United States Environmental Protection Agency
Science Advisory Board Washington, DC
EPA-SAB-EHC-99002 November 1998
www.epa.gov/sab

AN SAB REPORT: REVIEW OF THE RfC METHODS CASE STUDIES

REVIEW OF CASE STUDIES ASSOCIATED WITH THE DOCUMENT *METHODS FOR DERIVATION OF INHALATION REFERENCE CONCENTRATIONS AND APPLICATION OF INHALATION DOSIMETRY* (EPA/600/8-90/066F) BY THE ENVIRONMENTAL HEALTH COMMITTEE OF THE SCIENCE ADVISORY BOARD (SAB)

November 17, 1998

EPA-SAB-EHC-99-003

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

Subject: Review of the Sixteen Case Studies associated with the document *Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry,* October 1994, (EPA/600/8-90/066F)

Dear Ms. Browner:

At the request of the Office of Research and Development (ORD), National Center for Environmental Assessment, the Environmental Health Committee (EHC) of the Environmental Protection Agency's Science Advisory Board (SAB) reviewed the Agency's Inhalation Reference Concentrations (RfC) Methods Case Studies. The Committee met on June 9-10, 1998 at the EPA's Environmental Research Center in Research Triangle Park, North Carolina.

The ORD's National Center for Environmental Assessment (NCEA) developed the Inhalation Reference Concentrations in response to the Clean Air Act Amendments (CAAA) of 1990. The CAA requires sources to demonstrate negligible risk and lack of residual risk (after implementation of control technology) based on health risk estimates. It is anticipated that the RfCs will be used for CAAA, as part of the determination of negligible and residual risk for noncancer health effects of air toxics. In addition, it is anticipated that air pollution control offices at the regional, state and local level will continue to utilize RfC values in risk management programs.

The RfC is an estimate of a daily inhalation exposure to the human population, including sensitive subgroups, that are likely to be without an appreciable risk of deleterious noncancer effects during a lifetime. The methodology derives RfCs from dose-response estimates for noncancer effects. NCEA has estimated that the uncertainty associated with the RfC may span an order of magnitude.

The SAB Environmental Health Committee (in 1989 and 1990) reviewed previous versions of the inhalation RfC methodology. The current version of the methodology, *Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry*, represents the Agency's response to the EHC's comments arising from these two reviews, which

were incorporated in two reports: *Science Advisory Board's Comments on the Use of Uncertainty an Modifying Factors in Establishing Reference Dose Level*, January 17, 1990 (EPA-SAB-EHC-90-005); and *Science Advisory Board's Review of the Office of Research and Development Document Interim Methods for Development of Inhalation Reference Concentrations*, April 29, 1991 (EPA-SAB-EHC-91-008).

The EHC requested the opportunity to review case studies using the methods to demonstrate the application of the dosimetric adjustments and to illustrate the methodology applied to chemicals that are representative of the typical range of data available including those with human occupational or clinical information and those with databases considered to be insufficient for quantitative dose-response estimation (i.e., "not-verifiable). **This review was not intended to be a review of the RfC methods themselves or a review of the science regarding the specific chemicals addressed in the case studies, but rather of the conceptual framework of the approach as applied to representative data.**

The case studies reviewed by the Committee fell into one of four categories: a) particle case studies; b) category 1 gas case studies; c) category 3 gas case studies; and d) "not-verifiable" case studies (which had less satisfactory databases than most of the other case studies and for which the EPA did not set RfCs).

The Office of Research and Development requested that the EHC provide comment(s) on each of the following aspects of the RfC Case Studies:

a) Overall, are the concepts and applications of the RfC methodology clearly articulated in the documentation provided for the case studies? Do the decisions and choices in these files attain the Agency's goal of being "transparent, clear, and reasonable? If not, what are specific examples within these files that could be instituted to better attain this goal?

b) In derivation of the RfC in the specific case studies,

   (1) Are the study summaries presented in sufficient detail for reader evaluation?

   (2) Are the designations of the critical effect and effects levels: no-observable-adverse-effect-level, lowest-observable-adverse-effect level, benchmark dose/concentration (NOAEL/LOAEL/BMC), based on rationales that are clear and reasonable?

   (3) Of the studies presented in either the IRIS Summary or Toxicological Reviews of each chemical, has the Principal studies been selected in a consistent and rational manner? Does this choice reflect consideration on the current knowledge of potential human response?

(4) Have the underlying assumptions of the duration and dosimetry adjustments been presented clearly?

(5) Are the rationales presented for use of uncertainty factors clear, reasonable and consistent?

(6) Do the confidence statements reflect the strengths and limitations (e.g., relevancy to humans, comprehensiveness of the data base) of the RfC assessment in a manner consistent with the Agency's goals?

c) In the IRIS Summaries for the specific cases, numerous studies are included under the heading "Supporting/Additional Studies" that are meant to provide further support for designation of the critical effect (e.g., mechanistic data, human data) or for the effect level chosen in the Principal study, or to establish the completeness of the data base. Is the depth of presentation in this section sufficiently comprehensive to provide information supportive of the decisions made in the assessment (such as uncertainty factors and confidence levels)?

The Environmental Health Committee commends the Agency for demonstrating the application of both the dosimetric adjustments and the RfC methodology to chemicals representative of the typical range of data available (including those with human occupational or clinical information as well as those with databases considered to be insufficient for quantitative dose-response estimation).

The EHC found the concepts and application of the RfC methodology to be clearly articulated in some of the case studies and unclear in others. The same finding also held true with the derivation of the RfC. In general, the Committee found the concepts and application of the RfC methodology in the recently updated or created case studies, such as those for vinyl chloride and methyl methacrylate, to be clearly articulated. To the contrary, the case studies that did not include the more recent research findings were criticized by the EHC. Examples of those case studies include carbon disulfide and antimony trioxide. The IRIS Summaries for some of the case studies were sufficiently comprehensive while others were not. It is clear that the EPA knows how to prepare comprehensive IRIS Summaries. The main problem is how to update the old documents to meet current standards. For some RfC case studies, there was a difference of opinion amongst the Committee regarding the clarity of the document, the rational for the RfC derivation and the comprehensiveness of the summary. The Committee identified specific areas in the RfC case studies that should be improved and made the following overall recommendations:

a) In general, it was difficult to read the narrative for an RfC case study document and compare all the results from all the studies presented for a given chemical. To improve the clarity of the documents, the Agency should summarize some of the data using figures and tables.

b) When appropriate, the Agency should update the RfCs when more recent studies become available.

c) In some cases, the Agency did not include available human data when developing the RfC. The EPA should incorporate the human data, when available.

d) In developing the RfCs, the Agency should expand their review of the literature to include new models, both laboratory animal-derived and mathematical.

e) Each document should contain a section that addresses children and their unique exposures and vulnerabilities, and that delineates data gaps. Each document should also include a statement on whether the RfC is protective of children.

f) The definition of susceptible human populations should be consistent throughout all of the RfC documents. The EPA should also include a discussion on how it deals with susceptible subpopulations such as children with asthma or children with cystic fibrosis.

g) All available data reviewed for a given document should be listed and the reasons for inclusion or exclusion from the derivation of the RfC should be provided in an appendix.

h) Several of the RfC case studies used acronyms and scientific terminology that were not defined in the document. Each RfC document should stand on its own and should not require frequent referral to the RfC background documents. Therefore, all of the documents should have a glossary, explaining the scientific terminology. In addition, the acronyms should be accompanied by their full names when they are first used in the RfC documents.

i) Some of the calculations were unclear. An explanation of the calculations should be included, in some of the case studies, and improved, in other case studies.

j) The units of measure should be consistent throughout the RfC documents. If two units are used, one should be followed in parenthesis by the other. For example, 408 ppm (68 mg/m^3).

k) Each RfC case study document should include an illustration of the respective chemical structure.

l) The Agency should reassess the application of uncertainty factors in the development of the RfC. It appears that the Agency uses the same uncertainty factor whether or not there are data on other, possibly significant (but less frank)

endpoints, and when there is marginal dosimetry information or a fully developed PBPK model. This practice will tend to discourage additional research.

