National Advisory Committee (NAC)
for Acute Exposure Guideline Levels (AEGLs) for Hazardous Substances
Final Meeting 14 Highlights
The Old Post Office, Rm. M-09
1100 Pennsylvania Avenue
Washington, D.C.
June 14-16, 1999

INTRODUCTION

George Rusch (NAC Chairman) opened the meeting and welcomed all participants. The meeting agenda (Attachment 1) and participants (Attachment 2) are attached. The NAC/AEGL Meeting 13 highlights (Appendix A) were reviewed and approved unanimously as is (Appendix B) based on the motion made by Bob Benson, seconded by Dave Belluck.

STATUS REPORTS AND GENERAL INTEREST ITEMS

29th OECD Meeting Overview

Roger Garrett provided an overview of the OECD meeting held June 7-11, 1999, in Paris, France. Ten OECD countries (technical representatives), four international organizations, and one OECD secretariat were represented at the meeting. Roger Garrett explained that the meeting provided a good platform for a collective effort (both national and international) to improve the scope of support for the AEGL program. The Standing Operating Procedures (SOPs) and five interim status chemicals (aniline, arsine, chlorine, fluorine, and hydrazine) from the National Advisory Committee on Acute Exposure Guidelines Levels (NAC/AEGL) were presented at the OECD meeting. The two primary issues were: (1) to evaluate and reach a consensus on the scientific approach for developing AEGLs, and (2) to seek participation and resource support for the AEGL program. The AEGL program and its methodologies were favorably received and appreciated, and the participants were impressed with the "transparency" (openness) of the methodologies and rationales presented in the SOP, Technical Support Documents (TSDs), and Summary Tables. Questions arose regarding some aspects of the SOP although no consensus was achieved on these issues. These focused primarily on uncertainty factors (magnitude and justification), carcinogenicity, dosimetry, time scaling, and resource support for the AEGL program. George Rusch stated that there was a difference of opinion in the overall philosophy in application of uncertainty factors. For example, the National Academy of Sciences Committee on Toxicology (NAS/COT) has expressed some concern that the uncertainty factors may be to small while some OECD members said they are inappropriate and should not be used at all.

The need and usefulness of an international effort to develop AEGLs was recognized. The fact that chemical spills and emergencies do not recognize political borders necessitates the need for an international, universal approach to responding to such emergencies. Fritz Kalberlah said industry representatives at the OECD meeting were also supportive of the AEGL process and the need for international involvement. Roger Garrett stated that in such an environment, the AEGLs may be utilized in different ways by different countries and their application adjusted under different umbrellas of risk management.

National Academy of Sciences/Committee on Toxicology (NAS/COT)
The status of deliberations by the NAS/COT Subcommittee on AEGLs were discussed by Roger Garrett. The NAS/COT has been reviewing the SOPs and 10 interim-status AEGLs. Additionally, they have also been presented with 10 additional AEGL TSDs to provide a broader perspective of the NAC/AEGL work. An Interim Letter Report (Attachment 3) from the NAS/COT was distributed that provided information regarding their review of the SOP and the AEGL Interim values/TSDs (Attachment 4). Roger Garrett focused on the major issues of incomplete sections in the SOPs, uncertainty factor application/justification, time scaling, use of a NOEL, AEGL-1 issues (specifically, where AEGL-1 values were not developed) and cancer risk. A written response to NAS/COT concerns is planned.

Incomplete sections of the SOPs
Incomplete sections of the SOPs (carcinogenicity, hypersusceptible populations, clarification of precision of values, dosimetry adjustments, and alternate methodologies) will be expanded/revised as required and resubmitted to the NAS/COT in a timely fashion to the next NAS/COT meeting.

Time scaling
The NAS/COT suggested that when empirically derived values of n for the equation, $C^n \times t = k$, are unavailable, the AEGL values should be derived using an $n = 3$ when scaling from longer time periods to shorter periods and an $n = 1$ when scaling from shorter time periods to longer periods. This practice would encompass a greater range of possible concentration-time relationships and provide somewhat lower AEGL values than would be attained using a default of $n = 2$. It was the general consensus of the NAC/AEGL that this approach be adopted (Appendix C).

Dosimetry issues
Although the NAS/COT originally indicated some concern regarding the lack of dosimetric adjustment in the development of AEGLs, it was the consensus of the NAC/AEGL that dosimetry adjustments will not be routinely performed because the existing EPA dosimetry models for gases and vapors have not been validated. Consistent with NAS/COT recommendations, an attempt at dosimetry adjustment will be considered for particulate matter. The SOP will be amended to include brief discussion of methodologies such as particulate matter dosimetry and minute-volume scaling factors.

AEGL-1 issues
The NAS/COT expressed concern regarding the absence of AEGL-1 values for some chemicals. The NAC/AEGL will attempt to set AEGL-1 values where possible. However, for some chemicals the AEGL-l level simply may not be feasible or appropriate and would be of limited use and validity for the emergency planner.

Carcinogenicity
There was extensive discussion regarding the issue of how carcinogenic potential will factor into the development of AEGLs. This topic was discussed in-depth following Dr. Edward Calabrese's presentation/discussion of his single-exposure carcinogen database and is presented under the General Interest Items.

Uncertainty factors
For some uncertainty factors, more definitive justification is required. For example, an uncertainty factor of 3 for intraspecific variability for chemical irritants should not be routinely used with a justification of "mechanism of action is similar and unlikely to vary among individuals." Attention must also be given to consistency of uncertainty factor application and justification. In many cases, the uncertainty factor issues

are chemical-specific. A suggestion was made by George Alexeeff that the NAC/AEGL may, depending on availability of resources, want to investigate variability in responses to chemical irritants.

Alternate methodologies

A discussion of alternate methodologies (e.g., benchmark dose, categorical regression) will be added to the SOP as suggested by the NAS/COT. Collaborative efforts are currently underway with EPA/RTP regarding categorical regression. Where appropriate, these methodologies may be applied to the development of AEGLs.

Interim Chemical Status Reports

Chemical-specific comments from the NAS/COT were briefly discussed by Robert Young and Cheryl Bast. For most of the chemicals, aniline (Attachment 5), arsine (Attachment 6), chlorine (Attachment 7), hydrazine (Attachment 8), dimethylhydrazine (Attachment 9), and methyl hydrazine (Attachment 10), the discussions focused on the effect of calculating AEGL values using a time-scaling factor (n) of 1 or 3 rather than a default of 2 (see above discussion) or the fact that more extensive justification of uncertainty factors was required. Where applicable, tables were presented showing the effect of this adjustment. For 1,2-dichloroethene (Attachment 11), additional data (from a GLP industry study report) has become available necessitating revisit of the current AEGLs. James Barter (PPG) expressed concerns regarding the differential toxicity of the 1,2-dichloroethene isomers and that this may be a moot issue because little or none (<0.5%) of the *cis* isomer is used. Additional deliberations on this chemical was tabled until the new data become available. For phosphine (Attachment 12), NAS/COT concerns will be addressed (i.e., absence of AEGL-1, justification of rationale for previously approved AEGLs) and considered at the next NAC/AEGL meeting. The TSDs and summary tables for these chemicals will be revised accordingly.

General Interest Items

- Hypersusceptible/Hypersensitive Individuals

George Rodgers provided information in response to the NAS/COT request for a more definitive and thorough delineation of a hypersusceptible subpopulation as it pertains to the AEGL process. He noted that the hypersusceptible subpopulation may be defined as that which exhibits an idiosyncratic response or a response that lies outside of or is discontinuous with the range of normal responders. He provided information from the field of anesthesiology to demonstrate the effects of age on anesthetic gas effects. It is likely that the issue hypersusceptiblity may most often be a chemical-specific issue. The hypersusceptible individual may be impossible to identify and, therefore, difficult to protect. It has been estimated that in a chemical accident scenario involving perhaps 1,000-2,500 individuals, the hypersusceptible subpopulation may only encompass one or two individuals.

- Single-exposure carcinogen database

Edward Calabrese presented an overview of his Single Exposure Carcinogen Database (Attachment 13). Following an explanation of the need for such a database, the terms used in the database were defined and the procedure for identifying and extracting data elements for inclusion in the database were explained. The database contains approximately 5500 studies involving 800 chemicals. Positive responses were reported predominately via the oral, injection, and dermal routes by genotoxic carcinogens. Positive reports were reported following single exposures for a wide variety of chemicals on a broad range of species and strains. He will provide some search results to George Rusch on irritant chemicals requested by the NAC/AEGL.

• Acute exposure carcinogenicity issue

There was extensive discussion in response to the NAS/COT concerns regarding the use of cancer risk in the development of AEGLs. The NAS/COT indicated that a consensus on this issue by the NAC/AEGL was needed and that also should be incorporated into the SOP document. Additionally, chemical-specific cancer issues would need to be incorporated into the TSDs. Roger Garrett presented a synopsis of the scientific status of acute exposure cancer response issues. Following extensive discussion it was the consensus of the NAC/AEGL that a cancer notation be included in the Executive Summary AEGL table. The notation would include carcinogenic potential regardless of route and whether or not the risk is quantifiable. This notation would be especially relevant for those chemicals for which a cancer risk (determined by the method described by the NAS) comes within range of the AEGL values determined using noncancer endpoints. The Appendix currently included in TSDs on chemicals with quantifiable carcinogenicity data will be retained and will include 10^{-4}, 10^{-5}, and 10^{-6} risk levels. A discussion regarding the cancer risk and its relevance will be included in this Appendix, the Executive Summary, and text body of the TSD where appropriate. A motion to accept this position was made by Ernest Falke and seconded by Richard Niemeier (Appendix D). The motion passed unanimously. These issues will be included in the SOP.

AEGL PRIORITY CHEMICALS

Hydrogen sulfide, CAS No. 7783-06-4

Chemical Manager: Steven Barbee, Arch Chemical Corp.
Author: Cheryl Bast, ORNL

Cheryl Bast reviewed the previous NAC/AEGL deliberations on hydrogen sulfide (Attachment 14) explaining that the AEGL-1 was currently based on threshold for annoyance. Cheryl Bast presented exposure values provided by Zarena Post (unable to attend) that were obtained near an oil refinery. The described exposure was of approximately 0.5-8 hours duration and involved low levels of additional chemicals (sulfur dioxide, toluene, benzene, methyl-tert-butyl ether). The issue of discussion focused on whether or not to set AEGL-1 levels 5 times greater than the odor threshold or to set levels that are below ambient air levels (i.e., odor threshold). The issue will be revisited at the next meeting.

Perchloromethyl mercaptan, CAS No. 594-42-3

Chemical Manager: Zarena Post, Texas NRCC
Author: Claudia Troxel, ORNL

Claudia Troxel presented a summary of the limited available data on perchloromethyl mercaptan and also described the basis and rationale for the draft AEGL values (Attachment 15) (Loren Koller substituted for Zarena Post). AEGL values were presented using the traditionally applied default *n* of 2 for time scaling as well as the NAS/COT-suggested *n* values of 1 and 3. Comments to the chemical manager from those NAC members who responded to the previously circulated TSD suggested reduction of the total uncertainty factor from 100 to 30. Initially, concern was expressed regarding the validity of an AEGL-1 and several options were considered: (1) no value, (2) use odor threshold as presented in draft TSD, and (3) use subacute study and uncertainty factors. AEGL-1 values were based on the threshold for irritation of 0.079 ppm from a 13-week exposure. The resulting 30-min., 1-hr, 4-hr, and 8-hr AEGL-1 values were 0.018, 0.014, 0.009, and 0.006 ppm, respectively, and incorporated a total uncertainty factor of 10 (a long-term study was utilized to derive values for a short-term effect). The motion for these AEGL-1 values was provided by Bob Snyder

and seconded by John Hinz. The motion passed [YES: 18; NO: 7; ABSTAIN: 0] (Appendix E). Following extensive discussion, it was the consensus of the NAC/AEGL to base the AEGL-2 on minimal reversible effects in rats following repeated exposures to 0.58 ppm. The resulting 30-min., 1-hr, 4-hr, and 8-hr AEGL-2 values were 0.044, 0.035, 0.022, 0.014 ppm and incorporated a total uncertainty factor of 30 (10 for interspecies variability due to data limitations and a steep dose-response curve and 3 for intraspecies variability in response to an irritant). A motion by Bob Benson (seconded by Ernest Falke) to accept these values passed [YES: 20; NO: 6; ABSTAIN: 0] (Appendix E). AEGL-3 also involved extensive deliberations regarding the exposure-response determinant for the value and uncertainty factor application. A motion (made by Ernie Falke and seconded by Bob Benson) to accept the values of 0.38, 0.30, 0.075, and 0.038 ppm for the 30-min, 1 hr, 4 hr, and 8 hr AEGL-3, respectively, passed [YES: 21; NO: 4; ABSTAIN: 0] (Appendix E). These values were based on a nonlethal response of rats to 9 ppm and reflect a total uncertainty factor application of 30 (10 for interspecies and 3 for intraspecies).

SUMMARY OF REVISED AEGL VALUES (ppm) FOR PERCHLOROMETHYLMERCAPTAN					
Classification	**30-min**	**1-hr**	**4-hr**	**8-hr**	**Endpoint**
AEGL-1	0.018	0.014	0.009	0.006	threshold for irritation in rats from a 13-week study
AEGL-2	0.044	0.035	0.022	0.014	minimal reversible effects in rats following subchronic exposure to 0.58 ppm
AEGL-3	0.38	0.30	0.075	0.038	no effect level (9 ppm)for mortality in rats

Toluene, CAS No. 108-88-3

Chemical Manager: Larry Gephart, Exxon Biomedical Sciences, Inc.
Author: Tessa Long, ORNL

Larry Gephart provided an introduction (Attachment 16) and Tessa Long presented an overview of the extensive toluene database (Attachment 17). After discussion, the committee decided to base AEGL-1 values on eye and nose irritation and headache in humans exposed to 100 ppm for 6 hours. The resulting 30-min, 1-hr, 4-hr, and 8-hr AEGL-1 values were 120, 82, 41, and 29 ppm and incorporated a total uncertainty factor of 3 for intraspecies extrapolation. A motion by Loren Koller (seconded by David Belluck) to accept these values passed [YES: 20; NO: 1; ABSTAIN: 1] (Appendix F). The committee decided to base AEGL-2 values on confusion, uncoordination, nausea, and muscular weakness in humans exposed to 200 ppm for 8 hours. The resulting 30-min, 1-hr, 4-hr, and 8-hr AEGL-2 values were 270, 190, 94, and 67 ppm and incorporated a total uncertainty factor of 3 for intraspecies extrapolation. A motion was made by Loren Koller (seconded by David Belluck) to accept these values passed [YES: 21; NO: 1; ABSTAIN: 0] (Appendix F). The committee then decided to base AEGL-3 values on a 1-hour NOEL for death in mice of 6339 ppm. The resulting 30-min, 1-hr, 4-hr, and 8-hr AEGL-3 values were 900, 630, 320, and 220 ppm and incorporated a total uncertainty factor of 10 (3 for intraspecies and 3 for interspecies extrapolation). A motion by Loren Koller (seconded by Kyle Blackman) to unanimously accept these values (Appendix F).

SUMMARY OF PROPOSED AEGL VALUES (ppm) FOR TOLUENE					
Classification	**30-min**	**1-hr**	**4-hr**	**8-hr**	**Endpoint**

AEGL-1	120	82	41	29	eye and nose irritation and headache in humans
AEGL-2	270	190	94	67	confusion, nausea, muscular weakness, uncoordination in humans
AEGL-3	900	630	320	220	NOEL for death in mice

Tetrachloroethylene, CAS No. 127-18-4

Chemical Manager: William Bress, Vermont Dept. Health
Author: Claudia Troxel, ORNL

Claudia Troxel presented a review of the data available for tetrachloroethylene (Attachment 18). The committee discussed the validity of the value of the exponent n=2 obtained from the ten Berge reference, and decided to assume the value was correct. Ernie Falke will attempt to verify this value; if the value cannot be verified, the chemical will be brought back to the committee. After deliberation, the committee (remaining cognizant of CNS effects observed in humans exposed to 50 ppm for 4 hr) decided to base AEGL-1 values on irritation in humans exposed to 106 ppm for 1 hr. The resulting 30-min, 1-hr, 4-hr, and 8-hr AEGL-1 values were 50, 35, 18, and 12 ppm and incorporated a total uncertainty factor of 3 for intraspecies extrapolation. A motion by Steve Barbee (seconded by Richard Niemeier) to accept these values passed [YES: 21; NO: 2; ABSTAIN: 0] (Appendix G). The committee decided to base AEGL-2 values on a NOEL for ataxia in rats exposed to 1150 ppm for 4 hr. The resulting 30-min, 1-hr, 4-hr, and 8-hr AEGL-2 values were 330, 230, 120, and 81 ppm and incorporated a total uncertainty factor of 10 (3 for intraspecies and 3 for interspecies extrapolation). A motion by Bob Benson (seconded by Richard Niemeier) to accept these values passed [YES: 21; NO: 1; ABSTAIN: 0] (Appendix G). The committee decided to base AEGL-3 values on an estimated NOEL for death in mice and rats (highest concentration with no lethality). The resulting 30-min, 1-hr, 4-hr, and 8-hr AEGL-3 values were 690, 490, 240, and 170 ppm and incorporated a total uncertainty factor of 10 (3 for intraspecies and 3 for interspecies extrapolation). A motion was made by Tom Hornshaw (seconded by Steve Barbee). The committee unanimously accepted these values (Appendix G).

SUMMARY OF PROPOSED AEGL VALUES (ppm) FOR TETRACHLOROETHYLENE					
Classification	**30-min**	**1-hr**	**4-hr**	**8-hr**	**Endpoint**
AEGL-1	50	35	18	12	Irritation in humans
AEGL-2	330	230	120	81	NOEL for ataxia in rats
AEGL-3	690	490	240	170	Estimated NOEL for death (highest concentration with no lethality)

ADMINISTRATIVE ISSUES

Future meetings

The following meeting dates and locations have been proposed:

September 14-16, 1999 (Washington, D.C.)
December 6-8, 1999 (Washington, D.C.)
March 16-17, 2000 (Philadelphia or Rutgers University) (prior to SOT)

These highlights are submitted by Robert Young and Po-Yung Lu, ORNL.

LIST OF ATTACHMENTS

The attachments were distributed during the meeting and will be filed in the EPA Docket Office.

1. NAC/AEGL Meeting No. 14 Agenda
2. NAC/AEGL Meeting No. 14 Attendee List
3. Interim Letter Report of NAS/COT/AEGL
4. Summary of Chemical Specific Comments by NAS/COT/AEGL
5. Chemical Specific Comment Responses to NAS/COT/AEGL - Aniline
6. Chemical Specific Comment Responses to NAS/COT/AEGL - Arsine
7. Chemical Specific Comment Responses to NAS/COT/AEGL - Chlorine
8. Chemical Specific Comment Responses to NAS/COT/AEGL - Hydrazine
9. Chemical Specific Comment Responses to NAS/COT/AEGL - Dimethylhydrazine
10. Chemical Specific Comment Responses to NAS/COT/AEGL - Methylhydrzine
11. Chemical Specific Comment Responses to NAS/COT/AEGL - 1,2-Dichloroethene
12. Chemical Specific Comment Responses to NAS/COT/AEGL - Phosphine
13. The Single Exposure Carcinogen Database: Assessing the Circumstances During Which a Single Exposure to a Carcinogen Can Cancer - Edward Calabrese
14. Data Analysis of Hydrogen Sulfide - Cheryl Bast
15. Data Analysis of Perchloromethyl mercaptan - Claudia Troxel
16. Overview of Toluene - Larry Gephart
17. Data Analysis of Toluene - Tessa Long
18. Data Analysis of Tetrachloroethylene - Claudia Troxel

LIST OF APPENDICES

A. Approved NAC-AEGL-13 Meeting Highlights
B. Ballot for Minutes approval
C Ballot for approval on time scaling extrapolation
D. Ballot for approval on how to handle “carcinogenicity” issues in TSD
E. Ballot for Perchloromethyl mercaptan
F. Ballot for Toluene
G. Ballot for Tetrachloroethylene

National Advisory Committee for
Acute Exposure Guideline Levels for Hazardous Substances

Attachment 1

NAC/AEGL-14

The Old Post Office, 1100 Pennsylvania Avenue, Washington, D.C.

AGENDA

Monday, June 14, 1999

10:00 AM	Introductory remarks and approval of NAC/AEGL-13 Highlights (George Rusch, Roger Garrett, and Paul Tobin)
10:15	Status Reports (Roger Garrett, George Rusch, and Ernest Falke) ✦OECD Meeting ✦NAS/COT AEGL Subcommittee Report: • SOP Manual • Time scaling methodology • AEGL-1 level issues • Uncertainty factors • Hypersusceptible/hypersensitive individuals • Dosimetric adjustments • Other issues (benchmark doses, categorical analysis, etc.) • Carcinogenicity
12:30 PM	Lunch
1:30	✦NAS/COT AEGL Subcommittee Report (continued): focus on carcinogenicity
2:00	Single-exposure Carcinogen Database: presentation (Ed Calabrese, University of Massachusetts)
3:00	Break
3:15	Single-exposure Carcinogen Database: demonstration (continued)
3:45	Discussion of carcinogenicity as related to short term exposures
5:15	Administrative issues, future meetings
5:30	Adjourn for the day

Tuesday, June 15, 1999

8:00 AM	✦NAS/COT AEGL Subcommittee Report (continued)
9:00	Review of chemicals with "Interim" AEGL status and NAS/COT review and comment: Aniline, Arsine, Chlorine, Fluorine, Hydrazine, Methyl hydrazine, 1,1- and 1,2-dimethyl hydrazines, Phosphine, and 1,2-Dichloroethene
10:00	Break
10:15	Review of chemicals with "Interim" AEGL status and NAS/COT review and comment (continued)
12:00 PM	Lunch
1:00	Hydrogen sulfide (Steven Barbee/Cheryl Bast)
2:00	Perchloromethylmercaptan (Zarena Post/Claudia Troxel)
3:00	Break
3:15	Perchloromethylmercaptan (continued)
3:45	Toluene (Larry Gephart/Tessa Long)
5:00	Adjourn for the day

Wednesday, June 16, 1999

8:00 AM	Toluene (continued)
9:30	Tetrachloroethylene (Bill Bress/Claudia Troxel)
10:15	Break
10:30	Tetrachloroethylene (continued)
12:30 PM	Adjourn meeting

NAC/AEGL-14
6/13-16/99

Attachment 2

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OVER →

NAC/AEGL-14
6/14-16/99

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Attachment 3

INTERIM LETTER REPORT OF THE SUBCOMMITTEE ON ACUTE EXPOSURE GUIDELINE LEVELS

Subcommittee on Acute Exposure Guideline Levels

Committee on Toxicology

Board on Environmental Studies and Toxicology

Commission on Life Sciences

National Research Council

May 1999

NATIONAL RESEARCH COUNCIL
BOARD ON ENVIRONMENTAL STUDIES
AND TOXICOLOGY
2101 Constitution Avenue Washington, D.C. 20418

COMMITTEE ON TOXICOLOGY

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May 5, 1999

Roger Garrett, Ph.D.
Director, Special Science Program
Office of Pollution Prevention and Toxics, and
Director, AEGL Program
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MS 7403
401 M Street, SW
Washington, D.C. 20460

Dear Dr. Garrett:

This interim letter report was prepared by the Subcommittee on Acute Exposure Guideline Levels* of the National Research Council's Committee on Toxicology in response to a request from the National Advisory Committee (NAC) on Acute Exposure Guideline Levels (AEGLs)** for Hazardous Substances. The subcommittee is charged to review the scientific validity of the AEGLs developed by the NAC for extremely hazardous substances (EHSs), as defined pursuant to the Superfund Amendments and Reauthorization Act of 1986. The subcommittee held its first meeting on October 15-16, 1998. At that meeting, the NAC presented its standing operating procedures (SOP) document, which serves as the guidance document for developing AEGL documents for individual chemicals. The NAC's SOP document is generally based upon the COT's 1993 report entitled *Guidelines for Developing Community Exposure Levels for Hazardous Substances*.

The subcommittee reviewed the NAC's draft SOP document and concludes overall that it provides generally sound guidelines for developing AEGLs for EHSs. However, the subcommittee recommends certain revisions to particular sections of the document. These are discussed below under five headings: (1) incomplete sections, (2) derivation of AEGLs, (3) odor threshold and other nuisance effects, (4) uncertainty factors, and (5) time scaling.

Because the NAC is planning to prepare AEGL documents for approximately 200 chemicals over the next several years, the subcommittee believes it is important that the NAC revise its SOP document as recommended herein before continuing to produce individual

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*Appendix 1 contains the names and brief biographies of the subcommittee members.

**Appendix 2 contains a list of abbreviations used in this interim letter report.

AEGL documents; otherwise the subcommittee is likely to have the same concerns about all AEGL documents that it reviews in the future.

Sincerely,

Daniel Krewski, Ph.D.
Chair, Subcommittee on Acute
Exposure Guideline Levels

Bailus Walker, Jr., Ph.D., M.P.H.
Chair, Committee on Toxicology

c: Paul Tobin
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INTERIM LETTER REPORT OF THE SUBCOMMITTEE ON ACUTE EXPOSURE GUIDELINE LEVELS

BACKGROUND

In 1990, the U.S. Environmental Protection Agency (EPA) and the Agency for Toxic Substances and Disease Registry (ATSDR) asked the National Research Council (NRC) to develop guidelines that could be used to develop community emergency exposure levels (CEELs) for extremely hazardous substances (EHSs) pursuant to the Superfund Amendments and Reauthorization Act (SARA) of 1986.

In response to that request, a subcommittee of the NRC's Committee on Toxicology (COT) prepared a report in 1993 entitled *Guidelines for Developing Community Exposure Levels for Hazardous Substances*. That report provides step-by-step guidance for setting CEELs for EHSs (NRC 1993).

In 1995, EPA, together with several other federal and state agencies and several private organizations, convened an advisory committee—the National Advisory Committee (NAC) on Acute Exposure Guideline Levels (AEGLs) for Hazardous Substances—to develop AEGLs (analogous to CEELs) for up to 400 extremely hazardous substances (EHSs). To date, the NAC has reviewed and approved AEGLs for approximately 40 EHSs.

The AEGLs developed by the NAC potentially have a broad range of applications for federal, state, and local governments and for the private sector. AEGLs are needed for planning, response, and prevention applications related to the accidental releases of EHSs. It is also likely that the AEGL documents will be used by other groups to update workplace and ambient-air assessments of these materials.

CHARGE TO THE SUBCOMMITTEE

In 1998, EPA, DOD, and other agencies arranged for an independent NRC study to review AEGLs for EHSs for scientific validity, completeness, and conformance to the NRC's guidelines report (NRC 1993). The NRC was also asked to review the NAC's draft manual on standing operating procedures (SOP) (NAC 1998). That manual is based on the guidance provided by the NRC (1993) and contains further details and clarification of specific procedures, methods, criteria, and other guidelines used by the NAC in the development and interpretation of AEGLs.

In response to the NAC's 1998 request, COT convened the Subcommittee on Acute Exposure Guideline Levels to review the draft SOP manual and AEGL documents approved by the NAC. The subcommittee members were selected because of their expertise in toxicology, pharmacology, medicine, industrial hygiene, biostatistics, risk assessment, risk communication, and interpretation of the technical information.

This interim letter report presents the subcommittee's conclusions and recommendations for improving the SOP manual.

CONCLUSIONS AND RECOMMENDATIONS

The subcommittee concludes overall that the NAC's draft SOP manual provides generally sound guidelines for developing AEGLs for EHSs. However, the subcommittee recommends certain revisions to particular sections of the manual. These are discussed below under five headings: (1) incomplete sections, (2) derivation of AEGLs, (3) odor threshold and other nuisance effects, (4) uncertainty factors, and (5) time scaling.

1. Incomplete Sections

Some sections of the NAC's draft SOP manual are incomplete. For example, section 2.8 on guidelines for known and suspect carcinogens is still in preparation. It is anticipated that the guidance presented in that section will be helpful in estimating cancer risks from high-level, short-term exposures. The section on hypersusceptible or hypersensitive individuals (section 2.10.3) is also incomplete; the guidance presented in that section will be helpful in determining the magnitude of uncertainty factors for susceptible subpopulations.

The subcommittee recommends that both sections be completed as soon as possible.

2. Derivation of AEGLs

The NRC Committee on Toxicology has published several reports on estimating carcinogenic risk for short-term, high-level exposures from chronic bioassay data (NRC 1986a,b; 1992; 1993; 1999); that approach has been used for several years in Committee on Toxicology reports. Cancer risk is estimated on the basis of the average lifetime daily dose calculated from the total dose for a short-term exposure. The estimated cancer risk is often multiplied by an uncertainty factor of up to 10 to account for exposure during sensitive ages (e.g., infants and children). The subcommittee recommends that this approach be adopted by the NAC in estimating cancer risk for short-term exposure, when appropriate. For carcinogenic chemicals, the NAC primarily uses systemic toxicity for deriving AEGL values. The subcommittee recommends that the NAC develop exposure values corresponding to 10^{-4}, 10^{-5}, or 10^{-6} risk levels.

The subcommittee also recommends incorporation of certain new risk-assessment methods in the SOP manual. For example, the NAC said it did not use the dosimetric adjustments used by EPA for the determination of reference concentrations because they "have not been validated with experimental data." The subcommittee does not agree with that statement. The dosimetric adjustments of EPA were based in large part on a study of species differences in dosimetry of particles of different sizes conducted by EPA over 10 years. Thus,

the adjustments that EPA uses are in fact based on experimental data. In addition, the subcommittee believes that certain newer risk assessment methods such as the benchmark dose might be useful in the determination of AEGLs in the future and recommends that the NAC consider these methods within the current scheme.

The subcommittee recommends that the text in the SOP manual (page 47, section 2.10.1) on precision of risk values be clarified. Given the reliability of data used to establish AEGLs, the subcommittee recommends that the AEGLs be rounded to one or two significant figures, as appropriate.

3. Odor Threshold and Other Nuisance Effects

Distinctions should be drawn between odor perception, nuisance effects, and adverse health effects. The NAC should specify how irritation, nuisance effects (Cometto-Muñiz and Cain 1994; Abraham et al. 1996), and ratings of well-being (Seeber et al. 1997) are to be considered in the derivation of AEGLs.

AEGLs below the odor threshold should be indicated. AEGL-1 is the airborne concentration [expressed as ppm or mg/m^3] of a substance at or above which it is predicted that the general population, including "susceptible" but excluding "hypersusceptible" individuals, could experience notable discomfort. Airborne concentrations below AEGL-1 represent exposure levels that could produce mild odor, taste, or other sensory irritation. Exposures to chemicals at concentrations below the odor threshold could be of concern.

Olfactory fatigue and the decreased ability to detect odor over time need to be considered for each chemical of concern. When the AEGL-1 is set on the basis of odor, the subcommittee recommends that the NAC establish the value for the shortest time and indicate that the AEGL-1 value for longer exposures is not needed. However, this might not be the case if an adverse health effect were to occur (e.g., headache increasing with time).

4. Uncertainty Factors

In the absence of specific information on the magnitude of uncertainty factors for several extrapolations—(1) animal to human, (2) general human population to susceptible subpopulations, and (3) subchronic exposure to chronic exposure—the NAC uses a default uncertainty factor of 10 for each extrapolation. The NAC, however, uses uncertainty factors of less than 10 when relevant information—such as mechanism of action and consistency of effects at similar concentrations in several animal species—is available. At its next meeting, the subcommittee will continue to deliberate on the need for uncertainty factors for (1) lack of no-observed adverse-health-effect levels (NOAELs) and (2) inadequate data bases. The subcommittee's recommendations on those factors will be provided in its next report.

such extrapolations (i.e., derivation of an AEGL from RD_{10}) are questionable given the fact that extrapolation from even the RD_{50} have been shown to be problematic (Schaper 1993).

The rationale for using any particular uncertainty factor should be included in the discussion of the derivation of each AEGL, including justifications for not applying default uncertainty factors of 10.

