National Advisory Committee (NAC)
for Acute Exposure Guideline Levels (AEGLs) for Hazardous Substances

September 28-30, 2005

Final Meeting-38 Highlights

U.S. Department of Labor
Rooms 3437 A, B, & C
200 Constitution Ave., N.W.
Washington, DC 20210

INTRODUCTION

Chairman George Rusch welcomed the committee, and encouraged chemical managers to take notes on the staff scientists' presentations.

The draft NAC/AEGL-37 meeting highlights were not discussed because of the current issue on intentional dosing human data.

Richard Niemier discussed a practical use of AEGL values; AEGL-1 values were used for re-entry after a recent styrene release in Cincinnati, OH.

The highlights of the NAC/AEGL-38 meeting are summarized below along with the Meeting Agenda (Attachment 1) and the Attendee List (Attachment 2). The subject categories of the highlights do not necessarily follow the order listed in the NAC/AEGL-38 Agenda.

SUMMARY OF COT SUBCOMMITTEE MEETING

George Rusch led a discussion of the most recent COT subcommittee meeting (NAS-16; Aug. 31, Sept. 1-2, Woods Hole, MA). Major discussion points were as follows:

1. LOA (Level of Odor Awareness) paper needs to be published so that we can finalize the many TSDs where an LOA is calculated. Marc Ruijten stated that the paper is currently in the RIVM internal review process.

2. The COT subcommittee emphasized the need to track TSD revisions (red-line/cross out). This should also be used for revised TSDs discussed at NAC meetings.

3. The COT subcommittee showed an interest in the use of human data issue.

4. After incorporation of formal comments from the COT subcommittee, the PBPK white paper may be finalized and will become an addendum to the SOP.

5. The "Adjustment Factor" concept was discussed, and the consensus of the COT subcommittee appeared to be in conflict with discussions at previous COT subcommittee meetings. At NAS-15 (January, 2005), the suggestion was to apply an additional factor to obtain AEGL values consistent with available data. At NAS-16, subcommittee members seemed to think it was more appropriate to adjust the final AEGL values, and not to apply an additional "adjustment factor" to the derivation or to adjust the uncertainty factors. As this issue needs to be resolved, the NAC/AEGL staff will present options and request clear direction from COT subcommittee members at NAS-17.

6. Fifteen chemicals were presented at NAS-16, and ten of these were provisionally approved as "final."

7. The COT subcommittee was concerned about the use of animal developmental toxicity endpoints for derivation of AEGL-2 values, specifically, if reduced fetal body weight is the result of a single exposure or is a cumulative effect.

HUMAN STUDIES ISSUES

Iris Camacho presented information on the FY 2006 EPA Appropriations Act language and Proposed Rule, published on September 12, 2005, (Attachment 3) and on how this may impact the AEGL program. The appropriations act language prohibits use of 3rd party, intentional human dosing data for pesticides until a Final Rule on the topic is published. The Agency has interpreted this law to include both pesticides and industrial chemicals. Impacts on the AEGL program include: no discussion of chemicals/TSDs containing intentional human dosing data at NAC meetings (until publication of the final rule); a "hold" on the Federal Register package (FR09); and cancellation of the December meeting. The proposed rule has been published in the Federal Register and is open for public comment until December 12, 2005.

UNCERTAINTY FACTOR DATA BASE

Richard Williams, intern with the AEGL program, provided information and a demonstration of the Uncertainty Factor data base (Attachment 4). The data base is designed to store and categorize AEGL uncertainty factor application data and rationales. The data base should allow for the analysis of trends in UF application, evaluation of processes and rationales, and consistency in UF application. The data base was well received by the NAC members. Suggestions for improvement included addition of toxicity endpoints other that irritation,

identification of human or animal data used to adjust UFs, tracking dates when UFs were proposed, inclusion of chemical class information, addition of synonyms/CAS numbers, and inclusion of the value and source of the time scaling exponent 'n'.

RD_{50} METHODOLOGY

Peter Bos discussed the RD_{50} assay and relevance for setting AEGLs (Attachment 5). Discussion focused on whether or not the RD_{50} is an appropriate endpoint as a point-of-departure for AEGL value derivation, whether the RD_{50} may be an AEGL-1 or AEGL-2 endpoint, and how to handle scaling across time. The ASTM (2004) standard methodology was also discussed, as was the necessity of evaluating the raw data set used in calculating RD_{50} values. It was pointed out that use of the RD_{50} may amplify the uncertainty associated with scaling across time, and that in some cases, the RD_{50} methodology necessitates extrapolation over three orders of magnitude, also amplifying the uncertainty. A further challenge involves equating respiratory depression in animals with an equivalent effect in humans and distinguishing between stimulation of the olfactory versus trigeminal nerve. There was also a discussion about including a statement regarding use of the RD_{50} in the revised SOP; a suggestion was made that the RD_{50} could be used cautiously, acknowledging the limitations inherent in the method. A white paper regarding the relevance of the RD_{50} methodology for setting AEGL values will be drafted and included as an addendum to the SOP.

REVIEW AND RESOLUTION OF COT/AEGL COMMENTS ON INTERIM AEGL VALUES

Boron Trifluoride (CAS No. 7637-07-2)

Chemical Manager: George Rusch, Honeywell
Staff Scientist: Claudia Troxel, CMTox

George Rusch pointed out that Honeywell is the largest producer of boron trifluoride, and that he was responsible for all modern toxicology studies conducted with boron trifluoride. Dr. Rusch was chemical manager for this compound due to his familiarity with its' toxicology. He abstained from all votes, and presented the review of this chemical because the staff scientist, Claudia Troxel, was unable to attend the meeting. The AEGL values developed in the TSD and the presentation overheads were developed by Dr. Troxel. George Rusch then discussed the data set and COT/AEGL's comments (Attachment 6). The COT/AEGL suggested that the AEGL-1 and AEGL-2 derivations be revised, because these values were based on repeated-exposure studies. The COT/AEGL also suggested that the interspecies UF of 10, applied in the AEGL-3 derivation, be reduced. Dr. Rusch explained that the Honeywell Corporation conducted a 4-hour inhalation toxicity study in rats (Bowden et al., 2005) in response to the COT subcommittee comments. Proposed AEGL-1 values (2.5 mg/m^3 for all time points) were based on histological signs of

irritation noted in rats exposed to 74.4 mg/m^3 for 4 hours (Bowden et al., 2005). This was considered a NOAEL for notable irritation because there were no overt clinical signs of irritation. An interspecies UF of 10 (default) was applied, and intraspecies UF of 3 was applied because irritation is not expected to vary greatly within species. Values were held constant at all time points. Proposed AEGL-3 values (48 mg/m^3 for 10-min, 48 mg/m^3 for 30-min, 38 mg/m^3 for 1-hr, 24 mg/m^3 for 4-hr, and 12 mg/m^3 for 8-hr) were based on a 4-hour $BMCL_{05}$ in rats (Rusch et al., 1986). An interspecies UF of 10 was proposed because species differences exist in sensitivity to boron trifluoride, with the guinea pig being most sensitive. An intraspecies UF of 3 was applied due to the steep concentration-response curve and irritation endpoint. Time scaling was accomplished using default values of n=1 or n=3. The 30-min value was adopted as the 10-min value. Proposed AEGL-2 values (16 mg/m^3 for 10-min, 16 mg/m^3 for 30-min, 13 mg/m^3 for 1-hr, 8 mg/m^3 for 4-hr, and 4 mg/m^3 for 8-hr) were derived by dividing the proposed AEGL-3 values by 3; this approach was justified by the steep concentration-response curve. After discussion, a motion was made by Bob Benson and seconded by Nancy Kim to adopt AEGL-3 values of 140 mg/m^3 for 10-min, 140 mg/m^3 for 30-min, 110 mg/m^3 for 1-hr, 72 mg/m^3 for 4-hr, and 36 mg/m^3 for 8-hr. The values used the point-of-departure, intraspecies UF and time scaling as proposed. An interspecies UF of 3 was applied, because boron trifluoride is a highly-reactive, corrosive irritant. The motion carried (YES: 15; NO: 0; ABSTAIN: 1) (APPENDIX A). A motion was then made by Steve Barbee and seconded by Richard Thomas to derive AEGL-2 values (47 mg/m^3 for 10-min, 47 mg/m^3 for 30-min, 37 mg/m^3 for 1-hr, 24 mg/m^3 for 4-hr, and 12 mg/m^3 for 8-hr) by dividing the AEGL-3 values by 3. The motion carried (YES: 15; NO: 0; ABSTAIN: 1) (APPENDIX A). A motion was then made by Marc Ruijten and seconded by Richard Niemier to adopt an AEGL-1 value of 2.5 mg/m^3 at all time points based on the NOEL of 24.6 mg/m^3 in rats exposed for 4 hours. Uncertainty factors of 3 each were applied for inter- and intraspecies extrapolation. The motion carried (YES: 15; NO: 0; ABSTAIN: 1) (APPENDIX A).

Summary of AEGL Values for Boron Trifluoride						
Classification	**10-minute**	**30-minute**	**1-hour**	**4-hour**	**8-hour**	**Endpoint (Reference)**
AEGL–1	2.5 mg/m^3	2.5 mg/m^3	2.5 mg/m^3	2.5 mg/m^3	2.5 mg/m^3	NOEL in rats (Bowden et al., 2005)
AEGL–2	47 mg/m^3	47 mg/m^3	37 mg/m^3	24 mg/m^3	12 mg/m^3	1/3 the AEGL-3 values
AEGL-3	140 mg/m^3	140 mg/m^3	110 mg/m^3	72 mg/m^3	36 mg/m^3	4- hr. $BMCL_{05}$ in rats (Rusch et al., 1986)

JP-8 (Jet Fuel) (CAS No. 8008-20-6)

Chemical Manager: John Hinz, U.S. Air Force
Staff Scientist: Sylvia Talmage, ORNL

Sylvia Talmage and John Hinz discussed the data set and COT/AEGL's comments (Attachment 7). The COT/AEGL's main concerns were as follows: 1) Delete JP-4 discussions from the TSD; 2)

Improve the justification of the interspecies UF of 1; 3) Explain the Alaris 10-fold reduction factor; 4) Clarify the discussion of immune response to JP-8 with regard to vapors and aerosols; and 5) Discuss PBPK models and the lack of time scaling for AEGL-2 values. Much of the NAC discussion focused on the use of the RD_{50}. Sylvia explained that the AEGL values were based on a weight-of-evidence approach and that the values derived from the RD_{50} were supported by a lack of histopathology in other studies. The AEGL values will not change; however, the TSD will be revised so that the presentation of the RD_{50} data in the JP-8 TSD is not in conflict with the RD_{50}/SOP presentation (Attachment 5).

REVIEW of PRIORITY CHEMICALS

Ketene (CAS No. 463-51-4)

Staff Scientist: Peter Bos, RIVM
Chemical Manager: Jim Holler, ATSDR

Peter Bos reviewed the available data (Attachment 8). Proposed AEGL-1 values (0.24 ppm for 10-min, 0.24 ppm for 30-min, 0.19 ppm for 1-hour, 0.12 ppm for 4-hours, and 0.088 ppm for 8-hours) were based on no effects in mice exposed to 1 ppm for 7 hours (Treon et al., 1949). An interspecies UF of 3 was proposed because the mouse is the most sensitive species, and an intraspecies UF was also proposed because ketene acts directly at the port of entry. Time scaling was accomplished using the default values of n =1 or n = 3. The 30-min AEGL-1 was adopted as the 10-min AEGL-1. Proposed AEGL-2 values (0.83 ppm for 10-min, 0.83 ppm for 30-min, 0.66 ppm for 1-hour, 0.42 ppm for 4-hours, and 0.23 ppm for 8-hours) were based on one-third of the AEGL-3 values; this approach is supported by the steep concentration-response curve. Proposed AEGL-3 values (2.5 ppm for 10-min, 2.5 ppm for 30-min, 2.0 ppm for 1-hour, 1.2 ppm for 4-hours, and 0.68 ppm for 8-hours) were based on no mortality in mice exposed to 12 ppm for 4 hours (Treon et al., 1949). Uncertainty factor application and time scaling were proposed similar to AEGL-1. After discussion, a motion was made by Bob Benson and seconded by Marc Ruijten to accept AEGL values as proposed except that the point-of-departure for AEGL-2 will be the 12 ppm, 7 hour exposure of mice divided by three to estimate a NOAEL for effects defined by AEGL-2 (12 ppm ÷ 3 = 4 ppm). Time scaling and UF application are the same as for AEGL-1 and AEGL-3. (It is noted that the resulting AEGL-2 values are the same as proposed, but the rationale is different. The motion carried The motion carried (AEGL-1: YES: 12; NO: 1; ABSTAIN: 3) (AEGL-2: YES: 10; NO: 1; ABSTAIN: 6) (AEGL-3: YES: 10; NO: 1; ABSTAIN: 6) (APPENDIX B).

Summary of AEGL Values for Ketene						
Classification	**10-minute**	**30-minute**	**1-hour**	**4-hour**	**8-hour**	**Endpoint (Reference)**
AEGL–1	0.24 ppm	0.24 ppm	0.19 ppm	0.12 ppm	0.088 ppm	NOEL in mice (Treon et al., 1949)
AEGL–2	0.83 ppm	0.83 ppm	0.66 ppm	0.42 ppm	0.23 ppm	Estimated NOAEL for AEGL-2 effects in mice (Treon et al., 1949)
AEGL–3	2.5 ppm	2.5 ppm	2.0 ppm	1.2 ppm	0.68 ppm	4-hr NOEL for death in mice (Treon et al., 1949)

SELECTED CHLOROFORMATES

Methyl Chloroformate (CAS Reg. No. 79-22-1)
Ethyl Chloroformate (CAS Reg. No. 541-41-3)
Propyl Chloroformate (CAS Reg. No. 109-61-5)
Isopropyl Chloroformate (CAS Reg. No. 108-23-6)
Allyl Chloroformate (CAS Reg. No. 2937-50-0)
n-Butyl Chloroformate (CAS Reg. No. 593-34-7)
Isobutyl Chloroformate (CAS Reg. No. 543-27-1)
sec-Butyl Chloroformate (CAS Reg. No. 17462-58-7)
Ethyl Chlorothioformate (CAS Reg. No. 2941-64-2)
Diphosgene (CAS Reg. No. 503-38-8)

Staff Scientist: Cheryl Bast, ORNL
Chemical Manager: Ernest Falke, U.S. EPA

Cheryl Bast reviewed the sparse data set available in the published literature (Attachment 9). Dr. Roland Rossbacher, representing BASF, Germany, was in attendance and informed the NAC that there are new, unpublished chloroformate data developed by BASF Germany on many of the title chemicals. These data had not previously been available to the NAC. Dr. Rossbacher offered to submit these data to the NAC. These data will be included in a revised TSD which will be reviewed at NAC-39.

ARSENIC TRIOXIDE (CAS No. 1327-53-3)

Staff Scientist: Johan Schefferlie, RIVM
Chemical Manager: Richard Thomas, INTERCET, Ltd.

Johan Schefferlie reviewed the data set for arsenic trioxide (Attachment 10). AEGL-1 values were not proposed because of insufficient data. Proposed AEGL-2 values (2.5 mg/m^3 for 10-min, 2.5 mg/m^3 for 30-min, 2.0 mg/m^3 for 1-hr, 1.3 mg/m^3 for 4-hr, and 1.0 mg/m^3 for 8-hr) were based on 8-hour occupational exposures up to 1.0 mg/m^3. No UF was proposed because no acute AEGL-2 effects were expected at these concentration. The default value of n = 3 was used for time scaling. The proposed AEGL-3 values (11 mg/m^3 for 10-min, 11 mg/m^3 for 30-min, 9.1 mg/m^3 for 1-hr, 5.7 mg/m^3 for 4-hr, and 3.7 mg/m^3 for 8-hr) were based on a NOEL for lethality in rats exposed to 50 mg/m^3 for 6 hours (Holson et al., 1999). Uncertainty factors of 3 each were proposed for inter- and intraspecies extrapolation (total 10) because a larger total UF would yield AEGL-3 values within the range of some occupational exposure concentrations. Default time scaling (n = 1 or n = 3) was applied. After discussion, a motion was made by Marc Ruijten and seconded by Bob Benson to adopt AEGL-3 values as proposed. The motion carried (YES: 18; NO: 0; ABSTAIN: 0) (APPENDIX C). A motion was then made by Marc Ruijten and seconded by Richard Niemier to adopt AEGL-2 values of (3.7 mg/m^3 for 10-min, 3.7 mg/m^3 for 30-min, 3.0 mg/m^3 for 1-hr, 1.9 mg/m^3 for 4-hr, and 1.2 mg/m^3 for 8-hr) derived by dividing the AEGL-3 values by 3. This approach is supported because of the steep concentration-response curve (0/10 rats dead at 50 mg/m^3 and 10/10 rats dead at 100 mg/m^3). The motion carried (YES: 16; NO: 0; ABSTAIN: 0) (APPENDIX C). A motion was then made by Bob Benson and seconded by Marc Ruijten to not recommend AEGL-1 values because of insufficient data. The motion carried (YES: 16; NO: 0; ABSTAIN: 0) (APPENDIX C). A statement regarding use/non-use of the cancer values will be added to the TSD.

Summary of AEGL Values for Arsenic Trioxide

Classification	10-minute	30-minute	1-hour	4-hour	8-hour	Endpoint (Reference)
AEGL–1	NR	NR	NR	NR	NR	Not recommended due to insufficient data
AEGL–2	3.7 mg/m^3	3.7 mg/m^3	3.0 mg/m^3	1.9 mg/m^3	1.2 mg/m^3	1/3 the AEGL-3 values
AEGL-3	11 mg/m^3	11 mg/m^3	9.1 mg/m^3	5.7 mg/m^3	3.7 mg/m^3	6- hr. NOEL for lethality in rats (Holson et al., 1999)

CYCLOHEXYL ISOCYANATE (CAS No. 3173-53-3)

Staff Scientist: Carol Wood, ORNL
Chemical Manager: Marc Ruijten, RIVM

Marc Ruijten discussed the sparse data base for cyclohexyl isocyanate and proposed that no AEGL values be derived because of insufficient data. (Attachment 17). After discussion, a motion was made by Bob Benson and seconded by George Rodgers to adopt AEGL-3 values (0.14 ppm for 10-min, 0.14 ppm for 30-min, 0.11 ppm for 1-hour, 0.072 ppm for 4-hours, and 0.047 ppm for 8-hours) based on a calculated $BMCL_{05}$ (1.88 ppm) from a 6-hour rat study (Eastman Kodak, 1990, 1992). Inter- and intraspecies UFs of 3 each (total = 10) were applied because cyclohexyl isocyanate is highly irritating. A modifying factor of 3 was applied to account for the sparse data base. Default time scaling values of n =1 or n = 3 were applied; the 30-min value was adopted as the 10-min value. The motion carried (YES: 15; NO: 0; ABSTAIN: 2) (APPENDIX D). A motion was then made by Richard Niemier and seconded by George Woodall to derive AEGL-2 values by dividing the AEGL-3 values by 3. This motion did not carry (YES: 3; NO: 11; ABSTAIN: 4) (APPENDIX D). A motion was then made by Richard Niemier and Seconded by George Woodall to not recommend AEGL-1 or AEGL-2 values due to insufficient data. This motion carried (AEGL-1: YES: 15; NO: 0; ABSTAIN: 2) (AEGL-2: YES: 13; NO: 2; ABSTAIN: 1) (APPENDIX D).

The methyl isocyanate lethality should be included in the TSD for comparison. Mehyl isocyanate is more toxic than cyclohexyl isocyanate, so the derived cyclohexyl isocyanate values are protective. This TSD will be revisited if a SIDS is published and contains additional relevant data.

Summary of AEGL Values for Cyclohexyl Isocyanate

Classification	10-minute	30-minute	1-hour	4-hour	8-hour	Endpoint (Reference)
AEGL–1	NR	NR	NR	NR	NR	Not recommended: Insufficient data
AEGL–2	NR	NR	NR	NR	NR	Not recommended: Insufficient data
AEGL–3	0.14 ppm	0.14 ppm	0.11 ppm	0.072 ppm	0.047 ppm	6-hr $BMCL_{05}$ in rats (Eastman Kodak, 1990; 1992)

ADMINISTRATIVE MATTERS

The site and time of future meetings is as follows:

NAC/AEGL-39: February 1-3, 2006, Washington DC

All items in the agenda were discussed as thoroughly as the time permitted. The meeting highlights were prepared by Cheryl Bast and Sylvia Talmage, Oak Ridge National Laboratory, with input from the respective staff scientists, chemical managers, and other contributors.

LIST OF ATTACHMENTS

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

Attachment 1. NAC/AEGL-38 Meeting Agenda
Attachment 2. NAC/AEGL-38 Attendee List
Attachment 3. FY 2006 EPA Appropriations Act
Attachment 4. Uncertainty Factor Database
Attachment 5. RD_{50}: Relevance for Setting AEGLs
Attachment 6. Response to COT comments for Boron Trifluoride
Attachment 7. Response to COT comments for JP-8
Attachment 8. Data analysis for ketene
Attachment 9. Data analysis for selected chloroformates
Attachment 10. Data analysis for arsenic trioxide
Attachment 11. Data analysis for cyclohexyl isocyanate

LIST OF APPENDICES

Appendix A. Ballot for Boron Trifluoride
Appendix B. Ballot for Ketene
Appendix C. Ballot for Arsenic Trioxide
Appendix D. Ballot for Cyclohexyl Isocyanate
Appendix E. Committee chairman certification of minutes

ATTACHMENT 1

National Advisory Committee for Acute Exposure Guideline Levels for Hazardous Substances

NAC/AEGL-38
September 28-30, 2005

U.S. Department of Labor
Rooms 3437 A, B, & C
200 Constitution Ave., N.W.
Washington, DC 20210

Metro: Judiciary Square (Red Line)

AGENDA

Wednesday, September 28, 2005

10:00 a..m.	Introductory remarks and approval of NAC/AEGL-37 Highlights (George Rusch, Ernie Falke, and Paul Tobin)
10:30	Summary of COT Subcommittee Meeting (George Rusch)
11:00	Human Studies Issues (Iris Camacho)
11:30	Uncertainty Factor Database (Richard Williams)
12:00 p.m.	RD_{50} Methodology Update (Peter Bos)
12:30	Lunch
1:30	Review of Ketene (Jim Holler/Peter Bos)
3:30	Break
3:45	Revisit of Boron Trifluoride- New Data (George Rusch/Claudia Troxel)
5:30	Adjourn for the day

Thursday, September 29, 2005

8:30 a.m.	Review of Selected Chloroformates- Allyl chloroformate, Diphosgene, Ethyl Chloroformate, Ethyl chlorothioformate, Isobutyl chloroformate, Isopropyl chloroformate, Methyl chloroformate, n-Butyl chloroformate, Propyl chloroformate, sec-Butyl chloroformate (Ernie Falke/Cheryl Bast)
10:30	Break
10:45	Review of Selected Chloroformates (continued)
12:00 p.m.	Lunch
1:00	Review of Arsenic Trioxide (Richard Thomas/Johan Schefferlie)
3:00	Break
3:15	Revisit of Jet Fuels- Response to COT Comments (John Hinz/Sylvia Talmage)
4:30	Review of Cyclohexyl Isocyanate (Marc Ruijten/Carol Wood)
5:30	Adjourn for the day

Friday, September 30, 2005

8:00 a.m.	Unresolved Issues
10:00	Break
10:15	Unresolved Issues (continued)
11:10	Administrative matters
12:00 noon	Adjourn meeting

NAC/AEGL Meeting 38: September 28-30, 2005

Attendance 9/28/05 - 9/30/05

ATTACHMENT 2

Chemical: **CAS Reg. No.:**

Action: Proposed_____ **Interim**_____ **Other**_____

Chemical Manager: **Staff Scientist:**

NAC Member	AEGL1 (9/28)	AEGL2 (9/29)	AEGL3	LOA
Steven Barbee	✓	✓		
Lynn Beasley	✓	✓		
Robert Benson	✓	✓		
Jonathan Borak	✓	X		
William Bress	✓	✓		
George Cushmac	✓	✓		
Ernest Falke	✓	✓		
Alfred Feldt	✓	✓		
John Hinz	✓	✓		
Jim Holler	X	X		
Tom Hornshaw	✓	✓		
Warren Jederberg	X	X		
PETER BOS	✓	✓		
J. SCHEFFERLE	✓	✓		
Roland Rossbacher	✓	✓		

NAC Member	AEGL1	AEGL 2	AEGL3	LOA
Nancy Kim	✓	✓		
Glenn Leach	✓	✓		
John Morawetz	X	✓		
Richard Niemeier	✓	✓		
Marinelle Payton	X	X		
Susan Ripple	✓	✓		
George Rodgers	✓	✓		
Marc Ruijten	✓	✓		
George Rusch, Chair	✓	✓		
Richard Thomas	✓	✓		
George Woodall	✓	✓		
ALAN BECKER	✓	✓		
DIETER HEINZ	✓	✓		
CHERYL BAST & TALMAGE TALLY	✓	✓		
PASS/ FAIL				

PPM, (mg/m^3)	10 Min	30 Min	1 Hr	4 Hr	8 Hr
AEGL 1	, ( )	, ( )	, ( )	, ( )	, ( )
AEGL 2	, ( )	, ( )	, ( )	, ( )	, ( )
AEGL 3	, ( )	, ( )	, ( )	, ( )	, ( )
LOA					
* = ≥10% LEL					
** = ≥ 50% LEL					
*** = ≥100% LEL					

*Safety considerations against the hazard(s) of explosion(s) must be taken into account.
** and ***Extreme safety considerations against the hazard(s) of explosion(s) must be taken into account.

NR= Not Recommended due to_____

AEGL 1 **Motion by:** _____ **Second by:** _____
AEGL 2 **Motion by:** _____ **Second by:** _____
AEGL 3 **Motion by:** _____ **Second by:** _____
LOA **Motion by:** _____ **Second by:** _____

Approved by Chair: _____ **DFO:** _____ **Date:** _____

FY 2006 EPA Appropriations Act

On August 2, 2005, the President signed into law the Department of Interior, Environment, and Related Agencies Appropriations Act, 2006, Pub. L. No. 109-54 (Appropriations Act). Section 201 of the Appropriations Act includes the following provision:

None of the funds made available by this Act may be used by the Administrator of the Environmental Protection Agency to accept, consider or rely on third-party intentional dosing human toxicity studies for pesticides, or to conduct intentional dosing human toxicity studies for pesticides until the Administrator issues a final rulemaking on this subject. The Administrator shall allow for a period of not less than 90 days for public comment on the Agency's proposed rule before issuing a final rule. Such rule shall not permit the use of pregnant women, infants or children as subjects; shall be consistent with the principles proposed in the 2004 report of the National Academy of Sciences on intentional human dosing and the principles of the Nuremberg Code with respect to human experimentation; and shall establish an independent Human Subjects Review Board. The final rule shall be issued no later than 180 days after enactment of this Act.

Protections for Subjects in Human Research

[Federal Register: September 12, 2005 (Volume 70, Number 175)]
[Proposed Rules]
[Page 53837-53866]
From the Federal Register Online via GPO Access [wais.access.gpo.gov]
[DOCID:fr12se05-11]
[[Page 53838]]

ENVIRONMENTAL PROTECTION AGENCY
40 CFR Part 26
[OPP-2003-0132; FRL-7728-2]
RIN 2070-AD57

Protections for Subjects in Human Research

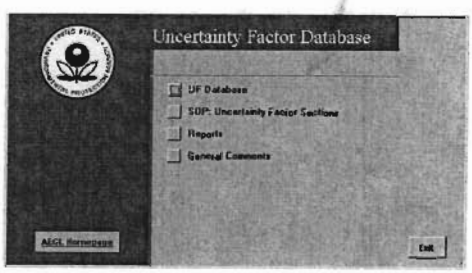
AGENCY: Environmental Protection Agency (EPA).
ACTION: Proposed rule.

SUMMARY: EPA proposes and invites public comment on a rulemaking to ban intentional dosing human testing for pesticides when the subjects are pregnant women or children, to formalize and further strengthen existing protections for subjects in human research conducted or supported by EPA, and to extend new protections to adult subjects in intentional dosing human studies for pesticides conducted by others who intend to submit the research to EPA. This proposal, the first of several possible Agency actions, focuses on third-party intentional dosing human studies for pesticides, but invites public comment on alternative approaches with broader scope.

