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

March 20-22, 2007

Meeting-42 Highlights

Arnold and Mabel Beckman Center
100 Academy Drive
Irvine, CA 92612

INTRODUCTION

Chairman George Rusch welcomed the committee. The draft NAC/AEGL-41 meeting highlights were reviewed. A motion was made by Richard Thomas and seconded by Dieter Heinz to accept the minutes as written with a date change for the next meeting, i.e., June 20-22, 2007. The motion passed unanimously by a show of hands (Appendix A). The final version of the NAC/AEGL-41 meeting highlights is attached (Appendix B).

George Rusch and Ernie Falke reported on the ACUTEX meeting in Ispra, Italy, on March 6-8, 2007. The E.U. Joint Chemical Research project includes members from JCR, The Netherlands, France, Germany, Finland, and The United Kingdom. Invited representatives of the U.S. were George Rusch, Ernie Falke, Richard Thomas and David Kelly, member of the National Research Council's Subcommittee to review AEGLs. ACUTEX was a research project addressing Development of Guideline Levels for European countries. Meeting attendees reviewed the completed ACUTEX report and discussed implementation of the guidance levels. Input from the U.S. representatives on several programs, including the AEGL program, led to a discussion of harmonization of the two programs.

The AEGL meeting began with Development Team meetings, a new protocol being tested to ensure consensus on individual chemicals among a NAC subgroup before opening discussions to the entire committee. The second meeting day also started with development team meetings. Interested members who were not part of the chemical manager/chemical reviewer team were encouraged to attend a subgroup meeting.

The highlights of the NAC/AEGL-42 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-42 Agenda.

REVIEW of FEDERAL REGISTER-09 COMMENTS

Aliphatic Nitriles
Acetonitrile (CAS No. 75-05-8)
Isobutyronitrile (CAS No. 78-82-0)
Propionitrile (CAS No. 107-12-0)
Chloroacetonitrile (CAS No. 107-14-2)
Malononitrile (CAS No. 109-77-3)

Chemical Manager: George Rodgers
Chemical Reviewers: Ernest Falke, George Rusch
Staff Scientist: Cheryl Bast

Cheryl Bast explained that many comments were received only on acetonitrile; all of these comments were from one commenter (INEOS Nitriles). (Attachment 3). However, the relative toxicity of all nitriles must be considered when addressing the FR comments. Also, AEGL-2 and AEGL-3 values for chloroacetonitrile and malononitrile were derived by a molar equivalence approach from the acetonitrile values. Therefore, if the acetonitriles are revised, the values for these two nitiriles must also be revised. In response to the comments, two additional studies will be added to the TSD, and a discussion of effects in the Pozzani et al. (1959) study will be modified. Following discussion, the AEGL-1 for acetonitrile will continue to be constant across exposure durations at 13 ppm. The points of departure for the AEGL-2 and the AEGL-3 remained the same. The point of departure for the AEGL-2 was the 4-hour 4000 ppm concentration that induced lung effects in rats (Pozanni et al. 1959), and the point of departure for the AEGL-3 remained the 4-hour LC_{01} for the rat of 8421 ppm (Monsanto 1986). The same inter- and intraspecies uncertainty factors of 3 and 10 were applied. In response to FR comments, the n value for AEGL-2 and -3 was changed from 2.5 to 1.6. The 'n' value of 2.5 was derived from linear regression of rat lethality data; whereas, the revised value of 1.6 was derived from the tenBerge program, and is more consistent with current NAC practices. The revised values are listed in the table below. It was moved by George Rodgers and seconded by Ernie Falke to move the acetonitrile AEGLs to Interim. The motion carried unanimously (Appendix C). Based on relative toxicity, the new acetonitrile values were in line with the values for proprionitrile and isobutyronitrile (derived with chemical-specific data), and therefore propionitrile and isobutyronitrile were moved to Interim status (moved by Rich Neimier and seconded by Dieter Heinz). The vote was unanimous (Appendix D). Based on molar equivalents and the reevaluated n value, the corresponding values for chloroacetonitrile and malononitrile were recalculated. It was moved by Rich Neimier and seconded by Dieter Heinz to move the modified chloroacetonitrile values to Interim. The motion passed unanimously (Appendix E). It was moved by Henry Anderson and seconded by Marc Baril to move the modified malononitrile values to Interim. The motion passed unanimously (Appendix F). Values for chloroacetonitrile and malononitrile are summarized in the table below.