5. Time Scaling

AEGLs for EHSs are derived for exposure durations of 30 min to 8 hr to meet a wide range of needs for government and private organizations. However, exposure-response data from experimental animals and from human-exposure incidents often involve exposure durations different from those specified for AEGLs. Therefore, extrapolation from the reported exposure period and chemical concentration is often required in the derivation of AEGLs.

Haber's rule (i.e., $c \times t = k$, where c is exposure concentration, t is exposure time, and k is a constant) has been used to relate exposure concentration and duration to a toxic effect (Rinehart and Hatch 1964). Basically, this concept states that exposure concentration and duration can be reciprocally adjusted to maintain a cumulative exposure constant (k), and that this cumulative exposure constant will always reflect a specific toxic response. This inverse relationship of concentration and time might be valid when the toxic response to a chemical is equally dependent upon the concentration and the exposure duration. But, several investigators have found that Haber's rule was not applicable to many chemicals; the concentration and time relationships were not always linear. The work by ten Berge et al. (1986) with acutely toxic chemicals revealed chemical-specific relationships between exposure concentration and time that were often exponential rather than linear. That relationship can be expressed by the equation $C^n \times t = k$, where n represents a chemical-specific exponent and even a toxic-end-point-specific exponent.

However, Druckrey (1967) and Rozman (1999) proposed, on the basis of experimental data, that the exponent in the equation—c × t = k—should be placed on t rather than c. The subcommittee believes that adequate research has not been done on time scaling and, therefore, it is unable to determine with confidence whether the exponent should be placed on c or t. At its next meeting, the subcommittee will hear presentations from the NAC and other scientists; those presentations might be useful in resolving this issue.

MISCELLANEOUS COMMENTS

The subcommittee believes that it is inappropriate to use the term "NOEL" when addressing frank toxicity (severe adverse effects) or mortality, because other less severe adverse effects are occurring at that level. The subcommittee recommends that the NAC use the term "no effect level for mortality or frank effects" instead of "NOEL."

NEXT STEPS

Because the NAC will be preparing AEGL documents for approximately 400 EHSs over the next several years and because the SOP manual will be used in the derivation of AEGLs, the subcommittee recommends that the draft SOP manual be revised as soon as possible. In subsequent reports that will assess the scientific validity of NAC AEGLs for several EHSs, the subcommittee may offer additional comments on the draft SOP manual.

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APPENDIX 1

SUBCOMMITTEE ROSTER AND BIOGRAPHIES
SUBCOMMITTEE ON ACUTE EXPOSURE GUIDELINE LEVELS

DANIEL KREWSKI *(chair),* Faculty of Medicine, University of Ottawa. Dr. Krewski is professor of medicine and of epidemiology and community medicine at the University of Ottawa, and adjunct research professor of statistics at Carleton University. Previously, he served as director of Risk Management and as director of the Bureau of Chemical Hazards with Health Canada. He received his M.Sc. and Ph.D. in mathematics and statistics from Carleton University, and his M.H.A. from the University of Ottawa. Dr. Krewski is associate editor of *Risk Analysis* and the *Journal of Epidemiology and Biostatistics*. He is currently a member of the NRC Board on Environmental Studies and Toxicology and its Committee on Toxicology. He recently chaired the NRC's Colloquium on Scientific Advances and the Future in Toxicologic Risk Assessment. He is also a member of the Committee on Research Priorities for Airborne Particulate Matter. Dr. Krewski has published more than 300 journal articles and book chapters in the areas of risk assessment, biostatistics, and epidemiology.

EDWARD C. BISHOP, Parsons Engineering Science, Inc. Dr. Bishop is a program manager at Parsons Engineering Science, Inc. He received his M.S. in engineering from the University of California, Los Angeles, and his Ph.D. in environmental health sciences from the University of California at Berkeley. Dr. Bishop has twenty-six years of experience as an industrial hygienist and environmental engineer. From 1986-1992, Lieutenant Colonel Bishop served as senior bioenvironmental engineering manager for the U.S. Air Force at Bolling Air Force Base in Washington, D.C. From 1983-1986, he was chief of industrial hygiene engineering for the U.S. Air Force in Europe. From 1980-1983, he served as bioenvironmental engineering consultant for the Air Force Occupational and Environmental Health Laboratory at Brooks Air Force Base in Texas. His experience includes program development, program management. technical consulting, and policy development in the areas of environmental compliance, remedial investigations, hazardous waste minimization, wastewater treatment, industrial process evaluation, pollution prevention, industrial hygiene, risk assessment, and radiation protection.

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JOHN DOULL, University of Kansas Medical Center. Dr. Doull is professor emeritus of pharmacology and toxicology at the University of Kansas Medical Center. He received his Ph.D. in pharmacology and an M.D. from the University of Chicago. At the University of

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DONALD E. GARDNER, Inhalation Toxicology Associates. Dr. Gardner is president of Inhalation Toxicology Associates. He received his Ph.D. in environmental health and toxicology in 1971 from the University of Cincinnati. Dr. Gardner's research interests include inhalation toxicology, environmental and occupational toxicology, immunotoxicology, and host defense mechanisms. He was division director of the EPA toxicology laboratory in Research Triangle Park, North Carolina. Later, he became vice president and chief scientist for ManTech Environmental Technology, Inc. Dr. Gardner was awarded the Society of Toxicology's 1992 Inhalation Toxicology Specialty Section Lifetime Achievement Award. He also served as president of the society's metals, immunology, and inhalation toxicology specialty sections. Dr. Gardner is currently the chair of the NRC's Subcommittee on Rocket Emission Toxicants and the Subcommittee on Guidelines for Spacecraft Maximum Allowable Concentrations (SMACs) for Space Station Contaminants. He is a member of the Subcommittee on Chronic Reference Doses for Selected Chemical Warfare Agents. Dr. Gardner serves on the board of directors for the Academy of Toxicological Sciences. He is editor-in-chief of the journal *Inhalation Toxicology*, and is on the editorial board of *Toxic Substance Journal, Environmental and Nutritional Interations*.

DAVID W. GAYLOR, U.S. Food and Drug Administration, Jefferson, Arkansas. Dr. Gaylor is associate director for Risk Assessment Policy and Research, National Center for Toxicological Research, U.S. Food and Drug Administration, Jefferson, Arkansas. He received his Ph.D. in statistics from North Carolina State University. He has been employed by the General Electric Company, General Dynamics Corporation, Research Triangle Institute, and the National Institute of Environmental Health Sciences previous to his current position. Dr. Gaylor serves on the editorial boards of Risk Analysis, Toxicological Industrial Health, Human Ecological Risk Assessment, and Regulatory Toxicology and Pharmacology. He received the Shewell Award and the Frank Wilcoxin Prize from the American Society for Quality Control and the Distinguished Achievement Medal from the Statistics and Environment Section of the American Statistical Association. Dr. Gaylor is a fellow of the American Statistical Society and the Society for Risk Analysis.

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Journal of Toxicology, Human and Ecological Risk Assessment, and *Human and Experimental Toxicology*.

FLORENCE K. KINOSHITA, Hercules Incorporated. Dr. Kinoshita is principal toxicology scientist of Safety, Health and Environment at Hercules Incorporated. She received her M.S. and Ph.D. in pharmacology from the University of Chicago. Presently, she is involved in safety assessment of industrial chemicals and food additives. She is a Diplomate of the American Board of Toxicology. She has served on numerous advisory committees of the U.S. Environmental Protection Agency, U.S. Food and Drug Administration, and the National Library of Medicine. She has also served on the National Institute of Health's Toxicology Study Section. She has served as the secretary of the Society of Toxicology from 1989-1992. Currently, she is a member of the NRC's Committee on Toxicology.

STEPHEN U. LESTER, Center for Health, Environment and Justice. Mr. Lester is the science director for the Center for Health, Environment and Justice. He received his M.S. in toxicology from the Harvard University School of Public Health and his M.S. in environmental health from the New York University Institute of Environmental Medicine. He served as a member of the NRC's Subcommittee on Zinc Cadmium Sulfide. Also, he served on the Technical Advisory Panel on Assessment of Superfund Implementation to the U.S. Congress Office of Technology Assessment; and on the National Institute of Environmental Health Sciences Special Review Committees for Superfund Basic Research and for Environmental Justice: Partnerships for Communication. Presently, he serves as a board member of the Love Canal Medical Trust Fund; is a member of the Technical Advisory Panel for the Oil, Chemical and Atomic Workers Hazardous Waste Training Program; is on the Love Canal Expert Advisory Committee to the New York State Department of Health; and is a member of the National Resource Council Committee on Intrinsic Remediation in Subsurface Environments. Mr. Lester has published many articles and chapters in several books.

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CALVIN C. WILLHITE, State of California, Department of Toxic Substances Control. Dr. Willhite is a toxicologist in the State of California Department of Toxic Substances Control. He received his M.S. in toxicology from Utah State University, and his Ph.D. in pharmacology from Dartmouth Medical School. Dr. Willhite has served on the Chemical Substances Threshold Limit Values (TLV) Committee of the American Conference of Governmental Industrial

Hygienists. He is currently a member of the Society of Toxicology Program Committee and the National Sanitation Foundation's Health Effects Task Group. He has served on several Regulatory/Advisory Panels, including the World Health Organization, International Agency for Research on Cancer (IARC), U.S. National Institutes of Health, and the U.S. Agency for International Development. Dr. Willhite has published primarily in developmental toxicology and is on the editorial board of the *Journal of Toxicology and Environmental Health, Critical Reviews*, *Toxicology*, and *Toxicology and Applied Pharmacology.*

APPENDIX 2

LIST OF ACRONYMS

AEGLS	Acute Exposure Guideline Levels
ATSDR	Agency for Toxic Substances and Disease Registry
c	Exposure concentration
CEELs	Community Emergency Exposure Levels
COT	Committee on Toxicology
EHSs	Extremely Hazardous Substances
EPA	United States Environmental Protection Agency
mg/m^3	milligrams per cubic meter
NAC	National Advisory Committee on Acute Exposure Guideline Levels
NOAEL	No Observed-Adverse-Effect Level
NRC	National Research Council
ppm	parts per million
RD_{10}	Respiratory Depression in 10% of the Animals
SARA	Superfund Amendment and Reauthorization Act
SOP	Standing Operating Procedures
t	exposure time

Summary of Chemical-Specific Comments by the NAS Subcommittee on AEGLs on NAC/AEGL Committee Technical Support Documents, AEGL Values, and Accompanying Rationale

NAS AEGL Subcommittee Meetings October 15-16, 1998 and April 19-20, 1999

A. FLUORINE

1. AEGL endpoint (AEGL-3 NOAEL) –

   The AEGL-3 NOAEL selected (15 ppm) is only ½ of the LC-50 value. Provide a strong scientific rationale for a value this close to the LC-50 or add an additional safety factor..

2. Interspecies Uncertainty Factors –

   More justification should be included

   a. No discussion in TSD under AEGL-2 rationale section

   b. Weak discussion in Executive Summary for AEGL-2

   c. Stronger discussion in Summary Table for AEGL-2

   d. More justification for UF of 1 for AEGL-3

3. Intraspecies Uncertainty FactorsIntraspecies Uncertainty Factors –

Inadequate justification for UF of 3

a. State how can we be sure that this covers asthmatics and children and infants.

b. What is an appropriate range of Ufs for asthmatics since all asthmatics are not the same?

c. What is the appropriate range for children and infants?

d. Include literature on asthmatics and/or susceptible individuals as part of the improved justification.

4. Interspecies Uncertainty Factors –

a. More justification for flat-lining ½ and 1 hr. AEGL-1 at 2 ppm and 4 and 8 hr. AEGL-1 at 1 ppm.

b. What is the justification for using a value of n = 1.77 derived from LC_{50} data for time scaling AEGL-2 values? Include this justification in the TSD.

5. Human Data --

Provide more discussion regarding the human experience as it relates to both AEGL-1 and AEGL-2. Contrast and compare data among individuals and various human studies.

6. Miscellaneous Procedures --

Issue of significant figures (position changed later)

B. ARSINE

1. AEGL-1 –

   Should try to develop an AEGL-1 value. If not, why not? Add a discussion, including a suggestion for further research in this area.

2. Intraspecies Uncertainty Factors –

   Question the use of UF of 3. Must provide more justification for Ufs that are less than 10. Refers author to work by Barnes, Hattis, etc. that should be included on the justification.

3. Time Scaling --

   Question use of n = 2 (see later formal comments recommending n = 1 and n = 3 as the lower and upper bounds, respectively).

4. Human Experience --

   Add more discussion to the human experience as it relates to AEGL-3.

5. Miscellaneous –

   Details and calculations should be provided in the TSD for the recommended AEGL values only. Derivations for alternative AEGL values should not be included in the TSD.

C. METHYL HYDRAZINE

1. Intraspecies UF of 3 for AEGL-3 and indirectly for AEGL-2 –

   Must provide a strong justification why the intraspecies UF for methyl hydrazine is 3 and the UF for the dimethyl hydrazines is 10.

2. Carcinogenicity

   Review the cancer risk assessment data for methyl hydrazine, hydrazine and the dimethylhydrazines and improve the discussion/rationale for not considering carcinogenicity as the basis for the methyl hydrazine AEGLs.

3. Miscellaneous

   Definition/description of AEGLs –

   Recommends language such as "rare exposures with complete recovery" rather than "one-time exposure." (See General Comments.)

D. DIMETHYLHYDRAZINES (1,1- and 1,2-)

1. Intraspecies UF of 10 fpr AEGL-2 and AEGL-3 Values

   Provide discussion/explanation why the intraspecies AEGL-2 and AEGL-3 UFs for the dimethylhydrazines are 10 and the UFs for methyl hydrazine are 3.

2. Carcinogenicity

   Review the cancer risk assessment data on dimethylhydrazines as well as multi-stage concepts and methodologies and other carcinogenicity information. Improve the discussion and the rationale for not using carcinogenicity as the basis for developing the AEGLs.

3. Attempts should be made to develop AEGL-1 Values.

4. Time Scaling

   a. Indicate the reference and toxicity endpoint used to derive the value of n in both the Summary Tables and the Executive Summary, as well as in the text of the TSD.

5. Human Condition –

   Although there does not appear to be any acute toxicity data, there should be some discussion regarding the human condition and the fact that the data from animal studies represent a credible approach to developing AEGL values for humans.

E. CHLORINE

1. Intraspecies Uncertainty Factors --

   a. Question the use of a UF of 1 for AEGL-1 and AEGL-2 based on effects observed in a single asthmatic, who is intended to represent the sensitive or susceptible populations. Should improve the justification, including the consideration of other susceptible individuals, such as children and infants, etc., the range of susceptibility of asthmatics as a subpopulation, and the consideration of the exercise mode of the test subjects.

   b. The use of a UF of 3 for AEGL-3 does not appear to be consistent with the use of a UF of 1 for AEGL-2. Provide justification for this apparent inconsistency or reconsider the UF values.

2. Time Scaling –

   Recommend using upper and lower bounds of n as 1 and 3. This would encompass 90 percent of the chemicals investigated by Ten Berge.

3. Delayed morbidity and mortality

   More information should be provided on the delayed morbidity and mortality observed in the mouse studies. How consistent was the observation of delayed effects across studies and how clear was the evidence that the mice died of bronchopneumonia? Improve the justification for not using the mouse data as the basis for AEGL-3.

F. HYDRAZINE

1. Intraspecies Uncertainty Factors and Irritant Effects –

   a. It is important for the NAC/AEGL Committee to make clear distinctions among irritants when selecting uncertainty factors for AEGL-1 to protect sensitive or susceptible individuals such as asthmatics. For example, there will be a wider range of adverse effects among more mild irritants such as sulfur dioxide as compared to more highly reactive irritants such as hydrogen sulfide. Therefore, it is important to consider UFs of 3 for chemicals such as SO_2 and Ufs of 10 for chemicals such as H_2S.

      In the case of hydrazine, it is important to emphasize that it is highly reactive as stated on lines 34-36 of the Executive Summary (should be sure that this statement and an appropriate discussion appear in the Summary Table and Text of the TSD, respectively). Would like to see same type of statements for highly reactive or mildly, moderate, etc., reactive chemicals and get away from the generic statement that "the mechanisms of action is believed to be similar."

   b. It appears that a UF of 3 for AEGL-2 is justifiable but a clear statement should be added that the UFs selected are considered adequate to protect children and infants.

   c. Include more discussion in the TSD regarding the "continuous" aspect of hydrazine exposure as reported by House, 1964. (??)

2. Carcinogenicity --

   a. Data and information on, or related to, carcinogenicity should be included in the TSD, even if it is not used to set the AEGL values. For example, include a discussion of MacEwen, et. al. In cancer section of TSD (page 20).

b .Hydrazine is a genotoxic carcinogen and, therefore, this fact should be added to the text, as well as the cancer assessments for 10^{-5} and 10^{-6} risk.

c. NAC/AEGL Committee is referred to the SMAC document and the discussion and treatment of hydrazine as a carcinogen in that document. The NAS Subcommittee on AEGLs believes the use of a UF of 2.8 in the cancer risk assessment calculation is protective of children. This UF was used in the SMAC document since it is not known what day in the course of human development is the most critical exposure period for inducing tumors. The Committee is referred also to Crump and Howe (1984), regarding the use of the uncertainty factor.

d. Further discussion by the NAS Subcommittee for AEGLs is summarized as following:

(1) Uncertainty of 30 to 50 fold is already built into the risk model.

(2) The NAS has used risk levels of 10^{-6} for the general population (SPEGLs) and 10^{-4} for occupational groups (EEGLs and SMACs).

(3) The fact that AEGLs are guideline levels for a rare event or single, one-time exposures and are limited to a local geographical area are good arguments for not settling AEGL values based on carcinogenic properties.

(4) To provide guidance to emergency planners and responders for risk management purposes, guidance can be developed either generically or on a case-by-case basis.

(5) Potential options for guidane might include comparisons of other carcinogens (known human vs. animal carcinogens, although both are likely), environmental justice issues (is the potentially exposed local population protected? Does a 10^{-4} risk

level protect children and infants, etc.?). The NAC/AEGL Committee is referred to the 1992 SMAC document that addresses guidelines for developing jshort-term exposure limits.

3. Time Scaling –

Use n = 3 for time scaling from 1 hour to 1./2 hour and N = 1 from 1 hour to 4 and 8 hours (see general comments).

G. ANILINE

1. Carcinogenicity --

   a. More comprehensive discussion on the carcinogenicity of aniline should be added to the TSD and the large amount of genotoxicity data available. It is recommended that the IRIS document on aniline be reviewed and that the relevant issues be addressed in the TSD.

   b. The NAS Subcommittee noted that EPA has classified aniline as a B-2 carcinogen while the TLV Committee has concluded that aniline is not a probable carcinogen. These observations could be included in the discussion in the TSD. The Subcommittee does not believe that aniline is a human carcinogen or is a very weak carcinogen (*i.e.,* 3000 ppm threshold).

2. Time Scaling –

   a. Extrapolating to shorter exposure periods from 8 hour empirical data points using n = 1 for AEGL-1 and AEGL-2 was supported by the NAS Subcommittee. However, because of the considerable span from 8 hours, the case should be strengthened with a discussion, including information in the Kim and Carlson paper.

   b. Question as to the use of n = 1 for time scaling AEGL-3. If this value is used, the NAC/AEGL Committee should obtain more information from the literature on lethality response over time and include it in the discussion and scientific rationale sections of the TSD.

3. Intraspecies Uncertainty Factors –

   The UFs are OK but need more discussion on children and infants and other susceptible subpopulations. Specifically, need to better document effects on children and infants with supporting studies. Recommended a better reference to, and information from, St. Louis hospital studies to support the UFs selected.

4. Miscellaneous –

   a. NAC/AEGL Committee should address hypersusceptibility and hypersensitivity (see general comments).

   b. A table and discussion on odor thresholds should be included in the TSD and should be separate from the non-lethal toxicity section. This should be done for all chemicals so that the levels for odor threshold can be compared to levels related to adverse effects, where this is possible (*i.e.,* the exposed population may smell the chemical but there is no concern for adverse effects). Suggests this should be included under physical/chemical properties.

   c. Add the aniline levels and the effects observed in the Price study and include this in a discussion of congenital sensitivity.

   d. Change graph to differentiate between empirical and extrapolated data.

H. 1,2 DICHLOROETHENE

1. Time Scaling --

   NAS Subcommittee feels that extrapolation from 5-minute data to 1-hour or longer is questionable since a steady state equilibrium has not been reached in 5 to 10 minutes. If the NAC/AEGL Committee wishes to stay with this approach, a value of n = 1 should be used for scaling all the way to 8 hours and the resultant values used unless other supporting data challenge the extrapolated values.

2. AEGL-3 Endpoint --

   a. It is believed that the endpoint for AEGL-3, fibrous swelling of cardiac tissue seen in only 2 of 6 animals, is flawed. This morphological change is not known, has not been reported as a toxicological endpoint, and is not considered to be a valid histopathological finding. The only credible effect was fatty infiltration of the liver, which may be more appropriate for AEGL-2. Recommends that the cardiac muscle endpoint be replaced with a credible endpoint, perhaps using the LC_{50} value as the basis.

3. .AEGL-2 Endpoint –

   a. Suggest using fatty infiltration of the liver as the AEGL-2 endpoint.

   b. AEGL-2 values and all AEGL-3 values are below the TLV value of 200 ppm. Statement in TSD that the TLV value is being updated is not really true. The TLV value was set in 1946 and it is not anticipated that the value will be changed in the near future. Hence, the possibility of change should be treated lightly in any discussion in the TSD.

4. Modifying Factor –

Question the use of a MF of 2 for differentiating the toxicity between the cis and trans isomers. The NAC Subcommittee questions whether there is a significant (*i.e.*, 2-fold) difference in the toxicity of the two isomers. If there are reported d differences, the data should be presented in the TSD. If there is no supporting data, the MF of 2 should be deleted.

I. PHOSPHINE

1. Odor Threshold --

   Additional data available on lower odor threshold levels. Dr. Florence Kinoshita will provide references. May be able to develop AEGL-2 values that are above the odor threshold.

2. Subchronic Data –

   Concerns regarding the use of subchronic data for developing AEGL-2 values. Should attempt to use acute toxicity data. If acute toxicity data from human or animal data is not adequate, suggested considering scaling back from 13 weeks to 8 hours with n = 3. However, the NAS Subcommittee does not want to encourage the use of subchronic data to develop AEGL values. Also, speculated that rat and mouse data with 2- week exposure reported by Morgan, et. al., 1995, may be more appropriate than a 13-week study.

3. Uncertainty Factors --

   Recommends review of UF of 3 in light of mouse data.

4. Miscellaneous –

   a. Improve the language in the "Confidence and Support" section of the Summary Tables for both AEGL-2 and AEGL-3.

   b. Recommend checking human data reported by Chafrika, et. al., 1976, regarding AEGL-2 values.

   c. Suggested human reference with 0.2 ppm causing headaches (Gering ? Jones?)

   d. Page 10 lines 6 and 7 (Devel./repro. tox.section), specify that there is no human data, as opposed to no animal data.

   e. NAS Subcommittee believes there is additional useful data available for both AEGL-2 and AEGL-3 development (some of which is referenced here).

J. GENERAL COMMENTS/GUIDELINES

1. All changes recommended by the NAS AEGL Subcommittee should be made in the text of the Technical Support Document as well as the Executive Summary and the Summary Table as appropriate.

2. AEGL definition or characterization –

   Recommends that NAC/AEGL Committee consider using the language "rare exposures with complete recovery" rather than a "one-time exposure." Recommends reviewing and using information in Kinkade, et. al., 1985.

3. Delete all alternative AEGL derivations from TSDs.

4. Attempt to develop AEGL-1 values in instances where they have not been developed.

5. Intraspecies uncertainty factors less than 10 --

   Improve the discussions and rationale that justify the use of UFs of less than 10, particularly with respect to children and infants, but also for other susceptible subpopulations. UFs of less than 10 should have a strong justification.

6. Provide justifications for using time-exposure relationships (values of n in $C^n x\ t = k$) derived from lethality (LC_{50}) data for time scaling AEGL-2 and AEGL-1 values.

7. NAC/AEGL Committee should address the issue of hypersensitivity/hypersusceptibility in the SOP Manual and in the TSDs as appropriate on a chemical-by-chemical basis.

8. Odor threshold levels should be included when available in all documents. Recommend placing odor data in other than the non-lethal toxicity section. NAS Subcommittee suggests placing the data under physical/chemical properties section.

ANILINE

The time-scaling value of n=1 is based on the **linear** relationship between aniline concentration and methemoglobin formation in the rat at 8 hours as well as the formation of methemoglobin over time at a constant concentration.

AEGL-1 FOR ANILINE (ppm)*				
	30-min	**1-hr**	**4-hr**	**8-hr**
n=1	**16**	**8.0**	**2.0**	**1.0**
AEGL-2 FOR ANILINE (ppm)*				
n=1	**24**	**12**	**3.0**	**1.5**
AEGL-3 FOR ANILINE (ppm)**				
n=1	**40**	**20**	**5.0**	**2.5**
n=3	***6.3***	***5.0***	***3.1***	***2.5***

*Based on an 8-hour study with rats.
**Values based on projections beyond the experimental data.

It was suggested that the conservative time-scaling value of n=3 be applied to the projected data (AEGL-3) only.

Using the value of n=3 for the projected data results in AEGL-3 values below the AEGL-1 values.

Older literature citations such as Henderson and Haggard (1943) state that concentrations of 100-160 ppm could be inhaled for 1 hour without serious symptoms and concentrations of 5-53 ppm produced slight symptoms after several hours.

ACUTE EXPOSURE GUIDELINE LEVELS FOR ANILINE (CAS NO. 62-53-3)

AEGL-1 VALUES

30 minutes	1 hour	4 hours	8 hours
16 ppm	8.0 ppm	2.0 ppm	1.0 ppm

Reference: Kim, Y.C. and G.P. Carlson. 1986. The effect of an unusual workshift on chemical toxicity. II. Studies on the exposure of rats to aniline. Fund. Appl. Toxicol. 7:144-152.

Test Species/Strain/Number: Adult male Sprague-Dawley rats, 5/exposure group.

Exposure Route/Concentrations/Durations: Inhalation: 0-150 ppm for 8 hours.

Effects:

Concentration (ppm)	Methemoglobin Formation (%)
0	1.1 (0.4-1.7)
10	1.1 (0.4-1.7)
30	1.6
50	4.7
100	22
150	41

Endpoint/Concentration/Rationale: The only effect of aniline administration was formation of methemoglobin. Administration of 100 ppm for 8 hours to rats resulted in elevation of methemoglobin to 22%. A review of the literature revealed that methemoglobin levels of 15% - 20% in humans results in clinical cyanosis but no hypoxic symptoms. This effect was considered to be within the definition of the AEGL-1. The 8-hour exposure to 100 ppm was chosen as the basis for the AEGL-1 calculations.

Uncertainty Factors/Rationale:
Total uncertainty factor: 100
Interspecies: 10 - A review of oral administration studies showed that humans are considerably more sensitive to methemoglobin formation than rats (up to 40 times based upon mg/kg doses).
Intraspecies: 10 - A review of infant poisonings determined that infants are considerably more sensitive to methemoglobin formation than adults.

Modifying Factor: Not applicable (1)

Animal to Human Dosimetric Adjustment: Not applied.

Time Scaling: $C^n \times t = k$ where $n = 1$; based on a review of three different lethality studies conducted at 4 and 7 hours, the ct product was reasonably consistent with a value of $n=1$.

Comments: The study was well conducted and documented. Values were presented graphically. Supporting data were sparse, probably because aniline is not a vapor at room temperature and poisonings have involved contact with the liquid. Because aniline is absorbed through the skin, a notation that direct skin contact with the vapor of liquid should be avoided has been added.

AEGL-2 VALUES

30 minutes	1 hour	4 hours	8 hours
24 ppm	12 ppm	3.0 ppm	1.5 ppm

Reference: Kim, Y.C. and G.P. Carlson. 1986. The effect of an unusual workshift on chemical toxicity. II. Studies on the exposure of rats to aniline. Fund. Appl. Toxicol. 7:144-152.

Test Species/Strain/Sex/Number: Adult male Sprague-Dawley rats, 5/exposure group.

Exposure Route/Concentrations/Durations: Inhalation: 0-150 ppm for 8 hours.

Effects:

Concentration (ppm)	Methemoglobin Formation (%)
0	1.1 (0.4-1.7)
10	1.1 (0.4-1.7)
30	1.6
50	4.7
100	22
150	41

Endpoint/Concentration/Rationale: Administration of 150 ppm for 8 hours to rats resulted in elevation of methemoglobin to 41%. A review of the literature revealed that methemoglobin levels of 20% to 45% in humans is associated with fatigue, lethargy, exertional dyspnea, and headache. These signs/symptoms were considered the threshold for disabling effects. The 8-hour exposure to 150 ppm was chosen as the basis for the AEGL-2 calculations.

Uncertainty Factors/Rationale:
Total uncertainty factor: 100
Interspecies: 10 - A review of oral administration studies showed that humans are considerably more sensitive to methemoglobin formation than rats (up to 40 times based upon mg/kg doses).
Intraspecies: 10 - A review of infant poisonings determined that infants are considerably more sensitive to methemoglobin formation than adults.

Modifying Factor: Not applicable (1)

Animal to Human Dosimetric Adjustment: Not applied.

Time Scaling: $C^n \times t = k$ where $n = 1$; based on a review of three different lethality studies conducted at 4 and 7 hours, the ct product was reasonably consistent with a value of n=1.

Comments: The study was well conducted and documented. Values were presented graphically. Supporting data were sparse, probably because aniline is not a vapor at room temperature and poisonings have involved contact with the liquid. Because aniline is absorbed through the skin, a notation that direct skin contact with the vapor of liquid should be avoided has been added.

AEGL-3 VALUES

30 minutes	1 hour	4 hours	8 hours
40 ppm	20 ppm	5.0 ppm	2.5 ppm

Reference: Kim, Y.C. and G.P. Carlson. 1986. The effect of an unusual workshift on chemical toxicity. II. Studies on the exposure of rats to aniline. Fund. Appl. Toxicol. 7:144-152.

Test Species/Strain/Sex/Number: Adult male Sprague-Dawley rats, 5/exposure group.

Exposure Route/Concentrations/Durations: 0-150 ppm for 8 hours.

Effects:

Concentration (ppm)	Methemoglobin Formation (%)
0	1.1 (0.4-1.7)
10	1.1 (0.4-1.7)
30	1.6
50	4.7
100	22
150	41

Endpoint/Concentration/Rationale: Because the exposures did not result in effects consistent with the definition of an AEGL-3, the concentration vs percent hemoglobin formation data presented by the authors was graphed and projected to a methemoglobin level of 70-80% which was considered the threshold for lethality in humans. This value was approximately 250 ppm. An 8-hour exposure to 250 ppm was chosen as the basis for the AEGL-3 calculations.

Uncertainty Factors/Rationale:
Total uncertainty factor: 100
Interspecies: 10 - A review of oral administration studies showed that humans are considerably more sensitive to methemoglobin formation than rats (up to 40 times based upon mg/kg doses).
Intraspecies: 10 - A review of infant poisonings determined that infants are considerably more sensitive to methemoglobin formation than adults.

Modifying Factor: Not applied (1)

Animal to Human Dosimetric Adjustment: Not applied.

Time Scaling: $C^n \times t = k$ where $n = 1$; based on a review of three different lethality studies conducted at 4 and 7 hours, the ct product was reasonably consistent with a value of n=1.

Comments: The study was well conducted and documented. Values were presented graphically. Supporting data were sparse, probably because aniline is not a vapor at room temperature and poisonings have involved contact with the liquid.
Because aniline is absorbed through the skin, a notation that direct skin contact with the vapor of liquid should be avoided has been added.