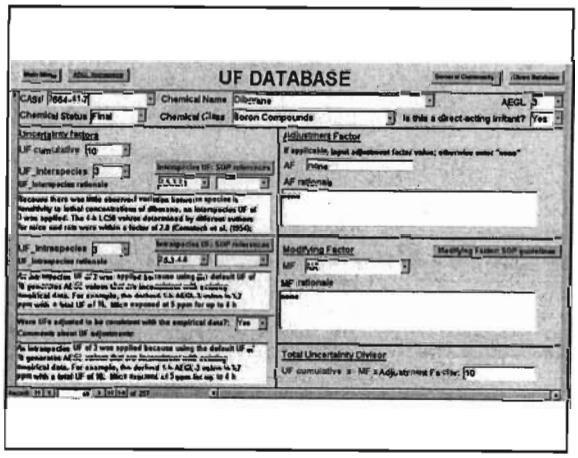
AEGL Uncertainty Factor Database

Richard Williams IV
Environmental Careers Organization
NAC/AEGL Meeting 38
Washington, D.C.
September 28-30, 2005

Uncertainty Factor Database



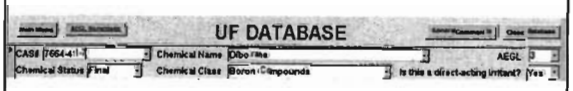
Outline of Presentation



AEGL Uncertainty Factor Database

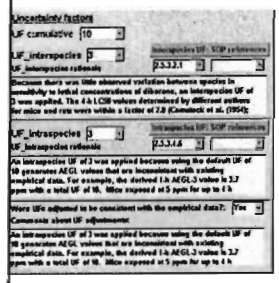
- Purpose
  - To store and categorize AEGL uncertainty data and the rationales for their derivation
- Applications
  - Analyze trends in the application of AEGL uncertainty values
  - Evaluate processes and rationales in assigning uncertainty values
  - Develop more standardized and consistent approaches for similar scenarios

Database Components



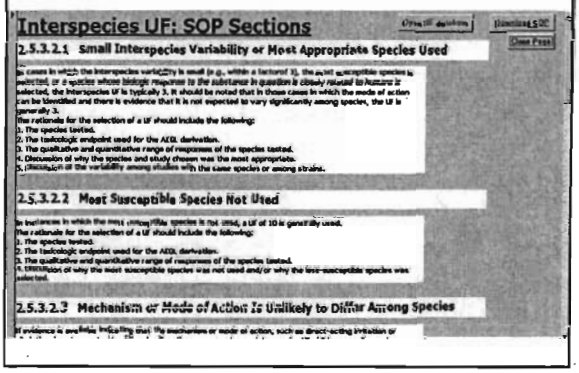
- Chemical Data
  - Name and CAS number
  - Chemical Class (47)
    - Ex. Acid Halides, Alcohols, Aldehydes, Aluminum Compounds, Amides, Amines, Anilines, Antimony Compounds, Arsenic Compounds, Boron Compounds etc...
  - Chemical Status
  - AEGL level
  - Direct-acting irritancy

Database Components



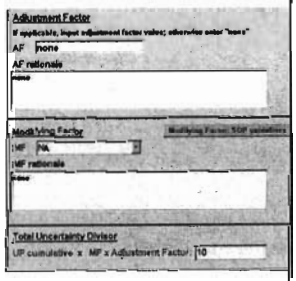
- Uncertainty Factors
  - Interspecies and Intraspecies
    - Values and rationales
    - SOP references
  - Uncertainty factor adjustments
    - Comments

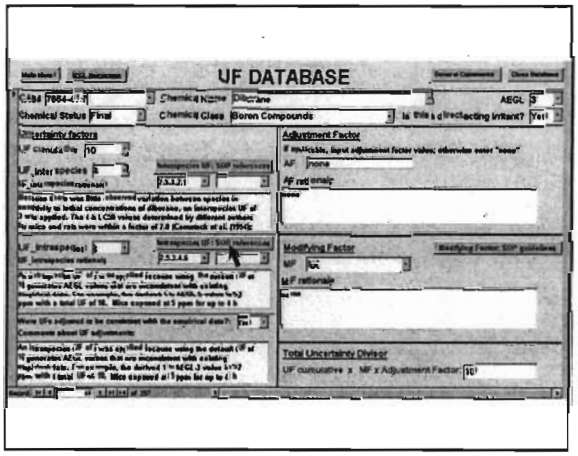
Database Components



Database Components

- Adjustment Factor
  - Selection is based upon a weight-of-evidence approach
  - Value and rationale
- Modifying Factor
  - Value and rationale
- Total Uncertainty Divisor
  - UF cumulative x MF x AF





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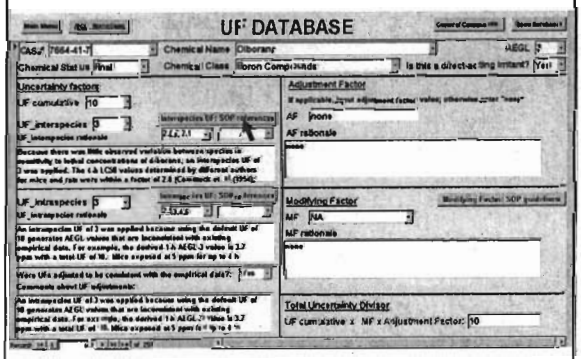

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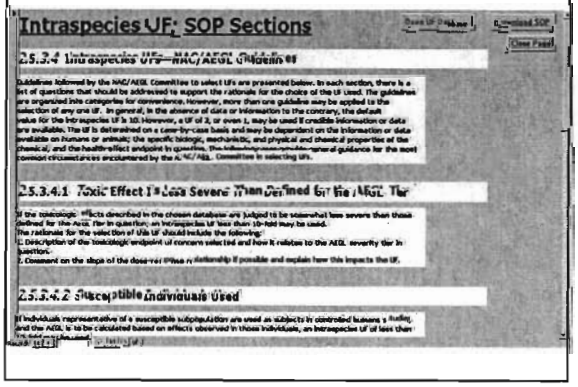

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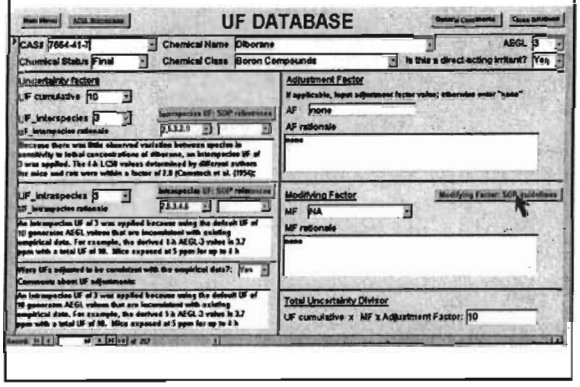

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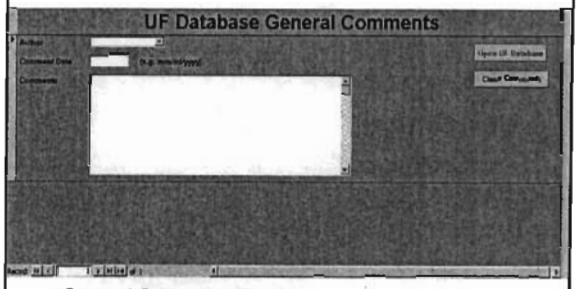
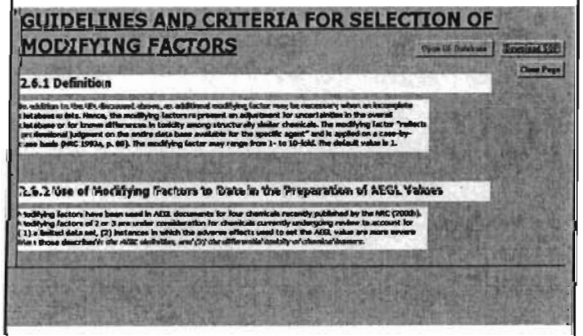


- General Comments Form
  - Accessible from the UF Database Form
  - Author, Date, and Comment Fields

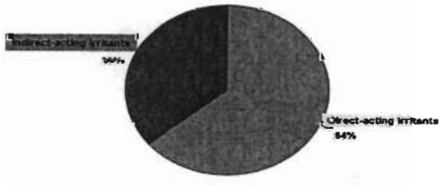
Database Components

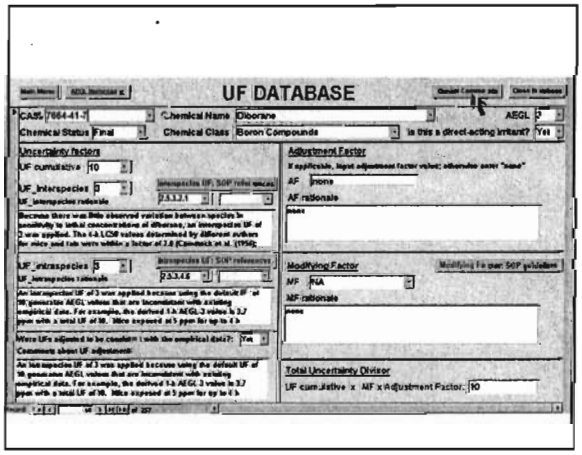


Sample Analysis Derived from AEGL Uncertainty Data

- 18% (47 / 257) of Final and Interim AEGLs have modifying factors
  - 64% (30 / 47) of AEGLs with modifying factors are classified as direct-acting irritants

AEGLs with Modifying Factors by Mechanism of Irritancy



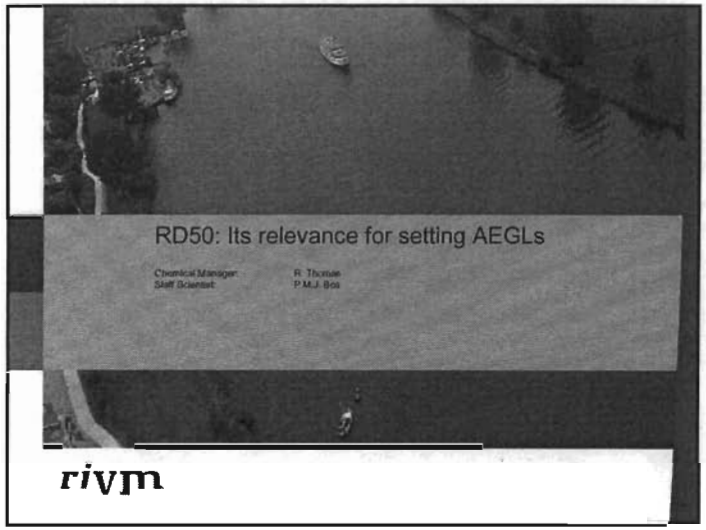


Further Applications and Analyses

- Examination of the uncertainty factor assignment for direct-acting chemical irritants, and solvents/CNS depressants
  - How often does existing empirical data require the reduction of the total UF to obtain reasonable AEGL values?
  - Does the database support the use of a generic approach?
- Analysis of uncertainty value assignment by chemical class classification

Acknowledgements

- AEGL Staff
  - Dr. Iris Camacho
  - Dr. Ernest Falke
  - Ms. Sharon Frazier
  - Dr. Marquea King
  - Dr. Paul Tobin
- NAC/AEGL Committee



RD50: Historical overview

- Developed in the 1960s by Dr. Yves Alarie for the US Department of Defense
  - Potency testing of nerve gases
- First published in 1966
  - "The method presented in this article permits the recognition of sensory irritation at concentration levels where cellular damage cannot be detected and thus represents a more sensitive means of revealing potentially irritating chemicals."

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RD50: Historical overview

- Detailed review of sensory irritation by Alarie in 1973
  - Sensory irritant
  - Pulmonary irritant
  - Bronchoconstrictor agent
  - Respiratory irritant
- Official ASTM method in 1984 (ASTM E 981)
  - Updated in 2004
- Up-to-date review by Alarie in 2000
  - Fully computerized system
    - Reproducible data analyses according to defined criteria
    - Distinction between different kind of responses
      - Sensory irritation, pulmonary irritation, airway constriction
    - Determination of Limit of detection (*Just Detectable Effect: JDE*)
    - Predictive equations for irritating potencies for non-reactive VOCs
      - based on physical-chemical properties

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RD50: Methodology

- Stimulation of free nerve endings
  - Direct stimulation of (trigeminal, vagal, or glossopharyngeal) nerve endings or smooth muscle
  - Indirect through (reversible) pathological changes like tissue inflammation
- Sensory irritation
  - Reversible change in breathing pattern
- Stimulation of the trigeminal nerve causing a characteristic pause following inspiration resulting in a delayed expiration

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RD50: Methodology

- Groups of mice are head-only exposed to a geometric series of concentrations
- RD50: The concentration inducing a 50% decrease in respiratory frequency, is used to determine the potency of a chemical
- Distinction between different kind of responses
  - Sensory irritation, pulmonary irritation, airway constriction or some combinations

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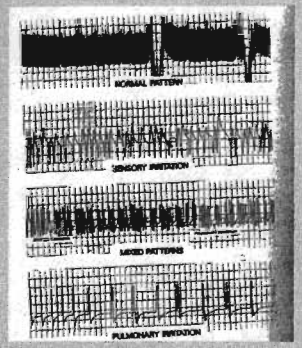
RD50: Methodology – breathing patterns



Obtained from Alarie et al., 2000

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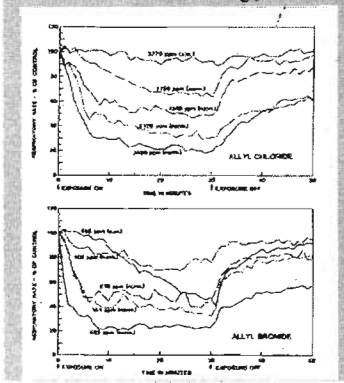
RD50: Methodology – time-response curve



Obtained from Nielsen and Bakbo, 1985

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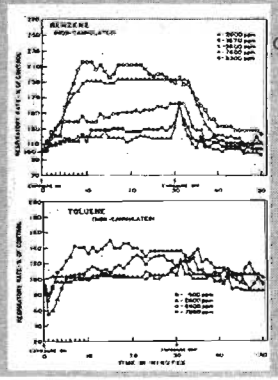
RD50: Methodology – time-response curve



Obtained from Nielsen and Alarie, 1982

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RD50: Methodology – log concentration-response curve

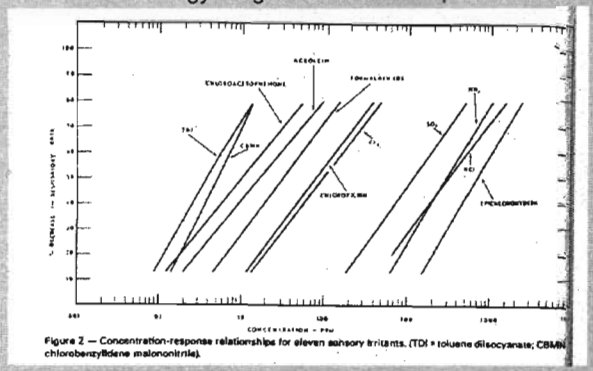

Figure 2 — Concentration-response relationships for eleven sensory irritants. (TDI = toluene diisocyanate; CBMN = chlorobenzylidene malononitrile).

Obtained from Kane et al., 1979

RD50: Predictive power

- Human equivalent
  - A burning or stinging sensation in eyes, nose, or throat
- Validation of the bioassay (qualitative)
  - Chemicals found to be a positive sensory irritant in male SW mice will be positive in human at a similar exposure concentration. A chemical found to be a non-sensory irritant will be negative in humans (Alarie, 1966; 1973).
- Calibration of the bioassay (quantitative)
  - High correlation of RD50 with 0.03*TLV (R^2=0.78; 89 chemicals)
    - E.g. Kane et al. (1979); Schaper, 1993)

RD50: Previous review *(Bos et al., 1992)*

- Concluding remarks:
  - Plateau response is not reached for every substance
  - Toxic effects may occur and interfere at the RD50 concentration
  - Large differences between strains and species (response characteristics)
  - Interlaboratory differences (response characteristics)
- Reproducibility
  - Differences in calculated RD50 values
  - Characteristics of time-response curve and log concentration-response curve

RD50: Previous review *(Bos et al., 1992)*

- Time-response
  - Graphical presentation of time-concentration-response necessary
  - Fast response (< 1 min) versus hours
    - Take into account in time-extrapolation from 10-min to 8-hours?
  - Fading of response
    - Sometimes increase in respiratory frequency Critical evaluation of the sensory irritation test for setting OELs
    - Verification of interfering factors and toxicity
- Recommendations
  - Time-response and log concentration response curves should be available
- Some recommendations have been met by computerized system

RD50: Use in AEGL-setting

- Hydrogen chlorine
  - 10-min AEGL-2: 1/3*RD50
- Jet propellant fuel-8
  - AEGL-1: 0.1*RD50; all time points
- Chloroformates
  - AEGL-1: 0.001* RD50; all time points
    - (0.01*RD50 would conflict with AEGL-2)

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RD50: To use or not to use in AEGL-setting

- Extrapolation of RD50 to human equivalent
  - Pungency versus odor
- Where does the animal bioassay find its place in the toxicity profile?
  - Where can the RD50 be placed on a gliding scale of increasing toxicity?
- Use of RD50 bioassay for AEGL-setting
  - AEGL-1 (nasal pungency) or AEGL-2 (severe eye irritation, lacrimation)

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RD50: Chemosensory effects

- Chemosensory stimulation
  - Odorous (olfactory stimulation)
  - Irritating (trigeminal stimulation)
- Stimulation of the olfactory system often occurs at concentrations well below that at which they will elicit trigeminal activation
  - Olfactory stimulation intermingles with sensory irritation in humans
    - Example of acetone (odor detection threshold: 20-400 ppm; threshold for sensory irritation between 10,000-40,000 ppm (Arts et al., 2003))
  - Distinction between olfactory and trigeminal stimulation necessary
    - Subjective versus objective responses

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RD50: Extrapolation to humans

- Human equivalent
  - A burning or stinging sensation in eyes, nose, or throat
  - Odor often a confounding factor in subjective measurements of sensory irritation in humans (e.g. acetone)
- Odor is not an endpoint in AEGL-setting
- Objective detection of sensory irritation
  - Use of anosmics and normosmics
  - Lateralization techniques
  - Measuring eye irritation along with olfactory stimulation
  - Recording of chemosensory potentials

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RD50: Validation for extrapolation to humans

- Alarie (1966, 1973)
  - 51 substances tested
  - 1-min exposure of mice to C^nt of (10 and) 40 min*mg/m^3
  - Humans exposed to C^nt between 5 and 80 (1 and 50) min*mg/m^3
  - Animal response: decrease in respiratory rate with characteristic pause at 40 min*mg/m^3
  - Human subjective response: eye, throat, skin, nose, or chest burning, conjunctivitis, lacrimation, coughing, gagging

- Comments
  - No details available on human study (e.g. on exposure conditions)
  - Olfactory stimulation is unknown but will have interfered
  - Very short exposures to a limited range of concentrations
    - "nonirritating" chemicals may induce irritation at higher concentrations

RD50: Calibration for extrapolation to humans

Table. Proposed relationship of RD_{50} concentrations and expected effect in humans (Kane et al, 1979)

Concentration	Expected response in humans
10 * RD_{50}	Possibly lethal
RD_{50}	Intolerable sensory irritation
0.1 * RD_{50}	Some sensory irritation
0.03 * RD_{50}	Suggested TLV, minor sensory irritation if any
0.01 * RD_{50}	No sensory irritation
0.001 * RD_{50}	No effect of any kind

*Proposal: 0.3*RD50 can serve as basis for an Emergency Exposure Limit (EEL)*

RD50: Calibration for extrapolation to humans

- Introduction of "steps of 10":
  - Based on the suggestion by Frazer (1953) that, from a pharmacological point of view, the general ratio of ineffective, effective, toxic, and lethal dosage in man is generally not greater than 1:10:100:1000
  - This suggestion is a theoretical assumption and has no valid scientific basis

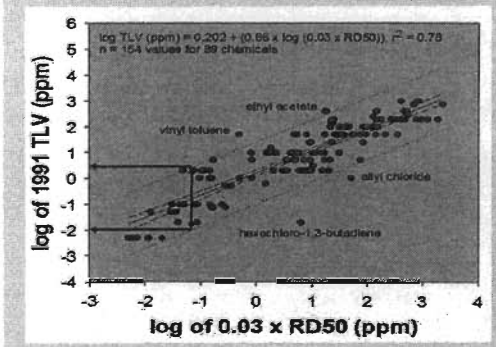
- Tested against data for 11 irritants
  - (acrolein, ammonia, chlorine, chloroacetophenone, CBMN, chloropicrin, epichlorohydrin, formaldehyde, hydrogen chloride, sulfur dioxide, TDI)
  - Overall reasonable agreement as to "steps of 10", variation present
  - At 0.001*RD50 no data for 8/11 chemicals
  - At 0.01*RD50 no data for 3/11 chemicals; no effects for 1 chemical; odor for 1 chemical
  - At 10*RD50 predominantly animal data and case studies
  - Human data: odor as confounding factor

RD50: Comparison with TLV

- Correlation with "human" TLVs is basis for quantitative validity of RD50 (calibration)

- Remarks:
  - Most TLVs based on irritation
  - 1990-1991TLVs
    - Approximately 25% based on analogy
    - Approximately 20% based on worker experience (generally old data)
    - Approximately 20% based on animal data (incl. repeated and oral data)
    - Approximately 5% based on Nelson data (1943)
    - Odor stimulation interferes in human data
    - TLV's have different levels of protection

RD50: Comparison with TLV



Obtained from Alarie et al., 2000

RD50: Comparison with TLV

- Correlation is not equal to association
- Many TLVs not based on adequate human data
- 0.03 * TLV is "best estimate" but variation by 2-3 orders of magnitude
  - AEGLs are predictive rather than protecting thresholds
- Additional "calibration" with human data is needed

RD50: Pungency thresholds (*Cometto-Muniz and coworkers*)

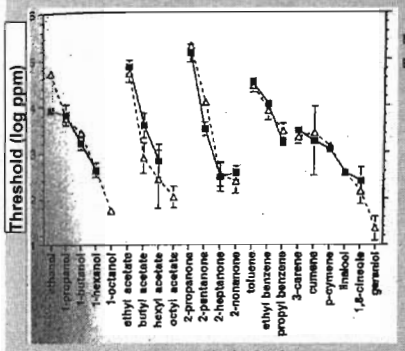
- Several series of homologous compounds
  - Acetates, alcohols, alkyl benzenes, aldehydes, ketones
- Odor thresholds
- Eye irritation in normosmics
- Nasal pungency thresholds (NPT) in anosmics

- Drawback: indirect concentration measurements
  - Absolute values are probably not accurate
  - Thresholds can be used in a relative sense

RD50: Comparison with NPT

- Good agreement of eye irritation in normosmics and NPT in anosmics
  - both effects reflect trigeminus stimulation
- Nasal Pungency Thresholds often are orders of magnitudes higher than odor thresholds
  - trigeminus versus olfactory stimulation

RD50: NPT versus eye irritation thresholds



NPT: filled squares, continuous lines
Eye irritation: triangles, broken lines

Obtained from Cometto-Muniz, 2000

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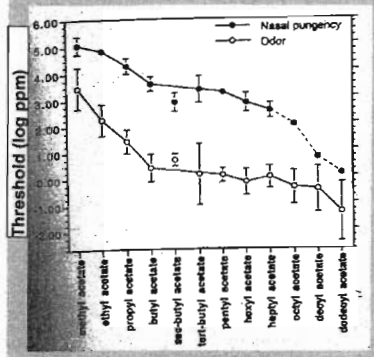
RD50: NPT versus odor thresholds: acetates



NPT: filled circles
Odor thresholds: empty circles

Obtained from Cometto-Muniz, 2000

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RD50: Comparison with NPT for acetates

Chemical	RD50 (ppm)	0.03 * RD50 (ppm)	Pungency threshold (ppm)
methyl acetate	830	25	112,358
ethyl acetate	580	17	67,272
propyl acetate	795	24	17,565
butyl acetate	730	22	3648
pentyl acetate	1565	47	1648
hexyl acetate	740	22	635

Pungency thresholds from Cometto-Muniz and coworkers

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RD50: Comparison with NPT for alcohols

Chemical	RD50 (ppm)	0.03 * RD50 (ppm)	Pungency threshold (ppm)
methanol	41,514	1245	35,000
ethanol	27,314	819	9000
n-propanol	12,704	381	2500
2-propanol	17,693	531	18,135
n-butanol	4784	144	1100
n-pentanol	4039	121	1700
n-hexanol	239	7	400
n-heptanol	98,4	3	210
n-octanol	47,2	1	70

Pungency thresholds from Cometto-Muniz and coworkers

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RD50: NPT for alkyl benzenes and aldehydes

Chemical	RD50 (ppm)	0.03 * RD50 (ppm)	Pungency threshold (ppm)
Alkyl benzenes			
toluene	5300	159	29,574
ethyl benzene	4060	122	10100
propyl benzene	1530	46	1487
butyl benzene	710	21	No NPT
hexyl benzene	125	4	No NPT
Aldehydes			
butanal	1015	30	*60,000*
pentanal	1121	34	*40,000*
hexanal	1029	31	*6000*
heptanal			*1700*
octanal			No NPT

Pungency thresholds from Cometto-Muniz and coworkers

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RD50: Comparison with NPTs

- Comparison of RD50 in mice and NPT in anosmics
  - Differences in duration and type of exposures
  - Absolute values for NPT do not match with "steps of 10" for sensory irritation based on mice, but are inaccurate
  - Pattern of NPTs over a homologous series of substances do not match with the pattern of RD50 values
- Data available (despite drawbacks) point to difficulties in direct extrapolation of RD50s to humans
  - Thresholds for eye irritation comparable with NPT but much higher than odor thresholds
  - Additional information is needed

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RD50: Its place in a toxicity profile

- Can sensory irritation be placed on a gliding scale of increasing toxicity in a general way?
- No relation was found between the sensory irritation potential as measured by the mouse bioassay and local tissue damage (histopathological changes) in the respiratory tract after single or repeated exposure *(Bos et al., 2002)*

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RD50: Its place in a toxicity profile

Comparison with mortality data

Chemical	RD_{50} ppm	Mortality	Species	LC_{50} (time) ppm	Species
Epichlorohydrin	687		mouse	369 (6-h) 820 (4-h)	rat mouse
Acetone	23,000 77,000		mouse	32,000 (4-h) 21,100 (8-h)	rat rat
*Chloroformates**					
Methyl	52.4	1/4 at 50 ppm	mouse	88 (1-h)	rat
Ethyl	77.5	3/4 at 100 ppm	mouse	145 (1-h)	rat
Propyl	83.5	1/4 at 50 ppm	mouse	410 (1-h)	rat
Isopropyl	104	1/4 at 50 ppm	mouse	300 (1-h)	rat
	375	2/4 at 283 ppm	mouse		
Isobutyl	97	No deaths	mouse		

** AEGL-1 was calculated by 0.001*RD50 rather than 0.01*RD50 because of conflict with AEGL-2 (1/3*AEGL-3)*

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RD50: Conclusions

- Extrapolation to a human equivalent needs further attention
  - Direct extrapolation to a human pungency threshold with a fixed factor is not recommended
  - Interference with odorous stimulation should always be taken into account
  - Quantitative comparison of RD50 values with adequate human data is urgently recommended, but these data have not been found (yet)
- Use of RD50 in AEGL-setting
  - Overly conservative approach will lead to conflicting AEGLs and/or too low action levels
  - Definition of a "sensory irritant" within AEGL-setting is needed
  - RD50 at the lower end of the toxicity profile
  - No interference with histopathological changes
  - No severe toxicity at concentrations below or comparable to the RD50
- Sensory irritation: AEGL-1 or AEGL-2?

BORON TRIFLUORIDE:DIMETHYL ETHER

- One of several complexes formed with boron trifluoride for ease of handling BF_3. Ether complexes consist of 1:1 molar ratio of BF_3 and the dimethyl or diethyl ether; can dissociate under proper temperature/ pressure conditions.

- Only one study addressed toxicity of BF_3:dimethyl ether - only nominal concentrations.

- Because complex can dissociate to form BF_3, the AEGL derivations are based upon this one chemical species alone.

ATTACHMENT 6

BORON TRIFLUORIDE (BF_3)

- Colorless gas - pungent suffocating odor

- Gas is stable in dry air, but immediately forms dense white cloud when exposed to moist air; upon exposure to even low levels of moisture in air, BF_3 reacts to form dihydrate, BF_3:$2H_20$. BF_3 dihydrate is strongly corrosive to the eyes and skin

- Excellent catalyst; has fire retardant and antioxidant properties, nuclear applications, and insecticidal properties

Toxicity Data:

- Human: odor detection
- Animal: acute toxicity data available in dogs, rats, mice, and guinea pigs, but exposure conc. generally expressed as nominal conc.

Effects of exposure in animals:

- short-term exposures - pulmonary irritation
- repeated exposures - pulmonary irritation and/or renal toxicity

Summary of AEGL Values for Boron Trifluoride (mg/m^3)					
Level	**10-min**	**30-min**	**1-hr**	**4-hr**	**8-hr**
AEGL-1	0.6	0.6	0.6	0.6	0.6
AEGL-2	21	21	16	10	6.8
AEGL-3	49	49	39	25	12

- **AEGL-1:** Value representing a no-effect level for irritancy following an acute exposure; exposures were in rats to 6 mg/m^3 for 6h/d, 5 d/wk, for 13 wk (Rusch et al., 1986; Hoffman and Rusch, 1982a)
  - UF=10; values set equal across time

- **AEGL-2:** Signs of irritation and renal toxicity (resulting in death) following exposure to 180 mg/m^3 for 6 h/d for 5 days (Rusch et al., 1986; Hoffman and Rusch, 1982b)
  - MF of 2: not known if rats had renal effects after single exposure; UF=10; default n=1,3

- **AEGL-3:** Calculated 4-hr LC_{01} in male and female rats of 736 mg/m^3 (Rusch et al., 1986; Hoffman, 1981)
  - UF=30; default n=1,3

Major Comments from COT:

AEGL-1

It is too much of a "stretch" to base < 1-day values (i.e., AEGL-1s) on effects (lacrimation) seen during the 2nd week of daily exposures. The steepness of the dose-response curve for renal toxicity is not relevant to, and thus not predictive of a dose-response curve for direct irritation. Moreover, most signs of direct irritation/respiratory distress on exposure day 5 in Table 3 (page 7) are not concentration-dependent. There are no data presented in this document that are suitable for calculating AEGL-1 values. Therefore, AEGL-1 values should not be determined at the present time.

