REPORT ON THE PEER REVIEW OF THE DIOXIN REASSESSMENT DOCUMENTS: TOXICITY EQUIVALENCY FACTORS FOR DIOXIN AND RELATED COMPOUNDS (CHAPTER 9) AND INTEGRATED RISK CHARACTERIZATION DOCUMENT

—Final Report—

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NOTE

This report was prepared by Eastern Research Group, Inc. (ERG), an EPA contractor, as a general record of discussion for the peer review meeting. This report captures the main points of scheduled presentations and highlights discussions among the reviewers. This report does not contain a verbatim transcript of all issues discussed during the peer review. Additionally, the report does not embellish, interpret, or enlarge upon matters that were incomplete or unclear. EPA will evaluate the reviewers' recommendations and determine what, if any, modifications are necessary to the current dioxin reassessment documents. Except as specifically noted, no statements in this report represent analyses by or positions of EPA or ERG.

TABLE OF CONTENTS

TABLE OF CONTENTS (Continued)

LIST OF ABBREVIATIONS

ATSDR	Agency for Toxic Substances and Disease Registry
AUC	area under the curve
CSF	cancer slope factor
ED_{01}	effective dose at the 1% response level
EPA	U.S. Environmental Protection Agency
ERG	Eastern Research Group, Inc.
GGT	gamma glutamyltransferase
IARC	International Agency for Research on Cancer
LED_{01}	lower bound of the effective dose at the 1% response level
MOE	margin of exposure
MRL	minimal risk level
NHATS	National Human Adipose Tissue Survey
PAH	polycyclic aromatic hydrocarbon
PBPK	physiologically based pharmacokinetic
PCB	polychlorinated biphenyl
PVC	polyvinyl chloride
RfC	reference concentration
RfD	reference dose
SAB	Science Advisory Board
SMR	standardized mortality ratio
TCDD	2,3,7,8-tetrachlorodibenzo-*p*-dioxin
TDI	tolerable daily intake
TEF	toxicity equivalence factor
WHO	World Health Organization

EXECUTIVE SUMMARY

Twelve independent peer reviewers critiqued the following two documents that the U.S. Environmental Protection Agency (EPA) prepared as part of its scientific reassessment of the health risks of exposure to dioxin and related compounds: "Part III: Integrated Summary and Risk Characterization for 2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin (TCDD) and Related Compounds" and "Chapter 9: Toxicity Equivalence Factors (TEFs) for Dioxin and Related Compounds." The reviewers were asked to give their individual opinions on these documents; no efforts were made to reach consensus on any issue.

During the 2-day peer review meeting, most reviewers commended EPA on its efforts in completing the documents for the reassessment, but they made several suggestions and recommendations for how the two documents can be improved or should be revised. The reviewers provided largely positive feedback on EPA's treatment of several issues (e.g., ambient and population exposures, toxicity equivalence factors, and inventory of sources); however, the reviewers had a range of opinions, including several criticisms, of EPA's treatment of other issues (e.g., cancer characterization, selection of a dose metric, and the risk characterization summary statement).

At the end of the meeting, the reviewers identified the following six topics as being the most critical for EPA to consider when completing the reassessment. The reviewers' specific comments on these topics are described in greater detail throughout this report, and briefly summarized in Section 2.1, which summarizes the reviewers' comments on 11 distinct topics. The topics of greatest concern to the reviewers are:

- Characterization of TCDD as a "human carcinogen" and related compounds as "likely human carcinogens"
- Validity of the range of cancer risk in the general population (i.e., 1 in 1,000 to 1 in 100) posed by ambient exposures to dioxin and related compounds

- Characterization of dioxin exposure levels at which noncancer effects are likely to occur and identification of specific noncancer effects expected to occur at ambient exposures
- The need for a distinction between dioxin-related effects of unknown clinical significance (e.g., biochemical changes) from effects with clinical manifestations of toxicity
- The need for more detail on what is known, and not known, about congener-specific toxicity
- Additional clarification on how various dose metrics (e.g., body burden, tissue levels, daily intake, and so on) differ; justification for the use of body burden, as opposed to other measures, as a dose metric; and greater discussion on how pharmacokinetic modeling is used to estimate body burdens from daily exposures

In addition to the aforementioned general issues of concern, the reviewers commented on a wide range of technical topics when responding to 21 charge questions that addressed various aspects of the two reassessment documents. Several cross-cutting suggestions came up during their discussions. Specifically, the reviewers suggested that EPA: use more tables to display results of studies and compare results of multiple studies on similar topics; discuss in greater detail how key decisions were made, including justification for why alternative approaches were not selected; and present a new section that states the various limitations, data gaps, and uncertainties in the current knowledge base on dioxin and identifies key research needs.

As stated earlier, a brief summary of the reviewers' key findings on specific topics is provided in Section 2.1 of this report; a more complete record of the reviewers' discussions is documented in Sections 2.2 through 2.13.

1.0 INTRODUCTION

This report summarizes an independent peer review by 12 experts of two documents, which the U.S. Environmental Protection Agency (EPA) released as part of its scientific reassessment of the potential health risks associated with exposures to dioxin and related compounds:

- The June 2000 release of "Part III: Integrated Summary and Risk Characterization for 2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin (TCDD) and Related Compounds" (EPA 2000a), referred to in this report simply as the "Integrated Summary"

- The June 2000 release of "Chapter 9: Toxicity Equivalence Factors (TEFs) for Dioxin and Related Compounds" (EPA 2000b), referred to in this report simply as the "TEF Chapter"

For additional reference, the reviewers were also given electronic copies of all other relevant chapters in the dioxin reassessment documents that EPA has previously released (EPA 2000c).

The peer review took place in Washington, D.C., on July 25–26, 2000, in a meeting that was open to the public. Eastern Research Group, Inc. (ERG), a contractor to EPA, organized the peer review and prepared this summary report. This introductory section provides background information on EPA's ongoing dioxin reassessment, the scope of the peer review, and the organization of this report.

1.1 Background

In April 1991, EPA announced that it would conduct a scientific reassessment of the potential health risks of exposure to dioxin and related compounds. The agency initiated the reassessment to review emerging scientific knowledge of the biological, human health, and environmental effects of these substances. In particular, EPA evaluated significant advances in the scientific understanding of mechanisms of dioxin toxicity, the carcinogenic and other adverse health effects of dioxin on people, human exposure pathways, and the toxic effects of dioxin to the environment.

The reassessment led to the publication of a multi-volume document titled "Exposure and Human Health Reassessment of 2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin (TCDD) and Related Compounds." The draft of this document was published in 1994. In 1995, this draft was reviewed by EPA's Science Advisory Board (SAB), which issued a fall 1995 report with the following four key recommendations:

- The review provided substantive comments on two sections in the reassessment documents: the chapter on Dose Response Modeling (Chapter 8) and the Risk Characterization document (identified as Chapter 9 in a previous draft).
- The review recommended that EPA develop a new chapter on toxicity equivalence factors (TEFs) to consolidate the discussion and scientific information on the use of TEFs for dioxin and related compounds.
- The review approved the health and exposure sections (Chapters 1–7), stating that there was no need for further SAB review as long as EPA updated these sections with any relevant new information before finalizing them.
- The review recommended that the revised chapters on Dose Response Modeling and Risk Characterization and the new chapter on TEFs undergo external peer review prior to the SAB's re-review.

To date, EPA has addressed the first three recommendations listed above and conducted an external peer review of the revised chapter on Dose Response Modeling (Chapter 8), but the agency has not yet conducted an external peer review of the updated Integrated Summary and Risk Characterization or the new chapter on TEFs. (These two documents are the Integrated Summary and TEF Chapter, mentioned above.) To ensure its assumptions, methods, and conclusions are based on sound scientific principles, EPA decided, as per policy, to have these two documents peer-reviewed. The remainder of this report describes the scope and findings of this independent peer review.

1.2 Scope of the Peer Review

ERG managed every aspect of the peer review, including selecting reviewers (see Section 1.2.1), briefing the reviewers (see Section 1.2.2), and organizing the peer review meeting (see Section 1.2.3). The following subsections describe what each of these tasks entailed.

1.2.1 Selecting the Reviewers

To organize a comprehensive peer review, ERG selected 12 independent peer reviewers with demonstrated expertise in any combination of the following technical fields:

- Risk characterization and communication
- Toxicology of dioxin and related compounds
- Epidemiology
- Sources of, and population exposures to, dioxin and related compounds
- Mechanisms and mode of action
- TEFs

Appendix A lists the 12 reviewers ERG selected for this peer review meeting, and Appendix C includes brief biographies that summarize most of the reviewers' areas of expertise. Recognizing that few individuals specialize in every technical area listed above, ERG ensured that the collective expertise of the selected peer reviewers covers the six technical areas (i.e., at least one reviewer has expertise in epidemiology, at least one reviewer has experience in mechanisms and mode of action, and so on). Moreover, ERG selected peer reviewers with various affiliations (e.g., state agencies, academia, and consulting companies), such that the expert panel offered a broad and balanced perspective on the scheduled discussions.

To ensure the peer review's independence, ERG only sought reviewers who could provide an objective and fair critique of EPA's work. As a result, ERG did not consider for selection individuals

who were associated in any way with preparing the dioxin reassessment documents or individuals who disclosed certain conflicts of interest.

1.2.2 Briefing the Reviewers

Because of the large volume of information in the dioxin reassessment, ERG worked with EPA to develop written guidelines for the technical review. ERG then distributed these guidelines (commonly called a "charge") and the relevant reassessment documents to the peer reviewers several weeks before the meeting. The charge to the reviewers addressed several specific topics, and included a question that asked the peer reviewers to comment on any topics not explicitly listed in the charge. A copy of this charge is included in this report as Appendix B.

In the weeks after the peer reviewers received the charge, ERG asked the reviewers to prepare their initial evaluations of the dioxin reassessment documents under review. ERG compiled these premeeting comments, distributed them to the reviewers, and made copies available to observers during the peer review meeting. These initial comments are included in this report, without modification, as Appendix C. As the appendix explains, ERG assigned "primary" and "secondary" reviewers to each charge question. It should be noted that the premeeting comments are preliminary in nature. Some reviewers' technical findings might have changed based on discussions during the meeting, so the premeeting comments should not be considered the reviewers' final opinions.

1.2.3 The Peer Review Meeting

The 12 peer reviewers and more than 100 observers attended the peer review meeting, which was held at the Holiday Inn Capitol hotel in Washington, D.C., on July 25–26, 2000. Appendix D lists the observers who confirmed their attendance at the meeting registration desk. The schedule of the peer review meeting generally followed the agenda, presented here as Appendix E. As the agenda indicates, the meeting began with introductory comments by the designated facilitators of the meeting. (These and other introductory comments are summarized below.) For the remainder of the meeting,

the reviewers provided many comments, observations, and recommendations when answering the questions in the charge. The agenda included two time slots for observer comments; Appendix F of this report presents these comments. An ERG writer attended the meeting and prepared this summary report.

On the first day of the meeting, Ms. Kate Schalk (ERG) welcomed the reviewers and observers to the meeting, stated the purpose of the peer review, identified the documents under review, and explained the procedure observers should follow to make comments, both orally at the meeting and in writing to EPA. Ms. Schalk then introduced Dr. Colin Park and Dr. Peter deFur, who were both peer reviewers and co-chairs of the meeting. In his opening comments, Dr. Park explained that the peer review meeting would take the form of a free-flowing discussion among the reviewers and that the meeting would not focus on reaching a consensus on any issue. Dr. deFur then asked the peer reviewers to introduce themselves, note their affiliations, and disclose relevant conflict of interest information. To ensure that the peer review remained independent, Dr. deFur asked the reviewers to discuss technical issues among themselves during the meeting and to consult with EPA only for necessary clarifications.

Following these opening remarks, Dr. William Farland (EPA), the Director of EPA's National Center for Environmental Assessment, gave a background presentation on the agency's ongoing reassessment of dioxin and related compounds. Dr. Farland first reviewed the schedule and scope of the overall dioxin reassessment, highlighting milestones in the project since 1995. Specifically, he explained how the current peer review and the public comment period fits into the reassessment and summarized how EPA has addressed major issues raised on earlier versions of the reassessment documents.

For the remainder of his presentation, Dr. Farland reviewed key findings in the current reassessment documents. For instance, he described EPA's inventory of sources of dioxin and related

compounds, stressing the potential importance of reservoir sources. Next, he reviewed exposure pathways to dioxins, focusing on ingestion of foods with trace levels of dioxin and related compounds. Dr. Farland then presented findings on current intakes, exposure doses, and body burdens, and explained how these various measures are interrelated. Finally, Dr. Farland presented general information on mechanisms of action, cancer characterization, the derivation and interpretation of upper bound cancer risks, and noncancer effects.

After Dr. Farland's presentation, Dr. deFur began the meeting's technical discussions. He first set guidelines for the discussions among the peer reviewers, then asked the reviewers to make a brief "bottom line" comment on the documents under review. Dr. deFur ensured that the reviewers' various comments were all covered at some point in the meeting agenda. For the remainder of the meeting, Dr. deFur and Dr. Park worked with the peer reviewers to answer the 21 charge questions. The remainder of this report summarizes the reviewers' discussions and documents their major findings and recommendations.

1.3 Report Organization

The structure of this report follows the order of reviewers' discussions during the meeting: Section 2 summarizes the reviewers' responses to the charge questions, and Section 3 describes how the reviewers reached their final recommendations. Section 4 lists all references cited in the text. These sections use the reviewers' initials to attribute technical comments and findings to the persons who made them.

As mentioned earlier, the appendices to this report include a list of the peer reviewers (Appendix A), the charge to the reviewers (Appendix B), the premeeting comments organized by author (Appendix C), a list of the observers who confirmed their attendance at the meeting registration desk (Appendix D), the meeting agenda (Appendix E), and the observers' comments (Appendix F).

2.0 RESPONSES TO CHARGE QUESTIONS

This section summarizes the peer reviewers' responses to the 21 charge questions listed in Appendix B. For each charge question, discussions began with a presentation by the peer reviewer to whom ERG assigned primary responsibility for addressing the particular topic. After the presentation, all of the peer reviewers engaged in free-flowing discussions on the topic of concern. The meeting co-chairs then summarized how the reviewers agreed and how their opinions differed. A general record of the discussions on each charge question follows. After discussing the charge questions, the reviewers identified several issues of greatest concern; these are documented in Section 3.

Readers interested in only a brief overview of the reviewers' responses to the charge questions should refer to the summary presented below in Section 2.1; a more detailed account of the responses to specific charge questions can be found in Sections 2.2 through 2.13.

Note: The reviewers' initials used to attribute comments are as follows: Dr. Peter deFur (PdF); Dr. Richard Dickerson (RD); Dr. Mark Harris (MH); Ms. Holly Hattemer-Frey (HHF); Dr. Brent Kerger (BK); Dr. Myrto Petreas (MP); Dr. Colin Park (CP); Dr. Christopher Rappe (CR); Dr. Lorenz Rhomberg (LR); Dr. Allan Smith (AS); Dr. Curtis Travis (CT); and Dr. Matti Viluksela (MV).

2.1 Overview of Responses

After the workshop, the meeting co-chairs worked with ERG to prepare brief summaries of the reviewers' responses to the charge questions. These summaries are presented below, and an account of the discussions that led to these summary statements is provided in Sections 2.2 through 2.13.

Question 1—Body Burdens (see Section 2.2). The issue of body burdens as a dose metric generated substantial discussions. The reviewers expressed several concerns about this issue, such as whether body burdens are the best or correct parameter to characterize exposures to dioxin and related compounds, whether EPA fully considered the Science Advisory Board's suggestion to

consider using "area under the curve" (AUC) as a dose metric, and if body burdens are an appropriate dose metric for all groups, particularly children. Though the reviewers expressed various opinions on EPA's proposed use of body burdens, nearly every reviewer agreed, by the end of the meeting, that body burden is an appropriate method to characterize dose. Some reviewers, however, still thought EPA should explain why peak blood concentration and AUC blood concentration were not selected as dose metrics; and some reviewers continued to have reservations about using the body burden dose metric for children. Several reviewers recommended that EPA explicitly explain, possibly in a figure, the relationship between daily intake, serum levels, tissue dose, and body burden; some suggested that EPA clearly define body burden and clarify how it is calculated or measured.

Questions 2 and 3—Use of a Margin of Exposure Approach to Evaluate Risks (see Section 2.3). Most reviewers agreed that the use of a margin of exposure to express exposures rather than comparing exposures to an RfD/RfC is a logical process, given the assumptions made in the assessment, but the implication of these assumptions need to be more clearly defined. Some reviewers, however, thought the Integrated Summary should provide more detailed information on the implications of this approach. For instance, the reviewers suggested that the document compare the margin of exposure approach to daily dose guidelines established by the Agency for Toxic Substances and Disease Registry (ATSDR) and the World Health Organization (WHO). Some reviewers had questions about exactly how the MOE approach will be applied to quantify cancer and noncancer risks.