The Committee appreciates the opportunity to review the RfC Methods Case Studies and looks forward to receiving a written response from the Assistant Administrator for Research and Development.

Sincerely,

/signed/
Dr. Joan M. Daisey, Chair
Science Advisory Board

Dr. Emil A. Pfitzer, Chair
Environmental Health Committee
Science Advisory Board

Dr. Mark J. Utell, Co-Chair,
Environmental Health Committee
Science Advisory Board

NOTICE

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ABSTRACT

The Environmental Health Committee (EHC) reviewed the EPA's Inhalation Reference Concentration (RfC) Methods Case Studies for selected chemicals. The Committee commends the Agency's efforts to demonstrate the application of the dosimetric adjustments and to illustrate the methodology.

The EHC found the concepts and application of the RfC methodology to be articulated clearly in some of the case studies and unclear in others. Similarly, the Committee concurred with the derivation of the RfC in some case studies and had concerns about the derivation in others. The same findings also held for the IRIS Summaries. For some of the case studies, there was a difference in opinion amongst the EHC regarding the clarity of the documents, the derivation of the RfC and/or the comprehensiveness of the summary.

The Committee made several recommendations for improvement: a) improve the clarity of the documents by summarizing some of the data using figures and tables; b) include more recent studies in the RfC case studies; c) incorporate human data into the derivation of the RfC, when available; d) expand the case studies to include a review of the newer models; e) include a statement on children, and whether the RfC is protective of children; f) explain the term susceptible population; g) give reasons for including or excluding available data; h) define scientific terminology used in the documents; i) clarify the calculations; j) make the units consistent; k) provide chemical structures; and l) reassess the application of uncertainty factors in the development of the RfC.

Keywords: Inhalation Reference Concentration (RfC), RfC methods case studies, Integrated Risk Information System (IRIS)

U.S. Environmental Protection Agency
Science Advisory Board
Environmental Health Committee
RfC Case Studies Review Panel

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[1]Did not attend the public meeting, but participated in the report preparation.
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1. EXECUTIVE SUMMARY

The Reference Concentration (RfC) is an estimate of a daily inhalation exposure to the human population, including sensitive subgroups, that are likely to be without an appreciable risk of deleterious noncancer effects during a lifetime. The uncertainty for the RfC estimates spans an order of magnitude. The EPA Office of Research and Development developed the RfC to meet the Agency's mandate under the Clean Air Act to demonstrate negligible risk and lack of residual risk (after implementation of control technology), based on human risk estimates.

On June 9-10, 1998, the Environmental Health Committee met at the EPA's Environmental Research Center in Research Triangle Park, North Carolina to review the Agency's RfC Methods Case Studies. There were four groups of case studies: a) particle case studies; b) category 1 gas case studies; c) category 3 gas case studies; and d) not-verifiable case studies. It is important to note that this was not a review of the science regarding the specific chemicals addressed in the case studies. This review also did not focus on the RfC methodology.

The Charge was to provide comments on each of the following aspects of the RfC Case Studies:

a) Overall, are the concepts and applications of the RfC methodology clearly articulated in the documentation provided for the case studies? Do the decisions and choices in these files attain the Agency's goal of being "transparent, clear, and reasonable? If not, what are specific examples within these files that could be instituted to better attain this goal?

b) In derivation of the RfC in the specific case studies:

   (1) are the study summaries presented in sufficient detail for the reader's evaluation?

   (2) are the designations of the critical effect and effects levels (NOAEL/LOAEL/BMC) based on rationales that are clear and reasonable?

   (3) of the studies presented in either the IRIS Summary or Toxicological Reviews of each chemical, have the Principal studies been selected in a consistent and rational manner? Does this choice reflect consideration on the current knowledge of potential human response?

   (4) Have the underlying assumptions of the duration and dosimetry adjustments been presented clearly?

(5) are the rationales presented for use of uncertainty factors clear, reasonable and consistent?

(6) do the confidence statements reflect the strengths and limitations (e.g., relevancy to humans, comprehensiveness of the data base) of the RfC assessment in a manner consistent with the Agency's goals?

c) In the IRIS Summaries for the specific cases, numerous studies are included under the heading "Supporting/Additional Studies" that are meant to provide further support for designation of the critical effect (e.g., mechanistic data, human data) or for the effect level chosen in the Principal study, or to establish the completeness of the data base. Is the depth of presentation in this section sufficiently comprehensive to provide information supportive of the decisions made in the assessment (such as uncertainty factors and confidence levels)?

The EHC found the concepts and application of the RfC methodology to be clearly articulated in some of the case studies and unclear in other case studies. The EHC concurred with the derivation of the RfC in some case studies and had concerns about the derivation of the RfC in other case studies. In general, the Committee found the concepts and application of the RfC methodology in the recently updated or created case studies, such as those for vinyl chloride and methyl methacrylate, to be clearly articulated. To the contrary, the case studies which did not include the more recent research findings were criticized by the EHC. Examples of those case studies include carbon disulfide and antimony trioxide. The IRIS Summaries for some of the case studies were sufficiently comprehensive while others were not. It is clear that the EPA knows how to prepare comprehensive IRIS Summaries. The main problem is how to update the old documents to meet current standards. For some RfC case studies, there was a difference of opinion amongst the Discussants regarding the clarity of the document, the rational for the RfC derivation and the comprehensiveness of the summary. The Committee identified specific areas in the RfC case studies that should be improved and makes the following overall recommendations:

a) In general, it was difficult to read the narrative on an RfC case study document and compare all the results from all the studies presented for a given chemical. To improve the clarity of the documents, the Agency should summarize some of the data using figures and tables.

b) When appropriate, the Agency should update the RfCs when more recent studies become available.

c) In some cases, the Agency did not include available human data when developing the RfC. The EPA should incorporate the human data, when available.

d) In developing the RfCs, the Agency should expand their review of the literature to include new models, both laboratory animal and mathematical.

e) Each document should contain a section on children and their unique exposures and vulnerabilities, and delineate data gaps. Each document should also include a statement on whether the RfC is protective of children.

f) The definition of susceptible human populations should be consistent throughout all of the RfC documents. The EPA should also include a discussion on how it

deals with susceptible subpopulations such as children with asthma or children with cystic fibrosis.

g) All available data reviewed for a given document should be listed and the reasons for inclusion or exclusion from the derivation of the RfC should be provided in an appendix.

