz and Bowman, 1992). The mothers had been fed a diet containing 5 ppt of TCDD. The offspring tested for learning, from two cohorts, were born a mean of 16 months or 36 months, respectively, from the initiation of exposure. Social behavior was assayed in the first cohort. On the basis of total TCDD consumed by the time of birth, the mothers had been exposed to about 0.125 ng/kg daily.

Copulatory behavior in male rats and measures of morphological and endocrine development showed adverse effects of prenatal exposure to TCDD at a dose of 64 ng/kg to the mother on gestation day (GD) 15 (Mably *et al.*, 1992). If a half-life in rats of 24 days was assumed for 1 ng/kg day^{-1}, steady state would be reached in about 120 days, and total body burden would be about 34 ng/kg. For this reason, because 64 ng/kg is actually a frank effects level (FEL), 1 ng/kg/day would be a dubious NOAEL. The problem lies in distinguishing between the acute effects of a dose delivered on GD 15 and an equivalent body burden stored largely in fat tissue. TCDD stored in this way might be viewed as functionally dormant, although the Schantz and Bowman data cited above argue against such an interpretation. Comparisons between acute and steady-state exposures for endpoints such as those above have not been carried out despite the significance of this issue. Such studies should be relatively straightforward, though tedious, to conduct.

In humans, TCDD and other lipophilic agents could enter the blood if fat stores were to be drawn upon during periods of caloric deficit. Weight-loss diet books consume enormous shelf space in bookstores and weight-loss regimens are not a guarantee against pregnancy. Although the increment in blood level of lipophilic toxicants during such a regimen may be small, it may not be insignificant, and fetal tissue might accumulate these increments. Release of such agents during gestation, in the small proportion of cases in which the mother fails to consume adequate nutrition, might lead to their accumulation in fetal tissue. Moreover, the fetus will deplete the mother of nutrients even at the cost of her own nutritional status. Lactation is another situation in which lipophilic agents are released and consumed, as discussed in the

document.[18] The lead parallel should again be considered. During pregnancy, lead is released from bone as a consequence of to hormonal changes. The same mechanism would not pertain to TCDD, but the details of gestational pharmacokinetics is a question that deserves to be further pursued.

Endpoints other than those discussed above (sexual function in rats and learning in monkeys) should also be considered. The role that developmental toxicity has assumed in risk assessment stems from an extensive body of literature indicating the exquisite vulnerability of the fetus. The developing brain is especially sensitive. But the rodent brain may not reflect all aspects of this sensitivity. Recall that rats are born, from the standpoint of brain development, at the end of the second human trimester. Processes that occur in humans during the third trimester, such as synaptogenesis and the maturation of neurotransmitter systems, occur postnatally in rats. For this reason, confining developmental treatments in rats to the prenatal period may underestimate the full impact in humans of gestational exposure. The behavioral pharmacology literature offers many examples of the sensitivity of the neonatal period in rodents and Bjerke *et al*. (1994) and Bjerke and Peterson (1994) reported that lactational as well as prenatal exposure proved necessary to induce feminization of male rat copulatory behavior.

Further, although sexual development has become a focus of TCDD toxicity research, it is crucial to recognize that the complex unfolding of brain developmental processes in the presence of certain levels of TCDD could also exert an impact on other indices of brain function and structure. The substantial levels of the Ah receptor in developing brain and its virtual disappearance later in life argue that sexual development is unlikely to be its only role. The report by Schantz and Bowman (1989) hints at additional outcomes. Note, further, that copulatory behavior and genital structure reflect only limited facets of sexual maturation. Copulatory behavior and reproductive morphology may not be the best endpoints to examine for prenatally-exposed females. Other sexually dimorphic behaviors, based on cognitive function, for example, might also reveal consequences of TCDD exposure if examined. And, for males, sexual motivation is an arena independent of copulation itself.

The preceding comments presume that the total exposure is to TCDD. They make no assumptions about the validity of TEQs, which is a separate, but related issue.

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[18] A study just published, and not available to the Committee at the time of the review, reports that higher levels of PCBs, PCDDs, and PCDFs in breast milk were related to reduced neurological optimality, and higher levels of planar PCBs were associated with a higher incidence of hypotonia (Huisman et al., 1995).

Chapter 5 of the reassessment document neither cited nor discussed the findings of several researchers on the effects of PCBs (e.g., Jacobson and Jacobson, 1994 and Gladen, *et al.*, 1988). Jacobson and Jacobson (1994) reported that higher gestational exposure to PCBs, as reflected by cord serum levels and maternal consumption of Lake Michigan fish, was correlated with lower scores on tests of psychological development. A large cohort in North Carolina was reported by Gladen *et al.* to show also evidence of poorer performance associated with higher prenatal exposure to PCBs. Jacobson and Jacobson suggested that the PCBs themselves, particularly the coplanar PCB congeners, could be more responsible for such effects than the much lower concentrations of dioxins or dibenzofurans in these mixtures, but the relative potency issue would have to be clarified. PCDFs in the Yusho and YuCheng exposures are currently held to be primarily responsible for the observed toxicities. The North Carolina and Lake Michigan studies, however, are significant because they indicate adverse neurobehavioral development associated with current environmental levels of this class of compounds.[19]

Another reason for reevaluating the current NOAEL are data strongly suggesting that TCDD is a more potent teratogen in mice than previously supposed, and that this effect occurs at doses considerably lower than those causing liver enzyme induction. (Bjerke *et al.*, 1994) These data are coupled with findings from various laboratories showing changes in hormone levels controlling reproductive and developmental processes and reproductive success in offspring of treated animals.

In summary, the current NOAEL of 1 ng/kg day^{-1} rests on a debatable foundation, and it would be appropriate to reevaluate it.[20] One reason for a fuller examination of these issues is that such a NOAEL is likely to be used in evaluating the risks of human exposures, given that crude clinical evidence for developmental and reproductive effects attributable to TCDD is necessarily quite limited. The neurobehavioral studies on PCBs offer directions for additional research, but forcing such studies into an effects level mold, as noted earlier, is a premature use of the data.

4.7 Human/Animal Databases: Potential for Immunotoxicity (Charge Question 15)

[19] These findings were not discussed at the Committee's public meeting, but came to light during the preparation of this report.

[20] Several Members of the Committee suggest that the immediate inference of this statement is that the NOAEL should be lowered.

There was a consensus among most Committee Members that, overall, Chapter 4 of the reassessment document provided an accurate, current summary of the immunotoxicology associated with TCDD and related compounds in humans and experimental animals. However, the Committee has some concerns (and noted some omissions) pertaining to immunology and the interpretation of certain experimental results, in Chapter 4, and particularly, Chapter 9. Although the overall data suggest that dioxin and related compounds can produce immune effects, there are insufficient supporting data to establish fully whether these effects can occur at or near two orders-of-magnitude above background levels.

The document hedges on whether there was sufficient evidence to state that this class of compounds can cause immune effects in humans. In some instances there was a "YES" and in other sections a statement of "UNSURE." **Based upon the extensive experimental animal, and the very limited human, database the majority of the Committee agreed that sufficient data exist to indicate immune effects could occur in the human population from exposure to dioxin or dioxin-like agents at some dose levels.** However, the large variability in the immune response in humans, the limited numbers of tests conducted, and the poor exposure characterization of the populations that have been studied prevent definitive conclusions as to sensitivity. This is not to say that humans are more or less sensitive than other species, only there are not sufficient clinical data to assess human sensitivity.

The most notable documented immune effects in humans occurred in the Taiwan population exposed to contaminated rice oil where both immunosuppression and increased infections were observed, presumably resulting from exposure to furans and PCBs (Wu *et al.*, 1984; Chang *et al.*, 1982a; Chang *et al.*, 1982b: Chang *et al.*, 1981). Some studies have reported changes in immunoglobin (Ig) levels (Jennings *et al.*, 1988) and NK cell activity (Jennings *et al.*,1988; Svensson *et al.*, 1991). Other studies have reported no effects (such as the Ranch Hand (USAF, 1991) and Seveso studies (Mocarelli *et al.,* 1986; Mocarelli *et al.,* 1991)). but, as with the positive studies, the actual exposure levels and study design, were not adequately addressed in the document nor were they critically reviewed.