The reviewers thought the Integrated Summary clearly presented the entire data set of dose-response data that met EPA's selection criteria, but they had several suggestions for improving this presentation. Most importantly, many reviewers thought EPA should attempt to differentiate effects that are "frank manifestations of toxicity" from effects with unknown clinical significance. Other suggestions included differentiating continuous effects from quantal effects, illustrating the significance of

the Hill curve fit parameters, and explaining why one observes a range of dose-responses that spans 10 orders of magnitudes in ED_{01}.

Questions 4 and 5—Mechanisms and Mode of Action (see Section 2.4). The reviewers agreed that the reassessment documents gives considerable attention to the mode and mechanism of dioxin action, and provided few suggestions for how discussion of these topics should be improved. Recognizing that the mode of action raises the possibility that other compounds mediated by the Ah receptor can modulate dioxin toxicity, several reviewers thought the reassessment should describe how naturally occurring dioxin-like compounds affect dioxin toxicity. Given that the cancer characterization is based in part on dioxins being "strong cancer promoters," some reviewers thought the Integrated Summary should discuss the mechanisms by which dioxins act as promoters. Some reviewers gave examples of how EPA can clarify and enrich its discussion on mode and mechanisms of action, such as by describing all factors that might explain differences in sensitivity to dioxin among species and individuals and by characterizing the mechanisms by which dioxin has disruptive effects on cell growth, cell differentiation, and other biochemical pathways.

Questions 6 and 7—Toxicity Equivalence Factors (see Section 2.5). The reviewers generally agreed that Chapter 9 adequately presents the history, rationale, and support for the TEQ approach for evaluating dioxin-like toxicity, but they had two specific concerns about this approach. Several reviewers were concerned that the TEQ approach attributes dioxin-like toxicity, albeit in relatively small amounts, to compounds for which little toxicologic data are available; and one reviewer thought Chapter 9 should explain why naturally occurring dioxin-like compounds (e.g., indole-3-carbinol) and other compounds that activate the Ah receptor (e.g., polycyclic aromatic hydrocarbons) are not included in the TEQ approach.

Though the reviewers felt that Chapter 9 establishes clear procedures for using, calculating, and interpreting TEQs, they listed certain topics this chapter should describe more clearly. The reviewers

suggested that EPA make the following revisions to Chapter 9: given that the various dioxin-like compounds have a wide range of chemical and physical properties, EPA should stress that risk assessors should characterize fate and transport of individual dioxin-like compounds separately, rather than modeling fate and transport of a complex mixture as TEQs; EPA should concisely state in the conclusions the reason why the agency selected the WHO 1998 TEFs over TEFs that have been used previously; and EPA should present example TEQ calculations as an appendix.

Question 8 and 9—Noncancer Effects (see Section 2.6). The reviewers thought the reassessment documents adequately assemble the information on noncancer effects in animals and humans and explain why effects observed in animals are of concern to humans. Some reviewers found the human epidemiologic data on noncancer effects to be unconvincing and consequently thought EPA was not justified in raising concern of dioxin-related noncancer effects occurring at ambient exposures. The reviewers recommended that EPA include a table displayed at the meeting but not in the reassessment documents (i.e., the table labeled "10.xx.xx") in the final reassessment to summarize the various noncancer effects observed in animals and humans at low-level exposures.

Most reviewers agreed that developmental, reproductive, immunological, and endocrinological noncancer effects could be seen in humans, given sufficient dose. Their concern and discussion on this point focused again on the extent to which the human epidemiological data suggest that noncancer effects occur at ambient exposures. The reviewers suggested that EPA improve its justification of this conclusion.

Question 10, 11, and 12—Cancer Effects (see Section 2.7). The reviewers agreed that 2,3,7,8-TCDD is clearly a potent multi-site carcinogen in multiple species of animals. The human epidemiology studies show increased cancer mortality in various studies, but the majority of the panel felt that the results are not consistent and specific enough to conclude a causal effect, and therefore, as EPA acknowledges, the human data by itself is "limited". With "limited" human epidemiology, the

characterization as a "human carcinogen" rests on sufficient knowledge of mode of action in animals and humans. Some panel members felt that the modes of action were not sufficiently well understood to meet this definition, while others felt that the modes of action were not sufficiently well explained to meet the requirement. For one of these two reasons the majority felt that the characterization as a "human carcinogen" was not justified.

One reviewer felt that the human epidemiology data combined with the animal data is sufficient for the characterization of 2,3,7,8-TCDD as a "human carcinogen" but the justification could be better presented.

A comment was made that the epidemiology sections for cancer and non-cancer effects are weakened by including studies which have virtually no exposure, but show positive effects. The presentation of these studies weakens the conclusions that could have been reached based upon studies with clearly documented excessive exposures. Examples include the GGT effects for Vietnam veterans and soft tissue sarcomas for phenoxy herbicide workers.

The reviewers listed several specific concerns about the cancer characterization: several reviewers thought EPA should analyze in detail only the human epidemiologic data collected among the most highly exposed cohorts, rather than grouping this data with studies that documented very low exposures; some reviewers questioned the biological plausibility that TCDD can be a promoter of all types of cancer; some reviewers thought the human epidemiologic data might suffer from recall bias, selection bias, and confounders from lifestyle choices (e.g., smoking) and exposures to many other carcinogens; and several reviewers thought the Integrated Summary should discuss in greater detail the strength of evidence for potential carcinogenicity for specific congeners.

Though the reviewers had different opinions on the cancer characterization, they mostly agreed that the Integrated Summary adequately describes the evolving point of departure methodology. The

reviewers recommended that the Integrated Summary present more detail (e.g., sample calculations) on exactly how the cancer slope factor was derived, and some reviewers thought the Integrated Summary should explain how the proposed approach differs from the agency's traditional approaches. Some reviewers argued that EPA should have used the results of the four epidemiologic studies of the highest exposed cohorts to derive its cancer slope factor, instead of relying on the single study with the most conservative finding, and that EPA should clearly describe why the LED_{01} is used as a point of departure, rather than other values (e.g., the LED_{10}, the ED_{01}, the ED_{10}).

The reviewers debated the validity of the upper bound cancer risks at length. Some reviewers thought the range of upper bound risks (1 in 1,000 to 1 in 100) seemed unrealistically high, but others argued that this risk level would be virtually impossible to observe given the high cancer mortality rate for the general population. Some reviewers were concerned that EPA's choice of dose metric, use of potentially biased epidemiologic studies, and assumption of linear dose-response might have led to an overstatement of upper bound risks. Revisions suggested by several reviewers included more clearly describing the derivation of the current cancer slope factor, explaining in detail why this CSF differs from previous estimates, and discussing the significance of the upper bound cancer risks to the public.

Given that the range of upper bound cancer risks is a major finding of the reassessment, the reviewers thought this conclusion must be explained, presented, and qualified more completely. Specific suggestions were as follows: presenting a "more central" estimate by using ED_{01}, rather than LED_{01}, and by using the results from multiple studies, rather than the result of a single study; reconsidering whether animal data should form the basis for the cancer slope factor; and revising the text to put the estimated range of upper bound cancer risks into perspective for the public.

The panel generally felt, albeit on an intuitive basis, that the upper bound cancer risk of 10^{-3} to 10^{-2} in the general population, implying an additional 3,000 to 30,000 deaths per year was alarmist, not

warranted, and not realistic. EPA should present a "reality check" on the 10^{-2} to 10^{-3} risk estimates relative to highly exposed past cohorts.

Question 13, 14, and 15—Background and Population Exposures (see Section 2.8). Given that "background" implies "normal and acceptable," the reviewers found the term "background exposure" inappropriate for exposure to dioxin and recommended that EPA instead use other terminology, possibly "ambient exposures" or "general population exposures." Though they agreed that the data presented on dioxin levels in food sources and contact rates are an improvement over those presented in earlier drafts, the reviewers suggested that EPA include more specific information (e.g., number of samples collected, sampling locations, ranges and standard deviations of observed levels, cumulative distributions, and so on) on the data presented in Tables 4-6 and 4-8. The reviewers suggested that EPA revise discussions of dioxin levels in food sources by: identifying levels of dioxin in other food sources for which data are available (e.g., fish oil); listing food sources that have not been extensively characterized (e.g., farm fish and marine fish); commenting on the rate at which dioxin levels in food sources have changed over the years, if sufficient data are available to quantify this rate of change; and presenting information from earlier chapters in the reassessment documents on how various cooking practices affect exposure concentrations.

The reviewers thought EPA adequately derived approaches to estimate average daily dose from both dietary intake and body burden. They thought the Integrated Summary needed only minor revisions to make these approaches more transparent. Suggested revisions included providing a clear definition of body burden and explaining how body burdens relate to tissue levels, presenting equations and sample calculations to illustrate how average daily dose can be estimated from dietary intake or from body burden, considering other sources of data for characterizing trends in body burden levels, and providing additional detail on the variability in the distribution of estimated average daily intakes. Some suggested the report include more discussion about how varying daily intakes over life, changes

in body fat with growth, and slow accumulation of dioxin in the body with ongoing lifetime exposure factor into the calculations of average daily dose from body burden.

The reviewers thought EPA identified important "special populations" of highly exposed individuals, and suggested that the agency consider including others, such as people who lose weight rapidly, fetuses, and people who eat large amounts of potentially contaminated food sources not explicitly considered in the reassessment (e.g., lamb). Exposures to the identified populations were not thoroughly characterized, owing largely to the fact that sparse data are available for doing so. Some reviewers gave references for additional data to consider when characterizing exposures to special populations, and several reviewers thought the Integrated Summary should more prominently acknowledge the current lack of extensive information as an important data gap.

Question 16—Children's Risk (see Section 2.9). The reviewers generally had a favorable impression of the presentation of children's risk in the Integrated Summary, and they agreed that not enough information is available to determine whether children are more or less sensitive than adults to dioxin-related health effects. They suggested several revisions for EPA to consider. The issue of greatest concern was whether EPA selected an appropriate dose metric for evaluating children's risk, especially considering that children's (especially nursing infants') doses can be much higher than those of adults, even thought their body burdens often are not. Though they did not agree on an appropriate exposure dose metric for evaluating children's risks, the reviewers did agree that the Integrated Summary needs additional discussion on the uncertainties associated with using various dose metrics specifically for evaluating children's risks. Additionally, some reviewers recommended EPA incorporate findings from the ongoing studies of Dutch cohorts to provide additional perspective on children's risks, and others thought the Integrated Summary should include greater discussion on *in utero* exposures and associated effects, though they noted few if any studies have extensively investigated this issue.

Question 17—Relative Risks of Breast Feeding (see Section 2.10). The reviewers agreed that the Integrated Summary adequately describes how daily exposure dose and body burden differ between nursing infants and non-nursing infants. They also agreed that the reassessment documents adequately characterize how the differences vary with age, noting that most of this information is presented in earlier chapters. The reviewers thought the Integrated Summary presented a reasonable argument that cancer risks associated with nursing are likely low, but they thought the document needs to provide a similar argument for noncancer effects, if the risks are indeed low. Other suggestions included describing how pharmacokinetic modeling of body burdens in infants compares to observed body burden levels and indicating which congeners account for the largest proportion of TEQs in breast milk.

Question 18 and 19—Risk Characterization Summary Statement (see Section 2.11). Some members of the panel believed that it was speculative to say that there are biochemical effects in humans at background levels, much less adverse effects. At a minimum, these statements should be qualified that effects are not seen and are based upon extrapolations from animals and include extrapolation assumptions. The reviewers thought the risk characterization summary statement could have been more effective at capturing and communicating the range of risks and related issues from dioxin and related compounds concerning cancer and noncancer effects. They thought this section needs to be more specific, give numerical risks and exposures (where possible), and clearly indicate what the health implications of exposure and effects. The reviewers were not in agreement over the way this section portrayed the previous material; some thought this section overstated the points raised in the early chapters, while others thought the section was consistent with the information presented earlier. Nonetheless, the disagreements among the reviewers in interpreting of the summary statement made it apparent that this section of the report needs to be more clear. The reviewers thought that specific information and references to numerical data would go a long way toward solving the difficulties with this section.

Several reviewers did not think EPA made an adequate case that current ambient exposures can lead to "adverse" health effects, although some were comfortable that the case was made. Some reviewers thought the Integrated Summary must explain why effects are believed to occur at current ambient exposures, when effects are not widely documented in highly exposed occupational cohorts; they recommended that EPA specify exactly which effects are currently occurring. To put the risk characterization into context, the reviewers also thought EPA should differentiate effects that are "frank manifestations of toxicity" from effects that have no known clinical significance (e.g., certain biochemical changes), the toxicity of TCDD from the toxicity of the other congeners that have not been studied as extensively, and conclusions based on animal studies from conclusions based on human studies.

The reviewers had different opinions on the extent to which additional information should be incorporated into the risk characterization summary statement. Some thought the quantitative cancer risk estimates should be in the final summary statement, but qualified as to their upper bound nature and uncertainties. Some also thought the summary statement should include margins of exposure for the noncancer endpoints of greatest concern. Others recommended that the impacts of breast feeding on exposure should be addressed in greater detail. Noting that a more objective summary statement could be crafted, some reviewers prepared language as alternate suggestions.

A number of the reviewers felt that the summary of the risk characterization on page 107 should be made more factual and more objective. It was felt that the summary was biased and was founded on unproven assumptions, rather than being founded on a more factual basis.

Question 20—Sources (see Section 2.12). The reviewers commended EPA on its efforts in compiling an adequate inventory of sources of dioxin and related compounds. They raised various minor points for EPA to consider, such as clarifying the extent to which polyvinyl chloride in municipal solid waste affects emissions from incinerators, stressing that landfill fires and backyard barrel burning, combined, account for more air emissions of dioxin than any other source identified in the inventory,

emphasizing the importance of quantifying emissions from primary magnesium production facilities, and reevaluating the statistical assumptions used to calculate releases of dioxin to land from land application of municipal wastewater treatment sludge.

2.2 Body Burdens (Question 1)

The first charge question addressed the issue of body burdens and asked the peer reviewers: "Did EPA adequately justify its use of body burden as a dose metric for inter-species scaling? Should the document present conclusions based on daily dose?" During their initial discussions, the reviewers expressed numerous concerns about the proposed use of body burden as a dose metric for dioxin and related compounds. However, by the end of the meeting, nearly every reviewer agreed that body burden is an appropriate dose metric, though they recommended that EPA better justify this selection and define how the various dose metrics are related. Some reviewers thought EPA should explain why peak blood concentration and AUC blood concentration were not selected as dose metrics. An overview of the reviewers' initial discussion on this issue follows, and their subsequent discussions on dose metrics are presented in responses to other charge questions (e.g., Sections 2.6 and 2.9):

- *The need for further documentation on the reasons for selecting body burden as a dose metric.* Though reviewers had various opinions on EPA's selection of dose metrics, most reviewers agreed that the Integrated Summary should present a more detailed account of why EPA selected body burden as a dose metric, and why the agency rejected other metrics. More specifically, reviewers suggested that the document should clearly present the advantages, disadvantages, and uncertainties of all dose metrics considered, and then explain why EPA considered body burden to be the most appropriate.

  Several reviewers gave specific examples of how the Integrated Summary should better defend the choice of dose metric. For instance, one reviewer thought EPA should have justified its selection by interpreting the results of a paper recently published in the scientific literature (e.g., Aylward et al., 1996) and other relevant studies (MH). Another reviewer thought the Integrated Summary should present a comparative analysis of how the various dose metrics perform for inter-species extrapolations on different endpoints, rather than just acknowledging that a single dose metric likely is not adequate for all endpoints (LR).

- *The need for definitions of terminology and clarifications on how various dose metrics are related*. When answering this question, the peer reviewers questioned how various dose metrics that EPA could have used (e.g., average plasma concentrations, maximum plasma concentrations, body burdens averaged over a specified time) relate to the proposed dose metric, body burden. After discussing these various measures at length, the reviewers eventually agreed that many metrics are essentially interchangeable. For instance, a reviewer explained that blood concentrations, breast milk concentrations, adipose concentrations, and body burdens are essentially proportional, once one accounts for lipid concentrations (AS). Another reviewer explained that body burdens can be calculated from daily doses, and vice versa, using physiologically based pharmacokinetic (PBPK) models (CT). With these concerns in mind, the reviewers recommended that EPA clearly indicate how the various dose metrics are related. Noting that the Integrated Summary refers to body burdens in various contexts, another reviewer suggested that EPA define body burden in the final report (see Section 2.8 for additional information on this comment) (MP).