h) Several of the RfC case studies used acronyms and scientific terminology that were not defined in the document. Each RfC document should stand on its own and should not require frequent referral to the RfC background documents. Therefore, all of the documents should have a glossary, explaining the scientific terminology. In addition, the acronyms should be accompanied by their full names when they are first used in the RfC documents.

i) Some of the calculations were unclear. An explanation of the calculations should be included, in some of the case studies, and improved, in other case studies.

j) The units of measure should be consistent throughout the RfC documents. If two units are used, one should be followed in parenthesis by the other. For example, 408 ppm (68 mg/m^3).

k) Each RfC case study document should include an illustration of the respective chemical structure.

l) The Agency should reassess the application of uncertainty factors in the development of the RfC. It appears that the Agency uses the same uncertainty factor whether or not there are data on more discriminating endpoints and when there is marginal dosimetry information or a fully developed PBPK model. This practice will tend to discourage additional research.

m) The underlying assumptions of the duration and dosimetry adjustments need further clarification in the calculation of a regional deposition dose ratio (RDDR) along with an explanation on the significance of the adjustments.

2. INTRODUCTION

2.1 Background

The RfC is an estimate, with uncertainty spanning an order of magnitude, of a daily inhalation exposure to the human population, including sensitive subgroups, that is likely to be without an appreciable risk of deleterious noncancer effects during a lifetime. The methodology derives RfCs from dose-response estimates for noncancer effects. The RfCs were developed by the Agency to meet its mandate under the Clean Air Act Amendments (CAAA) of 1990 to require sources to demonstrate negligible risk and lack of residual risk, after implementation of control technology, based on health risk estimates.

The inhalation RfC methodology was developed according to the oral reference dose (RfD) paradigm and emphasizes portal-of-entry considerations of comparative toxicity and inhalation dosimetry for particles and gases. Extrapolation modeling was added and factors are derived for adjustment of exposure concentrations that account for dosimetric differences between experimental animal species and humans. Previous versions of the RfC methodology have undergone external peer review, including reviews by the Environmental Health Committee in 1989 and 1990. These reviews generated two reports: *Science Advisory Board's Comments on the Use of Uncertainty an Modifying Factors in Establishing Reference Dose Level*, January 17, 1990 (SAB, 1990); and *Science Advisory Board's Review of the Office of Research and Development Document Interim Methods for Development of Inhalation Reference Concentrations*, April 29, 1991 (SAB, 1991).

The current version of the RfC methodology is described in *Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry* (EPA, 1994). This version incorporates the EPA's response to the EHC's previous comments.

At its 1990 review of the RfC methodology, the EHC requested the opportunity to review case studies using the methods in order to demonstrate the application of the dosimetric adjustments and illustrate the methodology applied to chemicals representative of the typical range of data available. The EHC recommended that the Agency include both case studies incorporating human occupational or clinical information, and those with databases considered to be insufficient for quantitative dose-response estimation ("not-verifiable"). The review was not intended to be a review of the RfC methods themselves but rather one of the conceptual framework of the approach as applied to representative data.

The Committee reviewed the following case studies which were separated into four categories:

a) group 1: particle case studies (diphenylmethane diisocyanate, antimony trioxide, and phosphoric acid)

b) group 2: category 1 gas case studies (methylmethacrylate, 1,3-dichloropropene, acetaldehyde, and chlorine dioxide)

c) group 3: category 3 gas case studies (carbon disulfide, n-hexane, hydrogen cyanide, vinyl chloride, and 2-ethoxyethanol)

d) group 4: not-verifiable case studies (acrylamide, bis(chloromethyl)ether, caprolactam, and methoxychlor).

In its briefing materials provided to the Committee, the Agency explained that there are differences in the level of documentation amongst the case studies and that the differences reflected changes made during a pilot program of the Integrated Risk Information System (IRIS) process. These changes are described in a paper by Mills and Foureman (in press). For some of the case studies, the background documentation describing the derivation of the RfC is embodied by the IRIS Summary alone. In the newer case studies, the documentation is described in the Toxicological Review. The complete IRIS file for the compounds that were reviewed is available at http://www.epa.gov/iris**.**

2.2 Charge

The review of the Inhalation Reference (RfC) Methods Case Studies was focused on the approach applied to the case studies. The review was not intended to focus on the RfC methodology or on the specific chemicals as independent critical reviews. However, in a few cases, the opinions of the reviewers on methodology or specific chemicals are included. The case studies that were reviewed by the Committee fell into one of four categories: a) particle case studies, b) category 1 gas case studies, c) category 3 gas case studies, and d) not-verifiable case studies. The Committee was charged to provide comments on each of the following aspects of the RfC Case Studies:

a) Overall, are the concepts and applications of the RfC methodology clearly articulated in the documentation provided for the case studies? Do the decisions and choices in these files attain the Agency's goal of being "transparent, clear, and reasonable? If not, what are specific examples within these files that could be instituted to better attain this goal?

b) In derivation of the RfC in the specific case studies,

(1) are the study summaries presented in sufficient detail for the reader evaluation?

(2) are the designations of the critical effect and effects levels (NOAEL/LOAEL/BMC) based on rationales that are clear and reasonable?

(3) of the studies presented in either the IRIS Summary or Toxicological Reviews of each chemical, have the Principal studies been selected in a consistent and rational manner? Does this choice reflect consideration on the current knowledge of potential human response?

(4) have the underlying assumptions of the duration and dosimetry adjustments been presented clearly?

(5) are the rationales presented for use of uncertainty factors clear, reasonable and consistent?

(6) do the confidence statements reflect the strengths and limitations (e.g., relevancy to humans, comprehensiveness of the data base) of the RfC assessment in a manner consistent with the Agency's goals?

c) In the IRIS Summaries for the specific cases, numerous studies are included under the heading "Supporting/Additional Studies" that are meant to provide further support for designation of the critical effect (e.g., mechanistic data, human data) or for the effect level chosen in the Principal study, or to establish the completeness of the data base. Is the depth of presentation in this section sufficiently comprehensive to provide information supportive of the decisions made in the assessment (such as uncertainty factors and confidence levels)?

3. RESPONSE TO THE CHARGE

3.1 General comments on the RfC Case Studies

The Environmental Health Committee commends the Agency's efforts to demonstrate the application of the dosimetric adjustments and to illustrate the methodology applied to chemicals representative of the typical range of data available.

The EHC found the concepts and application of the RfC methodology to be clearly articulated in some of the case studies, but unclear in others. Similarly, the Committee concurred with the derivation of the RfC in some case studies and had concerns about the derivation in others. The same findings also held true for the IRIS Summaries.

The Committee identified specific areas in the RfC case studies which should be improved and makes the recommendations discussed below for each group of chemicals.

3.2 Group 1: Particle Case Studies

3.2.1 Diphenylmethane Diisocyanate (MDI)

a) Is the RfC methodology clearly articulated? - The concepts and application of the RfC methodology are clearly put forth in the documentation.

b) Derivation of the RfC - The Reuzel *et al*. (1990; 1994) studies have the best characterization of exposure atmospheres in terms of size and concentration that can be related to observed effects in the animals. In particular, Reuzel *et al*. (1994) is the appropriate critical study for deriving the RfC. While the critical endpoint should be the production of asthma, there is no exposure information to allow the determination of critical exposure levels or duration for production of this condition. Thus, the endpoint selected for derivation of RfC (basal cell hyperplasia in the olfactory epithelium) is reasonable and does have good exposure data associated with it. However, the lack of this effect in another study at a higher concentration is of some concern in attempting to understand the rationale for the critical level selected.