AEGL-2

The rationale and calculation of AEGL-2s should be redone. It is not scientifically-defensible to assume that a single exposure to BTF will cause nephrotoxicity that is twice as severe (it is recommended in lines 29 & 30 that a modifying factor of 2 be used) as that produced by more than 5 consecutive days of inhalation of 180 mg/m^3. The NOAEL of 66 mg/m^3 in the study by Rusch et al. (1986) far exceeds the calculated 4- and 8-hour AEGL-2s of 10 mg/m^3 and 6.8 mg/m^3, respectively. In the absence of data applicable to AEGL-2 derivation, it is recommended that: (a) the NOAEL of 66 mg/m^3 be used as the basis for calculating AEGL-2 values; and (b) that the need for additional research to provide applicable data be emphasized.

AEGL-3

Page 24, lines 20 - 23: The degree of interspecies variability in LC_{50} values in Table 5 (page 15) is difficult to discern, due to the reporting of most exposures in nominal concentrations. It is clear, however, that guinea pigs are exquisitely sensitive. Rats appear to be more sensitive than mice to BTF lethality, but the mice data are quite limited. As guinea pigs are an atypical species, it is recommended that: (a) the 4-hour LC_{50} (1,200 mg/m^3) of Rusch et al. (1986) be utilized as the basis for calculating AEGL-3s; and (b) an interspecies uncertainty factor of 5 rather than 10 be employed.

TOXICITY DATA

- Human: no relevant data

- Animal - only three studies reporting measured concentrations: Bowden et al., 2005 (new); Rusch et al., 1986; Torkelson et al., 1961. These studies measured the exposure concentration and compared them to nominal concentration; found actual concentration ranged from 2.7-56% of nominal. Therefore, studies using nominal concentrations should not be used.

NEW - Bowden et al., 2005: Exposures to BF_3 dihydrate vapor/aerosol

ACUTE:

Groups of 10, SD rats/sex exposed for 4 hours to 0, 8.53, 24.6, or 74.4 mg/m^3

- No exposure-related effects on clinical signs during or after exposure, body weights, water consumption (visual inspection), gross necropsy findings, or liver and kidney weights
- Microscopic findings in 74.4 mg/m^3 group:

24 hours post exposure:

Larynx: Ventral cartilage necrosis: minimal to slight (4/5 ♂; 4/5 ♀, none affected in other groups)
Anterior ventral hemorrhage: 2/5 ♂
Ventral epithelial hyperplasia: ↑severity
Ventral inflammatory cell infiltration: ↑severity

2 weeks post exposure:

Larynx: Ventral cartilage necrosis: minimal in 1/5♂; moderate in 1/5♀

Conclusion: 74.4 mg/m^3 for 4 hours represents a concentration producing histological effects but no overt signs of irritation - AEGL-1

Rusch et al. 1986: Exposures to BF_3 dihydrate aerosol

ACUTE:

- Groups of 5, F344 rats/sex exposed for 4 hours to 0, 1010, 1220, 1320, or 1540 mg/m^3
- Clinical signs during and/or after exposure:
  ↓ activity, closed eyes, excessive lacrimation, oral/nasal discharge, gasping, moist/dry rales
- Wt loss; followed by wt gain by 14 days post exp.
- Red discoloration of lungs in several animals from all exposure groups
- Mortality:

Conc.	Mortality	Day of death
0	0/10	-
1010	3/10	0, 3, 6
1220	2/10	0, 3
1320	8/10	1,1,2,3,3,3,4,5
1540	9/10	0,0,0,1,2,3,4,5,5

- 4-hr LC_{50}: 1200 mg/m^3
- 4-hour LC_{01} (probit): 736 mg/m^3
- BMC_{01}: 1050 mg/m^3
- $BMCL_{05}$: 721 mg/m^3

Conclusion: 4-hr $BMCL_{05}$ of 721 mg/m^3 is selected for the POD for the AEGL-3; Use of this study is supported by Kasparov and Kiry (1972) study, which reported a 4-hr LC_{50} of 1180 mg/m^3 in rats

2-WEEK STUDY:

- Groups of 5 F344 rats/sex exposed for 6 h/d, 5 d/wk for 2 wk, to 0, 24, 66, or 180 mg/m^3
- Clinical signs during and/or after exposure:
  oral/nasal discharge, lacrimation, dry/moist rales, gasping, ano-genital staining, poor condition
- All 10 high-conc. rats died by 6^{th} exposure
- Wt loss in all exp. male groups and mid-and high-conc. females; followed by wt gain by 14 d post exp.
- Concentration-related ↑ lung wt.
- At 180 mg/m^3, necrosis and pyknosis of proximal tubular epithelium in kidneys
- 66 mg/m^3 is the no-effect level

SUBCHRONIC (13 -weeks):

- Groups of 20 F344 rats/sex exposed for 6 h/d, 5 d/wk for 13 wk, to 0, 2, 6, or 17 mg/m^3
- Clinical signs during and/or after exposure:
  ↑ dried red material around nose and mouth, lacrimation, and dry rales (mostly high-conc. grp)
- One high-conc. male rat died at wk 12
- No changes in body wt, ophthalmological findings, hematology analysis, organ wt, gross necropsy
- Concentration-related ↑ in fluoride levels in femurs
- Toxic renal tubular necrosis seen in high-conc. male rat with ↑ BUN levels and male rat that died early

Torkelson et al., 1961

4 mg/m^3 for 7 h/d, 5 d/wk for 127-128 exp.: No effects (appearance, bw, organ wts, gross necropsy)

- Rats 12/sex: areas of pneumonitis (slight), peribronchiole round cell infiltration, congestion
- Guinea pigs 10 /sex: slight pnuemonitis
- Rabbits 3/sex: no effects

8-11 mg/m^3 for 7 h/d, 5 d/wk for 29-33 exp:

- Rats- 5 Fe; exposed 33 times; normal in appearance and growth, ↑ fluoride in bones and teeth
- Guinea pigs- 10 M; exposed 29 times: 4 died - deaths accompanied by asthmatic attack; 6 survivors exhibited breathing difficulty

35 mg/m^3 (nominal) for 7 h/d for 42-60 exposures:

- Rats- 14 Fe; exposed 45 or 60 times; 1 rat died but cause undetermined; survivors: no effects on appearance or organ wt, chemical irritation of lungs - pnuemonitis
- Guinea pigs - 10 M; exposed 42-45 times; 7 died from respiratory failure or asphyxiation after 19th exp - ↑ lung wts, pneumonitis

New AEGL-1 Derivation

Key study: Bowden, 2005

Effects:
Histological signs of irritation at 74.4 mg/m^3; NOAEL for notable irritation because no overt clinical signs of irritation accompanying the histological findings

Uncertainty factors: 30
Interspecies UF: default of 10
Intraspecies UF: 3 because irritation is a direct contact effect and is not expected to vary greatly among individuals

Time scaling: Value set equal to all time periods

AEGL-1 Values for BF_3 (mg/m^3) [given in mg/m^3 because BF_3 gas becomes aerosol upon contact with moist air]				
10-min	**30-min**	**1-hr**	**4-hr**	**8-hr**
2.5	**2.5**	**2.5**	**2.5**	**2.5**

"New" AEGL-3 Derivation

Key study: Rusch et al., 1986

Effects:

4-hr LC_{01}: $BMCL_{05}$ of 721 mg/m^3

Uncertainty factors: 30

Interspecies UF: 10 - species differences exist in sensitivity to BF_3, with the guinea pig being the most sensitive to lethality (COT recommends 5)

Intraspecies UF: 3 - based on steep dose-response curve; primary effect is irritation

Time scaling: Default: n = 1 or 3; 10-min value set equal to 30-min (4-h exposure)

AEGL-3 Values for BF_3 (mg/m^3) [given in mg/m^3 because BF_3 gas becomes aerosol upon contact with moist air]					
POD; UF	**10-min**	**30-min**	**1-hr**	**4-hr**	**8-hr**
721; 10	**140**	**140**	**110**	**72**	**36**
721; 15 ***(COT)***	**96**	**96**	**76**	**48**	**38**
721; 30	**48**	**48**	**38**	**24**	**12**

- Rusch et al. (1986) study (4-hr LC_{50} of 1200 mg/m^3) supported by Kasparov and Kiry (1972) study (4-hr LC_{50} of 1180 mg/m^3)

AEGL-2 Derivation

AEGL-3 levels ÷ 3 to obtain an estimate of AEGL-2

- Data meeting definition of AEGL-2 endpoint not available
- Dose-response curve for lethality was steep (Rusch et al, 1986)

AEGL-2 Values for BF_3 (mg/m^3) [given in mg/m^3 because BF_3 gas becomes aerosol upon contact with moist air]					
POD; UF; ÷3	**10-min**	**30-min**	**1-hr**	**4-hr**	**8-hr**
721; 10	**47**	**47**	**37**	**24**	**12**
721; 15	**32**	**32**	**25**	**16**	**13**
721; 30	**16**	**16**	**13**	**8**	**4**

Note: 2-week repeated-exposure study (6 hr/d, 5 d/wk) in rats reported NOAEL of 66 mg/m^3 (Rusch et al., 1986).

Summary of AEGL Values for BF_3 (mg/m^3)						
Level	**UF**	**10-min**	**30-min**	**1-hr**	**4-hr**	**8-hr**
AEGL-1		2.5	2.5	2.5	2.5	2.5
AEGL-2	10	47	47	37	24	12
AEGL-3	10	140	140	110	72	36
AEGL-2	30	16	16	13	8	4
AEGL-3	30	48	48	38	24	12

Note on time scaling: When viewing the toxicity data in terms of $mg/m^3 \bullet hr$, it appears that n > 3; therefore, using the default n value of n=3 for scaling from longer to shorter durations is reasonable. The n=1 is still used to extrapolate from shorter to longer durations to err on the conservative side.

TABLE 6. Summary of Acute Lethal Inhalation Data in Laboratory Animals

Concentration mg/m^3	Exposure Duration	$mg/m^3 \bullet hr$	Effect	Reference
Rat				
1100*?	1 h	1100	LC_{50} in male rats	Vernot et al., 1977
1000*?	1 h	1000	LC_{50} in female rats	
1200	4 h	4800	LC_{50} in male and female rats	Rusch et al., 1986
1180*?	4 h	4720	LC_{50}	Kasparov and Kiry, 1972
3900*	4 h	15,600	2/2 rats died; one 148 minutes into exposure, the other within 24 hours of exposure	DuPont Co., 1948
2100*	5.5 h	11,550	1/10 rats died	Stokinger and Spiegl, 1953
Mouse				
3460*?	2 h	6920	LC_{50}	Kasparov and Kiry, 1972
2100*	5.5 h	11,550	1/10 mice died	Stokinger and Spiegl, 1953
Guinea pig				
2760*	5 min	230	2/2 guinea pigs died	DuPont Co., 1948
720*	3 h	2160	1/2 guinea pigs died	
109*?	4 h	436	LC_{50}	Kasparov and Kiry, 1972
2100*	5.5 h	11,550	10/10 died	Stokinger and Spiegl, 1953
970*	1.4 h	1358	7/10 died	
370*	10.9 h	4033	1/10 died	

* nominal concentration

*? Not known if nominal or measured concentrations

TABLE 7. Summary of Nonlethal Inhalation Data in Laboratory Animals [a]				
Concentration mg/m³	**Duration**	**mg/m³•hr [b]**	**Effect**	**Reference**
Dog				
1380-2760*	30 min		1 dog; gagged, wheezed, spit up frothy mucous during exposure; recovered after exposure	DuPont Company, 1948
	2 h		1 dog; similar clinical signs, necropsy 48 hours post exposure revealed edema of the larynx, emphysema in lungs, exudate in bronchi, renal capsular spaces and convoluted tubules distended with fluid	
Rat				
2760*	1 h	2760	2/2 rats survived; pulmonary congestion	DuPont Company, 1948
720*	3 h	2160	no clinical signs, no gross or microscopic changes	
370*	10.9 h	4033	10/10 rats survived	Stokinger and Spiegl, 1953
24	6 h/d, 5 d/wk for 2 wk		10/10 animals from each group survived, clinical signs included oral and nasal discharge, lacrimation, dry and moist rales, gasping, poor condition; increased lung weights	Rusch et al., 1986
66			10/10 survived; same clinical signs; decreased body weights; increased lung weights	
35*	7 h/d, 5 d/wk, up to 60 exp.		14 rats; no changes in appearance or organ weights; gross/ microscopic changes in lungs - pneumonitis	Torkelson et al., 1961
8-11	7 h/d, 5 d/wk, for 33 exp.		5 rats; no changes in appearance of body weights	
4	7 h/d, 5 d/wk, for 127-128 exp.		12 male, 12 female rats; no changes in appearance, body or organ weights, or gross necropsy findings	
Mouse				
370*	10.9 h	4033	10/10 mice survived	Stokinger and Spiegl, 1953
Guinea pig				
4	7 h/d, 5 d/wk, for 127-128 exp.		10 males, 10 females; no changes in appearance, body or organ weights, slightly increased incidence of pneumonitis	Torkelson et al., 1961
Rabbit				
4	7 h/d, 5 d/wk, for 127-128 exp.		3 male, 3 female rabbits; no changes in appearance, body or organ weights, or gross or microscopic findings	Torkelson et al., 1961

[a] Some repeated exposure studies are included in the table if the data were deemed relevant

[b] The concentrations in the repeated-exposure studies are not converted to mg/m³•hr.

* nominal concentration

JP-8: Summary of Response to Comments from National Research Committee
National Advisory Committee Meeting, September 28-30, 2005
John Hinz, Chemical Manager; Sylvia Talmage, Staff Scientist

1. Delete discussions/references to JP-4
These discussions have been either shortened or eliminated.

2. Justify interspecies uncertainty factor (UF) of 1
The justification for the interspecies UF of 1 has been rewritten. The basis for the interspecies UF of 1 is the higher respiratory rate and cardiac output in rodents relative to body weight (compared with humans), which results in more rapid uptake and higher blood concentrations (higher systemic dose) of the hydrocarbon components of jet fuel. Furthermore, the blood:air partition coefficient for several hydrocarbon components of jet fuel is higher in rodents than in humans (Gargas et al., Toxicol. Appl. Pharmacol. 98: 87-99, 1989). Metabolism may be faster in rodents than in humans, but the rapid metabolism is expected to be offset by the higher uptake.

The NRC has approved an interspecies UF of 1 for several other chemicals including fluorine, hydrogen fluoride, HFE-7100 (methyl nonafluorobutyl and nonafluoroisobutyl ethers), HFC-134a (1,1,1,2-tetrafluoroethane), and HCFC-141b (1,1-dichloro-1-fluoroethane). The NRC has suggested an interspecies UF of 1 for toluene based on the empirical data involving higher blood concentrations in rodents than in humans under the same exposure conditions. The same is true for methyl ethyl ketone, and 1,1,1-trichloroethane.

3. Explain the use of Alarie's 10-fold reduction factor.
The 10-fold reduction factor of Alarie et al. (1981) essentially includes a 3-fold factor for both intraspecies and interspecies variability.
The explanation for use of the Alarie reduction factor has been rewritten and supported with the extensive review of Schaper (Am. Ind. Hyg. Assoc. J. 54:488-544, 1993). Schaper (1993) shows that for 95 chemicals for which information was available, the ACGIH Threshold Limit Values (TLV) correlate with 0.03 x the RD_{50}. The smaller, 10-fold, reduction factor used for the AEGL-1 correlates with slight irritation which meets the definition of the AEGL-1.

4. Immune response to JP-8 and aerosols
The TSD focused on vapor exposure (with an aerosol component at high concentrations) because vapor is the probable exposure scenario for communities.
The immune studies were discussed, but not considered because (1) they used aerosols and (2) there is controversy concerning the analytical measurements in these studies. As reported in ACGIH (2003), "these publications do not provide adequate information to permit a judgment of aerosol size and stability nor do they speak to the extent to which the sampling systems distinguished between aerosol and vapor" (ACGIH 2003; Frank 2004).
Aerosols can and often do act more like particulate matter (Goetz 1961, Int. J. Air Water Pollut 4:168-184), thus initiating a greater response than vapor alone.

5. Discuss PBPK models... and lack of time-scaling for AEGL-2

The TSD notes that models for single and multiple components of fuels have been developed. The interactions of the multiple chemicals of fuels are complex and not fully understood. Depending on lipophilicity among other factors, the individual components are taken up at varying rates. At this time, the models are in a preliminary stage and are not useful for either setting AEGL values or time-scaling them.

The 30-minute clinical study of Astrand et al. (1975) was used as an example of rapid approach to steady-state in the blood for several chemical components common to Stoddard Solvent and jet fuels (*n*-decane). At steady-state, we have used the same value across time for solvents.

6. The AEGL-2 (1100 mg/m^3) may be too high

When the 1100 mg/m^3 value is converted to ppm for any individual component of JP-8, the values are quite low.

Examples:

avg. m.w. of JP-8 (167): 1100 mg/m^3 = 160 ppm

dodecane, undecane, nonane (the primary components): 1100 mg/m^3 = 158, 172, 210 ppm

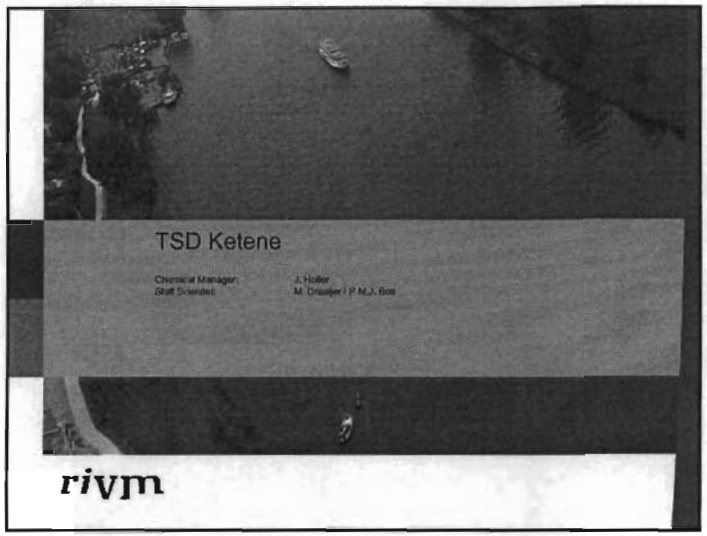
toluene: 1100 mg/m^3 = ~300 ppm (the interim AEGL-2 ranges from 990 to 510 ppm)

Many of the identified aliphatic hydrocarbons are of low toxicity.

n-nonane: 4-hour LC_{50} = 3200 ppm (mouse)

no change in respiratory rate of mouse: 1000-1500 ppm (5246-7869 mg/m^3)

For JP-8, we failed to identify a lethal concentration. Concentrations of 3430 mg/m^3 or 4440 mg/m^3 for 4 hours were not lethal. Dividing by 3 (an alternate way to set the AEGL-2) yields values close to 1100 mg/m^3.



Ketene: use and Physical-chemical properties

- Use: Acetylating agent in chemical synthesis
- Physical-chemical properties
  - Molecular weight: 42.04
  - Colorless gas
  - Water solubility: no
  - Boiling point: -56°C
  - Odor: penetrating
  - Flammability: no data

rivm 2

Ketene: available data

- No human data available
- Four animal studies available
  - Treon et al. 1949
    - Single and repeated exposures; several animal species
  - Wooster et al. 1947
    - Single 10-min exposures; several animal species
  - Cameron and Neuberger 1937
    - Single 5-min (several species) and 20-min exposures (mice)
  - Mendenhall and Stokinger 1959
    - Single 10-min exposures; mice

rivm 3

Ketene: animal experiments

- Treon et al. (1949)
  - Single 10-min exposures
    - ketene of high purity
    - static conditions, nominal concentrations
    - monkeys, cats, rabbits, guinea pigs, rats, mice (n=2-10/20)
  - Repeated exposures
    - ketene of high purity
    - dynamic conditions, nominal concentrations
    - monkeys, cats, rabbits, guinea pigs, rats, mice (n=1-10)
    - daily exposures range from 1 ppm (7 h) to 50 ppm (50 min)
    - general description of toxicity

rivm 4

Ketene: animal experiments

- Wooster et al. (1947)
  - Single 10-min exposures
    - purity unknown
    - cats, rabbits, guinea pigs, rats, mice (n=2-20/24)
    - calculated concentrations (70 – 815 ppm)
    - up to 15 days of observation
- Cameron and Neuberger (1937)
  - Single 5-min exposures (mice also 20-min)
    - co-exposure to methane (equivalent concentrations)
    - guinea pigs, rats, mice (n not given)
    - concentration range reported (100 – 2000 ppm)
- Mendenhall and Stokinger (1959)
  - Single 10-min exposures
    - tolerance test (ketene/ozone)
    - mixture (42% ketene, 42% methane, 16% other gases)
    - mice (actual concentrations: 1.1 ppm and higher)

rivm

5

Ketene: toxicity profile

- Toxicity profile comparable for all species tested
  - Sneezing, coughing, nasal discharge, eye irritation, labored breathing, lethargy, death
  - Greatest toxicity in mice, followed by rats, guinea pigs, cats and rabbits
- Steep concentration-response and time-response relation
- Main effects on lung and CNS
- CNS effects possibly due to cerebral anoxia secondary to severe alveolar damage
- Mortality due to respiratory failure

rivm

6

Ketene: toxicity profile

- Developmental / reproductive toxicity
  - No data available
- Genotoxicity
  - No data available
- Carcinogenicity
  - No data available
- Kinetics
  - No data available

rivm

7

Ketene: animal experiments

- Mendenhall and Stokinger (1959)
  - Single 10-min exposures
    - 5.0 ppm: highest concentration without mortality
    - 18.4 ppm: lowest concentration with 100% mortality
- Cameron and Neuberger (1937)
  - Single 5-min exposures (mice also 20-min)
    - only 100% mortality at all exposures
- Wooster et al. (1947)
  - Single 10-min exposures
    - cats, rabbits, guinea pigs, rats, mice (n=2-20/24)
    - calculated concentrations (70 – 815 ppm)

rivm

8

Ketene: Wooster et al. (1947)

Concentration (ppm)	Mortality	Time of death or observation period
Cats	(n=1-2)	
233	0/1	15 d
367	1/2	8-12 h
623	2/2	26 min and 8-12 h
815	1/1	135 min
Rabbits	(n=2)	
652	0/2	10 d
Guinea pigs	(n=2-4)	
367	2/4	8-12 h
	3/4	3 d
623	4/4	8-12 h
652	2/2	8-12 h
Rats	(n=4)	
122	0/4	10 d
250	4/4	150 min
774	4/4	135 min
Mice	(n=20-24)	
70	0/20	115 min
	20/20	240 min
122	16/20	180 min
	18/20	3 d
192	20/20	115 min
349	11/20	55 min
	20/20	80 min
815	24/24	60 min

rivm

Ketene: Treon et al. (1949)

Table: Acute Lethal Inhalation Data (dynamic exposure)

Concentration (ppm)	Intended exposure (time/d)	(d)	Mortality	Time of death
Mice			(n=7-10)	
50	50 min	1	10/10	0-94 min (7); 5.25-8.25 h (3)
53	100 min	1	10/10	0-92 min (10)
23	30 min	1	7/10	1.85-4.2 h (5); 7 and 16 h (2)
23	120 min	1	10/10	1.85-6.35 h (10)
23	4 h	2	10/10	during 1st exposure (3); less than 7 h after 1st exposure (7)
12	4.5-6 h	15	4/7	during 2nd exposure (3); during 7th exposure (1)
1	7 h	14	1/10	3 days after 10th exposure (1)
1	7 h	55	1/10	1 day after 49th exposure (1)

rivm

Ketene: AEGL-1

- Treon et al (1949): critical study
  - Other studies supporting for brief (10-min) exposures
  - Mice are most susceptible
  - Drawbacks: nominal concentrations and general description of toxicity
- No effects at 7-h exposure to 1 ppm
- Severe lung effects at 4.5-h exposure to 12 ppm cannot be ruled out

rivm

Ketene: AEGL-1

- Treon et al.(1949): point of departure
  - No effects at 7-h exposure to 1 ppm
  - Interspecies factor of 3 (mice: most susceptible species)
  - Intraspecies factor of 3 (mode of action: direct action at port of entry)
  - Total UF= 10
  - Default values of n
    - n=1 for extrapolation to 480 min
    - n=3 for extrapolation to 30 min – 240 min
    - 10-min AEGL-1 = 30-min AEGL-1

rivm

Ketene: AEGL-1

AEGL-1 Values for Ketene				
10-minute	30-minute	1-hour	4-hour	8-hour
0.24 ppm (0.41 mg/m³)	0.24 ppm (0.41 mg/m³)	0.19 ppm (0.33 mg/m³)	0.12 ppm (0.21 mg/m³)	0.088 ppm (0.15 mg/m³)

rivm

Ketene: AEGL-2

- Treon et al.(1949): point of departure
  - No effects at 7-h exposure to 1 ppm
  - No deaths in single 4.5 h exposure to 12 ppm
    - (3/7 deaths on second day during exposure)
  - Mortality preceded by severe lung damage, hence lung damage cannot be ruled out at 12 ppm (AEGL-2 effect)
  - No appropriate NOAEL for this effect
    - (NOAEL somewhere between 1 and 12 ppm)
  - Steep concentration-response curve:
    - AEGL-2 = AEGL-3/3
  - AEGL-2 levels are mid between AEGL-1 and AEGL-3

rivm

Ketene: AEGL-3

- Treon et al.(1949): point of departure
  - Mice most susceptible species
  - 100% mortality at 50-min exposure to 50 ppm
  - 7/10 deaths at 30-min exposure to 23 ppm
  - 100% mortality at 2-hour exposure to 23 ppm
  - No mortality in single 4.5 h exposure to 12 ppm
    - (3/7 deaths on second day during exposure)
- Point of departure: 4.5-h exposure to 12 ppm

rivm

Ketene: AEGL-3

- Treon et al. (1949)
  - Total UF= 10 (similar to AEGL-1)
  - Default values of n
    - n=1 for extrapolation to 480 min
    - n=3 for extrapolation to 30 min – 240 min
    - 10-min AEGL-1 = 30-min AEGL-1

AEGL-3 Values for Ketene				
10-minute	30-minute	1-hour	4-hour	8-hour
2.5 ppm (4.3 mg/m³)	2.5 ppm (4.3 mg/m³)	2.0 ppm (3.4 mg/m³)	1.2 ppm (2.1 mg/m³)	0.68 ppm (1.17 mg/m³)

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Ketene: Summary of AEGL-values

Summary of AEGL Values					
	Exposure Duration				
Classification	10-minute	30-minute	1-hour	4-hour	8-hour
AEGL-1 (Nondisabling)	0.24 ppm	0.24 ppm	0.19 ppm	0.12 ppm	0.046 ppm
AEGL-2 (Disabling)	0.83 ppm	0.83 ppm	0.66 ppm	0.42 ppm	0.23 ppm
AEGL-3 (Lethal)	2.5 ppm	2.5 ppm	2.0 ppm	1.2 ppm	0.68 ppm

rivm

17

ATTACHMENT 9

ACUTE EXPOSURE GUIDELINE LEVELS (AEGLs) FOR SELECTED CHLOROFORMATES

NAC/AEGL-38
September 28-30, 2005

ORNL Staff Scientist: Cheryl Bast

Chemical Manager: Ernest Falke

Chemical Reviewers: Lynn Beasley and Paul Tobin

- Hydrolyze in water or moist air to produce the parent hydroxy compound, hydrogen chloride, carbon dioxide, and a carbonate.
- All title chloroformates are direct-acting contact irritants, and are corrosive to the eyes, skin, gastrointestinal and respiratory tracts.

  Ethyl chlorothioformate may cause both portal of entry and systemic effects. These systemic effects are likely due to the ability of the thio moiety to interact with other biomolecules.

  Myocardial degeneration, nephrosis, hepatic necrosis, adrenal necrosis, spleen and lymph node necrosis, and lymphoid cell depletion noted in rats
- Values derived for six chloroformates
- In all cases the inter- and intra- species uncertainty factors were 3 and 3, respectively.
- In 2 cases a modifying factor was used for limited data and the possibility of systemic effects.
- Where an AEGL-2 was calculated it was determined by dividing the AEGL-3 by 3.