- *Arguments supporting the use of body burden as a dose metric*. When responding to the first charge question, the reviewers generally agreed that body burden is an appropriate dose metric for cancer effects, though some questioned its utility for addressing noncancer effects. One reviewer provided several arguments supporting the use of body burden as a dose metric (CT). For example, noting that average daily doses can be calculated from body burdens, this reviewer found using body burden as a dose metric to be quite practical, especially because detailed information on historical exposures (i.e., daily doses) often is not available to epidemiologists or risk assessors.

- *Potential shortcomings associated with using body burden as a dose metric*. Though most peer reviewers thought body burden is an appropriate dose metric, many noted its potential shortcomings as such. For instance, one reviewer thought, and other agreed, that use of body burdens (which present an integrated account of all past exposures) cannot adequately represent the effects of a single high-dose exposure (HHF). Moreover, this reviewer was concerned that the average daily dose of dioxins for nursing infants is considerably higher than the average daily dose of most adults—a fact she thought is not reflected in the body burden dose metric. Other reviewers found these arguments compelling (PdF,LR), and one suggested that it might be necessary to use multiple dose metrics to address the various types of exposures (LR). Another reviewer, on the other hand, thought body burden is an acceptable dose metric for children, given that body burdens can be calculated from daily dose estimates (CT).

  Another reviewer provided specific examples of potential shortcomings of the body burden dose metric (BK). Citing results from an analysis recently reported in the literature (Aylward et al., 1996), this reviewer showed how selected dose-response data for a cancer endpoint, in both rats and humans, varied considerably depending on the dose metric selected. Citing these data, he suggested that widely different conclusions can be drawn from inter-species

extrapolations using different dose metrics. As an example of his concern, this reviewer noted that liver sequestration of dioxins has been seen to vary considerably among species, making him wonder if extrapolations based on body burdens truly account for key pharmacokinetic concepts.

This reviewer commented on another issue, saying he did not think the body burden dose metric will be useful for characterizing threshold-based outcomes (such as noncancer effects) as evidenced by the fact that EPA does not propose a reference dose (RfD) or reference concentration (RfC) (BK). He thought threshold-based outcomes are consistent with a receptor-mediated toxic response.

- *Comments on the proposed use of a dose metric that has not been widely used.* One reviewer was troubled by EPA's selection of a dose metric that has not been used for any other chemical or drug (BK). This reviewer thought EPA should instead use approaches that have been demonstrated to model dose-response for other chemicals effectively, such as the use of PBPK modeling to evaluate exposures to lead. Another reviewer disagreed, saying that EPA should use whichever metric is best supported by the science, regardless of its precedent or lack thereof (CT).

- *Arguments supporting the use of blood concentrations as a dose metric.* Some reviewers argued in favor of using blood concentrations of dioxin as an appropriate dose metric. Referring to two reviewers' premeeting comments, one reviewer indicated that blood concentration is used more commonly than body burden as a dose metric for chemicals (drugs) with long half-lifes (BK). He added that the circulating blood concentration is a much more appropriate dose metric for chemicals with receptor-based modes of action. Though not disagreeing with these arguments, the reviewers eventually agreed that body burden and blood concentration can be easily calculated from each other, thus making the suggestion of using blood concentrations as a dose metric a moot point. Some reviewers added, however, that body burdens are not easily related to peak blood concentration or AUC blood concentration, and they recommended that EPA consider these dose metrics, as described in the next bulleted item (MH,BK).

- *Arguments supporting the use of an "area under the curve" (AUC) dose metric.* The reviewers briefly discussed whether an AUC dose metric might be more appropriate than body burden. Referring to two reviewers' premeeting comments, one reviewer thought AUC (or ppt-years) is the most appropriate and specific dose metric for chemicals with a receptor-based mode of action (BK). He also thought the AUC construct, unlike the body burden metric, provides an adequate scientific framework for a threshold-based dose-response model—an issue he considered important for evaluating noncancer effects. Another reviewer agreed, and suggested that EPA should have better justified its decision not to use an AUC dose metric, especially considering that the 1995 SAB review suggested that ". . . AUC is the preferred

dose metric for dealing with agents with long biological half-lives" (MH). This reviewer thought the Integrated Summary should have been more responsive to SAB's comment on this issue. On the other hand, a different reviewer did not support using AUC as a dose metric, partly because of its failure to model dose-response adequately for other types of exposures (e.g., cigarette smoking) (AS).

- *Comments on inter-species differences in pharmacokinetics*. Several reviewers thought the Integrated Summary should give more consideration to physiological and pharmacokinetic differences between animals and humans in the distribution, metabolism, and excretion of dioxin and related compounds. The reviewers paid the most attention to the inter-species differences in the half-life of dioxin and related compounds, and the implications of these differences on the risk characterization. The concern about this issue, as one reviewer explained (BK), is that half-life is a key parameter in inter-species extrapolations: if the half-life of dioxins in humans is shorter than the value EPA uses in the reassessment (i.e., roughly 7 years), then EPA has overstated body burden estimates and hence the exposure levels; if, on the other hand, the half-life of dioxins in humans is longer than the value used in the reassessment, then EPA has understated body burdens and exposure levels.

  Given these implications, some reviewers thought, the issue of the half-life of dioxins in humans deserves greater attention in the Integrated Summary. One reviewer, for example, thought the document should prominently acknowledge that dioxin and related compounds have half-lifes in humans that are disproportionately longer than one would expect from allometric scaling (CT). Another reviewer suggested that the Integrated Summary should at least explain or hypothesize why allometric scaling does not work effectively for dioxins (LR). Other reviewers thought the assumption of a constant half-life in humans may be flawed, citing data from the Yusho and Yucheng poisoning incidents and other sources that imply that half-lives may be dose-dependent or age-dependent (BK,CR). One of these reviewers was particularly concerned about the apparent dose-dependence of the half-life (i.e., the fact that the half-life may decrease with increased exposure dose, likely due to enzyme induction effects), given that many of the analyses in the Integrated Summary are based on highly dosed animals and humans (BK). Because of the various uncertainties associated with estimating the half-life of dioxins in humans, some reviewers thought EPA should make greater efforts to understand the pharmacokinetics of dioxins in humans rather than extrapolate data from highly dosed animals to humans (BK,AS).

  The reviewers eventually asked EPA to clarify issues pertaining to pharmacokinetics. Dr. Linda Birnbaum (EPA) responded, noting that three key factors—lipophilicity, induction of metabolism, and hepatic sequestration—largely dictate the pharmacokinetics of dioxin in all species that have been studied to date. She indicated that the difference in adipose volume in animals and humans appears to be a key factor in the failure of allometric scaling for dioxins. One reviewer thought the Integrated Summary should explain why half-life varies across

different species, why the half-life in humans is longer than one would expect from allometric scaling, and what these differences mean in terms of using body burden as a dose metric (LR).

One reviewer stressed that there are two questions about body burden as a dose metric that need to be addressed: (1) what is the value of a body burden metric in relating different exposures, rates, and durations to the outcome within a particular species (i.e., for use in dose-response modeling)? and (2) does a body burden dose metric serve well as a basis for expressing doses of expected equal toxicity across species? This reviewer thought these questions raise an important distinction in the appropriateness of body burdens, and he did not think the reassessment documents adequately address these questions (LR).

2.3 Use of Margin of Exposure Approach (Questions 2 and 3)

The charge included two questions on EPA's proposed use of a margin of exposure (MOE) approach to evaluate dioxin-related health risks. The first question asked the reviewers: "How might the rationale be improved for EPA's decision not to calculate an RfD/RfC, and for the recommended MOE approach for conveying risk information? Is an MOE approach appropriate, as compared to the traditional RfD/RfC? Should the document present an RfD/RfC?" Most reviewers supported EPA's proposed MOE approach, given the fact that applying RfDs in the traditional sense (i.e., for the most sensitive noncancer endpoint) would lead to values that are too low to be very helpful in making risk management decisions. The reviewers' specific comments and suggestions on this topic follow:

- *Arguments supporting the MOE approach.* The reviewers generally agreed that the traditional use of an RfD or RfC would not be meaningful for evaluating dioxin exposures, given that current ambient exposures to dioxin are already higher than the RfD or RfC that EPA would most likely select. In such a scenario, reviewers noted that using an MOE approach makes sense and developing an RfD or RfC for the most sensitive endpoint does not (CP,LR). The reviewers voiced several concerns about the MOE approach and how the Integrated Summary presents it. These concerns are described below.

- *Concerns with using the MOE approach for evaluating noncancer effects.* Given their concerns regarding the proposed EPA approach, as documented below, the reviewers suggested that EPA describe in greater detail the implications of the MOE approach and justify not using other approaches for evaluating dose-response. The reviewers had different opinions on which approach is most appropriate for evaluating the potential for noncancer health effects associated with exposures to dioxin and related compounds. One reviewer, for example,

supported the approach the Agency for Toxic Substances and Disease Registry (ATSDR) used to derive its minimal risk level (MRL) for dioxin (BK). He explained that this approach relies heavily on the weight of evidence of dioxin-related noncancer effects in humans, instead of basing health guideline doses exclusively on animal studies and overly conservative extrapolation factors, as is often done for chemicals that have been studied less extensively.

Another reviewer, however, did not fully support ATSDR's approach, noting that it relies on extrapolation factors that are considerably lower than have been used for any other chemical (AS). Specifically, he indicated that ATSDR's MRL, after being corrected for the inter-species differences in half-life of dioxins, is only nine times lower than the exposure doses observed to cause adverse noncancer effects in animals. He thought this margin of safety was unusually low, especially when compared to ATSDR's derivation of MRLs for other chemicals. The other reviewer argued, however, that ATSDR has used even lower extrapolation factors when deriving MRLs for other chemicals (e.g., arsenic) (BK).

One reviewer made a different suggestion: a more quantitative noncancer risk evaluation can be conducted using distributional approaches for deriving extrapolation factors (LR). He thought EPA should investigate the utility of such an approach, which he thought is particularly appropriate for evaluating chemicals for which population exposures are known to exceed RfDs.

- *Concerns with using the MOE approach for evaluating cancer effects.* The reviewers also had differing opinions on the utility of the MOE approach in cancer risk assessment. One reviewer, for example, noted that MOE has never been used to evaluate cancer in EPA risk assessments (BK).[1] He also thought this approach, which inherently incorporates ambient exposures, is inconsistent with EPA's traditional approach of evaluating the incremental cancer risks attributed to a specific source of exposure. Given that cancer risks associated with ambient exposures are estimated to be so high, this reviewer noted that the incremental risks from specific sources will consistently be marginal and may be viewed as insignificant. He also found the absence of considerably higher cancer risks in populations that were heavily exposed to dioxin and related compounds (e.g., in Seveso, Yucheng, and Yusho) to contradict key findings from the MOE approach—an issue the reviewers discussed in far greater detail when responding to charge questions 10, 11, and 12 (see Section 2.7).

  Another reviewer, on the other hand, thought the MOE approach to evaluating cancer risk is insightful, particularly in support of risk management decisions (AS). Specifically, he argued

[1] When asked to clarify issues raised in this question, Dr. Farland explained that EPA's proposed cancer guidance (1996) indicates that the MOE is a recommended approach for characterizing cancer risks, particularly as a "default" approach where nonlinear dose response cannot be further characterized.

that risk managers can make more informed decisions if they know the "background" contribution to dioxin-related cancer risks. As an example, risk managers might choose not to conduct an expensive clean-up for a site with an incremental dioxin cancer risk of 1 in 10,000, knowing that the general population already experiences much higher dioxin-related cancer risks (estimated in the range 1 in 1,000 to 1 in 100).

- *Differentiation of adverse effects from other effects with no apparent clinical significance*. During this discussion, several reviewers expressed concern about a lack of distinction between what they considered to be adverse effects (e.g., "frankly toxic effects") and effects with no apparent clinical significance (e.g., certain biochemical effects)—a concern the reviewers voiced several times during the peer review meeting. More specifically, one reviewer found the notion of a continuum of dioxin-related responses interesting, but he thought risk assessors and managers ultimately will be interested in understanding how dioxin exposures relate to frankly toxic effects, not to biochemical effects of unknown significance (CP). Another reviewer agreed, and suggested that EPA characterize effective doses at the 1% response level (ED_{01}) for specific endpoints (e.g., biochemical effects, chloracne, and so on), rather than focusing simply on the most sensitive one (LR). He thought such an approach is needed to allow risk assessors to conduct detailed, endpoint-specific analyses.

- *Consistency with other health guidelines*. Summarizing the premeeting comments on this question, one reviewer suggested that the Integrated Summary better explain how EPA's proposed MOE approach differs from dioxin dose guidance issued by other agencies, specifically ATSDR's MRL and the World Health Organization's (WHO's) tolerable daily intake (TDI) (CP). Another reviewer added that the 1995 SAB review of an earlier version of the reassessment made this same recommendation (MH). He did not think the Integrated Summary is adequately responsive to this particular SAB comment. When asked about this issue, Dr. Farland indicated that the Integrated Summary refers to the ATSDR and WHO guideline doses and briefly explains their differences, but does not extensively compare and contrast the various values.

The reviewers revisited some of the same comments when responding to the second charge question pertaining to EPA's proposed MOE approach. The question (charge question 3) asked:

> The SAB commented that previous dose-response modeling was too limited to biochemical endpoints (CYPIA1, IA2, . . .). Are the calculations of a range of ED_{01} body burden for noncancer effects in rodents responsive and clearly presented? Please comment on the weight of evidence interpretation of the body burden data associated with a 1% response rate for non-cancer effects that is presented in Chapter 8, Appendix I and Figure 8-1 (where EPA

considers that the data best support a range estimate for ED_{01} body burdens between 10 ng/kg to 50 ng/kg).

The reviewers' general response to this question was that the information presented in Appendix I and Figure 8-1 in the Integrated Summary adequately responds to SAB's request for more detailed dose-response information. However, the reviewers made several comments on how the presentation of information can be further improved, as described below:

- *General comments on the presentation of information.* Several reviewers agreed that the dose-response data presented in Appendix I and Figure 8-1, in a general sense, respond to the SAB comment that earlier reassessment documents were too limited to biochemical endpoints (PdF,CP,LR). One reviewer, for example, noted that EPA clearly specified the selection criteria used to identify relevant dose-response data and apparently considered all available data sets that met the selection criteria (LR). This reviewer added that he would have liked to have access to more information about the individual studies considered, but he did not think such detailed information is needed in the Integrated Summary. The following bulleted items describe the reviewers' concerns about how EPA currently presents dose-response data. At the end of the discussion, Dr. Farland indicated that EPA has considered other formats for presenting dose-response data. As an example, he distributed a draft version of a "Table 10.X.X.xx," which many reviewers thought would be an improved format for presenting the data.

- *The need to distinguish adverse effects from changes of unknown clinical significance.* The reviewers suggested that the presentation of dose-response data should clearly distinguish effects that are frank manifestations of toxicity (e.g., cancer) from effects that have unknown clinical significance (e.g., certain biochemical changes), though they acknowledged that making this distinction may be difficult and somewhat subjective. Explaining why this distinction is necessary, one reviewer said that a 1% change in enzyme induction, for example, should not necessarily form the basis of a noncancer risk assessment (LR). Similarly, another reviewer was concerned that the data in Figure 8-1 imply that dioxin-related hepatic effects occur at relatively low doses, although, she thought, most of the effects presented were increases in gamma glutamyltransferase (GGT)—an effect of unknown clinical significance (HHF). These and other reviewers agreed that the data presented in the Integrated Summary would be of greatest use to risk managers if some kind of distinction between the seriousness of the effects were made.

- *Importance of distinguishing quantal and continuous endpoints*. Several reviewers thought the data presented in Appendix I should clearly distinguish quantal effects (i.e., effects that either occur or do not occur, such as cleft palate) from continuous effects (i.e., effects that have a broad spectrum of responses, such as the degree of enzyme induction). One reviewer explained that this distinction is particularly important because toxicologists often use different models to characterize the two different types of dose-response (LR). He added that the ED_{01} has considerably different interpretations for the two types of effects: for continuous effects, the ED_{01} is the dose at which 1% of the maximum possible increase in a quantity is realized; for quantal effects, however, the ED_{01} is the dose at which 1% of the population has a response. This reviewer stressed that these two different interpretations of ED_{01} might explain, in part, why Figure 8-1 depicts such a broad range of dose-response data. Two other reviewers agreed with these arguments (BK,AS).