The rationale for the critical effect, namely that protection against nasal cell hyperplasia will likely protect against other effects, may be generally reasonable, unless of course the concentration needed to elicit this effect is much greater than that for responses in other areas of the lungs. The available database is not clear in this regard. Furthermore, it is possible that effects in the rat upper respiratory tract may occur to a greater extent than that in humans, due to differences in structure between the two species. Furthermore, for the same exposure concentration, there

could be greater effects in the lower respiratory tract in humans than in rats, depending upon inhaled particle size, due to lower efficiency of the human upper respiratory tract to collect particles. In this regard, there is concern with the statement that effects in the upper respiratory tract (ET) are reflective of the major health concern related to MDI exposure, which is asthma. This is not at all well justified in the toxicological review and this position could be a problem due to dosimetric differences between rat and human at the actual human exposure relevant size of 10 μm, which may not be reflective in the animal studies cited which used smaller particles. This is because particle deposition is more regionally uniform for the smaller 1 μm particles, upon which the RfC is based, than for the larger particles which may be more relevant to actual human exposure.

The critical animal study used particles around 1 μm, while actual human exposure is to particles around 10 μm. Thus, the ratio of ET doses from rat and human would not be the same for the larger particles as for the smaller ones, since the upper respiratory tract deposition efficiency for the larger particles is greater in rats than humans while the ET deposition is similar for rats and humans for the smaller particles. Thus, the regional deposition dose ratio (RDDR) would actually be different for each of these two size particles, but this discrepancy is not considered in the derivation of the human equivalent concentration (HEC) for the ET region.

c) Presentation of Additional Studies - At the public meeting, ORD staff provided additional information on particle deposition differences between rats and humans. This information should be included in the case study document. Also, occupational technology may produce finer particles of MDI in comparison to years ago. This issue should be explored because it would have implications to the applicability of the animal studies to human exposure to MDI.

3.2.2 Antimony trioxide

a) Is the RfC methodology clearly articulated? - As noted below, certain aspects of the antimony trioxide case study were clear and transparent. Other aspects were not as well developed and need further explanation or reorganization. For example, the summaries of the antimony trioxide studies were found to be presented in sufficient detail and the designation of critical effect and effects levels were determined to be clear and reasonable. The choice of the principal study for this chemical was well justified and supported by the limited human data.

On the other hand, transparency and clarity were hindered by the use of acronyms that were never defined in the document and the subsequent need to go back to the EPA document on RfCs to understand what was being done (Jarabek, 1994; 1995a; and 1995b). The Committee noted that the nomenclature and calculations

of the dosimetry adjustments could be improved. For example, the meaning of the acronym, RDDR(TH), was unknown and the acronym was never defined in the document. The term, HEC, "human equivalent concentration" was understood but the calculation of the HEC was unclear. The documentation for the calculation of the dosimetry adjustment could also be improved. These calculations appear in the section of the document with the subheadings "Scenario" and "Conversion factors." For example, it might be more logical to present the BMC(ADJ) conversion first since it is not apparent in the "Scenario" how this value is obtained. Additionally, it appears that the adjustment is to convert 6 hrs/day, 5 days/week into a continuous exposure (24 hr/day, 7 days/week). However, the conversion indicated that the hours and days are added/subtracted to the BMC (e.g., +/- 6 hrs/24 hrs) instead of the BMC being multiplied by the 6/24 ratio. A brief narrative, beyond that presented, might also be useful for individuals who are not familiar with these conversions to explain how the value of 0.46 (the RDDR(TH)) was obtained.

Although the use of the Benchmark Dose approach is highly encouraged, it would be useful for the narrative to contain a brief statement regarding the merits of both approaches (NOAEL and Benchmark Dose) and the rationale for the choice of the latter in this particular case. The calculation of the BMC also was unclear. The first sentence under the section on the BMC states that the incidence of chronic inflammation, etc. in the animals observed during the 1-year period were analyzed for the BMC. Is this the first or the second year of the study? The subtleties of the difference between relative versus additional risk models may be known to those in the field, but not to those outside the field. For the calculations to be transparent to a wider community than those who routinely do risk assessments, EPA will have to explain the risk models more fully. The Agency should define all of the acronyms when they are first used in the document and the calculations should be explained so that the antimony trioxide document stands on its own without frequent referral to the RfC document.

The first complete sentence at the top of page 5 of the review document suggests that standard operating procedures for calculating BMCs were not followed. The Agency should provide an explanation for not following the BMC standard operating procedures. How does the EPA know that "the best curve fits and the lowest corresponding lower 95% confidence levels" were those obtained for chronic inflammation in female rats if the Agency did not examine all of the endpoints? The EPA should revise this statement to clarify that this was the best curve fit and lowest 95% confidence value for those endpoints for which the BMC was calculated.

It was not clear as to how the 10% incidence level for calculating the BMC was chosen. There are three sequential sentences in the top paragraph on page 5 of the

review document (These sentences appear on lines 11-16) describing the choice of the 10% incidence level for the BMC. The subject text refers to studies by Faustman *et al*. (1994), Allen *et al*. (1993) and Allen and Chapman (1993), but does not state clearly which studies support the choice of the 10% incidence level. There is also a comment about the probability of response among a "subset," but this subset is not identified. The Committee suggests that this section of the report's text be revised to identify clearly the basis for the choice of the 10% incidence level.

b) Derivation of the RfC - Individual reviewers within the Committee did not agree fully as to the level of confidence on the RfC for antimony trioxide. Issues which concerned the whole Committee included the short duration of the principal study, and the lack of reproductive and developmental studies. As noted below, both of these issues generated uncertainty factors that did not appear to be well justified. Consequently, the EHC would like to see more details regarding the rationale for the choice of the uncertainty factors.

The designation of the critical effect and the effects level were clear for the NOAEL and the LOAEL but the effect level for the BMC were merely stated (line 16, page 5 of the review draft) making it difficult to evaluate the accuracy or reasonableness of the value. The choice of the critical study seemed reasonable. The assumption of the duration and dosimetry adjustments were understood except for the calculation of HEC, which was not described. The rationales for the uncertainty factors were clearly stated.

It was noted that the choice of a ten-fold intraspecies extrapolation factor to be supportable because it is a "standard" default factor; the use, however, of a three-fold factor for an incomplete data base was not well justified. It was unclear as to whether or not this uncertainty factor was an arbitrary default when reproductive/developmental studies have not been conducted regardless of the existence of data to indicate that this system may not be the most sensitive. For example, antimony trioxide appears to be a pulmonary toxicant as determined from the principal study. The additional studies support this observation. Toxicokinetic studies indicate long term retention in the lungs. The various toxicity studies conducted have not determined the reproductive organs to be target organs for absorbed antimony. The one animal study conducted determined no teratogenic effects. The only evidence for potential reproductive effects appears to be a questionable human study.