Attachment 6

ARSINE

AEGL-1 FOR ARSINE

- **not established by NAC/AEGL due to extreme toxicity**
  - **toxicity below odor threshold (0.5 ppm)**
  - **very steep exposure-response curve**

- **use detection limit as AEGL-1 value**
  - **0.010 ppm by GC in recent animal studies**
  - **0.025 to 0.05 ppm MSA and Draeger tubes**

AEGL-2 FOR ARSINE (ppm)				
	30-min	1-hr	4-hr	8-hr
n=2	0.24	0.17	0.083	0.059
n=3	0.21	0.17	-	-
n=1	-	-	0.04	0.03

- AEGL-2 based upon no hematologic findings in mice exposed for 1-hr to 5 ppm

- all AEGL values (regardless of *n* value) and their C x t products represent exposures that are below those indicative of notable toxic responses in animal models

AEGL-3 FOR ARSINE (ppm)				
	30-min	1-hr	4-hr	8-hr
n=2	0.7	0.5	0.25	0.18
n=3	0.63	0.5	-	-
n=1	-	-	0.13	0.063

- AEGL-3 based upon estimate of lethality threshold (15 ppm) in mice following 1-hr exposure
  - significant hematologic changes at 15 ppm
  - 100% lethality at 26 ppm

- all AEGL values (regardless of *n* value) and their C x t products represent exposures that are below those indicative of observable toxic responses in animal models

ACUTE EXPOSURE GUIDELINES FOR ARSINE
(CAS NO. 7784-42-1)

AEGL-1 VALUES			
30 minutes	1 hour	4 hours	8 hours
Not appropriate	Not appropriate	Not appropriate	Not appropriate

Reference: The available human and animal data indicate that there is very little margin between seemingly inconsequential exposures and lethal exposures. The mechanism of arsine toxicity (hemolysis and subsequent renal failure) and the fact that toxicity has been demonstrated at or below the odor threshold justify the inappropriateness of AEGL-1 values for any exposure period.

Test Species/Strain/Number: Not applicable

Exposure Route/Concentrations/Durations: Not applicable

Effects: Not applicable

Endpoint/Concentration/Rationale: Not applicable

Uncertainty Factors/Rationale: Not applicable

Modifying Factor: Not applicable (1)

Animal to Human Dosimetric Adjustment: Not applicable

Time Scaling: Not applicable

Confidence and Support for AEGL Levels: Not applicable

ACUTE EXPOSURE GUIDELINES FOR ARSINE
(CAS NO. 7784-42-1)

AEGL-2 VALUES			
30 minutes	1 hour	4 hours	8 hours
0.24 ppm	0.17 ppm	0.083 ppm	0.059 ppm

Reference: Peterson, D.P., M.H. Bhattacharyya. 1985. Hematological responses to arsine exposure: quantitation of exposure response in mice. Fundam. Appl. Toxicol. 5: 499-505.

Test Species/Strain/Sex/Number: Female B6C3F$_1$ mice, 8/group

Exposure Route/Concentrations/Durations: Inhalation: 0, 5, 9, 11, 15, or 26 ppm for1 hour

Effects: hematocrit level (as % of controls)

5 ppm	no significant effects (determinant for AEGL-2)
9 ppm	80.2 %
11 ppm	79.7%
15 ppm	61.4%
26 ppm	21.7% (100% mortality at 4 days postexposure)

Endpoint/Concentration/Rationale: 5 ppm for 1 hour considered as no-observed-effect-level for decreased hematocrit. A NOEL was used because of an extremely steep dose-response curve and the fact that the ultimate toxic effect, renal failure, is delayed for several days.

Uncertainty Factors/Rationale:
Total uncertainty factor: 30

Interspecies: 10 - The 10 minute LC_{50} value for the monkey was about 60% of the rat value and one third the rabbit value. A less sensitive species, the mouse, was used to calculate the AEGL levels because the data exhibited a good exposure response curve and the endpoint of decreased hematocrit can be considered a sensitive indicator of arsine toxicity. In addition, arsine has an extremely steep dose response curve giving little margin between no effects and lethality.

Intraspecies: 3 - the critical toxic effect (hemolysis) is not expected to differ greatly among individuals and is likely to occur in all individuals at extremely low arsine concentrations.

Modifying Factor: Not applicable

Animal to Human Dosimetric Adjustment: None applied, insufficient data

Time Scaling:	$C^n \times t = k$ where n = 2; The concentration-exposure time relationship for many irritant and systemically acting vapors and gases may be described by $C^n * t = k$, where the exponent n ranges from 0.8 to 3.5. In the absence of chemical specific data, an approximate midpoint value of n=2 was selected by the NAC/AEGL for time scaling. Although the use of a lower n value would provide lower AEGL-2 values for some time periods, the determinant used (no significant effects in mice exposed to 5 ppm for 1 hour) is considered a conservative representation for AEGL-2 effects.
Confidence and Support for AEGL Levels: The study was considered adequate for AEGL-2 derivation. It was carefully designed and performed, used adequate numbers of animals, used an appropriate exposure regimen, and identified an endpoint consistent with AEGL-2 definition and with the known effects of arsine.	

ACUTE EXPOSURE GUIDELINES FOR ARSINE
(CAS NO. 7784-42-1)

AEGL-3 VALUES			
30 minutes	1 hour	4 hours	8 hours
0.70 ppm	0.50 ppm	0.25 ppm	0.18 ppm

Reference: Peterson, D.P., M.H. Bhattacharyya. 1985. Hematological responses to arsine exposure: quantitation of exposure response in mice. Fundam. Appl. Toxicol. 5: 499-505.

Test Species/Strain/Sex/Number: Female B6C3F$_1$ mice, 8/group

Exposure Route/Concentrations/Durations: Inhalation: 0, 5, 9, 11, 15, or 26 ppm for 1 hour

Effects: hematocrit level (as % of controls) and lethality

5 ppm	no significant effects
9 ppm	80.2 % (no mortality)
11 ppm	79.7% (no mortality)
15 ppm	61.4% (no mortality) (determinant for AEGL-3)
26 ppm	21.7% (3/8 immediately following exposures; 100% mortality at 4 days postexposure)

Endpoint/Concentration/Rationale: 15 ppm for 1 hour induced a significant decrease in hematocrit that may be approaching a degree of hemolysis that can lead to renal failure. Given the steepness of the dose response curve this is justified as an estimate of the lethality threshold. An exposure of 26 ppm for 1 hour resulted in 100% lethality.

Uncertainty Factors/Rationale:

Total uncertainty factor: 30

Interspecies: 10 - The 10 minute LC_{50} value for the monkey was about 60% of the rat value and one third the rabbit value. A less sensitive species, the rat, was used to calculate the AEGL levels because the data exhibited a good exposure response curve and the endpoint of decreased hematocrit can be considered a sensitive indicator of arsine toxicity. In addition, arsine has an extremely steep dose response curve giving little margin between no effects and lethality.

Intraspecies: 3 - the critical toxic effect (hemolysis and subsequent renal failure) would be expected to occur in all individuals at extremely low arsine concentrations.

Modifying Factor: Not applicable

Animal to Human Dosimetric Adjustment:

Time Scaling:	$C^n \times t = k$ where n = 2; The concentration-exposure time relationship for many irritant and systemically acting vapors and gases may be described by $C^n * t = k$, where the exponent n ranges from 0.8 to 3.5. In the absence of chemical specific data, an approximate midpoint value of n=2 was used as a default for scaling across time. Although the use of a lower n value would provide lower AEGL-3 values for some time periods, the determinant used (no mortality and a 38.6% decrease in hematocrit in mice exposed to 15 ppm for 1 hour) is considered a conservative representation for AEGL-3 effects.
Confidence and Support for AEGL Levels: The study was considered adequate for AEGL-3 derivation. It was carefully designed and performed, used adequate numbers of animals, used an appropriate exposure regimen, and identified an endpoint consistent with AEGL-3 definition and with the known effects of arsine. The available data indicate that the exposure-response relationship for arsine is very steep, thereby justifying a conservative approach to deriving AEGL values.	

Attachment 7

CHLORINE

The n value of 2 is a derived value based on animal lethality data. The mechanism of action for lethality (severe irritation with edema) is the same as/similar to that for the AEGL-1 (slight irritation) and AEGL-2 (severe irritation with asthmatic-like symptoms).

AEGL-1 FOR CHLORINE (ppm)*				
	30-min	**1-hr**	**4-hr**	**8-hr**
n=2	**1.4**	**1.0**	**0.5**	**0.5**
n=3	***1.0***	***0.8***	***0.5***	***0.4***
n=1	***4.0***	***2.0***	***0.5***	***0.3***

*Based on 4-hour exposure of human subjects.

AEGL-2 FOR CHLORINE (ppm)*				
	30-min	**1-hr**	**4-hr**	**8-hr**
n=2	**2.8**	**2.0**	**1.0**	**0.7**
n=3	***2.0***	***1.6***	***1.0***	***0.8***
n=1	***8.0***	***4.0***	***1.0***	***0.5***

*Based on 4-hour exposure of human subjects.

AEGL-3 FOR CHLORINE (ppm)*				
	30-min	**1-hr**	**4-hr**	**8-hr**
n=2	**28**	**20**	**10**	**7.1**
n=3	***25***	***20***	***13***	***10***
n=1	***40***	***20***	***5.0***	***2.5***

*Based on a 1-hour exposure of mice and rats.

ACUTE EXPOSURE GUIDELINE LEVELS FOR CHLORINE (CAS No. 7782-50-5)

AEGL-1 VALUES			
30 minutes	1 hour	4 hours	8 hours
1.4 ppm	1.0 ppm	0.50 ppm	0.50 ppm

Reference: Rotman, H.H., M.J. Fliegelman, T. Moore, R.G. Smith, D.M. Anglen, C.J. Kowalski, and J.G. Weg. 1983. Effects of low concentrations of chlorine on pulmonary function in humans. J. Appl. Physiol. 54:1120-1124.

Test Species/Strain/Number: Nine human male subjects

Exposure Route/Concentrations/Durations: Inhalation: 0.0, 0.5, 1,0 ppm for 8 hours; break at 4 hours; subjects exercised for 15 minutes of every hour; sham exposures were included.

Effects:
- 0.5 ppm for 4 hours: no effects in eight of nine subjects; transient changes in pulmonary functions in one of nine subjects
- 1.0 ppm for 4 hours: transient changes in pulmonary functions in eight of nine subjects; asthmatic episode in one of nine subjects

Endpoint/Concentration/Rationale: 0.5 ppm for 4 hours resulted in no effects in healthy human subjects and transient changes in pulmonary functions for a sensitive individual who had obstructive airways disease prior to the exposure. The 0.5 ppm concentration was chosen as the next highest concentration produced coughing, wheezing, and a considerable increase in airways resistance in a sensitive individual.

Uncertainty Factors/Rationale:
Total uncertainty factor: 1
- Interspecies: Not applicable
- Intraspecies: 1 - A sensitive individual who had obstructive airways disease prior to the exposure was tested.

Modifying Factor: Not applicable (1)

Animal to Human Dosimetric Adjustment: Not applicable; human data used.

Time Scaling: $C^n \times t = k$ where $n = 2$ (range of 1.0 to 3.5); based on regression analysis of several animal LC_{50} studies conducted at exposure times of 5 minutes to seven hours.

Comments: The study was well conducted and documented and reinforces a study conducted earlier at the same facilities in which 31 male and female subjects were tested for sensory irritation. This study went into greater detail than the previous study, measuring 15 pulmonary function parameters before, during, and after exposures. Subjects were exercising and the study included a sensitive individual.

AEGL-2 VALUES			
30 minutes	1 hour	4 hours	8 hours
2.8 ppm	2.0 ppm	1.0 ppm	0.71 ppm

Reference: Rotman, H.H., M.J. Fliegelman, T. Moore, R.G. Smith, D.M. Anglen, C.J. Kowalski, and J.G. Weg. 1983. Effects of low concentrations of chlorine on pulmonary function in humans. J. Appl. Physiol. 54:1120-1124.

Test Species/Strain/Sex/Number: Nine human male subjects

Exposure Route/Concentrations/Durations: Inhalation: 0.0, 0.5, 1,0 ppm for 8 hours; break at 4 hours; subjects exercised for 15 minutes of every hour; sham exposures were included

Effects:
- 0.5 ppm for 4 hours: no/slight effects in eight healthy subjects; transient changes in pulmonary functions in one of nine subjects
- 1.0 ppm for 4 hours: transient changes in pulmonary functions in healthy subjects; asthmatic episode in one of nine subjects

Endpoint/Concentration/Rationale: 1 ppm for 4 hours resulted in an asthmatic attack in a sensitive exercising individual. The severity of the attack, as indicated by an increase in airways resistance, was considered to meet the definition of an AEGL-2.

Uncertainty Factors/Rationale:
Total uncertainty factor: 1
- Interspecies: Not applicable (1)
- Intraspecies: 1 - A sensitive individual who had obstructive airways disease prior to the exposure was tested.

Modifying Factor: Not applicable (1)

Animal to Human Dosimetric Adjustment: Not applicable, human data used.

Time Scaling: $C^n \times t = k$ where $n = 2$ (range of 1.0 to 3.5); based on regression analysis of several animal LC_{50} studies conducted at exposure times of 5 minutes to seven hours.

Comments: The study was well conducted and documented and reinforces a study conducted earlier at the same facilities in which 31 male and female subjects were tested for sensory irritation. This study went into greater detail than the previous study, measuring 15 pulmonary function parameters before, during, and after exposures. Subjects were exercising and the study included a sensitive individual.

AEGL-3 VALUES			
30 minutes	1 hour	4 hours	8 hours
28 ppm	20 ppm	10 ppm	7.1 ppm

References: (1) MacEwen, J.D. and E.H. Vernot. 1972, Toxic Hazards Research Unit Annual Technical Report. 1972. Wright-Patterson Air Force Base, Dayton, OH; (2) Zwart, A. and Woutersen. 1988. Acute inhalation toxicity of chlorine in rats and mice: time-concentration mortality relationships and effects on respiration. J. Hazard. Mater. 19:195-208; (3) O'Neil, C.E. 1991. Immune responsiveness in chlorine exposed mice. PB92-124478, Prepared for NIOSH, Cincinnati, OH.

Test Species/Strain/Sex/Number: (1) Sprague-Dawley rats, 10/exposure group;
(2) Wistar-derived rats, 10/exposure group;
(3) BALB/c mice, 10/exposure group

Exposure Route/Concentrations/Durations: Inhalation: (1) 213-427 ppm for 1 hour
(2) 322-595 ppm for 1 hour
(3) 50-250 ppm for 1 hour

Effects: (1) no deaths at 213 ppm for 1 hour (rat);
(2) no deaths at 322 ppm for 1 hour (rat);
(3) no deaths at 150 ppm for 1 hour (mouse)

Endpoint/Concentration/Rationale: 200 ppm for 1 hour (the approximate mean of experimental LC_0 the rat and mouse values) was chosen as the basis for the 1-hour AEGL-3. Mice appeared to be unusually sensitive to chlorine; and in some studies, delayed deaths were attributed to bronchopneumonia rather than direct effects of chlorine.

Uncertainty Factors/Rationale:
Total uncertainty factor: 10
Interspecies: 3 - The mouse and rat LC_{50} values did not differ by more than a factor of 2 - 3 with the mouse being consistently more sensitive. In some mouse studies delayed deaths were attributed to bronchopneumonia rather than direct effects of chlorine.
Intraspecies: 3 - The mechanism of action, irritation, is not expected to differ greatly among individuals because chlorine is a direct acting irritant.

Modifying Factor: Not applicable (1)

Animal to Human Dosimetric Adjustment: Not applied.

Time Scaling: $C^n \times t = k$ where $n = 2$ (range of 1.0 to 3.5); based on regression analysis of several animal LC_{50} studies conducted at exposure times of 5 minutes to seven hours.

Comments: The data base for chlorine is extensive with multiple studies of lethality, conducted at several exposure durations and involving several species. Studies with multiple dosing regimens showed a clear dose-response relationship. Longer-term studies that support the safety of the proposed values were also available. Tissue and organ pathology indicated that the toxic mechanism was the same across species.

Attachment 8

HYDRAZINE

AEGL-1 FOR HYDRAZINE

- **flat-lined; value of *n* inconsequential for current interim AEGL-1 values**

AEGL-2 FOR HYDRAZINE (ppm)				
	30-min	1-hr	4-hr	8-hr
n=2	18	13	6.2	4.4
n=3	15	13	-	-
n=1	-	-	3.1	1.6

- **AEGL-2 based upon reversible nasal lesions in rats following 1-hr exposure to 750 ppm**
  - **reversible lesions even after 10-week exposure**

AEGL-3 FOR HYDRAZINE (ppm)				
	30-min	1-hr	4-hr	8-hr
n=2	50	35	18	13
n=3	45	35	-	-
n=1	-	-	8.9	4.4

- **AEGL-3 based upon estimated lethality threshold in rats**
  - 1,064 ppm (3-fold reduction on 1-hr LC_{50})

HYDRAZINE ISSUES

- **Cancer risk**

  - **risk level ?**
    NAS: 10^{-4} for occupational groups
    10^{-6} for general population
  - **rare event, one-time single exposure to limited population may justify minimizing cancer risk as AEGL determinant**

- **Genotoxicity data and discussion**

ACUTE EXPOSURE GUIDELINES FOR HYDRAZINE
(CAS NO. 302-01-2)

AEGL-1 VALUES			
30 minutes	1 hour	4 hours	8 hours
0.1 ppm	0.1 ppm	0.1 ppm	0.1 ppm

Reference: House, W.B. 1964. Tolerance criteria for continuous inhalation exposure to toxic materials. II. Effects on animals of 90-day exposure to hydrazine, unsymmetrical dimethylhydrazine (UMDH), decaborane, and nitrogen dioxide. ASD-TR-61-519 (iii). Wright-Patterson AFB, Ohio, 84 pp.

Test Species/Strain/Number: 10 male rhesus monkeys

Exposure Route/Concentrations/Durations: Inhalation: 0.78 ppm (range: 0.25-1.38 ppm) continuous for 90 days; 0.4 ppm continuous for first 10 days (determinant for AEGL-1)

Effects: Eye and facial irritation within 24 hours

Endpoint/Concentration/Rationale: 0.4 ppm for 24 hours resulted in mild irritation which is a defined AEGL-1 endpoint

Uncertainty Factors/Rationale:
Total uncertainty factor: 10
Interspecies: 3 - Contact irritation is not likely to vary greatly among species because hydrazine is a highly reactive and direct acting irritant. Also, a nonhuman primate was the test species.
Intraspecies: 3 - The mechanism of action, irritation, is not expected to differ greatly among individuals because hydrazine is a highly reactive and direct acting irritant.

Modifying Factor: Not applicable

Animal to Human Dosimetric Adjustment: Not applied; surface contact

Time Scaling: $C^n \times t = k$ where $n = 2$ to scale from 24-hr exposure to 4-hr and 8-hr exposure periods. Due to the extreme reactivity of hydrazine, the effects were considered to be concentration dependent and, therefore, the 0.1 ppm concentration derived for the 4-hr and 8-hr periods was applied for all time periods.

Confidence and Support for AEGL Levels: Although the study used for AEGL-1 development was properly conducted and used an adequate number of an appropriate species, the confidence in the proposed values is low due to limited quantitative data pertaining to AEGL-1 type effects.

ACUTE EXPOSURE GUIDELINES FOR HYDRAZINE
(CAS NO. 302-01-2)

AEGL-2 VALUES			
30 minutes	1 hour	4 hours	8 hours
18 ppm	13 ppm	6.2 ppm	4.4 ppm

Reference: Latendresse, J.R., G.B. Marit, E.H. Vernot, C.C. Haun, C.D. Flemming. 1995. Oncogenic potential of hydrazine in the nose of rats and hamsters after 1 or 10 1-hr exposures. Fundam. Appl. Toxicol. 27: 33-48.

Test Species/Strain/Sex/Number: Male and female Fischer-344 rats and Syrian golden hamsters, 10/exposure group

Exposure Route/Concentrations/Durations: Inhalation: 750 ppm for 1 hour

Effects:

Exposure	Effect
750 ppm for 1 hour	nasal lesions (minimal necrosis, mild to moderate exfoliation, minimal to moderate acute inflammation, mild apoptosis; determinant for AEGL-2)

Endpoint/Concentration/Rationale: 750 ppm for 1 hour resulted in nasal lesions (minimal necrosis, mild to moderate exfoliation, minimal to moderate acute inflammation, mild apoptosis; determinant for AEGL-2).

Uncertainty Factors/Rationale:

Total uncertainty factor: 30

Interspecies: 10 - An uncertainty factor of 10 for interspecies variability was applied to account for the high degree of variability in the data due to the extreme reactivity of hydrazine that compromised exposure concentration measurements.

Intraspecies: 3 - The mechanism of action, port-of-entry contact irritation, is not expected to differ greatly among individuals because hydrazine is a highly reactive and direct acting irritant.

Modifying Factor: 2 for inadequacies in the database pertaining to AEGL-2 effects

Animal to Human Dosimetric Adjustment: Insufficient data

Time Scaling: $C^n \times t = k$ where $n = 2$; The concentration-exposure time relationship for many irritant and systemically acting vapors and gases may be described by $C^n \times t = k$, where the exponent n ranges from 0.8 to 3.5. In the absence of chemical specific data, an approximate midpoint value of $n=2$ was used for scaling across time.

Confidence and Support for AEGL Levels: The study was considered adequate for AEGL-2 derivation. It was carefully designed and performed, used adequate numbers of two test species and identified an endpoint consistent with AEGL-2 definition.

ACUTE EXPOSURE GUIDELINES FOR HYDRAZINE (CAS NO. 302-01-2)

AEGL-3 VALUES			
30 minutes	1 hour	4 hours	8 hours
50 ppm	35 ppm	18 ppm	13 ppm

Reference: HRC (Huntington Research Centre, Ltd.). 1993. Hydrazine 64% aqueous solution: acute inhalation toxicity in rats 1-hour exposure. Huntington Research Centre, Cambridge, England. CMA 8/930523.

Test Species/Strain/Sex/Number: Male and female Sprague-Dawley rats, 5/sex/group

Exposure Route/Concentrations/Durations: Inhalation: 0, 0.65, 2.04, 3.24, 4.9 mg/L for 1 hour (nose-only exposure to 64% aerosol)

Effects:

Concentration	Mortality
0.65 mg/L (496 ppm)	0/10
2.04 mg/L (1556 ppm)	0/10
3.24 mg/L (2472 ppm)	4/10
4.98 mg/L (6596 ppm)	6/10

LC_{50}: 4959 ppm (64% aerosol); 3192 ppm (hydrazine alone) (provided in reference)

Endpoint/Concentration/Rationale: When compared to the data from Latendresse et al. (1995), where rats survived multiple 1-hr exposures to 750 ppm, the calculated 1-hr LC_{01} of 334 ppm appeared to be unrealistically low and not scientifically defensible as an estimated lethality threshold. Therefore, a three-fold reduction in the 1-hr LC_{50} (3192 ppm/3 = 1064 ppm) was accepted by the NAC/AEGL Committee as an estimate of the lethality threshold for a 1-hr exposure duration that was consistent with the currently available data.

Uncertainty Factors/Rationale:

Total uncertainty factor: 30

Interspecies: 10 - An uncertainty factor of 10 for interspecies variability was applied to account for the high degree of variability in the data due to the extreme reactivity of hydrazine that compromised exposure concentration measurements.

Intraspecies: 3 - The mechanism of action, port-of-entry contact irritation, is not expected to differ greatly among individuals because hydrazine is a highly reactive and direct acting irritant.

Modifying Factor: Not applicable because lethality data in several species from multiple studies were available

Animal to Human Dosimetric Adjustment: Insufficient data

Time Scaling: $C^n \times t = k$ where $n = 2$; The concentration-exposure time relationship for many irritant and systemically acting vapors and gases may be described by $C^n \times t = k$, where the exponent n ranges from 0.8 to 3.5. In the absence of chemical specific data, an approximate midpoint value of $n=2$ was used for scaling across time.

Confidence and Support for the AEGL Levels: The study was properly conducted, used an adequate number of test animals, an adequate range of exposure concentrations, and an exposure regimen consistent with AEGL time frames. The study was considered adequate for AEGL-3 derivation.

Attachment 9

DIMETHYLHYDRAZINE

DIMETHYL HYDRAZINE ISSUES

- **AEGL-1 not established by NAC/AEGL due to extreme toxicity**
  - **toxicity below odor threshold (6-14 ppm)**
  - **use detection limit ? (0.3 - 0.5 ppm detector tubes)**

- **Cancer risk**

- **Intraspecies UF**
  - **justify UF of 10 for DMH and UF of 3 for MMH**

ACUTE EXPOSURE GUIDELINES FOR DIMETHYLHYDRAZINE
(CAS NO. 57-14-7; 1,1-DIMETHYLHYDRAZINE)
(CAS NO. 540-73-8; 1,2-DIMETHYLHYDRAZINE)

AEGL-1 VALUES			
30 minutes	1 hour	4 hours	8 hours
Not appropriate	Not appropriate	Not appropriate	Not appropriate

Reference: The available animal data indicate that toxic responses may occur at or below the odor threshold. Exposure-response relationships suggest little margin between exposures resulting in no observable effects and those producing significant toxicity. Therefore, AEGL-1 values were considered to be inappropriate.

Test Species/Strain/Number: Not applicable

Exposure Route/Concentrations/Durations: Not applicable

Effects: Not applicable

Endpoint/Concentration/Rationale: Not applicable

Uncertainty Factors/Rationale: Not applicable

Modifying Factor: Not applicable

Animal to Human Dosimetric Adjustment: Not applicable

Time Scaling: Not applicable

Confidence and Support for AEGL Values: Not aaplicable

ACUTE EXPOSURE GUIDELINES FOR DIMETHYLHYDRAZINE
(CAS NO. 57-14-7; 1,1-DIMETHYLHYDRAZINE)
(CAS NO. 540-73-8; 1,2-DIMETHYLHYDRAZINE)

AEGL-2 VALUES			
30 minutes	1 hour	4 hours	8 hours
6.0 ppm	3.0 ppm	0.75 ppm	0.38 ppm

Reference: Weeks, M.H., G.C. Maxey, M.E. Sicks, E.A. Greene. 1963. Vapor toxicity on UDMH in rats and dogs from short exposures. Am. Ind. Hyg. Assoc. J. 24: 137-143.

Test Species/Strain/Sex/Number: mongrel dogs, 2-4/group, sex not specified

Exposure Route/Concentrations/Durations: Inhalation; 1,200-4,230 ppm for 5 minutes; 360, 400 or 1,530 ppm for 15 minutes; 80-250 ppm for 60 minutes

Effects:

Exposure	Effect
15 min	
360 ppm	muscle fasciculations in 1 of 4 dogs (determinant for AEGL-2)
400 ppm	behavioral changes in 2 of 4 dogs
1,530 ppm	tremors, convulsions, vomiting in 2 of 2 dogs

Endpoint/Concentration/Rationale: 15-min exposure to 360 ppm considered a threshold for potentially irreversible effects or effects that would impair escape. At this exposure, muscle fasciculations were observed in 1 of 4 exposed dogs and at 400 ppm behavioral changes were observed.

Uncertainty Factors/Rationale:

Total uncertainty factor: 30

Interspecies: 3 - The toxic response to dimethylhydrazine (LC_{50} values) was similar across species. The 4-hr LC_{50} values for mouse, rat, and hamster differ by a factor of approximately 2 and were consistent with the dog data when extrapolated from 1 hr using n=1. The more sensitive species, the dog, was used to derive the AEGL-2 values.

Intraspecies: 10 – A broad spectrum of effects were seen which included behavioral effects, hyperactivity, fasciculations, tremors, convulsions, and vomiting. The mechanism of toxicity is uncertain and sensitivity among individuals may vary.

Modifying Factor: None

Animal to Human Dosimetric Adjustment: None applied, insufficient data

Time Scaling: $C^n \times t = k$ where n = 1; LC_{50} data were available for 5, 15, 30, 60, and 240-minute exposures in rats and 5, 15, and 60 minutes for the dog. Exposure-response data indicated a near linear concentration-response relationship (n=0.84 for rats, n=0.80 for dogs). For time-scaling, a linear relationship was assumed and a value where n=1 selected by the National Advisory Committee.

Confidence and Support for AEGL Values:
The study was considered marginally adequate for AEGL-2 derivation. The dog appeared to be a sensitive species exhibiting a critical response. The AEGL values for hydrazine, methylhydrazine and dimethylhydrazine were relationally consistent with respective toxicity data for these chemicals.

ACUTE EXPOSURE GUIDELINES FOR DIMETHYLHYDRAZINE
(CAS NO. 57-14-7; 1,1-DIMETHYLHYDRAZINE)
(CAS NO. 540-73-8; 1,2-DIMETHYLHYDRAZINE)

AEGL-3 VALUES			
30 minutes	1 hour	4 hours	8 hours
22 ppm	11 ppm	3 ppm	1.5 ppm

Reference: Weeks, M.H., G.C. Maxey, M.E. Sicks, E.A. Greene. 1963. Vapor toxicity of UDMH in rats and dogs from short exposures. Am. Ind. Hyg. Assoc. J. 24: 137-143.

Test Species/Strain/Sex/Number: mongrel dogs, 3-4/group; sex not specified

Exposure Route/Concentrations/Durations: Inhalation; exposure to various concentrations (80-22,300 ppm) for 5, 15, or 60 minutes

Effects:

1-hr LC_{50}	981 ppm (reduction by 1/3 was basis for AEGL-3 derivation)
15-min LC_{50}	3,580 ppm
5-min LC_{50}	22,300 ppm

Endpoint/Concentration/Rationale: 1-hr LC_{50} (981 ppm) reduced by 1/3 was considered an estimate of the lethality threshold (327 ppm).

Uncertainty Factors/Rationale:

Total uncertainty factor: 30

Interspecies: 3 -The toxic response to dimethylhydrazine (LC_{50} values) was similar across species. The 4-hr LC_{50} values for mouse, rat, and hamster differ by a factor of approximately 2 and were consistent with the dog data when extrapolated from 1 hr using n=1. The more sensitive species, the dog, was used to derive the AEGL-3 values.

Intraspecies: 10 – A broad spectrum of effects were seen which included behavioral effects, hyperactivity, fasciculations, tremors, convulsions, and vomiting. The mechanism of toxicity is uncertain and sensitivity among individuals may vary. A factor of 10 was also retained because experiments by Weeks et al. (1963) indicated that dogs that had been previously stressed (auditory stimuli) were more sensitive to the adverse effects of dimethylhydrazine.

Modifying Factor: None

Animal to Human Dosimetric Adjustment: None applied, insufficient data

Time Scaling: $C^n \times t = k$ where n = 1; LC_{50} data were available for 5, 15, 30, 60, and 240-minute exposures in rats and 5, 15, and 60 minutes for the dog. Exposure-response data indicated a near linear concentration-response relationship (n=0.84 for rats, n=0.80 for dogs). For time-scaling, a linear relationship was assumed and a value where n=1 selected by the National Advisory Committee.

Confidence and Support for AEGL Values:
The study was considered marginally adequate for AEGL-3 derivation. The dog appeared to be a sensitive species exhibiting a critical response. The AEGL values for hydrazine, methylhydrazine and dimethylhydrazine were relationally consistent with respective toxicity data for these chemicals.

Attachment 10

METHYLHYDRAZINE

METHYL HYDRAZINE ISSUES

- **AEGL-1 not established by NAC/AEGL due to extreme toxicity**
  - **toxicity below odor threshold (6-14 ppm)**
  - **use detection limit ? (0.3 - 0.5 ppm detector tubes)**

- **Cancer risk**

- **Intraspecies UF**
  - **justify UF of 3 for MMH and UF of 10 for DMH**

ACUTE EXPOSURE GUIDELINES FOR METHYLHYDRAZINE
(CAS NO. 60-34-4)

AEGL-1 VALUES			
30 minutes	1 hour	4 hours	8 hours
Not appropriate	Not appropriate	Not appropriate	Not appropriate

Reference: The available animal data indicate that toxic responses may occur at or below the odor threshold. Exposure-response relationships suggest that there is little margin between exposures resulting in no observable effects and those producing significant toxicity. Therefore, AEGL-1 values were considered to be inappropriate.

