UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

EPA-SAB-EHC-91-008

OFFICE OF
THE ADMINISTRATOR

April 29, 1991

Honorable William K. Reilly
Administrator
U.S. Environmental Protection Agency
401 M Street, S.W.
Washington, D.C. 20460

Subject: Science Advisory Board's review of the Office of Research and Development document Interim Methods for Development of Inhalation Reference Concentrations (EPA/600/8-90/066, August 1990)

Dear Mr. Reilly:

Inhalation Reference Concentrations (RfC) were developed to serve as a basis for health risk estimates for non-cancer effects (analogous to the Agency's Reference Dose (RfD) for orally ingested toxicants) resulting from exposure to airborne pollutants. It is anticipated that RfCs will be used for Clean Air Act regulatory activities as a part of the determination of negligible and residual risk for non-cancer health effects of air toxics.

The methodology to calculate inhalation RfCs follows the oral Reference Dose paradigm, with an added emphasis on portal-of-entry considerations of comparative toxicity and inhalation dosimetry for particles and gases. A draft of the interim methodology was reviewed at a public peer-review workshop in October, 1987 and the methodology has since been reviewed and implemented by the Agency's RfD/RfC work group. It was intended to review and update the methodology as the state-of-the-art progressed. Now that RfC values are being made available to the public on the Integrated Risk Information System (IRIS), and in anticipation of their aforementioned role in regulatory support, the EPA Office of Research and Development requested an SAB review in order to incorporate further expert opinion and recommendations on improving the interim methodology.

In response to this request, the SAB Environmental Health Committee (EHC) met on October 26, 1990 in Arlington, Virginia to receive briefings on the RfC methodology from Agency staff.

The following issues, comprising the Charge to the Committee, were discussed and are dealt with fully in the accompanying report:

1. Does the methodology utilize appropriate dosimetric extrapolations for particles and gases, respectively?

The Committee found the extrapolations and other factors used to be reasonable and well founded. Some specific suggestions for improvement are provided in the report.

2. Should the same uncertainty factors be used when dosimetric adjustments are incorporated?

Current methods for assessing the Reference Dose (RfD) call for applying an uncertainty factor of 10 to compensate for extrapolation from animal data to human data. The proposed Inhalation Reference Concentration methods are far more detailed in estimating respiratory exposure and, in fact, adjust for differences in interspecies dosimetry. The importance and accuracy of that adjustment is highly variable among compounds and among biological endpoints. Clearly the use of more precise methods should not be discouraged by applying the same uncertainty factors that would be applied to more general methods, but a general statement about the appropriate uncertainty factor is not possible, other than to state that this factor should be smaller with improved data and understanding.

Dealing with this issue could also be aided by a more detailed articulation of the intent of the various uncertainty factors. An understanding of the various uncertainties for which a specific factor is designed to compensate would allow a better evaluation of the influence of increased information on an uncertainty factor.

3. Are the concepts and applications of the methodology clearly articulated in its documentation?

The Committee believes that EPA Staff did an excellent job in defining and explaining a sophisticated approach to a complex problem. Specific observations for improving or clarifying the text have been forwarded to the appropriate EPA staff.

4. Is the research intended to support the methods appropriate for improving risk extrapolation procedures?

Suggestions for further research are given throughout the document. In some cases these are explicitly mentioned; in others they are inferred. It would be preferable to provide a special section outlining research needs and suggestions.

Overall, the Committee finds the referenced document to be useful and comprehensive. It advances considerably the previous approaches for calculating reference doses for inhaled toxicants. The Committee is concerned, however, about the emphasis given to the "No Observed Adverse Effects Level (NOAEL) plus uncertainty factor" approach, especially in view of the SAB's past urging that alternative methods, such as the benchmark approach (A statistical approach for deriving RfC or RfD, based on the entire set of relevant dose-response data,not only the NOAEL/LOAEL points. The lower ten percent confidence limit sets the RfC or RfD value.), be applied to the raw data. The draft document discusses the benchmark approach in Appendix A, but refers to this and other methods as "Novel." We consider these approaches to be alternative, and in some cases, more desirable, methods.