Summary of AEGL Values for Nitriles					
Classification	10-Minute	30-Minute	1-Hour	4-Hour	8-Hour
Acetonitrile					
AEGL-1	13 ppm	13 ppm	13 ppm	13 ppm	13 ppm
AEGL-2	490 ppm	490 ppm	320 ppm	130 ppm	86 ppm
AEGL-3	1000 ppm	1000 ppm	670 ppm	280 ppm	180 ppm
Chloroacetonitrile					
AEGL-1	NR	NR	NR	NR	NR
AEGL-2	49 ppm	49 ppm	32 ppm	13 ppm	8.6 ppm
AEGL-3	100 ppm	100 ppm	67 ppm	28 ppm	18 ppm
Malononitrile					
AEGL-1	NR	NR	NR	NR	NR
AEGL-2	7.5 ppm	7.5 ppm	4.9 ppm	2.0 ppm	1.3 ppm
AEGL-3	15 ppm	15 ppm	10 ppm	4.3 ppm	2.8 ppm

RD_{50} WHITE PAPER

Peter Bos discussed the RD_{50} assay and relevance for setting AEGLs (Attachment 4). A brief historical overview was given and the methodology was summarized, including a critical review of the proposed relationship of the RD_{50} concentration and the expected effect in humans. A challenge involves equating respiratory depression in animals with an equivalent effect in humans and distinguishing between stimulation of the olfactory versus trigeminal nerve. Discussion focused on whether or not the RD_{50} is an appropriate endpoint as a point-of-departure (POD) for AEGL derivation and how to handle scaling across time. It was concluded that appropriate human data on chemosensory effects (like effects following trigeminal nerve stimulation) are lacking; the available limited data on human nasal pungency thresholds do not support the use of the RD_{50} as POD for AEGL-derivation. As an alternative the following approach was adopted. The sensory irritation as measured by respiratory depression in the mouse bioassay was concluded to be an AEGL-1 endpoint. Criteria on minimal data requirements (regarding both data availability and quality) were laid down to judge the results of the bioassay on their suitability for AEGL-derivation. The RD_{10}, as a threshold for sensory irritation, was proposed as POD. Uncertainty factors are to be applied according to the SOP for local effects on the respiratory tract and one AEGL-1 value will be set for all exposure durations up to eight hour.

REVIEW OF PRIORITY CHEMICALS

Chlorobenzene (CAS No. 108-90-7)

Chemical Manager: Marinelle Payton
Chemical Reviewers: Steve Barbee, Marc Ruijten
Staff Scientist: J. Muller, Peter Bos

Peter Bos discussed the clinical and laboratory animal data for chlorobenzene and mentioned several approaches for development of AEGL-2 and -3 values, i.e., a PBPK modeling approach vs the traditional time scaling approach (Attachment 5). The different approaches resulted in conflicting values. Consensus as to a single approach had not been reached in the morning development team meeting, and there was much discussion among the committee later. Following initial writing of the document, new data from the Utah Biomedical Test Laboratory were located. The proposed AEGL-1 value was based on human data. The point of departure was a 10 ppm exposure of volunteers for 8 hours/day, 5 days/week which resulted in no complaints (Knecht and Woitowitz 2000). Because this was a conservative endpoint (only mild complaints were recorded at 60 ppm), an intraspecies UF of 1 was applied, and the value was not time-scaled. The point of departure for the AEGL-2 was a 30-minute exposure of rats and guinea pigs to 2990 ppm (Utah Biomedical Laboratory). Interspecies and intraspecies uncertainty factors of 3 each for a total of 10 were applied. Time scaling to the longer and shorter values used the default values of n of 3 and 1, respectively. Because chlorobenzene approaches steady-state in the blood of the rat in one hour, the same values were used for the one- through eight-hour exposure durations. Using the same study, the point of departure for the AEGL-3 was the highest non-lethal value in rats and guinea pigs – 8000 ppm for 30 minutes. Uncertainty factors and time scaling were the same as for the AEGL-2. A motion was made by Marc Ruijten and seconded by Marc Baril to accept the values. The motion passed unanimously (Appendix G).