- *The need for further interpretation of the dose-response data*. The primary reviewer for this charge question offered several suggestions for presenting and interpreting the dioxin dose-response data (LR). First, he thought EPA should attempt to explain the extremely broad range in dose-response data (i.e., ED_{01} values spanning ten orders of magnitude) depicted in Figure 8-1 (LR). He thought this was particularly important given his experience with receptor binding models, which generally predict a difference between low receptor occupancy and high receptor occupancy over a roughly 80-fold range of dose. Thus, this reviewer wondered how the underlying assumption of a receptor-based mode of action for dioxin could be consistent with such highly variable dose-response. He offered several potential explanations, such as inter-species differences, sex differences, use of various dosing protocols, and consideration of all different endpoints in one figure, but he could not examine any of these influences based solely on how EPA presents the dose-response data.

  Further, this reviewer thought EPA should provide some guidance on how to use the data shown in Appendix I and Figure 8-1 in a quantitative noncancer risk assessment. Another reviewer agreed, noting that these data summaries should clearly depict the range of dose-response levels observed in humans for specific endpoints, so that a risk assessor can quickly compare body burdens observed in a particular population to those that have been shown to be associated with adverse effects in humans (BK).

- *Comments on EPA's use of Hill equations*. The primary reviewer offered several comments on the use of Hill equations to interpret dose-response data in Appendix I. First, this reviewer thought, the Integrated Summary should describe the significance of the parameters of the Hill equations used to model dose-response (LR). Specifically, he thought EPA could have included a sample calculation and a figure to illustrate the significance of the shape parameter and exponent in a curve fit using the Hill equations. Second, considering the wide range of curve fit parameters presented in Appendix I, this reviewer noted a great diversity in the shape of dose-response curves among the various studies EPA selected to evaluate; he thought the

Integrated Summary should make some attempt to put these highly variable parameters into perspective. Third, noting that EPA used Hill equations that model doses received that are above background levels, this reviewer thought a case could be made for using an "additive to background" version of the Hill equations.

- *Other comments and questions on the presentation of the data.* Some reviewers had additional concerns that do not fall into the categories listed above. One reviewer, for example, worried about extrapolating results of animal studies to humans using the ED_{01}, considering that many animal studies have too few subjects for the 1% effect level to be calculated directly (particularly for quantal outcomes) (AS). When asked to respond to this concern, Dr. Farland explained that the ED_{01} fell within the range of observations for greater than 60% of the studies considered in Appendix I, and even a larger number fell within one order of magnitude of this range; this fact supports the use of the ED_{01}. Another reviewer was concerned that using body burden as a dose metric in Appendix I and Figure 8-1 would mask any notable differences associated with the duration of exposure (MH). When asked to clarify this point, Dr. Birnbaum explained that the data shown in Figure 8-1 are only for chronic and subchronic exposures, for which one can assume that steady-state body burdens have been achieved. Finally, another reviewer suggested that EPA present all data in Appendix I and Figure 8-1 in multiple dose metrics (e.g., body burden, maximum blood concentration, AUC blood concentration) to demonstrate how these metrics differ in modeling dose-response (BK).

2.4 Mechanisms and Mode of Action (Questions 4 and 5)

Two charge questions concerned how the Integrated Summary addresses the mechanisms and mode of action of dioxin toxicity. The first question asked the reviewers: "How might the discussion of mode of action of dioxin and related compounds be improved?" The reviewers who answered this question generally found the discussion on mode of action to be adequate and offered some minor comments on how EPA can clarify and enrich this discussion, primarily by characterizing how various molecular and cellular events (i.e., not just the Ah receptor) are affected by dioxin action. These comments addressed both mode of action and mechanisms of action of dioxin toxicity, and are outlined below:

- *Recommended revisions.* The reviewers made some specific recommendations for improving the discussion on mode of action and mechanism of action. First, two reviewers thought the discussion on mechanisms was too focused on the Ah receptor, failing to address other relevant mechanisms (HHF,CT). For instance, one reviewer thought earlier chapters in the overall

reassessment document should include detailed information, to the extent it is known, on the disruptive effects of dioxin on cell growth, cell differentiation, signal transduction, and other biochemical pathways (CT). He suggested that the Integrated Summary include only a brief summary of these mechanisms.

Another reviewer noted that the Integrated Summary describes some factors (e.g., binding affinity of the Ah receptor) that might explain inter-species variability of dioxin action, but he thought the document should acknowledge the role of other factors (MV). Specifically, he thought the document should note the role of the C-terminal end of the Ah receptor. He explained that recent studies have suggested that mutations in this part of the transactivation domain can lead to increased resistance to dioxin-related effects (Pohjanvirta et al., 1998).

Other suggestions for improving this section included acknowledging the role of naturally occurring dioxin-like compounds in affecting dioxin toxicity (MH), considering research being conducted on other species (e.g., clams) for more insights on mode of action (PdF), highlighting how mechanisms of action are known to differ between laboratory animals and humans (HHF), and making the editorial revisions listed in Dr. Harris' premeeting comments (MH).

- *Implications of the mode of action on the cancer characterization.* Two reviewers thought discussions on mode and mechanism of action for dioxin were particularly important, given that EPA bases its cancer characterization, at least in part, on the fact that dioxin and related compounds are believed to be "strong cancer promoters" (AS,CT). Because of this, one reviewer thought the dioxin reassessment—either in earlier chapters or in the Integrated Summary—should include detailed discussions on the mechanisms by which dioxin acts as a promoter (CT). The reviewers discussed this issue further when responding to charge questions on cancer characterization (see Section 2.7).

The second charge question pertaining to mechanisms and mode of action asked the reviewers: "Despite the lack of congener-specific data, does the discussion in the Integrated Summary and Risk Characterization support EPA's inference that these effects may occur for all dioxin-like compounds, based on the concept of toxicity equivalence?" The reviewers who answered this question generally agreed that the dioxin reassessment documents, taken as a whole, adequately support the use of toxicity equivalence to support the notion that TCDD toxicity may occur for all dioxin-like compounds. One reviewer, however, thought only the earlier chapters in the reassessment thoroughly address the issue, and he did not think the Integrated Summary provided enough detail (MH). He thought EPA

could easily address this issue by including in the Integrated Summary more of the relevant information presented in Chapters 2 and 9.

The reviewers made three specific comments on this question. First, three reviewers thought the concept of toxic effects of dioxin-like compounds should be expanded to explain how certain groups of compounds act differently. Specifically, one reviewer thought the reassessment needs to acknowledge the role of antagonistic, naturally occurring dioxin-like compounds (MH); another reviewer agreed, noting that the reassessment should describe how non-chlorinated compounds can modulate the dioxin toxic response (RD); and another reviewer thought the documents should explain that some dioxin-like compounds, such as polychlorinated biphenyls (PCBs), have toxic actions that are not mediated by the Ah receptor (PdF). Second, one reviewer suggested that EPA use ecotoxicologic data on non-experimental animals (i.e., mammalian wildlife) to support the inference of toxicity equivalence (PdF). Third, one reviewer suggested that EPA clarify text in the Integrated Summary (e.g., lines 23–25 on page 89 of the review draft) that imply congener-specific differences in toxicity, but do not explain in detail what these differences are (MP).

2.5 Toxicity Equivalence Factors (Questions 6 and 7)

The charge to the reviewers included two questions that pertained specifically to the new TEF Chapter (i.e., Chapter 9) in the dioxin reassessment. The reviewers' comments on these chapters were consistently favorable, though they offered several suggestions for revising the text.

The first charge question addressing the TEF Chapter asked: "Is the history, rationale, and support for the TEQ concept, including its limitations and caveats, laid out by EPA in a clear and balanced way in Chapter 9? Did EPA clearly describe its rationale for recommending adoption of the 1998 WHO TEFs?" The reviewers who answered this question generally agreed that the TEF Chapter adequately presents the history, rationale, and support for the TEQ approach for evaluating dioxin-like toxicity. They made few specific suggestions for improving this chapter. One suggestion was that EPA

should enhance the chapter by drawing from data on wildlife studies (PdF), but the issue that received the greatest attention was concern about whether the TEF approach should be applied strictly to dioxins, furans, and dioxin-like PCBs, or if it should consider other compounds that interact with the Ah receptor (e.g., naturally occurring dioxin-like compounds, polycyclic aromatic hydrocarbons [PAHs], and others).

One reviewer noted that the TEF Chapter currently acknowledges that many classes of compounds bind to the Ah receptor, but he questioned why this entire group of compounds was not included in the TEF approach (MH). As an example of his concern, this reviewer referred to a publication that reported that TEQ calculations found that PAHs account for roughly 80 percent of the total TEQ at a particular site. He and other reviewers wondered if the TEF approach documented in the TEF Chapter should be broadened to account for the many other compounds that interact with the Ah receptor (PdF,MH,AS).

The reviewers eventually asked Dr. Birnbaum to clarify why the TEF approach is limited to only dioxins, furans, and dioxin-like PCBs. Dr. Birnbaum explained that the entire TEF approach was developed to evaluate toxicity for a group of compounds that meet four criteria: they must bind to the Ah receptor, be structurally related, be persistent, and induce a common spectrum of biological responses. Noting that PAHs meet only the first criterion, she concluded that this group of compounds is correctly omitted from TEF analyses. She added that some subchronic studies in animals have recently shown that naturally occurring dioxin-like compounds (e.g., isoflavones) do not show Ah-mediated effects or modulate dioxin-related effects, despite the fact that these compounds are known to interact with the Ah receptor. A reviewer agreed, and added that naturally occurring dioxin-like compounds have been shown to cause enzyme induction *in vitro* but not *in vivo* (MV). This reviewer thought EPA adequately defended its use of TEFs to examine effects of only dioxin and related compounds.

The second question pertaining to the TEF Chapter asked the reviewers: "Does EPA establish clear procedures for using, calculating, and interpreting toxicity equivalence factors?" The reviewers agreed that the TEF Chapter establishes clear procedures for using, calculating, and interpreting TEFs using the approach outlined by WHO, and they recommended several minor revisions to the chapter. For instance, one reviewer thought the chapter should include an appendix with an example illustrating how TEFs are derived (MV); another reviewer suggested that EPA prepare a summary document that more concisely explains to risk managers how to apply the TEF approach (PdF); and another reviewer suggested that EPA expand the uncertainty section in Chapter 9.5 to acknowledge the uncertainties associated with congener-specific toxicities, chemical and biological properties, use of dose metric, and presence of other ligands that might modulate dioxin-like toxicity (BK).

The reviewers discussed two issues regarding how risk assessors should apply the TEF approach. First, one reviewer thought the TEF Chapter should clearly state that because dioxin congeners exhibit a wide range of chemical and physical properties, risk assessors must model the fate and transport of individual congeners before converting exposure concentrations to a TEQ (CP). Other reviewers debated whether such information belongs in the TEF Chapter (BK,AS), and another reviewer thought EPA should simply clarify this issue by adding to the text already found in Chapter 9.6 (in lines 14–26 on page 9-30 in the review draft) (PdF).

Second, another reviewer wondered how pharmacokinetic differences among congeners factor into the TEF approach (LR). Dr. Birnbaum clarified that TEFs take into account congener-specific clearance rates: all other factors (i.e., toxicity) considered equal, congeners with the shortest half-lifes have lower TEFs than congeners with longer half-lifes. The reviewer noted that, because it explicitly accounts for half-lifes, the TEF approach is inherently better for evaluating chronic effects than for acute effects (LR). He explained that calculating acute doses with TEFs may understate the actual short-term dose, because the rapid clearance of certain congeners will already be considered; he added that he was not sure if this is a significant problem.

2.6 Noncancer Effects (Questions 8 and 9)

The reviewers answered two questions regarding how the Integrated Summary addresses noncancer effects. The first asked: "Have the available human data been adequately integrated with animal information in evaluating likely effect levels for the noncancer endpoints discussed in the reassessment?" The reviewers commended EPA on its efforts in compiling the available animal data and applicable human data in Chapters 4, 5, and 7 of the reassessment documents, but most agreed that the integration of these data in the Integrated Summary needs improvement. Many reviewers thought EPA could accomplish better integration by presenting certain data summaries in the Integrated Summary. More detail on this suggestion and others follows:

- *Presentation of data*. The reviewers made two recommendations for better integrating animal and human data in the Integrated Summary. First, one reviewer thought including the ED_{01} table from Appendix I and the "Table 10.X.X.xx" that Dr. Farland displayed during the meeting in the Integrated Summary would be sufficient for providing a more integrated account of the animal and human noncancer data (RD). Second, two reviewers thought EPA should prepare a new table for the Integrated Summary that summarizes key aspects of the various human studies of noncancer effects (HHF,MP). These reviewers thought a table listing the sample size, dose metric, odds ratios, effects observed, and other features of the available human studies would be a useful reference to all readers.

  Other reviewers agreed with this second recommendation in concept, but were concerned about how such a table might be interpreted. For instance, one reviewer noted that a summary table cannot adequately characterize the impacts of confounding factors in epidemiologic studies (AS), and he added that confounding factors can be particularly important to those interpreting studies of populations with very low doses. Given this concern, he was not convinced that EPA needs to include a summary table of human studies of noncancer effects in the Integrated Summary. Another reviewer echoed this concern, noting that the quality and robustness of epidemiologic studies must be considered when interpreting their findings (BK). Because of these concerns, another reviewer thought a summary table of human studies in the Integrated Summary would need to be accompanied by additional text in the document (CP). A reviewer added that the Integrated Summary, when referring to discussions in earlier chapters, should give as specific citations as possible (e.g., refer to Chapter 4.2.2 rather than refer to Chapter 4) (LR).

- *Comments on interpreting epidemiologic studies*. The reviewers offered several general comments on how EPA should weigh the results of human epidemiologic studies against

findings from animal studies. First, one reviewer noted that, for endpoints that tend to be associated with exposures to women and children (e.g., developmental effects), epidemiologic data will provide little insight on effects occurring in humans, because most of the studies conducted to date have focused on highly exposed male workers (RD). Second, another reviewer thought EPA could have interpreted the epidemiologic data more critically (CP). For instance, he noted that some studies have reported observing dioxin-related noncancer effects that could just as easily be attributed to confounding factors. He thought the increased levels of GGT observed among Viet Nam veterans, for example, could have been associated with alcohol consumption, and not necessarily with dioxin exposure. Third, another reviewer thought EPA should carefully examine only those epidemiologic studies based on reliable estimates or measures of exposure dose (AS). He suggested that EPA mention in the reassessment all relevant studies, dismissing those that have critical weaknesses, such as unreliable dose information.

- *Concerns about selected noncancer effects observed in animals at low-dose exposures*. One reviewer indicated that researchers have observed certain noncancer effects, other than biochemical changes, in animals at body burdens not considerably lower than the current estimate of "background" body burdens in humans (AS). Specifically, he noted endometriosis in monkeys, decreased sperm production in the offspring of exposed rats, and immunosuppression in the offspring of exposed monkeys—all have occurred at body burdens within an order of magnitude of body burdens currently observed in humans. He thought these findings were of concern not only because of their public health implications, but also because the low-dose effects in humans might be difficult to verify with epidemiologic studies. Given these concerns, this reviewer thought the Integrated Summary should more prominently acknowledge the potential risks of these outcomes and the added importance of needing to reduce current levels of dioxins in the environment. Another reviewer commented that EPA should examine more carefully the possibility that certain animal species (e.g., rhesus monkeys) may be more susceptible to reproductive effects of TCDD than humans and that confounding influences in study design may impact the dose-response pattern shown in some of these studies (BK).

- *Relevance of studies on Dutch cohorts*. Several reviewers questioned whether the Integrated Summary, when it discusses the human data on noncancer effects, should include results from ongoing studies of cohorts in the Netherlands (MH,CP,AS). The reviewers asked EPA to give an overview of these studies. Dr. Birnbaum explained that the Dutch studies examined approximately 400 women and their children from an urban and rural area and correlated a wide range of noncancer effects among the children with the body burdens measured in their mothers. Dr. Birnbaum noted that several dose-dependent effects have been observed, including cognitive deficits and immune effects. Some effects correlated with TEQ exposures, but others correlated only with PCB exposures. Dr. Birnbaum added that researchers have

reported seeing similar results (i.e., dioxin-related noncancer effects occurring at "background" exposures) in other populations, but she noted that these results have not been published.

Some reviewers commented on the results of these Dutch studies. One reviewer was skeptical about the significance of the studies' findings, given the marginal difference in body burdens between the highest and lowest exposure quartiles (CP). Another reviewer was also skeptical about these findings, noting that even the occupational studies of highly dosed workers have not provided compelling evidence that dioxin-related noncancer effects might occur at such low levels of exposure (MH). Dr. Birnbaum noted, however, that the occupational studies do not examine the developmental effects being examined in the Dutch studies. She added that animal studies are suggesting that developmental effects might be the most sensitive endpoint for dioxin-related noncancer effects. Concluding the discussion, another reviewer cautioned about attaching too much significance to the Dutch studies (AS). Noting that many studies were needed to verify the low-dose effects associated with lead exposure, he thought the Dutch studies alone should not change the tone of the reassessment's account of noncancer effects.