Although not well-established, several studies of humans (Chang, *et al.*, 1981; Bekesi *et al.*,1985) exposed to halogenated aromatic hydrocarbons (HAH), as well as of monkeys (Hong *et a*l., 1989; Tryphonas *et al.*, 1989), reported that a slight reduction in $CD4^+$ cells occurred. Although this may or may not translate to a significant health effect, these cells are involved in regulating immune responses and reduced CD4/CD8 ratios are a hallmark of immunosuppression. It may be argued that any reduction in

CD4 cells could lead to such potential health effects as increases in infectious disease, given that a large population is affected. Of interest to this discussion is a recent study by Oughton *et al.* (1995) which found no decrease in total CD4+ cells in TCDD-treated mice following low-level chronic exposures. However, within the CD4+ subset, a modest decrease was observed in the proportion of CD4+ memory cells as defined by concomitant expression of Pgp-1 CD45RB. The clinical significance of this change on immunocompetence is presently unclear. Similar changes in immune system functioning have, however, been suggested by some investigators to be significant to HIV pathogenesis (Janossy *et al*., 1993; Lim *et al.*, 1993; Cameron *et al*., 1994; Jaleco *et al*., 1994), indicating that the decrease in these cells may be associated with a decrease in immunocompetence.

Although the immune system is a sensitive target to HAHs in experimental animal species, as presented, the EPA document does not provide convincing evidence to indicate that background or near background exposure levels to dioxin-like compounds in industrial countries are sufficient to affect the immune system. Given the current methods available for testing, it would be unlikely that this could even be determined in humans, and one would have to rely on experimental animal data or highly exposed populations to determine effects at the low-end of the dose-response curve, or in vitro approaches using primary isolated human lymphocytes and human lymphoid cell lines. Changes reported at very low levels of exposure in two or three of the experimental animal studies are certainly of concern, but need to be confirmed and reproduced and, until then, cannot yet be used to support a “background” level effect. However, the No Observed Eeffects Level (NOEL) and ED_{50} (dose effective for 50% of the recipients) for suppression of the T-dependent antibody response, in sensitive mouse strains, has been reproduced in many labs using different experimental designs and can be used to help support or refute that “background” or one to two orders above background is significant. In this respect, the recent paper by McGrath *et al*.(1994) is relevant to this issue.

Human studies undertaken to study the immune system of exposed populations have **not** used the appropriate test battery for this class of chemicals. The ”gold-standard” test (i.e., suppression of the primary antibody response following immunization) was not employed in any of the human test panels, although this is a hallmark in experimental animals. The exception to this is the as yet, unpublished study on the Inuit population (Dewailly, in press).

Chapter Four discussions pertaining to *in vitro* effects, although complete, concluded these tests have limited relevance as culture conditions may play a significant role (i.e., serum effects). The Committee felt that this was not a legitimate

argument as numerous investigators have successfully reproduced *in vivo* observations using well-defined *in vitro* culture conditions. The *in vitro* studies have provided considerable understanding of the cellular and molecular mechanisms of TCDD and should not be understated.

Although data exist suggesting that non-Ah receptor mechanisms may play some role in immunotoxicity, definitive evidence for this is lacking and will require using novel approaches such as receptor knockout mice or pure binding antagonists. The Committee agreed that the majority of evidence indicates that imununotoxicity (particularly suppression of the antibody response) by dioxins is presumably Ah-receptor dependent. The disappearance of quantitative differences in immunosuppression between Ah-low and Ah-high responsive mice after sub-chronic exposure suggests that chronicity can override acute exposure resistance and may suggest an even "greater" hazard. Based upon existing evidence, the involvement of an endocrine-related non-Ah receptor mechanism impacting on immunocompetence may be overstated in the document.

Numerous studies suggest that the immune system is a sensitive target for dioxin-like compounds in experimental animals. There are species/strain differences in the sensitivity, but the effects tend to be similar with the most sensitive indicator (at least in adult animals) being changes in the primary antibody responses; similar effects occur in many test species (guinea pig, rabbit, monkey, etc.). As such, it would be more appropriate to indicate that differences in animal sensitivity exists rather than "variability in response" as this suggests a different meaning. One might expect that similar variability would also exist in the human population, but this has not been examined when the limited clinical studies have been undertaken.

Multiple cellular targets exist for immunotoxicity by dioxin-like compounds including both T and B lymphocytes as well as lymphoid-associated tissue (e.g., thymus epithelium) and marrow stromal elements. Debate exists as to the "most sensitive" or "most proximate" target and not which cell is the target. The reassessment document should be more clear on this point. (Table 9-2 is incorrect as the immune system of rabbits and fish are also affected).

Studies conducted in a number of experimental species, including mice and monkeys, indicate that the antibody response to a T-dependent antigen is the most sensitive and reproducible indicator for immunotoxicity in adult animals. The ED_{50} in sensitive strains of mice is approx. 0.7 μg/kg. Several other responses have been shown to be more sensitive but have not been confirmed or reproduced by other research groups. **Chapter 9 gives undue weight to these unconfirmed or limited**

studies (see Table 9-5), and fails to discuss the highly reproducible and widely used primary antibody suppression studies.

Results for the host resistance tests are, for the most part, consistent with the immune affects. One obvious exception to this are the influenza challenge studies conducted in mice (G. Burelson, in press), where disease occurs at much lower dose levels than do immune changes. As this directly relates to human health, the mechanism and relevance of these observations, which of course were not available when the reassessment was developed, need to be addressed in the future revision. The recent observations reported by the same author in rats (G. Burleson, in press) should also be discussed.[21] This new study helps increase the validity of the preceding observation, although additional studies are warranted to help elucidate the mechanism. It would argue that a very specific component (perhaps immune/perhaps not) is altered, and at extremely low concentrations.

Chapter 9 should also include a table of confirmed laboratory results (i.e., the PFC primary response) which provide ED_{50}, ED_1, and/or NOELs. A separate table for suggestive results (not yet extended at low doses) can then be included and identified as such. The text of these tables should include a critical review of the data, the most reproducible and sensitive indicators, and a clear and logical presentation of how these data were used to determine that exposures at 1 or 2 orders-of-magnitude above background levels have potential human health effects.

4.8 Other Effects (Charge Question 16)

The Committee had no specific concerns with the manner in which the topic of "other effects" is covered in the reassessment document. There has been considerable expansion of the knowledge base since the document was issued, however, and these gains should be addressed in any revision.

Specifically, major growth has taken place in our understanding of the biological and biochemical effects of TCDD and related members of this class, and in the whole area of receptor biology and signaling biology, and these gains should be factored into the revision.

4.9 Dose-Response

[21] The two in-press studies noted here were not available to most Members of the Committee during the review process; several Members therefore cannot endorse these specific findings at this time.

4.9.1 Approaches to Dose-response Determination for Cancer (Charge Question 17)

There was public expectation that the reevaluation of the carcinogenic potency of dioxin would be comprehensive and would incorporate extensive new data generated for that purpose. The Committee was disappointed to see that, in addition to data from the Kociba *et al.* (1978) bioassay (which formed the basis for EPA's earlier estimate of cancer potency for TCDD), the only additional data used in EPA's quantitative analysis was from the Maronpot *et al.* (1993) gavage study.

The only use that EPA made of pharmacokinetic modeling in its quantitative analysis was in making correlations between estimates of two-stage model parameters and outputs of pharmacokinetic models (Appendix D of the reassessment document). This is a very limited use of the physiological and pharmacokinetic information (although the Committee is aware of the problems involved in using the extant PBPK models--see the discussion in sections 4.1.1 and 4.1.2); moreover, the description provided in Appendix D is not sufficient to enable the reader to understand what was done. This lack of clear exposition needs to be corrected in the revised document.

Not only is EPA's risk assessment of dioxin extremely important in its own right, it represents EPA's first application of so-called “biologically based” models. Consequently, it may set a precedent for future analyses. It is thus important that the analysis be clearly presented so that its scientific justification and usefulness can be assessed. **EPA should describe its analysis in sufficient detail that it can be fully understood by the reader, to the point of reproducing the analysis if desirable.** The reasoning and analysis that led EPA to propose its preferred model must be clearly explained. The sensitivity of the results to alternative models or assumptions must also be presented. Unfortunately, EPA's description of its analysis is lacking in clarity, in details, and in supporting documentation.

The description of the analysis relied upon by EPA consists of a single paragraph at the bottom of page 8-45. The resulting model is described in broad terms as the “most parsimonious two-stage model” that agrees with the tumor incidence data and focal lesion data. **EPA must describe its analysis in sufficient detail to allow the reader to understand how EPA arrived at its preferred model and how robust those results are -- i.e., to what extent would other assumptions be reasonable, adequately fit the data, and lead to different levels of risk.** For example, EPA's preferred analysis uses data from a feeding study and a gavage study and thus had to make assumptions in order to combine data from two different types of studies. EPA does not describe how this issue was handled, nor detail the necessary assumptions.