Test Species/Strain/Number: Not applicable

Exposure Route/Concentrations/Durations: Not applicable

Effects: Not applicable

Endpoint/Concentration/Rationale: Not applicable

Uncertainty Factors/Rationale: Not applicable

Modifying Factor: Not applicable

Animal to Human Dosimetric Adjustment: Not applicable

Time Scaling: Not applicable

Confidence and Support for the AEGL Values: Not applicable

ACUTE EXPOSURE GUIDELINES FOR METHYLHYDRAZINE (CAS NO. 60-34-4)

AEGL-2 VALUES			
30 minutes	1 hour	4 hours	8 hours
1.8 ppm	0.90 ppm	0.23 ppm	0.11 ppm

Reference: Haun, C.C., J.D. MacEwen, E.H. Vernot, G.F. Egan. 1970. Acute inhalation toxicity of monomethylhydrazine vapor. Am. J. Ind. Hyg. Assoc. 31: 667-677

Test Species/Strain/Sex/Number: Squirrel monkeys, 2-4 males/group

Exposure Route/Concentrations/Durations: Inhalation; exposure to 300, 340, or 376 ppm for 15 minutes; 130, 150, or 170 ppm for 30 minutes; 75, 85, or 90 ppm for 60 minutes

Effects: Data specifically identifying serious, irreversible effects consistent with AEGL-2 definition were not available. The lethalitiy data are shown in the summary table for AEGL-3.

Endpoint/Concentration/Rationale: In the absence of data specifically identifying AEGL-2 endpoints, the AEGL-2 was based upon a three-fold reduction of the AEGL-3 values for all time periods. Given the steepness of the exposure-dose curve it was the judgement of the AEGL Committee that a 3-fold downward adjustment would be reasonably protective against serious long-term, irreversible effects, or inability to escape.

Uncertainty Factors/Rationale:
Total uncertainty factor: 10
Interspecies: See discussion in the AEGL-3 section because the AEGL-2 is 1/3 of the AEGL-3.
Intraspecies: See discussion in the AEGL-3 section because the AEGL-2 is 1/3 of the AEGL-3.

Modifying Factor: None

Animal to Human Dosimetric Adjustment: None applied, insufficient data

Time Scaling: $C^n \times t = k$ where $n = 1$; See discussion for AEGL-3 because AEGL- 2 values were derived by 3-fold reduction of AEGL-3 values.

Confidence and Support for the AEGL Values:
In the absence of relevant data, the AEGL-2 values were derived by downward adjustment of the AEGL-3 values which compromises the confidence in these values. The AEGL values for methylhydrazine reflect the steep exposure-response relationship suggested by available data. The AEGL values for hydrazine, methylhydrazine and dimethylhydrazine were relationally consistent with respective toxicity data for these chemicals

ACUTE EXPOSURE GUIDELINES FOR METHYLHYDRAZINE
(CAS NO. 60-34-4)

AEGL-3 VALUES			
30 minutes	1 hour	4 hours	8 hours
5.5 ppm	2.7 ppm	0.68 ppm	0.34 ppm

Reference: Haun, C.C., J.D. MacEwen, E.H. Vernot, G.F. Egan. 1970. Acute inhalation toxicity of monomethylhydrazine vapor. Am. J. Ind. Hyg. Assoc. 31: 667-677.

Test Species/Strain/Sex/Number: Squirrel monkeys, 2-4 males/group

Exposure Route/Concentrations/Durations: Inhalation; exposure to 300, 340, or 376 ppm for 15 minutes; 130, 150, or 170 ppm for 30 minutes; 75, 85, or 90 ppm for 60 minutes

Effects:

Exposure	Lethality ratio		
15 min	300 ppm	1/4	
	340 ppm	1/2	
	376 ppm	3/3	
30 min	130 ppm	0/3	
	150 ppm	2/3	
	170 ppm	2/2	
60 min			
	75 ppm	0/2	
	85 ppm	2/4	60-min LC_{50} = 82 ppm
	90 ppm	2/2	

Endpoint/Concentration/Rationale: The 60-min LC_{50} of 82 ppm was reduced to 27.3 ppm as an estimate of the lethality threshold; the available data indicated the squirrel monkey to be the most sensitive species tested. This is a reasonable estimate of the lethality threshold since methlhydrazine has a steep exposure-response curve. For the one hour exposure 2/2 monkeys died at 90 ppm, 2/4 at 85 ppm, and 0/2 at 75 ppm. A similar spectrum of response is seen with the rhesus monkey and dog.

Uncertainty Factors/Rationale:

Total uncertainty factor: 10

Interspecies: 3 - One hour LC_{50}s were determined in the monkey, dog, rat, and mouse. The LC_{50} values ranged from 82 ppm in the squirrrel monkey to 244 ppm in the mouse, differing by a factor of approximately three. The squirrel monkey value of 82 ppm was used to determine the AEGL-3 value. Since the species used was the most sensitive to methylhydrazine toxicity, and the most closely related to humans, an uncertainty factor of 3 is justified.

Intraspecies: 3 - A broad spectrum of effects were seen which included vomiting, convulsions, pulmonary edema, hemolysis, contact irritation in the eye and nose. The mechanism of toxicity is uncertain and sensitivity among individuals may vary although the exposure-resposne relationship is steep suggesting limited variability in the toxic response to methylhydrazine.

Modifying Factor: None

Animal to Human Dosimetric Adjustment: None applied, insufficient data

Time Scaling: $C^n \times t = k$ where n = 1; A regression analysis of data from squirrel monkeys and dogs (Haun et al., 1970) for 15, 30, and 60-minutes indicated a near-linear relationship (n=0.97 and 0.99, respectively, for the monkey and dog data). It was the consensus of the National Advisory Committtee to assume linearity (n=1).

Confidence and Support for the AEGL Values:

The study was considered adequate for AEGL-3 derivation. Although all species tested appeared to be similarly responsive to the lethal effects of methylhydrazine, the squirrel monkey appeared to be somewhat more sensitive. The AEGL values for methylhydrazine reflect the steep exposure-response relationship suggested by available data. The AEGL values for hydrazine, methylhydrazine and dimethylhydrazine were relationally consistent with respective toxicity data for these chemicals

Attachment 11

1,2-DICHLOROETHENE

AEGL-1 FOR 1,2-DICHLOROETHENE (ppm)				
	30-min	1-hr	4-hr	8-hr
n=2	19	13	6.6	4.7
n=1	*7.6*	*3.8*	*0.95*	*0.48*

AEGL-2 FOR 1,2-DICHLOROETHENE(ppm)				
	30-min	1-hr	4-hr	8-hr
n=2	56	40	20	14
n=1	*23*	*12*	*2.9*	*1.4*

AEGL-3 FOR 1,2-DICHLOROETHENE (ppm)				
	30-min	1-hr	4-hr	8-hr
n=2	200	141	71	50
n=3	*126*	*100*	*63*	*50*

ACUTE EXPOSURE GUIDELINES FOR 1,2-DICHLOROETHENE (CAS NO. 540-59-0)

AEGL-1 VALUES

30 minutes	1 hour	4 hours	8 hours
19 ppm	13 ppm	6.6 ppm	4.7 ppm

Reference: Lehman, K. B., and Schmidt-Kehl, L. 1936. The thirteen most important chlorinated aliphatic hydrocarbons from the standpoint of industrial hygiene. Arch. Fur Hygiene. 116: 9-268.

Test Species/Strain/Number: Human subjects/ 2

Exposure Route/Concentrations/Durations: Inhalation: 275, 825, 950, 1000, 1200, 1700, or 2200 ppm for 5-30 minutes

Effects:

275 ppm	no effects (5 min. Total exposure); determinant for AEGL-1
825 ppm	slight dizziness after 5 min. (10 min. exposure)
950 ppm	slight burning of eyes (5 min.)
1000 ppm	dizziness after 10 min; slight burning of eyes (30 min exposure)
1200 ppm	Dizziness after 5 min; drowsiness; slight burning of eyes (10 min exposure)
1700 ppm	Dizziness after 3 min; slight burning of eyes; intracranial pressure; nausea (5 min exposure)
2200 ppm	Severe dizziness; intracranial pressure; nausea (5 min exposure)

Endpoint/Concentration/Rationale: 275 ppm for 5 min.; no effect level for narcosis; odor present.

Uncertainty Factors/Rationale:
Total uncertainty factor: 3
Interspecies: Not applicable, human data used.
Intraspecies: 3 - the mechanism of narcosis is not expected to differ greatly among individuals, including sensitive individuals.

Modifying Factor: 2; differential isomer toxicity, the *cis-* isomer has been reported to be approximately twice as toxic as the *trans-* isomer in producing narcosis. It is thought that commercial products may contain a significant amount of *cis-* isomer.

Animal to Human Dosimetric Adjustment: Not applicable; human data used

Time Scaling: $C^n \times t = k$ where $n = 2$; The concentration-exposure time relationship for many irritant and systemically acting vapors and gases may be described by $C^n * t = k$, where the exponent n ranges from 0.8 to 3.5 (ten Berge et al., 1986). In the absence of chemical specific data, an approximate midpoint value of n=2 was used for scaling across time.

Confidence and Support for AEGL values: Although the values developed are considered to be protective, confidence in the AEGL-1 values is moderate due to only two subjects and differential toxicity of the *cis-* and *trans-* isomers.

ACUTE EXPOSURE GUIDELINE FOR 1,2-DICHLOROETHENE (CAS NO. 540-59-0)

AEGL-2 VALUES

30 minutes	1 hour	4 hours	8 hours
56 ppm	40 ppm	20 ppm	14 ppm

Reference: Lehman, K. B., and Schmidt-Kehl, L. 1936. The thirteen most important chlorinated aliphatic hydrocarbons from the standpoint of industrial hygiene. Arch. Fur Hygiene. 116: 9-268.

Test Species/Strain/Number: Human subjects/ 2

Exposure Route/Concentrations/Durations: Inhalation: 275, 825, 950, 1000, 1200, 1700, or 2200 ppm for 5-30 minutes

Effects:		
	275 ppm	no effects (5 min. total exposure)
	825 ppm	slight dizziness after 5 min. (10 min. exposure); determinant for AEGL-2
	950 ppm	slight burning of eyes (5 min.)
	1000 ppm	dizziness after 10 min; slight burning of eyes (30 min exposure)
	1200 ppm	Dizziness after 5 min; drowsiness; slight burning of eyes (10 min exposure)
	1700 ppm	Dizziness after 3 min; slight burning of eyes; intracranial pressure; nausea (5 min exposure)
	2200 ppm	Severe dizziness; intracranial pressure; nausea (5 min exposure)

Endpoint/Concentration/Rationale: 825 ppm for 5 min.; slight dizziness was observed.

Uncertainty Factors/Rationale:
Total uncertainty factor: 3
Interspecies: Not applicable - human data used.
Intraspecies: 3 - the mechanism of narcosis is not expected to differ greatly among individuals, including sensitive individuals.

Modifying Factor: 2; differential isomer toxicity, the *cis-* isomer has been reported to be approximately twice as toxic as the *trans-* isomer in producing narcosis. It is thought that commercial products may contain a significant amount of *cis-* isomer.

Animal to Human Dosimetric Adjustment: Not applicable; human data used

Time Scaling: $C^n \times t = k$ where $n = 2$;The concentration-exposure time relationship for many irritant and systemically acting vapors and gases may be described by $C^n * t = k$, where the exponent n ranges from 0.8 to 3.5 (ten Berge et al., 1986). In the absence of chemical specific data, an approximate midpoint value of $n=2$ was used for scaling across time.

Confidence and Support for AEGL values: Although the values developed are considered to be protective, confidence in the AEGL-2 values is moderate due to only two subjects and differential toxicity of the *cis-* and *trans-* isomers.

ACUTE EXPOSURE GUIDELINES FOR 1,2-DICHLOROETHENE (CAS NO. 540-59-0)

AEGL-3 VALUES			
30 minutes	1 hour	4 hours	8 hours
200 ppm	141 ppm	71 ppm	50 ppm

Reference: Freundt et al. 1977.Toxicity studies on 1,2-dichloroethylene. Toxicology. 7: 141-153.

Test Species/Strain/Sex/Number: Female SPF Wistar rats, 6/exposure group

Exposure Route/Concentrations/Durations: Inhalation: 0, 200, 1000, 3000 ppm for 8 hours

Effects: Increased incidence of fatty liver degeneration, pulmonary capillary hyperemia, alveolar septum distension (200, 1000, 3000 ppm)
Fibrous swelling and hyperemia of cardiac muscle with poorly maintained striation (3000 ppm) determinant for AEGL-3

Endpoint/Concentration/Rationale: 3000 ppm for 8 hours. The LOAEL for fibrous swelling and hyperemia of cardiac muscle with poorly maintained striation, this effect was not seen at 1000 ppm.

Uncertainty Factors/Rationale:
Total uncertainty factor: 30
Interspecies: 10, The physiology and metabolism leading to the induction of cardiac pathology is unknown. Given an unknown mechanism and the potential for differences in metabolism between species, an uncertainty factor of 10 was chosen.
Intraspecies: 3, although a factor of 10 might be used, the total UF would drive the AEGL-3 values down to AEGL-2 values. Since AEGL-2 values are based on human data and thus considered most appropriate, an intraspecies UF of 3 has been applied

Modifying Factor: 2; differential isomer toxicity, the *cis-* isomer has been reported to be approximately twice as toxic as the *trans-* isomer in producing narcosis. It is thought that commercial products may contain a significant amount of *cis-* isomer.

Animal to Human Dosimetric Adjustment: Insufficient data

Time Scaling: $C^n \times t = k$ where $n = 2$;The concentration-exposure time relationship for many irritant and systemically acting vapors and gases may be described by $C^n * t = k$, where the exponent n ranges from 0.8 to 3.5 (ten Berge et al., 1986). In the absence of chemical specific data, an approximate midpoint value of $n=2$ was used for scaling across time.

Confidence and Support for AEGL values: Although the values developed are considered to be protective, confidence in the AEGL-3 values is moderate due to species variability and differential toxicity of the *cis-* and *trans-* isomers.

Attachment 12

PHOSPHINE

ACUTE EXPOSURE GUIDELINES FOR PHOSPHINE (CAS NO. 7803-51-2)

AEGL-1 VALUES			
30 minutes	1 hour	4 hours	8 hours
Not appropriate	Not appropriate	Not appropriate	Not appropriate

Reference: Data unavailable

Test Species/Strain/Number: Not applicable

Exposure Route/Concentrations/Durations: Not applicable

Effects: Not applicable

Endpoint/Concentration/Rationale: Not applicable

Uncertainty Factors/Rationale: Not applicable

Modifying Factor: Not applicable

Animal to Human Dosimetric Adjustment: Not applicable

Time Scaling: Not applicable

Confidence and Support for AEGL values: Appropriate data were not available for derivation of AEGL-1 values. Lethality has been observed in animals exposed to phosphine below the odor threshold.

ACUTE EXPOSURE GUIDELINES FOR PHOSPHINE (CAS NO. 7803-51-2)

AEGL-2 VALUES			
30 minutes	1 hour	4 hours	8 hours
0.36 ppm	0.25 ppm	0.13 ppm	0.089 ppm

Reference: Newton et al. 1993. Inhalation toxicity of phosphine in the rat: acute, subchronic, and developmental. Inhalation Toxicol. 5: 223-239.

Test Species/Strain/Number: F344 rats/ 30/sex/concentration

Exposure Route/Concentrations/Durations: Inhalation: 0, 0.37, 1.0, 3.1, or 10 ppm, 6 hr/day, 5 days/week for 13 weeks

Effects:

0.37 ppm	no effects
1.0 ppm	decreased body weights and food consumption in males & females
3.1 ppm	decreased body weights and food consumption in males & females (determinant for AEGL-2)
10 ppm	lung congestion and kidney histopathology in both sexes, more severe in males than in females

Endpoint/Concentration/Rationale: 3.1 ppm,Exposure was for 6 hours a day, 5 days a week for 13 weeks.; no-effect-level for kidney pathology

Uncertainty Factors/Rationale:
Total uncertainty factor: 30

Interspecies:	3; Toxicity data exist for an AEGL-2 level effect in rats, but not mice, therefore the rat was used. Since data are from a multiple-exposure 13 week study in which no rats died, an uncertainty factor of 3 is used for the acute levels.
Intraspecies:	10 - Children appear to be more sensitive than adults to the effects of phosphine. There were two case reports where exposed children died but adults exposed under similar conditions survived.

Modifying Factor: NA

Animal to Human Dosimetric Adjustment: None; insufficient data

Time Scaling: $C^n \times t = k$ where $n = 2$; The concentration-exposure time relationship for many irritant and systemically acting vapors and gases may be described by $c^n * t = k$, where the exponent n ranges from 0.8 to 3.5 (ten Berge et al., 1986). In the absence of chemical specific data, an approximate midpoint value of $n=2$ was used for scaling across time.

Confidence and Support for AEGL values: The AEGL-2 values are considered to be protective since they are based on a no-effect-level for serious effects in a repeated-exposure study.

ACUTE EXPOSURE GUIDELINES FOR PHOSPHINE (CAS NO. 7803-51-2)

AEGL-3 VALUES

30 minutes	1 hour	4 hours	8 hours
2.1 ppm	1.5 ppm	0.74 ppm	0.52 ppm

Reference: Newton, P.E. 1991. Acute inhalation exposures of rats to phosphine. Bio/Dynamics, Inc. East Millstone, NJ. Project No. 90-8271.

Test Species/Strain/Sex/Number: Sprague-Dawley rats, 5/sex/concentration or 10 males/concentration

Exposure Route/Concentrations/Durations: Inhalation: 0, 1.3, 6.0, or 28 ppm for 6 hr (5/sex/group); 0, 3.1, 10, or 18 ppm for 6 hr (10 males/group)

Effects: Exposure was for 6 hours.

Concentration	Mortality
0 ppm	0/10
1.3 ppm	0/10
3.1 ppm	0/10
6.0 ppm	0/10
10 ppm	0/10
18 ppm	0/10 (determinant for AEGL-3)
28 ppm	5/10

LC_{50}: 28 ppm

Endpoint/Concentration/Rationale: No-effect-level for death; 18 ppm, 6 hr./This study was chosen because the use of other studies would have resulted in AEGL-3 levels which overlapped the AEGL-2 levels. Further, the AEGL-2 levels were set based upon data from a subchronic study with multiple exposures.

Uncertainty Factors/Rationale:
Total uncertainty factor: 30
Interspecies: 3; The OSHA PEL of 0.28 ppm was reported to have been exceeded in 5 separate human-exposure cases. Since adult humans can apparently tolerate this level without death a less conservative uncertainty factor of 3 is justified.
Intraspecies: 10 - Children appear to be more sensitive than adults to the effects of phosphine. There were two case reports where exposed children died but adults exposed under similar conditions survived.

Modifying Factor: Not applicable

Animal to Human Dosimetric Adjustment: Insufficient data

Time Scaling: $C^n \times t = k$ where $n = 2$; The concentration-exposure time relationship for many irritant and systemically acting vapors and gases may be described by $c^n * t = k$, where the exponent n ranges from 0.8 to 3.5 (ten Berge et al., 1986). In the absence of chemical specific data, an approximate midpoint value of $n=2$ was used for scaling across time.

Confidence and Support for AEGL values: Study is considered appropriate for AEGL-3 derivation since exposures are over a wide range of phosphine concentrations and utilize a sufficient number of animals.

AEGL-2 FOR PHOSPHINE (ppm)				
	30-min	**1-hr**	**4-hr**	**8-hr**
n=2	**0.36**	**0.25**	**0.13**	**0.09**
n=3	***0.23***	***0.19***	***0.11***	
n=1				***0.078***

AEGL-3 FOR PHOSPHINE (ppm)				
	30-min	**1-hr**	**4-hr**	**8-hr**
n=2	**2.1**	**1.5**	**0.74**	**0.52**
n=3	***1.4***	***1.1***	***0.69***	
n=1				***0.45***

The Single Exposure Carcinogen Database:

Assessing the Circumstances During Which a Single Exposure to a Carcinogen can Cause Cancer

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Abstract

A relational retrieval database has been developed compiling toxicological studies assessing whether a single dose of a chemical or physical agent without exogenous promotional stimuli could cause tumor development in animal models. This database allows for an evaluation of these studies over numerous parameters important to tumor outcome and/or type of the quality of the studies as well as physical/chemical properties of the agents. An assessment of the database, which currently contains approximately 5,500 studies involving approximately 800 chemicals from 2,000 articles, reveals that a single dose of an agent can cause tumors to develop in males and females of numerous animal models and all principal age groups. In addition, the range of the 426 agents causing a positive response was chemically diverse with representatives from over several dozen chemical classes. The dose causing a tumor endpoint was generally not acutely life threatening and frequently a low proportion of the LD50 (i.e., less than 1/50 LD50). Positive responses also were reported via multiple routes of exposure, mainly oral, injection, and dermal. These findings indicate that the phenomenon of single exposure carcinogenesis is widespread and highly generalizable across chemical class, route, dose range, species, age and gender. Single exposure carcinogenesis, a concept long de-emphasized by regulatory agencies, requires a careful and formal consideration, especially as it may pertain to accidental spills, leaks, fires, explosions, and exposure excursions, but not necessarily limited to these.

Introduction

The issue of whether an exposure of a very limited duration could cause cancer has long been debated in the toxicological community. In fact, various attempts have been made by the USEPA (Albert, 1994) and the US NAS (National Research Council, 1993) to provide methods to estimate risk from less than lifetime exposures including those as limited as a single administration. Such statements were enacted to provide assistance in assessing risk from intermittent spills, leaks, explosions and other acute exposures of limited duration. Despite these activities, only limited documentation was provided that supported the assumption that very limited or single exposures to carcinogens could cause tumor development.

The following paper presents a detailed summary of a recently developed relational retrieval data base concerning peer-reviewed studies of the toxicological/cancer literature that have explored whether a single administration of chemical or physical agents could cause cancer without the use of exogenous promotional stimuli. An analysis of the data base reveals that (1) hundreds of investigators have assessed whether a single exposure can cause cancer in animal models, (2) have found this to be a common phenomenon and (3) a number of these experimental protocols have evolved into standard highly reproducible cancer bioassays depending on the type of tumor and/or process designed for study. This data base is designed to include, in a comprehensive manner, such single exposure studies from the near conception of the cancer bioassay to the present. Consequently, the data base reflects the many and progressive advances in research design and study conduct, statistical evaluation, and molecular toxicological techniques over approximately three generations of toxicologists spanning from the 1930's to the present. Given the relational nature of the data base, one is able to not only explore the question

of whether a single exposure to a carcinogen can cause cancer and its public health implications, but also use the data base to gage and assess the historical unfolding of the concept of single exposure carcinogenesis, the differential advances in various technical areas (sample size, nature of control groups, statistical analysis, etc.) and interpretations of the cancer bioassay over the decades. Thus, the intention of the data base is not only to be broadly inclusive of studies that set forth to assess single exposure carcinogenesis but also to use its query capacity to differentiate amongst studies not only on the basis of quality and rigor, and historical framework but also specific technical areas addressed by the studies.

The development of the data base has evolved over a decade involving the evaluation of over 5,576 articles, 2,000 of which were determined to have experimentally addressed the concept of single exposure carcinogenesis. The task of identifying and assembling these papers was made particularly difficult because the concept of "single" exposure is not readily used as a likely keyword and much of the search strategy necessitated non-electronic means. While it has taken considerable time to develop the current data base to its present status, it should be acknowledged that over 20 presentations were made by one of use (EJC) at various professional society, government, industry, and university settings over the past decade in order to obtain constructive criticism with most notable components relating to histopathological evaluation and the inclusion of negative findings.

While we believe that the data base provides irrefutable evidence to the question of whether single exposure carcinogenesis exists and is widely generalizable, we acknowledge that differences will exist amongst toxicologists concerning entry criteria and decisions over what may constitute a "positive" result. This should not be unexpected given the several decades of

debate on this topic by prestigious U.S. and international toxicological committees on this general issue as well. Thus, despite possible professional disagreements on specific study interpretations, the overwhelming nature of the conclusion is that single exposure carcinogenesis is a commonly explored and a highly reproducible phenomenon.

Despite the widespread experimental evaluation of the concept of single exposure carcinogenesis, this paper represents the first attempt to genuinely assemble and review the relevant literature. While a preliminary paper has been recently published on this topic (Calabrese and Blain, 1998), the present paper represents a more detailed and considerably expanded analysis of the data.

Description of the Database

The relational retrieval database contains the findings of approximately 6,000 studies from 2,000 articles that employed a single-exposure carcinogen experimental protocol reported in the peer reviewed open-literature. The studies were overwhelmingly found in mainstream publications of the toxicological and cancer research communities (Table 1). Once it was established that a study satisfied the single exposure carcinogen bioassay criteria (i.e., the agent was only administered once without any additional treatment and tumors were examined as an endpoint), information was obtained from multiple areas, including citation information (including authors, journal, year of publication), chemical information (including the chemical name and synonyms, chemical class, and CAS number), study design (including type and quality of controls and treatment groups, the animal model, the subject's age and gender, the extent and type of pathological analyses, the route of exposure, dose-response relationships, statistical

analysis performed), group information (including sample size), and positive or negative[1] tumor information. Additionally, the database provides the capacity for time to tumor evaluations, the ability to assess single versus fractionated doses, and the relationship of a single dose to the dose at which 50% of the animals die within a specific time (LD50). Information on multiple physical and chemical parameters of each chemical are also included in the database. Given the large number of technical areas, a wide array of queries can be made using the database. This query system was employed to yield the descriptive assessment offered in this article.

General Findings

A very significant finding of the database assessment is that 426 chemicals were reported to cause tumor formation with but a single exposure across a very broad spectrum of animal models. These 426 chemical agents are derived from a very wide range of chemical classes (Table 2), many of which are known to have long standing exposure relevance to community-based and industrial populations. An analysis of each agent affecting a positive response in a single exposure carcinogen bioassay has revealed that most, if not all, are genotoxic carcinogens

[1]Determination of whether a response was considered positive or negative involved a weight-of-evidence judgement of the authors which was designed to be generally consistent with the guidance offered by EPA for carcinogen evaluation (U.S. EPA, 1986). Amongst those factors heavily weighted were the judgments and interpretations of the investigators, quality of study, internal consistency of data, as well as histological and statistical evaluations.

requiring either bioactivation to an ultimate carcinogen form or are direct acting.

Another important observation is that positive responses have been reported on a wide range of species or strains. Table 3, which summarizes the positive responses across species, reveals that more than 450 strains or substrains of mice and more than 140 strains or substrains of rats responded positively in single exposure protocol bioassays. In addition to the enormous number of strains/substrains of mice and rats displaying carcinogenic responses in a single exposure protocol, similar positive results were observed in hamsters, gerbils, rabbits, guinea pigs, opossum, and fish. Of particular note is that species of widely differing susceptibility to carcinogenic agents have been used in these studies leading one to conclude that there is no solid foundation for the premise that only highly sensitive models respond positively in single exposure carcinogen bioassays.

A complementary approach for assessing the role of species or strain susceptibility in single exposure carcinogen protocol studies is the determination of how many different species or strains have been studied within the context of assessing a particular carcinogen. Table 4 provides 10 different single exposure carcinogens and the animal models in which each chemical tested positively. The principal point that the information in this table emphasizes is the large number of different species and strains in which each of these agents has been tested positively. Such a consistently positive response involving a large number and a broad range of animal models offers a compelling argument supporting the broad interspecies generalizability of the single exposure carcinogen findings. The fact that positive single exposure responses are observed in chemicals of such structural diversity as well as in all principal animal models, strongly supports the hypothesis that susceptibility to a single exposure of a carcinogen may be

broadly generalizable, implying that humans are also likely to respond in a qualitatively comparable fashion.

Despite the fact that single exposure carcinogen studies have been conducted and reported over the decades with over two thousand papers published on specific experiments, it is most striking that there has been essentially no summarization of these findings prior to the present efforts. This section, therefore, will provide general considerations of the database that provide insight on the nature and quality of the studies comprising the single exposure carcinogen database. The issues that speak to quality involving concepts such as peer-review, study design (i.e., number of doses, controls, sample size, and statistical analysis), dose-response, and reproducibility will now be considered.

Peer Review

The widespread publications of the positive single exposure studies reveal that the phenomenon of positive single exposure carcinogen bioassays repeatedly passed the peer-review process of multiple editorial boards (Table 1) and individual reviews over several generations of scientists. Furthermore, the majority of the studies (56%) in the database have been published in the more recent times such as the past 25 years as overall research quality markedly improved.

Study Design Considerations

a. Number of doses

Of the 5,576 experiments in the database 76% utilized only a single treatment group. One hundred and forty-three (143, 3%) involved experiments with >5 doses. The remaining

1,163 (21%) studies had 2-5 doses. Such studies provide substantial opportunities to investigate the nature of dose-response relationships (Table 5). In fact, based on an analysis in Table 6 a clear trend exists indicating that the more treatment groups employed in an experiment the more likely a positive response will occur. Thus, for the ten agents assessed in Table 6, positive responses occurred in 85.4% of the studies using only one treatment group, 93.8% for those using from 2-5 treatment groups, and 95.7% for those with >5 treatment groups.

b. Controls

Another important consideration in assessing the overall quality of the database is the use of proper and adequate controls. Of the 5,576 studies 2,824 had concurrent controls (either untreated or vehicle), while an additional 327 studies reported the use of historical controls which substituted for concurrent controls. However, 39% (2,175) of the total studies did not use a control group. While this would appear to be a marked limitation, it is important to consider the possible reasons why an investigator would not include a control group and why such papers would pass through a normally rigorous peer-review. First, as expected there was a decline over the years of studies that used no controls (Figure 1) and an increase in studies that used vehicle controls (Figure 2), while the proportion of untreated controls remained steady (at approximately 25% of the studies each year) over the decades. This suggests that there has been an increasing importance placed on the presence and quality of controls. Still there is a large portion of studies even in the current literature that did not use controls. The reason for the lack of controls were generally attributed to the fact that the response was well known and a very high tumor response was expected (e.g., DMBA induced mammary tumors in Sprague-Dawley female rats when the dose was administered when the rat was 40-55 days of age). In fact, the single exposure group

was often used as the comparison group, especially in studies assessing modulatory influences, such as, chemopreventive influences on tumor response. Several studies were also conducted of a short duration (less than 3 months) in young animals (pubescent or younger). Therefore, no tumors would be expected to develop in controls. Nonetheless, some 396 studies with no control group were considered as providing a negative response even when tumors developed in a few animals. In such cases, the tumor incidence was of a magnitude that the authors did not feel the study warranted a causal effect.

c. Sample Size

Sample size is also an important factor in assessing the overall quality of the database. Of the 5,576 positive and negative studies in the database 1,114 (20%) had $\geq$50 subjects per group while 2,367 (42%) had $\geq$30 subjects per group and 4,883 (88%) had $\geq$10 subjects per group.

d. Statistical Analysis

Statistical significance was also considered important in deriving judgements on cause and effect relationships. Figure 3 provides an assessment of the percent of studies where hypothesis testing was performed by study publication year in the single exposure carcinogen database. The data clearly establish the progressive importance that hypothesis testing has played in assessing these cancer studies. However, despite the application of hypothesis testing statistical methodologies to the single exposure protocol, the proportion of studies being positive has been maintained relatively consistent over the decades (Figure 4). Thus, the incorporation of hypothesis testing did not notably affect the proportion of positive studies.

e. Reproducibility

Another striking finding in the database is the extensive reproducibility of some of the specific cancer bioassays. Such reproducibility speaks to conditions of both a general nature, that is, when the response was with a different animal model, or within a context of a highly specific replication. In fact, several single exposure protocols have been widely used as model experimental systems in order to evaluate a variety of hypotheses especially with respect to factors that may modify the cancer response (e.g., chemopreventative aspects). In such instances, the focus of the authors has not been that a single exposure caused the cancer response, but on the capacity to alter the cancer response. It is this use of such standard protocols that contributed to both the high number of studies as well as the relatively high proportion of positive studies without an unexposed and/or vehicle control group, and the high number of studies utilizing a single chemical treatment group. That is, in such standard experimental protocols a fixed tumor-inducing scheme was typically used, but multiple doses of the modifying factor (i.e., dietary factor) was employed. This utilization of a model single carcinogen exposure system also contributes in part for the very high (i.e., 3:1) ratio of positive to negative findings. This conclusion is supported by the fact that the ten most tested agents comprised 60% (i.e., 3,373) of the 5,576 studies in the database and that 87.5% of these studies were positive (Table 6). Such widespread use of standard protocols helps to explain the greater occurrence of positive studies involving females (42%) as compared to males (30%), (Table 7) especially given the interest in mammary tumors.