Summary of AEGL Values for Chlorobenzene

Classification	10-minute	30-minute	1-hour	4-hour	8-hour	Endpoint (Reference)
AEGL–1	10 ppm	10 ppm	10 ppm	10 ppm	10 ppm	No effect – humans (Knecht and Woitowitz 2000)
AEGL–2	430 ppm	300 ppm	150 ppm	150 ppm	150 ppm	Slight eye and nasal irritation -rat (Utah Biomedical Test Laboratory)
AEGL–3	1100 ppm	800 ppm	400 ppm	400 ppm	400 ppm	Highest non-lethal value – rat (Utah Biomedical Test Laboratory)

Toluene (CAS No. 108-88-3)

Chemical Manager: George Woodall
Chemical Reviewer: Marquea King
Staff Scientist: Sylvia Talmage

Sylvia Talmage discussed the development of toluene AEGL values over the period 1999-2007 (Attachment 6). In response to a National Academy of Science AEGL Subcommittee recommendation concerning the originally-derived values, PBPK modeling was used to derive AEGL-2 and AEGL-3 values. The first modeled values were based on a human study (AEGL-2) and a rat lethality study (AEGL-3). Because the human exposure did not involve an endpoint

consistent with the definition of an AEGL-2, the AEGL-2 values were reconsidered. Discussions and suggestions among the NAC members prior to and during the presentation led to consideration of other studies for both the AEGL-2 and -3. Jim Dennison of Century Environmental, Inc., was called upon to model the data for the suggested studies. Of two studies considered for development of AEGL-2 values, the study of Oshiro and Bushnell (2004) was chosen. The point of departure was the threshold for narcosis in a 70-minute exposure of Long-Evans rats to 2400 ppm. A single intraspecies uncertainty factor of 3 was applied because modeling accounted for the rat to human extrapolation, and the threshold for narcosis does not differ by more than three-fold among humans. The AEGL-3 point of departure remained the highest non-lethal value of 6250 ppm in the rat in a 2-hour study by Mullin and Krivanek (1982). Scaling to the other exposure durations were based on modeling. A motion to accept all three sets of AEGL values was made by Marc Ruijten and seconded by Richard Thomas. The motion passed: YES: 18; NO: 0; Abstain: 1 (Appendix H). The values appear in the table below. Although these values were accepted, further discussions focused on the AEGL-3. Jim Dennison will run the PBPK model for a rat lethality study (Wada et al. 1989), and the newly modeled values will be considered at the next meeting.

Summary of AEGL Values for Toluene						
Classification	**10-minute**	**30-minute**	**1-hour**	**4-hour**	**8-hour**	**Endpoint (Reference)**
AEGL–1	200 ppm	200 ppm	200 ppm	200 ppm	200 ppm	No effects above AEGL-1 definition-clinical studies
AEGL–2	3100 ppm *	1600 ppm *	1200 ppm	790 ppm	650 ppm	Threshold for narcosis – rat (Oshiro and Bushnell 2004)
AEGL–3	**	6100 ppm *	4500 ppm *	3000 ppm *	2500 ppm *	Highest non-lethal value – rat (Mullin and Krivanek 1982)

* The 10- and 3-minute AEGL-2 and 30-minute through 8-hour AEGL-3 values are higher than 1/10 of the lower explosive limit (LEL) of toluene in air (LEL = 14,000 ppm). Therefore, safety considerations against the hazard of explosion must be taken into account.

** The 10-minute AEGL-3 value of 13,000 ppm is higher than 50% of the LEL of toluene in air (LEL = 14,000 ppm). Therefore, extreme safety considerations against the hazard of explosion must be taken into account.

Bromine Chloride (CAS No. 13863-41-7)

Chemical Manager: George Cushmac
Chemical Reviewers: Alan Becker, Daniel Sudakin
Staff Scientist: Sylvia Talmage

Sylvia Talmage commented on the sparse data base for bromine chloride. The toxicity of bromine chloride is predicted to be between that of bromine and chlorine. Because no data were available for development of AEGL-1 values, it was suggested that the AEGL-1 for bromine chloride be set equal to the AEGL-1 values for the slightly more toxic chlorine. A single lethality study with the rat was available for development of AEGL-2 and -3 values (Dow Chemical Co. 1977). During a 7-hour exposure, respective mortalities of rats at 20, 40, 80, and 120 ppm were

0/6, 0/6, 1/6, and 5/6. Suggestions of using the 80 ppm value or using the graphed threshold for mortality of 70 ppm were rejected in favor of the benchmark-dose approach. The $BMDL_{05}$ was 39.5 ppm. Uncertainty factors 3 and 3 for a total of 10 were applied as the mechanism of action is direct irritation. The resulting value was time-scaled to the other exposure durations using default n values of 3 and 1 for shorter and longer exposure durations, respectively. Because of the long exposure duration, the 10-minute value was set equal to the 30-minute value. In accordance with Standing Operating Procedures for chemicals with sharp dose-response curves, the AEGL-2 was derived by dividing the AEGL-3 by 3. A motion was made by Dieter Heinz and seconded by Marc Baril to accept the suggested values. The motion passed unanimously (Appendix I). The values are summarized below.