  Justified by steep concentration-response curve (SOP Section 2.2.2.3)

CHEMICAL	AEGL-1 POD	AEGL-2 POD	AEGL-3 POD	1-hr Rat LC_{50} Data Available *POD	COMMENTS
Methyl chloroformate	RD_{50}/1000	1/3 AEGL-3	1/3 LC_{50}	Analytical *Male- 88 ppm (Vernot et al., 1977) Male- 92-123 ppm (Fisher et al., 1981) Female- 103 ppm (Vernot et al., 1977) Female- 100 ppm (Fisher et al., 1981) Nominal 163 ppm (Bio-Test, 1975)	
Ethyl chloroformate	RD_{50}/1000	1/3 AEGL-3	1/3 LC_{50}	Analytical *Male- 145 ppm (Vernot et al., 1977) Male- 189 ppm (Fisher et al., 1981) Female- 170 ppm (Vernot et al., 1977) Female- 200 ppm (Fisher et al., 1981)	
Propyl chloroformate	RD_{50}/1000	1/3 AEGL-3	$BMCL_{05}$	Nominal 410 ppm (Bio-Test, 1970) *($BMCL_{05}$ = 216 ppm)	MF=3 for limited data
Isopropyl chloroformate	RD_{50}/1000	1/3 AEGL-3	1/3 LC_{50}	Nominal 300 ppm (Bio-Test, 1970)	No MF- support from repeat-exposure data
Allyl chloroformate	NR	1/3 AEGL-3	$BMCL_{05}$	Analytical 65.1 ppm (Stillmeadow, 1987) *($BMCL_{05}$ = 21 ppm)	No MF- analytical concentration
n-Butyl chloroformate	NR	NR	NR		
Isobutyl chloroformate	NR	NR	NR		
sec-Butyl chloroformate	NR	NR	NR		
Diphosgene	NR	NR	NR		
				4-Hour POD	
Ethyl chlorothio-formate	NR	1/3 AEGL-3	$BMCL_{05}$	Analytical Male- 51 ppm (Stauffer, 1983) Female- 41 ppm (Stauffer, 1983) *($BMCL_{05}$ = 21 ppm)	MF=3 for systemic effects of thio moiety

AEGL-1 VALUES: METHYL CHLOROFORMATE				
10 minute	30 minute	1 hour	4 hour	8 hour
0.052 ppm	0.052 ppm	0.052 ppm	0.052 ppm	0.052 ppm

Species: Male Swiss-Webster Mouse
Concentration: 52.4 ppm (RD_{50})
Endpoint: Predicted no effect of any kind on the respiratory system
Reference: Carpenter, 1982

Rationale: The RD_{50} multiplied by 0.1 corresponds to "some sensory irritation".

The RD_{50} value multiplied by 0.01 corresponds to "no sensory irritation"

The RD_{50} value multiplied by 0.001 corresponds to "no effect of any kind on the respiratory system" Alarie (1981)

The multiplier of 0.001, rather than 0.01, was chosen because use of 0.01 would yield AEGL-1 values greater than AEGL-2 values at the longer time points and because 1/4 mice died at a concentration of 50 ppm (Carpenter, 1982).

Time Scaling: Value held constant across the 10- and 30-minute, and 1-, 4-, and 8-hour exposure times because mild irritancy generally does not vary greatly over time, and because it is not expected that prolonged exposure will result in an enhanced effect.

AEGL-2 VALUES: METHYL CHLOROFORMATE				
10 minute	30 minute	1 hour	4 hour	8 hour
1.8 ppm	1.2 ppm	0.97 ppm	0.24 ppm	0.12 ppm

Endpoint: ⅓ The AEGL-3 values

Endpoint is justified based on the steep concentration-response curve:

1-hr rat LC_{50} is approximately 100 ppm
Rats exposed to 26 ppm for 1-hr were clinically-normal (Fisher et al., 1981)

Support: Values are considered protective because rats showed no effect when exposed to 0.38 ppm repeatedly (6 hours/day, 5 days/week for 4 weeks), and showed only laryngeal lesions when exposed to 1.01 ppm for 6 hours/day, 5 days/week for 4 weeks (BASF, 1993).

AEGL-3 VALUES: METHYL CHLOROFORMATE				
10 minute	30 minute	1 hour	4 hour	8 hour
5.3 ppm	3.7 ppm	2.9 ppm	0.73 ppm	0.37 ppm

Species: Rat (10 males/group)
Concentration: 29 ppm
Time: 1-hour
Endpoint: Estimated lethality threshold: ⅓ of the most conservative 1-hr LC_{50} value in rats (88 ppm x ⅓ =29 ppm)
Reference: Vernot et al., 1977

Time Scaling: $C^n \times t = k$, where $n = 3$ for the 10- and 30-minute time periods, and $n = 1$ for the 4- and 8-hour time periods, to provide AEGL values that would be protective of human health (NRC, 2001).

Uncertainty Factors:

Interspecies = 3 Intraspecies = 3

Highly reactive and clinical signs are likely caused by a direct chemical effect on the tissues; this type of portal-of-entry effect is not expected to vary greatly between species or among individuals.

Support: POD supported by the fact that no deaths were observed in rats exposed to 26 ppm for 1 hour (Fisher et al., 1981).

Derived values are considered protective because:

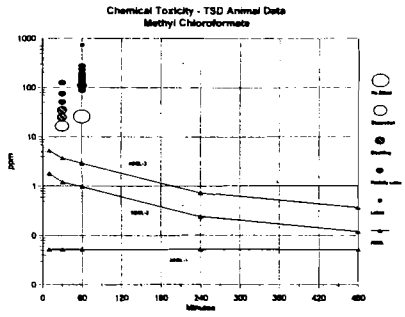
Rats showed no deaths until week 4 when exposed to 8.8 ppm repeatedly (6 hours/day, 5 days/week for 4 weeks)

No deaths and only nasal turbinate histopathology and larynx lesions in rats repeatedly exposed to 3.1 ppm

Only larynx lesions when exposed to 1.01 ppm for 6 hours/day, 5 days/week for 4 weeks (BASF, 1993).

THERE ARE NO OTHER EXTANT STANDARDS AND GUIDELINES FOR METHYL CHLOROFORMATE!

Summary of Proposed AEGL Values for Methyl Chloroformate					
Guideline	Exposure Duration				
	10-minutes	30-minutes	1-hour	4-hours	8-hours
AEGL-1	0.052 ppm	0.052 ppm	0.052 ppm	0.052 ppm	0.052 ppm
AEGL-2	1.8 ppm	1.2 ppm	0.97 ppm	0.24 ppm	0.12 ppm
AEGL-3	5.3 ppm	3.7 ppm	2.9 ppm	0.73 ppm	0.37 ppm



AEGL-1 VALUES: ETHYL CHLOROFORMATE				
10 minute	30 minute	1 hour	4 hour	8 hour
0.078 ppm	0.078 ppm	0.078 ppm	0.078 ppm	0.078 ppm

Species: Male Swiss-Webster Mouse
Concentration: 77.5 ppm (RD_{50})
Endpoint: Predicted no effect of any kind on the respiratory system
Reference: Carpenter, 1982

Rationale: The RD_{50} multiplied by 0.1 corresponds to "some sensory irritation"

The RD_{50} value multiplied by 0.01 corresponds to "no sensory irritation"

The RD_{50} value multiplied by 0.001 corresponds to "no effect of any kind on the respiratory system" Alarie (1981)

The multiplier of 0.001, rather than 0.01, was chosen because use of 0.01 would yield AEGL-1 values greater than AEGL-2 values at the longer time points.

Time Scaling: Value held constant across the 10- and 30-minute, and 1-, 4-, and 8-hour exposure times because mild irritancy generally does not vary greatly over time, and because it is not expected that prolonged exposure will result in an enhanced effect.

AEGL-2 VALUES: ETHYL CHLOROFORMATE				
10 minute	30 minute	1 hour	4 hour	8 hour
2.9 ppm	2.0 ppm	1.6 ppm	0.40 ppm	0.20 ppm

Endpoint: ⅓ The AEGL-3 values

Endpoint is justified based on the steep concentration-response curve:

1-hr rat LC_{50} is 189-200 ppm
Rats exposed to 47 ppm for 1-hr were clinically-normal (Fisher et al., 1981)

AEGL-3 VALUES: ETHYL CHLOROFORMATE				
10 minute	30 minute	1 hour	4 hour	8 hour
8.8 ppm	6.1 ppm	4.8 ppm	1.2 ppm	0.60 ppm

Species: Rat (10 males/group)
Concentration: 48 ppm
Time: 1-hour
Endpoint: Estimated lethality threshold: ⅓ of the most conservative 1-hr LC_{50} value in rats (145 ppm x ⅓ =48 ppm)
Reference: Vernot et al., 1977

Time Scaling: $C^n \times t = k$, where n= 3 for the 10- and 30-minute time periods, and n= 1 for the 4- and 8-hour time periods, to provide AEGL values that would be protective of human health (NRC, 2001).

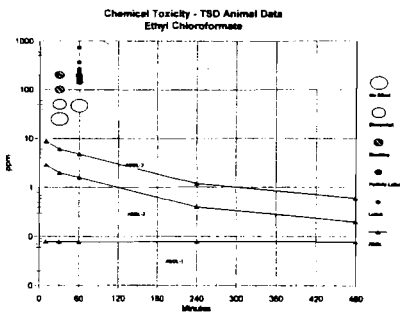
Uncertainty Factors:

Interspecies = 3 Intraspecies = 3

Highly reactive and clinical signs are likely caused by a direct chemical effect on the tissues; this type of portal-of-entry effect is not expected to vary greatly between species or among individuals.

Support: POD supported by the fact that no deaths were observed in rats exposed to 47 ppm for 1 hour (Fisher et al., 1981).

Summary of Proposed AEGL Values for Ethyl Chloroformate					
Guideline	Exposure Duration				
	10-minutes	30-minutes	1-hour	4-hours	8-hours
AEGL-1	0.078 ppm	0.078 ppm	0.078 ppm	0.078 ppm	0.078 ppm
AEGL-2	2.9 ppm	2.0 ppm	1.6 ppm	0.40 ppm	0.20 ppm
AEGL-3	8.8 ppm	6.1 ppm	4.8 ppm	1.2 ppm	0.60 ppm
Dutch MAC					1 ppm



AEGL-1 VALUES: PROPYL CHLOROFORMATE				
10 minute	30 minute	1 hour	4 hour	8 hour
0.084 ppm	0.084 ppm	0.084 ppm	0.084 ppm	0.084 ppm

Species: Male Swiss-Webster Mouse
Concentration: 83.5 ppm (RD_{50})
Endpoint: Predicted no effect of any kind on the respiratory system
Reference: Carpenter, 1982

Rationale: The RD_{50} multiplied by 0.1 corresponds to "some sensory irritation"

The RD_{50} value multiplied by 0.01 corresponds to "no sensory irritation"

The RD_{50} value multiplied by 0.001 corresponds to "no effect of any kind on the respiratory system" Alarie (1981)

The multiplier of 0.001, rather than 0.01, was chosen because use of 0.01 would yield AEGL-1 values greater than AEGL-2 values at the longer time points.

Time Scaling: Value held constant across the 10- and 30-minute, and 1-, 4-, and 8-hour exposure times because mild irritancy generally does not vary greatly over time, and because it is not expected that prolonged exposure will result in an enhanced effect.

AEGL-2 VALUES: PROPYL CHLOROFORMATE				
10 minute	30 minute	1 hour	4 hour	8 hour
4.3 ppm	3.0 ppm	2.4 ppm	0.6 ppm	0.30 ppm

Endpoint: ⅓ The AEGL-3 values

Endpoint is justified based on the steep concentration-response curve:

1-hr exposures(Bio-Test, 1970)

0/10 dead at 249 ppm

2/10 dead at 333 ppm

10/10 dead at 1000 ppm

AEGL-3 VALUES: PROPYL CHLOROFORMATE				
10 minute	30 minute	1 hour	4 hour	8 hour
13 ppm	9.1 ppm	7.2 ppm	1.8 ppm	0.90 ppm

Species: Rat (5/sex/group)
Concentration: 216 ppm
Time: 1-hour
Endpoint: Estimated lethality threshold: $BMCL_{05}$
Reference: Bio-Test, 1970

Time Scaling: $C^n \times t = k$, where $n = 3$ for the 10- and 30-minute time periods, and $n = 1$ for the 4- and 8-hour time periods, to provide AEGL values that would be protective of human health (NRC, 2001).

Uncertainty Factors:

Interspecies = 3 Intraspecies = 3

Highly reactive and clinical signs are likely caused by a direct chemical effect on the tissues; this type of portal-of-entry effect is not expected to vary greatly between species or among individuals.

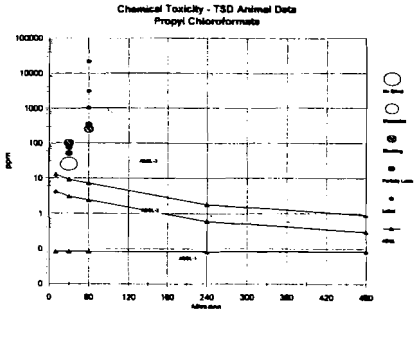
Modifying Factor = 3

Key study reported nominal, not analytical, concentrations

No other confirmatory studies

THERE ARE NO OTHER EXTANT STANDARDS AND GUIDELINES FOR PROPYL CHLOROFORMATE!

Summary of Proposed AEGL Values for Propyl Chloroformate					
Guideline	Exposure Duration				
	10-minutes	30-minutes	1-hour	4-hours	8-hours
AEGL-1	0.084 ppm	0.084 ppm	0.084 ppm	0.084 ppm	0.084 ppm
AEGL-2	4.3 ppm	3.0 ppm	2.4 ppm	0.6 ppm	0.30 ppm
AEGL-3	13 ppm	9.1 ppm	7.2 ppm	1.8 ppm	0.90 ppm



AEGL-1 VALUES: ISOPROPYL CHLOROFORMATE				
10 minute	30 minute	1 hour	4 hour	8 hour
0.10 ppm	0.10 ppm	0.10 ppm	0.10 ppm	0.10 ppm

Species: Male Swiss-Webster Mouse
Concentration: 104 ppm (RD_{50})
Endpoint: Predicted no effect of any kind on the respiratory system
Reference: Carpenter, 1982

Rationale: The RD_{50} multiplied by 0.1 corresponds to "some sensory irritation"

The RD_{50} value multiplied by 0.01 corresponds to "no sensory irritation"

The RD_{50} value multiplied by 0.001 corresponds to "no effect of any kind on the respiratory system" Alarie (1981)

The multiplier of 0.001, rather than 0.01, was chosen because use of 0.01 would yield AEGL-1 values greater than AEGL-2 values at the longer time points.

Time Scaling: Value held constant across the 10- and 30-minute, and 1-, 4-, and 8-hour exposure times because mild irritancy generally does not vary greatly over time, and because it is not expected that prolonged exposure will result in an enhanced effect.

AEGL-2 VALUES: ISOPROPYL CHLOROFORMATE				
10 minute	30 minute	1 hour	4 hour	8 hour
6.0 ppm	4.3 ppm	3.3 ppm	0.83 ppm	0.43 ppm

Endpoint: ⅓ The AEGL-3 values

Support: Values are considered protective because rats showed only nasal irritation when exposed to 20 ppm repeatedly (6 hours/day for 20 days) (Gage, 1970)

AEGL-3 VALUES: ISOPROPYL CHLOROFORMATE				
10 minute	30 minute	1 hour	4 hour	8 hour
18 ppm	13 ppm	10 ppm	2.5 ppm	1.3 ppm

Species: Rat (5/sex/group)
Concentration: 100 ppm
Time: 1-hour
Endpoint: Estimated lethality threshold: ⅓ x LC50: ⅓ x 300 ppm = 100 ppm
Reference: Bio-Test, 1970

Time Scaling: $C^n \times t = k$, where $n = 3$ for the 10- and 30-minute time periods, and $n = 1$ for the 4- and 8-hour time periods, to provide AEGL values that would be protective of human health (NRC, 2001).

Uncertainty Factors:

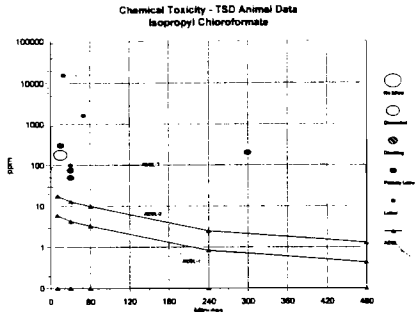
Interspecies = 3 Intraspecies = 3

Highly reactive and clinical signs are likely caused by a direct chemical effect on the tissues; this type of portal-of-entry effect is not expected to vary greatly between species or among individuals.

Support:

Values considered protective because no deaths were noted in rats exposed to 42 ppm isopropyl chloroformate 6 hours/day for 5 days (Collins and Proctor, 1984).

Extant Standards and Guidelines for Isopropyl Chloroformate					
Guideline	Exposure Duration				
	10 minutes	30 minutes	1 hour	4 hours	8 hours
AEGL-1	0.10 ppm	0.10 ppm	0.10 ppm	0.10 ppm	0.10 ppm
AEGL-2	6.0 ppm	4.3 ppm	3.3 ppm	0.83 ppm	0.43 ppm
AEGL-3	18 ppm	13 ppm	10 ppm	2.5 ppm	1.3 ppm
ERPG-1[a]	Insufficient Data				
ERPG-2[a]	5 ppm				
ERPG-3[a]	20 ppm				
Dutch MAC[b]					1 ppm



AEGL-1 VALUES: ALLYL CHLOROFORMATE				
10 minute	30 minute	1 hour	4 hour	8 hour
NR	NR	NR	NR	NR

Not Recommended due to insufficient data.

AEGL-2 VALUES: ALLYL CHLOROFORMATE				
10 minute	30 minute	1 hour	4 hour	8 hour
1.3 ppm	0.87 ppm	0.70 ppm	0.18 ppm	0.09 ppm

Endpoint: ⅓ the AEGL-3 values

Endpoint is justified based on the steep concentration-response curve:

1-hr rat exposures (Stillmeadow, 1987)

0/10 dead at 33.7 ppm

6/10 dead at 65 ppm

10/10 dead at 175.7 ppm

AEGL-3 VALUES: ALLYL CHLOROFORMATE				
10 minute	30 minute	1 hour	4 hour	8 hour
3.8 ppm	2.6 ppm	2.1 ppm	0.53 ppm	0.26 ppm

Species: Rat (5/sex/group)
Concentration: 21 ppm
Time: 1-hour
Endpoint: Estimated lethality threshold: $BMCL_{05}$
Reference: Stillmeadow, 1987

Time Scaling: $C^n \times t = k$, where $n = 3$ for the 10- and 30-minute time periods, and $n = 1$ for the 4- and 8-hour time periods, to provide AEGL values that would be protective of human health (NRC, 2001).

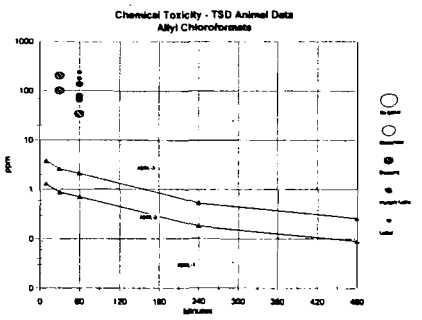
Uncertainty Factors:

Interspecies = 3 Intraspecies = 3

Highly reactive and clinical signs are likely caused by a direct chemical effect on the tissues; this type of portal-of-entry effect is not expected to vary greatly between species or among individuals.

THERE ARE NO OTHER EXTANT STANDARDS AND GUIDELINES FOR ALLYL CHLOROFORMATE!

Summary of Proposed AEGL Values for Allyl Chloroformate					
Guideline	Exposure Duration				
	10-minutes	30-minutes	1-hour	4-hours	8-hours
AEGL-1	NR	NR	NR	NR	NR
AEGL-2	1.3 ppm	0.87 ppm	0.70 ppm	0.18 ppm	0.09 ppm
AEGL-3	3.8 ppm	2.6 ppm	2.1 ppm	0.53 ppm	0.26 ppm



Summary of AEGL Values for n-butyl Chloroformate						
Classification	10-Minute	30-Minute	1-Hour	4-Hour	8-Hour	Endpoint (Reference)
AEGL-1 (Nondisabling)	NR	NR	NR	NR	NR	Insufficient data
AEGL-2 (Disabling)	NR	NR	NR	NR	NR	Insufficient data
AEGL-3 (Lethality)	NR	NR	NR	NR	NR	Insufficient data

Summary of AEGL Values For Isobutyl Chloroformate						
Classification	10-Minute	30-Minute	1-Hour	4-Hour	8-Hour	Endpoint (Reference
AEGL-1 (Nondisabling)	NR	NR	NR	NR	NR	Insufficient data
AEGL-2 (Disabling)	NR	NR	NR	NR	NR	Insufficient data
AEGL-3 (Lethality)	NR	NR	NR	NR	NR	Insufficient data

Summary of AEGL Values For sec-Butyl Chloroformate						
Classification	10-Minute	30-Minute	1-Hour	4-Hour	8-Hour	Endpoint (Reference)
AEGL-1 (Nondisabling)	NR	NR	NR	NR	NR	Insufficient data
AEGL-2 (Disabling)	NR	NR	NR	NR	NR	Insufficient data
AEGL-3 (Lethality)	NR	NR	NR	NR	NR	Insufficient data

AEGL-1 VALUES: ETHYL CHLOROTHIOFORMATE				
10 minute	30 minute	1 hour	4 hour	8 hour
NR	NR	NR	NR	NR

Not Recommended due to insufficient data.

AEGL-2 VALUES: ETHYL CHLOROTHIOFORMATE				
10 minute	30 minute	1 hour	4 hour	8 hour
0.47 ppm	0.47 ppm	0.37 ppm	0.23 ppm	0.12 ppm

Endpoint: ⅓ the AEGL-3 values

Endpoint is justified based on the steep concentration-response curve:

4-hr rat exposures (Stauffer, 1983)

4/20 dead at 33 ppm

14/20 dead at 59 ppm

20/20 dead at 65 ppm

AEGL-3 VALUES: ETHYL CHLOROTHIOFORMATE				
10 minute	30 minute	1 hour	4 hour	8 hour
1.4 ppm	1.4 ppm	1.1 ppm	0.70 ppm	0.35 ppm

Species: Rat (10/sex/group)
Concentration: 21 ppm
Time: 4-hour
Endpoint: Estimated lethality threshold: $BMCL_{05}$
Reference: Stauffer, 1983

Time Scaling: $C^n \times t = k$, where $n = 3$ for the 30-minute and 1-hour time periods, and $n = 1$ for the 8-hour time period, to provide AEGL values that would be protective of human health (NRC, 2001). The 30-minute value was adopted as the 10-minute value.

Uncertainty Factors:

Interspecies = 3 Intraspecies = 3

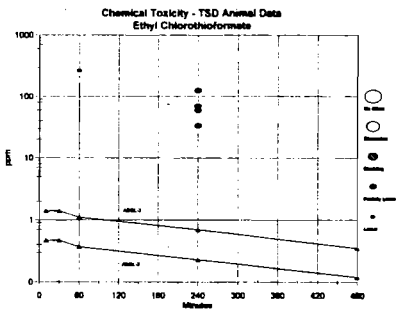
Highly reactive and clinical signs are likely caused by a direct chemical effect on the tissues; this type of portal-of-entry effect is not expected to vary greatly between species or among individuals.

Modifying Factor: 3

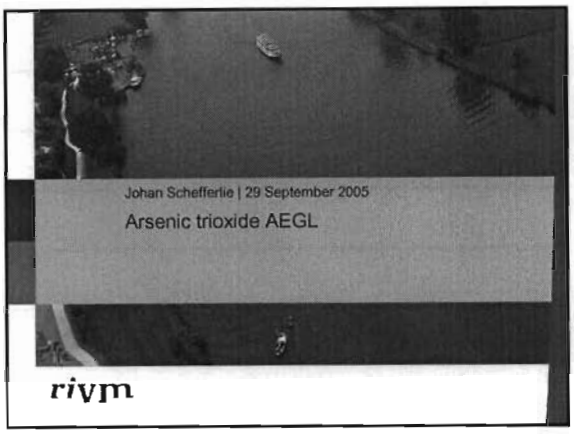
To protect against potential delayed systemic effects from the thio moitey.

THERE ARE NO OTHER EXTANT STANDARDS AND GUIDELINES FOR ETHYL CHLOROTHIOFORMATE!

Summary of AEGL Values for Ethyl Chlorothioformate					
Classification	10-minute	30-minute	1-hour	4-hour	8-hour
AEGL-1 (Nondisabling)	NR	NR	NR	NR	NR
AEGL-2 (Disabling)	0.47 ppm	0.47 ppm	0.37 ppm	0.23 ppm	0.12 ppm
AEGL-3 (Lethal)	1.4 ppm	1.4 ppm	1.1 ppm	0.70 ppm	0.35 ppm



Summary of AEGL Values For Diphosgene						
Classification	10-Minute	30-Minute	1-Hour	4-Hour	8-Hour	Endpoint (Reference)
AEGL-1 (Nondisabling)	NR	NR	NR	NR	NR	Insufficient data
AEGL-2 (Disabling)	NR	NR	NR	NR	NR	Insufficient data
AEGL-3 (Lethality)	NR	NR	NR	NR	NR	Insufficient data



Arsenic trioxide

- Solid at ambient temperatures
  - Inhalation exposure to dust
- Knowledge of toxicity mainly from oral data
- The most toxic one of all arsenic species
- 90% use as wood preservative
  - Phase out in 2003!
- Other uses mainly in pesticides

rivm

Diergeneesmiddelen

Reported effects in humans following inhalation

- Occupational long term exposure (not related to exposure concentration)
  - Peripheral neuropathy
  - Perforation of nasal septum
  - Pigmentation of the skin

rivm

Relevant data for AEGL

- No data on AEGL-1 or AEGL-2 effects
- Lethality data from a rat developmental study (range-finding)
- Knowledge about normal occupational exposure concentrations (personal breathing zone sampling) from 6 studies involving 356 workers

rivm

Lethality

- Single 6-h exposure
  - 25 mg/m³ 0/10
  - 50 mg/m³ 0/10
  - 100 mg/m³ 10/10
  - 150 mg/m³ 10/10
  - 200 mg/m³ 10/10

(Holson et al. 1999, see TSD page 10)

- 50 mg/m³ is a NOEL for lethality in rats in this study

rivm

AEGL-3

- The NOEL of 50 mg/m³ is the point of departure
- Total UF of 10 (3x3)
  - Larger factors (100 or 30) result in AEGL-3 values within or just above the range of normal occupational exposure concentrations
  - The resulting 6-h value is 5 mg/m³
- Time-scaling with $C^n \times t = k$
  - No data on time-concentration effects
  - Default n=3 for shorter time points, n=1 for longer time points
  - Starting point 6-h, so 10-min value is equal to 30-min value

10-minute	30-minute	1-hour	4-hour	8-hour
11 mg/m³	11 mg/m³	9.1 mg/m³	5.7 mg/m³	3.7 mg/m³

Expressed as mg/m³ As_2O_3 rather than mg/m³ As

rivm

AEGL-2

- Occupational long term 8-h exposures are up to 1.0 mg/m³
- No acute AEGL-2 effects expected at these concentrations
- Proposal to use 1.0 mg/m³ (8-h) as point of departure
- No UF is proposed
  - 1.0 mg/m³ is considered a sub-AEGL-2 concentration and it is not known hor far this is below the concentration that will produce AEGL-2 effects
- Default time-scaling as for AEGL-3

10-minute	30-minute	1-hour	4-hour	8-hour
2.5 mg/m³	2.5 mg/m³	2.0 mg/m³	1.3 mg/m³	1.0 mg/m³

rivm

Summary

Classification	10-minute	30-minute	1-hour	4-hour	8-hour
AEGL-1	Not proposed	Not proposed	Not proposed	Not proposed	Not proposed
AEGL-2	2.5 mg/m³	2.5 mg/m³	2.0 mg/m³	1.3 mg/m³	1.0 mg/m³
AEGL-3	11 mg/m³	11 mg/m³	9.1 mg/m³	5.7 mg/m³	3.7 mg/m³

These values are expressed as arsenic trioxide (mg As_2O_3/m^3)

rivm

CYCLOHEXYL ISOCYANATE

AEGL values are
NOT RECOMMENDED

¶

TABLE 1. Acute lethality in rats exposed to cyclohexyl isocyanate

Conc. (ppm)	Duration	Lethality	Clinical and necropsy findings	Reference
17.79	6 hrs	1/3 on day 7	irritation, lacrimation, dypsnea; inflammation in lungs, congestion of kidney and liver	Eastman Kodak Co. 1990, 1992
53.2	6 hrs	2/3 during exposure; 1/3 on day 12	as above plus salivation, gasping	Eastman Kodak Co. 1990, 1992
1017	6 hrs	3/3 after 4 hours	as above, more severe	Eastman Kodak Co. 1990, 1992
1401	1-2.5 hrs	6/6	irritation; hemorrhage in lungs	Mobay Corp. 1990a

¶

¶

TABLE 2. Acute lethality in rats exposed to saturated cyclohexyl isocyanate

Conc. (ppm)	Duration	Lethality	Clinical and necropsy findings	Reference
saturated	2 hrs	8/8	none stated	Mobay Corp. 1990b
saturated	3 min	0/10	irritation; dark spots on lungs	Mobay Corp. 1990c
saturated	10 min	10/10 within 11 days	respiratory problems; enlarged lungs with red spots, fluid, lobulated liver	Mobay Corp. 1990c
saturated	1 hr	10/10 during exposure	as above	Mobay Corp. 1990c

¶

DATA DEFICIENCIES

- No data with the appropriate endpoints were found.
- No human data were found.
- Lethality studies in rats:
  - Lacked concentration-response information;
  - Deaths occurred at all concentrations;
  - Nominal not analytical concentrations;
  - Lacked method details.