The reviewers then discussed charge question 9, which asked: "Do reviewers agree with the characterization of human developmental, reproductive, immunological, and endocrinological hazard? What, if any, additional assumptions and uncertainties should EPA embody in these characterizations to make them more explicit?" The reviewers briefly discussed this issue, and generally agreed that, given sufficient dioxin dose, developmental, reproductive, immunological, and endocrinological effects could be observed in humans. One reviewer noted that dioxin-related developmental and immunotoxic effects have been clearly demonstrated in human studies in the Netherlands, Yusho, and Yucheng (RD). He added that evidence of these effects and reproductive and endocrinological effects are also well documented in various vertebrate species.

The reviewers suggested few revisions to the noncancer characterization. One reviewer thought EPA should consider the suggestions raised in the primary and secondary reviewers' premeeting comments (PdF); another reviewer suggested that mentioning the Dutch studies in the reassessment would be appropriate, but he cautioned weighing the results of this study too heavily in the reassessment (see above) (MH); and another reviewer favored exercising caution when interpreting the Dutch studies, but added that EPA might consider thoroughly evaluating the results from the several

ongoing studies of many different cohorts with only ambient exposures to dioxin and related compounds (AS).

2.7 Cancer Effects (Questions 10, 11, and 12)

The charge included three questions regarding how EPA characterized cancer effects in the Integrated Summary. The first question asked: "Do you agree with the characterization in this document that dioxin and related compounds are carcinogenic hazards for humans?" Of all questions discussed during the meeting, charge question 10 clearly generated the greatest debate among the reviewers, and the reviewers' opinions on the cancer characterization greatly varied. For instance, when summarizing the premeeting comments, a reviewer noted the following: one reviewer agreed with EPA's cancer characterization; one indicated that the human epidemiology is inadequate; one said the human epidemiology does not demonstrate a strong dose-dependent relationship; one thought only TCDD could be characterized as a human carcinogen; one did not think the Integrated Summary presented adequate evidence supporting the characterization; and others commented that the evidence of carcinogenicity overall is weak, except perhaps for people exposed at highest doses (AS).

During the discussions on this issue, the reviewers unanimously agreed that dioxin is a strong, multi-site carcinogen in many animal species. The reviewers had different opinions, however, on the conclusions that can be drawn from the human data and the current knowledge of the mode of carcinogenic action. Some reviewers commented that EPA's characterization, at least for TCDD, can be defended with the available data (PdF,CR,AS,MV), but others did not think the characterization is consistent with the criteria outlined in the agency's most current cancer guidelines (HHF,BK,CP,CT). When reaching this point, the reviewers debated many relevant issues, such as the strengths and weaknesses of the human epidemiologic data, consistency with animal data, and modes and mechanism of carcinogenic action. These discussions are summarized below:

- *Strengths of epidemiologic studies*. Though they agreed that epidemiologic studies should weigh heavily in EPA's characterization of dioxin carcinogenicity, the reviewers clearly had

differing interpretations of these studies' results. Some reviewers thought the studies of the most highly exposed occupational cohorts provided compelling evidence of dioxin's carcinogenicity, but others had criticisms of these findings. The following paragraphs present the comments summarizing the strength of the epidemiologic studies, and the next bulleted item outlines the debate over the studies' weaknesses.

Highlighting the strengths of the epidemiologic studies, one reviewer summarized the rationale used by the International Agency for Research on Cancer (IARC) in its classification of dioxin carcinogenicity (AS). Of particular importance, he noted that IARC's review focused on the findings of the four studies of the most highly exposed occupational cohorts (Becher et al., 1996; Fingerhut et al., 1991; Hooiveld at al., 1998; Ott and Zober et al., 1996). In fact, the most highly exposed individuals in these cohorts were found to have body burdens more than two orders of magnitude higher than those of the general population. The reviewer then explained that cancer mortality in each of the cohorts, and in all cohorts combined, was significantly elevated. Specifically, the standardized mortality ratio (SMR) for all cancers for the combined population of the four cohorts was 1.4, with a confidence interval of 1.2 to 1.6. This SMR was shown to be statistically significant ($p<0.001$). The reviewer added that this increase was observed for all cancer deaths; and considerable increases in any one type of cancer death were generally not observed.

When interpreting this finding of increased cancer mortality, the reviewer stepped through several criteria widely used to assess whether environmental factors might cause disease (Hill, 1965):

– He stressed that the 40% increase in all cancers is almost certainly not due to chance alone, as the association was shown to be highly statistically significant (again, $p<0.001$).

– He suspected that the increase in all cancer is likely not biased by other factors, such as smoking or exposure to other occupational carcinogens. Specifically, he noted that the one study that looked explicitly at the issue found smoking not to be a confounding factor in the increased cancer mortality (Fingerhut et al., 1991). Further, he suspected that the presence of other occupational carcinogens cannot explain the overall increases in cancer, because most of these chemicals are often associated with increases in just one or a few types of cancer and generally are associated with decreased incidence of other cancers, due to the "healthy worker effect."

– He found the association between dioxin and cancer mortality to be very strong. Though he acknowledged that an SMR between 1 and 2 for a specific type of cancer is often viewed as a relatively weak association, he stressed that the SMR of 1.4, or a 40% increase, for all types of cancers is a very strong association given the large

number of added cancer cases. To illustrate this, the reviewer noted that the current general population risk for dying of cancer is roughly 1 in 5, and a 40% increase in this risk amounts to an added 8 in 100 cancer risk—or nearly 1 in 10—among the highly exposed cohorts (that is, 0.2 [1 in 5 general population cancer risk] x 0.4 [40% increase in risk] = 0.08 [8 in 100 increased cancer risk]).

– To give evidence of the consistency of the finding, this reviewer noted that the increased cancer risk has been observed in four cohorts and more recently some increased risk was observed in those with high exposure in the Seveso cohort study, according to an article to be released in an upcoming issue of the *American Journal of Epidemiology*.

– He added that the cancer mortality was shown to be dose-dependent, as the most highly exposed individuals within the four occupational cohorts have been found to have the highest cancer risks.

– This reviewer acknowledged that the findings of these studies are not well supported by biologic plausibility, though IARC provides several arguments on this issue. These arguments are summarized briefly in the bulleted item on modes and mechanisms of action, below.

Based on these arguments, this reviewer thought, limited epidemiologic evidence exists to support a causal association between dioxin exposure and increased cancer mortality. Another reviewer agreed that this evidence is compelling, particularly for the most highly exposed populations (MV).

- *Weaknesses of epidemiologic studies.* Following the presentation on the epidemiologic studies, summarized above, other reviewers identified potential weaknesses in the studies. Each identified weakness generated further discussion and debate. Opening this discussion, a reviewer noted that one of the occupational studies cited in the opening presentation (Fingerhut et al., 1991) has been updated (Steenland et al., 1999), and the updated study found a lower SMR (1.13) than reported in the original study (1.5) (BK). Clarifying this issue, Dr. Farland agreed that the update reported a lower SMR, but the update study continued to find a highly dose-dependent response, as illustrated by a plot of SMR versus exposure septile.

  Another issue discussed was bias in the occupational studies. One reviewer commented on two potential sources of bias (BK). First, he indicated that recall bias might have entered some studies, particularly the German studies, in which retired and elderly workers were reportedly asked to identify their former colleagues, including those who had died of cancer. (Another reviewer, who had reviewed the same studies, did not think the results were biased as suggested [AS]). Second, the reviewer questioned whether the studies were biased in their selection of comparison populations for calculating SMRs (BK). Giving an example of his

concern, he noted that comparing cancer mortality for an occupational cohort to the national average cancer mortality can yield considerably different findings than comparing cancer mortality for a cohort to the mortality experienced by individuals living in the vicinity of the cohort (BK). Thus, he wondered if the SMR for the four occupational cohorts combined might be biased by not comparing plant-specific cancer mortality to the mortality of the surrounding population. Another reviewer agreed with this argument in principle, but doubted that such a bias could possibly explain a 40% increase in all cancers for a relatively large occupational cohort (AS).

Some reviewers questioned whether the epidemiologic results might have been biased by lifestyle factors (e.g., smoking), especially given that a large portion of the identified cancer deaths were the result of lung cancer (BK,CP). One reviewer, for instance, thought nearly every cancer case in one of the occupational cohorts was due to lung cancer (Ott and Zober et al., 1996) (CP). Dr. Farland later clarified that lung cancer accounted for fewer than one third of the total cancers in this cohort. A reviewer added that, though he agreed that lung cancers were elevated among the highly exposed occupational cohorts, the SMR for all cancers in the four studies was comparable to that of just lung cancer (AS). In short, he stressed that the general increase in cancer mortality cannot be attributed solely to lung cancer.

The issue of biological plausibility was particularly troubling to one reviewer, who knew of no fundamental mechanism that could explain a general increase in all types of cancers (BK). Noting that no other chemicals, even the most potent known carcinogens, are believed to be promoters of all cancers, this reviewer stressed that no known mechanism supports the epidemiologic findings from the most highly exposed cohorts. Another reviewer agreed, and suggested that exposures to a wide array of occupational carcinogens might explain the general increased cancer mortality (MH). On the other hand, noting that many carcinogens (e.g., asbestos, benzene, vinyl chloride) are known to cause cancer at multiple sites and are suspected of causing cancer at others, one reviewer was not as troubled by a suggestion that one chemical might cause an increase in all cancers, without a pronounced increase in just one type of cancer (AS).

- *Comments on EPA's interpretation of the epidemiologic studies.* Two reviewers thought that including the results of low-exposure occupational cohorts with the results of highly exposed occupational cohorts weakens EPA's cancer characterization for dioxin and related compounds (BK,CP,AS). To give an example of this concern, one reviewer noted that apparent increases in cancer in low-exposure cohorts imply that highly exposed cohorts would experience dramatically higher cancer risks—a trend the data do not support (AS). In short, another reviewer noted, the findings from low-exposure cohorts taken with the findings from highly exposed cohorts do not suggest a dose-dependent cancer response (BK). Agreeing with this concern, another reviewer recommended that EPA list the various epidemiologic studies in the Integrated Summary, but only interpret those with well-documented, high

exposures to support the cancer characterization (CP). Finally, one reviewer suggested that EPA revise its interpretation of his epidemiologic study of New Zealand farmers to be more consistent with his conclusions (AS).

- *Comments on presentation of the epidemiologic studies in the Integrated Summary*. The reviewers suggested several ways EPA could improve the presentation of epidemiologic studies in the Integrated Summary. First, echoing an earlier comment, a reviewer said that presenting results of epidemiologic studies from low-exposure occupational cohorts alongside results from highly exposed cohorts ultimately weakens the analysis of human data in the Integrated Summary (CT). He and another reviewer suggested revising the Integrated Summary to focus only on the most highly exposed individuals (AS,CT). Second, another reviewer thought EPA could best summarize the epidemiologic studies in a table that lists the number of subjects, exposure levels, types of cancers observed, SMRs, and other key features of the studies (HHF). Third, one reviewer commented, adequate data support EPA's current cancer characterization, but the agency may need to bring more supporting information from earlier chapters in the reassessment to support its conclusion (PdF).

- *Integration of findings from human studies and animal studies*. When discussing results from the epidemiologic studies, the reviewers questioned whether the multi-site cancers observed in human studies are consistent with those observed in animal studies. One reviewer noted that every animal study he has reviewed has found positive associations between cancer incidence and dioxin exposure (PdF). Stressing that evidence of dioxin-related multi-site cancers has now been observed in various species of mammals, birds, fish, and shellfish, this reviewer thought dioxin may have a different mode of carcinogenic action than has been observed with chemicals studied previously. Another reviewer thought this type of evidence can be better conveyed in the Integrated Summary, possibly with a table that compares the dose-response relationship for cancers observed across the various animal and human epidemiologic studies (HHF).

  During this discussion, one reviewer focused on notable differences between dioxin-related cancers in animals and those in humans (BK). Specifically, he noted that a recent study has reported that humans may be 10- to 100-fold less sensitive to the carcinogenic action of dioxin than are rats (Aylward et al., 1996). Moreover, he noted that a widely cited study of rats found increases in liver cancer (Kociba et al., 1978)—a type of cancer that, he said, has not been notably increased in the human occupational cohorts. Another reviewer agreed that this particular study of rats might not be a good model of the types of cancer observed in humans who have been highly exposed to dioxins, which he thought was a compelling reason to base the cancer characterization on the human studies (AS).

- *Consistency of the cancer characterization with EPA's criteria*. The reviewers' discussion was hampered by the fact that EPA has not yet finalized its 1999 "Proposed Guidelines for

Carcinogenic Risk Assessment." Many reviewers wondered exactly what EPA's criteria were for characterizing cancer hazards in the Integrated Summary. Citing EPA's most recent guidelines, one reviewer indicated that the agency characterizes chemicals as carcinogens either when causal data are available for humans or when the following three criteria are met: carcinogenicity has been established in animal studies; "modes of carcinogenic action and associated key events in animals have been determined;" and "the same key events that precede carcinogenicity in animals have also been observed in exposed humans" (CP).

The reviewers' comments on whether these criteria are met for dioxin and related compounds differed: one reviewer did not think the cancer characterization met these three criteria (HHF); another reviewer thought EPA should include a table in the Integrated Summary that steps through these characterization criteria for dioxin (CT); and another reviewer thought the Integrated Summary already gives an overview of these criteria on pages 20 and 21 (CP), though he did not necessarily agree with the arguments presented.

- *Comments on the modes and mechanisms of action.* After reviewing EPA's latest criteria for cancer characterization, the reviewers discussed the extent to which information on the mode of carcinogenic action is available, though this discussion also considered information on mechanisms of carcinogenic action.

  Regarding mechanisms, one reviewer provided several arguments that great uncertainty remains as to the true mechanisms of carcinogenic action of dioxin and related compounds (CT). For instance, he noted that dioxin is not believed to be a strong initiator and therefore is believed to act through a promotional mechanism, though this mechanism has not been characterized. He added that some studies suggest that dioxin may be a negative promoter (i.e., it decreases cell proliferation at certain dose levels). Without knowing exactly how dioxin acts as a promoter, or whether cancer is an Ah-mediated response, he thought, EPA knows too little to base a cancer characterization on knowledge of mechanisms. Supporting this comment, another reviewer agreed that the mechanisms of carcinogenic action for dioxin are poorly understood, because researchers have yet to characterize the pathway of biochemical events to cancer (MV). Though not disagreeing with these comments, another reviewer stressed that researchers still do not know the mechanisms of action for even some of the most widely studied carcinogens (e.g., asbestos, cigarette smoke, vinyl chloride) (AS).

  Focusing on the modes of action, one reviewer commented on the extent to which researchers have characterized "key events" in how dioxin and related compounds may cause cancer (CT). He thought the Integrated Summary should document many key events in addition to activation of the Ah receptor in order to convey a greater understanding of the modes of carcinogenic action. For instance, he thought, a more compelling account of the mode of action would include information on activation of oncogenes, molecular level changes that affect the cell cycle, dioxin-related cell apoptosis, increased cellular proliferation, and other cellular changes.

In short, he thought the Integrated Summary needs to document much more information on modes of action to support the current cancer characterization. Though not disagreeing with these comments, another reviewer indicated that earlier chapters in the reassessment documents address many of the issues raised by the other reviewer (PdF).

The reviewers offered several recommendations for revising the Integrated Summary's discussions on mode of action, specifically as it relates to cancer characterization. First, one reviewer suggested that EPA create a table that clearly summarizes the various arguments regarding modes of carcinogenic action and key events in the cancer pathway (AS); another reviewer agreed, and suggested that the table also specify important data gaps (PdF). Second, one reviewer recommended that EPA refer to IARC's documentation of cancer classification, which includes a similar discussion on the current state of the science of mode of carcinogenic action (AS). Third, a reviewer thought the Integrated Summary should describe the distribution of Ah receptors across tissue types in various species, and explain how this might relate to the different types of cancers observed in the animal and human studies (LR).

- *Characterization for chemicals other than TCDD.* Noting that limited toxicologic and epidemiologic data exist for the dioxin-related compounds, some reviewers questioned the cancer characterization for these congeners (BK,CP,CR). One reviewer, for example, thought the cancer characterization should parallel IARC's cancer classification, which finds TCDD to be a known human carcinogen but does not have enough data on the other dioxins, furans, and dioxin-like PCBs to make a similar classification (CR). Another reviewer disagreed with this reasoning, primarily because IARC and EPA have notably different criteria for characterizing and classifying carcinogenicity (AS).