Summary of AEGL Values for Bromine Chloride						
Classification	**10-minute**	**30-minute**	**1-hour**	**4-hour**	**8-hour**	**Endpoint (Reference)**
AEGL–1	0.50 ppm	0.50 ppm	0.50 ppm	0.50	0.50 ppm	Analogy with chlorine
AEGL–2	3.2 ppm	3.2 ppm	2.5 ppm	1.6 ppm	1.2 ppm	One-third of the AEGL-3 values
AEGL–3	9.5 ppm	9.5 ppm	7.6 ppm	4.8 ppm	3.5 ppm	$BMDL_{05}$ – rat (Dow Chemical Co. 1977)

Boron Tribromide (CAS No. 10294-33-4)

Chemical Manager: Bob Benson
Chemical Reviewers: Marc Baril, Calvin Willhite
Staff Scientist: Sylvia Talmage

Bob Benson, the chemical manager, made a few introductory remarks. Sylvia Talmage then briefly discussed the TSD for the chemical (Attachment 8). There are no data available for the chemical. The draft TSD derived values based on analogy with hydrogen bromide with the assumption that hydrolysis of boron tribromide gives three moles of hydrogen bromide. After brief discussion of the issues, the NAC recommended that ORNL write a letter to the manufacturer asking for any acute toxicity data on the chemical as well as any information on the breakdown of the chemical in air. The chemical was tabled until additional information is received.

Diketene (CAS No. 674-82-8)

Chemical Manager: Bob Benson
Chemical Reviewers: John Hinz, Dieter Heinz
Staff Scientist: Kowetha Davidson

Bob Benson, the new chemical manager for diketene, summarized the status of the TSD for diketene. Diketene was discussed at NAC-36. No formal action was taken on the chemical at that time. The NAC requested that Kowetha Davidson try to get information on the original data from Danishevskii (1948). The study was cited in a secondary source (Fel'dman, 1967). At NAC-36 Susan Ripple also volunteered to search her sources for additional data. At NAC-42 Susan Ripple reported that no additional data are available. Cheryl Bast led the discussion (Attachment 9) and reported that Kowetha was unable to get additional information on Danishevskii (1948). During the discussion it was noted that the Benchmark Dose modeling in the TSD was done with the nominal concentration, rather than the analytical concentration, from the lethality study of Katz (1987). Appendix D will be revised accordingly. The recalculated value of the $BMCL_{05}$ for lethality (181 ppm, for a 1-hour exposure) was used to derive the AEGL-3. There are no data to derive a value of n. Therefore, the default time scaling was used. There are no appropriate data to derive AEGL-2 values. Accordingly, the AEGL-2 values were derived by dividing AEGL-3 values by 3. As the study used to derive AEGL-1 values could not be located, AEGL-1 values are not recommended. The proposed values are listed in the table below. Bob Benson made a motion to accept these values. The motion was seconded by Rick Niemeyer. The motion passed unanimously (Appendix J).

Summary of AEGL Values for Diketene						
Classification	**10-minute**	**30-minute**	**1-hour**	**4-hour**	**8-hour**	**Endpoint (Reference)**
AEGL–1	NR	NR	NR	NR	NR	No data
AEGL–2	11 ppm	7.7 ppm	6.0 ppm	1.5 ppm	0.77 ppm	One-third of the AEGL-3 values
AEGL–3	33 ppm	23 ppm	18 ppm	4.5 ppm	2.3 ppm	$BMDL_{05}$ – rat (Katz 1987)

Silicon Tetrafluoride (CAS No. 7783-61-1)

Chemical Manager: Ernie Falke
Chemical Reviewers: George Rusch, Paul Tobin
Staff Scientist: Cheryl Bast

Cheryl Bast discussed the sparse data set for silicon tetrafluoride (Attachment 10). Some of the studies are old, provide conflicting results, and are incompletely reported. Although silicon tetrafluoride may break down into hydrogen fluoride and silicon, the data do not support a hydrogen fluoride molar equivalent approach. Cheryl presented values with the available data, but in view of the conflicting data and incomplete reports, the chemical was tabled until the June meeting. Richard Thomas will contact the Japanese researchers to try to obtain data from an LC_{50} study.