Also, EPA does not describe clearly what data were used in its preferred analysis. It states only that the tumor incidence data from the Kociba *et al.* (1978) study and the focal lesion data from Maronpot *et al.* (1993) were used. The precise form of the tumor data (whether individual animal time-to-tumor data or summary data) is not stated. Similarly, the reader is not informed as to whether the data from Maronpot. *et al.* involving initiation with DEN or the data not involving such initiation were used in EPA's preferred analysis.

The focal lesion data used in developing EPA's cancer risk model are not from the published Maronpot *et al.* (1993) paper but are unpublished results from that study. That fact should be clearly indicated. More importantly, the actual data used by EPA should be made accessible to the reader, by including them in an appendix, if necessary.

If time-to-tumor data were used, an assumption was required as to the context in which the hepatocellular tumors from the Kociba *et al.* (1978; 1979) studies were observed (whether incidental, fatal or some combination). This assumption is not stated, and it may have an important effect upon EPA's conclusions regarding the fits to the data of various models.

Appendix C contains additional details of some analyses, but not the ones used to derive EPA's preferred cancer model. A considerable portion of Appendix C is devoted to discussing the non-identifiability of some parameters in certain applications of the two-stage model. In some of these instances, EPA is attempting to estimate up to 16 parameters from what are essentially four data points. It is not surprising that some of the parameters are not identifiable. The last paragraph in Appendix C is particularly disturbing. It starts with the assertion that the calculations have "hidden assumptions" that can have a bearing on the interpretation of the results. It then goes on to list some of these "hidden assumptions" and ends with the statement that the analysis is very sensitive to the choice of values for the radius of a cell and to the (assumed) minimum size of a detectable focus. This paragraph (and particularly the last statement re sensitivities of the analysis) raises serious questions as to the reliability of EPA's cancer risk assessment. No information is provided on the cell radius or minimum detectable focus size assumed in EPA's analysis. In fact, this is the only mention that either of these two quantities are required at all in the analysis. **EPA must provide enough detail in its analysis to permit the reader to determine how these values were used in the analysis, how EPA selected those values, what values were selected, and the sensitivity of EPA's risk assessment to those selections.**

EPA must clearly distinguish between what is being assumed (i.e., what is going into the modeling) and what is being concluded as a result of the modeling. **Although EPA's preferred dose response model is linear, it seems clear that a threshold model would provide an equivalent or nearly equivalent description of the data. This is the most important issue in the dose response-modeling and should be thoroughly explored in EPA's analysis.**

Even if EPA's risk assessment based on the animal data is correct, without additional assumptions regarding the relative sensitivities to dioxin of various types of tumors in humans and animals, the risk assessment based upon animal data only provides estimates of the risk of liver tumors in a single strain of female rats. Therefore, despite limitations in the human data for dioxin, it would have been appropriate for EPA to have conducted a more comprehensive analysis of the human data. EPA's risk assessment based on human data is derived from the published data from three studies. Reliance on these published data necessitated a number of assumptions and approximations by EPA that could have been avoided by use of the raw data from other studies. The Committee also recommends that the data from the Ranch Hand cohort, when published, be considered for inclusion in this analysis.

The cancer risk assessment models applied to the human data by EPA are conceptually flawed.[22] Both the additive and multiplicative models express the cancer mortality rate at a given age as a function of a summary measure of exposure. Clearly, this summary measure should involve only prior exposures and not future exposures. However, the summary exposure measure used by EPA is average lifetime exposure, which involves both past and future exposures. A practical consequence of this model misspecification is that in the case of the additive model, the increased mortality rate under constant exposure is independent of age (e.g., a person has the same probability of dying of a dioxin-induced cancer between the ages of one and two as between the ages of 70 and 71), which is clearly inappropriate. EPA appeared to recognize this and made a compensating *ad hoc* adjustment to the risk estimate obtained from the additive risk model. The Committee recommends that both the additive and multiplicative models be reformulated to incorporate more biologically plausible summary exposure measures (e.g., cumulative past exposure).

In EPA's cancer risk calculations based upon epidemiological data, exposures in dioxin-exposed subcohorts were summarized by the median exposure. The stated reason for choosing the median (over, say, the mean) was that body levels were “quite

[22] Several Members of the Committee contend that the cancer risk model is not particularly “flawed,” but represents an acceptable approach.

variable and not symmetrically distributed." Neither of these assertions appear to be supported by the draft document. At any rate, these are not appropriate reasons for selecting the median over the mean as a summary measure of exposure, and there appears to be no clear reason stated for preferring the median over the mean. This choice would not be required if the raw data were used in the analysis, which illustrates an advantage of basing an analysis upon the raw data.

Given the problems and limitations identified with the analysis, it is not clear that this work added significantly to our understanding of the dose-response for TCDD. Rather than giving a high priority to refining these techniques at the present time, the Committee recommends that EPA review this effort, and communicate clearly the strengths and limitations of the work. The Agency should evaluate critically the potential for future work in this area to elucidate the dose-response for TCDD in humans.

4.9.2 Use of the RfD in Evaluating Incremental Exposures (Charge Question 18)

The question of possibly rejecting of the Reference Dose (threshold) approach for evaluating incremental exposure because of the existing background levels relates also to health Charge questions 14 and 17 (as noted earlier). All three issues are part of a more fundamental problem which has not been addressed and needs to be included to provide balance to the reassessment document. **This fundamental issue concerns the basis for the selection of the dose response relationship to be used in assessing the (non-cancer) adverse effects of dioxin.** The selection of the dose response function clearly distinguishes the EPA approach from that of some (but not all) other agencies and bodies which have carried out similar risk assessments on dioxin. Although all of these groups used the same toxicologic and epidemiologic data bases as EPA, all except EPA have elected to use some type of threshold and safety factor methodology for their health risk evaluation. **Chapter 8 of the reassessment document needs to describe and evaluate this alternative dose response relationship, discuss the approaches and findings of the other relevant agencies, and justify the basis for selecting another approach.**

Although the Agency concludes (page 8-13 of the reassessment document) that the use of the linear multistage model (LMS) needs to be re-evaluated, the re-evaluation consists of enhancing the LMS approach with a $P_B P_K$ analysis and a 2-stage analysis rather than a discussion of alterative approaches. A discussion of such alternative approaches, and their results, should also be reflected in the appropriate

places in the summary chapter 9. As noted earlier in this report (see sections 4.5.2 and 4.5.3), dioxin is not an initiator and thus is not a complete carcinogen. Dioxin is a non-genotoxic promotor which acts at least in part via the Ah receptor and exhibits numerous U-shaped dose responses (Kociba, *et al.*, 1978; Pitot *et al.*, 1987; Fang *et al.*, in press; Maronpot *et al.*, 1993; Teegaurden *et al.*, 1995). Thus, the document cannot ignore a possible threshold dose-response relationship and claim to be comprehensive in its presentation.

As noted in the Committee's response to health question 14 (section 4.6.1), the available information on TCDDs suggest that use of the benchmark approach, rather than the reference dose, is probably more appropriate. This approach has been recommended in several previous SAB reports (SAB, 1990; SAB, 1995). The EPA, along with the International Life Sciences Institute (ILSI), has sponsored workshops on this topic, and various EPA staff are among the most progressive and knowledgeable experts in the use of this methodology.

The Committee (with the exception of one Member) agrees that, in concept, the reference dose is not designed to evaluate the risk from incremental exposures (however, if background exposures are not accounted for in the population from which data are obtained for calculating a reference dose, the resulting reference dose may represent doses in excess of that background). Although EPA's current methodology for cancer risk assessment allows one to assess risks from incremental exposures, the RfD methodology is not well-suited for this particular use. **The Committee recommends that EPA work towards developing and implementing a methodology that would allow the assessment of non-cancer risk resulting from incremental exposures.**

4.9.3 Continuum of Response Postulate (Charge Question 19)

EPA postulates a continuum of response from events seen at low doses that are not toxic but cause the subsequent development of toxic effects. This idea is expressed several times in the document, but it is not supported by a full discussion. As it stands now, the basis for this statement regarding a continuum of responses is unclear. The statement is far too general and could be taken as implying that all (or any) early changes will necessarily lead to ultimate toxicity. The statement is only defensible in reference to a limited number of specific case examples, but cannot be taken as universally proven. Until a full mechanism of action has been mapped out, the reassessment's position remains unproved in general. The statement should not be presented as a "postulate" (which is widely accepted as a universal truth not requiring proof) but as a "current hypothesis" (subject to change as new data are discovered).