Also, the Committee wishes to stress that there can be considerable differences in the extent of information available, and in toxicity mechanisms for various toxicant-endpoint combinations. This situation gives rise to two additional suggestions:

(1) When the subject interim document is revised, we propose that its title be changed to identify the approaches set forth as guidelines, not fixed "cookbook formulas," thus retaining flexibility needed to deal with varying toxicants and conditions.

(2) Given the need to accommodate knowledge for specific toxicants, the Committee believes that it would be useful for the SAB to review some toxicant-specific derivations of the RfC. This would increase our understanding of the overall methodology and its data base requirements, and enhance our ability to review the dosimetric adjustments.

Finally, the Committee would appreciate learning of the Agency's plans and schedule to revise the current interim document. We stand ready to review the specific applications noted above, as well as a future revision of the document itself.

The Science Advisory Board is pleased to have had the opportunity to review the draft document and to offer its advice. We would appreciate your response to the major points we have raised.

Raymond C. Loehr

Dr. Raymond Loehr, Chairman
Science Advisory Board

Arthur C. Upton

Dr. Arthur Upton, Chairman
Environmental Health Committee

ENCLOSURE

EPA

U.S. Environmental Protection Agency

Washington, DC
EPA-SAB-EHC-91-008

REPORT OF THE ENVIRONMENTAL HEALTH COMMITTEE

REVIEW OF THE OFFICE OF RESEARCH AND DEVELOPMENT'S DRAFT DOCUMENT "INTERIM METHODS FOR DEVELOPMENT OF INHALATION REFERENCE CONCENTRATIONS"

(EPA/600/8-90/066, AUGUST, 1990)

APRIL, 1991

A SCIENCE ADVISORY BOARD REPORT

ABSTRACT

Inhalation Reference Concentrations (RfCs) were developed to serve as a basis for health risk estimates for non-cancer effects (analogous to the oral Reference Dose (RfD)) resulting from exposure to airborne pollutants. On October 26, 1990, the Science Advisory Board (SAB) reviewed the methodology for development of inhalation RfC values (as described in the document "Interim Methods for Development of Inhalation Reference Concentrations," (EPA/600/8-90/066, August 1990), as requested by EPA's Office of Research and Development.

The Committee found the proposed methods for deriving RfCs to be reasonable, although some specific improvements, such as the use of the benchmark dose in place of the No Observed Adverse Effects Level/Lowest Observed Adverse Effects Level (NOAEL/LOAEL), were proposed. Methods to determine RfCs should retain flexibility to accommodate the specific information and characteristics of various toxic substances, and could incorporate a tiered approach in which simpler methods are applied before the more sophisticated methods defined in the documents reviewed are used.

Keywords: RfC; Inhalation Reference Concentration; Benchmark dose; Dosimetry; Methodology.

U. S. ENVIRONMENTAL PROTECTION AGENCY

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U.S. ENVIRONMENTAL PROTECTION AGENCY
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October 26, 1990

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1.0 Executive Summary

Inhalation Reference Concentrations (RfCs) were developed to serve as health risk estimates for non-cancer effects (analogous to the oral Reference Dose (RfD)) resulting from exposure to airborne pollutants. The RfC is an estimate (with uncertainty spanning perhaps 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 non-cancer effects during a lifetime.

SAB review of the methodology for development of inhalation RfC values, as described in the document "Interim Methods for Development of Inhalation Reference Concentrations," (EPA/600/8-90/066, August 1989) was requested by EPA's Office of Research and Development in order to incorporate further expert opinion and recommendations on the methodology, as well as suggestions for its improvement.