Acrylonitrile (CAS No. 107-13-1)

Chemical Manager: George Rodgers
Chemical Reviewers: Ernest Falke, George Rusch
Staff Scientist: Robert Young

Bob Young presented the data involving human exposures and laboratory animal studies (Attachment 11). The AEGL-3 values, adopted as presented, were based on the calculated $BMCL_{05}$ values from rat studies involving several time points: 30-minutes, and 1 and 8 hours (Appel et al. 1981; Dudley and Neal 1942). Inter- and intraspecies uncertainty factors of 3 each for a total of 10 were applied. The empirically-derived n value was 1.1. The 4-hour value was time-scaled from the 8-hour value. The values are supported by a recent study by WIL Research Laboratories (2005). It was moved by Ernie Falke and seconded by Richard Thomas to accept the values. The motion passed: YES: 13; NO: 4; Abstain: 0 (Appendix K). The AEGL-2 values were based on slight transitory effects in rats exposed to 305 ppm for 2 hours (Dudley and Neal 1942). Uncertainty factors and time-scaling were the same as for the AEGL-3 above. A motion was made by Marc Ruijten and seconded by Dieter Heinz to accept the values. The motion passed unanimously (19/19) (Appendix K). The AEGL-1 was based on monitoring data from DuPont Chemical Co. (unpublished). In that report, workers exposed to 16-20 ppm had no complaints of irritation. The value of 15 ppm was chosen as the point of departure. An uncertainty factor of 3 was applied and the resulting value of 4.6 ppm was used across all exposure durations because there is adaptation to the slight irritation that defines the AEGL-1. The value is supported by the study of Jakubowski et al. (1987) in which no effects were reported by male volunteers exposed to 4.6 ppm for 8 hours. The motion to accept 4.6 ppm was made by Richard Thomas and seconded by Ernie Falke. The motion passed: YES: 18; NO: 1; Abstain: 0 (Appendix K). Susan Ripple will supply the DuPont data.

Summary of AEGL Values for Acrylonitrile						
Classification	**10-minute**	**30-minute**	**1-hour**	**4-hour**	**8-hour**	**Endpoint (Reference)**
AEGL–1	4.6 ppm	4.6 ppm	4.6 ppm	4.6 ppm	4.6 ppm	Monitoring data; clinical study (DuPont Chemical Co; Jakubowski et al. 1987)
AEGL–2	290 ppm	110 ppm	57 ppm	16 ppm	8.6 ppm	Slight transitory effects – rat (Dudley and Neal 1942)
AEGL–3	480 ppm	180 ppm	100 ppm	35 ppm	19 ppm	Calculated $BMDL_{05}$ – rat (Dudley and Neal 1942; Appel et al. 1981)

Oxygen Difluoride (CAS No. 7783-41-7)

Chemical Manager: Iris Camacho
Chemical Reviewers: Al Feldt, Henry Anderson
Staff Scientist: Robert Young

Bob Young presented the data base, pointing out that lethality was related to body size, i.e., a 17-fold difference among four species (Attachment 12). No AEGL-1 values were proposed due to insufficient data. AEGL-2 values were derived as one-third of the AEGL-3 values. The AEGL-2 values are supported by limited human data. The AEGL-3 values were based on the threshold for lethality, the 1-hour $BMCL_{05}$ of 7.48 ppm in the rhesus monkey (Davis 1971). The non-human primate was not considered more sensitive than humans (the rhesus monkey is the same size as a small child). This observation was used to justify a single uncertainty factor of 3. Analysis of data from Davis (1970) and Lester and Adams (1965) with the software of ten Berge provided an *n* value of 1.1 for time scaling. The resulting values, listed in the table below, are supported by limited human data. It was moved by Richard Thomas and seconded by Dieter Heinz to accept values as proposed. The vote to accept was unanimous (Appendix L).

Summary of AEGL Values for Oxygen Difluoride						
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	4.3 ppm	1.6 ppm	0.83 ppm	0.24 ppm	0.13 ppm	One-third of the AEGL-3 values
AEGL–3	13 ppm	4.7 ppm	2.5 ppm	0.71 ppm	0.38 ppm	One-hour $BMCL_{05}$ in rhesus monkey (Davis 1971)

The final technical support document should contain tables of all fluoride AEGL values.