  Another reviewer thought a more appropriate characterization would consider three groups of congeners separately: congeners that have been widely studied (TCDD); congeners that have some toxicologic or epidemiologic data available (tetra-, penta-, and hexa-substituted dioxins and furans); and congeners for which few or no data are available (the remaining dioxins and furans and certain dioxin-like PCBs) (BK). Because limited information is available on many congeners, one reviewer thought the Integrated Summary should acknowledge the data gaps and clearly describe the basis for the cancer characterization in the absence of congener-specific information (CP). Given the concerns about congener-specific carcinogenicity, one reviewer found using TEQs to calculate cancer risks problematic (BK)—an issue the reviewers revisited when responding to charge question 12.

- *Other comments.* The reviewers raised several additional comments when discussing the cancer characterization of dioxin and related compounds. First, one reviewer thought the Integrated Summary should provide more detailed information on the apparent association between dioxin exposure and soft tissue sarcomas (MH). Specifically, he suggested the Integrated Summary specify what tissues are considered "soft tissues" and whether the Ah

receptor is found in them. Second, another reviewer thought evidence of the "anti-carcinogenesis" of dioxin should be included in the discussions of cancer characterization (LR). (One reviewer thought the Integrated Summary already addresses this issue [CP]). Finally, another reviewer noted that the issue of whether dioxin and related compounds are carcinogenic may be somewhat of a moot point to risk managers if noncancer endpoints are found to be more sensitive (RD). Other reviewers agreed with this argument in principle, but thought they should still thoroughly evaluate how the reassessment characterizes potential cancer risks.

The second charge question on cancer effects (charge question 11) asked the reviewers: "Does the document clearly present the evolving approaches to estimating cancer risk (e.g., margin of exposure and the LED_{01} as a point of departure), as described in the EPA "Proposed Guidelines for Carcinogenic Risk Assessment" (EPA/600/P-92/003C; April 1996)? Is this approach equally as valid for dioxin-like compounds?" The reviewers had various comments on the proposed margin of exposure approach for characterizing cancer risks. Most reviewers found the proposed approach acceptable, but some thought the Integrated Summary needs to explain in greater detail why other approaches are not used. The reviewers' specific comments on this issue follow:

- *Comments on the appropriateness of the margin of exposure approach.* Overall, one reviewer commended EPA's approach for estimating cancer risk as a "good job on a complex topic" (AS). Another reviewer found the proposed use of a margin of exposure approach acceptable for dioxin and related compounds (CP). He acknowledged that this is a rather new approach, but advocated the use of such approaches if they are supported by the available dose-response data. Another reviewer thought earlier chapters in the reassessment document adequately present the evolving approaches to estimating cancer risk and adequately defended EPA's use of the lower bound of the effective dose at the 1% response level (LED_{01}), but he did not think the Integrated Summary (see Chapter 5.1.1) succeeds in this regard (CT). To document the proposed approach more completely, he suggested, the Integrated Summary should describe the approach traditionally used to estimate cancer risk, explain how the ED approach differs from the traditional approach, and then explain why an LED_{01} was selected for the point of departure, as opposed to other possible choices (e.g., the LED_{10}, the ED_{01}, the ED_{10}).

  One reviewer thought the Integrated Summary did not provide a balanced account of the evolving approaches to estimate cancer risk (BK). As an example of his concerns, this

reviewer noted that EPA's 1996 cancer guidelines recommend the use of LED_{10} as a point of departure, though this recommendation is not mentioned or explored in the Integrated Summary. He was also concerned that EPA selected an approach without considering if it is consistent with the underlying mechanisms of action. A threshold dose-response approach, according to this reviewer, is more consistent with a receptor-based mechanism of action. He thought the Integrated Summary did not present or evaluate such an approach, or any other evolving approaches for estimating cancer risk.

- *Pros and cons of basing cancer risks on human data*. Referring to the weaknesses in the human epidemiologic data described earlier, one reviewer was surprised that EPA derived cancer risks from the human data, rather than the animal data (BK). He thought using animal data would be more consistent with the agency's derivation of cancer risks for many other chemicals. Another reviewer, on the other hand, commended EPA for deriving its point of departure estimate from human epidemiologic data, rather than from studies on laboratory animals (AS). He cited several reasons for doing so: results of rodent studies are often an extremely poor model for estimating cancer risks in humans; inter-species extrapolations between rats and mice have been shown to be highly uncertain, leaving questions about extrapolations to humans; and tumor classifications in laboratory animals can be inaccurate, considerably more so than in humans. Though he acknowledged that evaluating human data clearly involves uncertainties, he thought in this case that those uncertainties are far less than those involved in extrapolating cancer dose-response from laboratory animals to humans. This debate continued when the reviewers responded to charge question 12 (see below).

- *Comments on using a single human study for deriving cancer risks*. Three reviewers did not support EPA's use of the single epidemiologic study with the most conservative finding to derive its point of departure (BK,LR,AS). One reviewer found the approach somewhat arbitrary, and suggested that EPA derive a point of departure either from a meta-analysis of the four occupational cohorts with the highest exposures or from the one study found to be most robust and reliable, and not necessarily the one with the highest SMR (AS). Another reviewer agreed, noting that a more balanced approach would examine all available studies and derive the point of departure from the one found to be the strongest (BK). He suggested that EPA specifically consider an approach to evaluating cancer risks of dioxin documented in the literature (Aylward et al., 1996). Another reviewer added his concern about basing cancer risk assessment on the most sensitive human study (LR), and discussed his concern in greater detail when responding to charge question 12.

- *Comments on the proposed use of LED_{01} as a point of departure*. Two reviewers had specific questions about EPA's selection of the LED_{01} as a point of departure. First, though he acknowledged that the Integrated Summary makes a good case for using the 1% response level rather than the 10% response level for the point of departure, one reviewer did not think EPA adequately defended using the LED_{01} rather than the ED_{01} (LR). He thought use of the LED_{01}

introduced conservatism into the calculations, and suggested that EPA instead base the point of departure on the ED_{01} and quantify the uncertainties about that value. Second, one reviewer suggested that EPA call the point of departure the toxic dose at the 1% response level, or TD_{01}—a term he defined in an earlier publication (AS).

- *Suggested revisions to the Integrated Summary and other comments.* Two reviewers suggested specific revisions to the Integrated Summary to respond, in part, to the comments summarized above. First, one reviewer thought the Integrated Summary should specify all assumptions and show sample calculations to make the derivation of the point of departure more transparent (BK). Second, another reviewer thought EPA should consider an approach that he published on conducting "public health risk assessments" that account for general population exposures (AS). He said a reference to this approach can be found in his premeeting comments.

The third question on cancer effects asked the reviewers to: "Please comment on the presentation of the range of upper bound risks for the general population based on this reassessment. What alternative approaches should be explored to better characterize quantitative aspects of potential cancer risk? Is the range that is given sufficient, or should more weight be given to specific data sources?" The reviewers had many opinions on the upper bound dioxin-related cancer risks presented for the general population. Some reviewers were concerned that choosing dose metric, using potentially biased epidemiologic studies, and assuming linear dose-response might have led to an overstatement of upper bound risks. Some reviewers thought the range of upper bound risks (1 in 1,000 to 1 in 100) seemed unrealistically high, but others argued that this risk level would actually be virtually impossible to observe given the high cancer mortality rate for the general population. Revisions suggested by several reviewers included more clearly describing the derivation of the current cancer slope factor (CSF), explaining in detail why this CSF differs from previous estimates, and discussing the significance of the upper bound cancer risks to the public. These and other comments, suggestions, and recommendations are outlined below:

- *The need for more detail in explaining how EPA derived the CSF.* One reviewer thought the description of the derivation of the CSF in the Integrated Summary (pages 89–90) was too brief, and should clearly state exactly how the value was derived (HHF). Another reviewer

agreed, and added that the 1995 SAB review of the reassessment suggested that EPA make the CSF derivation more transparent, so that a reader can follow the derivation and reproduce the numbers (MH). A reviewer thought EPA could include more context on the latest CSF by comparing and contrasting it to slope factors derived from other studies (HHF). For instance, she wondered if the same dose observed to cause cancer in certain animals have been shown to cause similar effects in humans.

- *Comments on revisions to the CSF and the upper bound population risk.* Several reviewers thought the Integrated Summary should explicitly account for the factors that contributed to the roughly 10-fold increase in the CSF since the release of the earlier reassessment documents. One reviewer, for example, thought the Integrated Summary should explain what portion of the increase in the CSF can be attributed to using a different dose metric, basing the value on human studies rather than animal studies, and any other relevant factors (CT). He added that Chapter 5.2.1.2 (page 78) in the Integrated Summary would be a logical place for such information.

  Similarly, another reviewer was concerned that an uninformed reader might be confused by the higher estimate of upper bound cancer risk published in the current reassessment document, even though environmental releases of dioxin and related compounds and therefore human exposures to these chemicals are decreasing (HHF). She thought EPA could address this concern with minor revisions to the Integrated Summary.

- *Comments on potential biases from basing the CSF on the human epidemiologic data.* The reviewers differed on whether EPA should base the CSF on human epidemiologic studies or animal studies and on the potential implications of this decision. On one hand, a reviewer was surprised that EPA would base its CSF on human studies, given the uncertainties in the derivation, the level of scrutiny the human studies have received, and the potential biases in the human studies (BK). He thought this approach not only rests on a study of weak evidence of carcinogenicity in humans but also breaks a long tradition of deriving CSFs from highly controlled animal studies. Though not disagreeing that the human data have uncertainties, another reviewer argued that extrapolating CSFs from studies of laboratory animals is just as uncertain, if not more so (AS). As an example of his concern, this reviewer questioned the uncertainties introduced by laboratory studies, because these studies typically examine animals having only one genetic strain, living in highly controlled environments, and eating foods they might not typically eat otherwise. He added that tumors observed in studies in rodents often have no relevance to humans and that animal models in some cases actually underestimate the carcinogenicity of some toxins (e.g., effects of cigarette smoke on lung cancer). No other reviewers commented on this debate.

  One reviewer thought basing the CSF on the average SMR of an epidemiologic study involves an inherent statistical bias (CP). Specifically, he noted that the CSF for dioxin and related

compounds is derived from the average SMR observed in the entire cohort of a human study. He explained that this study-average SMR probably overstates the actual SMR for the least-exposed individuals in the cohort and understates the actual SMR for the most-exposed individuals—a trend he thought might cause EPA to overstate cancer risks for the general population (i.e., people exposed at levels considerably lower than in the occupational cohorts). He added that bias introduced by this approach is most pronounced when the distribution of doses is extremely broad and suggested that EPA consider using the SMR calculated for the least-exposed individuals in the occupational cohorts to estimate upper bound cancer risks for the general population. Another reviewer thought using such an approach would be assuming nonlinear dose-response for cancer risks (AS).

Revisiting responses to charge question 10, some reviewers had concerns about potential confounding effects in the human epidemiologic studies. Explaining this concern, one reviewer thought the epidemiologic data are useful for supporting the cancer characterization, but only in a qualitative fashion (CP). Using the epidemiologic data to derive CSFs, this reviewer argued, essentially attributes all cancer risk observed in the human studies to dioxin toxicity and none to potential confounding factors—an assumption he found particularly troubling given that occupational studies inevitably have many potential confounding factors, such as cigarette smoking and exposures to other chemicals. Another reviewer was less concerned about potential biases introduced by confounding factors (AS). He explained that one occupational study attributed only 4% of the increased cancer risks to cigarette smoking (Fingerhut et al., 1991), and he estimated that all confounding factors combined likely account for no more than 10% of the increased cancers observed in the human studies.

- *Concerns about contributions of non-TCDD congeners to upper bound cancer risks*. One reviewer had concern, and other reviewers echoed this concern later in the meeting, with basing the upper bound cancer risk estimate on TEQs (CT). His concern centered on the fact that TEQ calculations attribute cancer toxicity to dioxin, furan, and dioxin-like PCB congeners for which little toxicologic or epidemiologic data are available. As an example of his concern, this reviewer noted that all congeners with TEFs of 0.1, given the 10-fold increase in the CSF for TCDD, now essentially have CSFs equal to the one EPA previously used for TCDD. He thought the implications of this scenario are particularly troublesome, given that TCDD is often viewed as an extremely potent carcinogen.

- *Comments on the realism of the upper bound cancer risk and associated risk communication issues*. Some reviewers commented on whether the Integrated Summary's upper bound cancer risk estimates are realistic. First, one reviewer noted that the range of upper bound cancer risks (1 in 1,000 to 1 in 100) suggest that roughly 64,000 cancer deaths in the United States each year can be attributed to dioxin exposure—a conclusion she did not find realistic (HHF). Other reviewers suspected otherwise (AS,CT). One reviewer, for instance, noted that even a 1 in 100 increased cancer risk might be difficult to detect if the current cancer

mortality rate is 20 in 100 (CT). Another reviewer added that the upper bound cancer risk estimate would be quite difficult to observe in the population, even though the numbers seem very high (AS). To support his argument, this reviewer noted that roughly 15 years of research were needed to establish the 1 in 100 cancer risks for "passive smoking" and many occupational studies were needed to determine the apparent cancer risks associated with dioxin exposure. Given the significance of the range of upper bound cancer risks, reviewers suggested that EPA use arguments such as these to put the risk estimates into perspective (HHF,AS).

Another argument on the realism of the cancer risk estimates addressed the consistency between the risks to the general population and those to highly exposed occupational cohorts. Noting that the upper bound cancer risk estimate may be as high as 1 in 100, and that the highly exposed occupational cohorts have considerably higher doses of dioxin and related compounds, two reviewers thought a linear dose-response model would imply that a majority of the workers in these cohorts would have already died from cancer (HHF,CT). When asked to clarify this issue, Dr. Farland explained that the difference in exposure between the occupational cohorts and the general population—on a TEQ body burden basis—are within roughly an order of magnitude and therefore not as pronounced as might be suspected. To clarify this point, the reviewers thought the Integrated Summary should include some discussion on how the general population cancer risks compare to those observed in the highly exposed occupational cohorts.

Based on these concerns on perceptions of the upper bound cancer risk estimate, one reviewer suggested that EPA include text in the Integrated Summary to explain the implications of the risk estimates more clearly and to keep the document from sounding alarmist (HHF). She added that the current risk estimates might be very unsettling to the public and that some additional context is needed to put the reported values into perspective.

- *Suggestion that EPA calculate most likely cancer risk as well as upper bound cancer risk.* Some reviewers noted that EPA derived the CSF using several conservative assumptions, such as selecting the human study with the highest cancer risk, using a 1% response level instead of a 10% response level as a point of departure, and using an LED instead of an ED to calculate risks (CP,AS,MV). One reviewer thought EPA should not only present the upper bound risk estimate, but should also present a more realistic estimate of cancer risk that does not invoke the conservative assumptions (MV). Another reviewer agreed, noting that a more realistic estimate can be derived from a meta-analysis of the four occupational studies and using the ED_{01} for the point of departure, instead of the LED_{01} (CP). Revisiting a comment raised earlier, a third reviewer argued that EPA, when working with human studies, should not base its CSF on the most sensitive one (AS). He thought deriving CSFs from the most sensitive study is appropriate when only animal studies are available; however, in cases where human data are available, he advocated deriving CSFs from all epidemiologic studies combined.

- *Questions about the assumption of linear dose-response*. One reviewer disagreed with arguments in the Integrated Summary that reportedly support the use of linear dose-response models for cancer effects (MV). He thought the observation that certain biochemical effects exhibit linear dose-response behavior does not necessarily imply that cancer will do so as well. To illustrate his concern, he indicated that toxic responses of some chemicals do not follow a linear dose-dependent relationship, even though biochemical effects of the exposures may be linear. Specifically, he noted that carboxy-hemoglobin levels increase in a linear fashion with exposure to carbon monoxide, but a linear dose-response relationship is not observed for certain toxic effects (e.g., lethality).

- *Other comments*. The reviewers provided several additional comments when commenting on the upper bound cancer risks to the general population. First, one reviewer suggested that EPA consider using the highest achieved body burden as a dose metric for estimating cancer risks (AS). On the issue of dose metrics, another reviewer suspected that the apparent convergence of CSFs calculated for a variety of human and animal studies might be dependent on the dose metric selected and that use of other dose metrics might not reveal a dose-response relationship as consistent as reported in the Integrated Summary (BK). Second, one reviewer recommended that EPA review all sections describing how cancer risks, CSFs, body burdens, and average daily intakes have changed since previous releases of the reassessment documents; this reviewer suspected that some of the increases or decreases (e.g., "10-fold change") might not be cited accurately throughout the various volumes of the reassessment (LR).