The Committee finds the proposed methods for deriving RfCs to be reasonable, although some specific improvements, such as the use of the benchmark dose in place of the No Observed Adverse Effects Level/Lowest Observed Adverse Effects Level (NOAEL/LOAEL), are proposed. Methods to determine RfCs should retain flexibility to accommodate the specific information and characteristics of various toxic substances, and could incorporate a tiered approach in which simpler methods are applied before the more sophisticated methods defined in the documents reviewed are employed.

The Committee recommends review of RfC derivations for several specific chemicals that illustrate each of the dosimetric adjustments, demonstrate inadequate data bases for derivation ("not verifiable" status) or represent difficult scientific issues (e.g., sensitizing agents like toluene diisocyanate)."

The Committee also notes that:

1. The magnitude of uncertainty factors used for a specific agent should decrease as more data are incorporated into a given RfC assessment.

2. A clear articulation of the definition and intent of the various uncertainty factors is needed.

3. Research needs are not clearly described. A special section or report should be drafted to detail these needs.

2.0 Introduction

The Clean Air Act Amendments (CAAA) recently passed by the Congress identifies 189 substances and classes of chemicals, which, if emitted at specified quantities (10 or more tons of a specific substance, or 25 or more tons of of several chemicals), are subjected to Maximum Achievable Control Technology (MACT). Additional chemicals may be listed, and listed chemicals may be delisted, depending on health risks. In addition, the CAAA require emitting sources to demonstrate that, based on health risk estimates, only negligible risks (and no residual risk) exist after implementation of control technology. Inhalation Reference Concentrations (RfCs) have been developed to serve as base-line health risk estimates for non-cancer effects (analogous to the Agency's Reference Dose (RfD) for orally ingested toxicants) resulting from exposure to airborne pollutants. The RfC is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily inhalation exposure in the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious non-cancer effects during a lifetime. It is anticipated that RfCs will be used for CAAA regulatory activities as a part of the determination of listing/delisting decisions, lesser quantity cutoffs, and residual risk for non-cancer health effects of air toxics. Additionally, regional, state and local air pollution control offices have begun to utilize RfC values in risk management programs.

The inhalation RfC methodology follows the oral Reference Dose (RfD) paradigm with an added emphasis on portal-of-entry considerations of comparative toxicity and inhalation dosimetry for particles and gases. Extrapolation modeling has been used to derive factors that have been incorporated in the methodology to adjust exposure concentrations for dosimetric differences between experimental animal species and humans. A draft of the interim methodology was reviewed at a public peer-review workshop in October, 1987 and has since been reviewed and implemented by the Agency's RfD/RfC work group. The methodology was interim and intended to be reviewed and updated as the state-of-the-art progressed. Since the RfC values are now being made available to the public on the Integrated Risk Information System (IRIS), and anticipating their aforementioned role in regulatory support, the EPA Office of Research and Development requested an SAB review to

receive further expert opinion and recommendations on improving the methodology.

In response to this request, the SAB Environmental Health Committee (EHC) met on October 26, 1990 in Arlington Virginia to receive briefings on the RfC methodology from Agency staff, discuss the issues devolving from the Charge to the Committee (see following), and to initiate development of a report responding to these issues. Dr. Ronald Wyzga served as Chair, in the absence of Dr. Arthur Upton.

3.0 Detailed Charge

The SAB was requested to review the methodology for development of inhalation RfC estimates, as described in the document "Interim Methods for Development of Inhalation Reference Concentrations," (EPA/600/8-90/066, August 1990) and its associated documentation, Appendix B to the IRIS (essentially an executive summary to the methodology which also serves as a quick reference for the calculations). Key issues for the review were:

1. Does the methodology utilize appropriate dosimetric extrapolations for particles and gases, respectively?

2. Should the same uncertainty factors be used when dosimetric adjustments are incorporated?

3. Are the concepts and applications of the methodology clearly articulated in its documentation?

4. Is the intended research to support the methods appropriate to improving risk extrapolation procedures?

4.0 Findings

4.1 Overall Findings The document is useful and comprehensive, and it advances considerably the previous approaches for deriving reference concentrations for inhaled toxicants. The proposed dosimetric adjustment factors are relatively sophisticated, however, and require the development and consideration of significant quantities of detailed information; often information at this level of detail may be incongruent with some of the cruder aspects of the methodology, e.g., the application of roughly defined uncertainty factors to numbers of several significant digits. The Agency should give consideration to the development of an iterative approach, in which simpler methods are first applied; only when human exposures appear to be significant, given these initial results, would more detailed methods then be considered. The Committee is also concerned about the emphasis given to the "NOAEL plus uncertainty factor" technique, despite the SAB's past urging that alternative approaches, such as the benchmark method[1], be applied to the raw data[2]. The draft Document discusses the bench-mark method in Appendix A, but refers to this and other approaches as "Novel." We believe these approaches to be alternative, and in some cases, more desirable, methods.

The proposed methods emphasize the importance of the effect of cumulative dose (concentration x time) on response. Although this emphasis may be reasonable for many toxicant-endpoint combinations, the Committee cautions that there are many known examples in the literature when this assumption is not correct and urges flexibility in utilizing alternatives to the cumulative dose concept.

The methods should recognize that there can be considerable differences in the extent of information available, and in toxicity mechanisms for various toxicant-endpoint combinations. This requires flexibility in the methods. Given the need to accommodate knowledge for specific toxicants, the Committee believes it would

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[1] A statistical approach for deriving RfC or RfD, based on the entire set of relevant dose-response data,not only the NOAEL/LOAEL points. The lower ten percent confidence limit sets the RfC or RfD value.

[2] SAB Report "Comments on The Use of Uncertainty and Modifying Factors in Establishing Reference Dose Levels," EPA-SAB-EC-005, January 17, 1990

be useful for the SAB to review some toxicant-specific derivations of the RfC. This would increase our understanding of the overall methodology and its data base requirements and enhance our ability to review the dosimetric adjustments.

The methods should also more explicitly communicate the degree of uncertainty associated with the derivations of the various RfCs. Factors which could be so addressed might include issues such as the validity of the RfC to particles of different sizes, changes in assumptions about breathing mode, applicability of results for children, differences in alternative lung deposition models, and whether deposited dose should be normalized on the basis of lung surface area or per gram of lung tissue. It would be desirable to use 95% confidence intervals for deposition of particles to derive a similar 95% confidence interval for RfCs. In addition, several sizes of particles could be grouped together rather than being detailed so specifically as in the draft document. For example, particle sizes could be categorized in a number of appropriate ranges, based on their aerodynamic size. Finally, the role of, and assumptions about, clearance should also be discussed in more detail.

4.2 <u>Appropriateness of dosimetric extrapolations</u> Overall, we find the methodology to be reasonable. There are some areas, however, where improvements can be made. For example, it is assumed that there are linear relationships between breathing parameters used to derive the Regional Retained Dose Ratios (RDDR) and other sets of breathing parameters. The proposed method also assumes that all of a gas inspired goes to the region of concern. This simplification could be improved by having available two uptake values for the gas, one where only physical absorption is assumed, and another where instantaneous chemical reactions are assumed. These two values would then define bounds for the deposition of the gas.

The methodology might also take note of the fact that there is a close continuum between ultrafine particles and gases. This "continuity" may suggest ways to modify the gas approaches in order to address ultrafine particles.

In the case of the many inhaled chemicals which impact organs other than the lung, toxicity is sometimes related to metabolites of the chemicals, rather than the inhaled chemicals themselves. Application of physiological-biological and pharamacokinetic models

in these cases will require detailed information on the nature of the mechanisms of action for the specific chemical of concern. Methods should be sufficiently flexible to allow more sophisticated pharmacokinetic modeling to be incorporated when required.