OTHER ISSUES

Allyl Alcohol (CAS No. 107-18-6)

Bob Benson gave a brief update on the status of allyl alcohol. Allyl alcohol was not on the agenda for NAC-42. Comments from the COT were discussed at NAC-41 and the company representative, Dr. Marcy Banton, agreed to ask Lyondell Chemical to conduct additional research. Dr. Banton has received approval from the company to conduct the necessary research and she is developing a detailed protocol for an acute study.

GENERAL ISSUES

The value of the Development Team meetings prior to the formal meeting was evaluated by the committee members and scientific staff. For some chemicals, a consensus of opinion shortened the formal discussion sessions. In other cases, consensus could not be reached during the team meetings, and discussion during the formal session reflected the diverse opinions. For the June meeting, it was decided to continue with pre-meetings as necessary. NAC members interested in specific chemicals should ask to be assigned to the small Development Team groups.

ADMINISTRATIVE MATTERS

The site and time of future meetings is as follows:

NAC/AEGL-43: June 20-22, 2007, Rotterdam, Netherlands
NAC/AEGL-44: September 5-7, 2007, Washington, DC

All items in the agenda were discussed as thoroughly as the time permitted. The meeting highlights were prepared by Sylvia Talmage, Cheryl Bast, and Robert Young, Oak Ridge National Laboratory, and Robert Benson, U.S. EPA, 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-42 Meeting Agenda
Attachment 2. NAC/AEGL-42 Attendee List
Attachment 3. Review of FR-09 comments for Aliphatic Nitriles
Attachment 4. RD_{50}- Relevance for AEGL Derivation
Attachment 5. Data analysis for chlorobenzene
Attachment 6. Data analysis for toluene
Attachment 7. Data analysis for bromine chloride
Attachment 8. Data analysis for boron tribromide
Attachment 9. Data analysis for diketene
Attachment 10. Data analysis for silicon tetrafluoride
Attachment 11. Data analysis for acrylonitrile
Attachment 12. Data analysis for oxygen difluoride

LIST OF APPENDICES

Appendix A. Ballot for NAC-41 meeting summary
Appendix B. Final NAC-41 Meeting Highlights
Appendix C. Ballot for acetonitrile
Appendix D. Ballot for propionitrile and isobutyronitrile to Interim
Appendix E. Ballot for chloroacetonitrile
Appendix F. Ballot for malononitrile
Appendix G. Ballot for chlorobenzene
Appendix H. Ballot for toluene
Appendix I. Ballot for bromine chloride
Appendix J. Ballot for diketene

Appendix K. Ballot for acrylonitrile
Appendix L. Ballot for oxygen difluoride

National Advisory Committee for Acute Exposure Guideline Levels for Hazardous Substances

NAC/AEGL-42
March 20-22, 2007

Arnold and Mabel Beckman Center
100 Academy Drive
Irvine, CA 92612

AGENDA

Tuesday, March 20, 2007

10:00 a.m.	*Development team meetings: Aliphatic nitriles, Chlorobenzene, Toluene, Oxygen Difluoride
10:45	Development team meetings: Acrylonitrile, Bromine chloride, Diketene
11:15	Introductory remarks and approval of NAC/AEGL-41 and Highlights (George Rusch, Ernie Falke, and Paul Tobin)
11:30	RD_{50} Discussion (Peter Bos, Marquea King)
12:30 p.m.	Lunch
1:30	Review of Chlorobenzene (Marinelle Payton/Peter Bos)
3:30	Break
3:45	Response to FR09 Comments- Aliphatic Nitriles (George Rodgers/Cheryl Bast)
5:00	Adjourn for the day

Wednesday, March 21, 2007

8:30 a.m.	Development team meetings: Silicon Tetrafluoride, Boron tribromide
9:15	Development team meetings: As needed
10:00	Developmental Toxicity Update (Marcel van Raaij)
11:00	Revisit of Toluene- PBPK Approach (George Woodall/Sylvia Talmage)
12:00 p.m.	Lunch
1:00	Review of Acrylonitrile (George Rodgers/Bob Young)
2:30	Review of Bromine Chloride (George Cushmac/Sylvia Talmage)
3:30	Break
3:45	Revisit of Diketene (Bob Benson/Kowetha Davidson)
5:30	Adjourn for the day

Thursday, March 22, 2007

8:30 a.m.	Review of Silicon Tetrafluoride (Ernest Falke/ Cheryl Bast)
9:30	Review of Oxygen difluoride (Iris Camacho/Bob Young)
10:30	Break
10:45	Review of Boron Tribromide (Bob Benson/ Sylvia Talmage)
11:45	Administrative matters
12:00 noon	Adjourn meeting

*See Page 2.