AEGL values for cyclohexyl isocyanate

Class.	10-min	30-min	1-hr	4-hr	8-hr
AEGL-1	NR	NR	NR	NR	NR
AEGL-2	NR	NR	NR	NR	NR
AEGL-3	NR	NR	NR	NR	NR

Chemical: BORON TRIFLUORIDE **CAS Reg. No.:** 7637-07-2

Action: Proposed_____ **Interim**_____ **Other** REVISE AEGLs based on COT comments and new data

Chemical Manager: G. RUSCH **Staff Scientist:** C. TROXEL

NAC Member	AEGL1	AEGL2	AEGL3	LOA	NAC Member	AEGL1	AEGL2	AEGL3	LOA
Steven Barbee	Y	Y	Y		Nancy Kim	Y	Y	Y	
Lynn Beasley	A	A	A		Glenn Leach	A	A	A	
Robert Benson	Y	Y	Y		John Morawetz	A	A	A	
Jonathan Borak	Y	Y	Y		Richard Niemeier	Y	Y	Y	
William Bress	Y	Y	Y		Marinelle Payton	A	A	A	
George Cushmac	Y	Y	Y		Susan Ripple	Y	Y	Y	
Ernest Falke	A	A	A		George Rodgers	Y	Y	Y	
Alfred Feldt	Y	Y	Y		Marc Ruijten	Y	Y	Y	
John Hinz	Y	Y	Y		George Rusch, Chair	P	P	A*	
Jim Holler	A	A	A		Richard Thomas	Y	Y	Y	
Tom Hornshaw	Y	Y	Y		George Woodall	Y	Y	Y	
Warren Jederberg	A	A	A						
					TALLY				
					PASS/ FAIL	15/15	15/15	15/15	

*P = ABSTAIN

(mg/m^3)

PPM, (mg/m^3)	10 Min	30 Min	1 Hr	4 Hr	8 Hr
AEGL 1	,(2.5)	,(2.5)	,(2.5)	,(2.5)	,(2.5)
AEGL 2	,(47)	,(47)	,(37)	,(24)	,(12)
AEGL 3	,(140)	,(140)	,(110)	,(72)	,(36)
LOA					
* = ≥10% LEL					
** = ≥ 50% LEL					
*** = ≥100% LEL					

*Safety considerations against the hazard(s) of explosion(s) must be taken into account.
** and ***Extreme safety considerations against the hazard(s) of explosion(s) must be taken into account.

NR= Not Recommended due to_____

AEGL 1 Motion by: RUIJTEN **Second by:** NIEMEIER
AEGL 2 Motion by: ~~BOB BENSON~~ BARBEE **Second by:** G. WOODALL THOMAS
AEGL 3 Motion by: BOB BENSON **Second by:** N. KIM
LOA Motion by:_____ **Second by:**_____

Approved by Chair: [signature] **DFO:** [signature] **Date:** 9/28/05

Chemical: KETENE **CAS Reg. No.:** 463-51-4

Action: Proposed ✓ **Interim**_____ **Other**_____

Chemical Manager: [redacted] **Staff Scientist:**

NAC Member	AEGL1	AEGL2	AEGL3	LOA
Steven Barbee	Y	P	P	
Lynn Beasley	Y	Y	Y	
Robert Benson	Y	Y	Y	
Jonathan Borak	P	P	P	
William Bress	Y	Y	Y	
George Cushmac	Y	Y	Y	
Ernest Falke	Absent			
Alfred Feldt	Y	Y	Y	
John Hinz	P	P	P	
Jim Holler	Absent			
Tom Hornshaw	Y	P	P	
Warren Jederberg	Absent			

NAC Member	AEGL1	AEGL 2	AEGL3	LOA
Nancy Kim	N	N	N	
Glenn Leach	Absent			
John Morawetz	Absent			
Richard Niemeier	Y	Y	Y	
Marinelle Payton	Absent			
Susan Ripple	Y	Y	Y	
George Rodgers	P	P	P	
Marc Ruijten	Y	Y	Y	
George Rusch, Chair	Y	Y	Y	
Richard Thomas	Y	Y	Y	
George Woodall	Y	P	P	
TALLY				
PASS/ FAIL				

PPM, (mg/m^3)	10 Min	30 Min	1 Hr	4 Hr	8 Hr
AEGL 1	, (0.24 ppm)	, (0.24 ppm)	, (0.19 ppm)	, (0.12 ppm)	, (0.083 ppm)
AEGL 2	, (0.83 ppm)	, (0.83 ppm)	, (0.66 ppm)	, (0.42 ppm)	, (0.23 ppm)
AEGL 3	, (2.5 ppm)	, (2.5 ppm)	, (2.0 ppm)	, (1.2 ppm)	, (0.68 ppm)
LOA					
* = ≥10% LEL					
** = ≥ 50% LEL					
*** = ≥100% LEL					

*Safety considerations against the hazard(s) of explosion(s) must be taken into account.
** and ***Extreme safety considerations against the hazard(s) of explosion(s) must be taken into account.

NR= Not Recommended due to_____

AEGL 1 Motion by: [redacted] Robert Benson **Second by:** Marc Ruijten
AEGL 2 Motion by: Robert Benson **Second by:** Marc Ruijten
AEGL 3 Motion by: Robert Benson **Second by:** Marc Ruijten.
LOA Motion by:_____ **Second by:**_____

Approved by Chair: [signature] **DFO:** [signature] **Date:** 9/28/05

Chemical: ARSENIC TRIOXIDE **CAS Reg. No.:** 1327-53-3

Action: Proposed ✓ **Interim**_____ **Other**_____

Chemical Manager: **Staff Scientist:**

NAC Member	AEGL1	AEGL2	AEGL3	LOA
Steven Barbee	Y	A	Y	
Lynn Beasley	Y	Y	Y	
Robert Benson	Y	Y	Y	
Jonathan Borak	A	A	A	
William Bress	Y	Y	Y	
George Cushmac	A	Y	Y	
Ernest Falke	A	A	Y	
Alfred Feldt	Y	Y	Y	
John Hinz	A	A	A	
Jim Holler	A	A	A	
Tom Hornshaw	Y	Y	Y	
Warren Jederberg	A	A	A	

NAC Member	AEGL1	AEGL 2	AEGL3	LOA
Nancy Kim	Y	Y	Y	
Glenn Leach	Y	Y	Y	
John Morawetz	Y	Y	Y	
Richard Niemeier	Y	Y	Y	
Marinelle Payton	A	A	A	
Susan Ripple	Y	Y	Y	
George Rodgers	Y	Y	Y	
Marc Ruijten	Y	Y	Y	
George Rusch, Chair	Y	Y	Y	
Richard Thomas	Y	Y	Y	
George Woodall	Y	Y	Y	
TALLY	16/16	16/16	16/16	
PASS/ FAIL	Pass	Pass	Pass	

PPM, (mg/m³)	10 Min	30 Min	1 Hr	4 Hr	8 Hr
AEGL 1	,(NR)	,(NR)	,(NR)	,( )	,( )
AEGL 2	,(3.7)	,(3.7)	,(3.0)	,(1.9)	,(1.2)
AEGL 3	,(11)	,(11)	,(9.1)	,(5.7)	,(3.7)
LOA					
* = ≥10% LEL					
** = ≥ 50% LEL					
*** = ≥100% LEL					

*Safety considerations against the hazard(s) of explosion(s) must be taken into account.
** and ***Extreme safety considerations against the hazard(s) of explosion(s) must be taken into account.

NR= Not Recommended due to Insufficient data

AEGL 1 Motion by: Benson **Second by:** Ruijten
AEGL 2 Motion by: Ruijten **Second by:** Niemeier
AEGL 3 Motion by: Marc Ruijten **Second by:** Bob Benson
LOA Motion by:_____ **Second by:**_____

Approved by Chair: [signature] **DFO:** Paul S Tobin **Date:** 9/29/05

Chemical: CYCLOHEXYL ISOCYANATE **CAS Reg. No.:** 3173-53-3

Action: Proposed ✓ **Interim** _____ **Other** _____

Chemical Manager: MARC RUIJTEN **Staff Scientist:**

NAC Member	AEGL1	AEGL2		AEGL3	LOA
Steven Barbee	P	A	P	P	
Lynn Beasley	Y	Y	Y	Y	
Robert Benson	Y	N	Y	Y	
Jonathan Borak	A	A	A	A	
William Bress	Y	N	Y	Y	
George Cushmac	Y	N	Y	Y	
Ernest Falke	A	A	A	A	
Alfred Feldt	P	P	Y	P	
John Hinz	A	A	A	A	
Jim Holler	A	A	A	A	
Tom Hornshaw	Y	N	Y	Y	
Warren Jederberg	A	A	A	A	

NAC Member	AEGL1	AEGL2		AEGL3	LOA
Nancy Kim	Y	N	Y	Y	
Glenn Leach	Y	N	Y	Y	
John Morawetz	Y	N	Y	Y	
Richard Niemeier	Y	Y	N	Y	
Marinelle Payton	A	A	A	A	
Susan Ripple	Y	P	Y	Y	
George Rodgers	Y	N	N	Y	
Marc Ruijten	Y	N	Y	Y	
George Rusch, Chair	Y	N	Y	Y	
Richard Thomas	Y	N	Y	Y	
George Woodall	Y	Y	N	Y	
TALLY					
PASS/ FAIL	15/15	13/16		13/15	

PPM, (mg/m³)	10 Min	30 Min	1 Hr	4 Hr	8 Hr
AEGL 1	,(NR)	,(NR)	,(NR)	,(NR)	,(NR)
AEGL 2 ** 2nd batch	~~,(0.23)~~ NR	NR ~~,(0.03)~~	NR ~~(0.02)~~	NR ~~,(0.01)~~	NR ~~(0.01)~~ NR
AEGL 3 *	,(0.14)	,(0.14)	,(0.11)	,(0.072)	,(0.047)
LOA					
* = ≥10% LEL					
** = ≥ 50% LEL					
*** = ≥100% LEL					

*Safety considerations against the hazard(s) of explosion(s) must be taken into account.
** and ***Extreme safety considerations against the hazard(s) of explosion(s) must be taken into account.

NR= Not Recommended due to Lack of Data

AEGL 1 Motion by: Niemeier **Second by:** Woodall
AEGL 2 Motion by: Niemeier **Second by:** Woodall
AEGL 3 Motion by: Benson **Second by:** Woodall
LOA Motion by: _____ **Second by:** _____

Approved by Chair: _____ **DFO:** _____ **Date:** 9/29/05

ATTACHMENT 1

National Advisory Committee for Acute Exposure Guideline Levels for Hazardous Substances

NAC/AEGL-38
September 28-30, 2005

U.S. Department of Labor
Rooms 3437 A, B, & C
200 Constitution Ave., N.W.
Washington, DC 20210

Metro: Judiciary Square (Red Line)

AGENDA

Wednesday, September 28, 2005

10:00 a..m.	Introductory remarks and approval of NAC/AEGL-37 Highlights (George Rusch, Ernie Falke, and Paul Tobin)
10:30	Summary of COT Subcommittee Meeting (George Rusch)
11:00	Human Studies Issues (Iris Camacho)
11:30	Uncertainty Factor Database (Richard Williams)
12:00 p.m.	RD_{50} Methodology Update (Peter Bos)
12:30	Lunch
1:30	Review of Ketene (Jim Holler/Peter Bos)
3:30	Break
3:45	Revisit of Boron Trifluoride- New Data (George Rusch/Claudia Troxel)
5:30	Adjourn for the day

Thursday, September 29, 2005

8:30 a.m.	Review of Selected Chloroformates- Allyl chloroformate, Diphosgene, Ethyl Chloroformate, Ethyl chlorothioformate, Isobutyl chloroformate, Isopropyl chloroformate, Methyl chloroformate, n-Butyl chloroformate, Propyl chloroformate, sec-Butyl chloroformate (Ernie Falke/Cheryl Bast)
10:30	Break
10:45	Review of Selected Chloroformates (continued)
12:00 p.m.	Lunch
1:00	Review of Arsenic Trioxide (Richard Thomas/Johan Schefferlie)
3:00	Break
3:15	Revisit of Jet Fuels- Response to COT Comments (John Hinz/Sylvia Talmage)
4:30	Review of Cyclohexyl Isocyanate (Marc Ruijten/Carol Wood)
5:30	Adjourn for the day

Friday, September 30, 2005

8:00 a.m.	Unresolved Issues
10:00	Break
10:15	Unresolved Issues (continued)
11:10	Administrative matters
12:00 noon	Adjourn meeting

NAC/AEGL Meeting 38: September 28-30, 2005

Attendance 9/28/05 - 9/30/05

ATTACHMENT 2

Chemical: **CAS Reg. No.:**

Action: Proposed_____ **Interim**_____ **Other**_____

Chemical Manager: **Staff Scientist:**

NAC Member	AEGL1 (9/28)	AEGL2 (9/29)	AEGL3	LOA
Steven Barbee	✓	✓		
Lynn Beasley	✓	✓		
Robert Benson	✓	✓		
Jonathan Borak	✓	X		
William Bress	✓	✓		
George Cushmac	✓	✓		
Ernest Falke	✓	✓		
Alfred Feldt	✓	✓		
John Hinz	✓	✓		
Jim Holler	X	X		
Tom Hornshaw	✓	✓		
Warren Jederberg	X	X		
PETER BOS	✓	✓		
J. SCHEFFERLE	✓	✓		
Roland Rossbacher	✓	✓		

NAC Member	AEGL1	AEGL 2	AEGL3	LOA
Nancy Kim	✓	✓		
Glenn Leach	✓	✓		
John Morawetz	X	✓		
Richard Niemeier	✓	✓		
Marinelle Payton	X	X		
Susan Ripple	✓	✓		
George Rodgers	✓	✓		
Marc Ruijten	✓	✓		
George Rusch, Chair	✓	✓		
Richard Thomas	✓	✓		
George Woodall	✓	✓		
ALAN BECKER	✓	✓		
DIETER HEINZ	✓	✓		
CHERYL BAST & TALMAGE TALLY	✓	✓		
PASS/ FAIL				

PPM, (mg/m^3)	10 Min	30 Min	1 Hr	4 Hr	8 Hr
AEGL 1	, ( )	, ( )	, ( )	, ( )	, ( )
AEGL 2	, ( )	, ( )	, ( )	, ( )	, ( )
AEGL 3	, ( )	, ( )	, ( )	, ( )	, ( )
LOA					
* = ≥10% LEL					
** = ≥ 50% LEL					
*** = ≥100% LEL					

*Safety considerations against the hazard(s) of explosion(s) must be taken into account.
** and ***Extreme safety considerations against the hazard(s) of explosion(s) must be taken into account.

NR= Not Recommended due to_____

AEGL 1 **Motion by:** _____ **Second by:** _____
AEGL 2 **Motion by:** _____ **Second by:** _____
AEGL 3 **Motion by:** _____ **Second by:** _____
LOA **Motion by:** _____ **Second by:** _____

Approved by Chair: _____ **DFO:** _____ **Date:** _____

FY 2006 EPA Appropriations Act

On August 2, 2005, the President signed into law the Department of Interior, Environment, and Related Agencies Appropriations Act, 2006, Pub. L. No. 109-54 (Appropriations Act). Section 201 of the Appropriations Act includes the following provision:

None of the funds made available by this Act may be used by the Administrator of the Environmental Protection Agency to accept, consider or rely on third-party intentional dosing human toxicity studies for pesticides, or to conduct intentional dosing human toxicity studies for pesticides until the Administrator issues a final rulemaking on this subject. The Administrator shall allow for a period of not less than 90 days for public comment on the Agency's proposed rule before issuing a final rule. Such rule shall not permit the use of pregnant women, infants or children as subjects; shall be consistent with the principles proposed in the 2004 report of the National Academy of Sciences on intentional human dosing and the principles of the Nuremberg Code with respect to human experimentation; and shall establish an independent Human Subjects Review Board. The final rule shall be issued no later than 180 days after enactment of this Act.

Protections for Subjects in Human Research

[Federal Register: September 12, 2005 (Volume 70, Number 175)]
[Proposed Rules]
[Page 53837-53866]
From the Federal Register Online via GPO Access [wais.access.gpo.gov]
[DOCID:fr12se05-11]
[[Page 53838]]

ENVIRONMENTAL PROTECTION AGENCY
40 CFR Part 26
[OPP-2003-0132; FRL-7728-2]
RIN 2070-AD57

Protections for Subjects in Human Research

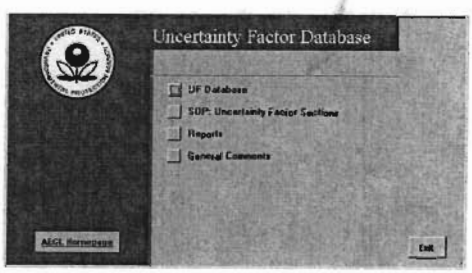
AGENCY: Environmental Protection Agency (EPA).
ACTION: Proposed rule.

SUMMARY: EPA proposes and invites public comment on a rulemaking to ban intentional dosing human testing for pesticides when the subjects are pregnant women or children, to formalize and further strengthen existing protections for subjects in human research conducted or supported by EPA, and to extend new protections to adult subjects in intentional dosing human studies for pesticides conducted by others who intend to submit the research to EPA. This proposal, the first of several possible Agency actions, focuses on third-party intentional dosing human studies for pesticides, but invites public comment on alternative approaches with broader scope.

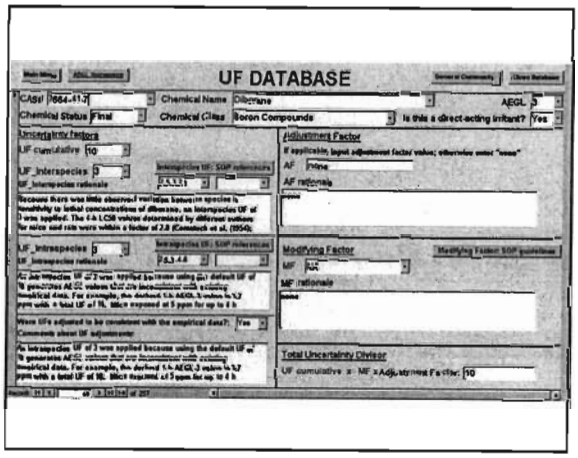
AEGL Uncertainty Factor Database

Richard Williams IV
Environmental Careers Organization
NAC/AEGL Meeting 38
Washington, D.C.
September 28-30, 2005

Uncertainty Factor Database



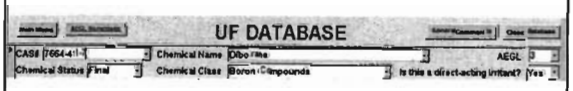
Outline of Presentation



AEGL Uncertainty Factor Database

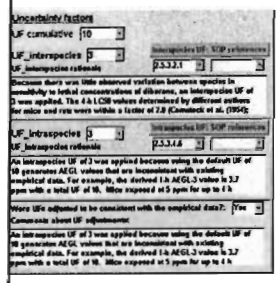
- Purpose
  - To store and categorize AEGL uncertainty data and the rationales for their derivation
- Applications
  - Analyze trends in the application of AEGL uncertainty values
  - Evaluate processes and rationales in assigning uncertainty values
  - Develop more standardized and consistent approaches for similar scenarios

Database Components



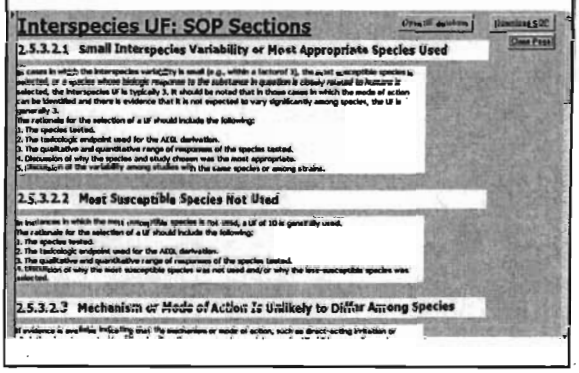
- Chemical Data
  - Name and CAS number
  - Chemical Class (47)
    - Ex. Acid Halides, Alcohols, Aldehydes, Aluminum Compounds, Amides, Amines, Anilines, Antimony Compounds, Arsenic Compounds, Boron Compounds etc...
  - Chemical Status
  - AEGL level
  - Direct-acting irritancy

Database Components



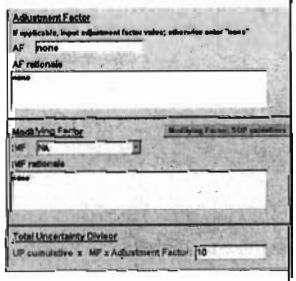
- Uncertainty Factors
  - Interspecies and Intraspecies
    - Values and rationales
    - SOP references
  - Uncertainty factor adjustments
    - Comments

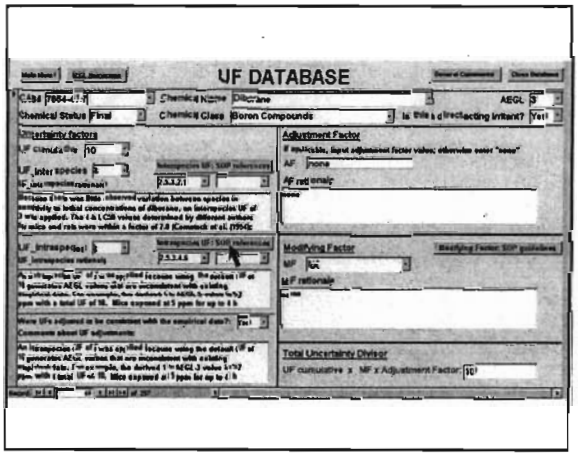
Database Components



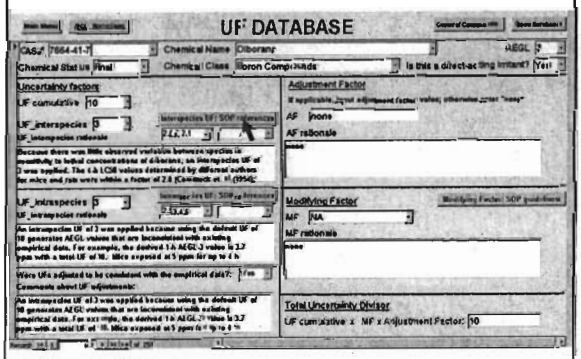
Database Components

- Adjustment Factor
  - Selection is based upon a weight-of-evidence approach
  - Value and rationale
- Modifying Factor
  - Value and rationale
- Total Uncertainty Divisor
  - UF cumulative x MF x AF

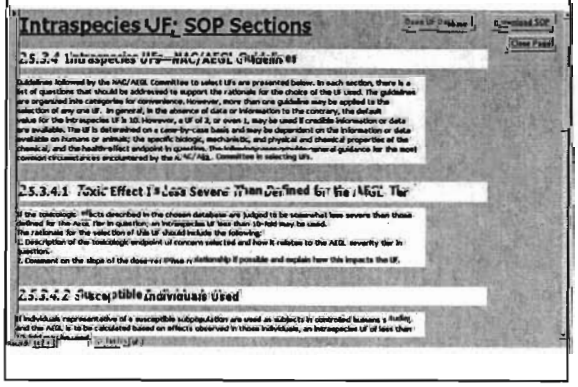




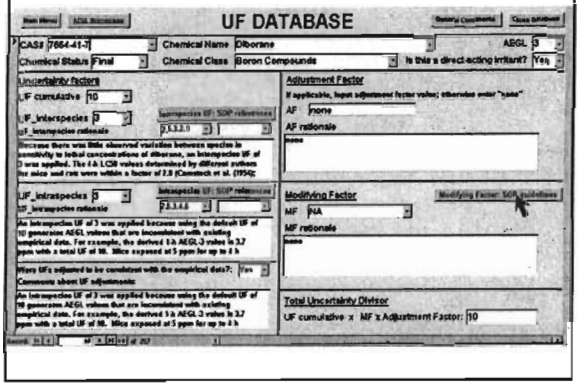
Database Components



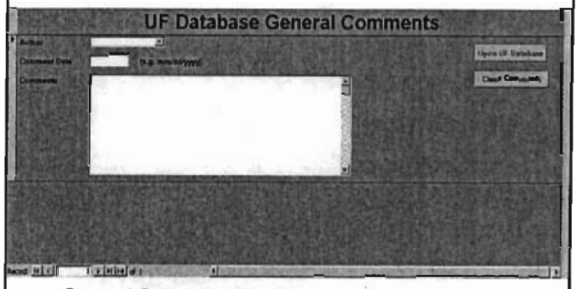
Database Components



Database Components

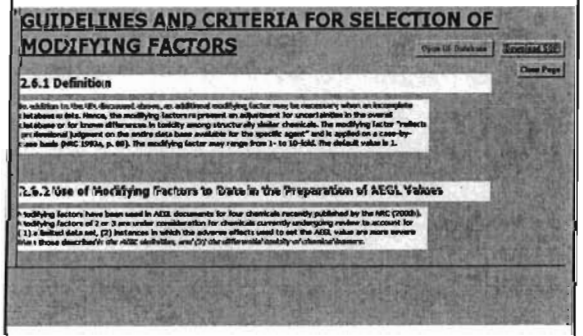


Database Components



- General Comments Form
  - Accessible from the UF Database Form
  - Author, Date, and Comment Fields

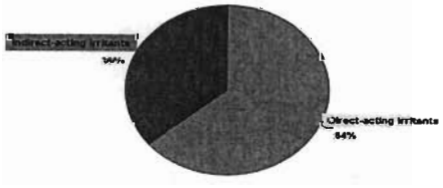
Database Components

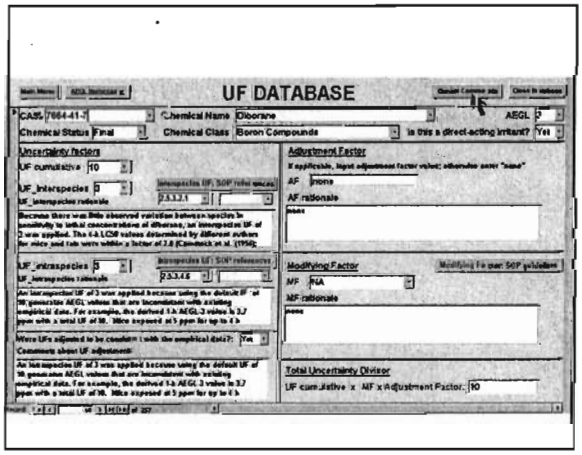


Sample Analysis Derived from AEGL Uncertainty Data

- 18% (47 / 257) of Final and Interim AEGLs have modifying factors
  - 64% (30 / 47) of AEGLs with modifying factors are classified as direct-acting irritants

AEGLs with Modifying Factors by Mechanism of Irritancy



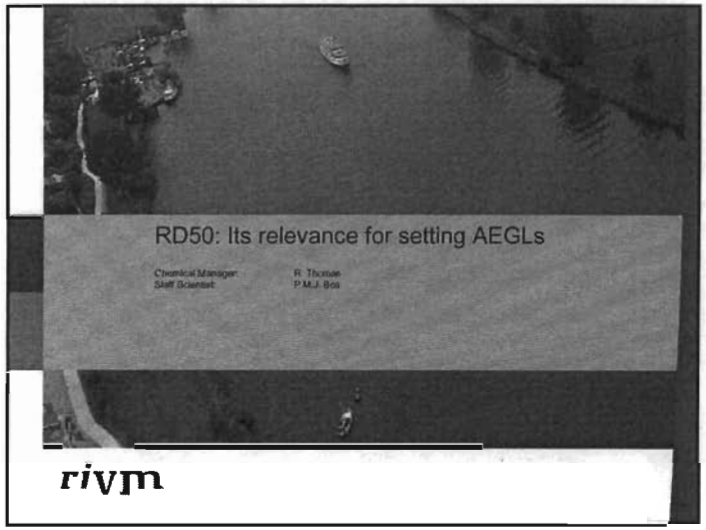


Further Applications and Analyses

- Examination of the uncertainty factor assignment for direct-acting chemical irritants, and solvents/CNS depressants
  - How often does existing empirical data require the reduction of the total UF to obtain reasonable AEGL values?
  - Does the database support the use of a generic approach?
- Analysis of uncertainty value assignment by chemical class classification

Acknowledgements

- AEGL Staff
  - Dr. Iris Camacho
  - Dr. Ernest Falke
  - Ms. Sharon Frazier
  - Dr. Marquea King
  - Dr. Paul Tobin
- NAC/AEGL Committee



RD50: Historical overview

- Developed in the 1960s by Dr. Yves Alarie for the US Department of Defense
  - Potency testing of nerve gases
- First published in 1966
  - "The method presented in this article permits the recognition of sensory irritation at concentration levels where cellular damage cannot be detected and thus represents a more sensitive means of revealing potentially irritating chemicals."

rivm

RD50: Historical overview

- Detailed review of sensory irritation by Alarie in 1973
  - Sensory irritant
  - Pulmonary irritant
  - Bronchoconstrictor agent
  - Respiratory irritant
- Official ASTM method in 1984 (ASTM E 981)
  - Updated in 2004
- Up-to-date review by Alarie in 2000
  - Fully computerized system
    - Reproducible data analyses according to defined criteria
    - Distinction between different kind of responses
      - Sensory irritation, pulmonary irritation, airway constriction
    - Determination of Limit of detection (*Just Detectable Effect: JDE*)
    - Predictive equations for irritating potencies for non-reactive VOCs
      - based on physical-chemical properties

rivm

RD50: Methodology

- Stimulation of free nerve endings
  - Direct stimulation of (trigeminal, vagal, or glossopharyngeal) nerve endings or smooth muscle
  - Indirect through (reversible) pathological changes like tissue inflammation
- Sensory irritation
  - Reversible change in breathing pattern
- Stimulation of the trigeminal nerve causing a characteristic pause following inspiration resulting in a delayed expiration

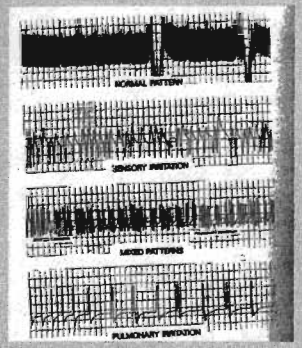
rivm

RD50: Methodology

- Groups of mice are head-only exposed to a geometric series of concentrations
- RD50: The concentration inducing a 50% decrease in respiratory frequency, is used to determine the potency of a chemical
- Distinction between different kind of responses
  - Sensory irritation, pulmonary irritation, airway constriction or some combinations

rivm

RD50: Methodology – breathing patterns



Obtained from Alarie et al., 2000

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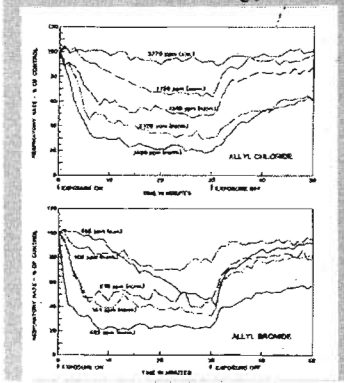
RD50: Methodology – time-response curve



Obtained from Nielsen and Bakbo, 1985

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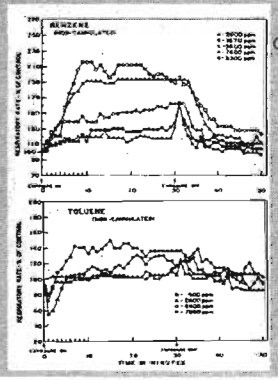
RD50: Methodology – time-response curve



Obtained from Nielsen and Alarie, 1982

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RD50: Methodology – log concentration-response curve

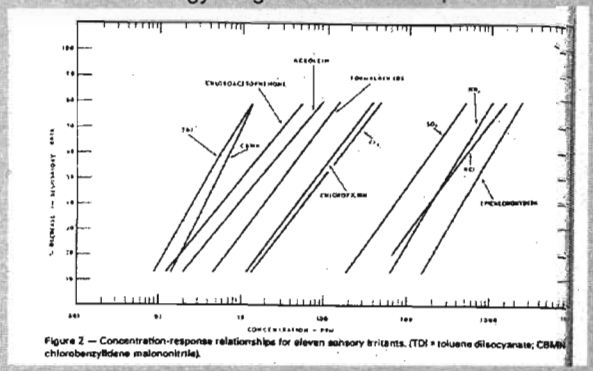

Figure 2 — Concentration-response relationships for eleven sensory irritants. (TDI = toluene diisocyanate; CBMN = chlorobenzylidene malononitrile).