2.8 Background and Population Exposures (Questions 13, 14, and 15)

The charge to the reviewers included three questions pertaining to background and population exposures to dioxin and related compounds. First, the charge asked: "Have the estimates of background exposures been clearly and reasonably characterized?" The reviewers gave consistently positive feedback on this question, with some suggestions for minor revisions and clarifications. An overview of their key findings follows:

- *Terminology*. Given that "background" implies "normal and acceptable," the reviewers found the term "background exposure" inappropriate for exposure to dioxin and related compounds. They recommended that EPA instead use other terminology, possibly "ambient exposure" or "general population exposure."

- *Comments on levels of dioxin in food*. One reviewer thought EPA's summary of dioxin levels in food sources was a significant improvement over the data presented in earlier releases

of the reassessment (MP). Specifically, she noted that EPA used results from statistically based surveys to comment on dioxin levels in beef, poultry, milk, and dairy; also acknowledging that data on dioxin levels in fish and eggs are limited. This reviewer thought Table 4-6, which summarizes the levels of dioxins in food, should either include additional data (e.g., the number of samples collected, the range of measured concentrations, and so on) or refer to the sections in earlier chapters of the reassessment that present this information.

One reviewer identified two sources of dioxin in food that were not included in the Integrated Summary (CR). First, he noted that a graduate thesis published data on dioxin levels in fish oil—a food source used by industry to prepare other foods, such as hamburgers. Second, he added that he has reported fish tissue concentrations for farm fish collected from the southern states. This reviewer thought information on these foods should be included in the document, since prepared foods and farm fish may be sold widely in the United States. One reviewer made a final comment: some information presented in earlier chapters of the reassessment relevant to dioxins in food (e.g., effects of cooking practices) is important to include in the Integrated Summary (MP).

- *Comments on contact rates*. One reviewer commented that the Integrated Summary's data on contact rates are defensible and acceptable (MP). She explained that the data currently reported are now based on 3-day dietary surveys conducted by the U.S. Department of Agriculture—an improvement, she thought, over the 1-day surveys that previously formed the basis for contact rates. She added that the contact rates for beef, pork, poultry, fish, egg, water, soil, and air are appropriately based on current data summarized in the most recent release of EPA's Exposure Factors Handbook.

- *Comments on average daily intake*. Given that EPA presented quality data on dioxin levels in food and contact rates, one reviewer had confidence that the reported average daily intakes were reasonable (MP). This reviewer thought Table 4-8 in the Integrated Summary should include more quantitative information from earlier chapters in the reassessment documents, such as the range and quartiles of estimated intakes. Another reviewer agreed, and suggested that presenting probability distributions for estimated intakes would provide the best perspective on the variability in ambient exposures (HHF). Two reviewers noted that the Integrated Summary has minor inconsistencies in the intake levels (and body burdens) it lists; they suggested that EPA identify and correct these (CP,CT).

- *Expanding on statements that dioxin levels in food and intakes are decreasing*. One reviewer thought EPA not only should state that body burdens and dioxin levels in food are going down, but should also attempt to characterize the rate of these decreases, if adequate data are available for doing so (AS). He stressed that the rates at which dioxin levels are decreasing in the environment may be important considerations for future risk management actions. Other reviewers commented that information on the rate of decrease of dioxin

emissions, dioxin body burdens in selected European and New Zealand populations, and dioxin levels in Baltic salmon and piscivorous birds have all been published (CP,CR,AS), but they were unsure if data are adequate to permit comment on the rate at which dioxin body burdens are decreasing in the U.S. population.

The second question on general population exposures asked: "Has the relationship between estimating exposures from dietary intake and estimating exposure from body burden been clearly explained and adequately supported?" The reviewers thought EPA derived adequate approaches to estimating average daily dose from both dietary intake and body burden. They thought the Integrated Summary needed only minor revisions to make these approaches more transparent. The reviewers' discussions and specific recommendations on this topic follow:

- *Need for definitions and minor clarifications.* A reviewer suggested that the Integrated Summary include a clear definition of body burden and explain how the body burden relates to tissue levels of dioxin (MP). One reviewer suggested using the term "body concentration" instead of "body burden" (AS). To clarify how average daily dose relates to dietary intake and body burden, reviewers suggested, the Integrated Summary should include equations and sample calculations. One reviewer suggested that the Integrated Summary also document the assumptions made when estimating dose from dietary intake or body burden (MP). Examples of such assumptions include the average lipid content and half-life of dioxins.

- *Comments on data presented on body burdens in the population.* None of the reviewers took exception with the data EPA presented on dioxin body burdens measured in the population. However, one reviewer questioned whether EPA could have cited additional data in the Integrated Summary when discussing how dioxin body burdens have changed with time (MP). Because the Integrated Summary does not document the criteria EPA used to select and reject studies that have measured body burdens, this reviewer was not sure why the agency did not consider some data sets she thought were relevant. For instance, this reviewer noted that the National Human Adipose Tissue Survey (NHATS) has shown a decrease in dioxin and furan levels in cadavers between 1982 and 1987. She also noted that the California Air Resources Board commissioned a study in the 1980s to determine average levels of dioxin and furan in tissues of individuals who were admitted to hospitals for surgeries not related to cancer. This reviewer thought comparing the results from these various studies, possibly in a table, would be useful. When asked to comment on these issues, Dr. Dwain Winters (EPA) noted that NHATS was not a statistically based survey. Due to the National Academy of Sciences'

criticisms of the survey, EPA decided not to rely on the data for information on long-term trends in body burden levels.

- *Comments on variability in the average daily intake.* Several reviewers thought the Integrated Summary could present more information characterizing the variability in the distribution of average daily intakes (HHF,AS,CT). Specifically, they wondered how EPA defends the statement that the upper range of ambient exposures may be three times higher than the reported average daily intake. For instance, one reviewer thought such statements should be supported by more specific descriptions (e.g., "the 99th percentile exposure is believed to be three times higher than the mean exposure") (AS); another reviewer thought the Integrated Summary should include a table showing the assumed distribution of average daily intakes (CT). One reviewer, on the other hand, thought the Integrated Summary already presented sufficient information on the assumed variability of exposures and how it was derived (CP).

  Some reviewers eventually asked EPA to clarify how it characterized the variability in exposures. Dr. Winters explained that the distribution of average daily intake is based on the known distribution of daily fat consumption. That data set, according to Dr. Winters, suggests that the 99th percentile of the fat consumption distribution is roughly three times greater than the mean consumption level. One reviewer questioned whether the variability in fat consumption should be viewed as a surrogate of the variability in the average daily intake of dioxin, noting that the concentration of dioxin in various food types also varies (AS). Dr. Winters agreed in principle, but indicated that the concentration of dioxin in the fat that people eat from the commercial food supply is not nearly as variable as one might expect, largely because the United States has a highly distributed food supply. Dr. Farland added that the variability observed in the limited body burden data currently available is very consistent with the variability in fat consumption rates.

The third question on general population exposures asked: "Have important 'special populations' and age-specific exposures been identified and appropriately characterized?" The reviewers thought EPA identified important "special populations" of highly exposed individuals, and suggested that the agency consider including others. The reviewers felt that exposures to the identified populations were not thoroughly characterized, largely because sparse data are available for doing so. Some reviewers gave references for additional data to consider when characterizing exposures to special populations, and several thought the Integrated Summary should more prominently acknowledge the current lack of extensive information as an important data gap. An overview of the reviewers' comments on special populations follows:

- *General comments.* The reviewers agreed that the special populations identified in the Integrated Summary—nursing infants, subsistence farmers, people who consume large quantities of fish from contaminated sources, occupational cohorts, and others—are likely to have increased exposures to dioxin. The reviewers suggested that EPA consider adding to this list people with rapid weight loss (RD), fetuses (HHF), and people who eat large amounts of potentially contaminated food sources not explicitly considered in the reassessment (e.g., lamb) (CR).

  The reviewers offered several other general comments and suggestions: one reviewer noted that the Integrated Summary does not identify smokers as a special population, even though earlier chapters in the reassessment documents do (MP); another thought workers with low levels of exposure (e.g., phenoxy herbicide sprayers) should not be included in the special populations (AS); and another suggested that the Integrated Summary indicate that other special populations may still be identified (PdF). At the end of the discussion, one reviewer suggested that the Integrated Summary should present data on age-specific body burdens, if available (MV). He thought such data are needed as a reference for identifying special populations.

- *Comments on fish consumption.* Much of the reviewers' discussion on special populations addressed EPA's characterization of subsistence or recreational fishers who regularly consume fish from contaminated sources. For instance, one reviewer thought the Integrated Summary should have cited the results of many studies in addition to that conducted on fishers in the Great Lakes region (MP). She suggested that EPA should compile data from all relevant studies of dioxin in fishing populations into a summary table, though, she added, such a table might be more appropriate for earlier chapters in the reassessment documents. One reviewer suggested that EPA consider adding body burden data recently reported for cohorts of fisherman in Finland to the Integrated Summary (Kiviranta et al., 2000) (MV). He noted that some tissue levels observed in these cohorts were comparable to those observed among people exposed to dioxins during the Seveso incident. Another reviewer agreed, and suggested that EPA consider including data compiled on cohorts of fishermen on the west and east coast of Sweden (CR).

  During this discussion, one reviewer was concerned that studies conducted to date might not have characterized exposures to all of the highest fish consumption groups in the United States (PdF). As an example of his concern, this reviewer noted that fishers in states along the Gulf of Mexico consume a wide variety of species from local waters throughout the year. Noting that this population, and perhaps many others, have yet to be adequately characterized, this reviewer thought the Integrated Summary should more prominently acknowledge that other special populations may exist. Another reviewer agreed, and thought the Integrated Summary

should specify the data gaps and research needs for identifying and characterizing all special populations (MP).

2.9 Children's Risk (Question 16)

One charge question addressed the issue of children's risk of dioxin exposure. It asked: "Is the characterization of increased or decreased childhood sensitivity to possible cancer and noncancer outcomes scientifically supported and reasonable? Is the weight of evidence approach appropriate?" Summarizing the premeeting comments, the primary reviewer for this question suggested that the reviewers generally had a favorable impression of the presentation of children's risk in the Integrated Summary. The issue of greatest concern was whether EPA selected an appropriate dose metric for evaluating this risk. A summary of the reviewers' discussion on this and other issues follows:

- *Concern that the selected dose metric (body burden) is inappropriate for evaluating children's risks.* Several reviewers raised concern about whether the dose metric adopted in the Integrated Summary (body burden) is appropriate for evaluating children's risks. Noting that children's body burdens are typically lower than those of adults, yet children's (especially nursing infants') doses are often higher than those of adults, one reviewer thought the use of body burden as a dose metric is inappropriate for evaluating children's risk (HHF). Though he did not disagree, another reviewer added that daily dose is also an inappropriate dose metric for children, given that nursing infants likely have exposures considerably higher than the ED_{01} for various noncancer effects (AS). This reviewer thought the dose to the target site might be the most important dose metric for evaluating children's risks. Another reviewer said peak plasma concentrations at critical stages of organogenesis or tissue development have been shown to be the most reliable indicator of toxicity for other developmental toxins (MH).

  One reviewer thought the Integrated Summary could present additional information on the pharmacokinetics of dioxin and related compounds in children to put the issue of dose metric into perspective (BK). He noted that a recent study identified three mechanisms explaining why children's body burdens of dioxin and related compounds may be lower than estimates from exposure levels imply: children have less efficient absorption of fatty materials from their gut than do adults, children excrete relatively higher amounts of fatty materials than do adults, and children's rapid growth and shifts in relative amounts of adipose tissue can skew their body burdens. Judging from his review of this and other studies, this reviewer thought peak or AUC blood concentrations of dioxin and related compounds would be the most appropriate metric of absorbed dose for children.

Though they did not agree on an appropriate exposure dose for evaluating children's risks, the reviewers did agree that the Integrated Summary needs additional discussion on the uncertainties associated with using various dose metrics to evaluate children's risks (HHF,BK). They also suggested that EPA highlight the issue of developing approaches to evaluate children's risk as a research need.

- *Comments on whether children are most sensitive to dioxin than are adults.* Agreeing with the conclusions in the Integrated Summary, several reviewers commented that not enough information is available to indicate whether children are more or less sensitive than adults to dioxin-related health effects (RD,HHF,AS). Expanding on this comment, one reviewer noted that the Integrated Summary correctly states that children (primarily nursing infants) have higher exposure doses than adults and therefore can be assumed to have greater risks, but he stressed that research has yet to establish that children have increased or decreased sensitivity to dioxins for any endpoint (RD). One reviewer thought the Integrated Summary could have reached this conclusion with a much shorter section on children's risk (AS), but another reviewer suggested that a longer section on this topic is necessary given heightened sensitivity on children's health issues (HHF). Regardless of the level of detail, another reviewer thought the Integrated Summary should stress that the current lack of information on children's sensitivity as a data gap and identify associated research needs (MV).

- *Suggestions of other studies for EPA to consider.* The reviewers suggested that EPA review the findings of three studies to provide additional perspective on children's exposures and risks. First, one reviewer suggested that the Integrated Summary incorporate the findings of the various Dutch studies that have been published to date (MV). Another reviewer, however, cautioned EPA against weighing these studies too heavily in the hazard characterization, given his concern about uncertainties in the results and the possibility that confounding factors might account for some of the observed effects (AS). Second, a reviewer recommended that the Integrated Summary present findings from a study he conducted on how body burdens of dioxins and related compounds in nursing infants relate to breast milk concentrations and the duration of breast feeding (Smith, 1987) (AS); he thought the results of this study might be an important consideration in the debate about appropriate dose metrics. Third, another reviewer recommended that EPA include the results of a 1999 publication by La Kind (full citation not provided) that suggests that body burdens in nursing infants are often lower than estimates (CP).

- *Comments on in utero exposures and effects.* Given that dioxin and related compounds can transfer from mother to fetus via the placenta, one reviewer thought the Integrated Summary should include greater discussion on *in utero* exposures and associated effects, though she acknowledged that few if any studies have extensively investigated this issue (HHF). Another reviewer added that *in utero* exposures may be particularly important if they occur during

critical windows of organogenesis or tissue development (PdF). He thought the lack of information on this issue should be noted as a data gap.

2.10 Relative Risks of Breast Feeding (Question 17)

The charge to the reviewers included one question on the relative risks of breast feeding, which asked: "Has EPA adequately characterized how nursing affects short-term and long-term body burdens of dioxins and related compounds?" The primary reviewer for this charge question noted that the Integrated Summary presents estimates of daily intake and body burden for nursing infants and non-nursing infants and indicates that the differences in body burden cannot be distinguished once children reach age 10. In that sense, he thought the Integrated Summary adequately characterizes how nursing affects short-term and long-term body burdens of dioxin and related compounds. He and the other reviewers had two specific comments on this issue:

- *The need to address the noncancer health implications of nursing.* One reviewer thought the Integrated Summary should not only describe how nursing affects long-term body burdens of dioxin and related compounds, but also comment on the health implications of nursing (CT). He thought the Integrated Summary presented a reasonable argument that cancer risks associated with nursing are likely low, because the long-term body burdens of nursing and non-nursing infants are similar and because dioxin is believed to act via a promotional mechanism. This reviewer was concerned, however, that the Integrated Summary does not adequately address the issue of potential noncancer effects as a result of nursing. Given that body burdens of nursing infants are roughly four times higher than those of non-nursing infants, he thought a case could be made that the increased risk of noncancer effects among nursing infants is low. He thought this case is strengthened by hypotheses that the most sensitive noncancer endpoints might be linked to *in utero* exposures. Regardless of the actual argument presented, this reviewer recommended that EPA include in the Integrated Summary some information on the noncancer health implications of breast feeding.

- *Suggestions on presenting more detailed information on the time-dependence of children's body burdens.* Though the reviewers agreed that the Integrated Summary currently presents some general information on how body burdens of dioxin and related compounds differ between nursing and non-nursing children, several reviewers suggested that this document include more information on the subject (BK,CP,AS). One reviewer, for example, recommended that EPA copy a plot showing how body burdens vary with age for nursing and non-nursing infants from earlier chapters in the reassessment documents to the Integrated

Summary (CP). Another reviewer suggested that EPA compare its estimates of body burdens in nursing infants with modeling results he has published in the literature (Smith, 1987) (AS). Noting the difficulties associated with modeling body burdens, however, another reviewer recommended that the Integrated Summary present data from a study of how adipose levels of dioxin and related compounds changed with age among a group of infants in Germany (Kreuzer et al., 1997) (BK). He thought EPA should compare the observed changes in body burdens to the age-dependent body burdens predicted by models. One reviewer added that this section should clearly indicate which congeners account for the largest proportion of TEQs in breast milk (CR).