Factors Affecting Response in a Single Exposure Protocol

Dose-response

In the course of discussing the principal findings of the Single Exposure Carcinogen Database, it has often been stated that it is expected that a single exposure to a carcinogen could cause cancer if the dose was sufficiently high. This assumption is often closely linked to a further assumption that the single dose must be exceedingly high and approach that causing acute toxicity. These assumptions were assessed by analyzing the dose that a single exposure causes cancer in mammalian models in relation to the dose causing the LD50. Even though many studies in the database do not provide information on the LD50 estimate for the specified agent in the animal model used under the conditions for their single exposure carcinogen bioassay, such information does exist for a number of agents. More specifically, it was commonly observed that the doses used in the single exposure protocols approached the LD50, that is, doses between 0.1 of the LD50 to the estimated LD50 value itself. In such cases, a very high tumor response was often reported. Nonetheless, a number of studies were found in which the dose employed was less than 1/50 of the LD50 with some studies approaching levels as low as 1/125 of the LD50 were determined to cause tumor formation in the animal models (e.g., Druckrey et al., 1967; Swenberg et al., 1972; Mohr and Hilfrich, 1972).

Such observations bring up the question of what is considered a "low" dose. While this represents a potentially subjective assessment, it may be best to phrase it in an operational framework that fits into a generalized risk assessment paradigm. That is, a dose maybe considered "low" if it is below the so-called no observed adverse effect level (NOAEL). Within

this context, a report by Layton et al. (1987) demonstrated that the ratio of the chronic NOAEL to the oral LD50 for a large number of agents approached 1/50 to 1/75 of the LD50 using the geometric mean as the measure of central tendency. By analogy, it follows that a positive single response at or below 1/50 of the LD50 could be reasonably agreed as a "low" dose. Furthermore, even in studies where the LD50 estimates were not provided, the dose employed generally caused no lethality in the initial months after treatment. These observations support the conclusion that doses that cause tumors following a single administration typically did not cause measurable additional risk of short-term mortality.

While the above analysis indicates that single non-life threatening doses can cause tumors, it must be emphasized that a single exposure at a dose far less than the LD50 and with no measurable risk of mortality from acute toxicity may still be considerably above what may be considered ambient exposures. More specifically, a dose 1/50-1/500 of the LD50, which is a "low" dose by the above definition, may still be far greater than normal community or even typical workplace exposures. Consequently, it is necessary to evaluate the entire dose response relationship. Even though U.S. regulatory agencies have assumed cancer risk is linear at low doses, sufficient examples exist in the cancer bioassay literature to challenge the generalizability of this highly influential belief. In fact, dose response relationships for various stages of cancer (i.e., initiation, promotion, and tumor formation or progression) have been observed to follow a U or J shaped response in numerous animal experimental studies (e.g., initiation:Camurri et al., 1983; Kitchin and Brown, 1994, 1995, and 1996; Kleczkowska and Althaus, 1996; Liu et al, 1997; promotion: Conolly and Andersen, 1997; Downs and Frankowski, 1982; Goldsworthy et al., 1984; Lutz et al., 1997; OTA, 1977; Pitot et al., 1987; tumor: Broerse et al., 1978, 1982, and

1987; Cook, 1994; Kociba et al., 1978; Nesnow et al., 1994; O'Gara et al., 1965; Prahalad et al., 1997; Waalkes et al., 1988). In these instances the low doses employed displayed a noticeable reduction in response as compared to the controls, while at a higher point in the dose response spectrum caused an enhancement of the tumor related endpoint was noted. This type of U-J shaped response occurs for both single and chronic exposure protocols. This type of dose response is referred to as hormesis, which has also been studied extensively in the literature (review by Calabrese and Baldwin, 1997, 1997a, 1998) with a database currently under construction. Although these two concepts (i.e., hormesis and single exposure carcinogen) appear to be contradictory, each generally emphasizes different parts of the dose-response continuum and are both important concepts in risk assessment.

Route of Administration

A wide range of routes of administration has been used in experiments evaluating single exposure to carcinogens. These have included oral exposure (12%), typically via gavage, dermal exposure via skin application (4%), injection by any of a variety of routes (including, subcutaneously, 30%; intraperitoneal, 22%; intramuscular, 12%; or intravenous, 8%), respiratory via inhalation (0.5%) or injection directly into the respiratory tract (1%), and select types of implantation (9%). While implantation and injection exposures have limited quantitative relevance for environmental exposures, oral, inhalation, and dermal routes of administration are more likely related to typical human exposures.

Role of Sex and Age

In the majority of the articles the authors reported the response by sex or only examined a single sex, allowing for the sexes to be evaluated as separate studies (3,917 studies allowed for a single sex to be evaluated), although on a large number of cases (i.e., 1,659, 30%) the results of both sexes were combined by the authors or the author did not mention the sex of the animals used. In such cases the information was recorded as a single study for the agent tested. Also, if the experiment tested multiple age groups, each age group was treated as a separate study for the purposes of the database.

Chemically induced cancer has long been known to be affected by age. Numerous examples exist in the single exposure carcinogen database of positive response with fetal, (transplacental), neonatal, and adult strains. As indicated in Table 7, the number of agents evaluated was much greater for adults, followed by neonates and then transplacental exposure. Table 8 lists the chemicals that were tested on both newborns and adults, therefore, allowing for comparisons to be made on the susceptibility to a specific compound due to age. In addition the database allows for the assessment of narrow ages (i.e., specific days of age) which may allow for the examination of different developmental periods (e.g., puberty). Of 47 chemicals by age comparisons, the most extensive testing has been with DMBA, MCA, ethyl carbamate, ENU, MNU, DBA, and BP (Table 8). Given the current U.S. federal agency interest in children's health, the capacity to assess single exposure carcinogen studies by age or age-sex interaction may be a useful tool.

Dose Fractionation

There has been much debate over how to estimate lifetime cancer risk from short-term exposures. Approaches to assess such risks have typically partitioned the total dose received over a short period of exposure, such as a single dose, for an equal cumulative but considerably lower exposure on a daily basis for an entire lifetime. This methodology as followed under the cancer bioassay is typically based on near lifetime exposures. Upton (1968) initially reported that fractionation of dose for low linear energy transfer radiation yields a lower cancer incidence than a single, massive exposure. While such findings may challenge the validity of risk assessment methods with practices that fractionate a single dose over a lifetime, the single exposure carcinogen database may permit a comparison of this hypothesis for a number of chemical carcinogens. More specifically, several dozen studies concerning single exposure carcinogenesis and dose-fractionation are included in the database (Table 9).

Other Issues

Time to Tumor Evaluation

An important consideration in modeling cancer risk has been that of time to tumor. Detailed consideration was given to the issue as far back as Druckrey (1967) who first proposed an inverse relationship between dose and tumor latency. The database provides information on whether interim sacrifices were performed and this can be linked with other interests such as chemical, tumor types, age, sex, etc. Approximately 10% of the studies in the database incorporated an interim sacrifice component in their protocol. The issue of the number of interim sacrifices within an experiment is also important. As provided in Table 10, the number is highly

variable ranging from 1 to over 20. These types of findings provide ample opportunity to investigate this concept of time to tumor with the single exposure carcinogen bioassay. The duration of a study can also be useful in determining time to tumor in cases where there were no interim sacrifices. Several authors report the increasing incidence of palpable tumors overtime instead of histological evaluation. Many authors used sufficiently short durations for their experiments, therefore determining a short time to tumor when the results were positive.

Negative versus Positive Outcomes

Even though 4,271 of the 5,576 studies were positive in the Single Exposure Carcinogen Database (Table 7), we believe that it is instructive to compare the findings of the nearly 1,300 negative studies with those judged to be positive. In the principal areas of comparison, both groups (i.e., positive and negative studies; Tables 7 and 11) were remarkably similar with respect to the proportion of males (30 vs 29%) and females (42 vs 35%), histology (79% vs 84%), newborns (10% vs 8%), and transplacental (6% vs 5%) studies. However, some differences were noted between the groups including the proportion using hypothesis testing (48% vs 35%), use of controls (58% vs 69%), the number of subjects per group (i.e., >10, 89 vs 79%; >30, 40 vs 28%; and >50, 19 vs 14%), and the proportion assessing a response for mammary tumors (19 vs 6%). The difference in the assessment of the mammary gland may be related to the differential use of Sprague-Dawley rats (15 vs 7%). This trend provides some inside for the basis of positive and negative responses. The greater use of concurrent and histological controls in the negative studies may provide an improved basis for drawing conclusions as to outcome. In contrast, the positive studies had a higher proportion of studies with larger number of subjects. This tendency

for larger sample sizes in the positive studies was reinforced with a tendency for greater use of hypothesis testing. Thus, it appears that the negative and positive studies were generally similar, but with greater emphasis on controls and less on sample size and statistical analysis in studies with negative findings. While study design may, therefore, have contributed to the occurrence of both positive and negative studies, so to may model and endpoint selection. For example, there is a greater tendency for the use of Sprague-Dawley rats (mainly females) and the strain A mouse in the positive studies, both of these models are recognized as having an enhanced risk for cancer with the Sprague-Dawley female being susceptible to mammary cancer and the strain A mouse susceptible to pulmonary tumors.

Environmental Relevance

Of the 818 chemicals listed in the Single Exposure Carcinogen Database, many have been recognized as having environmental and/or societal relevance. This is exemplified by the inclusion of many of these chemicals in formal priority-type chemical listings with various governmental programs such as Resource Conservation and Recovery Act (RCRA), Clean Water Act (CWA), Safe Water Drinking Act (SWDA), and Occupational Safety and Health Act (OSHA, Table 12). As is listed in Table 12, many of the chemicals tested in a single exposure protocol have been judged to provide a positive response in single exposure bioassays. Depending on the specific listing in Table 12, the proportion of positive chemicals to the total number of chemicals listed is variable but ranges from approximately 40-80%. While most of the listings emphasize concerns with chronic toxic outcome, including cancer, and or the possibility of acute toxic response, very little consideration has been given to the possibility that

a limited exposure may enhance cancer risk. The present findings indicate that this possibility needs to be carefully considered along with other health concerns.

Time Trends in Cancer Bioassays

Other considerations of interest with respect to the single exposure cancer database include the trends over time for chemicals that have been tested. Table 13 reports that PAHs, which have been so dominant in the testing, have progressively declined going from 46% of the studies published in the 1930-1940s to less than 10% in the 1990s. In contrast, the nitro compounds were not evaluated until the 1950s and by the 1990s comprised 17% of the total studies.

Single Exposure Carcinogenesis is not the Same as the Single Hit Theory of Carcinogenesis

Even though over 4,200 of the nearly 6,000 studies in the single exposure carcinogen database were positive, it does not necessarily follow that the single hit theory of carcinogenesis is now overwhelmingly supported or in fact directly relevant to the single exposure carcinogen database. The nature of the relationship of these two concepts to each other has been addressed in detail in the comprehensive study by Driver et al. (1987) that sought to assess whether the process of carcinogenesis was more consistent with the single hit or multistage theory of carcinogenesis. They assessed the capacity of the carcinogen DMN to cause kidney tumors in a model that is refractory to spontaneous kidney tumors (i.e., zero percent kidney tumors in controls). Following exposure to a single dose of DMN, the rats were sacrificed at various times corresponding to the various stages of carcinogenesis (i.e., initiation (early stage)-DNA adduct

formation, promotion (middle stage)-kidney foci formation, and progression to malignant tumor (final stage)-tumor formation). According to the single hit theory, DNA-adduct formation will occur during the early stage, foci formation would occur during the middle stage and tumor formation would occur during the late stage. Therefore, all stages would follow the same dose-response relationship. The data supported a linear dose response relationship for both adduct and foci formation. Such findings were consistent under the single hit theory of carcinogenesis. However, this was not the case for the kidney tumor response, which was decidedly nonlinear. The tumor response data were clearly more consistent with the traditional sigmoidal nature of the dose-response curve. These findings demonstrated that the process of carcinogenesis is multistage rather than single hit in nature. Of particular relevance to this paper is that the protocol of Driver et al (1987) established that a single exposure experimental protocol does not necessarily follow the single hit theory of carcinogenesis, therefore, separating the two concepts.

Mechanistic Considerations

Despite extensive interest in developing biologically motivated models of carcinogenesis over the past several decades, surprisingly little attention has addressed how specific agents cause benign and malignant tumors to develop with a single dose. Most research has focused on the hypothesis that the process of carcinogenesis is a multistage phenomenon including initiation, promotion, and progression (Boutwell, 1974; Slaga, 1980). It has generally been recognized that the process of carcinogenesis involves an initiation stage including "fixation" of the genetic alteration followed by a rather prolonged period of promotional stimulation. Despite the strong emphasis on understanding the multistage process of tumorigenesis involving exposure to

initiating, promoting, and progressing agents, little attention has been directed to understanding how specific carcinogens are able to cause benign and malignant tumors to develop with but a single exposure. However, the most likely conceptual framework to explain the occurrence of single exposure induced cancers is to assume a genetic lesion (i.e., mutational event) is accompanied by substantial tissue necrosis followed by extensive reparative synthesis. This conceptual framework is similar to the two-stage initiation-promotion system of the rat liver. While it offers a credible framework to explain some findings in the single exposure carcinogen database, it does not offer an adequate explanation for a large proportion of the positive studies. Other mechanisms may be proposed to occur for such positive findings that do not necessarily require any damage or injury based on promotional mechanisms. For example, such possible mechanisms could enable (1) cell-cycle alterations and oncogene activation in epidermal cells (Olsen and Iverson, 1987; Kirkhus et al, 1987; and Kirkhus and Clausen, 1987); (2) cell proliferation (Ames and Gold, 1990); (3) receptor mediated promotion by an initiator (Ivanovic and Weinstein, 1981); (4) endogenous promotional stimuli (Diwan et al, 1997; and Russo et al., 1977 and 1979); or (5) activation of obligatory biochemical events in promotion (O'Brien, 1976). A detailed follow-up paper addressing mechanistic foundations of single exposure carcinogens is under development.

Epidemiology

The single exposure carcinogen database is designed to consider animal bioassay data. Nonetheless, the question will arise as to how relevant the single exposure carcinogen concept is to the human experience. While it has been argued here that the phenomenon is highly

generalizable across species and is likely to be directly relevant to humans, it is of interest to examine actual human data pertinent to this issue.

As expected, information relevant to single exposure carcinogenesis in humans is very limited, since epidemiology studies such as with cancer endpoints are usually addressing prolonged exposures. Cancer epidemiology studies are likely to overlook single exposures either by requiring several years of exposure for entry into a cohort or confronted with the real possibility that persons having very limited exposures may tend to forget such exposures at the reporting as compared to the more prolonged exposures. Since it takes several (possibly as many as 20 years) for cancer to develop after an exposure, it makes it difficult to associate a single exposure to the cancer endpoint. Therefore, it makes it more difficult to relate a cancer endpoint with a specific exposure, especially if that exposure was of a short duration.

Despite such problems of practically relating the single exposure carcinogen concept to cancer epidemiology, we have set forth to identify studies in the occupational epidemiology domain where a limited exposure was linked to the development of cancer. The term "limited" exposure is a subjective term and as employed here describes durations lasting less than one year. Several agents were identified in which a limited occupational exposure lasting less than one year was implicated as the causal factor in the development of human cancer. These agents are benzene (Bond et al., 1986), beryllium (Monson, 1980; Wagoner et al., 1978; Infante et al., 1980; and Mancuso, 1980), vinyl chloride (Fishbein, 1979), and aromatic amines of benzidine (Case et al., 1954), and arsenic (Ott et al., 1974). Even though these investigations yielded suggestive, but not conclusive, evidence of a causal relationship between a "limited" exposure and cancer development, the data associated with medical exposure to diethylstilbestrol (DES) are

considerably more substantial and convincing.

Considerable research supports the conclusion that administration of DES during pregnancy may cause clear-cell adenocarcinoma of the vagina in young females (Greenwald et al., 1971; Herbst et al., 1971, 1974). An assessment of the DES registry revealed 170 cases of this very rare tumor overwhelmingly associated with the intrauterine exposure to DES. Further assessment revealed a 50-fold variation in the total dose, with 300 mg being the lowest cumulative positive dose. The duration of DES treatment associated with vaginal cancer in these subjects varied from as few as seven days to nearly the entire nine months of pregnancy.

Discussion

The concept that a single exposure to a carcinogen can cause cancer has been shown to have been widely assessed in the toxicological literature for individual compounds as evidenced by the nearly 6,000 studies in the database. Yet it is remarkable that such a widely studied concept has never been the object of a substantial review. This concept has, however, been more theoretically discussed under the context of risk assessment procedures to estimate risk to any limited carcinogen exposures. Even in these instances, such discussion has not taken into account the copious data available on the topic.

The collective findings indicate that very limited exposures to some toxic carcinogens of a non-life threatening or even of an apparently nontoxic nature may result in the development of cancer for numerous compounds in a large range of animal models. Such a collective weight of evidence suggests that the role of episodic exposures in cancer may be more significant than previously thought. Moreover, these findings suggest that heightened attention should be directed

to defining exposure patterns during accidental spills at work or in the environment.

The implications of these findings for taking exposure histories in epidemiological studies may be particularly noteworthy. For example, a large episodic exposure to a chemical carcinogen during a summer job during high school or college years may be easily neglected 30 or 40 years later. Yet, the present assessment suggests such a single large exposure maybe an important potential risk factor to consider.

Given the recognition of developmental and age susceptibility to a carcinogenic agent, the database may allow a more rapid identification of relevant studies as the formulation of improved specific hypotheses for assessing cancer risks in children (Table 7 & 8). Of particular importance in the overall assessment of single exposure carcinogens is the concern of linking exposure with periods of high endogenous promotion as is widely recognized for being responsible for a high incidence of breast cancer in Sprague-Dawley rats during the window of susceptibility, 40-55 days of age (Meites, et al, 1971; Nagasawa and Yanai, 1973; Shellabarger and Soo, 1973; Sinha and Dao, 1974 and 1975; Russo et al., 1977; Russo et al. 1979; Moore et al., 1981, Sinha et al., 1988; Cohen et al., 1993; and Diwan et al., 1997). The occurrence of different windows of susceptibility as a result of variable endogenous promotional stimuli represents a significant biological and risk assessment challenge. The concept of single exposure carcinogenesis also has potentially important implications for how the cancer bioassay is designed and conducted. The Single Exposure Carcinogen Database can be a tool to develop broad prospective on trends in cancer bioassays. For example, while 40% of the positive studies have used more than 30 animals per treatment group only 24% of positive studies have utilized 2 or more doses. Another interesting finding is that newborn and transplacental models were

evaluated in only 16% of the positive studies (Table 7). With respect to rat models used in positive single exposure response studies, the Sprague-Dawley strain was used more than twice as often as both the Wistar and F344 strains combined (Table 7).

While many may think that the concept of single exposure carcinogenesis is controversial, the fact is that over 4,200 positive studies have been reported by hundreds of researchers over multiple generations of toxicologists. The real controversial aspect is not the body of data, but how this information may be utilized in the process of risk assessment. However, neither the current paper nor limited efforts of the EPA and NAS has placed such findings in a stable interpretable context. This clearly represents a need for an important follow-up assessment.

Table 1: List of journals that have published studies using a single exposure protocol in the Single Exposure Carcinogen Database.

Journal title	Number of citations and studies	% of total citations and studies
Cancer Research	citations: 503 studies: 1421	25% 25%
Journal of the National Cancer Institute	citations: 287 studies: 961	14% 17%
Carcinogenesis	citations:233 studies:547	12% 10%
British Journal of Cancer	citations:117 studies:468	6% 8%
Cancer Letters	citations: 85 studies: 143	4% 3%
International Journal of Cancer	citations: 52 studies: 151	3% 3%
Japanese Journal of Cancer Research (GANN)	citations: 57 studies: 133	3% 2%
Nature	citations: 33 studies: 81	2% 2%
American Journal of Pathology	citations: 24 studies: 41	1% 1%
Toxicology and Applied Pharmacology	citations: 17 studies: 58	1% 1%
additional 221 journals	citations:592 studies: 1572	30% 28%
Total	citation: 2000 studies: 5576	101% 100%

Table 2: Listing of chemical classes with the number of chemicals per class that were demonstrated to be positive in at least one study in the Single Exposure Carcinogen Database

Chemical Class(es)	# of positive chemicals per chemical class
PAH	67
Inorganic	49
Nitrosamine	35
Ether	17
Amide, Fibers/Minerals	16
Polymer	15
Halocarbon, Phenol	14
Aromatic Amine, Azo compound, Heterocyclic compound	13
Alcohol, Carboxylic acid	10
Hydrazine, Nitrosourea, Triazene	7
Nitro compounds	6
Aldehyde, Anthracycline Antitumor Antibiotic, Carbamate, Ester, Ketone, Steroid	5
Alkaloid, Epoxide	4
Amine, Azoxy compound, Mycotoxin, Radionuclide, Sulfate Ester	3
Glutamic acid pyrrolysate, Sulfide, Sulfonate	2
Coumarin, Cyclic sultone, Imide, Lactone, Nitrile, Organometal, PBB, Pyrrolizidine alkaloid, Sulfonic acid, Thiol	1
Miscellaneous	18

Table 3: List of species with the number of strains and/or substrains that had positive results in the Single Exposure Carcinogen Database

Species	Number of strains and/or substrains with positive results
Mice	464
Rats	141
Hamsters	20
Fish	9
Rabbits	9
Guinea Pigs	5
Primates	3
Gerbils	2
Birds	5
Dogs	1
Opossum	1

Table 4: List of selected chemicals with the strains of animals where the chemical was found to be positive in the Single Exposure Carcinogen Database

Chemical Name	Strains or substrains of Animals where the chemical was positive
Dibenzanthracene	Mice (49 different strains or substrains), albino rabbits, OM/N rats, Strain 2 guinea pigs
Urethane (Ethyl Carbamate)	Mice (123 different strains or substrains), albino rats
Benzo(a)pyrene	Mice (39 different strains or substrains), Rats (11 different strains or substrains), Hamsters (14 different strains or substrains), Shasta Rainbow trout, Tupaia glis (tree shrews)
Diethylnitrosamine	Mice (69 different strains or substrains), Rats (10 different strains or substrains), gerbils, Rivulus maroratus (fish), Syrian Golden Hamsters
Methylcholanthrene	Mice (155 different strains or substrains), Rats (16 different strains or substrains), albino rabbits, hamsters (14 different strains or substrains), guinea pigs (4 different strains or substrains), Peking Ducks, Tupaia glis (tree shrews), snails
DMBA	Mice (93 different strains or substrains), Rats (59 different strains or substrains), guinea pigs (2 different strains), rabbits (3 different strains), hamsters (12 different strains or substrains), Chickens, Japanese House Musk Shrews
Methylnitrosourea	Mice (39 different strains or substrains), Rats (32 different strains or substrains), Syrian Golden hamsters
Ethylnitrosourea	Mice (66 different strains or substrains), Rats (36 different strains or substrains), Gerbils (2 different strains), Rabbits (9 different strains), Opossum, Syrian Golden Hamster, Xiphorphorine fish
Dimethylnitrosamine	Mice (32 different strains or substrains), Rats (10 different strains or substrains), Mastomys (Praoys) natalensis, Rainbow trout, Syrian Golden hamsters
Radiation	Rats (12 different strains or substrains), Mice (11 different strains or substrains), beagle

Table 5: The Number and Percent of Studies by the number of treatment (doses) groups the Study used

Number of doses/experiment	Number of studies	% of total studies (5,576)
1	4257	76
2	609	11
3	298	5
4	164	3
5	92	2
6	48	0.9
7	19	0.3
8	32	0.6
9	11	0.2
10	7	0.1
>10	26	0.5

Table 6: Most used chemicals in the database with the number of studies they were used as well as the number of positive studies, given as total numbers and broken down by the number of treatment groups used for each.

Chemical	Total number of studies where chemical was used (% of studies in database; 5576)		Number of positive studies where the chemical was used	
DBA	all studies	158 (3%)	all studies	134
	1 group	136	1 group	116
	2-5 groups	18	2-5 groups	14
	> 5 groups	4	> 5 groups	4
Urethane	all studies	367 (7%)	all studies	339
	1 group	294	1 group	266
	2-5 groups	63	2-5 groups	63
	> 5 groups	10	> 5 groups	10
Benzo(a)pyrene	all studies	205 (4%)	all studies	176
	1 group	134	1 group	112
	2-5 groups	64	2-5 groups	57
	> 5 groups	7	> 5 groups	7
DEN	all studies	198 (4%)	all studies	175
	1 group	156	1 group	135
	2-5 groups	38	2-5 groups	36
	> 5 groups	4	> 5 groups	4
MCA	all studies	615 (11%)	all studies	548
	1 group	470	1 group	408
	2-5 groups	131	2-5 groups	126
	> 5 groups	14	> 5 groups	14
DMBA	all studies	971 (17%)	all studies	831
	1 group	767	1 group	635
	2-5 groups	178	2-5 groups	170
	> 5 groups	26	> 5 groups	26
MNU	all studies	305 (6%)	all studies	278
	1 group	200	1 group	175
	2-5 groups	98	2-5 groups	96
	> 5 groups	7	> 5 groups	7

ENU	all studies 1 group 2-5 groups > 5 groups	340 (6%) 275 59 6	all studies 1 group 2-5 groups > 5 groups	307 245 56 6
DMN	all studies 1 group 2-5 groups > 5 groups	120 (2%) 96 20 4	all studies 1 group 2-5 groups > 5 groups	97 76 19 2
Radiation	all studies 1 group 2-5 groups > 5 groups	97 (2%) 57 28 12	all studies 1 group 2-5 groups > 5 groups	66 39 17 10
Total	all studies 1 group 2-5 groups > 5 groups	3373 (60%) 2585 697 94	all studies 1 group 2-5 groups > 5 groups	2951 2207 654 90

Table 7: Description of the Single Exposure Carcinogen database with number and percent of studies in various categories where a single dose was used with a positive outcome

	Number of chemicals (% of total positive; 426)	Number of citations (% of total positive; 1802)	Number of studies (% of total positive; 4271)
Sex:			
Males	221 (52%)	635 (35%)	1285 (30%)
females	195 (46%)	1001 (56%)	1796 (42%)
both	197 (46%)	483 (27%)	1189 (28%)
histology	377 (88%)	1462 (81%)	3384 (79%)
statistics (hypothesis testing)	219 (51%)	954 (53%)	2039 (48%)
used controls	ND	975 (54%)	2492 (58%)
Concurrent	ND	950 (53%)	2151 (50%)
Vehicle	248 (58%)	585 (32%)	1318 (31%)
Historical	53 (12%)	63 (3%)	242 (6%)
Subjects in groups			
>10	372 (87%)	1547 (86%)	3607 (84%)
>30	216 (50%)	840 (47%)	1696 (40%)
>50	121 (28%)	478 (27%)	820 (19%)
Age			
Newborn	60 (14%)	165 (9%)	425 (10%)
Transplacental	37 (9%)	138 (8%)	277 (6%)
Most reported organs			
liver	97 (23%)	244 (14%)	613 (14%)
mammary	62 (14%)	517 (29%)	800 (19%)
skin	53 (12%)	213 (12%)	577 (14%)
Respiratory	143 (34%)	430 (24%)	1220 (29%)
Most examined animal models			
Rats	226 (53%)	928 (51%)	1659 (39%)
Sprague-Dawley	64 (15%)	451 (25%)	621 (15%)
Wistar	60 (14%)	101 (6%)	188 (4%)
Fisher 344	37 (9%)	92 (5%)	124 (3%)
Mice	237 (56%)	736 (41%)	2260 (53%)
Swiss	47 (11%)	75 (4%)	151 (4%)
Strain A	61 (14%)	118 (7%)	259 (6%)
C3H	23 (5%)	36 (2%)	76 (2%)

Table 8: Chemicals that have been tested with a single exposure in Adults (animals 50 days old or older) and newborns (animals 7 days old or younger) with the number of citations and studies for each circumstance. The positive responses are denoted with a + while the negative response with a -.

Chemical name	+ adult	+ newborn	- adult	- newborn
3-hydroxyxanthine	citations 1 studies 1	citations 2 studies 2	citations 0 studies 0	citations 2 studies 4
4-nitroquinoline-1-oxide	citations 3 studies 5	citations 6 studies 7	citations 2 studies 2	citations 1 studies 1
aflatoxin B1	citations 3 studies 5	citations 3 studies 5	citations 2 studies 2	citations 1 studies 1
azoxymethane	citations 2 studies 2	citations 2 studies 2	citations 0 studies 0	citations 0 studies 0
benzo(a)pyrene	citations 29 studies 67	citations 11 studies 19	citations 7 studies 7	citations 3 studies 4
bis-(2-hydroxypropyl)nitrosamine	citations 0 studies 0	citations 1 studies 2	citations 1 studies 1	citations 0 studies 0
cycasin	citations 3 studies 4	citations 11 studies 15	citations 0 studies 0	citations 0 studies 0
diethylnitrosamine	citations 12 studies 15	citations 11 studies 16	citations 4 studies 4	citations 3 studies 4
dimethylnitrosamine	citations 17 studies 27	citations 15 studies 22	citations 5 studies 6	citations 0 studies 0
DMBA	citations 389 studies 492	citations 44 studies 94	citations 52 studies 59	citations 3 studies 5
ethyl carbamate	citations 77 studies 240	citations 31 studies 65	citations 4 studies 5	citations 2 studies 3
ethylnitrosourea	citations 27 studies 200	citations 27 studies 73	citations 1 studies 6	citations 2 studies 3
methylcholanthrene	citations 165 studies 456	citations 19 studies 37	citations 14 studies 36	citations 3 studies 3
methylnitrosourea	citations 101 studies 172	citations 10 studies 18	citations 10 studies 11	citations 3 studies 3
Radiation	citations 25 studies 33	citations 7 studies 8	citations 12 studies 14	citations 0 studies 0

1,2-dimethylhydrazine	citations 2 studies 2	citations 2 studies 4	citations 0 studies 0	citations 0 studies 0
1,3,6,8-tetrachloro-2,7-diacetamidofluorene	citations 0 studies 0	citations 1 studies 1	citations 1 studies 1	citations 1 studies 2
2-amino-5-azotoluene	citations 2 studies 2	citations 1 studies 2	citations 0 studies 0	citations 0 studies 0
2-naphthylamine	citations 0 studies 0	citations 2 studies 2	citations 2 studies 3	citations 1 studies 1
3,4,9,10-dibenzopyrene	citations 3 studies 6	citations 0 studies 0	citations 0 studies 0	citations 1 studies 2
aflatoxins	citations 1 studies 1	citations 0 studies 0	citations 0 studies 0	citations 1 studies 1
benz(a)anthracene	citations 5 studies 9	citations 1 studies 3	citations 4 studies 16	citations 0 studies 0
bis(chloromethyl)ether	citations 0 studies 0	citations 1 studies 2	citations 1 studies 1	citations 0 studies 0
butylnitrosourea	citations 0 studies 0	citations 3 studies 5	citations 1 studies 1	citations 0 studies 0
chloroform	citations 0 studies 0	citations 0 studies 0	citations 1 studies 2	citations 1 studies 1
croton oil	citations 0 studies 0	citations 0 studies 0	citations 1 studies 1	citations 1 studies 1
DDT	citations 0 studies 0	citations 0 studies 0	citations 1 studies 1	citations 1 studies 1
dibenzanthracene	citations 27 studies 79	citations 8 studies 14	citations 8 studies 8	citations 1 studies 1
estradiol	citations 0 studies 0	citations 1 studies 1	citations 1 studies 2	citations 1 studies 1
ethyl methane sulphonate	citations 3 studies 3	citations 1 studies 1	citations 2 studies 2	citations 1 studies 1
iron	citations 0 studies 0	citations 0 studies 0	citations 2 studies 2	citations 1 studies 2
MCA-11,12-oxide	citations 0 studies 0	citations 0 studies 0	citations 1 studies 1	citations 1 studies 2

methyl-bis(2-chloroethyl) amine hydrochloride	citations 2 studies 2	citations 1 studies 1	citations 1 studies 1	citations 0 studies 0
methylnitrosourethane	citations 0 studies 0	citations 1 studies 1	citations 1 studies 1	citations 0 studies 0
MNNG	citations 1 studies 1	citations 5 studies 9	citations 5 studies 5	citations 0 studies 0
N-hydroxy-2-fluorenylacetamide	citations 4 studies 4	citations 3 studies 5	citations 1 studies 1	citations 1 studies 1
N-hydroxy-2-naphthylamine	citations 1 studies 1	citations 3 studies 3	citations 0 studies 0	citations 0 studies 0
N-hydroxy-4-acetylaminobiphenyl	citations 0 studies 0	citations 2 studies 3	citations 1 studies 1	citations 1 studies 1
N-nitrosomethyl(2-oxopropyl)amine	citations 2 studies 4	citations 1 studies 1	citations 0 studies 0	citations 0 studies 0
phenanthrene	citations 0 studies 0	citations 0 studies 0	citations 1 studies 1	citations 2 studies 3
phenobarbital	citations 0 studies 0	citations 0 studies 0	citations 1 studies 1	citations 1 studies 2
tobacco	citations 1 studies 1	citations 2 studies 4	citations 1 studies 1	citations 1 studies 2
4-(methylnitrosoamino)-1-(3-pyridyl)-1-butanone	citations 1 studies 1	citations 1 studies 2	citations 0 studies 0	citations 1 studies 1
1-naphthylamine	citations 0 studies 0	citations 1 studies 1	citations 1 studies 1	citations 0 studies 0
2-acetylaminofluorene	citations 1 studies 1	citations 4 studies 6	citations 1 studies 1	citations 1 studies 1
4-dimethylaminoazobenzene	citations 0 studies 0	citations 1 studies 1	citations 1 studies 1	citations 1 studies 1
safrole	citations 0 studies 0	citations 1 studies 2	citations 1 studies 1	citations 0 studies 0

Table 9: Chemicals where dose fractionation was performed sorted by the results of a single dose as compared to the dose fractionation.