Obtained from Kane et al., 1979

RD50: Predictive power

- Human equivalent
  - A burning or stinging sensation in eyes, nose, or throat
- Validation of the bioassay (qualitative)
  - Chemicals found to be a positive sensory irritant in male SW mice will be positive in human at a similar exposure concentration. A chemical found to be a non-sensory irritant will be negative in humans (Alarie, 1966; 1973).
- Calibration of the bioassay (quantitative)
  - High correlation of RD50 with 0.03*TLV (R^2=0.78; 89 chemicals)
    - E.g. Kane et al. (1979); Schaper, 1993)

RD50: Previous review *(Bos et al., 1992)*

- Concluding remarks:
  - Plateau response is not reached for every substance
  - Toxic effects may occur and interfere at the RD50 concentration
  - Large differences between strains and species (response characteristics)
  - Interlaboratory differences (response characteristics)
- Reproducibility
  - Differences in calculated RD50 values
  - Characteristics of time-response curve and log concentration-response curve

RD50: Previous review *(Bos et al., 1992)*

- Time-response
  - Graphical presentation of time-concentration-response necessary
  - Fast response (< 1 min) versus hours
    - Take into account in time-extrapolation from 10-min to 8-hours?
  - Fading of response
    - Sometimes increase in respiratory frequency Critical evaluation of the sensory irritation test for setting OELs
    - Verification of interfering factors and toxicity
- Recommendations
  - Time-response and log concentration response curves should be available
- Some recommendations have been met by computerized system

RD50: Use in AEGL-setting

- Hydrogen chlorine
  - 10-min AEGL-2: 1/3*RD50
- Jet propellant fuel-8
  - AEGL-1: 0.1*RD50; all time points
- Chloroformates
  - AEGL-1: 0.001* RD50; all time points
    - (0.01*RD50 would conflict with AEGL-2)

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RD50: To use or not to use in AEGL-setting

- Extrapolation of RD50 to human equivalent
  - Pungency versus odor
- Where does the animal bioassay find its place in the toxicity profile?
  - Where can the RD50 be placed on a gliding scale of increasing toxicity?
- Use of RD50 bioassay for AEGL-setting
  - AEGL-1 (nasal pungency) or AEGL-2 (severe eye irritation, lacrimation)

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RD50: Chemosensory effects

- Chemosensory stimulation
  - Odorous (olfactory stimulation)
  - Irritating (trigeminal stimulation)
- Stimulation of the olfactory system often occurs at concentrations well below that at which they will elicit trigeminal activation
  - Olfactory stimulation intermingles with sensory irritation in humans
    - Example of acetone (odor detection threshold: 20-400 ppm; threshold for sensory irritation between 10,000-40,000 ppm (Arts et al., 2003))
  - Distinction between olfactory and trigeminal stimulation necessary
    - Subjective versus objective responses

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RD50: Extrapolation to humans

- Human equivalent
  - A burning or stinging sensation in eyes, nose, or throat
  - Odor often a confounding factor in subjective measurements of sensory irritation in humans (e.g. acetone)
- Odor is not an endpoint in AEGL-setting
- Objective detection of sensory irritation
  - Use of anosmics and normosmics
  - Lateralization techniques
  - Measuring eye irritation along with olfactory stimulation
  - Recording of chemosensory potentials

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RD50: Validation for extrapolation to humans

- Alarie (1966, 1973)
  - 51 substances tested
  - 1-min exposure of mice to C^nt of (10 and) 40 min*mg/m^3
  - Humans exposed to C^nt between 5 and 80 (1 and 50) min*mg/m^3
  - Animal response: decrease in respiratory rate with characteristic pause at 40 min*mg/m^3
  - Human subjective response: eye, throat, skin, nose, or chest burning, conjunctivitis, lacrimation, coughing, gagging

- Comments
  - No details available on human study (e.g. on exposure conditions)
  - Olfactory stimulation is unknown but will have interfered
  - Very short exposures to a limited range of concentrations
    - "nonirritating" chemicals may induce irritation at higher concentrations

RD50: Calibration for extrapolation to humans

Table. Proposed relationship of RD_{50} concentrations and expected effect in humans (Kane et al, 1979)

Concentration	Expected response in humans
10 * RD_{50}	Possibly lethal
RD_{50}	Intolerable sensory irritation
0.1 * RD_{50}	Some sensory irritation
0.03 * RD_{50}	Suggested TLV, minor sensory irritation if any
0.01 * RD_{50}	No sensory irritation
0.001 * RD_{50}	No effect of any kind

*Proposal: 0.3*RD50 can serve as basis for an Emergency Exposure Limit (EEL)*

RD50: Calibration for extrapolation to humans

- Introduction of "steps of 10":
  - Based on the suggestion by Frazer (1953) that, from a pharmacological point of view, the general ratio of ineffective, effective, toxic, and lethal dosage in man is generally not greater than 1:10:100:1000
  - This suggestion is a theoretical assumption and has no valid scientific basis

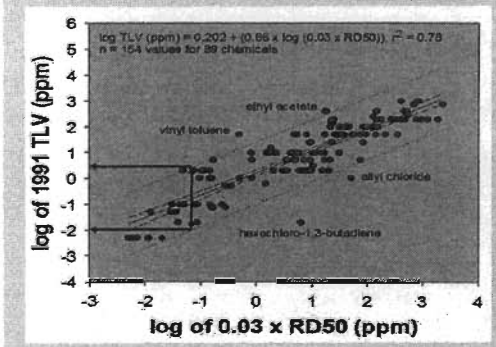
- Tested against data for 11 irritants
  - (acrolein, ammonia, chlorine, chloroacetophenone, CBMN, chloropicrin, epichlorohydrin, formaldehyde, hydrogen chloride, sulfur dioxide, TDI)
  - Overall reasonable agreement as to "steps of 10", variation present
  - At 0.001*RD50 no data for 8/11 chemicals
  - At 0.01*RD50 no data for 3/11 chemicals; no effects for 1 chemical; odor for 1 chemical
  - At 10*RD50 predominantly animal data and case studies
  - Human data: odor as confounding factor

RD50: Comparison with TLV

- Correlation with "human" TLVs is basis for quantitative validity of RD50 (calibration)

- Remarks:
  - Most TLVs based on irritation
  - 1990-1991TLVs
    - Approximately 25% based on analogy
    - Approximately 20% based on worker experience (generally old data)
    - Approximately 20% based on animal data (incl. repeated and oral data)
    - Approximately 5% based on Nelson data (1943)
    - Odor stimulation interferes in human data
    - TLV's have different levels of protection

RD50: Comparison with TLV



Obtained from Alarie et al., 2000

RD50: Comparison with TLV

- Correlation is not equal to association
- Many TLVs not based on adequate human data
- 0.03 * TLV is "best estimate" but variation by 2-3 orders of magnitude
  - AEGLs are predictive rather than protecting thresholds
- Additional "calibration" with human data is needed

RD50: Pungency thresholds (*Cometto-Muniz and coworkers*)

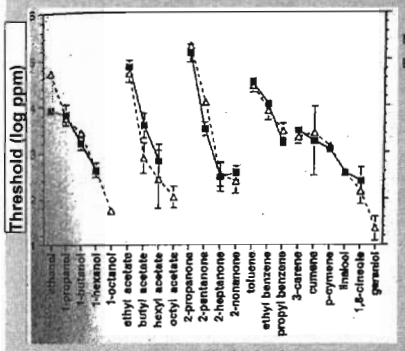
- Several series of homologous compounds
  - Acetates, alcohols, alkyl benzenes, aldehydes, ketones
- Odor thresholds
- Eye irritation in normosmics
- Nasal pungency thresholds (NPT) in anosmics

- Drawback: indirect concentration measurements
  - Absolute values are probably not accurate
  - Thresholds can be used in a relative sense

RD50: Comparison with NPT

- Good agreement of eye irritation in normosmics and NPT in anosmics
  - both effects reflect trigeminus stimulation
- Nasal Pungency Thresholds often are orders of magnitudes higher than odor thresholds
  - trigeminus versus olfactory stimulation

RD50: NPT versus eye irritation thresholds



NPT: filled squares, continuous lines
Eye irritation: triangles, broken lines

Obtained from Cometto-Muniz, 2000

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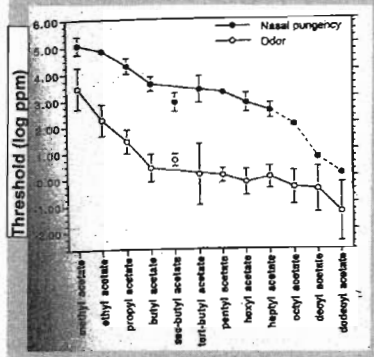
RD50: NPT versus odor thresholds: acetates



NPT: filled circles
Odor thresholds: empty circles

Obtained from Cometto-Muniz, 2000

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RD50: Comparison with NPT for acetates

Chemical	RD50 (ppm)	0.03 * RD50 (ppm)	Pungency threshold (ppm)
methyl acetate	830	25	112,358
ethyl acetate	580	17	67,272
propyl acetate	795	24	17,565
butyl acetate	730	22	3648
pentyl acetate	1565	47	1648
hexyl acetate	740	22	635

Pungency thresholds from Cometto-Muniz and coworkers

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RD50: Comparison with NPT for alcohols

Chemical	RD50 (ppm)	0.03 * RD50 (ppm)	Pungency threshold (ppm)
methanol	41,514	1245	35,000
ethanol	27,314	819	9000
n-propanol	12,704	381	2500
2-propanol	17,693	531	18,135
n-butanol	4784	144	1100
n-pentanol	4039	121	1700
n-hexanol	239	7	400
n-heptanol	98,4	3	210
n-octanol	47,2	1	70

Pungency thresholds from Cometto-Muniz and coworkers

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RD50: NPT for alkyl benzenes and aldehydes

Chemical	RD50 (ppm)	0.03 * RD50 (ppm)	Pungency threshold (ppm)
Alkyl benzenes			
toluene	5300	159	29,574
ethyl benzene	4060	122	10100
propyl benzene	1530	46	1487
butyl benzene	710	21	No NPT
hexyl benzene	125	4	No NPT
Aldehydes			
butanal	1015	30	*60,000*
pentanal	1121	34	*40,000*
hexanal	1029	31	*6000*
heptanal			*1700*
octanal			No NPT

Pungency thresholds from Cometto-Muniz and coworkers

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RD50: Comparison with NPTs

- Comparison of RD50 in mice and NPT in anosmics
  - Differences in duration and type of exposures
  - Absolute values for NPT do not match with "steps of 10" for sensory irritation based on mice, but are inaccurate
  - Pattern of NPTs over a homologous series of substances do not match with the pattern of RD50 values
- Data available (despite drawbacks) point to difficulties in direct extrapolation of RD50s to humans
  - Thresholds for eye irritation comparable with NPT but much higher than odor thresholds
  - Additional information is needed

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RD50: Its place in a toxicity profile

- Can sensory irritation be placed on a gliding scale of increasing toxicity in a general way?
- No relation was found between the sensory irritation potential as measured by the mouse bioassay and local tissue damage (histopathological changes) in the respiratory tract after single or repeated exposure *(Bos et al., 2002)*

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RD50: Its place in a toxicity profile

Comparison with mortality data

Chemical	RD_{50} ppm	Mortality	Species	LC_{50} (time) ppm	Species
Epichlorohydrin	687		mouse	369 (6-h) 820 (4-h)	rat mouse
Acetone	23,000 77,000		mouse	32,000 (4-h) 21,100 (8-h)	rat rat
*Chloroformates**					
Methyl	52.4	1/4 at 50 ppm	mouse	88 (1-h)	rat
Ethyl	77.5	3/4 at 100 ppm	mouse	145 (1-h)	rat
Propyl	83.5	1/4 at 50 ppm	mouse	410 (1-h)	rat
Isopropyl	104	1/4 at 50 ppm	mouse	300 (1-h)	rat
	375	2/4 at 283 ppm	mouse		
Isobutyl	97	No deaths	mouse		

** AEGL-1 was calculated by 0.001*RD50 rather than 0.01*RD50 because of conflict with AEGL-2 (1/3*AEGL-3)*

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RD50: Conclusions

- Extrapolation to a human equivalent needs further attention
  - Direct extrapolation to a human pungency threshold with a fixed factor is not recommended
  - Interference with odorous stimulation should always be taken into account
  - Quantitative comparison of RD50 values with adequate human data is urgently recommended, but these data have not been found (yet)
- Use of RD50 in AEGL-setting
  - Overly conservative approach will lead to conflicting AEGLs and/or too low action levels
  - Definition of a "sensory irritant" within AEGL-setting is needed
  - RD50 at the lower end of the toxicity profile
  - No interference with histopathological changes
  - No severe toxicity at concentrations below or comparable to the RD50
- Sensory irritation: AEGL-1 or AEGL-2?

BORON TRIFLUORIDE:DIMETHYL ETHER

- One of several complexes formed with boron trifluoride for ease of handling BF_3. Ether complexes consist of 1:1 molar ratio of BF_3 and the dimethyl or diethyl ether; can dissociate under proper temperature/ pressure conditions.

- Only one study addressed toxicity of BF_3:dimethyl ether - only nominal concentrations.

- Because complex can dissociate to form BF_3, the AEGL derivations are based upon this one chemical species alone.

ATTACHMENT 6

BORON TRIFLUORIDE (BF_3)

- Colorless gas - pungent suffocating odor

- Gas is stable in dry air, but immediately forms dense white cloud when exposed to moist air; upon exposure to even low levels of moisture in air, BF_3 reacts to form dihydrate, BF_3:$2H_20$. BF_3 dihydrate is strongly corrosive to the eyes and skin

- Excellent catalyst; has fire retardant and antioxidant properties, nuclear applications, and insecticidal properties

Toxicity Data:

- Human: odor detection
- Animal: acute toxicity data available in dogs, rats, mice, and guinea pigs, but exposure conc. generally expressed as nominal conc.

Effects of exposure in animals:

- short-term exposures - pulmonary irritation
- repeated exposures - pulmonary irritation and/or renal toxicity

Summary of AEGL Values for Boron Trifluoride (mg/m^3)					
Level	**10-min**	**30-min**	**1-hr**	**4-hr**	**8-hr**
AEGL-1	0.6	0.6	0.6	0.6	0.6
AEGL-2	21	21	16	10	6.8
AEGL-3	49	49	39	25	12

- **AEGL-1:** Value representing a no-effect level for irritancy following an acute exposure; exposures were in rats to 6 mg/m^3 for 6h/d, 5 d/wk, for 13 wk (Rusch et al., 1986; Hoffman and Rusch, 1982a)
  - UF=10; values set equal across time

- **AEGL-2:** Signs of irritation and renal toxicity (resulting in death) following exposure to 180 mg/m^3 for 6 h/d for 5 days (Rusch et al., 1986; Hoffman and Rusch, 1982b)
  - MF of 2: not known if rats had renal effects after single exposure; UF=10; default n=1,3

- **AEGL-3:** Calculated 4-hr LC_{01} in male and female rats of 736 mg/m^3 (Rusch et al., 1986; Hoffman, 1981)
  - UF=30; default n=1,3

Major Comments from COT:

AEGL-1

It is too much of a "stretch" to base < 1-day values (i.e., AEGL-1s) on effects (lacrimation) seen during the 2nd week of daily exposures. The steepness of the dose-response curve for renal toxicity is not relevant to, and thus not predictive of a dose-response curve for direct irritation. Moreover, most signs of direct irritation/respiratory distress on exposure day 5 in Table 3 (page 7) are not concentration-dependent. There are no data presented in this document that are suitable for calculating AEGL-1 values. Therefore, AEGL-1 values should not be determined at the present time.

AEGL-2

The rationale and calculation of AEGL-2s should be redone. It is not scientifically-defensible to assume that a single exposure to BTF will cause nephrotoxicity that is twice as severe (it is recommended in lines 29 & 30 that a modifying factor of 2 be used) as that produced by more than 5 consecutive days of inhalation of 180 mg/m^3. The NOAEL of 66 mg/m^3 in the study by Rusch et al. (1986) far exceeds the calculated 4- and 8-hour AEGL-2s of 10 mg/m^3 and 6.8 mg/m^3, respectively. In the absence of data applicable to AEGL-2 derivation, it is recommended that: (a) the NOAEL of 66 mg/m^3 be used as the basis for calculating AEGL-2 values; and (b) that the need for additional research to provide applicable data be emphasized.

AEGL-3

Page 24, lines 20 - 23: The degree of interspecies variability in LC_{50} values in Table 5 (page 15) is difficult to discern, due to the reporting of most exposures in nominal concentrations. It is clear, however, that guinea pigs are exquisitely sensitive. Rats appear to be more sensitive than mice to BTF lethality, but the mice data are quite limited. As guinea pigs are an atypical species, it is recommended that: (a) the 4-hour LC_{50} (1,200 mg/m^3) of Rusch et al. (1986) be utilized as the basis for calculating AEGL-3s; and (b) an interspecies uncertainty factor of 5 rather than 10 be employed.

TOXICITY DATA

- Human: no relevant data

- Animal - only three studies reporting measured concentrations: Bowden et al., 2005 (new); Rusch et al., 1986; Torkelson et al., 1961. These studies measured the exposure concentration and compared them to nominal concentration; found actual concentration ranged from 2.7-56% of nominal. Therefore, studies using nominal concentrations should not be used.

NEW - Bowden et al., 2005: Exposures to BF_3 dihydrate vapor/aerosol

ACUTE:

Groups of 10, SD rats/sex exposed for 4 hours to 0, 8.53, 24.6, or 74.4 mg/m^3

- No exposure-related effects on clinical signs during or after exposure, body weights, water consumption (visual inspection), gross necropsy findings, or liver and kidney weights
- Microscopic findings in 74.4 mg/m^3 group:

24 hours post exposure:

Larynx: Ventral cartilage necrosis: minimal to slight (4/5 ♂; 4/5 ♀, none affected in other groups)
Anterior ventral hemorrhage: 2/5 ♂
Ventral epithelial hyperplasia: ↑severity
Ventral inflammatory cell infiltration: ↑severity

2 weeks post exposure:

Larynx: Ventral cartilage necrosis: minimal in 1/5♂; moderate in 1/5♀

Conclusion: 74.4 mg/m^3 for 4 hours represents a concentration producing histological effects but no overt signs of irritation - AEGL-1

Rusch et al. 1986: Exposures to BF_3 dihydrate aerosol

ACUTE:

- Groups of 5, F344 rats/sex exposed for 4 hours to 0, 1010, 1220, 1320, or 1540 mg/m^3
- Clinical signs during and/or after exposure:
  ↓ activity, closed eyes, excessive lacrimation, oral/nasal discharge, gasping, moist/dry rales
- Wt loss; followed by wt gain by 14 days post exp.
- Red discoloration of lungs in several animals from all exposure groups
- Mortality:

Conc.	Mortality	Day of death
0	0/10	-
1010	3/10	0, 3, 6
1220	2/10	0, 3
1320	8/10	1,1,2,3,3,3,4,5
1540	9/10	0,0,0,1,2,3,4,5,5

- 4-hr LC_{50}: 1200 mg/m^3
- 4-hour LC_{01} (probit): 736 mg/m^3
- BMC_{01}: 1050 mg/m^3
- $BMCL_{05}$: 721 mg/m^3

Conclusion: 4-hr $BMCL_{05}$ of 721 mg/m^3 is selected for the POD for the AEGL-3; Use of this study is supported by Kasparov and Kiry (1972) study, which reported a 4-hr LC_{50} of 1180 mg/m^3 in rats

2-WEEK STUDY:

- Groups of 5 F344 rats/sex exposed for 6 h/d, 5 d/wk for 2 wk, to 0, 24, 66, or 180 mg/m^3
- Clinical signs during and/or after exposure:
  oral/nasal discharge, lacrimation, dry/moist rales, gasping, ano-genital staining, poor condition
- All 10 high-conc. rats died by 6^{th} exposure
- Wt loss in all exp. male groups and mid-and high-conc. females; followed by wt gain by 14 d post exp.
- Concentration-related ↑ lung wt.
- At 180 mg/m^3, necrosis and pyknosis of proximal tubular epithelium in kidneys
- 66 mg/m^3 is the no-effect level

SUBCHRONIC (13 -weeks):

- Groups of 20 F344 rats/sex exposed for 6 h/d, 5 d/wk for 13 wk, to 0, 2, 6, or 17 mg/m^3
- Clinical signs during and/or after exposure:
  ↑ dried red material around nose and mouth, lacrimation, and dry rales (mostly high-conc. grp)
- One high-conc. male rat died at wk 12
- No changes in body wt, ophthalmological findings, hematology analysis, organ wt, gross necropsy
- Concentration-related ↑ in fluoride levels in femurs
- Toxic renal tubular necrosis seen in high-conc. male rat with ↑ BUN levels and male rat that died early

Torkelson et al., 1961

4 mg/m^3 for 7 h/d, 5 d/wk for 127-128 exp.: No effects (appearance, bw, organ wts, gross necropsy)

- Rats 12/sex: areas of pneumonitis (slight), peribronchiole round cell infiltration, congestion
- Guinea pigs 10 /sex: slight pnuemonitis
- Rabbits 3/sex: no effects

8-11 mg/m^3 for 7 h/d, 5 d/wk for 29-33 exp:

- Rats- 5 Fe; exposed 33 times; normal in appearance and growth, ↑ fluoride in bones and teeth
- Guinea pigs- 10 M; exposed 29 times: 4 died - deaths accompanied by asthmatic attack; 6 survivors exhibited breathing difficulty

35 mg/m^3 (nominal) for 7 h/d for 42-60 exposures:

- Rats- 14 Fe; exposed 45 or 60 times; 1 rat died but cause undetermined; survivors: no effects on appearance or organ wt, chemical irritation of lungs - pnuemonitis
- Guinea pigs - 10 M; exposed 42-45 times; 7 died from respiratory failure or asphyxiation after 19th exp - ↑ lung wts, pneumonitis

New AEGL-1 Derivation

Key study: Bowden, 2005

Effects:
Histological signs of irritation at 74.4 mg/m^3; NOAEL for notable irritation because no overt clinical signs of irritation accompanying the histological findings

Uncertainty factors: 30
Interspecies UF: default of 10
Intraspecies UF: 3 because irritation is a direct contact effect and is not expected to vary greatly among individuals

Time scaling: Value set equal to all time periods

AEGL-1 Values for BF_3 (mg/m^3) [given in mg/m^3 because BF_3 gas becomes aerosol upon contact with moist air]				
10-min	**30-min**	**1-hr**	**4-hr**	**8-hr**
2.5	**2.5**	**2.5**	**2.5**	**2.5**

"New" AEGL-3 Derivation

Key study: Rusch et al., 1986

Effects:

4-hr LC_{01}: $BMCL_{05}$ of 721 mg/m^3

Uncertainty factors: 30

Interspecies UF: 10 - species differences exist in sensitivity to BF_3, with the guinea pig being the most sensitive to lethality (COT recommends 5)

Intraspecies UF: 3 - based on steep dose-response curve; primary effect is irritation

Time scaling: Default: n = 1 or 3; 10-min value set equal to 30-min (4-h exposure)

AEGL-3 Values for BF_3 (mg/m^3) [given in mg/m^3 because BF_3 gas becomes aerosol upon contact with moist air]					
POD; UF	**10-min**	**30-min**	**1-hr**	**4-hr**	**8-hr**
721; 10	**140**	**140**	**110**	**72**	**36**
721; 15 ***(COT)***	**96**	**96**	**76**	**48**	**38**
721; 30	**48**	**48**	**38**	**24**	**12**

- Rusch et al. (1986) study (4-hr LC_{50} of 1200 mg/m^3) supported by Kasparov and Kiry (1972) study (4-hr LC_{50} of 1180 mg/m^3)

AEGL-2 Derivation

AEGL-3 levels ÷ 3 to obtain an estimate of AEGL-2

- Data meeting definition of AEGL-2 endpoint not available
- Dose-response curve for lethality was steep (Rusch et al, 1986)

AEGL-2 Values for BF_3 (mg/m^3) [given in mg/m^3 because BF_3 gas becomes aerosol upon contact with moist air]					
POD; UF; ÷3	**10-min**	**30-min**	**1-hr**	**4-hr**	**8-hr**
721; 10	**47**	**47**	**37**	**24**	**12**
721; 15	**32**	**32**	**25**	**16**	**13**
721; 30	**16**	**16**	**13**	**8**	**4**

Note: 2-week repeated-exposure study (6 hr/d, 5 d/wk) in rats reported NOAEL of 66 mg/m^3 (Rusch et al., 1986).

Summary of AEGL Values for BF_3 (mg/m^3)						
Level	**UF**	**10-min**	**30-min**	**1-hr**	**4-hr**	**8-hr**
AEGL-1		2.5	2.5	2.5	2.5	2.5
AEGL-2	10	47	47	37	24	12
AEGL-3	10	140	140	110	72	36
AEGL-2	30	16	16	13	8	4
AEGL-3	30	48	48	38	24	12

Note on time scaling: When viewing the toxicity data in terms of $mg/m^3 \bullet hr$, it appears that n > 3; therefore, using the default n value of n=3 for scaling from longer to shorter durations is reasonable. The n=1 is still used to extrapolate from shorter to longer durations to err on the conservative side.