The specific case developed by EPA to support this hypothesis was the binding of ligand to the Ah receptor, which is then assumed to lead to all, or most, of the toxic responses. The possibility that the Ah receptor system may be a sensing pathway to protect the cell, not an integral part of the machinery associated with the toxic response of a cell to TCDD, is not considered.[23] Only in the mechanism of action chapter is there any suggestion that this association may not be universally accepted. However, Ah receptor binding may not be the ultimate mechanistic step in all responses. It is not proven for all possible toxic endpoints; the association is strongest for enzyme induction in mice, but may not hold in other species. Different strains of rat show remarkably diverse sensitivities to dioxin while possessing active Ah receptors. Although enzyme induction in mice is the classic Ah receptor mediated response, there may be other responses that do not involve Ah receptor. For example, although some immuno-responses are Ah associated in mice, others are apparently not.[24] Ah receptor binding may not be a rate-limiting response. The recent development of "knock out" mice lacking functional Ah receptors may help clarify these points. EPA needs to leave itself some flexibility so that the assessment can remain valid in light of future discoveries.

The EPA response at the public review meeting suggested that Ah receptor binding could be considered as "necessary but not sufficient." Other events may well also be needed for toxicity to occur. Because of this, TEFs should be based solely on Ah receptor data only when other data are unavailable. There are a variety of individual effects yielding a likelihood of response, a cascade of events.

The Committee is not taking the position that EPA is wrong in its view that Ah receptor binding is a critical early event leading to eventual toxicity, but rather that the Agency stated the idea too strongly and without sufficient consideration of toxic immune system effects that have not been shown to be Ah receptor associated. Alternative mechanisms that have been suggested in the published literature were not considered in the document. The evidence for Ah receptor-linked effects (and their role in toxicity), and (for balance) the evidence suggesting a lack of involvement of Ah receptor binding in some effects, should be discussed in the document to support acceptance of this continuum as a current hypothesis. Furthermore, the continuum theory needs further explanation, some discussion of the merits and limitations, and an indication of the acceptance of this idea

[23] One Member of the Committee asserts that "The Ah receptor system is probably part of the normal cellular second messenger regulating systems and its inappropriate activation by dioxin (and dioxin-like compounds) can lead to assorted toxic outcomes through a variety of pathways. Any suggestion that this inappropriate activation has positive outcomes is strictly speculative at this time."

[24] One of the Committee's immunologist participants believes that "The evidence for receptor independence from this data is insufficient to contradict the majority of evidence for receptor dependence."

in the scientific community. EPA needs to be more flexible in its statements, to allow adaptability to scientific evidence that may be developed in the future.

4.10 Use of Toxicity Equivalence Factors (TEFs) (Charge Question 20)

In general, the Committee agrees that the use of a TEF is a valid approach provided that the contribution to the TEQ from: a) TCDD; b) other dioxins and furans; and c) coplanar PCBs are explicitly stated. **However, when assessing the toxicity of complex mixtures that are not well-defined, the Committee believes that presenting the results using alternative methods may be warranted whenever possible.** It must be noted however, that other than the suggestion (see Section 4.13 below) to apply TEQs separately for 2,3,7,8-TCDD, other dioxins and furans, and co-planar PCBs, as well as for environmental mixtures as a whole, the Committee has no specific proposals for such alternative methods.

Although the assessment acknowledges some of the uncertainties associated with the use of TEFs/TEQs, these issues have not been satisfactorily addressed. **Since the TEQ approach has been used throughout the assessment document, and many of its conclusions (e.g.,, the position that levels 10-100 times over background pose a possible human health hazard) hinge on the validity of the TEF values and assumptions used, the Committee advises EPA to include a peer-reviewed appendix that will comprehensively review EPA's use of the TEF/TEQ approach in the exposure and health assessment documents**. This appendix should clearly outline the assumptions and TEF values used throughout the documents as well as address the following issues:

The reassessment document acknowledges that dioxin-like compounds other than TCDD represent greater than 90% of the calculated TEQ value in some instances. Consequently, the applicability of using TEFs for mixtures containing PCBs with partial agonist and antagonist activities should be addressed. The EPA assumes that there is additivity among TEQs calculated from the TEF values for 7 of the 75 dioxins, 10 of the 135 dibenzofurans, and 13 of the 209 PCBs. However, these dioxin-like congeners constitute a small percentage of the total congeners present in an environmentally relevant mixture. Therefore, the EPA should address the issue of possible interactions, since there is evidence that non-dioxin-like PCBs antagonize several biochemical (e.g. enzyme induction) and toxic responses (e.g., teratogenic and immunotoxic effects) elicited by more potent congeners. Possible synergies should also be considered.

New data, which became available since the release of the document have resulted in adjustments to several of the TEF values. The Committee suggests that a comprehensive review of all TEF values be summarized within the appendix for each congener that has previously been assigned a value. In addition, EPA should clearly state the species and responses (e.g., ligand binding, enzyme induction, immunotoxicity) used to derive the TEF value. Finally, since TEF values can vary dramatically based upon the species and response examined, EPA should justify the TEF value that has been selected for evaluating human risk.

EPA should document clearly the studies that demonstrate additivity among dioxins, dibenzofurans and PCBs and that the TEF/TEQ approach accurately predicts both short-term (e.g., immunotoxic effects, enzyme induction) and long-term (e.g., carcinogenic, teratogenic, reproductive effects) responses elicited by these complex mixtures. In the event there are insufficient data demonstrating the applicability of the approach for specific toxic endpoints, EPA should justify its position for the use of the TEF/TEQ approach.

Although the reassessment recognized that humans are not overly sensitive or resistant to the effects of dioxin-like compounds relative to other species, there is a lack of discussion regarding the differences between human and rodent receptors. Such information should be included in the appendix. EPA should also outline how this information is taken into account when assigning TEF values to congeners. Also, recent studies indicate that there are differences in congener uptake, metabolism, elimination, and storage. This should be acknowledged followed by a discussion of how this information is taken into account when assigning TEF values to congeners.

The reassessment document lacks discussion regarding naturally occurring dioxin-like compounds such as benzo[a]pyrene and indole[3,2-b]carbazole. The EPA should comment on the exclusion of these compounds. These agents are not persistent or bioaccumulative, but the precursor of indole[3,2-b]carbazole is present at high levels in the diet, and this constant level of exposure should be reported. Furthermore, there is (very preliminary) evidence that some of these compounds (e.g., indole[3,2-b]carbazole) may have an anticarcinogenic effect (Bjeldanes *et al.*, 1991; Bradlow *et al.*, 1991; Liu *et al.*, 1994; and Wattenberg *et al.*, 1978).

As mentioned in the health assessment document (p 9-70), “A more detailed description of these issues is contained in U.S. EPA (1989).” This referenced document (TITLE, EPA/625/3-89/016), once updated and modified to address the issues listed above, and peer reviewed, could be used as a basis for the appendix and therefore, could reasonably accommodate the Committee's above suggestions. In

addition, a balanced comprehensive review should clearly state the assumptions and limitations of the TEF/TEQ approach as well as highlight the areas that warrant further investigation. Examination of the Summary of the Public Comments related to the Exposure and Health documents (EPA/600/6-88/005Ca, Cb, Cc and EPA/600/BP-92/001a, 001b, 001c) indicates that EPA is already aware of the concern surrounding this issue (i.e. the statement that "This issue was the single most addressed issue among all of the comments on the risk characterization" on page 25 of the Health Comments Summary). Therefore, the addition of a peer reviewed appendix dealing with the TEF/TEQ approach should satisfy several of the concerns raised, or at least indicate which items are still points of contention.

4.11 Laboratory Animals/ Human Response

4.11.1 Animal Data and Weight-of-Evidence Conclusions for Human Risk (Charge Question 21)

The present state of our knowledge of TCDD as a toxic agent is largely derived from studies with animals. Thus, there is, by definition, a heavy reliance on the results of numerous animal studies designed to define the plethora of effects of TCDD. **By default one is compelled to use these animal data.** However, these data must be used in perspective. Studies using animals as surrogates for humans show almost a 10,000-fold range in their response to dioxin exposure for a number of different adverse effects, depending on the animal species and endpoints selected. The reasons for these large differences in response by different species of animals are not known (even though they are all presumed to have the Ah receptor), but this breadth of sensitivity may serve as an indicator of the range of response that might be seen in the human population.