Chemicals where a single dose caused fewer tumors than that dose fractionated	Chemicals where a single dose caused more tumors than that dose fractionated	Chemicals where there was similar results between the single dose and the dose fractionation
DMBA Benzo(a)pyrene radiation MCA 3-hydroxyxanthine PBB potassium bromate N-nitrosobis(2-acetoxypropyl)amine cadmium chloride	1,2-Dimethylhydrazine methylnitrosourea procarbazine DMBA methyl(acetoxymethyl)nitrosamine	3-hydroxyxanthine DMBA procarbazine N-OH-2-FAA Benzo(a)pyrene Ethyl carbamate methyl-bis(2-chloroethyl)amine hydrochloride DMN

Table 10: Number and percent of positive studies that had different numbers of interim sacrifices (these numbers do not include the final sacrifices)

Number of interim sacrifices	Number of studies	% of total positive studies with interim sacrifice
1	91	21%
2	74	17%
3	62	14%
4	20	5%
5	23	5%
6	11	2.5%
7	14	3%
8	8	2%
9-19	37	8.5%
more than 19	4	1%
not specified*	90	21%
total	434	100%

* Sometimes the authors were vague about the number of times they sacrificed. They may state animals were routinely sacrificed, they were sacrificed from 2-23 weeks, or that they were sacrificed at various intervals. In any of these cases a specific number of sacrifices cannot be determined even though it is clear that the authors performed interim sacrifices.

Table 11: Description of the Single Exposure Carcinogen database with number and percent of studies in various categories where a single dose was used with a negative outcome

	Number of chemicals (% of total negative; 539)	Number of citations (% of total negative; 506)	Number of studies (% of total negative; 1295)
Sex:			
males	197 (37%)	201 (40%)	366 (28%)
females	231 (43%)	252 (50%)	459 (35%)
both	260 (48%)	146 (29%)	470 (36%)
histology	483 (90%)	412 (81%)	1084 (84%)
statistics (hypothesis testing)	206 (38%)	208 (41%)	454 (35%)
used controls	ND	378 (75%)	869 (67%)
Concurrent	ND	275 (54%)	744 (57%)
Vehicle	248 (58%)	166 (33%)	505 (39%)
Historical	53 (12%)	19 (4%)	85 (7%)
Subjects in groups			
>10	471 (87%)	409 (81%)	1027 (79%)
>30	178 (33%)	146 (71%)	418 (32%)
>50	93 (17%)	82 (16%)	177 (14%)
Age			
Newborn	63 (12%)	42 (8%)	106 (8%)
Transplacental	22 (4%)	30 (6%)	63 (5%)
Most reported organs			
liver	60 (11%)	61 (12%)	131 (10%)
mammary	31 (6%)	50 (10%)	81 (6%)
skin	42 (8%)	80 (16%)	139 (11%)
Respiratory	120 (22%)	65 (13%)	175 (14%)
Most examined animal models			
Rats	192 (36%)	193 (38%)	364 (28%)
Sprague-Dawley	62 (12%)	39 (8%)	85 (7%)
Wistar	38 (7%)	39 (8%)	66 (5%)
Fisher 344	21 (4%)	25 (5%)	30 (2%)
Mice	376 (70%)	272 (54%)	785 (61%)
Swiss	65 (12%)	45 (9%)	99 (8%)
Strain A	42 (8%)	30 (6%)	50 (4%)
C3H	36 (7%)	8 (2%)	40 (3%)

Table 12: Occurrence of chemicals in the Single Exposure Carcinogen Database in Environmental Pollutant Listings

Listing	Total number of chemicals	Number of positive chemicals
RCRA- Appendix VIII and IX	130	82
CERCLA- hazardous substances	205	132
Clean water act toxic pollutants	136	98
clean air act-61 hazardous air pollutants	44	18
SDWA original 83	88	65
IARC	224	127
OSHA	132	67
AGCIH	84	37
DOT	60	24
California Prop 65	207	119
Mass. Right to know	196	105
NJ right to know	270	162
NTP bioassay	121	53

Table 13: Listing of chemical classes that were tested under a single exposure protocol with the number of chemicals per class by time period

Chemical Class	30-40	40-50	50-60	60-70	70-80	80-90	90-98
PAH	21 (46%)	28 (31%)	19 (23%)	47 (19%)	49 (13%)	25 (10%)	13 (9%)
Inorganic	5 (11%)	5 (5.5%)	8 (10%)	31 (12%)	32 (9%)	35 (14%)	24 (16%)
Fibers/Minerals	0	0	2 (2%)	6 (2%)	14 (4%)	14 (6%)	4 (3%)
Heterocyclic Compound	3 (7%)	3 (3%)	2 (2%)	6 (2%)	12 (3%)	9 (4%)	4 (3%)
Amine and/or Aromatic Amine	0	2 (2%)	1 (1%)	21 (8%)	27 (7%)	3 (1%)	0
Amide	0	2 (2%)	3 (4%)	15 (6%)	13 (3.5%)	8 (3%)	6 (4%)
Phenol	2 (4%)	4 (4%)	6 (7%)	13 (5%)	14 (4%)	9 (4%)	3 (2%)
Nitro compound, Nitrosamine and/or Nitrosourea	0	0	1 (1%)	14 (6%)	39 (11%)	25 (10%)	26 (17%)
Carboxylic acid	4 (9%)	9 (10%)	7 (9%)	8 (3%)	8 (2%)	3 (1%)	2 (1%)
Epoxide	0	0	0	5 (2%)	9 (2.5%)	7 (3%)	0
Alcohol	0	0	0	3 (1%)	8 (2%)	7 (3%)	2 (1%)
Azoxy compound and/or azo compound (including azo dye)	1 (2%)	2 (2%)	4 (4%)	12 (5%)	7 (2%)	5 (2%)	3 (2%)
Aldehyde	1 (2%)	1 (1%)	0	2 (1%)	4 (1%)	3 (1%)	2 (1%)
Ester	0	2 (2%)	0	3 (1%)	3 (1%)	5 (2%)	3 (2%)
Ether	4 (9%)	6 (7%)	0	6 (2%)	7 (2%)	8 (3%)	2 (1%)
Halocarbon	2 (4%)	2 (2%)	0	4 (2%)	16 (5%)	17 (7%)	0
Miscellaneous	2 (4%)	5 (5.5%)	5 (6%)	9 (4%)	12 (3%)	14 (6%)	14 (9%)

Carbamate	0	1 (1%)	1 (1%)	3 (1%)	5 (1%)	3 (1%)	3 (2%)
Isocyanate, Isothiocyanate, and or Thiocyanate	0	8 (9%)	0	0	0	1 (0.5%)	8 (5%)
Nitrile	1 (2%)	3 (3%)	0	0	2 (0.5%)	0	0
Steroid	0	1 (1%)	2 (2%)	1 (0.5%)	9 (2.5%)	5 (2%)	5 (3%)
Polymer	0	1 (1%)	12 (15%)	4 (2%)	4 (1%)	3 (1%)	2 (1%)
Other classes	0	5 (5.5)	9 (11%)	35 (14%)	69 (19%)	29 (12%)	21 (14%)
Total	46	90	82	248	365	244	150

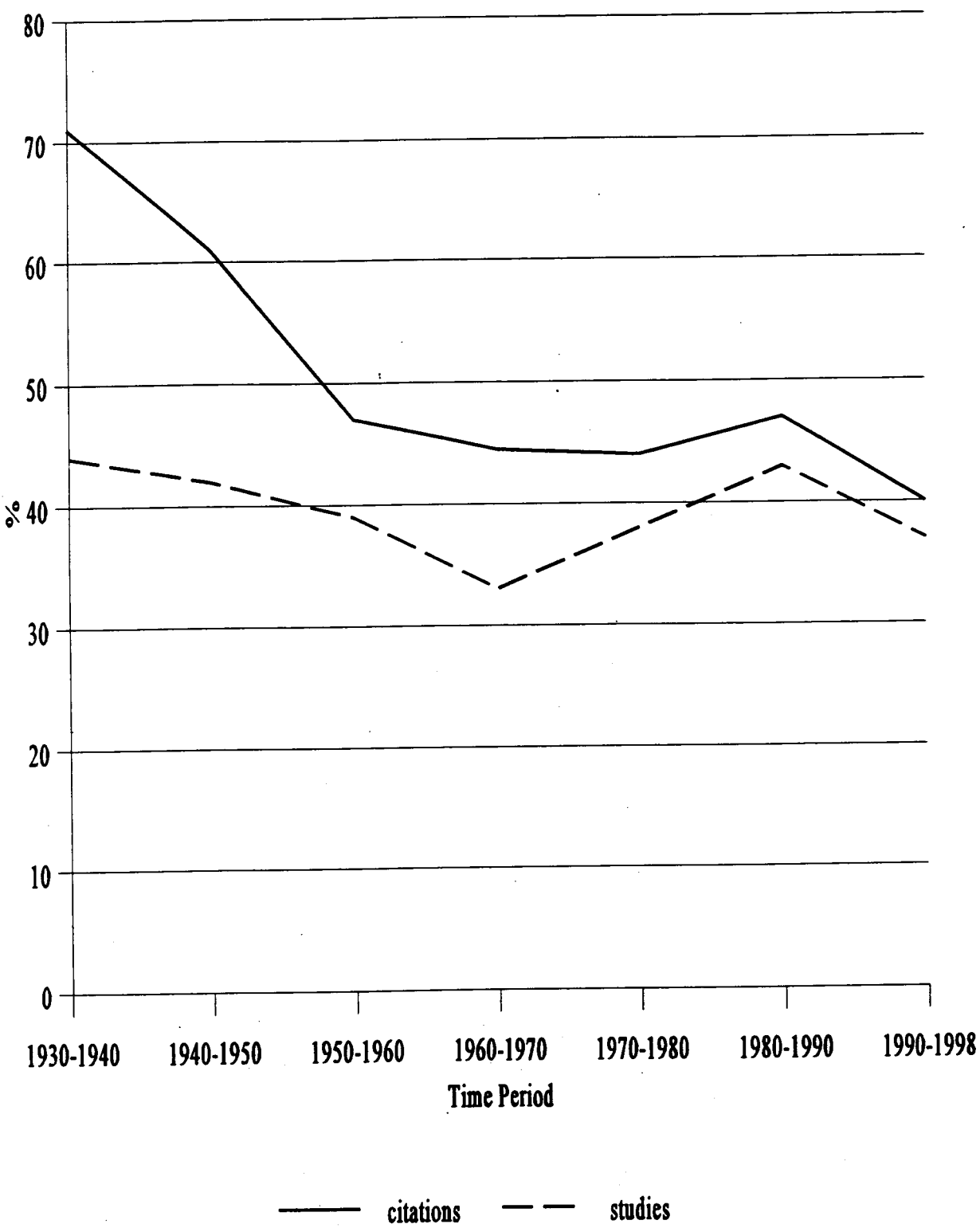

Figure 1: The percent of citations and studies that did not use a control in their experimentation for the period 1930-1998.

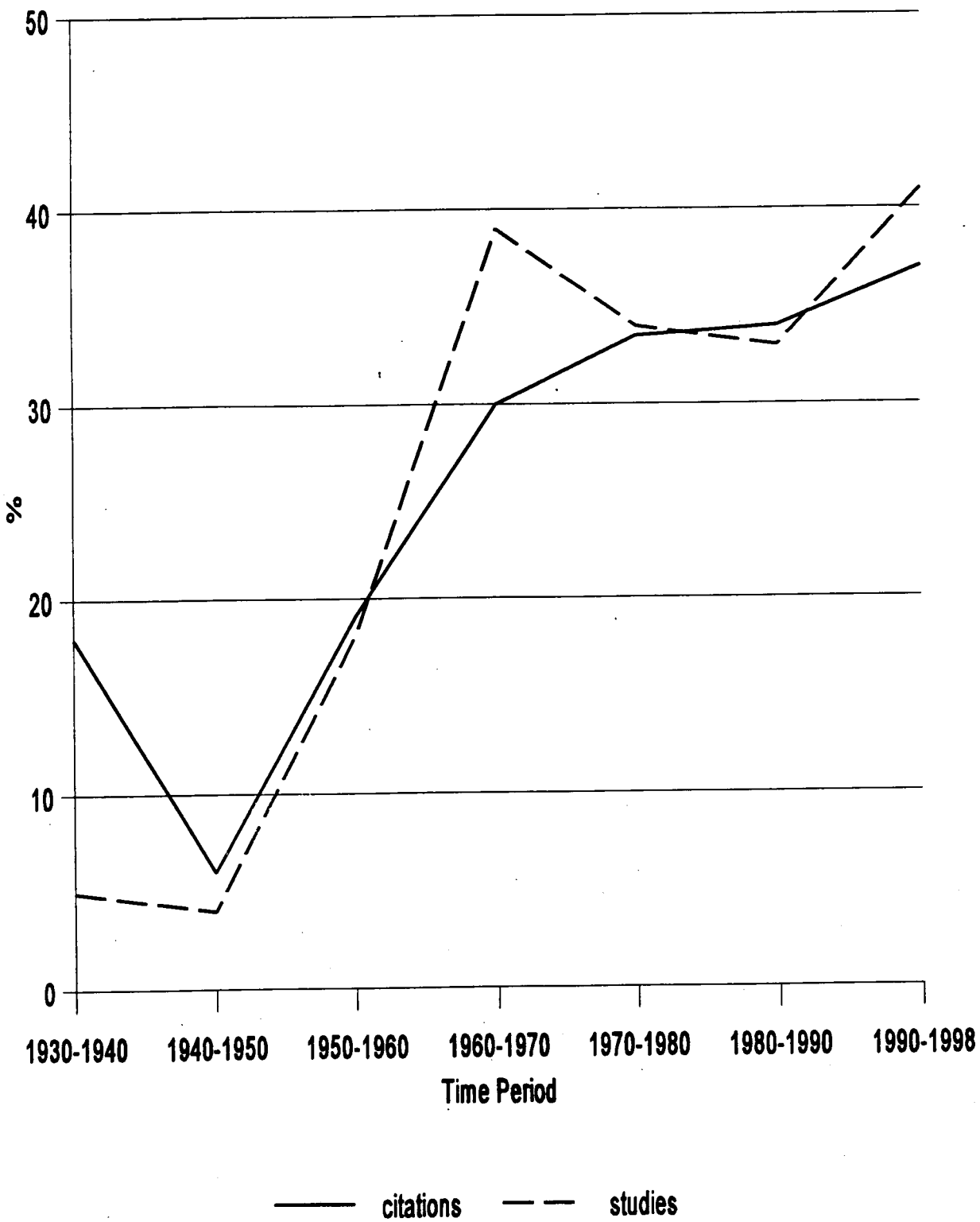

Figure 2: The percent of citations and studies that used a vehicle control for the period 1930-1998

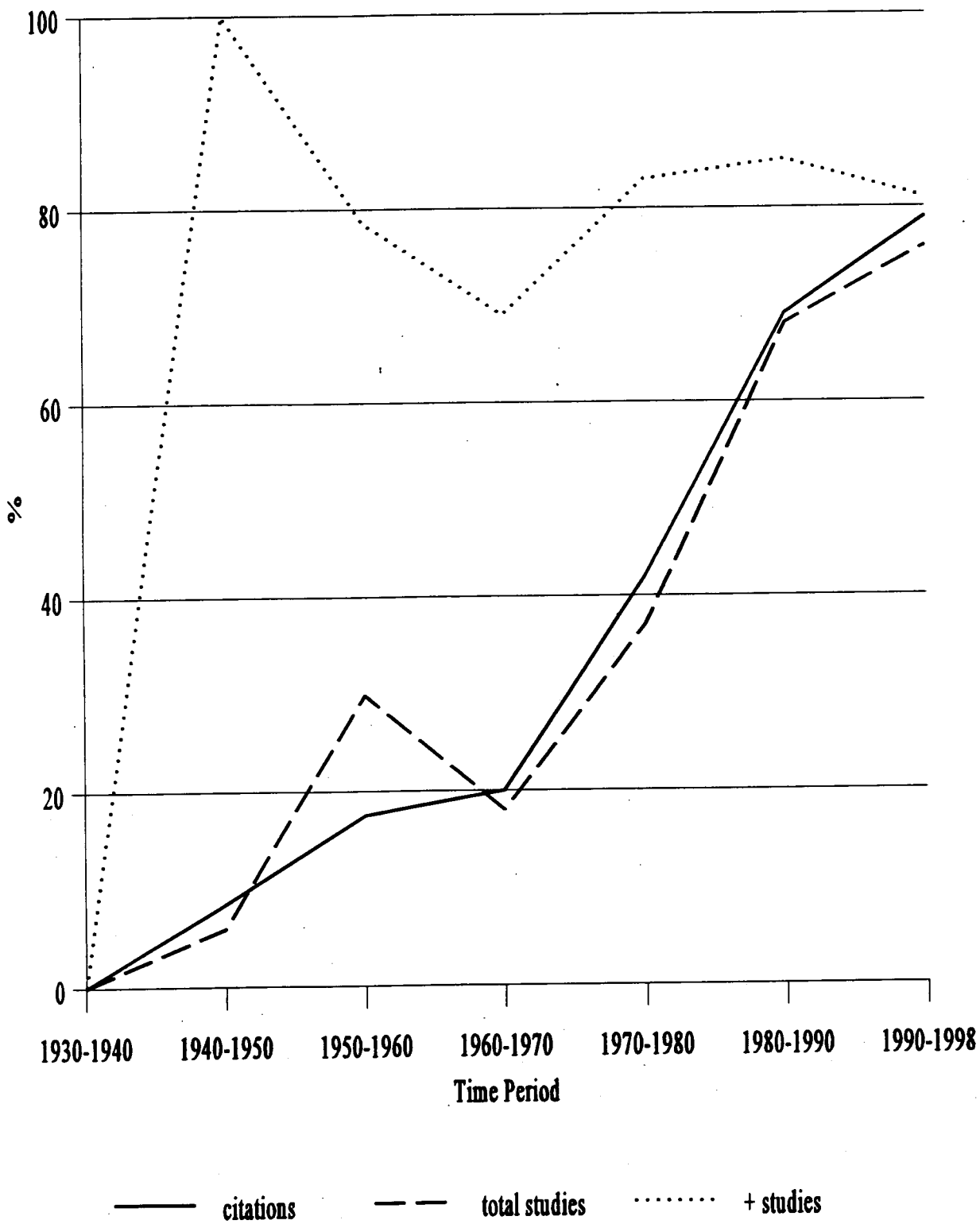

Figure 3: Percent of citations, total studies, and positive studies that performed hypothesis testing reported for the period 1930-1998

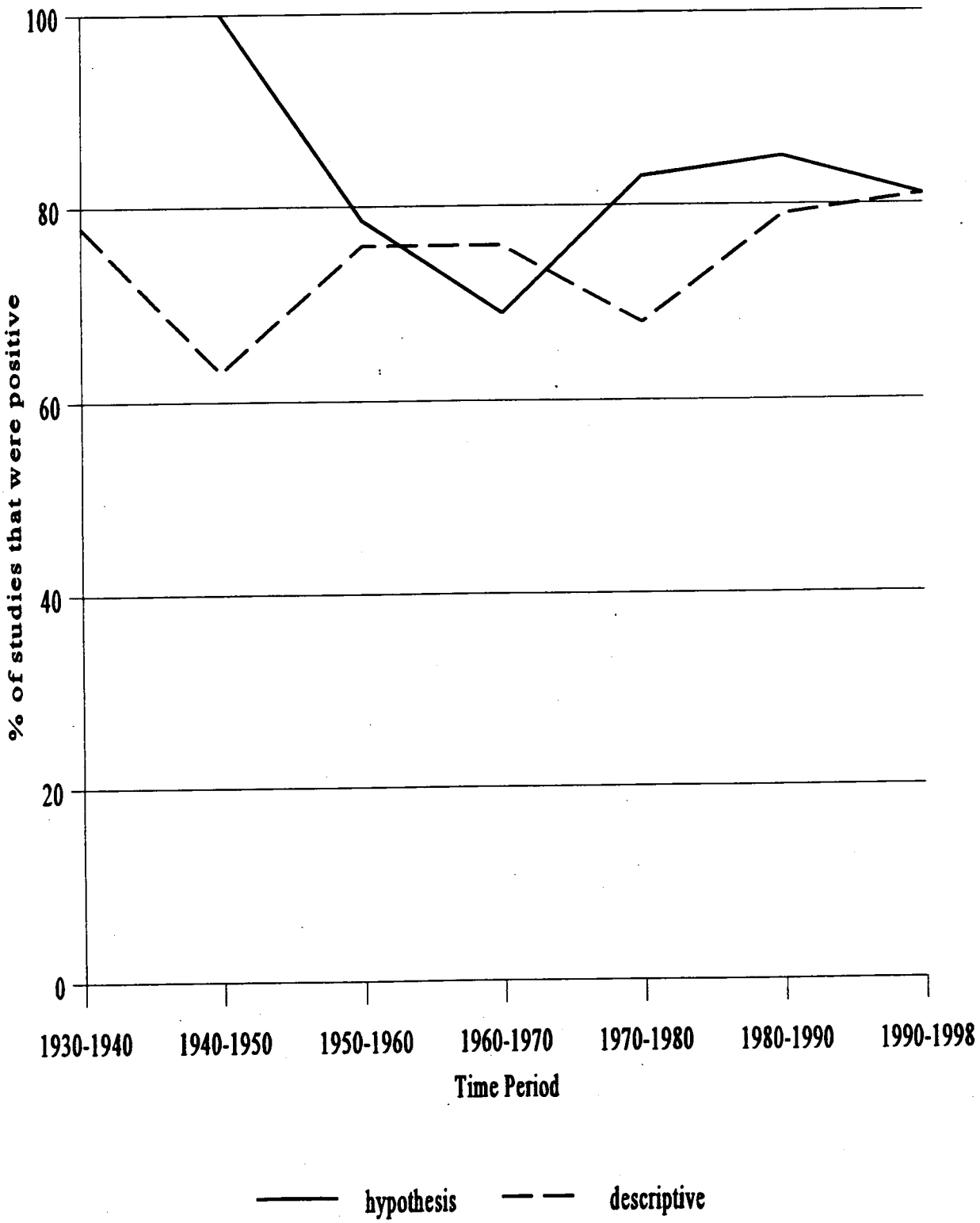

Figure 4:Percent of studies that were positive broken down by whether the authors performed hypothesis or descriptive analysis reported for the period 1930-1998

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Attachment 14

HYRDOGEN SULFIDE: REVISITING AEGL-1

NAC/AEGL-14
JUNE 14-16, 1999

CHEMICAL MANAGER: STEVE BARBEE
ORNL STAFF SCIENTIST: CHERYL BAST

"Data summarized by the Health Department and experiments carried out by its staff showed that the geometric mean of threshold odor concentration for hydrogen sulfide was about 0.03 ppm."

"Factors responsible for annoyance can be categorized as the unpleasant odor sensation itself, its effects on social life, and the instigation of headache or nausea. As a provisional rule, it appears that when an unpleasant odor reaches about 5 times its detection threshold concentration, then this is the median threshold for odor annoyance."

The Perception of Hydrogen Sulfide Odor in Relation to Setting an Ambient Standard. California Air Resources Board. April 10, 1985.

AEGL-1 FOR HYDROGEN SULFIDE (ppm [mg/m^3])					
AEGL Level	10-min	30-min	1-hr	4-hr	8-hr
AEGL-1	0.15 [0.21]	0.15 [0.21]	0.15 [0.21]	0.15 [0.21]	0.15 [0.21]

Species: Human
Concentration: 0.03 ppm
Time: All
Endpoint: 5 times odor threshold to estimate odor annoyance
Reference: State of California, 1985

H_2S concentrations measured downwind of a refining company

Measurement Parameters	H_2S Concentration	Comments
30-minute downwind average	0.095 ppm	Upwind monitoring not conducted
30-minute downwind average	0.084 ppm	Upwind monitoring <0.003 ppm
5-hour downwind average (8 separate 30-minute averages)	0.091 ppm	Upwind monitoring for 6 of 8 30-minute periods was 0.002-0.003 ppm
30-minute downwind average	0.094 ppm	Upwind monitoring not conducted
30-minute downwind average	0.084 ppm	Upwind monitoring <0.002 ppm

Maximum Continuous monitor single point concentration: 0.276 ppm

Maximum Continuous monitor 30-minute concentration: 0.118 ppm

Six monitoring staff members experienced:

- Persistent odors
- Eye irritation
- Throat irritation
- Headache
- Nausea

Symptoms subsided, in most cases, within a few hours after leaving the sampling site. Throat irritation persisted in two staff members through the following day.

Exposure duration?
Exposure to additional chemicals likely downwind from a refinery?

Additional Chemicals Detected:

Sulfur Dioxide: 0.168 ppm (highest 30-min. Downwind average)

Benzene: 18 ppb (highest 1-hr. average)
5.3 ppb (highest 3-hr. composite)

Methyl t-Butyl Ether: 110 ppb (highest 1-hr. average)
19 ppb (highest 3-hr. composite)

Toluene: 11 ppb (highest 1-hr. average)
11 ppb (highest 3-hr. composite)

PERCHLOROMETHYL MERCAPTAN AEGLs

Zarena Post/ Loren Koller
Claudia M. Troxel

PERCHLOROMETHYL MERCAPTAN

- **PROPERTIES**
  Oily, yellow liquid
  Unbearable acrid odor
  Irritant, lacrimator

- **USES**
  Used in early 1900s as chemical warfare gas (Clarisit)
  Intermediate in synthesis of dyes and fungicides (Captan, Folpet)

- **PRODUCTION**
  Manufacturers of the chemical in U.S. sell in 5 or 25 g quantities

- **AVAILABLE DATA**
  Humans: case reports, secondary sources
  Nonlethal and lethal studies limited to rats

HUMAN DATA

- **LETHAL EFFECTS:**

  Case report - exposure to unquantified amount of vapor and liquid: massive hemorrhaging lung edema with simultaneous heart, circulatory, and kidney failure from resultant hypoxia

- **NONLETHAL EFFECTS:**

  Odor threshold:

  Secondary sources: 0.001 ppm
  0.24 ppm

ANIMAL DATA

- **LETHAL EFFECTS:**
  Rat 1-Hour LC_{50}:

  Vernot et al., 1977
  11 ppm (males)
  16 ppm (females)
  13.5 ppm (combined)

  Stauffer Chemical Co., 1971
  13 ppm (combined)

  9 ppm: no deaths
  18 ppm: 7/10 died
  Clinical signs: eye and mucosa irritation, dyspnea, gasping, "acute depression" [severity of signs not provided]

- **NONLETHAL EFFECTS:**

Knapp, MacAskill, Axicker, and Sprague. 1987. Effects in rats of repeated inhalation exposure to PMM (Abstract 762).

15 male and female SD rats/group exposed to "cumulative" mean air concentrations of **0, 0.02, 0.13, or 1.15 ppm,** for **6 h/d, 5 d/wk** for **2 wks**.

RESULTS:

0.02 ppm	No effects
0.13 ppm	Mild nasal epithelial changes
1.15 ppm	Haircoat stains, labored breathing, tremors, decreased b.w., increased lung wts, pulmonary edema, increased mucous secretions, alveolitis, interstitial fibroplasia; mild nasal epithelial changes

Knapp and Thomassen, 1987. Subchronic inhalation study with PMM in rats.

18 SD rats/sex/group, exposed to **0.014, 0.079, 0.580 ppm** for **6 h/d, 5 d/wk** for **70 to 72 d**

RESULTS:

0.014 ppm	No effects
0.079 ppm	1 male, 1 female had residues of purulent or serum exudate
0.58 ppm	Salivation (d 18) and sneezing (d 59); decreased female b.w., increased male and female lung wts relative to b.w., mucous in trachea, respiratory nasal epithelium changes, residues of purulent or serum exudate, focal subacute interstitial pneumonia

SUMMARY OF INHALATION DATA IN LABORATORY RATS			
Conc. (ppm)	Duration	Effects	References
Lethal Effects			
13	1 h	Calculated LC_{50} [males and females]	Stauffer Chemical Co., 1971
18	1 h	Lowest exposure causing mortality (7/10)	
11	1 h	LC_{50} [males]	Vernot et al., 1977
16	1 h	LC_{50} [females]	
Nonlethal Effects			
9	1 h	Eye and mucosa irritation, dyspnea, gasping, "acute depression" (severity of signs not defined)	Stauffer Chemical Co., 1971
0.13	6 h/d, 5d/wk for 2 wk	Mild nasal epithelial changes	Knapp et al., 1987
1.15	6 h/d, 5d/wk for 2 wk	Haircoat stains, labored breathing, tremors, decreased b.w., increased lung wts, pulmonary edema, increased mucous secretions, alveolitis, interstitial fibroplasia; mild nasal epithelial changes	
0.58	6 h/d, 5d/wk for 70-72 d	Salivation (d 18) and sneezing (d 59) Mild changes: decreased female b.w., increased male and female lung wts relative to b.w., mucous in trachea, respiratory nasal epithelium changes, focal subacute interstitial pneumonia	Knapp and Thomassen, 1987

POSSIBLE MECHANISM OF TOXICITY

- Direct damage of tissues from HCl:

$$CCl_3\text{-}S\text{-}Cl + H_2O \rightarrow CCl_3\text{-}SOH + HCl$$

PMM is insoluble in water, so large amounts of HCl not likely to be produced

- Inactivation of key enzymes by interaction with functional groups:

$$R\text{-}NH_2 + CCl_3\text{-}S\text{-}Cl \rightarrow CCl_3\text{-}S\text{-}NH\text{-}R + HCl$$

or

$$R\text{-}OH + CCl_3\text{-}S\text{-}Cl \rightarrow CCl_3\text{-}S\text{-}O\text{-}R + HCl$$

AEGL-1 (ppm)			
30 min	1 hour	4 hours	8 hours
0.001	0.001	0.001	0.001

- **Reference:** Ruth, 1986. Odor thresholds and irritation levels of several chemical substances: a review.