TABLE 6. Summary of Acute Lethal Inhalation Data in Laboratory Animals

Concentration mg/m^3	Exposure Duration	$mg/m^3 \bullet hr$	Effect	Reference
Rat				
1100*?	1 h	1100	LC_{50} in male rats	Vernot et al., 1977
1000*?	1 h	1000	LC_{50} in female rats	
1200	4 h	4800	LC_{50} in male and female rats	Rusch et al., 1986
1180*?	4 h	4720	LC_{50}	Kasparov and Kiry, 1972
3900*	4 h	15,600	2/2 rats died; one 148 minutes into exposure, the other within 24 hours of exposure	DuPont Co., 1948
2100*	5.5 h	11,550	1/10 rats died	Stokinger and Spiegl, 1953
Mouse				
3460*?	2 h	6920	LC_{50}	Kasparov and Kiry, 1972
2100*	5.5 h	11,550	1/10 mice died	Stokinger and Spiegl, 1953
Guinea pig				
2760*	5 min	230	2/2 guinea pigs died	DuPont Co., 1948
720*	3 h	2160	1/2 guinea pigs died	
109*?	4 h	436	LC_{50}	Kasparov and Kiry, 1972
2100*	5.5 h	11,550	10/10 died	Stokinger and Spiegl, 1953
970*	1.4 h	1358	7/10 died	
370*	10.9 h	4033	1/10 died	

* nominal concentration

*? Not known if nominal or measured concentrations

TABLE 7. Summary of Nonlethal Inhalation Data in Laboratory Animals [a]				
Concentration mg/m³	**Duration**	**mg/m³•hr [b]**	**Effect**	**Reference**
Dog				
1380-2760*	30 min		1 dog; gagged, wheezed, spit up frothy mucous during exposure; recovered after exposure	DuPont Company, 1948
	2 h		1 dog; similar clinical signs, necropsy 48 hours post exposure revealed edema of the larynx, emphysema in lungs, exudate in bronchi, renal capsular spaces and convoluted tubules distended with fluid	
Rat				
2760*	1 h	2760	2/2 rats survived; pulmonary congestion	DuPont Company, 1948
720*	3 h	2160	no clinical signs, no gross or microscopic changes	
370*	10.9 h	4033	10/10 rats survived	Stokinger and Spiegl, 1953
24	6 h/d, 5 d/wk for 2 wk		10/10 animals from each group survived, clinical signs included oral and nasal discharge, lacrimation, dry and moist rales, gasping, poor condition; increased lung weights	Rusch et al., 1986
66			10/10 survived; same clinical signs; decreased body weights; increased lung weights	
35*	7 h/d, 5 d/wk, up to 60 exp.		14 rats; no changes in appearance or organ weights; gross/ microscopic changes in lungs - pneumonitis	Torkelson et al., 1961
8-11	7 h/d, 5 d/wk, for 33 exp.		5 rats; no changes in appearance of body weights	
4	7 h/d, 5 d/wk, for 127-128 exp.		12 male, 12 female rats; no changes in appearance, body or organ weights, or gross necropsy findings	
Mouse				
370*	10.9 h	4033	10/10 mice survived	Stokinger and Spiegl, 1953
Guinea pig				
4	7 h/d, 5 d/wk, for 127-128 exp.		10 males, 10 females; no changes in appearance, body or organ weights, slightly increased incidence of pneumonitis	Torkelson et al., 1961
Rabbit				
4	7 h/d, 5 d/wk, for 127-128 exp.		3 male, 3 female rabbits; no changes in appearance, body or organ weights, or gross or microscopic findings	Torkelson et al., 1961

[a] Some repeated exposure studies are included in the table if the data were deemed relevant

[b] The concentrations in the repeated-exposure studies are not converted to mg/m³•hr.

* nominal concentration

JP-8: Summary of Response to Comments from National Research Committee
National Advisory Committee Meeting, September 28-30, 2005
John Hinz, Chemical Manager; Sylvia Talmage, Staff Scientist

1. Delete discussions/references to JP-4
These discussions have been either shortened or eliminated.

2. Justify interspecies uncertainty factor (UF) of 1
The justification for the interspecies UF of 1 has been rewritten. The basis for the interspecies UF of 1 is the higher respiratory rate and cardiac output in rodents relative to body weight (compared with humans), which results in more rapid uptake and higher blood concentrations (higher systemic dose) of the hydrocarbon components of jet fuel. Furthermore, the blood:air partition coefficient for several hydrocarbon components of jet fuel is higher in rodents than in humans (Gargas et al., Toxicol. Appl. Pharmacol. 98: 87-99, 1989). Metabolism may be faster in rodents than in humans, but the rapid metabolism is expected to be offset by the higher uptake.

The NRC has approved an interspecies UF of 1 for several other chemicals including fluorine, hydrogen fluoride, HFE-7100 (methyl nonafluorobutyl and nonafluoroisobutyl ethers), HFC-134a (1,1,1,2-tetrafluoroethane), and HCFC-141b (1,1-dichloro-1-fluoroethane). The NRC has suggested an interspecies UF of 1 for toluene based on the empirical data involving higher blood concentrations in rodents than in humans under the same exposure conditions. The same is true for methyl ethyl ketone, and 1,1,1-trichloroethane.

3. Explain the use of Alarie's 10-fold reduction factor.
The 10-fold reduction factor of Alarie et al. (1981) essentially includes a 3-fold factor for both intraspecies and interspecies variability.
The explanation for use of the Alarie reduction factor has been rewritten and supported with the extensive review of Schaper (Am. Ind. Hyg. Assoc. J. 54:488-544, 1993). Schaper (1993) shows that for 95 chemicals for which information was available, the ACGIH Threshold Limit Values (TLV) correlate with 0.03 x the RD_{50}. The smaller, 10-fold, reduction factor used for the AEGL-1 correlates with slight irritation which meets the definition of the AEGL-1.

4. Immune response to JP-8 and aerosols
The TSD focused on vapor exposure (with an aerosol component at high concentrations) because vapor is the probable exposure scenario for communities.
The immune studies were discussed, but not considered because (1) they used aerosols and (2) there is controversy concerning the analytical measurements in these studies. As reported in ACGIH (2003), "these publications do not provide adequate information to permit a judgment of aerosol size and stability nor do they speak to the extent to which the sampling systems distinguished between aerosol and vapor" (ACGIH 2003; Frank 2004).
Aerosols can and often do act more like particulate matter (Goetz 1961, Int. J. Air Water Pollut 4:168-184), thus initiating a greater response than vapor alone.

5. Discuss PBPK models... and lack of time-scaling for AEGL-2

The TSD notes that models for single and multiple components of fuels have been developed. The interactions of the multiple chemicals of fuels are complex and not fully understood. Depending on lipophilicity among other factors, the individual components are taken up at varying rates. At this time, the models are in a preliminary stage and are not useful for either setting AEGL values or time-scaling them.

The 30-minute clinical study of Astrand et al. (1975) was used as an example of rapid approach to steady-state in the blood for several chemical components common to Stoddard Solvent and jet fuels (*n*-decane). At steady-state, we have used the same value across time for solvents.

6. The AEGL-2 (1100 mg/m^3) may be too high

When the 1100 mg/m^3 value is converted to ppm for any individual component of JP-8, the values are quite low.

Examples:

avg. m.w. of JP-8 (167): 1100 mg/m^3 = 160 ppm

dodecane, undecane, nonane (the primary components): 1100 mg/m^3 = 158, 172, 210 ppm

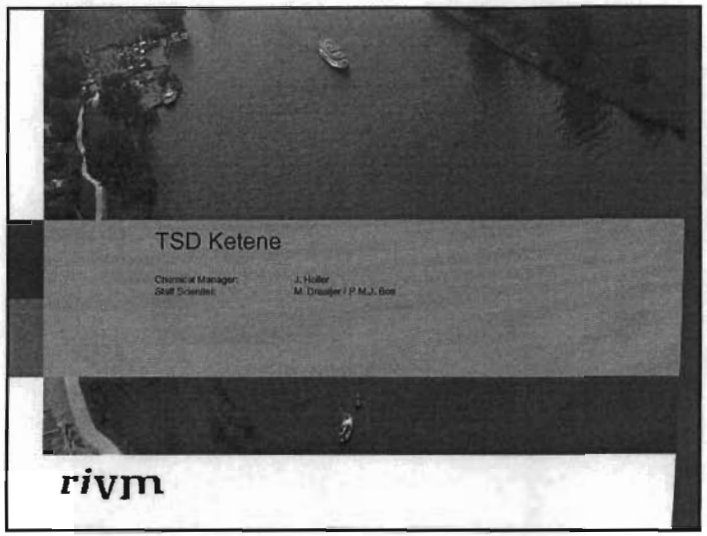
toluene: 1100 mg/m^3 = ~300 ppm (the interim AEGL-2 ranges from 990 to 510 ppm)

Many of the identified aliphatic hydrocarbons are of low toxicity.

n-nonane: 4-hour LC_{50} = 3200 ppm (mouse)

no change in respiratory rate of mouse: 1000-1500 ppm (5246-7869 mg/m^3)

For JP-8, we failed to identify a lethal concentration. Concentrations of 3430 mg/m^3 or 4440 mg/m^3 for 4 hours were not lethal. Dividing by 3 (an alternate way to set the AEGL-2) yields values close to 1100 mg/m^3.



Ketene: use and Physical-chemical properties

- Use: Acetylating agent in chemical synthesis
- Physical-chemical properties
  - Molecular weight: 42.04
  - Colorless gas
  - Water solubility: no
  - Boiling point: -56°C
  - Odor: penetrating
  - Flammability: no data

rivm 2

Ketene: available data

- No human data available
- Four animal studies available
  - Treon et al. 1949
    - Single and repeated exposures; several animal species
  - Wooster et al. 1947
    - Single 10-min exposures; several animal species
  - Cameron and Neuberger 1937
    - Single 5-min (several species) and 20-min exposures (mice)
  - Mendenhall and Stokinger 1959
    - Single 10-min exposures; mice

rivm 3

Ketene: animal experiments

- Treon et al. (1949)
  - Single 10-min exposures
    - ketene of high purity
    - static conditions, nominal concentrations
    - monkeys, cats, rabbits, guinea pigs, rats, mice (n=2-10/20)
  - Repeated exposures
    - ketene of high purity
    - dynamic conditions, nominal concentrations
    - monkeys, cats, rabbits, guinea pigs, rats, mice (n=1-10)
    - daily exposures range from 1 ppm (7 h) to 50 ppm (50 min)
    - general description of toxicity

rivm 4

Ketene: animal experiments

- Wooster et al. (1947)
  - Single 10-min exposures
    - purity unknown
    - cats, rabbits, guinea pigs, rats, mice (n=2-20/24)
    - calculated concentrations (70 – 815 ppm)
    - up to 15 days of observation
- Cameron and Neuberger (1937)
  - Single 5-min exposures (mice also 20-min)
    - co-exposure to methane (equivalent concentrations)
    - guinea pigs, rats, mice (n not given)
    - concentration range reported (100 – 2000 ppm)
- Mendenhall and Stokinger (1959)
  - Single 10-min exposures
    - tolerance test (ketene/ozone)
    - mixture (42% ketene, 42% methane, 16% other gases)
    - mice (actual concentrations: 1.1 ppm and higher)

rivm

5

Ketene: toxicity profile

- Toxicity profile comparable for all species tested
  - Sneezing, coughing, nasal discharge, eye irritation, labored breathing, lethargy, death
  - Greatest toxicity in mice, followed by rats, guinea pigs, cats and rabbits
- Steep concentration-response and time-response relation
- Main effects on lung and CNS
- CNS effects possibly due to cerebral anoxia secondary to severe alveolar damage
- Mortality due to respiratory failure

rivm

6

Ketene: toxicity profile

- Developmental / reproductive toxicity
  - No data available
- Genotoxicity
  - No data available
- Carcinogenicity
  - No data available
- Kinetics
  - No data available

rivm

7

Ketene: animal experiments

- Mendenhall and Stokinger (1959)
  - Single 10-min exposures
    - 5.0 ppm: highest concentration without mortality
    - 18.4 ppm: lowest concentration with 100% mortality
- Cameron and Neuberger (1937)
  - Single 5-min exposures (mice also 20-min)
    - only 100% mortality at all exposures
- Wooster et al. (1947)
  - Single 10-min exposures
    - cats, rabbits, guinea pigs, rats, mice (n=2-20/24)
    - calculated concentrations (70 – 815 ppm)

rivm

8

Ketene: Wooster et al. (1947)

Concentration (ppm)	Mortality	Time of death or observation period
Cats	(n=1-2)	
233	0/1	15 d
367	1/2	8-12 h
623	2/2	26 min and 8-12 h
815	1/1	135 min
Rabbits	(n=2)	
652	0/2	10 d
Guinea pigs	(n=2-4)	
367	2/4	8-12 h
	3/4	3 d
623	4/4	8-12 h
652	2/2	8-12 h
Rats	(n=4)	
122	0/4	10 d
250	4/4	150 min
774	4/4	135 min
Mice	(n=20-24)	
70	0/20	115 min
	20/20	240 min
122	16/20	180 min
	18/20	3 d
192	20/20	115 min
349	11/20	55 min
	20/20	80 min
815	24/24	60 min

rivm

Ketene: Treon et al. (1949)

Table: Acute Lethal Inhalation Data (dynamic exposure)

Concentration (ppm)	Intended exposure (time/d)	(d)	Mortality	Time of death
Mice			(n=7-10)	
50	50 min	1	10/10	0-94 min (7); 5.25-8.25 h (3)
53	100 min	1	10/10	0-92 min (10)
23	30 min	1	7/10	1.85-4.2 h (5); 7 and 16 h (2)
23	120 min	1	10/10	1.85-6.35 h (10)
23	4 h	2	10/10	during 1st exposure (3); less than 7 h after 1st exposure (7)
12	4.5-6 h	15	4/7	during 2nd exposure (3); during 7th exposure (1)
1	7 h	14	1/10	3 days after 10th exposure (1)
1	7 h	55	1/10	1 day after 49th exposure (1)

rivm

Ketene: AEGL-1

- Treon et al (1949): critical study
  - Other studies supporting for brief (10-min) exposures
  - Mice are most susceptible
  - Drawbacks: nominal concentrations and general description of toxicity
- No effects at 7-h exposure to 1 ppm
- Severe lung effects at 4.5-h exposure to 12 ppm cannot be ruled out

rivm

Ketene: AEGL-1

- Treon et al.(1949): point of departure
  - No effects at 7-h exposure to 1 ppm
  - Interspecies factor of 3 (mice: most susceptible species)
  - Intraspecies factor of 3 (mode of action: direct action at port of entry)
  - Total UF= 10
  - Default values of n
    - n=1 for extrapolation to 480 min
    - n=3 for extrapolation to 30 min – 240 min
    - 10-min AEGL-1 = 30-min AEGL-1

rivm

Ketene: AEGL-1

AEGL-1 Values for Ketene				
10-minute	30-minute	1-hour	4-hour	8-hour
0.24 ppm (0.41 mg/m³)	0.24 ppm (0.41 mg/m³)	0.19 ppm (0.33 mg/m³)	0.12 ppm (0.21 mg/m³)	0.088 ppm (0.15 mg/m³)

rivm

Ketene: AEGL-2

- Treon et al.(1949): point of departure
  - No effects at 7-h exposure to 1 ppm
  - No deaths in single 4.5 h exposure to 12 ppm
    - (3/7 deaths on second day during exposure)
  - Mortality preceded by severe lung damage, hence lung damage cannot be ruled out at 12 ppm (AEGL-2 effect)
  - No appropriate NOAEL for this effect
    - (NOAEL somewhere between 1 and 12 ppm)
  - Steep concentration-response curve:
    - AEGL-2 = AEGL-3/3
  - AEGL-2 levels are mid between AEGL-1 and AEGL-3

rivm

Ketene: AEGL-3

- Treon et al.(1949): point of departure
  - Mice most susceptible species
  - 100% mortality at 50-min exposure to 50 ppm
  - 7/10 deaths at 30-min exposure to 23 ppm
  - 100% mortality at 2-hour exposure to 23 ppm
  - No mortality in single 4.5 h exposure to 12 ppm
    - (3/7 deaths on second day during exposure)
- Point of departure: 4.5-h exposure to 12 ppm

rivm

Ketene: AEGL-3

- Treon et al. (1949)
  - Total UF= 10 (similar to AEGL-1)
  - Default values of n
    - n=1 for extrapolation to 480 min
    - n=3 for extrapolation to 30 min – 240 min
    - 10-min AEGL-1 = 30-min AEGL-1

AEGL-3 Values for Ketene				
10-minute	30-minute	1-hour	4-hour	8-hour
2.5 ppm (4.3 mg/m³)	2.5 ppm (4.3 mg/m³)	2.0 ppm (3.4 mg/m³)	1.2 ppm (2.1 mg/m³)	0.68 ppm (1.17 mg/m³)

rivm

Ketene: Summary of AEGL-values

Summary of AEGL Values					
	Exposure Duration				
Classification	10-minute	30-minute	1-hour	4-hour	8-hour
AEGL-1 (Nondisabling)	0.24 ppm	0.24 ppm	0.19 ppm	0.12 ppm	0.046 ppm
AEGL-2 (Disabling)	0.83 ppm	0.83 ppm	0.66 ppm	0.42 ppm	0.23 ppm
AEGL-3 (Lethal)	2.5 ppm	2.5 ppm	2.0 ppm	1.2 ppm	0.68 ppm

rivm

17

ATTACHMENT 9

ACUTE EXPOSURE GUIDELINE LEVELS (AEGLs) FOR SELECTED CHLOROFORMATES

NAC/AEGL-38
September 28-30, 2005

ORNL Staff Scientist: Cheryl Bast

Chemical Manager: Ernest Falke

Chemical Reviewers: Lynn Beasley and Paul Tobin

- Hydrolyze in water or moist air to produce the parent hydroxy compound, hydrogen chloride, carbon dioxide, and a carbonate.
- All title chloroformates are direct-acting contact irritants, and are corrosive to the eyes, skin, gastrointestinal and respiratory tracts.

  Ethyl chlorothioformate may cause both portal of entry and systemic effects. These systemic effects are likely due to the ability of the thio moiety to interact with other biomolecules.

  Myocardial degeneration, nephrosis, hepatic necrosis, adrenal necrosis, spleen and lymph node necrosis, and lymphoid cell depletion noted in rats
- Values derived for six chloroformates
- In all cases the inter- and intra- species uncertainty factors were 3 and 3, respectively.
- In 2 cases a modifying factor was used for limited data and the possibility of systemic effects.
- Where an AEGL-2 was calculated it was determined by dividing the AEGL-3 by 3.

  Justified by steep concentration-response curve (SOP Section 2.2.2.3)

CHEMICAL	AEGL-1 POD	AEGL-2 POD	AEGL-3 POD	1-hr Rat LC_{50} Data Available *POD	COMMENTS
Methyl chloroformate	RD_{50}/1000	1/3 AEGL-3	1/3 LC_{50}	Analytical *Male- 88 ppm (Vernot et al., 1977) Male- 92-123 ppm (Fisher et al., 1981) Female- 103 ppm (Vernot et al., 1977) Female- 100 ppm (Fisher et al., 1981) Nominal 163 ppm (Bio-Test, 1975)	
Ethyl chloroformate	RD_{50}/1000	1/3 AEGL-3	1/3 LC_{50}	Analytical *Male- 145 ppm (Vernot et al., 1977) Male- 189 ppm (Fisher et al., 1981) Female- 170 ppm (Vernot et al., 1977) Female- 200 ppm (Fisher et al., 1981)	
Propyl chloroformate	RD_{50}/1000	1/3 AEGL-3	$BMCL_{05}$	Nominal 410 ppm (Bio-Test, 1970) *($BMCL_{05}$ = 216 ppm)	MF=3 for limited data
Isopropyl chloroformate	RD_{50}/1000	1/3 AEGL-3	1/3 LC_{50}	Nominal 300 ppm (Bio-Test, 1970)	No MF- support from repeat-exposure data
Allyl chloroformate	NR	1/3 AEGL-3	$BMCL_{05}$	Analytical 65.1 ppm (Stillmeadow, 1987) *($BMCL_{05}$ = 21 ppm)	No MF- analytical concentration
n-Butyl chloroformate	NR	NR	NR		
Isobutyl chloroformate	NR	NR	NR		
sec-Butyl chloroformate	NR	NR	NR		
Diphosgene	NR	NR	NR		
				4-Hour POD	
Ethyl chlorothio-formate	NR	1/3 AEGL-3	$BMCL_{05}$	Analytical Male- 51 ppm (Stauffer, 1983) Female- 41 ppm (Stauffer, 1983) *($BMCL_{05}$ = 21 ppm)	MF=3 for systemic effects of thio moiety

AEGL-1 VALUES: METHYL CHLOROFORMATE				
10 minute	30 minute	1 hour	4 hour	8 hour
0.052 ppm	0.052 ppm	0.052 ppm	0.052 ppm	0.052 ppm

Species: Male Swiss-Webster Mouse
Concentration: 52.4 ppm (RD_{50})
Endpoint: Predicted no effect of any kind on the respiratory system
Reference: Carpenter, 1982

Rationale: The RD_{50} multiplied by 0.1 corresponds to "some sensory irritation".

The RD_{50} value multiplied by 0.01 corresponds to "no sensory irritation"

The RD_{50} value multiplied by 0.001 corresponds to "no effect of any kind on the respiratory system" Alarie (1981)

The multiplier of 0.001, rather than 0.01, was chosen because use of 0.01 would yield AEGL-1 values greater than AEGL-2 values at the longer time points and because 1/4 mice died at a concentration of 50 ppm (Carpenter, 1982).

Time Scaling: Value held constant across the 10- and 30-minute, and 1-, 4-, and 8-hour exposure times because mild irritancy generally does not vary greatly over time, and because it is not expected that prolonged exposure will result in an enhanced effect.

AEGL-2 VALUES: METHYL CHLOROFORMATE				
10 minute	30 minute	1 hour	4 hour	8 hour
1.8 ppm	1.2 ppm	0.97 ppm	0.24 ppm	0.12 ppm

Endpoint: ⅓ The AEGL-3 values

Endpoint is justified based on the steep concentration-response curve:

1-hr rat LC_{50} is approximately 100 ppm
Rats exposed to 26 ppm for 1-hr were clinically-normal (Fisher et al., 1981)

Support: Values are considered protective because rats showed no effect when exposed to 0.38 ppm repeatedly (6 hours/day, 5 days/week for 4 weeks), and showed only laryngeal lesions when exposed to 1.01 ppm for 6 hours/day, 5 days/week for 4 weeks (BASF, 1993).

AEGL-3 VALUES: METHYL CHLOROFORMATE				
10 minute	30 minute	1 hour	4 hour	8 hour
5.3 ppm	3.7 ppm	2.9 ppm	0.73 ppm	0.37 ppm

Species: Rat (10 males/group)
Concentration: 29 ppm
Time: 1-hour
Endpoint: Estimated lethality threshold: ⅓ of the most conservative 1-hr LC_{50} value in rats (88 ppm x ⅓ =29 ppm)
Reference: Vernot et al., 1977

Time Scaling: $C^n \times t = k$, where $n = 3$ for the 10- and 30-minute time periods, and $n = 1$ for the 4- and 8-hour time periods, to provide AEGL values that would be protective of human health (NRC, 2001).

Uncertainty Factors:

Interspecies = 3 Intraspecies = 3

Highly reactive and clinical signs are likely caused by a direct chemical effect on the tissues; this type of portal-of-entry effect is not expected to vary greatly between species or among individuals.

Support: POD supported by the fact that no deaths were observed in rats exposed to 26 ppm for 1 hour (Fisher et al., 1981).

Derived values are considered protective because:

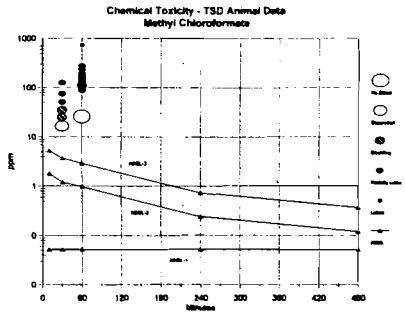
Rats showed no deaths until week 4 when exposed to 8.8 ppm repeatedly (6 hours/day, 5 days/week for 4 weeks)

No deaths and only nasal turbinate histopathology and larynx lesions in rats repeatedly exposed to 3.1 ppm

Only larynx lesions when exposed to 1.01 ppm for 6 hours/day, 5 days/week for 4 weeks (BASF, 1993).

THERE ARE NO OTHER EXTANT STANDARDS AND GUIDELINES FOR METHYL CHLOROFORMATE!

Summary of Proposed AEGL Values for Methyl Chloroformate					
Guideline	Exposure Duration				
	10-minutes	30-minutes	1-hour	4-hours	8-hours
AEGL-1	0.052 ppm	0.052 ppm	0.052 ppm	0.052 ppm	0.052 ppm
AEGL-2	1.8 ppm	1.2 ppm	0.97 ppm	0.24 ppm	0.12 ppm
AEGL-3	5.3 ppm	3.7 ppm	2.9 ppm	0.73 ppm	0.37 ppm



AEGL-1 VALUES: ETHYL CHLOROFORMATE				
10 minute	30 minute	1 hour	4 hour	8 hour
0.078 ppm	0.078 ppm	0.078 ppm	0.078 ppm	0.078 ppm

Species: Male Swiss-Webster Mouse
Concentration: 77.5 ppm (RD_{50})
Endpoint: Predicted no effect of any kind on the respiratory system
Reference: Carpenter, 1982

Rationale: The RD_{50} multiplied by 0.1 corresponds to "some sensory irritation"

The RD_{50} value multiplied by 0.01 corresponds to "no sensory irritation"

The RD_{50} value multiplied by 0.001 corresponds to "no effect of any kind on the respiratory system" Alarie (1981)

The multiplier of 0.001, rather than 0.01, was chosen because use of 0.01 would yield AEGL-1 values greater than AEGL-2 values at the longer time points.

Time Scaling: Value held constant across the 10- and 30-minute, and 1-, 4-, and 8-hour exposure times because mild irritancy generally does not vary greatly over time, and because it is not expected that prolonged exposure will result in an enhanced effect.

AEGL-2 VALUES: ETHYL CHLOROFORMATE				
10 minute	30 minute	1 hour	4 hour	8 hour
2.9 ppm	2.0 ppm	1.6 ppm	0.40 ppm	0.20 ppm

Endpoint: ⅓ The AEGL-3 values

Endpoint is justified based on the steep concentration-response curve:

1-hr rat LC_{50} is 189-200 ppm
Rats exposed to 47 ppm for 1-hr were clinically-normal (Fisher et al., 1981)

AEGL-3 VALUES: ETHYL CHLOROFORMATE				
10 minute	30 minute	1 hour	4 hour	8 hour
8.8 ppm	6.1 ppm	4.8 ppm	1.2 ppm	0.60 ppm

Species: Rat (10 males/group)
Concentration: 48 ppm
Time: 1-hour
Endpoint: Estimated lethality threshold: ⅓ of the most conservative 1-hr LC_{50} value in rats (145 ppm x ⅓ =48 ppm)
Reference: Vernot et al., 1977

Time Scaling: $C^n \times t = k$, where n= 3 for the 10- and 30-minute time periods, and n= 1 for the 4- and 8-hour time periods, to provide AEGL values that would be protective of human health (NRC, 2001).

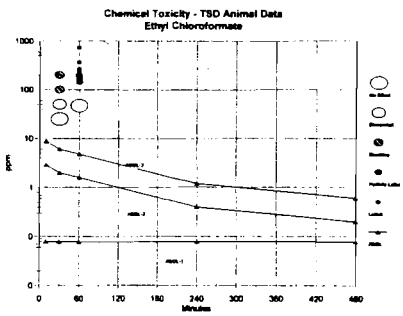
Uncertainty Factors:

Interspecies = 3 Intraspecies = 3

Highly reactive and clinical signs are likely caused by a direct chemical effect on the tissues; this type of portal-of-entry effect is not expected to vary greatly between species or among individuals.

Support: POD supported by the fact that no deaths were observed in rats exposed to 47 ppm for 1 hour (Fisher et al., 1981).

Summary of Proposed AEGL Values for Ethyl Chloroformate					
Guideline	Exposure Duration				
	10-minutes	30-minutes	1-hour	4-hours	8-hours
AEGL-1	0.078 ppm	0.078 ppm	0.078 ppm	0.078 ppm	0.078 ppm
AEGL-2	2.9 ppm	2.0 ppm	1.6 ppm	0.40 ppm	0.20 ppm
AEGL-3	8.8 ppm	6.1 ppm	4.8 ppm	1.2 ppm	0.60 ppm
Dutch MAC					1 ppm



AEGL-1 VALUES: PROPYL CHLOROFORMATE				
10 minute	30 minute	1 hour	4 hour	8 hour
0.084 ppm	0.084 ppm	0.084 ppm	0.084 ppm	0.084 ppm

Species: Male Swiss-Webster Mouse
Concentration: 83.5 ppm (RD_{50})
Endpoint: Predicted no effect of any kind on the respiratory system
Reference: Carpenter, 1982

Rationale: The RD_{50} multiplied by 0.1 corresponds to "some sensory irritation"

The RD_{50} value multiplied by 0.01 corresponds to "no sensory irritation"

The RD_{50} value multiplied by 0.001 corresponds to "no effect of any kind on the respiratory system" Alarie (1981)

The multiplier of 0.001, rather than 0.01, was chosen because use of 0.01 would yield AEGL-1 values greater than AEGL-2 values at the longer time points.