Likewise, the uncertainty factor for study duration is also not well justified. The statement that steady state concentrations of antimony were not reached in the lung conflicts with information presented in the narrative which states that the clearance half time for the low dose in the Newton *et al*. (1994) study was 2.3

months. With this half time, antimony levels in the lungs at the low dose should have been close to steady state.

The Committee agreed with the case study narrative finding that the ocular effects in the Newton study were inappropriate for consideration, whereas the pulmonary inflammation was the appropriate response for the application of benchmark dose methodology (Newton *et al.*, 1994). The EHC also found that sufficient detail was presented with regard to the experimental protocol and major findings of the study selected for determination of the RfC (e.g., Newton *et al*., 1994). The narrative related to the decision not to choose an endpoint (ocular toxicity, for example) along with the narrative related to the endpoint of choice for human extrapolation (pulmonary toxicity, chronic interstitial inflammation) was found to be useful. In conclusion, the presentation on both of these extremes was found to be useful and helped to convince the Discussant of the Agency's derivation of the RfC.

c) Presentation of Additional Studies - The Committee noted no problems with the depth of presentation of the additional studies. The supporting/additional studies provide a useful and valuable perspective for the determination of the RfC. Even though these studies cannot be used to determine the RfC, they do provide consistency regarding the toxic effects and mechanistic insights, particularly in the dosimetry area, that serve to support the choice of study and endpoint for effect. The Agency is encouraged to continue to include supporting studies, (particularly the inclusion of human studies) in the case studies.

There are some editorial comments. On page 10, line 16, "smelters" should be changes to "smelter workers." Also, care should be taken to describe the particle size in each exposure. This was not done consistently. On page 8, the term "Ferret's diameter" was unfamiliar. Is there a more common term?

3.2.3 Phosphoric Acid

a) Is the RfC methodology clearly articulated? - The study summaries are given in sufficient detail. In addition, the rationale for the designations of the critical effect and the effects levels (NOAEL etc.) are presented clearly. However, the case study, as written, was somewhat difficult to read and, therefore, was not transparent. Who is the audience for these reports? Even assuming some degree of toxicology background, some clarification is still in order. The Committee recommends that the abbreviations be defined when they are first used, calculations be explained, and where applicable, the importance of calculations should be noted. For example,

(1) Abbreviations need to be defined (e.g. RDDR, MMAD, and BMC10 (HEC)).

(2) It is not clear where some numbers used in the calculations come from, example, in the scenario, the BMC10 (HEC) = 5.4 mg/m^3 X 0.64.

(3) Some explanation of the importance of certain calculations would be clarifying. For example, there is discussion on the nonaerodynamic diameter of the aerosol particles at the lesion site. How is this related or important to the calculation of the BMC10?

(4) The underlying assumptions of the duration and dosimetry adjustments need further clarification in the calculation of an RDDR along with an explanation on the significance of the adjustments.

Also, the rationale was unclear on how the Agency applied the information on the hygroscopic growth of the acid aerosols to estimate the diameter of the particles (based upon initial mass median aerodynamic diameter (MMAD) of the aerosol) at the proposed site of the critical lesion, which is the tracheobronchial tree.

Phosphoric acid is being compared in a number of instances with another particulate acid for which there is more data, namely sulfuric acid. In the case of the latter, high concentration exposures are associated with alveolitis, bronchial and/or bronchiolar edema and epithelial desquamation. There is little evidence for bronchiolar fibrosis. Also, the sensitivity of the morphological endpoints is dependent upon the animal species, with the rat the least sensitive to sulfuric acid. Thus, the critical dose for rat may be much higher than that for other species, including humans; the latter may respond with similar lesions at lower concentrations. The EPA should note for clarification purposes that the maximum uncertainty factor for both dosimetry response is 3. Together these factors comprise the interspecies uncertainty factor of 10.

b) Derivation of the RfC - The study summaries are given in sufficient detail. The rationale for the designations of the critical effect and effects levels (NOAEL, etc.) are presented clearly. Given those studies described, the principal study appears appropriately chosen. However, the choice of the appropriate study, and indeed the studies which are presented, lack any consideration of the current knowledge of the potential human response in that no discussion of developmental effects is given. There is potential that the most sensitive endpoint (i.e., a developmental endpoint) has not been studied. Given that the newborn lung is primarily made up of terminal bronchioles with alveolarization only beginning, and given that children breathe more air per unit body weight than adults, the potential for lung developmental effects is great. This issue should be addressed under uncertainty factors, where little explanation is given. There was a concern about the adequacy of the uncertainty factor of 10. The Agency should clarify who are considered

sensitive human subpopulations, if children are considered a sensitive human subpopulation, and if children with chronic lung disease such as bronchopulmonary dysplasia, or children with asthma, are considered sensitive human subpopulations.

3.3 Group 2: Category 1 Gas Case Studies

3.3.1 Methymethacrylate

a) Is the RfC methodology clearly articulated? - This document was described as "by far, the clearest in its presentation of the methodology" during the Committee's discussions. It could serve as a model for the other compounds. However, there were still some areas that could be made clearer. On page 7, the abbreviations used in the footnote to the table should be defined. At the bottom of page 7, the exposure concentrations should be rounded to 100 and 400 ppm as they are on the next page as opposed to the numbers cited in the review document, 99.79 and 396.07. The same holds for the calculated values for the concentrations in mg/m^3. On page 8, line 11, "effect" should be "affect." The chemical structure for methylmethacrylate should be added to the document.

It is confusing that the critical study is described as having 70 rats of each sex per group but the observations described at the bottom of page 7 refer to incidences per 10 animals or even in one case in only 4 animals. This inconsistency should be corrected or explained. On page 9, the data for degeneration of the olfactory epithelium in males is described for groups ranging in number from 38 to 48. What happened to the rest of the animals? On page 9, in the middle paragraph, on the 4^{th} from the bottom line: the EPA should explain what is meant by an "environmentally protective RfC?" The RfC is meant to protect human health, not the environment. On the top of page 10, the Agency should define the abbreviations here. Otherwise, the paragraph in which this appears is quite well written and close to being the transparent report that the EPA desires.

Concepts and application of RfC methodology are explained in detail in the documentation in a sort of boiler-plate manner. However, when it comes to establishing the RfC, there are numerous data gaps and places where there are more than enough data but no clear indication of how the data were used to establish the value. Documentation needs to be more reader-friendly. Some figures and tables that summarize the data and make comparisons are recommended. To meet its goal of improving the utility and credibility of the IRIS process, these documents need to become more understandable to all levels of users of these documents. The methylmethacrylate document was clearly one of the best of the IRIS documents included in the Committee's background material but even it needs editing. As recommended for other RfC documents, the

methylmethacrylate Document should use full description with first encounter (e.g., adjusted for ADJ, and human exposure concentration for HEC).

b) Question 2: Derivation of the RfC - The study summaries were in sufficient detail. The choice of critical effect and effect level seemed reasonable. The choice took into account current knowledge of human responses. The underlying assumption of the duration and dosimetry adjustments were presented quite clearly in this document - much more so than for acetylaldehyde and hydrogen cyanide. The considerations for the choice of uncertainty factors were clearly presented and appeared to be carefully thought through. The statement on confidence was clear and logical.