NAC/AEGL Meeting 42: March 20-22, 2007

Chemical: Attendance **CAS Reg. No.:** ATTACHMENT 2

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

Chemical Manager: **Staff Scientist:**

NAC Member	AEGL1	AEGL2	AEGL3	LOA
Henry Anderson				
Steven Barbee				
Marc Baril				
Lynn Beasley				
Alan Becker				
Robert Benson				
George Cushmac				
Ernest Falke				
~~Alfred Feldt~~				
Roberta Grant				
Dieter Heinz				
~~John Hinz~~				
Jim Holler				
David Freshwater DOE				
Sylvia Talmage ORNL				

NAC Member	AEGL1	AEGL 2	AEGL3	LOA
~~Warren Jederberg~~				
~~Glenn Leach~~				
Richard Niemeier				
~~Marinelle Payton~~				
Susan Ripple				
George Rodgers				
Marc Ruijten				
George Rusch, Chair				
~~Daniel Sudakin~~				
Richard Thomas				
Calvin Willhite				
George Woodall				
Cheryl Bast ORNL				
Bob Young ORNL				
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:** _____

ATTACHMENT 3

ALIPHATIC NITRILES:

RESPONSE TO FR09 COMMENTS ON ACETONITRILE

NAC/AEGL-42
March 20-22, 2007
Irvine, CA

ORNL: Staff Scientist: Cheryl Bast
Chemical Manager: George Rodgers
Chemical Reviewers: Ernest Falke and George Rusch

Selected Aliphatic Nitriles TSD discussed by the NAC in September, 2003 (NAC-30) and published in FR09

TSD contains AEGL value derivations for five chemicals:

Acetonitrile
Isobutyronitrile
Propionitrile
Chloroacetonitrile
Malononitrile

Received many comments on acetonitrile only

Even though we only received comments on acetonitrile, we need to keep the whole TSD in perspective.

AEGL-2 and AEGL-3 values for chloroacetonitrile and malononitrile were derived by analogy to acetonitrile using i.p. lethality data and a relative potency approach.

Values for isobutyronitrile and propionitrile were based on chemical-specific data; however, we need to make sure that the relative toxicity of all nitriles is appropriate

Acetonitrile< Chloroacetonitrile< Propionitrile< Isobutyronitrile< Malononitrile

All comments from:
INEOS Nitriles
INEOS USA LLC
2600 South Shore Blvd.
Suite 250
League City, Texas 77573

COMMENT: Several unpublished studies were provided for consideration.

RESPONSE: All of these studies have been reviewed and are well-conducted, GLP studies. However only two of the studies will be incorporated into the TSD, because the others are not inhalation studies and are not directly related to AEGL value derivation/support. COT has recommended that this type of information be limited in the TSD.

Studies to be Added to the TSD:

MPI Research. An Acute Inhalation Toxicity Study of Acetonitrile in Mice. Study 780-006, April 27, 1998.

To be added to Section II.3.1.2: Acute lethality- mice

E.I. du Pont de Nemours and Company. In Vitro Dermal Absorption Rate Testing of Acetonitrile. Project 17521, October 27, 2005.

To be added to Section I.1: Absorption, Metabolism, Disposition, and Excretion.

The following studies are well conducted but will not be added to the TSD:

MPI Research. An Acute Dermal Toxicity Study of Acetonitrile in Rabbits. Study 780-003, November 24, 1997.

MPI Research. A Dermal Irritation Study of Acetonitrile in Rabbits. Study 780-004, November 20, 1997.

Hilltop Research Inc. Delayed Contact Hypersensitivity Study of Acetonitrile in Guinea Pigs. Project 97-8472-21, August 18, 1997.

MPI Research. An Eye Irritation Study of Acetonitrile in Rabbits. Study 780-005, November 24, 1997.

MPI Research. An Acute Oral Toxicity Study of Acetonitrile in Mice. Study 780-002, April 27, 1998.

Central Toxicology Laboratory. Mouse Bone Marrow and Peripheral Blood Micronucleus Test of Acetonitrile. Report CTL/P/6051, October 27, 1998.

Bioassay Systems Corporation. In Vitro Gene Mutation Assay (HGPRT Locus) of Acetonitrile in Cultured Chinese Hamster Ovary Cells. Project 11725, April 27, 1984.