The Committee also notes that a new set of physiological parameters (e.g., lung volumes and breathing rates) is to be published in the International Committee for Radiological Protection Reference Manual. These up-dated values should be incorporated into the methodology.

4.3 Appropriate uncertainty factors The oral Reference Dose (RfD) paradigm, on which this proposed methodology is based, applies (generally) ten-fold uncertainty factors to account for uncertainties engendered by the various extrapolations performed to arrive at daily human exposure estimates from the available experimental data. The proposed Inhalation Reference Concentration methods are far more detailed in estimating respiratory exposure and, in fact, adjust for differences in inter-species dosimetry as far as deposition is concerned. The importance and accuracy of that adjustment is highly variable among compounds and among biological endpoints. Clearly the use of more precise methods should not be penalized by applying the same uncertainty factors that would be applied to more general methods, but a general statement about the appropriate uncertainty factor is not possible, other than to expect that improved data and understanding of uptake, as opposed to intake, should lead to smaller uncertainty factors. In general, there will be less uncertainty associated with the dose to the respiratory region than to organs outside the respiratory tract; for that reason, the uncertainty factors associated with respiratory effects would in general be smaller than those associated with effects in the more distal organs.

Dealing with this issue could also be aided by a more detailed articulation of the intent of the various uncertainty factors. An understanding of the various uncertainties for which a specific factor is designed to compensate would allow a better evaluation of the influence of increased information on an uncertainty factor. An alternative scheme that does not require uncertainty factors might use the benchmark dose variant to calculate risk specifically.

4.4 Is the document clearly articulated? The Committee believes that EPA Staff did an excellent job in defining and explaining a sophisticated approach to a complex problem. Many specific detailed observations for improving or clarifying the text were made by Committee members; these have been forwarded to the appropriate EPA Staff. Other considerations are addressed above.

4.5 Appropriateness of suggested research Suggestions for further research are given throughout the document. In some cases these are explicitly mentioned; in others they are inferred. It would be preferable to provide a special section outlining research needs and suggestions. The research suggested should include ways to address many of the uncertainties raised by the Committee. The Committee does, however, wish to indicate that in some cases required research will be compound-specific; the report should acknowledge the need for this research as well for more generic methods research.

5.0 Conclusions and Recommendations

The proposed methods to derive Inhalation Reference Concentrations are reasonable, although some specific improvements, such as the use of the benchmark dose (or other alternative approach) in place of the NOAEL/LOAEL, have been proposed. It is important that the methods to determine RfCs retain flexibility to accommodate the specific information and characteristics of various toxic substances (in light of this, future iterations of the interim methods document could be entitled as "Guidelines" to reinforce the idea that the methods are not "cookbook formulas"). The methods could also incorporate a tiered approach in which simpler methods are applied before the more sophisticated methods defined in the documents reviewed are utilized. Also, a review of the applications of the proposed RfC methods for several specific chemicals would facilitate the evaluation of these methods, and the Committee would be pleased to assist in such reviews.

The Committee also notes that:

1. In general, as the amount of scientific information incorporated into RfC determination increases, the magnitude of the overall uncertainty factor, applied in the RfC derivation, should decrease.

2. A clear articulation of the definition and intent of the various uncertainty factors is needed. This would help define the correct uncertainty factors to be used for RfCs. A review of RfC estimates that illustrate the different dosimetric adjustments and that illustrate the use of different uncertainty factors (e.g., laboratory animal to human, subchronic to chronic, LOAEL to NOAEL, etc.) would aid in the formulation of any recommendations concerning the uncertainty factors.

3. The methodology is reasonably well described. The inclusion of case studies for specific toxicants, as noted above, would improve this description.

4. Research needs are not clearly described. A special section or report should be drafted to detail these needs.

5. The detailed RDDR tables in Appendix H of the draft document provide an inappropriate sense of precision by displaying four significant figures after the decimal point. The tables should be revised to display less detailed data, perhaps giving ranges of particle sizes and RDDRs generated with other deposition models.