The use of animal data to establish a potency value for TCDD which may then be used for calculating human risk is of particular concern to this Committee. The assignment of "oral intake risk-specific doses of slightly less than 0.01 pg TCDD/kg/day, corresponding to unit risk estimates of 1×10^{-4} per pg TCDD/kg/day" (pages 9-67 and 9-83) must be rigorously analyzed to satisfy the scientific community that these values, derived solely from animal studies, are adequately justified and defensible. These critical values will serve as the elements for human risk assessment calculations by risk managers when determining acceptable levels of human exposure. It is not obvious how these values of potency were derived and how vigorously the value can be defended as the critical number used for human risk calculations. **The document requires a more extensive discussion (in Chapter 9) of how this**

calculation was derived, which default assumptions were used, and why daily dose is the proper dosimetric parameter.

4.11.2 Animal vs. Human Data (Charge Question 22)

The strengths and weaknesses of extrapolation to humans are discussed in the dioxin document, in the responses by those submitting comments, and in the TCDD literature. In general terms, the arguments advanced from both positions are widely recognized. Little is novel in the TCDD context and the debate remains relatively superficial. EPA's assertions in favor of species extrapolation are based on the weight-of-evidence argument, which points to some shared mechanisms among species, the presence of a functional Ah receptor in humans, similar biochemical responses in multiple species, and the correspondence in certain outcomes of high dose exposures, primarily chloracne, in both humans and animals. Commonalities in certain outcomes among several species of laboratory animals (but not yet humans), particularly in the growing developmental literature, also support this position.

The opposing position asserts that postulating homologous outcomes among species is not a fruitful avenue to risk assessment. This position objects particularly to the lack of cogent human data on indices such as sexual behavior, immune dysfunction, and others, and notes species heterogeneity in the Ah receptor. Lack of human data, however, should not be interpreted to mean that humans are unaffected, because appropriate human studies are yet to be performed. Although it will be a difficult task, EPA should perhaps consider, in future revisions, what human studies might be undertaken to shed light on this issue.

The animal data indicate TCDD to be a potent developmental toxicant capable of inducing functional and morphological aberrations in male rats (Mably *et al.*, 1992; Bjerke *et al.*, 1994; Bjerke and Peterson, 1994). Because such outcomes can occur at low doses, and therefore are much more relevant to general environmental levels, most Committee Members think that a revised Chapter 9 should feature developmental toxicity with as much emphasis as is allocated to cancer and reproductive toxicity. Animal data will have to be relied on for developmental questions linked to TCDD because the human database is so limited. These data, however, can be supplemented by the PCB data from the Lake Michigan (Jacobson and Jacobson, 1994) (as discussed in section 4.6.1) and North Carolina (Gladen *et al.,* 1988) studies because, unlike the Japanese and Taiwanese episodes, they are based on prevailing environmental levels and were revealed by neuropsychological indices rather than clinical abnormalities. The evolution of our understanding of the developmental toxicity of lead should be cited as a model.

A lamentable stimulus to this debate is the somewhat loose and impressionistic manner in which Chapter 9 is framed. Had its tenets been offered in a more precise, organized manner, with appropriate documentation and depth, and with a clear presentation and evaluation of conflicting points of view, it could have served as a structure on which to build a more defensible risk characterization. Although the case for extrapolation is argued more cogently in Chapter 8, its fragmentation in Chapter 9 leads to questions about its validity. In defense of EPA, however, the insistence on human evidence for every assertion about a possible hazard based on animal data is unrealistic. One comment submitted to EPA contends that clinical evidence of disordered human sexual behavior, corresponding to Mably *et al.* (1992), has yet to appear (however, complaints of impotence have been received from exposed workers, although adults seem to be a rather less sensitive population). It further argues that the preponderance of social and environmental determinants in human sexual behavior makes it unlikely that effects homologous to Mably *et al.* would ever emerge as a consequence of prenatal TCDD exposure. No cogent attempt to make such a comparison has been carried out; in addition, it would be naive to expect exactly the same outcomes. If such studies are undertaken seriously, they should be designed to illuminate small functional differences; the lead, ethanol, and PCB literature offer suitable models (e.g., Streissguth *et al.*, 1990 re ethanol).

Chapter 9 needs to offer a balanced perspective on these issues, especially by recognizing that, for developmental toxicity, arguing from simple homologous responses is unproductive. An appropriate translation, especially for functional endpoints, is essential. Chapter 9 should be organized in accordance with Wilson's principle, i.e., that functional effects of gestational exposure are likely to emerge at lower dose levels than those provoking overt structural teratologies (Wilson, 1977). Chapter 5 might also benefit by a wider discussion of developmental questions beyond the narrow domain of TCDD.

4.12 Overall Scientific Foundations of the Health Reassessment Document

4.12.1 Evaluation of the Risk Assessment Chapter (Charge Question 23)

The stated purpose of the Risk Characterization Chapter (9) is to provide “a balanced picture of the scientific findings of the health and exposure assessments for use by risk managers in selecting risk management options . . . “ (pg. 9-2). The risk management implications of the draft conclusions could certainly be significant. If there are public health consequences of current exposures to dioxin-like compounds, intensified regulatory actions may be appropriate. Given the large public health and

economic stakes in the dioxin reassessment, the Agency is well-advised to make sure that its final conclusions about dioxin-like compounds have a high degree of support within the scientific community. Otherwise, risk managers will not be in a strong position to perform their roles with competence and credibility.

Overall, the analytic strengths of the draft conclusions rest in the innovative approach that the Agency has taken to deal with this class of compounds. The weaknesses rest in the lack of discussion of alternative low-dose models and serious uncertainties, and the absence of quantitative information that can be useful to risk managers in comparing the incremental benefits of regulatory alternatives aimed at reducing exposures to dioxin-like compounds.

Looking at the strengths of the conclusions, three major points are apparent. **First, by focusing serious attention on various non-cancer effects, the Agency has dispelled any mis-impression that EPA's risk assessment process is overly preoccupied with carcinogenic effects.** In order to emphasize this point, the Agency may want to reorder the discussion of health effects on pp. 9-39 through 9-53, so that the discussions of non-cancer effects precede that of the cancer effects.

Second, by evaluating an entire group of compound classes (with a common attribute), rather than a single compound, the Agency responds to the generally-mistaken criticism that its risk assessment process can only address issues on a chemical-by-chemical basis. In this case, the compound classes are defined in terms of common biological responses, since the human body is presumed to be responding to the cumulative exposure to numerous agents that act through a common mechanism involving the Ah receptor. This leads to the Agency's use of TEFs as a numerical device to describe the relative importance of various dioxin-like compounds. In the final assessment, EPA should emphasize further the ambitious and somewhat speculative nature of this ground-breaking approach to risk assessment, as well as the consequences of not using a TEQ approach.

Third, in the opinion of most Committee Members, a useful comparative perspective is provided in the draft conclusions where the Agency highlights the fact that the margin of safety (between background exposures and levels of exposure where effects have been observed in test animals) for dioxin-like compounds is smaller than the EPA usually sees for many other compounds.

Three major weaknesses were also noted. **First, the presentation of scientific findings portrayed in the draft conclusions is not balanced.**[25] A tendency to overstate the evidence of danger is apparent in the following:

a) **There is an inference that humans are at risk from background and near- background exposures. The term "background," because of its implications in ordinary discourse, needs to be amplified in the context of the dioxin reassessment. "Background" typically refers to exposure levels that are not out of the ordinary experience. The populations described by Jacobson and Jacobson (1994)** (as discussed in section 4.6.1**), Gladen *et al.* (1988), and Huisman *et al.* (1995), which demonstrate associations between PCB (and in the Huisman study, PBBs and dioxins) exposure and neuro-developmental deficits, would be classified at the high end of the "background' distribution. This distinction needs to made clear by EPA**.

b) The Agency's decision to propose a uniform carcinogen classification for all dioxin-like compounds (even though the weight-of-the-evidence on TCDD is more persuasive than for many other compounds included in the report).

c) The Health Reassessment document's presentation of quantitative estimates of carcinogenic potency without presenting any quantitative estimates of anti-carcinogenic action (even though available data suggest protective effects are occurring at low levels of exposure) and biological plausibility for such effects (As noted in section 4.2.1 however, several Members of the Committee suggest that possible protective effects may be related to anti-estrogenic activity, rather than any general chemoprotective effect. One Member does not believe that the evidence for protective effects is statistically significant.).