- Odor threshold: odor said to be unbearable, acrid, and disagreeable

- **Uncertainty Factors/Rationale:**
  Total uncertainty factor: 1
  Interspecies: NA
  Intraspecies: NA

- **Time scaling:** none: flat-lined across time because odor threshold

AEGL-2 (ppm)				
UF	30 min.	1 hour	4 hours	8 hours
100	0.020	0.014	0.0071	0.0050
30	0.067	0.047	0.024	0.017
10	0.20	0.14	0.071	0.050

- **Reference:** Knapp and Thomassen, 1987. Subchronic inhalation study with PMM in rats.

- 18 SD rats/sex/group

- **Concentration/Time Selection/Rationale:** 0.58 ppm, 6 h/d, 5 d/wk, for 70 d: mild effects: mild focal subacute interstitial pneumonia. Conc. between 0.13 ppm (mild nasal epithelial changes) and 1.15 ppm (severe effects)

- **Uncertainty Factors/Rationale:**
  Total uncertainty factor: 100
  Interspecies: 10 - only rat data
  Intraspecies: 10 - interindividual differences not known

- **Time scaling:** $C^n \times t = k$ where n = 2 ("default")

- ACGIH & OSHA TWA: 0.1 ppm; IDLH: 10 ppm

AEGL-2 (ppm) [UF = 10]				
n	30 min.	1 hour	4 hours	8 hours
2	0.20	0.14	0.071	0.050
1*				0.044
3*	0.13	0.11	0.066	

* n = 1 when extrapolating from short to long time periods

n = 3 when extrapolating from long to short time periods

Knapp and Thomassen, 1987. Subchronic inhalation study with PMM in rats.

0.58 ppm for 6 hours

AEGL-3 (ppm)				
UF	30 min.	1 hour	4 hours	8 hours
100	0.062	0.044	0.022	0.016
30	0.21	0.15	0.073	0.052
10	0.62	0.44	0.22	0.16

- **Reference:** Vernot et al., 1977; Stauffer Chemical Co., 1971

- **Concentration/Time Selection/Rationale:**
  ⅓ of the combined 1-hour LC_{50} in rats (4.4 ppm)

- **Uncertainty Factors/Rationale:**
  Total uncertainty factor: 10
  Interspecies: 10 - only rat data
  Intraspecies: 10 - interindividual differences not known

- **Time scaling:** $C^n \times t = k$ where n = 2 ("default')

- ACGIH & OSHA TWA: 0.1 ppm; IDLH: 10 ppm (IDLH based upon statement by Prentiss (1937) that PMM is one-sixth as toxic as phosgene)

AEGL-3 (ppm) [UF = 10]				
n	30 min.	1 hour	4 hours	8 hours
2	0.62	0.44	0.22	0.16
1*			0.11	0.055
3*	0.55	0.44		

* n = 1 when extrapolating from short to long time periods

n = 3 when extrapolating from long to short time periods

Vernot et al., 1977; Stauffer Chemical Co., 1971:

⅓ the 1-hour LC_{50} = 4.4 ppm

- ACGIH & OSHA TWA: 0.1 ppm, IDLH: 10 ppm

AEGL-2 (ppm)				
UF	30 min.	1 hour	4 hours	8 hours
100	0.040	0.028	0.014	0.010
30	0.13	0.94	0.047	0.033
10	0.40	0.28	0.14	0.10
n = 1, 3				
10	0.26	0.21	0.13	0.086

- Knapp, MacAskill, Axicker, and Sprague. 1987. Effects in rats of repeated inhalation exposure to PMM (Abstract 762).

- **1.15 ppm for 6h/d, 5 d/wk for 2 wk**: Haircoat stains, labored breathing, tremors, decreased b.w., increased lung wts, pulmonary edema, increased mucous secretions, alveolitis, interstitial fibroplasia; mild nasal epithelial changes

- **ACGIH & OSHA TWA: 0.1 ppm, IDLH: 10 ppm**

AEGL-3 (ppm)				
UF	30 min.	1 hour	4 hours	8 hours
100	0.13	0.009	0.045	0.032
30	0.42	0.30	0.15	0.11
10	1.3	0.90	0.45	0.32
n = 1, 3				
10	1.1	0.90	0.23	0.11

- Stauffer Chemical Co., 1971:
- **9 ppm for 1 hour**: No mortality
- **ACGIH & OSHA TWA: 0.1 ppm, IDLH: 10 ppm**

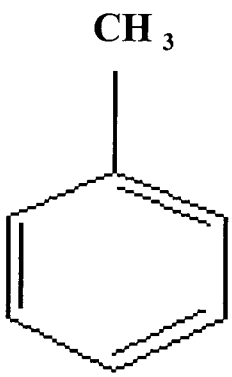
TOLUENE

- VERY GOOD HEALTH EFFECTS DATABASE
- PRIMARY TARGET ORGAN: CNS
- CHALLENGES FOR DEVELOPING AEGLs
  - Which effects meet the AEGL definitions?
  - Which studies should we use?
  - How much uncertainty exists?
  - How should we perform time-scaling?

Attachment 17

TOLUENE AEGLs

CAS Reg. No. 108-88-3



C7H8
MW 92.140

Larry Gephart
Tessa Long

TOLUENE

- PROPERTIES

  Volatile, colorless liquid

  Flammable and explosive

  Sweet pungent odor (similar to benzene)

  Isolated from pyrolized petroleum and coal tar

- USES

  Chemical manufacturing of benzene, benzyl chloride, benzoic acid, phenol, cresols, vinyl toluene, TNT, and toluene diisocyanate.

  Back-blending into gasoline to increase the octane rating, most toluene remains a in a mixture of benzene-toluene-xylene for use in gasoline

  Solvent for paints, adhesives, inks, coatings, and pharmaceuticals

- PRODUCTION

  1997 World Production, 12.9 million tons

  1997 U.S. Production, 4.3 million tons

- AVAILABLE DATA
  - Human Inhalation Exposures

    Abuse data (lethal and nonlethal)

    Accidental (lethal and nonlethal)

    Occupational (nonlethal)

    Experimental (nonlethal, low conc. exposures)
  - Animal Inhalation Exposures

    Acute LC_{50}s

    Acute Neurobehavioral

    Developmental/Reproductive

    Subchronic and Chronic

LETHALITY IN HUMANS

ABUSE SITUATIONS and ONE ACCIDENTAL EXPOSURE

- Cardiac arrest

ABUSE SITUATIONS

- Bilateral adrenal hemorrhage
- Severe CNS depression
- Asphyxia
- Renal Failure

LETHALITY IN ANIMALS

LC_{50} DATA

- Initial excitation phase followed by CNS depression, narcosis, and death

- Interspecies Sensitivity

Table 1. Acute lethal toluene inhalation exposures in rats and mice.				
Reference	**Concen. (ppm)**	**Duration**	**Effects**	**Species**
Pryor et al., 1978	26700	1 hr	LC_{50}	rat
Cameron et al., 1938	24400	1.5 hr	60% mortality	rat
Kojima and Kobayashi, 1973	15000	2.5 hr	80% mortality	rat
Cameron et al., 1938	12200	6.5 hr	100% mortality	rat
Carpenter et al., 1976	8800	4 hr	LC_{50}	rat
Smyth et al., 1969	4000	4 hr	16% mortality	rat
Bonnet et al., 1979	6940	6 hr	LC_{50}	mouse
Svirbely et al., 1943	5320	7 hr	LC_{50}	mouse
Moser and Balster, 1985	38465	10 min	LC_{50}	mouse
"	21872	30 min.	LC_{50}	mouse
"	19018	60 min.	LC_{50}	mouse

- < 3-fold difference between rat and mouse

SUBLETHAL EFFECTS IN HUMANS

- PRIMARY EFFECT - CNS depression

  Acute inhalation exposures
  - fail to produce residual organ damage
  - produce mental confusion, incoordination, and impaired performance on neurobehavioral tasks

  Chronic inhalation exposures
  - CNS disturbances and impaired neuromuscular function
  - Long-term high exposures can produce permanent cerebral and cerebellar effects

- SYSTEMIC EFFECTS
  - Sensory irritation, nausea
  - Cardiovascular
  - Hematological
  - Renal (Metabolic acidosis)

- Hepatic
- Ocular (⇓ color discrimination)

◆ DEVELOPMENTAL/REPRODUCTIVE
- Case reports indicate a fetal syndrome similar to Fetal Alcohol Syndrome among infants whose mothers abused toluene during pregnancy
- Reports of reproductive toxicity are inconclusive among occupationally exposed men and women.

◆ GENOTOXICITY/CARCINOGENICITY
- Reports of genotoxicity are inconclusive among occupationally exposed workers
- In vitro studies are negative
- IARC stated toluene is not classifiable as a human carcinogen

SUBLETHAL EFFECTS IN ANIMALS

PRIMARY EFFECT - CNS depression

- Initial hyperactivity (⇑ responding)
- Decrease in activity (⇓ responding)
- Decrease dopamine conc. and NE utilization in brain
- Changes in patterns of sleep and wakefulness
- Narcosis

SYSTEMIC EFFECTS

- Lung atelectasis
- Hematological
- Cardiac
- Liver
- Renal
- Hearing loss
- ⇓ Body weight (subchronic, chronic)

- Gastrointestinal
- Immunological and Lymphreticular

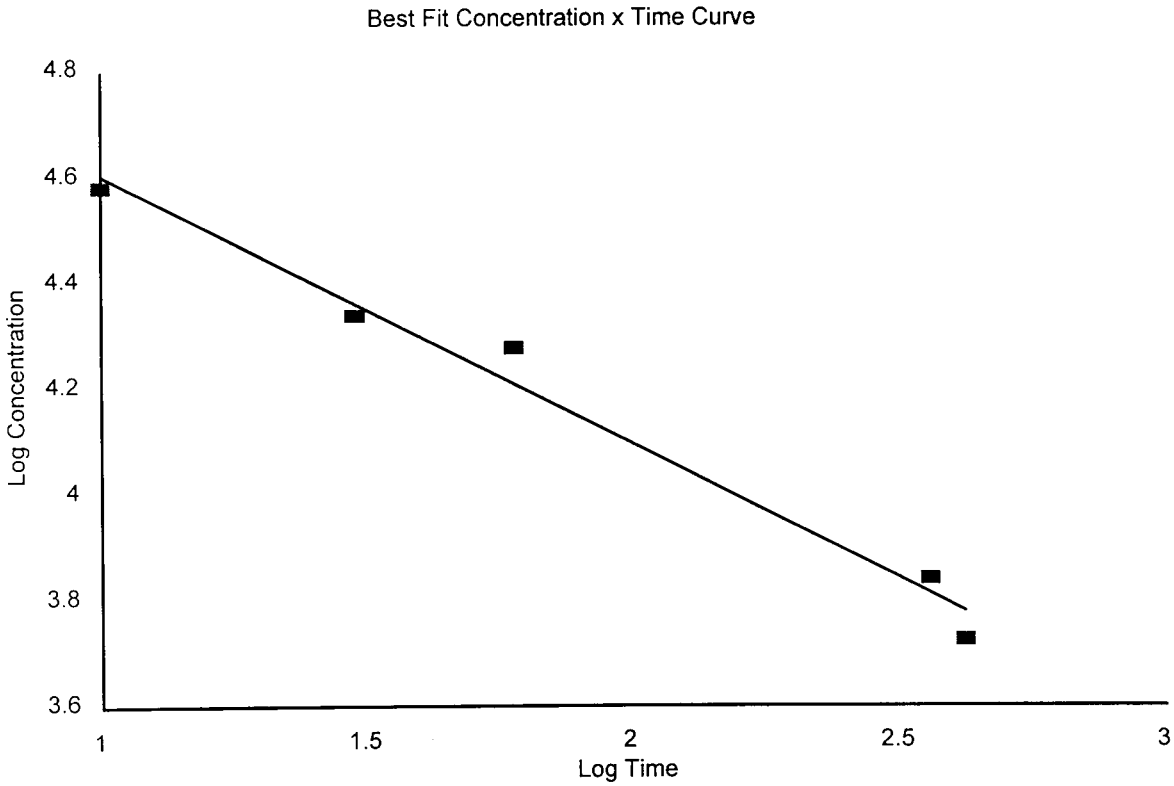
DEVELOPMENTAL/REPRODUCTIVE

- No reproductive effects have been identified in rodents
- Developmental delays
- ⇑Fetal mortality

GENOTOXICITY/CARCINOGENICTY

- Reports suggest toluene does not have genotoxic/carcinogenic potential in rodents

DERIVATION OF *n*



n=2

R^2=0.98

Correlation coeff. = 0.99

FIGURE 1. Regression curve for mouse lethality data.

10-, 30-, and 60-min (Moser and Balster, 1985)

6- and 7-hr (Bonnet et al., 1979)

TABLE 2: AEGL-1 VALUES FOR TOLUENE (ppm [mg/m^3])				
AEGL level	30-min	1-hr	4-hr	8-hr
AEGL-1	115 [432]	82 [308]	41 [154]	29 [109]

Species: Human
Concentration: 100 ppm
Time: 6 hr
Endpoint: Eye and nose irritation, headache
Reference: Andersen et al., 1983

n = 2

Uncertainty Factor = 3

Intraspecies = 3 (Mechanism of irritation and headache not expected to vary greatly between indiv.)

Supporting data:

Baelum et al., 1990

Human subjects, 7 hr at 100 ppm, sensory irritation headache, dizziness, ⇓ visual vigilance

Echeverria et al., 1991

Human subjects, 7 hr at 150 ppm, sensory irritation, headache, fatigue, ⇓ 2/12 neurobehavioral tasks

Rahill et al., 1996

Human subjects, 6 hr at 100 ppm, slight ⇓ on one cognitive task

Cherry et al., 1983

Human subjects, 4 hr at 80 ppm, no impairment on neurobehavioral tasks

TABLE 3: AEGL-2 VALUES FOR TOLUENE (ppm [mg/m^3])				
AEGL level	30-min	1-hr	4-hr	8-hr
AEGL-2	267 [1004]	189 [711]	94 [354]	67 [252]

Species: Human
Concentration: 200 ppm
Time: 8 hr
Endpoint: Incoordination, mental confusion, neurobehavioral deficits
References: Wilson, 1943; von Oettingen et al., 1942

n = 2
Uncertainty Factor = 3
Intraspecies = 3 (Mechanism of action for CNS effects is not expected to vary greatly between individuals)

Supporting Data:

Gambarale and Hultengren, 1972

Human subjects, 700 ppm for 20 min., CNS threshold for ⇑ reaction time, decreased perceptual speed

Taylor and Evans, 1985

Macaque monkeys, 2000 ppm for 50 min, significantly impaired reaction time and matching to sample accuracy

TABLE 4: AEGL-3 VALUES FOR TOLUENE (ppm [mg/m^3])				
AEGL level	30-min	1-hr	4-hr	8-hr
AEGL-3	897 [3373]	634 [2384]	317 [1192]	224 [842]

Species: Mouse
Concentration: 6339.33 ppm
Time: 1 hr
Endpoint: 1/3 of the LC_{50}
Reference: Moser and Balster, 1985

n = 2
Uncertainty Factor = 10
Interspecies = 3 (little species variability for lethal and nonlethal effects)
Intraspecies = 3 (mechanism of CNS depression is not expected to vary greatly between individuals)

Supporting Data:

Meulenbelt et al., 1990

Human accidental exposure which resulted in unconsciousness, estimated exposure conc. of 1842 ppm for 2-3 hr.

TABLE 5. SUMMARY OF PROPOSED AEGL VALUES (ppm)					
Classification	**30-minute**	**1-hour**	**4-hour**	**8-hour**	**Endpoint (Reference)**
AEGL-1	115	82	41	29	Eye irritation, headache in humans (Andersen et al., 1983)
AEGL-2	267	189	94	67	Incoordination, mental confusion, neurobehavioral deficits in humans (Wilson, 1943; von Oettingen et al., 1942)
AEGL-3	897	634	317	224	Lethality, 1/3 mouse 1-hour LC_{50} (Moser and Balster, 1985)

Table 6. Standards and guidelines for Toluene.	
ACGIH TLV-TWA (ACGIH 1998)	50 ppm
ACGIH TLV-STEL (ACGIH 1998)	postponed until more data are available
OSHA PEL-TWA (NIOSH 1997)	200 ppm
OSHA Ceiling (NIOSH 1997)	300 ppm
OSHA 10-min max peak (NIOSH 1997)	500 ppm
NIOSH REL-TWA (NIOSH 1997)	100 ppm
NIOSH STEL (NIOSH 1997)	150 ppm
NIOSH IDLH (NIOSH 1997)*	500 ppm
1-hour EEGL (NRC 1987)	200 ppm
24-hour EEGL (NRC 1987)	100 ppm
ERPG-1 (AIHA-ERPG, 1996)	50 ppm
ERPG-2 (AIHA-ERPG, 1996)	300 ppm
ERPG-3 (AIHA-ERPG, 1996)	1000 ppm

* IDLH is based on acute inhalation toxicity data in humans (Gamberale and Hultengren 1972; von Oettingen et al., 1942; Wilson 1943)

TETRACHLOROETHYLENE (PCE) AEGLs

Bill Bress
Claudia M. Troxel

PCE

- **PROPERTIES**
  Colorless, nonflammable liquid
  Ethereal odor; thresholds of 2-71 ppm

- **USES**
  Dry cleaning solvent, degreaser, chemical intermediate, veterinary antithelminitic

- **INHALATION TOXICITY**
  Humans: primarily reversible CNS effects and irritation
  Animals: reversible CNS effects predominate: also hepatotoxicity in mice and nephrotoxicity in rats

- **AVAILABLE DATA**
  Data addressing effects consistent with definitions for AEGL endpoints were limited

HUMAN DATA

- **LETHAL EFFECTS:**

  Autopsy reports following exposure to unquantified amount of vapor

- **NONLETHAL EFFECTS:**

  Controlled exposures: detection of odor, slight eye and nasal irritation, and CNS effects such as headaches, dizziness, mental sluggishness, nauseousness, feelings of exhilaration or inebriation, faintness, sleepiness, vertigo, tinnitus, and reduced motor coordination

  Case reports: one of more cases of unconsciousness, reversible liver damage, pulmonary edema, cardiac arrhythmias, optic neuritis

- **DEVELOPMENTAL AND REPRODUCTIVE EFFECTS:**

  Inconclusive results

- **GENOTOXICITY:**

  No evidence of genotoxicity in humans

- **CARCINOGENICITY:**

  IARC classified PCE as probably carcinogenic to humans: positive association between exposure and esophageal and cervical cancer and non-Hodgkin's lymphoma

ANIMAL DATA

- **LETHAL EFFECTS**: [LC_{50} in ppm]

Rats:	6 h	4100	Mice:	4 h	5200
	8 h	5000		6 h	2978

- **NONLETHAL EFFECTS**:

Acute:

Reversible CNS effects - hyperactivity, hypoactivity, drowsiness, ataxia, anesthesia

Repeated Exposure:

Mice: Hepatoxicity - fat infiltration, congestion, increased liver weights

Rats: Nephrotoxicity - increased kidney weights, hyalin droplet formation

- **DEVELOPMENTAL/ REPRODUCTIVE:**

  No developmental anomalies; no clear reproductive effects

  Decreases in fetal b.w. in mice and rats

  Neurobehavioral testing of offspring from exposed dams: inconsistent decrements

- **GENOTOXICITY**:
  Generally tested negative in mutagenicity tests; equivocal evidence of DNA binding

  PCE epoxide less reactive than epoxides of unsymmetrically substituted chlorinated ethylenes

- **CARCINOGENICITY**:

  Rats: Mononuclear cell leukemia, uncommon renal tubular cell neoplasms

  Mice: hepatocellular adenomas and carcinomas

MECHANISMS OF "SPECIES SPECIFIC" TOXICITY/CARCINOGENICITY

Nephrotoxicity/carcinogenicity in rats:

Chronic toxicity

Hyalin droplet nephropathy

Gluthathione/β-lyase pathway

Hepatotoxicity/carcinogenicity in mice:

Increased production of TCA

cytotoxicity

peroxisomal proliferation

Rat hepatocytes: interference with energy-dependent hepatic transport functions

Categorical Regression Analysis of PCE:

- Rao et al., 1993: Regression analysis based on entire data base of PCE identified CNS effects as the more sensitive noncancer endpoint in both the <14 day and 15-365 day exposure duration studies.

- Guth et al., 1997: Review of all available acute exposures to PCE (single exposures under 24 h)

  CNS effects: NE - no effect, AE - adverse effect, SE -includes lethality (considered severe CNS effect: narcosis precedes death, recovery occurs if animals removed from exposure)

  Variable slope model (stratified on species) applied to CNS data to predict a probability of 0.1 that an adverse or severe effect would be observed (ET-T10)

  Rat and human show similar slopes for severe and adverse effect EC-T10

AEGL-1

- Stewart et al., 1981. Tetrachloroethylene: development of a biologic standard for the industrial worker by breath analysis.

- 4 male and 5 female volunteers:
  0 ppm PCE for 1 or 2 days
  100 ppm PCE for **7½ hours** for 5 days

RESULTS:

- EEG changes consistent with cortical depression/first stages of anesthesia measurable on first day in 3/4 males and 4/5 females

No other effects:

- Equal number of subjective responses on exposure and 0 ppm exposure days

- No changes in neurological, blood chemistry, cardio-pulmonary function tests

- **Uncertainty Factors/Rationale:**
  Total uncertainty factor: 3
  Interspecies: NA
  Intraspecies: 3 - Mechanism of action for CNS effects not expected to vary greatly

- **Time scaling:** $C^n \times t = k$ where $n = 2$ (as calculated in ten Berge et al., 1986)

AEGL-1 (ppm)			
30 min	1 hour	4 hours	8 hours
130	91	46	32

[100 ppm for 7.5 h] SUPPORTED BY:

- Stewart et al., 1981: Exposure to 150 ppm for 7.5 h - reduced score in coordination test

- Stewart et al., 1977 - 6 volunteers/sex exposed to 100 ppm for 5.5 h had reduced score in coordination test

AEGL-2

- Carpenter et al., 1937. The chronic toxicity of tetrachloroethylene.

- 4 volunteers: **475 ppm** for **130 min**.

RESULTS:

- Volunteers reported salivation, slight eye and nasal irritation, tightness in frontal sinuses, increased hand perspiration

- **Uncertainty Factors/Rationale:**
  Total uncertainty factor: 3
  Interspecies: NA
  Intraspecies: 3 - Mechanism of action for CNS effects not expected to vary greatly

- **Time scaling:** $C^n \times t = k$ where $n = 2$ (as calculated in ten Berge et al., 1986)

AEGL-2 (ppm)			
30 min	1 hour	4 hours	8 hours
130	91	46	32

[475 ppm for 130 min] SUPPORTED BY:

- Mattsson et al., 1998: Rats exposed to **800 ppm** for **6 h**/d, for 4 days had changes in flash and somatosensory evoked potentials and in an EEG on the 4th day

- NTP, 1986 - Rats and mice exposed to 800 ppm for **6 h**/d, 5 d/wk for 13 wks had liver congestion or lesions. Panting and irritation were noted in mice on 2nd exposure day

- Offspring of pregnant rats exposed to **900 ppm** for **7 h**/d during GD 7-13 had poorer performance in ascent and rotorod test on certain testing days

AEGL-3

- Goldberg et al., 1964. Effect of repeated inhalation of vapors of industrial solvents on animal behavior.

- Rats exposed to **2300 ppm** for **4 h** had reversible ataxia

- **Uncertainty Factors/Rationale:**
  Total uncertainty factor: 10
  - Interspecies: 3 - does not appear to be much variation across species for CNS effects
  - Intraspecies: 3 - mechanism of action for CNS effects not expected to vary greatly

- **Time scaling:** $C^n \times t = k$ where $n = 2$ (as calculated in ten Berge et al., 1986)

AEGL-3 (ppm)			
30 min	1 hour	4 hours	8 hours
650	460	230	160

[2300 ppm for 4 h] SUPPORTED BY:

- Carpenter, 1937: 4 volunteers exposed to **934 ppm** for **95 min** reported tightness of frontal sinuses, increased hand perspiration, nostril irritation, congestion of eustachian tubes, lassitude, slight mental fogginess, stinging eyes, exhilaration; tip of nose and lips anesthetized in one subject.

- Friberg, 1953 - No mortality in mice exposed to **2450 ppm** for **4 h**

- NTP, 1986 - No mortality in rats exposed to **2445 ppm** for **4 h**: hypoactivity, ataxia, anesthesia

Summary of Lethal Inhalation Data in Laboratory Animals			
Conc. (ppm)	Duration	Mortality and Other Effects	Reference
Rat			
4100	6 h	LC_{50}	Bonnet et al., 1980
5000	8 h	LC_{50}	Pozzani et al., 1959
3786	4 h	Lowest exposure concentration causing death (1/5 males; 4/5 females); no mortality at 2445 ppm	NTP, 1986
1750	6 h/d, 5d/wk for 2 wk	Killed 5/10; no mortality at 875 ppm or less	NTP, 1986
1600	6 h/d, 5d/wk for 13 wk	Killed 11/20; No mortality at 800 ppm or less	NTP, 1986
Mouse			
5200	4 h	LC_{50}	Friberg et al., 1953
2978	6 h	LC_{50}	Bonnet et al., 1980
3000	4 h	Lowest exposure concentration causing death (2/8) No mortalities at 2450 ppm	Friberg et al., 1953
2613	4 h	Lowest exposure concentration causing death in males; 2/5 females died at lowest dose of 2328 ppm	NTP, 1986
1600	6 h/d, 5d/wk for 13 wk	Killed 6/20; No mortality at 800 ppm or less	NTP, 1986
3700	various time periods	Effective exposure duration for 50% of the animals was as follows: for the onset of anesthesia: 24.0 min; for hepatotoxicity: 470 min; for death: 730 min. Therefore, determined that CNS effects occur well before liver damage	Gehring, 1968

Summary of Nonlethal Inhalation Data in Laboratory Animals			
Conc. (ppm)	Duration	Effects	References
Monkey			
400	7 h/d for 179 exp.	No effects	Rowe et al., 1952
Rat			
10,520-11,430	25 min	Increased respiratory rate	Janssen, 1990
2445	4 h	Highest concentration causing no mortality; Hypoactivity, ataxia, and anesthesia	NTP, 1986
2300	4 h	Overt ataxia during first exposure resulting in 80% loss of both avoidance and escape responses, disappeared during subsequent exposures; no effects at 1150 ppm	Goldberg et al., 1964
800	6 h/d for 4 d	Changes in flash and somatosensory evoked potential and in EEG	Mattsson et al., 1998
100, 350, 1225	18 h/d, 3 d or 3 wks	Reversible decreases in psychomotor speed and motor activity; exposure concentration-related severity	Kulig et al., 1992
1600	7 h/d, 5 d/wk for 18 exp.	Animals appeared drowsy or stuporous upon removal from the chamber during the first week of exposure	Rowe et al., 1952
875	6 h/d, 5d/wk for 2 wk	Highest concentration causing no mortality; No clinical signs	NTP, 1986
800	6 h/d, 5d/wk for 13 wk	Highest concentration causing no mortality; No clinical sign; Dose-related hepatic congestion in 200, 400, or 800 ppm animals	NTP, 1986
1000	4 or 7 h/d, 4 d/wk for 2 wk	Increased kidney weights with minimal to moderate hyalin droplet formation in renal cortex; minimal to moderate hepatic central fatty metamorphosis	Piper and Sparschu, 1969
Mouse			
2445	4 h	Highest concentration causing no mortality in males (2/5 females died at 2328 ppm but none at 2445 ppm); Hypoactivity and anesthesia	NTP, 1986
200 400	4 h	Moderate hepatic fat infiltration 24 h post exp, but not 3 days post exp. Moderate to massive hepatic fat infiltration	Kylin et al., 1963
713	4 h	ID_{50}: 50% decrease in the total duration of immobility in behavioral despair swimming test	De Ceaurriz et al., 1983
875 1750	6 h/d, 5 d/wk for 2	Hepatic cytoplasmic vacuolation (fat) in males Dyspnea, hypoactivity, hyperactivity, anesthesia, ataxia, lower final body wts; hepatic cytoplasmic vacuolation (fat)	NTP, 1986
200 400 800	6 h/d, 5d/wk for 13 wk	No clinical signs or pathological lesions Hunched over posture and no movement on day 2; liver lesions Highest conc. with no mortality; panting, irritation on day 2; liver lesions	NTP, 1986

Appendix A

National Advisory Committee (NAC)
for Acute Exposure Guideline Levels (AEGLs) for Hazardous Substances
Final Meeting 13 Highlights
Wyndham Riverfront Hotel, 701 Convention Center Blvd.
New Orleans, Louisiana 70130
March 11-12, 1999

INTRODUCTION

George Rusch (NAC Chairman) opened the meeting and welcomed all participants. Attached are the meeting agenda (Attachment 1) and the attendee list (Attachment 2).

The NAC/AEGL Meeting 12 highlights were reviewed and minor changes were requested by John Morawetz and David Belluck. A motion to accept the meeting summary passed unanimously (Appendix A).

STATUS REPORTS AND GENERAL INTEREST ITEMS

National Academy of Sciences (NAS)/Committee on Toxicology (COT)

Roger Garrett (Program Director) stated that the NAS/COT Subcommittee on Acute Exposure Guideline Levels has prepared a preliminary report and was waiting for the completion of the thorough NAS review process. This report addresses the Standing Operating Procedures (SOPs) and eight interim AEGL assessments. A more definitive characterization of hypersusceptible subpopulations and the integration of cancer risk for acute exposures were among the issues the COT identified as topics of concern. He also stated that the SOPs and the five interim assessments will be presented to OECD in response to their interest in the AEGL program.

General Interest Items

- Ceiling Levels
  There was discussion regarding the interpretation of AEGLs especially regarding ceiling level terminology (Attachment 3). It was suggested by George Rusch (NAC/AEGL Chairman) that an official definition needed to be established and practical applications of AEGLs needed to be explored.

- Compilation of AEGL-1 Endpoints
  Deferred until the next meeting.

- AEGL Dose-Response Family Curves
  Ernest Falke gave a brief overview of dose-response data (Attachment 4) for some of the AEGL chemicals and stated that a considerable amount of data were available. This will be an ongoing effort.

- NORA Proposal
  Discussion was deferred.

- Children vs. Adults Sensitivity
  Bill Pepelko stated that pharmacokinetics may be an important factor regarding variable toxicity between children and adults. Brief discussion ensued regarding the intraspecies uncertainty factor as it pertains to children. The Childrens' Environmental Health Web site (www.cehn.org) was mentioned as a possible source of information.

- Piperidine Reference
  Mark McClanahan indicated that the original references in question will be obtained and the findings summarized. (Note: no additional information can be used to expand the current version of TSD).