The data needed for the recommendation is included and can be "teased out" by the diligent reader. Some summary tables and figures would be helpful. The crucial study is the Hazelton inhalation rat study with effects at 400 ppm, histopathological changes at 100 ppm and NOAEL at 25 ppm. The uncertainty factor of 10 (intraspecies) and modifying factor (MF) of 1 seem appropriate.

c) Presentation of Additional Studies - The depth of the presentation of the additional studies was adequate except for the lack of references for the second paragraph under “Supporting Studies.” Supporting studies do not add a great deal. It would be helpful to have specific sensitization data in humans and some methodology to quantitate an exposure-response for methylmethacrylate.

3.3.2 1,3-Dichloropropene

a) Is the RfC methodology clearly articulated? - The case study for 1,3-dichloropropene is transparent and clear.

b) Derivation of the RfC - The Agency should explain, in the document, why it did not use the benchmark dose.

c) Presentation of Additional Studies - The depth of the presentation in this document is sufficiently comprehensive, providing information supportive of the decisions made in the assessment. However, a statement on children, and whether the RfC is protective of children, should be added.

3.3.3 Acetaldehyde

a) Is the RfC methodology clearly articulated? - The acetaldehyde document is more typical of IRIS documents and when compared with the Agency for Toxic Substances and Disease Registry (ATSDR) documents or the occupational exposure limit documentation, is much less readable. In general, the Discussants

found the methodology to be well articulated. However, the methodology could be made clearer in several ways. The acronyms used at the top of page 2 should be defined. The method for calculating the HEC should be described. On page 1, the term, critical dose, would be more appropriately called, critical exposure concentration. A value that has the units "mg/m^3" should not be called a dose. Why is the critical effect listed twice (as 1 and 2)? Perhaps it refers to the two critical studies. However, it is confusing to list the same effect twice. The critical effect was degeneration of olfactory epithelium, period.

b) Derivation of the RfC - The study summaries were presented in sufficient detail. The designation of critical effects were clear and reasonable. The Discussants agree with the choice of a critical effect. The duration and dosimetry adjustments were clear for the most part, but the method of conversion to an HEC was not described. The description of both the uncertainty factors and the confidence statements were clear and reasonable.

The use of the Appleman studies to define critical effects is adequate but there is a lot of human data that could be used (Appleman *et al*., 1982; Appleman and Woutersen, 1986). The use of human data would avoid the interspecies extrapolation factor of 10. If the EPA uses the human data to derive the RfC for acetaldehyde, the factor of 10 between subchronic and chronic may also vanish.

c) Presentation of Additional Studies - The presentation of the additional studies was in sufficient depth for the evaluation of the choice of the critical study. The Committee agree with the low confidence value. For a compound of this importance (since it is an IARC carcinogen) the IRIS document should be improved.

No discussion of the common genetic polymorphism of acetaldehyde dehydrogenase is presented. The inability or relative inability to metabolize acetadeldehyde is common amongst Asian populations. Are there any data that suggest that such individuals are at increased risk of an adverse effect to acetaldehyde gas exposure? The Agency should address this issue.

3.3.4 Chlorine dioxide

a) Is the RfC methodology clearly articulated? - The RfC methodology was found to be clearly articulated. However, the definition of thoracic respiratory effects should be included in the document.

b) Derivation of the RfC - The Committee was unclear about the significance of deriving an RfC when there was clearly zero confidence. During the public

meeting, the Agency responded that it was required by the Clean Air Act to set an exposure limit for chlorine dioxide.

c) Presentation of Additional Studies - The chlorine dioxide presentation provided in the Agency's document is sufficiently comprehensive to provide information supportive of the decision made in the assessment.

3.4 Group 3: Category 3 Gas Case Studies

3.4.1 Carbon disulfide

a) Is the RfC methodology clearly articulated? - This case study was very clearly written. However, the units were not consistent. This should be corrected.

b) Derivation of the RfC - The methods used to calculate the BMC is not consistent with methods described for continuous data sets in other EPA documents. EPA has recommended either a "hybrid approach" or conversion of continuous data to quantal data. EPA may want to revisit this and compare its methods for calculating the BMC with other guidance the EPA has put forward for continuous data.

It will be helpful to report the magnitude of change in the maximum motor conduction velocity (MCV) and to clearly state that the original authors (and not just a peer reviewer) questioned the biological significance of the findings in the study. The authors stated that "all reductions are within range of clinical normal values."

An additional 10-fold uncertainty factor was added because of effects seen in a developmental neurotoxicity study. In the n-hexane RfC, (described in section 3.4.2), a 10-fold uncertainty factor was added because there were no data at all. Yet in this carbon disulfide case study, an experiment was conducted with more sensitive endpoints at different stages of development. The EPA added a 10-fold factor because minimal effects were noted. If the developmental effects are truly a concern, then the RfC should be based on these effects, rather than adding a 10-fold uncertainty factor to a different endpoint. It appears that the Agency adds the same uncertainty factor whether or not additional data are available. This practise will discourage registrants from better understanding mechanisms and evaluating more discriminating endpoints.

On the other hand, another Committee Member concluded that the direct acting mechanism of carbon disulfide toxicity should not lessen an uncertainty factor for susceptible populations. The rationale was that a susceptible populations does not just mean metabolic polymorphisms and that an axon which is growing and then

cross-linked has more potential for an adverse outcome(s) than one which is static. The EPA should define the term "sensitive subpopulations" and use it consistently throughout the documents. It was also concluded that, in the Tabacova studies, an increase in narrow-path crossing slips and falls is reported at 10 mg/m^3, although not at higher concentrations, and that this may be enough evidence to require an uncertainty factor for developmental effects of at least three if not ten.

c) Presentation of Additional Studies - As explained above, the depth of the presentation for carbon disulfide is not sufficiently comprehensive to provide information that is supportive of the uncertainty factors or the confidence limits.

3.4.2 n-Hexane

a) Is the RfC methodology clearly articulated? - The concepts and applications of the RfC methodology are clearly articulated in the documentation. However, it was not transparent to the reviewers that the RfC is based on a study in which the effects are of questionable biological significance. The change in MCV was less than a 5% change. The authors of the study state that there were "no apparent abnormalities in any one person" (Sanagi and Seki, 1980). Thus, on an individual basis in the present study, no objective signs indicating damage to the nervous system that could have been due to the n-hexane exposure were detected." The authors also state that "it cannot be determined that even on a group basis, toxic effects on the peripheral nervous system were demonstrated at the given exposure level." Finally, they state that the "number of subjects examined and the differences noted between the groups were really too small to come to any decisive conclusion." These conclusions from the original authors need to be included in the documentation so it can be clearly understood that the RfC is based on very questionable changes.

The EPA's decision to use these "effects" as a LOAEL from which to set the RfC is not completely consistent with the Agency's approach to setting the RfC for carbon disulfide. In the carbon disulfide example (addressed in section 3.4.1), the benchmark dose approach was used to extrapolate **above** the dose range to a 10% change because the EPA concluded that the minimal effects observed in the study were not considered biologically meaningful. If the Agency chooses to use less than a 5% change in MCV for risk assessment purposes because these findings are consistent with other changes seen at higher doses, then it is important for the Agency to state this and make transparent the uncertainties surrounding the effect observed in Sanagi and Seki (1980).

b) Derivation of the RfC - The 3-fold uncertainty factor was added for lack of data on reproductive and chronic respiratory effects. There have been several studies submitted to the Agency on commercial hexane (55% n-hexane) including

developmental studies in two species, a 2-generation reproductive study, and a chronic study (Ladefoged and Perbellin, 1986; Ladefoged *et al*., 1989; Ladefoged *et al*., 1994; and Patten *et al.*, 1986). The Agency should review these studies and consider removing the 3-fold uncertainty factor since the database is quite rich.