2.11 Risk Characterization Summary Statement (Questions 18 and 19)

During their final discussions, the reviewers discussed at length the risk characterization summary statement in the Integrated Summary. They addressed the two charge questions on this topic simultaneously. These questions asked: "Does the summary and analysis support the conclusion that enzyme induction, changes in hormone levels, and indicators of altered cellular function seen in humans and laboratory animals, represent effects of unknown clinical significance, but they may be early indicators of toxic response?" and "Has the short summary statement in the risk and hazard characterization on page 107 adequately captured the important conclusions, and the areas where further evaluation is needed? What additional points should be made in this short statement?"

The reviewers agreed that the risk characterization summary statement is a critical section of the Integrated Summary, because some readers may read only this section and because the media is more likely to quote this section than other sections in the reassessment documents. Given this concern, the reviewers stressed the importance of having a clear, specific, factual, objective, unbiased, quantitative (where possible), and unambiguous risk characterization summary statement. Some reviewers added that the summary statement should be "more factual and less speculative."

Though they acknowledged the challenges of condensing the findings of the reassessment into a brief statement, the reviewers generally felt that EPA needs to clarify and strengthen the current version of the summary statement. The nature of the suggested improvements varied from reviewer to

reviewer. Some reviewers thought EPA needs to make significant revisions to correct the tone and content of the summary statement (i.e., substantial revisions), but other reviewers thought the main task EPA faces is carefully rewording this part of the Integrated Summary (i.e., stylistic revisions). A detailed summary of the reviewers' specific comments follows:

- *Concerns about the implication that adverse effects are associated with ambient exposures to dioxin and related compounds.* The reviewers discussed at length how the risk characterization summary statement describes health risks associated with ambient exposures to dioxin and related compounds, and several reviewers thought EPA needs to clarify the existing summary statement to avoid overstating dioxin-related risks (HHF,BK,CP,CT). The reviewers' comments on this issue centered on two topics: the distinction between biochemical changes and effects of clinical significance and the inconsistency between effects occurring at ambient exposure and the apparent absence of effects in highly exposed occupational cohorts.

  As one example of their concern, the reviewers took exception to a quote in the risk characterization summary statement (page 107): "Some of these effects may be occurring in humans at general population background levels and may be resulting in adverse impacts on human health." Several reviewers disagreed with this statement, as described below; and most reviewers agreed that statements such as this are open to various interpretations. One reviewer was troubled by the implication of health risks resulting from ambient exposures to dioxin and related compounds for a couple of reasons (HHF). First, she thought the summary statement should state clearly what type of effects are believed to be occurring, because she did not think the Integrated Summary should attribute too much weight to effects of unknown clinical significance, such as increased GGT levels. Second, she argued that the implication of adverse effects associated with ambient exposures seems to contradict the findings of the epidemiologic studies—an inconsistency she thought was highlighted by another quote in the summary statement: "There have been a few human cohorts identified with TCDD exposures high enough to raise body burdens significantly over background levels, and when these cohorts have been examined, relatively few clinically significant effects were detected" (pages 85–86).

  Some reviewers agreed with these comments and added, in short, that EPA did not make an adequate case for concluding that adverse effects might be associated with ambient exposures (BK,CP). These reviewers had several concerns: they thought the summary statement should specify exactly what "adverse impacts on human health" EPA expects will occur from ambient exposures. One reviewer explained further that EPA needed to present more convincing arguments on the mechanisms of action and greater understanding of how various dose metrics affect dose-response interpretations to support its theory of continuum of effects (i.e., that biochemical changes may be an early indicator of a toxic response) (BK).

Two reviewers had different perspectives on this issue (PdF,AS). Given the body burdens of dioxin and related compounds that have been shown to be associated with adverse effects in animals, these reviewers found it conceivable that humans at the highest end of the body burden distribution could have exposures consistent with points of departure derived from the animal studies. They were not sure, however, if EPA was basing its summary statement on this logic.

- *Comments on presentation of animal vs. human data, biochemical vs. other effects, and toxicity of TCDD vs. toxicity of other congeners.* Based on the reviewers' questions about the health implications of ambient exposures, two reviewers thought EPA should revise the risk characterization summary statement to distinguish important factors that affect the overall conclusions (BK,CT). Echoing comments raised during responses to other charge questions, these reviewers thought the summary statement should clearly distinguish conclusions based on animal studies from those based on human studies; and one reviewer added that EPA's conclusions should clearly distinguish health effects that are biochemical changes from those that are frank manifestations of toxicity and the conclusions should clearly distinguish the toxicity of TCDD from the toxicity of other congeners.

- *Suggestions that the wording in the summary statement be clearer, more specific, and more precise.* Apart from their comments on the technical content of the risk characterization summary statement, most every reviewer recommended that EPA revise the wording in this section to be as clear, specific, and precise as possible. Regarding specificity, two reviewers reiterated an earlier suggestion that EPA indicate in the summary statement exactly what kinds of dioxin-related effects are believed to be associated with ambient exposures (HHF,AS). Another reviewer noted that many terms used in the summary statement (e.g., "likely," "near," and "very high") are subjective and should be replaced with more precise terms (e.g., "order of magnitude" or "three times higher"), to the extent possible (AS). The reviewers had other recommendations for how EPA could improve the wording of the summary statement: using more caveats that caution the reader about findings that are highly uncertain (BK); including language in the final cancer characterization that is consistent with the agency's current guidelines (BK), and ensuring the conclusion statements in the summary statement are consistent with the main findings of earlier versions of the reassessment (CP).

  As an example of concerns about the wording in the summary statement, the reviewers had differing opinions on how to interpret a sentence discussed earlier: "Some of these effects may be occurring in humans at general population background levels and may be resulting in adverse impacts on human health" (page 107). One reviewer thought this sentence was based on findings earlier in the reassessment that biochemical effects of unknown clinical significance (and not all effects) might be associated with exposures at or near ambient exposures (and not necessarily at general population background levels) (CP). Though he acknowledged that the differences between "at" and "at or near" and "these effects" and "biochemical effects" might seem minor, this reviewer thought these distinctions are important to make to convey an

understanding of dioxin toxicity to the reader. Though some reviewers questioned the accuracy of a statement that ambient exposures are associated with dioxin-related effects, one reviewer noted that the sentence of concern says that ". . . effects may be occurring . . .", which is different from saying ". . . effects are occurring . . ." (AS). Nonetheless, given the reviewers' concerns, several suggested that EPA carefully revise the summary statement to strengthen and clarify findings that are unclear and open to interpretation.

- *Proposed alternate language for the summary statement*. When discussing the language EPA should use in the risk characterization summary statement, two reviewers provided examples of alternate language the agency should consider when revising the Integrated Summary (CP,AS). One reviewer thought EPA should focus on identifying findings the agency can state with confidence and clearly stating uncertainties (CP). He thought the following summary statements might be more appropriate for the risk characterization:

  – "TCDD is highly toxic to many animal species across a variety of cancer and noncancer endpoints."

  – "Other 2,3,7,8-substituted dioxins and furans are expected to have similar effects, albeit at different doses and with different degrees of uncertainty."

  – "There is no reason to expect, in general, that humans would not be similarly affected at some dose."

  – "Based upon the animal data, current margins of exposure are too low, especially for more highly exposed populations."

  – "The human data base is less certain. Occupationally and accidentally exposed cohorts exposed at higher levels show correlations with exposure, albeit inconsistently."

  – "The human data, in general, do not contradict the animal data."

  – "There is uncertainty as to the distinction between biochemical changes and adverse effects."

  – "Releases to the environment from sources that have been characterized have decreased significantly over the last decade and are expected to continue to decrease, but other sources are still poorly characterized."

  The one reviewer who commented on these proposed summary statements thought they, too, could be more specific and better tied to the data that form the basis of EPA's conclusions (AS). He added that the summary statements listed above do not include any characterization

of carcinogenicity—an issue he thought could be summarized least ambiguously with a statement like: "Using best available estimates of cancer risks, the [upper bound general population] risks might be on the order of 1 in 1,000 to 1 in 100, and EPA has traditionally sought to have cancer risks be no higher than 1 in 100,000." He thought the agency could make a similar statement about noncancer outcomes by listing the specific effects of clinical significance observed in animals at low doses (e.g., reduced sperm production, immunosuppression, endometriosis), comparing general population body burdens to the body burdens in animals believed to be associated with these effects, and adding that EPA traditionally seeks to have human exposures at least one or two orders of magnitude lower than the doses observed in animals to generate the most sensitive effects.

- *The need for more quantitative information in the summary statement.* The reviewers had differing opinions on the extent to which quantitative information is available on noncancer endpoints. One reviewer noted that the only quantitative information presented in the risk characterization summary document is for cancer endpoints (BK). He thought the absence of quantitative information on noncancer endpoints (i.e., an RfD) suggests that EPA will focus future risk management decisions on only the cancer endpoint, under the assumption that such an approach would also protect against dioxin-related noncancer effects. Other reviewers disagreed, noting that EPA's derivation of points of departure and margins of exposure was a quantitative treatment of noncancer risks (PdF,CP).

- *Comments on the implications of the selected dose metric.* When evaluating the risk characterization summary statement, three reviewers revisited an earlier debate on the implications of the dose metric (i.e., body burden) EPA selected for the reassessment. One reviewer thought the summary statement should acknowledge that analyses of dose-response based on dose metrics other than body burden might lead to different conclusions (MH). Reviewing an earlier finding that blood concentrations of dioxin and related compounds are proportional to body burdens, another reviewer wondered what dose metrics could lead to different results (CT). Two reviewers suggested that using peak blood concentrations or AUC blood concentrations, rather than just a one-time measure of blood concentration (or body burden), might be more appropriate for modeling dose-response (MH,BK).

- *Other comments.* The reviewers offered several additional comments on the content of the risk characterization summary statement. For instance, one reviewer thought EPA should integrate findings from ecotoxicologic studies into the summary statement (PdF) (see Section 2.13 for additional detail on this comment). Further, another reviewer thought the summary statement should provide more detailed information on exposures and body burdens for nursing infants (AS). Another reviewer thought the final summary statement (on page 107) should address the carcinogenicity characterization, the upper bound cancer risks at ambient exposures, and health implications of breast feeding (CT).

2.12 Sources (Question 20)

The charge question on the inventory of dioxin sources asked the peer reviewers: "Are these sources adequately described and are the relationships to exposure adequately explained?" When responding to this question, several reviewers commended EPA on its efforts in compiling the inventory (CP,CR,CT). These reviewers noted that the agency will likely continue to revise and update the inventory as new information becomes available, and they provided only minor comments on the topic:

- *Comments on sources of air emissions*. Referring to his own and other reviewers' premeeting comments, the primary reviewer for this charge question listed several comments on estimates of air emissions in EPA's inventory of dioxin sources (CR). First, this reviewer suspected that dioxin emissions from municipal solid waste incinerators have continued to decrease since 1994, the most recent year for which EPA has estimated emissions from this source. He suggested that the Integrated Summary acknowledge that current dioxin emissions from municipal solid waste incinerators are likely lower than the inventory reports. Second, this reviewer suggested that EPA carefully revise text in the Integrated Summary regarding how polyvinyl chloride (PVC) in municipal solid waste affects dioxin emissions from municipal solid waste incinerators. He noted that his own research has shown that the presence of PVC has little effect on dioxin emissions from incinerators, primarily because municipal solid waste typically includes other chlorine donors. Third, this reviewer recommended that the Integrated Summary more prominently acknowledge the fact that landfill fires and backyard barrel burning, combined, account for more air emissions of dioxin than any other source identified in the inventory—a finding he thought had important implications on future risk management decisions. Fourth, noting that source tests on sintering plants in Europe have found dioxin emissions to be highly dependent on process temperature and chlorine content in the feed, this reviewer questioned EPA's estimates of air emissions from sintering plants, because no information was provided on either process temperature or chlorine content for the two facilities tested in the United States. Finally, this reviewer was concerned that EPA has not quantified emissions from primary magnesium production facilities, particularly because two of the three U.S. facilities in this source category use the same industrial process as a magnesium production facility in Norway that has been found to produce extremely high dioxin emissions.

- *Comments on releases of dioxin to land*. One reviewer suspected that EPA overestimated the amount of dioxin releases to land in 1994 as a result of land application of municipal wastewater treatment sludge (CR). This reviewer presented the original data used in the release estimate, which were collected from a land application site in Billerica, Massachusetts. He then showed that a release estimate derived from the mean sampling result is considerably different than the estimate derived from the median sampling result. He eventually suggested

that EPA reevaluate the data for this source category and consider using the median of the sampling results to derive an annual release estimate.

- *Discussion on whether modeling can be used to fill data gaps.* Noting that emissions estimates for roughly two thirds of the source categories in the inventory are based on a limited number of measurements, one reviewer wondered if EPA should have relied more heavily on models to estimate emissions from source categories that have not been extensively characterized (HHF). Though they agreed in principle that models can be used to estimate air emission rates from measured ambient air concentrations or soil concentrations, two reviewers found these types of modeling exercises to be highly uncertain, sometimes inaccurate, and therefore not appropriate for the inventory of dioxin sources (CP,CR).

2.13 General Comments (Question 21)

At the end of the meeting, the reviewers were asked to: "Please provide any other comments or suggestions relevant to the two review documents, as interest and time allow." The reviewers commented on three issues when responding to this question. First, one reviewer thought incorporating findings from ecotoxicologic studies of dioxin-related effects on wildlife would strengthen the evidence for dioxin toxicity in animals, and by inference, in humans (PdF). He thought the wildlife literature has a much larger volume of information on congeners that have not been studied extensively in laboratory animals and humans. Another reviewer supported this suggestion in principle, but cautioned EPA about basing firm conclusions on toxicity observed in non-mammalian wildlife (e.g., birds and fish) (BK).

Second, noting that nonlinear dose-response models may be more appropriate for characterizing receptor-based mechanisms, two reviewers thought EPA should justify its decision for using linear dose-response models, and consider using nonlinear models, to characterize dioxin toxicity (BK,MV). Other reviewers were not convinced that nonlinear models would be an improvement to the reassessment (PdF,AS). One of the meeting co-chairs suggested that the debate on the utility of linear and nonlinear dose-response models was beyond the scope of this peer review (CP).

Third, one reviewer thought the Integrated Summary should include a figure that illustrates how dioxin and related compounds distribute within various tissue types in humans (RD).

3.0 REVIEWERS' OVERALL RECOMMENDATIONS

After answering the charge questions, the reviewers, as a group, listed the topics they thought were most critical for EPA to consider when completing the reassessment. The reviewers did not prepare summary statements for these topics, but rather suggested that EPA refer to the record of discussion (i.e., Section 2 of this report) for specific suggestions, comments, and recommendations. The reviewers' identified the following topics as being of greatest concern for finalizing the Integrated Summary:

- Characterization of TCDD as a "human carcinogen" and related compounds as "likely human carcinogens"
- Validity of the range of cancer risk in the general population (i.e., 1 in 1,000 to 1 in 100) posed by ambient exposures to dioxin and related compounds
- Characterization of dioxin exposure levels at which noncancer effects are likely to occur and identification of specific noncancer effects expected to occur at ambient exposures
- The need for a distinction between dioxin-related effects of unknown clinical significance (e.g., biochemical changes) from effects with clinical manifestations of toxicity
- The need for more detail on what is known, and not known, about congener-specific toxicity
- Additional clarification on how various dose metrics (e.g., body burden, tissue levels, daily intake, and so on) differ; justification for the use of body burden, as opposed to other measures, as a dose metric; and greater discussion on how pharmacokinetic modeling is used to estimate body burdens from daily exposures

In addition to the aforementioned topics of concern, the reviewers made numerous comments, suggestions, and recommendations throughout the workshop. The following suggestions were made during responses to multiple questions: EPA should use more tables to display results of studies and compare results of multiple studies on similar topics; EPA should discuss in greater detail how key decisions were made, including justification for why alternative approaches were not selected; and EPA

should consider including a new section in the Integrated Summary that states the various limitations, data gaps, and uncertainties in the current knowledge base on dioxin and identifies key research needs.

4.0 REFERENCES

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APPENDIX A

LIST OF EXPERT PEER REVIEWERS

APPENDIX B

CHARGE TO EXPERT PEER REVIEWERS

APPENDIX C

PREMEETING COMMENTS, ALPHABETIZED BY AUTHOR

APPENDIX D

LIST OF REGISTERED OBSERVERS OF THE PEER REVIEW MEETING

APPENDIX E

AGENDA FOR THE PEER REVIEW MEETING

APPENDIX F

OBSERVER COMMENTS