- Categorical Regression in AEGL Development
  Judy Strickland (USEAP/NCEA) presented results of a categorical regression analysis of propylene oxide (Attachment 5). A comparison of this approach to that used by the NAC/AEGL indicated similar determinations of AEGL-1 and AEGL-2 values. AEGL-3 values varied somewhat but not greatly. It was suggested that the results of the categorical regression analysis be incorporated into the appendix section of the propylene oxide Technical Support Document (TSD). Furthermore, Judy offered the results of a categorical regression analysis for methyl isocyanate which had been performed by Dan Guth in 1997. With the application of an uncertainty factor of 6, the results for mild adverse effects, which approximate AEGL-1 values, were comparable to the proposed AEGL-1s.

- IDLH Values and their Relation to AEGLs
  Following a statement of the definition of the IDLH (Zarena Post), there was brief discussion regarding the relevance of the IDLH to AEGL levels 2 and 3 (Attachment 6). Richard Niemeier (NIOSH) (absent) would likely be able to provide greater insight into this subject.

- Scientific Judgement in AEGL Development
  George Rusch commented on the value of scientific judgement in development of AEGLs. Although graphic presentation of data and modeling techniques are useful, good individual and group judgements are cornerstones of good risk assessment. The NAC/AEGL should continue to rely on the expertise that various members bring to the discussions.

- AEGL Applications
  Ernest Falke distributed a draft of the AEGL application write-up (Attachment 3) and requested comments. An attempt to reach consensus on all or part of the draft was deferred. It was suggested that individuals from other agencies/organizations be invited to a future NAC/AEGL meeting to discuss how the AEGLs may be applied.

- Paul Tobin (DFO) indicated that a list of new NAC/AEGL priority chemicals was being drafted and distributed (Attachment 7).

AEGL PRIORITY CHEMICALS

Ethylenediamine, CAS No.107-15-3

Chemical Manager: Mark McClanahan, CDC
Author: Sylvia Milanez, ORNL

Sylvia Milanez provided an overview of data pertinent to developing AEGL values (Attachment 8). There was some discussion regarding the sensitivity characterization (hypersusceptible or not) of individuals sensitized by ethylenediamine. Following discussion regarding the apparently insufficient data relative to AEGL-1, it was decided to address AEGL-2 and AEGL-3 values first. A motion for AEGL-2 by Steven Barbee; seconded by Loren Koller) entailed the use of the NOEL of 59 ppm from a 30-day study in rats exposed for 7 hrs/day, an uncertainty factor of 10 (3 for interspecies and 3 for intraspecies), and using a value of *n*=2 to extrapolate down to 30 min. The proposed values were 30-min, 22 ppm; 1 hr, 16 ppm; 4 hr, 7.8 ppm; and 8 hr, 5.5 ppm. It was noted that this is consistent with the case report of the sensitized human who was exposed as a challenge to ethylenediamine. The values are also consistent with using a 100-fold safety factor with an acute 8-hr study. The motion passed unanimously. A motion was made by Ernest Falke (seconded by Richard Thomas) to develop AEGL-3 values using the same study as used for AEGL-2 (i.e., Pozzani and Carpenter). The determinant for AEGL-3 was the 7-hr, 132-ppm exposure at which there was toxicity seen in only one animal and there was no lethality. This provides a conservative estimate of the lethalty threshold and is consistent with the fact that at 225 ppm, the next highest level, there was lethality. Using an *n* of 2 and a total uncertainty factor of 10 (3 for intraspecies and 3 for interspecies), the resulting AEGL-3 values are: 49 ppm for 30 min, 35 ppm for 1 hr, 17 ppm for 4 hrs, 12 ppm for 8 hrs. The motion passed [YES: 24; NO: 1, ABSTAIN: 0]. A motion was made by Bob Benson (seconded by Ernest Falke) that we do not establish AEGL-1 values for ethylenediamine because there is insufficient data on which to base them. The motion passed [YES: 24; NO: 2; ABSTAIN 0] (Appendix B). John Morawetz indicated that a note should accompany the AEGL values regarding sensitive individuals.

SUMMARY OF REVISED AEGL VALUES FOR ETHYLENEDIAMINE					
Classification	**30-min**	**1-hr**	**4-hr**	**8-hr**	**Endpoint**
AEGL-1	ND	ND	ND	ND	Not determined; insufficient data.
AEGL-2	22 ppm 54 mg/m^3	16 ppm 38 mg/m^3	7.8 ppm 19 mg/m^3	5.5 ppm 14 mg/m^3	NOEL for rats exposed 30 days to 59 ppm for 7 hrs/day
AEGL-3	49 ppm 121 mg/m^3	35 ppm 86 mg/m^3	17 ppm 43 mg/m^3	12 ppm 30 mg/m^3	7-hr exposure of rats (toxicity but no deaths) to 132 ppm for 30 days used as a conservative estimate of lethality threshold

Phosphorus trichloride, CAS No. 7719-12-2

Chemical Manager: Tom Hornshaw, Illinois EPA
Author: Robert Young, ORNL

Robert Young provided an overview of the physico-chemical properties and limited toxicity data on phosphorus trichloride (Attachment 9). The deficiencies were especially prevalent regarding exposure-response data for nonlethal endpoints. Draft values for all three AEGL levels were, however, developed to provide strawman reference points as a basis for discussion. Tom Hornshaw presented an overview of several accidental industrial/transport releases of phosphorus trichloride and the responses to these releases. Following discussion regarding the available lethality data, a motion was made by Bob Benson (seconded by Bill Pepelko) that we adopt AEGL-3 values for phosphorous trichloride of 1.6 ppm for 30-min; 1.1 ppm for 1-hr; 0.56 ppm for
4 hr; 0.39 ppm for 8 hr. These are based on a one-third reduction of the 4-hr LC_{50} in the guinea pig of 50 ppm as an estimate of the non-lethal threshold of 16.7 ppm. Theses values reflect an uncertainty factor of 10 for interspecies variability, a factor of 3 for intraspecies uncertainty, and a time scaling exponent (n) of 2. The motion passed [YES: 18; NO: 8; ABSTAIN 0]. (Appendix C). The motion that we will have insufficient data to derive AEGL-1 and AEGL-2 values and that was made by Dave Belluck and seconded by Kyle Blackman. The motion passed unanimously.

SUMMARY OF PROPOSED AEGL VALUES FOR PHOSPHORUS TRICHLORIDE					
Classification	**30-min**	**1-hr**	**4-hr**	**8-hr**	**Endpoint**
AEGL-1	ND	ND	ND	ND	Not determined; insufficient data
AEGL-2	ND	ND	ND	ND	Not determined; insufficient data
AEGL-3	1.6 ppm 8.9 mg/m^3	1.1 ppm 6.2 mg/m^3	0.56 ppm 3.1 mg/m^3	0.39 ppm 2.2 mg/m^3	Estimated lethality threshold based upon 1/3 reduction of guinea pig 4-hr LC_{50} (50 ppm/3 = 16.7 ppm).

Phosphorus oxychloride, CAS No. 10025-87-3

Chemical Manager: Tom Hornshaw, Ilinois EPA
Author: Robert Young, ORNL

An overview of available data on phosphorus oxychloride was presented by Robert Young (Attachment 10). Quantitative data sufficient for developing AEGL-1 and AEGL-2 values were unavailable and no draft values were presented. Tom Hornshaw also presented information on an accidental release of phosphorus oxychloride (Attachment 11). Lethality data were limited to 4-hr LC_{50} values in rats and guinea pigs. Draft AEGL-3 values were developed based upon a three-fold reduction of the 4-hr LC_{50} in rats as an estimated of the lethality threshold (i.e., 48.4 ppm/3 = 16.1 ppm). The draft values were developed using an uncertainty factor of 10 for interspecies variability (no human exposure data and limited animal data in only two species) and an intraspecies uncertainty factor of 3 (mechanism of toxicity appears to be a function of hydrogen chloride and phosphonic acid production resulting in contact irritation and tissue destruction and is not likely

to vary among individuals). Due to uncertainties regarding time-dose relationships, the draft values were developed using an *n* of 2 for extrapolation from 4 hrs to 1 hr and to 30 min. and an *n* of 1 for extrapolation to 8 hrs. However, it was the consensus of the NAC/AEGL that the *n* exponent remain constant at 2. A motion was made Bob Benson (seconded by Bob Snyder) to adopt AEGL-3 values for phosphorus oxychloride of 1.5 ppm for 30-min; 1.1 ppm for 1-hr; 0.54 ppm for 4 hr; and 0.38 ppm for 8 hr based upon the 16.1 lethality threshold estimate, an *n* of 2 and uncertainty factors as described above. The motion passed [YES: 18; NO: 8; ABSTAIN: 0] (Appendix D).

SUMMARY OF PROPOSED AEGL VALUES FOR PHOSPHORUS OXYCHLORIDE					
Classification	**30-min**	**1-hr**	**4-hr**	**8-hr**	**Endpoint**
AEGL-1	ND	ND	ND	ND	Not determined; insufficient data
AEGL-2	ND	ND	ND	ND	Not determined; insufficient data
AEGL-3	1.5 ppm 9.4 mg/m^3	1.1 ppm 6.9 mg/m^3	0.54 ppm 3.4 mg/m^3	0.38 ppm 2.4 mg/m^3	Estimated lethality threshold based upon 1/3 reduction of rat 4-hr LC_{50} (48 ppm/3 = 16 ppm).

Tetranitromethane, CAS No. 509-14-8

Chemical Manager: Kyle Blackman, FEMA
Author: Sylvia Milanez, ORNL

Sylvia Milanez presented a summary of data relevant to the development of AEGL values for tetranitromethane (Attachment 12). A motion was made by Loren Koller (seconded by Bill Bress/Richard Thomas) that the values as originally proposed for AEGL-1 be adopted. These values were: 30-min, 0.69 ppm; 1 hr, 0.49 ppm, 4 hr, 0.24 ppm, 8 hrs, 0.17 ppm. For AEGL-2: 30-min, 1.7 ppm; 1 hr, 1.2 ppm; 4 hr, 0.61 ppm, and 8 hr, 0.43 ppm. AEGL-3: 30-min, 3.5 ppm ; 1 hr, 2.4 ppm; 4 hr, 1.2 ppm; 8 hr, 0.87 ppm. All of these values are based on the NTP 1990 study. AEGL-1 values are based upon the no-observed-effect threshold of 2 ppm for rats and mice. AEGL-2 values were based upon an exposure level that induced reddening of the lungs in mice (5 ppm). The AEGL-3 values were based upon lethality thresholds in rats and mice (10 ppm). The key study was a 2-week study with a 6-hr/day exposure for 5/days/week. The value for *n* was 2 and it was pointed out that the value of *n* fits both the Kincaid and the Korbakova data. The motion passed (each AEGL level was subject to a separate vote). These votes were AEGL-1 [YES: 21; NO: 5, ABSTAIN 0]; AEGL-2 [YES: 24; NO: 2; ABSTAIN: 0]; AEGL-3 [unanimously] respectively (Appendix E).

SUMMARY OF PROPOSED AEGL VALUES FOR TETRANITROMETHANE					
Classification	**30-min**	**1-hr**	**4-hr**	**8-hr**	**Endpoint**

AEGL-1	0.69 ppm 5.6 mg/m^3	0.49 ppm 3.9 mg/m^3	0.24 ppm 2.0 mg/m^3	0.17 ppm 1.4 mg/m^3	Threshold for no observable effects in rats and mice (NTP, 1990)
AEGL-2	1.7 ppm 14 mg/m^3	1.2 ppm 9.8 mg/m^3	0.61 ppm 4.9 mg/m^3	0.43 ppm 3.5 mg/m^3	Pulmonary irritation in mice (NTP, 1990)
AEGL-3	3.5 ppm 28 mg/m^3	2.4 ppm 20 mg/m^3	1.2 ppm 9.8 mg/m^3	0.87 ppm 6.9 mg/m^3	Lethality threshold in mice (NTP, 1990)

Jet Fuels

Chemical Manager: John Hinz, USAF (AL/OEMH)
Author: Sylvia Talmage, ORNL

John Hinz gave a brief overview of jet fuels and delineated the major issues (a complex mixture with variable composition, vapor vs. aerosol exposure, military vs civilian exposure) impacting AEGL development (Attachment 13 and 14). Previous assessments on fuels other than JP-8 and the fact that some of the jet fuels (e.g., JP-4, JP-7) will no longer be used were noted. He emphasized that the AEGL assessment should focus on JP-8. A presentation of current knowledge on various jet fuels was provided by Maj. Les Smith and Maj. Don Christensen, M.D. (Brooks AFB) (Attachment 15). These overviews included characterization of the various jet fuels (application, composition, inventories, etc.) as well as results of USAF worker exposure surveys, and current and future health-related studies (especially on JP-8). Sylvia Talmage then presented a summary of currently available data on JP-4, JP-5, JP-7, and JP-8 (Attachment 16). It was noted that much of the toxicity data are from long-term exposures and that development of AEGL values would be difficult and of uncertain validity, especially for the 30-min, 1-hr, and 4-hr exposure periods. Draft 8-hr AEGL values for all three levels were presented (300 mg/m^3, 1700 mg/m^3, and 3000 mg/m^3, respectively, for AEGL-1, AEGL-2, and AEGL-3). It was the consensus of the NAC/AEGL, however, that the AEGL development for jet fuels be tabled pending availability of information from ongoing and soon-to-be-conducted studies by the USAF.

Sulfur tetrafluoride, CAS No. 7783-60-0

Chemical Manager: Kyle Blackman, FEMA
Author: Carol Forsyth, ORNL

Carol Forsyth reported that the only available information on this chemical was limited to a secondary source and an accident report with no details (Attachment 17). The relevance of sulfuric acid as a decomposition product and the use of hydrogen fluoride as a surrogate were briefly discussed. Because of the lack of chemical-specific data, the uncertainty regarding the breakdown to hydrogen fluoride, and the fact that sulfuric acid has not yet been addressed by the NAC/AEGL, deliberations on sulfur tetrafluoride were deferred indefinitely.

Methyl isocyanate, CAS No. 624-83-9

Chemical Manager: Loren Koller, Oregon State Univ.
Author: Carol Forsyth, ORNL

Carol Forsyth gave a brief summary of available data for methyl isocyanate and presented draft AEGL values (Attachment 18). Judy Strickland stated that categorical regression analysis provided 30-min and 1-hr AEGL values that were lower (analysis not provided). A discussion on the mechanism of action of methyl isocyanate focused on the irritation and possible developmental effects as inferred by spontaneous abortion rates in the Bhopal incident. A motion to accept the following AEGL-3 values was made by Bob Benson (seconded by Ernest Falke): 0.4 ppm for 30 min; 0.2 ppm for 1 hr; 0.05 ppm for 4 hrs; 0.025 ppm for 8 hrs. These values were based upon an increased number of deaths in rat pups born from mothers who were exposed to 3 ppm during gestation. At 1 ppm there was no increase in death of pups compared to the controls. An *n* of 1 for time scaling is based upon an extrapolation of lethality data. An uncertainty factor of 3 for interspecies variability was applied because there was agreement between two species and two separate laboratory reports. An uncertainty factor of 10 was applied for intraspecies variability because of uncertainties regarding the mechanism of action. The motion passed unanimously (Appendix F). Further deliberations were tabled due to lack of time.

SUMMARY OF PROPOSED AEGL VALUES FOR METHYL ISOCYANATE					
Classification	**30-min**	**1-hr**	**4-hr**	**8-hr**	**Endpoint**
AEGL-1*					
AEGL-2*					
AEGL-3	0.4 ppm 0.95 mg/m^3	0.2 ppm 0.42 mg/m^3	0.05 ppm 0.12 mg/m^3	0.025 ppm 0.06 mg/m^3	Neonate lethality in rats following gestational exposure of dams to 3 ppm (Schwetz et al., 1987)

*To be determined at next meeting

ADMINISTRATIVE ISSUES

Future meetings

The following meeting dates and locations have been proposed:

June 14-16,1999 (Washington, D.C.)
September 14-16, 1999 (Rutgers University, N.J.)
December 6-8, 1999 (Washington, D.C.)

These highlights were prepared by Robert Young and Po-Yung Lu, ORNL.

LIST OF ATTACHMENTS

The attachments were distributed during the meeting and will be filed in the EPA Docket Office.

1. NAC/AEGL Meeting No. 13 Agenda
2. NAC/AEGL Meeting No. 13 Attendee List
3. Draft of AEGL Application Write-up - Ernest Falke
4. Dose- response family curve - Ernest Falke
5. Categorical Regression Analysis of Propylene Oxide - Judy Strickland
6. Definition of IDLH - Zarena Post
7. Second list of draft NAC/AEGL priority chemicals - Paul Tobin
8. Data Analysis of Ethylenediamine - Sylvia Milanez
9. Data Analysis of Phosphorus trichloride - Robert Young
10. Data Analysis of Phosphorus oxychloride - Robert Young
11. Accidental Release Data of Phosphorus oxychloride - Tom Hornshaw
12. Data Analysis on Tetranitromethane - Sylvia Milanez
13. Overview of Jet Fuels - John Hinz
14. Factors impacting the development of AEGLs of Jet Fuels - John Hinz
15. Current Knowledge on Jet Fuels - Les Smith and Don Christiansen
16. Data Analysis of JP-4, JP5- JP-7, and JP-8 - Sylvia Talmage
17. Data Analysis of Sulfur Tetrafluoride - Carol Forsyth
18. Data Analysis of Methyl Isocyanate - Carol Forsyth

LIST OF APPENDICES

A. Approved NAC-AEGL-12 Meeting Highlights
B. Ballot for Ethylenediamine
C Ballot for Phosphorus trichloride
D. Ballot for Phosphorus oxychloride
E. Ballot for Tetranitromethane
F. Ballot for Methyl isocyanate

Appendix B

NAC/AEGL Meeting: 6/14-16/99 **Chemical:** MINUTES

NAC Member	AEGL 1	AEGL 2	AEGL 3	NAC Member	AEGL 1	AEGL 2	AEGL3
George Alexeeff				Loren Koller			
Steven Barbee				Glenn Leach			
Lynn Beasley				Mark A. McClanahan			
David Belluck				John S. Morawetz			
Robert Benson				Deirdre L. Murphy			
Kyle Blackman				Richard W. Niemeier			
Jonathan Borak				William Pepelko			
William Bress				Zarena Post			
Luz Claudio				George Rodgers			
George Cushmac				George Rusch, Chair			
Ernest Falke				Michelle Schaper	Absent	Absent	Absent
Larry Gephart				Bob Snyder			
John Hinz				Thomas Sobotka			
Jim Holler				Kenneth Still			
Thomas C. Hornshaw				Patricia Ann Talcott			
Nancy Kim				Richard Thomas			
				Thomas Tuccinardi/ Doan Hansen			
				TALLY			

ACCEPTED - UNANIMOUS

PPM, (mg/m³)	30 Min	60 Min	4 Hr	8Hr
AEGL 1	,( )	,( )	,( )	,( )
AEGL 2	,( )	,( )	,( )	,( )
AEGL 3	,( )	,( )	,( )	,( )

AEGL 1 Motion: Benson **Second:** Belluck

AEGL 2 Motion: _____ **Second:** _____

AEGL 3 Motion: _____ **Second:** _____

Approved by Chair: _____ **DFO:** Paul S. Tobin **Date:** 6/14/99

In the absence of supporting data use default of n=3 and n=1 to interpolate to shorter and longer exposure times, resp.

NAC/AEGL Meeting: 6/14-16/99 **Chemical:**

Appendix C

NAC Member	AEGL 1	AEGL 2	AEGL 3	NAC Member	AEGL 1	AEGL 2	AEGL3
George Alexeeff				Loren Koller			
Steven Barbee				Glenn Leach			
Lynn Beasley				Mark A. McClanahan			
David Belluck				John S. Morawetz			
Robert Benson				Deirdre L. Murphy			
Kyle Blackman				Richard W. Niemeier			
Jonathan Borak				William Pepelko			
William Bress				Zarena Post			
Luz Claudio				George Rodgers			
George Cushmac				George Rusch, Chair			
Ernest Falke				Michelle Schaper	Absent	Absent	Absent
Larry Gephart				Bob Snyder			
John Hinz				Thomas Sobotka			
Jim Holler				Kenneth Still			
Thomas C. Hornshaw				Patricia Ann Talcott			
Nancy Kim				Richard Thomas			
				Thomas Tuccinardi/ Doan Hansen			
				TALLY			

UNANIMOUS, EXCEPT LARRY GEPHART

PPM, (mg/m³)	30 Min	60 Min	4 Hr	8Hr
AEGL 1	,( )	,( )	,( )	,( )
AEGL 2	,( )	,( )	,( )	,( )
AEGL 3	,( )	,( )	,( )	,( )

AEGL 1 Motion: Alexeeff **Second:** Thomas

AEGL 2 Motion: _____ **Second:** _____

AEGL 3 Motion: _____ **Second:** _____

Approved by Chair: _____ **DFO:** _____ **Date:** 6/15/99

ASTERISK (*) ALL INHALATION AND ORAL ROUTE AEGL CHEMICALS AND INDICATE CALCULATION IN EXECUTIVE SUMMARY, BODY TEXT AND APPENDIX (AS APPROPRIATE, CASE BY CASE), BUT BASE AEGL VALUES ON TOX DATA

NAC/AEGL Meeting: 6/14-16/99 **Chemical:**

NAC Member	AEGL 1	AEGL 2	AEGL 3
George Alexeeff	Y		
Steven Barbee	Y		
Lynn Beasley	Y		
David Belluck	Y		
Robert Benson	PASS		
Kyle Blackman	Y		
Jonathan Borak	A		
William Bress	Y		
~~Luz Claudio~~			
George Cushmac	Y		
Ernest Falke	Y		
Larry Gephart	Y		
John Hinz	PASS		
Jim Holler	Y		
Thomas C Hornshaw	Y		
Nancy Kim	Y		

NAC Member	AEGL 1	AEGL 2	AEGL3
Loren Koller	PASS		
Glenn Leach	A		
Mark A. McClanahan	Y		
John S. Morawetz	A		
Deirdre L. Murphy			
Richard W. Niemeier	Y		
William Pepelko	A		
Zarena Post	A		
George Rodgers	A		
George Rusch, Chair	Y		
Michelle Schaper	PASS Absent	Absent	Absent
Bob Snyder	Y		
Thomas Sobotka	Y		
Kenneth Still	Y		
Patricia Ann Talcott	A		
Richard Thomas	A		
~~Thomas Tuccinardi~~ Doan Hansen	A Y		
TALLY			

Appendix D

PPM, (mg/m³)	30 Min		60 Min	4 Hr	8Hr
AEGL 1	,( )		,( )	,( )	,( )
AEGL 2	,( )		,( )	,( )	,( )
AEGL 3	,( )		,( )	,( )	,( )

AEGL 1 **Motion:** FALKE **Second:** NIEMEIER

AEGL 2 **Motion:** _____ **Second:** _____

AEGL 3 **Motion:** _____ **Second:** _____

Approved by Chair: _____ **DFO:** _____ **Date:** 6/14/99

Appendix E

NAC/AEGL Meeting: 6/14-16/99 **Chemical:** 594-42-3 PERCHLOROMETHYL MERCAPTAN

NAC Member	AEGL 1	AEGL 2	AEGL 3
George Alexeeff	N	N	Y
Steven Barbee	Y	Y	Y
Lynn Beasley	Y	Y	Y
David Belluck	Y	Y	Y
Robert Benson	Y	Y	Y
Kyle Blackman	N	N	Y
Jonathan Borak	A	A	A
William Bress	N	Y	Y
~~Luz Claudio~~			
George Cushmac	Y	Y	Y
Ernest Falke	Y	Y	Y
Larry Gephart	Y	Y	Y
John Hinz	Y	N	Y
Jim Holler	Y	Y	A
Thomas C. Hornshaw	Y	N	N
Nancy Kim	Y	Y	Y

NAC Member	AEGL 1	AEGL 2	AEGL3
Loren Koller	Y	Y	Y
Glenn Leach	Y	Y	Y
Mark A. McClanahan	N	N	N
John S. Morawetz	A	A	A
Deirdre L. Murphy			
Richard W. Niemeier	Y	Y	Y
William Pepelko	Y	Y	Y
Zarena Post	A	A	A
George Rodgers	A	A	A
George Rusch, Chair	Y	Y	Y
Michelle Schaper	N Absent	Absent Y	Absent Y
Bob Snyder	Y	Y	Y
Thomas Sobotka	N	Y	N
Kenneth Still	Y	Y	Y
Patricia Ann Talcott	A	A	A
Richard Thomas	N	Y	Y
~~Thomas Tuccinardi~~ Doan Hansen	A N	A N	A ~~A~~ N
TALLY	18/25	20/26	21/25

PPM, (mg/m³)	30 Min	60 Min	4 Hr	8Hr
AEGL 1	0.018 ,( )	0.014 ,( )	0.009 ,( )	0.006 ,( )
AEGL 2	0.044 ,( )	0.035 ,( )	0.022 ,( )	0.014 ,( )
AEGL 3	0.38 ,( )	0.30 ,( )	0.075 ,( )	0.038 ,( )

AEGL 1 Motion: R. Snyder **Second:** L. Koller

AEGL 2 Motion: R Benson **Second:** Falke

AEGL 3 Motion: Falke **Second:** R. Benson

Approved by Chair: [signature] **DFO:** Paul S. Tobin **Date:** 6/15/99

Appendix F

NAC/AEGL Meeting: 6/14-16/99 **Chemical:** TOLUENE 108-88-3

NAC Member	AEGL 1	AEGL 2	AEGL 3
George Alexeeff	A	A	A
Steven Barbee	Y	Y	Y
Lynn Beasley	Y	Y	Y
David Belluck	Y	Y	Y
Robert Benson	Y	Y	Y
Kyle Blackman	Y	Y	Y
Jonathan Borak	A	A	A
William Bress	Y	Y	Y
~~Luz Claudio~~			
George Cushmac	Y	Y	Y
Ernest Falke	Y	Y	Y
Larry Gephart	Y	Y	Y
John Hinz	PASS	Y	Y
Jim Holler	Y	A	Y
Thomas C. Hornshaw	Y	Y	Y
Nancy Kim	N	Y	Y

NAC Member	AEGL 1	AEGL 2	AEGL3
Loren Koller	Y	Y	Y
Glenn Leach	Y	Y	Y
Mark A. McClanahan	Y	Y	Y
John S. Morawetz	A	A	A
Deirdre L. Murphy			
Richard W. Niemeier	Y	Y	Y
William Pepelko	Y	Y	Y
Zarena Post	A	A	A
George Rodgers	A	A	A
George Rusch, Chair	Y	Y	Y
Michelle Schaper	Absent Y	Absent Y	Absent Y
Bob Snyder	Y	Y	Y
Thomas Sobotka	N	N	Y
Kenneth Still	Y	Y	Y
Patricia Ann Talcott	A	A	A
Richard Thomas	A	A	A
Thomas Tuccinardi/ Doan Hansen	A A	A A	A A
TALLY	20/22	21/22	22/22

PPM, (mg/m³)	30 Min	60 Min	4 Hr	8Hr
AEGL 1	120 ,( )	82 ,( )	41 ,( )	29 ,( )
AEGL 2	270 ,( )	190 ,( )	94 ,( )	67 ,( )
AEGL 3	900 ,( )	630 ,( )	320 ,( )	220 ,( )

AEGL 1 Motion: L. Koller **Second:** D. Belluck

AEGL 2 Motion: L. Koller **Second:** D Belluck

AEGL 3 Motion: L. Koller **Second:** K. Blackman

Approved by Chair: [signature] **DFO:** Paul S. Tobin **Date:** 6/16/99

Appendix E

NAC/AEGL Meeting: 6/14-16/99 **Chemical:** 594-42-3 PERCHLOROMETHYL MERCAPTAN

NAC Member	AEGL 1	AEGL 2	AEGL 3
George Alexeeff	N	N	Y
Steven Barbee	Y	Y	Y
Lynn Beasley	Y	Y	Y
David Belluck	Y	Y	Y
Robert Benson	Y	Y	Y
Kyle Blackman	N	N	Y
Jonathan Borak	A	A	A
William Bress	N	Y	Y
~~Luz Claudio~~			
George Cushmac	Y	Y	Y
Ernest Falke	Y	Y	Y
Larry Gephart	Y	Y	Y
John Hinz	Y	N	Y
Jim Holler	Y	Y	A
Thomas C. Hornshaw	Y	N	N
Nancy Kim	Y	Y	Y

NAC Member	AEGL 1	AEGL 2	AEGL3
Loren Koller	Y	Y	Y
Glenn Leach	Y	Y	Y
Mark A. McClanahan	N	N	N
John S. Morawetz	A	A	A
Deirdre L. Murphy			
Richard W. Niemeier	Y	Y	Y
William Pepelko	Y	Y	Y
Zarena Post	A	A	A
George Rodgers	A	A	A
George Rusch, Chair	Y	Y	Y
Michelle Schaper	N Absent	Absent Y	Absent Y
Bob Snyder	Y	Y	Y
Thomas Sobotka	N	Y	N
Kenneth Still	Y	Y	Y
Patricia Ann Talcott	A	A	A
Richard Thomas	N	Y	Y
~~Thomas Tuccinardi~~ Doan Hansen	A N	A N	A ~~A~~ N
TALLY	18/25	20/26	21/25

PPM, (mg/m³)	30 Min	60 Min	4 Hr	8Hr
AEGL 1	0.018 ,( )	0.014 ,( )	0.009 ,( )	0.006 ,( )
AEGL 2	0.044 ,( )	0.035 ,( )	0.022 ,( )	0.014 ,( )
AEGL 3	0.38 ,( )	0.30 ,( )	0.075 ,( )	0.038 ,( )

AEGL 1 Motion: R. Snyder **Second:** L. Koller

AEGL 2 Motion: R Benson **Second:** Falke

AEGL 3 Motion: Falke **Second:** R. Benson

Approved by Chair: [signature] **DFO:** Paul S. Tobin **Date:** 6/15/99

Appendix G

127-18-4

NAC/AEGL Meeting: 6/14-16/99 **Chemical:** TETRACHLOROETHYLENE

NAC Member	AEGL 1	AEGL 2	AEGL 3	NAC Member	AEGL 1	AEGL 2	AEGL3
George Alexeeff	A	A	A	Loren Koller	Y	Y	Y
Steven Barbee	Y	Y	Y	Glenn Leach	Y	Y	Y
Lynn Beasley	Y	Y	Y	Mark A. McClanahan	N	Y	Y
David Belluck	Y	Y	Y	John S. Morawetz	A	A	A
Robert Benson	Y	Y	Y	Deirdre L. Murphy			
Kyle Blackman	Y	Y	Y	Richard W. Niemeier	Y	Y	Y
Jonathan Borak	A	A	A	William Pepelko	Y	Y	Y
William Bress	Y	Y	Y	Zarena Post	A	A	A
Luz Claudio				George Rodgers	A	A	A
George Cushmac	Y	Y	Y	George Rusch, Chair	Y	Y	Y
Ernest Falke	Y	Y	Y	Michelle Schaper	~~Absent~~ Y	~~Absent~~ Y	~~Absent~~ Y
Larry Gephart	Y	Y	Y	Bob Snyder	Y	Y	Y
John Hinz	Y	Y	Y	Thomas Sobotka	Y	N	Y
Jim Holler	Y	Y	Y	Kenneth Still	Y	Y	Y
Thomas C. Hornshaw	Y	Y	Y	Patricia Ann Talcott	A	A	A.
Nancy Kim	N	Bress	Y	Richard Thomas	A	A	A
				Thomas Tuccinardi/ Doan Hansen	A A	A A	A A
				TALLY	21/23	21/22	23/23

PPM, (mg/m³)	30 Min	60 Min	4 Hr	8Hr
AEGL 1	50 ,( )	35 ,( )	18 ,( )	12 ,( )
AEGL 2	330 ,( )	230 ,( )	120 ,( )	81 ,( )
AEGL 3	690 ,( )	490 ,( )	240 ,( )	170 ,( )

AEGL 1 Motion: S. Barbee **Second:** R. Niemeier

AEGL 2 Motion: R. Benson **Second:** R. Niemeier

AEGL 3 Motion: T. Hornshaw **Second:** S. Barbee

Approved by Chair: [signature] **DFO:** [signature] **Date:** 6/16/99