A 10-fold uncertainty factor was added for the use of a LOAEL rather than a NOAEL. The full 10-fold factor should be reduced to take into account the fact that the "LOAEL" was actually based on effects that are of questionable biological significance which were considered to be a "NOAEL" in the carbon disulfide case. In addition, these effects, if real, could be a result of exposure to both acetone and hexane. This leaves an uncertainty factor of 10 for sensitive populations, which is appropriate and should not be reduced.

The definition of teratogen would be helpful since sometimes it is defined to mean functional defects (which were not examined in this study). It is not clear from the discussion whether the brain or spinal cord (for pyramidal tracts or ascending tracts) were examined. It is not clear whether any developmental neurotoxicity testing was done. The Agency should clarify all of these issues in the n-hexane RfC document.

c) Presentation of Additional Studies - The n-hexane RfC document did not address the significant acetone exposure. There is evidence to suggest that acetone might potentiate the effects of n-hexane (Ladefoged and Perbellin, 1986; Ladefoget *et al*., 1989, 1994; and Patten *et al*., 1986). Thus, if one makes the conservative assumption that the statistically significant effects in the Sanagi and Seki (1980) study are biologically meaningful, these effects may be a result of exposure to both acetone and hexane. Based on this evidence, the minimal changes in MCV would likely be observed at levels above 58 ppm for n-hexane alone.

3.4.3 Hydrogen cyanide

a) Is the RfC methodology clearly articulated? - The Committee was disappointed with the hydrogen cyanide RfC document in terms of the uncertainty factors and the focus on rat data rather than human studies. The ATSDR document on cyanide has a more extensive human database and uses the trans-species information in a more rational manner.

b) Derivation of the RfC - The dose response relationship for cyanide is steeper than for almost any other chemical. It is known that hydrogen cyanide acts almost instantaneously by producing cyanohemoglobin, and that all species react similarly. Thus, an uncertainty factor of 1000 is not considered to be justified.

c) Presentation of Additional Studies - The Agency should revise the hydrogen cyanide document to focus on the human studies.

3.4.4 Vinyl chloride

a) Is the RfC methodology clearly articulated? - In contrast to the document on carbon disulfide, this document is clearly presented and defended. The IRIS summary is a most valuable support to the toxicology summary. The IRIS Summary and Toxicological Profiles are more up to date than most IRIS documents and generally do a better job than most such documents.

The RfC of 0.1 mg/m^3 is clearly defined as limited to non-cancer effects applications. Since the quantitative estimate of cancer risk is 0.000001 per microgram/cu.m., it appears that a cancer risk of 0.0001 is present at the RfC. If this is the case, the Agency should make this explicit in the RfC document, since most readers of the document will assume that the RfC is a "no adverse effects" level

b) Derivation of the RfC - Vinyl chloride clearly presents health problems. It produces angiosarcoma in both rats and workers. However, since the Occupational Safety and Health Administration (OSHA) reduced the Permissible Exposure Limit (PEL) to 1 ppm several decades ago, there has not been a single new case of angiosarcoma in the registry at Louisville. This clearly indicates that there is at least a pragmatic or practical threshold for vinyl chloride angiosarcoma in man and the RfC methodology is more appropriate for assessing noncancer risks than the slope factor approach using a linear multistage model. Storm and Rozman (1997) have compared the dose response data for rats and man to vinyl chloride and demonstrated that the linear multistage approach is inappropriate, that rats are more sensitive than man and that there is clearly a threshold for angiosarcoma in both rats and man. This paper needs to be incorporated into the database for vinyl chloride.

Uncertainty factors seem to be limited to 1, 3 and 10 (although the first two 3's (3x3) are equated to 10). Vinyl chloride is given a factor of 3 based on the failure of PBPK modeling to address the potential for different tissue sensitivities between species. While this sounds reasonable it also appears that other chemicals with the same factor of 3 have more serious deficiencies. The Agency should consider using a further gradation in uncertainty factors. Given the significant effort required to develop and apply a PBPK model, there does not seem to be a practical benefit for the use of these models if no reduction in uncertainty (and corresponding uncertainty factors) is obtained. The confidence level of medium for the database also seems more severe than the same confidence level for other

chemicals. This is particularly true based on the stated unlikelihood of reproductive effects.

c) Presentation of Additional Studies - The EHC found that the use of a two-year dietary admix study in rats as the principal study for an inhalation RfC is justified based on the qualitative and quantitative dose-response relationship with a one-year inhalation study in rats, the accepted reliability of PBPK modeling to calculate levels of metabolites per liver volume in rats and humans, and the lower doses of the oral study. One Member was concerned that the inhalation RfC is based upon an oral feeding study when inhalation exposure study data are available and would like to see this issue discussed in the document and a justification presented for the use of an ingestion study. It may be the most appropriate, but this decision should be defended. In the case of vinyl chloride, human data are not only available but are adequate to establish causality with exposure-response information. In such cases the rat data become irrelevant or are of value only as corroborative information. It is informative with vinyl chloride to note the comparison of the rat-human data and it helps us define the utility of animal tests as predictors of human effects.

3.4.5 2-Ethoxyethanol

a) Is the RfC methodology clearly articulated? - The RfC methodology was clearly articulated with the exception of the inconsistency in the units. The units of ppm or mg/m^3 need to be made consistent throughout the document. In the description of the Doe (1984) study, the parameters which assess fetal toxicity included fetal body weight, and external, visceral and skeletal examinations. The Agency should clarify whether the term "visceral" includes the brain and whether this study was the standard toxicological assessment defined by Wilson.

b) Derivation of the RfC - In one study, the NOAEL (HEC) was 47 mg/m^3. The EHC was a concerned that this value was lower than the adjusted value for the testicular effects. The rationale for choosing the testicular atrophy as the critical endpoint should be explained in this piece.

c) Presentation of Additional Studies - The RfC for ethoxyethanol would be more convincing if it were based on the human data (Clapp and Smallwood, 1987) rather than on the rabbit data. In setting the RfCs, the Agency's goal is not to protect rabbits or rats but to improve human health. The Committee recommends that the EPA pay more attention to data from the target species available.

3.5 Group 4: Not-Verifiable Case Studies

These following four chemicals have less satisfactory databases than most of the other case studies; subsequently, the EPA did not set RfCs for these chemicals.

3.5.1 Acrylamide

Although there is some useful information in this document, there was agreement that there are insufficient data for developing an RfC. A chronic oral (drinking water) study in rats has been used to estimate carcinogenic potency for both the oral and inhalation routes. The Agency should explore the possibility of using the noncancer findings in that study to estimate an RfC. The Agency should also consider giving more prominence to the dermal route for this chemical and other chemicals where there is insufficient inhalation data. In the acrylamide case, it was shown that peripheral neuropathy has been produced with exposure by the dermal route.