Time Scaling: Value held constant across the 10- and 30-minute, and 1-, 4-, and 8-hour exposure times because mild irritancy generally does not vary greatly over time, and because it is not expected that prolonged exposure will result in an enhanced effect.

AEGL-2 VALUES: PROPYL CHLOROFORMATE				
10 minute	30 minute	1 hour	4 hour	8 hour
4.3 ppm	3.0 ppm	2.4 ppm	0.6 ppm	0.30 ppm

Endpoint: ⅓ The AEGL-3 values

Endpoint is justified based on the steep concentration-response curve:

1-hr exposures(Bio-Test, 1970)

0/10 dead at 249 ppm

2/10 dead at 333 ppm

10/10 dead at 1000 ppm

AEGL-3 VALUES: PROPYL CHLOROFORMATE				
10 minute	30 minute	1 hour	4 hour	8 hour
13 ppm	9.1 ppm	7.2 ppm	1.8 ppm	0.90 ppm

Species: Rat (5/sex/group)
Concentration: 216 ppm
Time: 1-hour
Endpoint: Estimated lethality threshold: $BMCL_{05}$
Reference: Bio-Test, 1970

Time Scaling: $C^n \times t = k$, where $n = 3$ for the 10- and 30-minute time periods, and $n = 1$ for the 4- and 8-hour time periods, to provide AEGL values that would be protective of human health (NRC, 2001).

Uncertainty Factors:

Interspecies = 3 Intraspecies = 3

Highly reactive and clinical signs are likely caused by a direct chemical effect on the tissues; this type of portal-of-entry effect is not expected to vary greatly between species or among individuals.

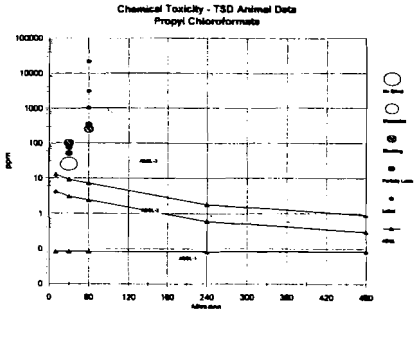
Modifying Factor = 3

Key study reported nominal, not analytical, concentrations

No other confirmatory studies

THERE ARE NO OTHER EXTANT STANDARDS AND GUIDELINES FOR PROPYL CHLOROFORMATE!

Summary of Proposed AEGL Values for Propyl Chloroformate					
Guideline	Exposure Duration				
	10-minutes	30-minutes	1-hour	4-hours	8-hours
AEGL-1	0.084 ppm	0.084 ppm	0.084 ppm	0.084 ppm	0.084 ppm
AEGL-2	4.3 ppm	3.0 ppm	2.4 ppm	0.6 ppm	0.30 ppm
AEGL-3	13 ppm	9.1 ppm	7.2 ppm	1.8 ppm	0.90 ppm



AEGL-1 VALUES: ISOPROPYL CHLOROFORMATE				
10 minute	30 minute	1 hour	4 hour	8 hour
0.10 ppm	0.10 ppm	0.10 ppm	0.10 ppm	0.10 ppm

Species: Male Swiss-Webster Mouse
Concentration: 104 ppm (RD_{50})
Endpoint: Predicted no effect of any kind on the respiratory system
Reference: Carpenter, 1982

Rationale: The RD_{50} multiplied by 0.1 corresponds to "some sensory irritation"

The RD_{50} value multiplied by 0.01 corresponds to "no sensory irritation"

The RD_{50} value multiplied by 0.001 corresponds to "no effect of any kind on the respiratory system" Alarie (1981)

The multiplier of 0.001, rather than 0.01, was chosen because use of 0.01 would yield AEGL-1 values greater than AEGL-2 values at the longer time points.

Time Scaling: Value held constant across the 10- and 30-minute, and 1-, 4-, and 8-hour exposure times because mild irritancy generally does not vary greatly over time, and because it is not expected that prolonged exposure will result in an enhanced effect.

AEGL-2 VALUES: ISOPROPYL CHLOROFORMATE				
10 minute	30 minute	1 hour	4 hour	8 hour
6.0 ppm	4.3 ppm	3.3 ppm	0.83 ppm	0.43 ppm

Endpoint: ⅓ The AEGL-3 values

Support: Values are considered protective because rats showed only nasal irritation when exposed to 20 ppm repeatedly (6 hours/day for 20 days) (Gage, 1970)

AEGL-3 VALUES: ISOPROPYL CHLOROFORMATE				
10 minute	30 minute	1 hour	4 hour	8 hour
18 ppm	13 ppm	10 ppm	2.5 ppm	1.3 ppm

Species: Rat (5/sex/group)
Concentration: 100 ppm
Time: 1-hour
Endpoint: Estimated lethality threshold: ⅓ x LC50: ⅓ x 300 ppm = 100 ppm
Reference: Bio-Test, 1970

Time Scaling: $C^n \times t = k$, where $n = 3$ for the 10- and 30-minute time periods, and $n = 1$ for the 4- and 8-hour time periods, to provide AEGL values that would be protective of human health (NRC, 2001).

Uncertainty Factors:

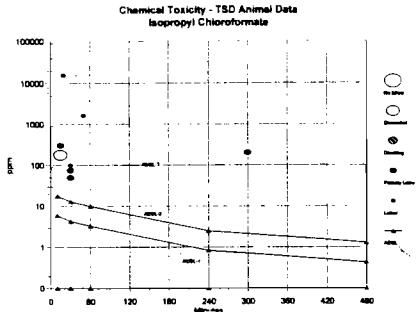
Interspecies = 3 Intraspecies = 3

Highly reactive and clinical signs are likely caused by a direct chemical effect on the tissues; this type of portal-of-entry effect is not expected to vary greatly between species or among individuals.

Support:

Values considered protective because no deaths were noted in rats exposed to 42 ppm isopropyl chloroformate 6 hours/day for 5 days (Collins and Proctor, 1984).

Extant Standards and Guidelines for Isopropyl Chloroformate					
Guideline	Exposure Duration				
	10 minutes	30 minutes	1 hour	4 hours	8 hours
AEGL-1	0.10 ppm	0.10 ppm	0.10 ppm	0.10 ppm	0.10 ppm
AEGL-2	6.0 ppm	4.3 ppm	3.3 ppm	0.83 ppm	0.43 ppm
AEGL-3	18 ppm	13 ppm	10 ppm	2.5 ppm	1.3 ppm
ERPG-1[a]	Insufficient Data				
ERPG-2[a]	5 ppm				
ERPG-3[a]	20 ppm				
Dutch MAC[b]					1 ppm



AEGL-1 VALUES: ALLYL CHLOROFORMATE				
10 minute	30 minute	1 hour	4 hour	8 hour
NR	NR	NR	NR	NR

Not Recommended due to insufficient data.

AEGL-2 VALUES: ALLYL CHLOROFORMATE				
10 minute	30 minute	1 hour	4 hour	8 hour
1.3 ppm	0.87 ppm	0.70 ppm	0.18 ppm	0.09 ppm

Endpoint: ⅓ the AEGL-3 values

Endpoint is justified based on the steep concentration-response curve:

1-hr rat exposures (Stillmeadow, 1987)

0/10 dead at 33.7 ppm

6/10 dead at 65 ppm

10/10 dead at 175.7 ppm

AEGL-3 VALUES: ALLYL CHLOROFORMATE				
10 minute	30 minute	1 hour	4 hour	8 hour
3.8 ppm	2.6 ppm	2.1 ppm	0.53 ppm	0.26 ppm

Species: Rat (5/sex/group)
Concentration: 21 ppm
Time: 1-hour
Endpoint: Estimated lethality threshold: $BMCL_{05}$
Reference: Stillmeadow, 1987

Time Scaling: $C^n \times t = k$, where $n = 3$ for the 10- and 30-minute time periods, and $n = 1$ for the 4- and 8-hour time periods, to provide AEGL values that would be protective of human health (NRC, 2001).

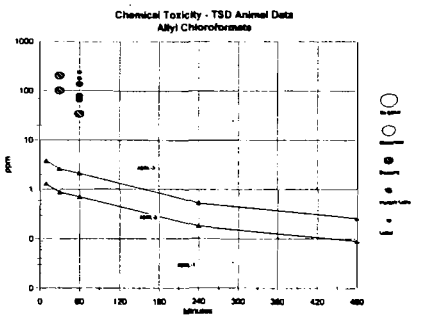
Uncertainty Factors:

Interspecies = 3 Intraspecies = 3

Highly reactive and clinical signs are likely caused by a direct chemical effect on the tissues; this type of portal-of-entry effect is not expected to vary greatly between species or among individuals.

THERE ARE NO OTHER EXTANT STANDARDS AND GUIDELINES FOR ALLYL CHLOROFORMATE!

Summary of Proposed AEGL Values for Allyl Chloroformate					
Guideline	Exposure Duration				
	10-minutes	30-minutes	1-hour	4-hours	8-hours
AEGL-1	NR	NR	NR	NR	NR
AEGL-2	1.3 ppm	0.87 ppm	0.70 ppm	0.18 ppm	0.09 ppm
AEGL-3	3.8 ppm	2.6 ppm	2.1 ppm	0.53 ppm	0.26 ppm



Summary of AEGL Values for n-butyl Chloroformate						
Classification	10-Minute	30-Minute	1-Hour	4-Hour	8-Hour	Endpoint (Reference)
AEGL-1 (Nondisabling)	NR	NR	NR	NR	NR	Insufficient data
AEGL-2 (Disabling)	NR	NR	NR	NR	NR	Insufficient data
AEGL-3 (Lethality)	NR	NR	NR	NR	NR	Insufficient data

Summary of AEGL Values For Isobutyl Chloroformate						
Classification	10-Minute	30-Minute	1-Hour	4-Hour	8-Hour	Endpoint (Reference
AEGL-1 (Nondisabling)	NR	NR	NR	NR	NR	Insufficient data
AEGL-2 (Disabling)	NR	NR	NR	NR	NR	Insufficient data
AEGL-3 (Lethality)	NR	NR	NR	NR	NR	Insufficient data

Summary of AEGL Values For sec-Butyl Chloroformate						
Classification	10-Minute	30-Minute	1-Hour	4-Hour	8-Hour	Endpoint (Reference)
AEGL-1 (Nondisabling)	NR	NR	NR	NR	NR	Insufficient data
AEGL-2 (Disabling)	NR	NR	NR	NR	NR	Insufficient data
AEGL-3 (Lethality)	NR	NR	NR	NR	NR	Insufficient data

AEGL-1 VALUES: ETHYL CHLOROTHIOFORMATE				
10 minute	30 minute	1 hour	4 hour	8 hour
NR	NR	NR	NR	NR

Not Recommended due to insufficient data.

AEGL-2 VALUES: ETHYL CHLOROTHIOFORMATE				
10 minute	30 minute	1 hour	4 hour	8 hour
0.47 ppm	0.47 ppm	0.37 ppm	0.23 ppm	0.12 ppm

Endpoint: ⅓ the AEGL-3 values

Endpoint is justified based on the steep concentration-response curve:

4-hr rat exposures (Stauffer, 1983)

4/20 dead at 33 ppm

14/20 dead at 59 ppm

20/20 dead at 65 ppm

AEGL-3 VALUES: ETHYL CHLOROTHIOFORMATE				
10 minute	30 minute	1 hour	4 hour	8 hour
1.4 ppm	1.4 ppm	1.1 ppm	0.70 ppm	0.35 ppm

Species: Rat (10/sex/group)
Concentration: 21 ppm
Time: 4-hour
Endpoint: Estimated lethality threshold: $BMCL_{05}$
Reference: Stauffer, 1983

Time Scaling: $C^n \times t = k$, where $n = 3$ for the 30-minute and 1-hour time periods, and $n = 1$ for the 8-hour time period, to provide AEGL values that would be protective of human health (NRC, 2001). The 30-minute value was adopted as the 10-minute value.

Uncertainty Factors:

Interspecies = 3 Intraspecies = 3

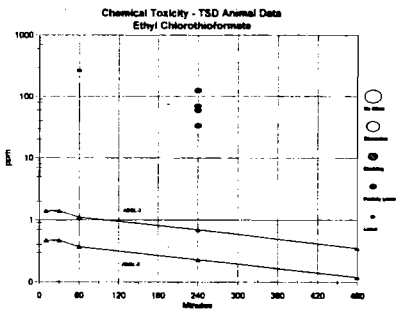
Highly reactive and clinical signs are likely caused by a direct chemical effect on the tissues; this type of portal-of-entry effect is not expected to vary greatly between species or among individuals.

Modifying Factor: 3

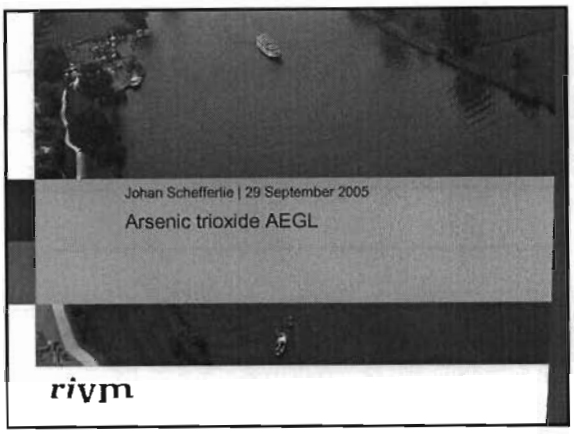
To protect against potential delayed systemic effects from the thio moitey.

THERE ARE NO OTHER EXTANT STANDARDS AND GUIDELINES FOR ETHYL CHLOROTHIOFORMATE!

Summary of AEGL Values for Ethyl Chlorothioformate					
Classification	10-minute	30-minute	1-hour	4-hour	8-hour
AEGL-1 (Nondisabling)	NR	NR	NR	NR	NR
AEGL-2 (Disabling)	0.47 ppm	0.47 ppm	0.37 ppm	0.23 ppm	0.12 ppm
AEGL-3 (Lethal)	1.4 ppm	1.4 ppm	1.1 ppm	0.70 ppm	0.35 ppm



Summary of AEGL Values For Diphosgene						
Classification	10-Minute	30-Minute	1-Hour	4-Hour	8-Hour	Endpoint (Reference)
AEGL-1 (Nondisabling)	NR	NR	NR	NR	NR	Insufficient data
AEGL-2 (Disabling)	NR	NR	NR	NR	NR	Insufficient data
AEGL-3 (Lethality)	NR	NR	NR	NR	NR	Insufficient data



Arsenic trioxide

- Solid at ambient temperatures
  - Inhalation exposure to dust
- Knowledge of toxicity mainly from oral data
- The most toxic one of all arsenic species
- 90% use as wood preservative
  - Phase out in 2003!
- Other uses mainly in pesticides

rivm

Diergeneesmiddelen

Reported effects in humans following inhalation

- Occupational long term exposure (not related to exposure concentration)
  - Peripheral neuropathy
  - Perforation of nasal septum
  - Pigmentation of the skin

rivm

Relevant data for AEGL

- No data on AEGL-1 or AEGL-2 effects
- Lethality data from a rat developmental study (range-finding)
- Knowledge about normal occupational exposure concentrations (personal breathing zone sampling) from 6 studies involving 356 workers

rivm

Lethality

- Single 6-h exposure
  - 25 mg/m³ 0/10
  - 50 mg/m³ 0/10
  - 100 mg/m³ 10/10
  - 150 mg/m³ 10/10
  - 200 mg/m³ 10/10

(Holson et al. 1999, see TSD page 10)

- 50 mg/m³ is a NOEL for lethality in rats in this study

rivm

AEGL-3

- The NOEL of 50 mg/m³ is the point of departure
- Total UF of 10 (3x3)
  - Larger factors (100 or 30) result in AEGL-3 values within or just above the range of normal occupational exposure concentrations
  - The resulting 6-h value is 5 mg/m³
- Time-scaling with $C^n \times t = k$
  - No data on time-concentration effects
  - Default n=3 for shorter time points, n=1 for longer time points
  - Starting point 6-h, so 10-min value is equal to 30-min value

10-minute	30-minute	1-hour	4-hour	8-hour
11 mg/m³	11 mg/m³	9.1 mg/m³	5.7 mg/m³	3.7 mg/m³

Expressed as mg/m³ As_2O_3 rather than mg/m³ As

rivm

AEGL-2

- Occupational long term 8-h exposures are up to 1.0 mg/m³
- No acute AEGL-2 effects expected at these concentrations
- Proposal to use 1.0 mg/m³ (8-h) as point of departure
- No UF is proposed
  - 1.0 mg/m³ is considered a sub-AEGL-2 concentration and it is not known hor far this is below the concentration that will produce AEGL-2 effects
- Default time-scaling as for AEGL-3

10-minute	30-minute	1-hour	4-hour	8-hour
2.5 mg/m³	2.5 mg/m³	2.0 mg/m³	1.3 mg/m³	1.0 mg/m³

rivm

Summary

Classification	10-minute	30-minute	1-hour	4-hour	8-hour
AEGL-1	Not proposed	Not proposed	Not proposed	Not proposed	Not proposed
AEGL-2	2.5 mg/m³	2.5 mg/m³	2.0 mg/m³	1.3 mg/m³	1.0 mg/m³
AEGL-3	11 mg/m³	11 mg/m³	9.1 mg/m³	5.7 mg/m³	3.7 mg/m³

These values are expressed as arsenic trioxide (mg As_2O_3/m^3)

rivm

CYCLOHEXYL ISOCYANATE

AEGL values are
NOT RECOMMENDED

¶

TABLE 1. Acute lethality in rats exposed to cyclohexyl isocyanate

Conc. (ppm)	Duration	Lethality	Clinical and necropsy findings	Reference
17.79	6 hrs	1/3 on day 7	irritation, lacrimation, dypsnea; inflammation in lungs, congestion of kidney and liver	Eastman Kodak Co. 1990, 1992
53.2	6 hrs	2/3 during exposure; 1/3 on day 12	as above plus salivation, gasping	Eastman Kodak Co. 1990, 1992
1017	6 hrs	3/3 after 4 hours	as above, more severe	Eastman Kodak Co. 1990, 1992
1401	1-2.5 hrs	6/6	irritation; hemorrhage in lungs	Mobay Corp. 1990a

¶

¶

TABLE 2. Acute lethality in rats exposed to saturated cyclohexyl isocyanate

Conc. (ppm)	Duration	Lethality	Clinical and necropsy findings	Reference
saturated	2 hrs	8/8	none stated	Mobay Corp. 1990b
saturated	3 min	0/10	irritation; dark spots on lungs	Mobay Corp. 1990c
saturated	10 min	10/10 within 11 days	respiratory problems; enlarged lungs with red spots, fluid, lobulated liver	Mobay Corp. 1990c
saturated	1 hr	10/10 during exposure	as above	Mobay Corp. 1990c

¶

DATA DEFICIENCIES

- No data with the appropriate endpoints were found.
- No human data were found.
- Lethality studies in rats:
  - Lacked concentration-response information;
  - Deaths occurred at all concentrations;
  - Nominal not analytical concentrations;
  - Lacked method details.

AEGL values for cyclohexyl isocyanate

Class.	10-min	30-min	1-hr	4-hr	8-hr
AEGL-1	NR	NR	NR	NR	NR
AEGL-2	NR	NR	NR	NR	NR
AEGL-3	NR	NR	NR	NR	NR

Chemical: BORON TRIFLUORIDE **CAS Reg. No.:** 7637-07-2

Action: Proposed_____ **Interim**_____ **Other** REVISE AEGLs based on COT comments and new data

Chemical Manager: G. RUSCH **Staff Scientist:** C. TROXEL

NAC Member	AEGL1	AEGL2	AEGL3	LOA	NAC Member	AEGL1	AEGL2	AEGL3	LOA
Steven Barbee	Y	Y	Y		Nancy Kim	Y	Y	Y	
Lynn Beasley	A	A	A		Glenn Leach	A	A	A	
Robert Benson	Y	Y	Y		John Morawetz	A	A	A	
Jonathan Borak	Y	Y	Y		Richard Niemeier	Y	Y	Y	
William Bress	Y	Y	Y		Marinelle Payton	A	A	A	
George Cushmac	Y	Y	Y		Susan Ripple	Y	Y	Y	
Ernest Falke	A	A	A		George Rodgers	Y	Y	Y	
Alfred Feldt	Y	Y	Y		Marc Ruijten	Y	Y	Y	
John Hinz	Y	Y	Y		George Rusch, Chair	P	P	A*	
Jim Holler	A	A	A		Richard Thomas	Y	Y	Y	
Tom Hornshaw	Y	Y	Y		George Woodall	Y	Y	Y	
Warren Jederberg	A	A	A						
					TALLY				
					PASS/ FAIL	15/15	15/15	15/15	

*P = ABSTAIN

(mg/m^3)

PPM, (mg/m^3)	10 Min	30 Min	1 Hr	4 Hr	8 Hr
AEGL 1	,(2.5)	,(2.5)	,(2.5)	,(2.5)	,(2.5)
AEGL 2	,(47)	,(47)	,(37)	,(24)	,(12)
AEGL 3	,(140)	,(140)	,(110)	,(72)	,(36)
LOA					
* = ≥10% LEL					
** = ≥ 50% LEL					
*** = ≥100% LEL					

*Safety considerations against the hazard(s) of explosion(s) must be taken into account.
** and ***Extreme safety considerations against the hazard(s) of explosion(s) must be taken into account.

NR= Not Recommended due to_____

AEGL 1 Motion by: RUIJTEN **Second by:** NIEMEIER
AEGL 2 Motion by: ~~BOB BENSON~~ BARBEE **Second by:** G. WOODALL THOMAS
AEGL 3 Motion by: BOB BENSON **Second by:** N. KIM
LOA Motion by:_____ **Second by:**_____

Approved by Chair: [signature] **DFO:** [signature] **Date:** 9/28/05

Chemical: KETENE **CAS Reg. No.:** 463-51-4

Action: Proposed ✓ **Interim**_____ **Other**_____

Chemical Manager: [redacted] **Staff Scientist:**

NAC Member	AEGL1	AEGL2	AEGL3	LOA
Steven Barbee	Y	P	P	
Lynn Beasley	Y	Y	Y	
Robert Benson	Y	Y	Y	
Jonathan Borak	P	P	P	
William Bress	Y	Y	Y	
George Cushmac	Y	Y	Y	
Ernest Falke	Absent			
Alfred Feldt	Y	Y	Y	
John Hinz	P	P	P	
Jim Holler	Absent			
Tom Hornshaw	Y	P	P	
Warren Jederberg	Absent			

NAC Member	AEGL1	AEGL 2	AEGL3	LOA
Nancy Kim	N	N	N	
Glenn Leach	Absent			
John Morawetz	Absent			
Richard Niemeier	Y	Y	Y	
Marinelle Payton	Absent			
Susan Ripple	Y	Y	Y	
George Rodgers	P	P	P	
Marc Ruijten	Y	Y	Y	
George Rusch, Chair	Y	Y	Y	
Richard Thomas	Y	Y	Y	
George Woodall	Y	P	P	
TALLY				
PASS/ FAIL				

PPM, (mg/m^3)	10 Min	30 Min	1 Hr	4 Hr	8 Hr
AEGL 1	, (0.24 ppm)	, (0.24 ppm)	, (0.19 ppm)	, (0.12 ppm)	, (0.083 ppm)
AEGL 2	, (0.83 ppm)	, (0.83 ppm)	, (0.66 ppm)	, (0.42 ppm)	, (0.23 ppm)
AEGL 3	, (2.5 ppm)	, (2.5 ppm)	, (2.0 ppm)	, (1.2 ppm)	, (0.68 ppm)
LOA					
* = ≥10% LEL					
** = ≥ 50% LEL					
*** = ≥100% LEL					

*Safety considerations against the hazard(s) of explosion(s) must be taken into account.
** and ***Extreme safety considerations against the hazard(s) of explosion(s) must be taken into account.

NR= Not Recommended due to_____

AEGL 1 Motion by: [redacted] Robert Benson **Second by:** Marc Ruijten
AEGL 2 Motion by: Robert Benson **Second by:** Marc Ruijten
AEGL 3 Motion by: Robert Benson **Second by:** Marc Ruijten.
LOA Motion by:_____ **Second by:**_____

Approved by Chair: [signature] **DFO:** [signature] **Date:** 9/28/05

Chemical: ARSENIC TRIOXIDE **CAS Reg. No.:** 1327-53-3

Action: Proposed ✓ **Interim**_____ **Other**_____

Chemical Manager: **Staff Scientist:**

NAC Member	AEGL1	AEGL2	AEGL3	LOA
Steven Barbee	Y	A	Y	
Lynn Beasley	Y	Y	Y	
Robert Benson	Y	Y	Y	
Jonathan Borak	A	A	A	
William Bress	Y	Y	Y	
George Cushmac	A	Y	Y	
Ernest Falke	A	A	Y	
Alfred Feldt	Y	Y	Y	
John Hinz	A	A	A	
Jim Holler	A	A	A	
Tom Hornshaw	Y	Y	Y	
Warren Jederberg	A	A	A	

NAC Member	AEGL1	AEGL 2	AEGL3	LOA
Nancy Kim	Y	Y	Y	
Glenn Leach	Y	Y	Y	
John Morawetz	Y	Y	Y	
Richard Niemeier	Y	Y	Y	
Marinelle Payton	A	A	A	
Susan Ripple	Y	Y	Y	
George Rodgers	Y	Y	Y	
Marc Ruijten	Y	Y	Y	
George Rusch, Chair	Y	Y	Y	
Richard Thomas	Y	Y	Y	
George Woodall	Y	Y	Y	
TALLY	16/16	16/16	16/16	
PASS/ FAIL	Pass	Pass	Pass	

PPM, (mg/m³)	10 Min	30 Min	1 Hr	4 Hr	8 Hr
AEGL 1	,(NR)	,(NR)	,(NR)	,( )	,( )
AEGL 2	,(3.7)	,(3.7)	,(3.0)	,(1.9)	,(1.2)
AEGL 3	,(11)	,(11)	,(9.1)	,(5.7)	,(3.7)
LOA					
* = ≥10% LEL					
** = ≥ 50% LEL					
*** = ≥100% LEL					

*Safety considerations against the hazard(s) of explosion(s) must be taken into account.
** and ***Extreme safety considerations against the hazard(s) of explosion(s) must be taken into account.

NR= Not Recommended due to Insufficient data

AEGL 1 Motion by: Benson **Second by:** Ruijten
AEGL 2 Motion by: Ruijten **Second by:** Niemeier
AEGL 3 Motion by: Marc Ruijten **Second by:** Bob Benson
LOA Motion by:_____ **Second by:**_____

Approved by Chair: [signature] **DFO:** Paul S Tobin **Date:** 9/29/05

Chemical: CYCLOHEXYL ISOCYANATE **CAS Reg. No.:** 3173-53-3

Action: Proposed ✓ **Interim** _____ **Other** _____

Chemical Manager: MARC RUIJTEN **Staff Scientist:**

NAC Member	AEGL1	AEGL2		AEGL3	LOA
Steven Barbee	P	A	P	P	
Lynn Beasley	Y	Y	Y	Y	
Robert Benson	Y	N	Y	Y	
Jonathan Borak	A	A	A	A	
William Bress	Y	N	Y	Y	
George Cushmac	Y	N	Y	Y	
Ernest Falke	A	A	A	A	
Alfred Feldt	P	P	Y	P	
John Hinz	A	A	A	A	
Jim Holler	A	A	A	A	
Tom Hornshaw	Y	N	Y	Y	
Warren Jederberg	A	A	A	A	

NAC Member	AEGL1	AEGL2		AEGL3	LOA
Nancy Kim	Y	N	Y	Y	
Glenn Leach	Y	N	Y	Y	
John Morawetz	Y	N	Y	Y	
Richard Niemeier	Y	Y	N	Y	
Marinelle Payton	A	A	A	A	
Susan Ripple	Y	P	Y	Y	
George Rodgers	Y	N	N	Y	
Marc Ruijten	Y	N	Y	Y	
George Rusch, Chair	Y	N	Y	Y	
Richard Thomas	Y	N	Y	Y	
George Woodall	Y	Y	N	Y	
TALLY					
PASS/ FAIL	15/15	13/16		13/15	

PPM, (mg/m³)	10 Min	30 Min	1 Hr	4 Hr	8 Hr
AEGL 1	,(NR)	,(NR)	,(NR)	,(NR)	,(NR)
AEGL 2 ** 2nd batch	~~,(0.23)~~ NR	NR ~~,(0.03)~~	NR ~~(0.02)~~	NR ~~,(0.01)~~	NR ~~(0.01)~~ NR
AEGL 3 *	,(0.14)	,(0.14)	,(0.11)	,(0.072)	,(0.047)
LOA					
* = ≥10% LEL					
** = ≥ 50% LEL					
*** = ≥100% LEL					

*Safety considerations against the hazard(s) of explosion(s) must be taken into account.
** and ***Extreme safety considerations against the hazard(s) of explosion(s) must be taken into account.

NR= Not Recommended due to Lack of Data

AEGL 1 Motion by: Niemeier **Second by:** Woodall
AEGL 2 Motion by: Niemeier **Second by:** Woodall
AEGL 3 Motion by: Benson **Second by:** Woodall
LOA Motion by: _____ **Second by:** _____

Approved by Chair: _____ **DFO:** _____ **Date:** 9/29/05