Second, important uncertainties associated with the Agency's conclusions are not fully recognized and subjected to feasible analyses. Examples of this problem include instances in which:

[25] Several Members of the Committee do not agree with this statement and regard the EPA presentation and the inferences drawn as appropriately conservative within the context of public health protection.

a) The document did not acknowledge the biologic plausibility of a threshold model for some or all of the effects.

b) Sensitivity analyses of the TEF values reported in Table 9.1 were not provided (incorporation of such analyses were suggested and illustrated in the comments provided by the public).

c) The document repeatedly referred to "average body burden" as a biologically meaningful dose metric, even though other measures of dose associated with peak intake may be more important for some effects, and that “area under the curve” is the preferred dosimetric for dealing with agents with long biologic half-lives.

d) The document reported "conservative" numerical values (e.g., for the potency figure) without any realistic or central estimates to provide a broader perspective.

Finally, the characterization of non-cancer risk is not performed in a manner that allows meaningful analysis of the incremental benefits of risk management alternatives.[26] The risk manager is provided with no quantitative indication of how the severity or frequency of non-cancer effects (e.g., reproductive and developmental toxicity) in the human population might be affected by incremental reductions in either intake rates or average body burdens. Although the Agency is correct in pointing out the weaknesses in a traditional "reference dose" approach to this class of compounds, it has not provided risk managers with any means to perform dose-response analyses of the non-cancer effects. Unless such information is provided, there is a danger that the real possibility of non-cancer effects will be downplayed or ignored or, conversely, overstated, in regulatory impact analyses and future cost-benefit analyses.

From a presentational perspective, more thought needs to be given to how the information is presented in Tables 9-3 through 9-5. These are arguably the most important tables in the entire report, but they are not constructed in a manner that is helpful to the reader looking for information about how responses are related to dose range. Without information about dose range, the effects reported are easily misinterpreted. One fruitful idea might be to start with background exposures, report the most sensitive endpoint first, and then order all of the effects along a continuum of dose. A

[26] A minority within the Committee finds the non-cancer risk characterization to be appropriate for use within a public health perspective. However, they agree that the reassessment document’s characterization is not performed in a manner which will be very useful in the analysis of the incremental benefits of risk management alternatives by those who are also concerned with the micro-level economic costs.

"Comments Section" should be added to the table to highlight key uncertainties in the database on particular effects.

4.12.2 Evaluation of Major Conclusions (Charge Question 1)

Five major conclusions related to the health effects of .2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD or dioxin) are contained in Chapter 9. These conclusions purport to draw on the extensive data base on TCDD and related compounds presented in Chapters 1 through 7 and part of Chapter 8.

The comments following the quotation of each of Chapter 9's conclusions (in italic text) presented below reflect the Committee's concerns with that conclusion.

a) *The scientific community has identified and described a series of common biological steps that are necessary for most (if not all) of the observed effects of dioxin and related compounds in vertebrates, including humans. Binding of dioxin-like compounds to a cellular protein called the Ah receptor represents the first step in a series of events attributable to exposure to dioxin-like compounds, including biochemical, cellular, and tissue level changes in normal biological processes. Binding to the Ah receptor appears to be necessary for all well-studied effects of dioxin but is not sufficient, in and of itself. to elicit these responses. This reassessment concludes that the effects elicited by exposure to 2,3,7,8-TCDD are shared by other chemicals that have a similar structure and Ah receptor-binding characteristics. Consequently, the biological system responds to the cumulative exposure of Ah receptor-mediated chemicals rather than to the exposure to any single dioxin-like compound.* (Chapter 9, page 78)

The conclusion that some responses to TCDD and structurally related compounds are initiated by binding to (and activation of the Ah receptor) is clearly supported by an extensive body of data on many, if not all, relevant endpoints. The acceptance that toxicities of potential concern are receptor-associated provides the opportunity to draw upon the principles of receptor action that have been developed and validated within the disciplines of immunology, biochemistry, and pharmacology. These principles are not unique to TCDD, but rather apply to all ligand receptor interactions (however, see the discussion in section 4.2.1 concerning the relationship of the binding of TCDD to the Ah receptor and the manifestation of toxicity). Receptor theory provides the basis for the development of quantitative descriptions of these interactions that take into account both the **affinity** of the ligand for its cognate receptor and **efficacy**. The latter is based on the experimental observation that not all ligands produce the same

quantitative response as a function of receptor occupancy. The extremes range from full agonist to antagonist. Although the conclusion that TCDD toxicity is receptor-associated is straight-forward and supported by the data, the broader implications for environmental mixtures that contain synergists, agonists, partial agonists, and antagonists need to be more fully considered--both qualitatively (What compounds are present?) and quantitatively (in what amounts?). In the overall context of the exposure-dose-response paradigm, it is necessary also to incorporate pharmacokinetic data that will allow a qualitative and quantitative description of the presence of the various compounds (and their metabolites) in potential target tissues. Clearly, not all dioxin-like compounds are alike in their metabolic stability, tissue distribution patterns, or biologic half-life.

The conclusion that "the biological system responds to the cumulative exposure of Ah receptor-mediated chemicals" needs to be more specifically defined to incorporate the above concerns. The implication of simple additivity ignores individually and collectively the chemical and biological properties of these chemicals as well as the well-established and experimentally verified principles of receptor-ligand interactions.

b) *There is adequate evidence based on all available information, including studies in human populations as well as in laboratory animals and from ancillary experimental data, to support the inference that humans are likely to respond with a broad spectrum of effects from exposure to dioxin and related compounds--if exposures are high enough. These effects will likely range from adaptive change at or near background levels of exposure to adverse effects with increasing severity as exposure increases above background levels.* (Chapter 9, page 79).

Effects and exposure levels need to be specified. For example, are *all* effects negative as implied by the term *increasing severity?* Here, it is imperative that the entire database be explicitly considered in the document, on an end-point specific basis. For example, there is evidence from bioassays in rodents that TCDD could be chemoprotective against breast cancer (Kociba *et al.*, 1978) -- although not all Members of the Committee accept this finding. Recent studies from Seveso (Bertazzi *et al.,* 1993) seem to show a pattern of **decreasing** relative risk values for breast cancer in women when comparing exposure zones R to B to A (i.e., from lower to higher estimated exposure). It must be noted, however, that these relative risk estimates are extremely unstable, and, as is the case with cancer exceedences, are based on very small numbers (e.g., one case of breast cancer in zone A). In addition, no other epidemiological studies have reported such effects, so the issue of the nature of effects remains problematical.

The overall impact of certain biochemical changes (e.g., increased levels of phase I and phase II metabolizing enzymes) seen at lower levels is not fully understood at this time. Current knowledge of the mechanisms of TCDD toxicity has not identified the biological determinants of specificity that would allow one to extrapolate toxicities across species with confidence.

In summary, there is not reason nor sufficient evidence to reject completely the EPA's statement above, but it should be revised to sharpen its message, better indicate areas of uncertainty, and reflect (with appropriate caveats) the *total* extant database.

c) *In TCDD-exposed men, subtle changes in biochemistry and physiology, such as enzyme induction, altered levels of circulating reproductive hormones, or reduced glucose tolerance, have been detected in a limited number of available studies. These findings, coupled with knowledge derived from animal experiments, suggest the potential for adverse impacts on human metabolism and developmental and/or reproductive biology and perhaps, other effects in the range of current human exposures. Given the assumption that TEQ intake values represent a valid comparison with TCDD exposure, some of these adverse impacts may be occurring at or within one order of magnitude of average background TEQ intake or body-burden levels (equal to 3-6 pg TEQ/kg body weight/day or 40-60 to 600 ppt in lipid). As body burdens increase within and above this range, the probability and severity as well as the spectrum of human non-cancer effects most likely increase. It is not currently possible to state exactly how or at what levels humans in the population will respond, but the margin of exposure (MOE) between background levels and levels where effects are detectable in humans in terms of TEQs is considerably smaller than previously estimated.*(Chapter 9, page 81)

Potential adverse effects are stated without a clear definition of the doses or exposure levels at which they occur. EPA's revision should attempt to provide a range of exposures linked to a range of adverse effects, much like it has done with lead toxicity, and incorporate some identification as to what adverse effects could be expected.