3.5.2 Bis(chloromethyl)ether (BCME)

In general, the Discussants also agreed that the information on bis(chloromethyl)ether was insufficient to develop an RfC. However, a six-month inhalation study to BCME vapors showed no noncancer effects at the highest dose tested. It may be possible to use this to estimate an RfC. While the RfC is clearly designed for noncancer endpoints, the RfC should reference carcinogenicity when cancer is the crucial endpoint as it is for BCME. There is little justification for an RfC based on available data.

3.5.3 Caprolactam

The Committee agreed that an RfC should not be derived at this time, given the paucity of data on caprolactam. Although an oral RfD from animal studies and some worker information is available, very limited human inhalation data are available. Several workplace studies with a small number of employees are presented; however, no meaningful exposure information is available. It should be also noted in the caprolactam document that an oral RfD has been derived based on reduced body weight.

In order to make the report more understandable to the reader, several clarifications are required in the caprolactam RfC document:

a) On page 6 of 15 (paragraphs #3 and #4), does the reference to intubation with Caprolactam or water in these two paragraphs refer to oral or inhalation studies? Although at first glance these would appear to be gavage studies, it is not clear from the remainder of the paragraphs. The EPA should clarify this.

b) On page 7 of 15, line 4: how do you have menstrual disturbances in pregnant women? This statement also needs clarification.

3.5.4 Methoxychlor

The Committee concurs that the database is inadequate to derive an RfC for methoxychlor at this time. There is only one case report of an aplastic anemia after using a tomato dust pesticide containing methoxychlor.

3.6 General Findings from RfC Case Studies

It was difficult to read the narrative on an RfC case study document and compare all the results from all the studies presented for a given chemical. It is suggested that the EPA consider using tabular or pictorial presentation of data similar to ATSDR in addition to using narrative.

In discussing critical effects that are statistically significant, the magnitude and hence severity of the effect should be reported. It was the absence of this information in the n-hexane review that led one of the reviewers to check the original paper and discover that the effect was less than a 5% effect that would not typically be regarded as biologically significant. Inclusion of this type of data will make the risk assessment process more transparent and improve the scientific rigor of the discussion.

The Agency should reconsider how uncertainty factors are added when the critical effects have variable levels of concern. The carbon disulfide and n-hexane case studies illustrate this problem in two different ways:

a) A 10-fold uncertainty factor was added for n-hexane because there were no developmental toxicity data. Yet a 10-fold safety factor was added to carbon disulfide which had developmental toxicity data using functional endpoints because slight equivocal effects were noted. This is not a consistent application of uncertainty factors.

b) A 10-fold uncertainty factor was added to n-hexane because the critical effect was a LOAEL. Although this effect was statistically significant it was not regarded by the authors as biologically meaningful. All values were within normal clinical range. If the critical effect is an equivocal effect then it is difficult to justify the full 10-fold safety factor to extrapolate from LOAEL and NOAEL. In fact, one might challenge the need for an additional safety factor at all.

In conclusion, there should be less uncertainty if experiments were conducted to elucidate mechanisms and as more sensitive endpoints are used that refine the NOAEL. This should be considered in the selection of uncertainty factors.

4. SUMMARY OF RECOMMENDATIONS

The Committee had the following thoughts and recommendations for EPA to consider in revising the document and their approaches to RfC calculations:

a) In general, it was difficult to read the narrative on an RfC case study document and compare all the results from all the studies presented for a given chemical. To improve the clarity of the documents, the Agency should summarize some of the data using figures and tables.

b) The Agency should include more recent studies to derive the RfCs which were based on studies that were done in the past and may be outdated..

c) In some cases, the Agency did not include available human data when developing the RfC. The EPA should pay more attention to the human data, when available.

d) In developing the RfCs, the Agency should expand their review of the literature to include new models, both laboratory and mathematical.

e) Each document should contain a section on children and their unique exposures and vulnerabilities, and delineate data gaps. Each document should also include a statement on whether the RfC is protective of children

f) The definition of susceptible human populations should be consistent throughout all of the RfC documents. The EPA should also include a discussion on how it deals with susceptible subpopulations such as children with asthma or children with cystic fibrosis.

g) All available data reviewed for a given document should be listed and the reasons for inclusion or exclusion from the derivation of the RfC should be provided in an appendix.

h) Several of the RfC case studies used acronyms and scientific terminology that were not defined in the document. Each RfC document should stand on its own and should not require frequent referral to the RfC background documents. Therefore, all of the documents should have a glossary, explaining the scientific terminology. In addition, the acronyms should be accompanied by their full names when they are first used in the RfC documents.

i) Some of the calculations were unclear. An explanation of the calculations should be included in some of the case studies and improved, in other case studies.

j) The units of measure should be consistent throughout the RfC documents. If two units are used, one should be followed in parenthesis by the other. For example, 408 ppm (68 mg/m^3).

k) Each RfC case study document should include an illustration of the respective chemical structure.

l) The Agency should reassess the application of uncertainty factors in the development of the RfC. It appears that the Agency uses the same uncertainty factor whether or not there are data on other, possibly significant (but less frank) endpoints and when there is marginal dosimetry information or a fully developed PBPK model. This practice will tend to discourage additional research.

APPENDIX A - ACRONYMS AND ABBREVIATIONS

ACGIH	-	American Conference of Governmental Industrial Hygienists
ADJ	-	Adjusted
ATSDR	-	Agency for Toxic Substances and Disease Registry
BCME	-	Bis(chloromethyl)ether
BMC	-	Benchmark Concentration
BMD	-	Benchmark Dose
CAAA	-	Clean Air Act Amendments
CFD-PBPK	-	Computational Fluid Dynamics-Physiologically-Based Pharmacokinetic
EHC	-	Environmental Health Committee
ET	-	Upper Respiratory Tract
HEC	-	Health Equivalent Concentration
IARC	-	International Agency for Research on Cancer
IRIS	-	Integrated Risk Information System
LOAEL	-	Lowest-Observed-Adverse Effect Level
MMAD	-	mass median aerodynamic diameter
MAK	-	German Maximum Allowable Concentration
MCV	-	maximum motor conduction velocity
MDI	-	Diphenylmethane Diisocyanate
MEK	-	Methyl Ethyl Ketone
MF	-	Modifying Factor
mg/m^3	-	milligrams per cubic meter
MLE	-	Central Estimate
Mva	-	minute volume for the laboratory animal
Mvh	-	minute volume for humans
NCEA	-	National Center for Environmental Assessment
NOAEL	-	No-Observed-Adverse Effect Level
ORD	-	Office of Research and Development
OSHA	-	Occupational Safety and Health Administration
PBPK	-	Physiologically-Based-Pharmacokinetic
PEL	-	Permissible Exposure Limit
ppm	-	parts per million
RDDR	-	Regional Deposition Dose Ratio
REL	-	Recommended Exposure Limit
RfC	-	Inhalation Reference Concentration
RfD	-	Inhalation Reference Dose
RGDR	-	regional gas deposition ratio
Sa	-	surface area for the laboratory animal
SAB	-	Science Advisory Board
Sh	-	surface area for humans
TLV	-	Threshold Limit Value

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