A critical issue throughout the risk characterization chapter is the assumption of the validity of the TEQ approach. Employment of TEQs assumes that all dioxin-like compounds have equal efficacy and in the context of the receptor occupancy theory (i.e., linear stimulus transfer), simple additivity can be used. Experimental evidence does not support the position of equal efficacy (which would rule out the presence of

partial agonists or antagonists). With the knowledge that dioxin-like compounds have differing receptor affinity, the well-documented difference in the levels of the Ah receptor in various tissues would determine whether synergism or antagonism would predominate. Finally, *in vivo,* dioxin-like compounds differ significantly in their distribution and metabolism. **Despite these caveats, the sense of almost all of the Committee was that the TEQ approach is, until some better alternative is developed, the best *available* vehicle for performing risk assessment involving complex mixtures of dioxins, furans, and co-planar PCBs. To address the caveats noted above, EPA should conduct a peer review of the TEF/TEQ approach, with particular attention to the role of partial agonists and antagonists.**

The last sentence of the above quoted EPA conclusion ("*It is not currently possible to state exactly how or at what levels humans in the population will respond, but the margin of exposure (MOE) between background levels and levels where effects are detectable in humans in terms of TEQs is considerably smaller than previously estimated.")* is (in the opinion of most, but not all of the Committee) thought to be speculative and needs to be reexamined. In effect, it states that we don't know what will occur, or at what level this unknown [response] will occur, but we know that it will occur (in terms of TEQs) closer to background levels than previously estimated.

d) *With regard to carcinogenicity, a weight-of-the-evidence evaluation suggests that dioxin and related compounds (CDDs, CDFs, and dioxin-like PCBs are likely to present a cancer hazard to humans. While major uncertainties remain, efforts of this reassessment to bring more data into the evaluation of cancer potency have resulted in a risk-specific dose estimate (1 X 10^{-6}) risk or one additional cancer in one million exposed of approximately 0.01 pg TEQ/kg body weight/day, This risk-specific dose estimate represents a plausible upper bound on risk based on the evaluation of animal and human data. "True" risks are not likely to exceed this value, may be less, and may even be zero for some members of the population.* (Chapter 9, page 85)

Existing epidemiological methodologies, coupled with the available database, simply do not have the power to identify possible cancer/dioxin links at background levels. Consequently, the conclusion that dioxin and related compounds are likely to present a cancer hazard to humans at exposure levels within one or two orders-of-magnitude above background is not well-supported by the existing human epidemiologic database.

The previous (and apparently still current) position of the EPA has been to use a linear extrapolation approach. This approach employs TEQ additivity and, to some extent, is contrary to the principles applicable to the quantitative modeling of receptor-mediated processes, most of which assume the absence of a threshold. There is a considerable body of peer-reviewed data, including the bioassay data in Sprague-Dawley rats (Kociba *et al.*, 1978) and more recent studies on the TCDD-dependent changes in hepatocyte proliferation (Fox *et al.*, 1992) and preneoplastic foci (Maronpot *et al.*, 1993), which challenges both of these assumptions. Thus, the risk-specific dose estimate (at the 10^{-6} level of risk) of 0.01 pg, TEQ/kg body weight/day is not supported by the available data.

All of the above notwithstanding, the main cancer hazard issue for EPA and other risk managers is to identify and gain a better understanding of those conditions of exposure wherein dioxin can be a human carcinogen. The Agency should revise its conclusions so as to state background risk in terms of a range from lower to higher, and should identify the range of risks for specific exposures above background exposures that may pose a human hazard.

e) *Based on all of the data reviewed in this reassessment and scientific inference, a picture emerges of TCDD and related compounds as potent toxicants in animals with the potential to produce a spectrum of effects. Some of these effects may be occurring in humans at very low levels, and some may be resulting in adverse impacts on human health.* (Chapter 9, page 87)

TCDD is a potent animal toxicant, producing a spectrum of effects dependent on the dose, context of exposure, and the genetic background. Not all responses in animals can be classified as adverse. In humans under conditions of high exposure, the most well-documented response is chloracne. Adverse effects attributable to chronic low level exposure have not yet been adequately demonstrated. The neuropsychological abnormalities reported in the Lake Michigan (Jacobson and Jacobson, 1994) (as discussed in section 4.6.1) and North Carolina (Gladen *et al.,* 1988) PCB exposure studies are suggestive, even though the exposures (albeit at “environmental levels”) are probably higher than one would consider to be near general background levels. The overarching issue here is the validity of extrapolation of animal data on dioxin to humans (which assumes rodents and humans to be equivalent in sensitivity) and the default assumptions applied to the analysis of the animal data which form the basis of the positions taken in the risk characterization.

It is difficult to determine what EPA is inferring in the last sentence in the above-cited conclusion. If it is intended to state that adverse effects in humans may be occurring near current exposure levels, it is the Committee's judgement that EPA has not presented findings that support this conclusion adequately.

4.13 Other Issues and Future Steps

In the preceding text, the Health Panel of the Dioxin Reassessment Review Committee responded to the 23 explicit questions contained in its charge. During the course of the Panel's deliberations however, some generic issues not addressed in the 23 questions arose. These are:

a) The advantages and disadvantages of expressing overall risks for 2,3,7,8-TCDD, other dioxins and furans, and co-planar PCBs together and separately.

The basis of this issue is, of course, the use of TEQ/TEF in formulating a risk assessment for a broad range of related agents. Although there are many concerns about the assumptions underlying the application of TEF/TEQ in this manner, neither this Committee nor the public commentors who addressed this topic can propose an approach better than that used by EPA. The sense of most of the Committee, developed as this review was prepared, was that EPA and other interested parties would be better served if the risk assessments for 2,3,7,8-TCDD, other dioxins and furans, and co-planar PCBs were done separately, **as well for environmental mixtures as a whole**.[27] Having these risk assessment calculations provided side-by-side in a single document will help risk managers, since control strategies and options may differ substantially for the separate categories, while recognizing that most human exposures will be to complex mixtures.

b) The implications to the risk assessment of alternate forms for the exposure-response relationship at low (environmentally relevant) levels of exposure.

The Committee urges EPA to examine fundamental principles of receptor theory, and the evidence from the epidemiological and toxicological data bases in the low exposure ranges for their consistency with its assumption of a linear, non-threshold carcinogenic risk. In addition, the Committee (with several exceptions) believe that the

[27] Several Committee Members believe that keeping dioxin-like PCBs together with the dioxins and furans in a single overall reassessment is appropriate and consistent with EPA's role of managing health risks to the general public.

Agency should at least consider the suggestions from the public[28] regarding evidence for reduced cancer risks associated with very low levels of exposure. Although such a concept seems to be counterintuitive, there is a body of literature (albeit debatable, and both pro and con) on the concept of hormesis and ionizing radiation biological effects; this concept was not discussed during the review meeting, but is mentioned as a possible area of future investigation.[29]

c) The extent to which revisions in the draft reassessment document will be needed to warrant the endorsement of SAB in terms of the appropriate utilization of scientific knowledge in the preparation of the risk assessment.

The Committee concluded that EPA reviews of the background and relevant literature in Chapters 1-7 were thorough and objective, and that, subject to revision to incorporate changes made in response to specific technical input from the Committee and others, no further SAB review was needed.

By contrast, the Committee concluded that more substantial revisions would be needed in Chapter 8 on modeling, and in Chapter 9 on risk assessment, and a further SAB public review session would be needed before any SAB endorsement of EPA's judgments on the extent of health risk posed by 2,3,7,8-TCDD, other dioxins and furans, and co-planar PCBs. In view of the major public health and economic implications of the ultimate judgments on the extent of these risks, the Committee recommends that this further effort be undertaken as soon as possible.

The importance of this revision to the reassessment of dioxin risks demands that the highest standards of peer-review extend to the risk characterization itself. Although it can be argued that this is in fact being carried out by this SAB Committee, submitting the risk characterization chapter for external peer review prior to final review by the SAB would serve to strengthen the document, and assure a greater likelihood of its acceptance by the scientific community-at-large. It is recommended strongly that: a) the risk characterization chapter undergo major revision; and b) the revised document be peer reviewed by a group of preeminent scientists, including some researchers from outside the dioxin “community” before returning to the SAB. It is particularly important

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[28] Based on an analysis of data in Fingerhut *et al.*, 1990.

[29] Several Members of the Committee believe that the evidence of “hormesis” for dioxin-lime compounds is not statistically or experimentally significant at this time, and that until more solid evidence is obtained, this issue is irrelevant. These Members also contend that the putative “hormesis” effects are occurring at the levels of exposure at which the developmental and immunological alterations are seen.

to include individuals with outstanding credentials and experience in basic research and quantitative modeling of receptor-mediated processes, as well as other scientists with broad toxicological, epidemiological, and public health, perspectives in such a review.

5. CONCLUSIONS

5.1 Exposure Assessment Document

EPA has done a very credible and thorough job on a large and complex task. The Agency is commended on the work that has been done to assemble, integrate, and analyze a very large body of data on source emissions, environmental levels, exposures, and human body burdens in a framework of human exposure assessment. In so doing, they have uncovered key data gaps and issues, developed some reasonable priorities for future efforts, and begun research efforts to address key information gaps. In general, the work has been clearly presented, and uncertainties and limitations in the data are generally well described. Thus, the recommendations of the Committee largely address refinements, corrections and clarifications that should be made to the Exposure Assessment draft document rather than substantive revisions.

In general, the emissions inventory has identified the major known sources of dioxins and provided a reasonable estimate of total emissions, given the available data. The Committee recommends that the new information on emissions from incineration of medical waste, which became available after this draft document was prepared, be reviewed and the emissions estimates be revised if appropriate. The Committee also recommends adding an explicit statement to the final document noting that the fractional contributions of various types of emissions sources to total emissions cannot be assumed to be identical to the fractional contributions of those sources to human exposures.

At present, it is difficult to evaluate the relative contributions of local and more distant sources to the levels of dioxin in food. When better data become available from on-going EPA measurements of dioxin concentrations in food, the Committee suggests that the Agency considering using a Geographical Information System (GIS) for analysis of these data. With such a system, the geographic distributions of dioxin emissions sources and dioxin levels in food could be mapped and quantitative questions asked (and tested statistically) regarding the probable influences of local and more distant sources.

In the Exposure document, total estimated dioxin-like emissions for the U.S. have been directly compared to an estimate of the total amount of dioxin deposited to the surface of the U.S., based on available measured deposition factors. However, a scientifically-valid mass balance comparison would require estimating deposition of the emitted dioxins using atmospheric dispersion and deposition modeling and then comparing this estimate to the estimate obtained from measured and representative

deposition data. The Committee's concurs with EPA's position (Volume II, p. 3-166) that it is not scientifically valid to infer that there are (based on the simple mass balance comparison) missing sources of dioxins. The Committee also recommends that this section of the document be modified substantially so that the simple direct mass balance comparison is not provided, and that the scientific problems with this procedure, which are given, be modified appropriately to reflect this revision.

The Committee agrees that the available scientific evidence strongly indicates that current levels of dioxin-like compounds in the environment derive from anthropogenic sources and that the air-to-plant-to-animal pathway is most probably the primary way in which the food chain is impacted and humans are exposed. However, the environmental data are limited and EPA should not loose sight of other potentially important exposure pathways that may impact on some parts of the population, e.g., point source to water to fish, and cigarette smoking. Furthermore, there is a very large gap in our understanding of the potential atmospheric transformation of vapor-phase dioxin-like compounds and of the air to plant transfer coefficients of these compounds. Environmental measurements of deposition of particulate and vapor-phase dioxin-like compounds to the surface are also extremely limited, although we understand that there are now some efforts to address this lack.

The reassessment document indicated that it is possible that dioxins from historic reservoir sources might be re-introduced through various exposure pathways. The Committee agreed that the potential contributions from reservoirs might indeed be important and that these sources should be evaluated more thoroughly.

The Exposure document defines a “background” exposure based on existing monitoring data obtained from sites removed from known contaminant sources (or from food representative of the general supply). The Committee had two concerns with the “background exposures” as so defined. The first is that this term be used consistently throughout the document. The second concern was that the comparison of estimated exposures from a single planned facility to this “background” might not be adequate if the region already had a higher level of exposure than the “background” due to the presence of multiple existing sources. The Committee recommended that a “baseline” exposure assessment also be made for the local area or region for comparison to the “background,” and that the Agency consider providing guidance for performing “baseline” exposure assessments, as well as assessments of the exposure increment from a proposed facility.

Although the Committee supports EPA’s use of TEQs for exposure analysis, it also recommends that EPA carefully review the draft Exposure Assessment report and

ensure that the congener-specific data are used in all instances (such as transport, transformation, and deposition processes) in which differences in the physical and chemical properties of the congeners are likely to be important. The Committee has noted several such cases in this report.

The Exposure Assessment document provides a reasonable central estimate of dioxin exposure but the estimate has substantial uncertainties at this time because of to the very limited data that are available. The assessment does not (and, given currently available data, cannot) provide an estimate of the complete distribution of exposures for the U.S. population which is needed to provide a strong scientific basis for a judging whether there are currently significant adverse health risks to the U.S. population from the dioxins. Nor are the body burden data adequate for time trend analysis. The Committee commends and fully supports EPA's efforts to develop more current and representative data on concentrations of dioxins in food and in human tissue. These are very high priority research needs.

5.2 Health Assessment Document

The first seven chapters of this three-volume document present a comprehensive and careful review of the scientific literature on the biological mechanisms leading to: uptake of dioxin and related compounds; their binding to receptor sites; their metabolism and retention in tissues; and cellular, organic, and whole body responses. The Committee commends the EPA staff for this considerable accomplishment, and has made a number of comments and suggestions for relatively minor changes, corrections, and citations to additional literature that should sharpen and clarify the content of these chapters further. It is confident that EPA will use this guidance to produce improved final versions of these chapters that will not need further review by SAB.

The document represents a departure from the earlier EPA risk assessment for dioxin, which dealt primarily with 2,3,7,8-TCDD. In addressing a broad range of dioxin-like compounds having the common property of binding to the Ah receptor, and producing related responses in cells and whole animals, it creates opportunities for a holistic assessment of the cumulative impacts of these broadly distributed anthropogenic pollutants. Thus, while the environmental concentrations of each compound alone may be too low to produce effects of concern, the combined exposures may be producing effects that warrant concern. The use of the concept of toxicity equivalence factors (TEFs), and the concentrations of the compounds in foods and environmental media, to produce an overall index of public health risk is clearly justifiable. Its practical application depends on the reliability of the TEFs and the availability of

representative and reliable exposure data. This review of the Health Assessment Document calls for clarifications in the specifications for TEFs of the various dioxin-like compounds for various health outcomes of concern. Having such specifications on TEFs, combined with exposure data for the specific compounds, the contributions to the overall risk of the various compounds and compound classes can then be determined with sufficient confidence for risk management decisions. In other words, when the risk manager concludes that the overall health risk from dioxin and related compounds requires a decision to reduce the risk, such decisions can be based on knowledge of which control options can produce the greatest increments of risk reduction for these several classes of compounds covered in this document.

It is on the basis of the preceding discussion that the Committee calls for more explicit treatment, in the revised document, of the major compound classes, i.e., 2,3,7,8-TCDD, other dibenzodioxins and furans, and coplanar PCBs. Each has different sources and options for source and exposure reduction.

The eighth chapter on modeling is a critical one in the document. The interpretation of the available bioeffects data from controlled exposure studies in the laboratory depends largely on cross-species and high dose to-low dose extrapolations. The interpretation of the human experience, largely (but not exclusively) from relatively high dose industrial workers exposures and acute exposures of populations to accidental releases, requires knowledge of, and corrections for, dose-related responses, and for the influence of confounding factors such as exposures to other toxicants, differences in population distributions of age, sex, ethnic background, diet, etc. Since each set of relevant data is inadequate, by itself, for estimating the human health risks of chronic, low-dose environmental exposures to dioxin and related compounds, models that are based on all of the relevant data are essential.

The modeling chapter does an adequate job summarizing the current state-of-the-art of modeling relevant to dioxin and related compounds. Its major deficiency, from the perspective of the SAB review Committee, was its reliance on the standard EPA default assumption of a linear non-threshold model for carcinogenic risk. Many Members of the Committee were impressed by the possibility of using the available data, primarily the low-dose data of Kociba *et al.* (1976; 1978; 1979) for rats, and the Bertazzi *et al.* (1993) data for humans, to construct an alternate model allowing for minimal response at low environmental levels of exposure that would be consistent with the body of available epidemiological and bioassay data, and recommend that the feasibility of such a model be discussed in the revised draft chapter.

The final chapter on risk assessment had, of necessity, the limitations imposed on it by its reliance on the contents of the first eight chapters. Also, having been prepared after the external peer reviews devoted to the earlier chapters, it was not as thoroughly reviewed as were the preceding chapters. It needs to be revised to reflect the changes being made in Chapters 1-8, and the areas of weakness discussed above in Sections 4.12.1 and 4.12.2. Chapter 9 would greatly benefit from an external peer review by a group including: scientists active in dioxin research; other scientists with broad toxicological (including experience in basic research and modeling of receptor-mediated processes); and scientists with epidemiological and public health perspectives, to place the risks of dioxin and related compounds in perspective. It may also be desirable to invite, as observers, risk managers, who may have to contend with concerns of the larger public in addressing regulatory options for these compounds.[30]

[30] Several Committee Members believe that EPA should consider in a threshold model the possibility of other toxic effects occurring in the "threshold region."

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