COMMENT: **Section I.6 Temporal Extrapolation**

Suggest using n value (1.550) derived from acute rat lethality data in Tables II.2 and II.3 using Dose Resp program of tenBerge.

RESPONSE: Agree with comment. Currently an n value of 2.5 is applied (from 5 rat LC_{50} data points ranging from 15-min through 8-hr). Where appropriate, AEGL values will be scaled across time using n = 1.55.

COMMENT: **Summary, page II-5- more information on uses/production is provided.**

RESPONSE: This information will be added to TSD.

COMMENT: Section II.3.2.4 Monkeys

The cited report by Pozzani et al (1959) of hemorrhage of the superior and inferior sagittal sinuses of the brain has been further investigated by Dr. Robert Garman, DVM, in cooperation with Dr. Karl Jensen of the US EPA. This involved recovery and re-evaluation of the original brain sections from the monkeys exposed by Pozzani. Dr. Garman's full report and Dr. Jensen's response are provided separately as attachments. In summary it has been concluded upon re-evaluation that the hemorrhage reported in Pozzani et al is not a manifestation of acetonitrile toxicity, but rather an artifact of postmortem alteration and tissue handling procedures at the time of the study.

RESPONSE: Text will be revised to reflect new findings.

COMMENT: Section II.4.3 Derivation of AEGL-1

We question the justification for holding the concentration constant across all time points because no human data exists for periods less than 4 hours. There are ample experimental toxicity data on acetonitrile demonstrating that responses are concentration dependent. It is also interesting to note that in human case reports cited in the draft technical support document that have resulted in fatalities, there was apparently no avoidance stimuli triggered by the exposures to acetonitrile vapor. Given that the odor threshold is well below the lethal concentrations, this suggests that exposure to acetonitrile vapor may not induce notable discomfort or irritation at relatively high levels.

We recommend that the AEGL-1 values be scaled across time in a manner similar to the AEGL-2 and AEGL-3 values.

RESPONSE: The current AEGL-1 values and justification and possible revision and justification are presented below. Either of these sets of AEGL-1 values is consistent with possible AEGL-2 and AEGL-3 values for acetonitrile, as well as values for the other nitriles in this TSD.

	10-min	30-min	1-hr	4-hr	8-hr	Endpoint
Current AEGL-1	13 ppm	13 ppm	13 ppm	13 ppm	13 ppm	Values held constant
Possible Revision	53 ppm	53 ppm	34 ppm	13 ppm	8.4 ppm	Time scaling: n = 1.55

Current Text:

The slight chest tightness and cooling sensation in the lungs noted by one of three human male volunteers exposed to 40 ppm acetonitrile for 4 hours (Pozzani et al., 1959) will be used as the basis for AEGL-1 values. No intraspecies uncertainty factor will be applied. This approach is considered justified because the mild effect (slight chest tightness and cooling sensation) is considered to have occurred in a sensitive subject since no symptoms were reported by two other subjects exposed to this same regimen and no effects were noted at 80 ppm for four hours in these two individuals. A modifying factor of 3 was applied to account for the sparse data base.

The resulting 13 ppm concentration will be held constant across all time points because no human data exist for periods of less than 4-hours; thus, time-scaling to shorter durations could yield values eliciting symptoms above those defined by AEGL-1.

Possible Revision:

The values will be scaled across time using an n value of 1.55, derived from rat lethality data. The 30-min value will be adopted as the 10-min value because the POD is 4-hours. Values are supported by the fact that only minor chest tightness and a cooling sensation were noted in one of three subjects exposed to 40 ppm acetonitrile for 4-hours, and only minor effects were noted in two (less-sensitive) subjects exposed to 80 or 160 ppm for 4-hours.

COMMENT: **Section II.5.3 Derivation of AEGL-2**

The human data published by Pozzani et al 1959 and cited in the draft report show that volunteers exposed to 160 ppm acetonitrile vapor for 4 hours did not produce adverse effects. Applying the 30x uncertainty factor derived in the draft technical support document for setting human values based on rat data, in a reverse fashion, suggests that rats would tolerate 4 hour exposures to 4800 ppm with no serious effects. However, the Union Carbide data cited in the draft document reports 10% mortality in rats exposed to 4000 ppm acetonitrile vapor for 4 hours. This demonstrates that the 30x uncertainty factor for establishing AEGL values based on rat data is larger than is warranted by the data.

RESPONSE: The total uncertainty factor of 30 appears to be appropriate, and resulting values ARE supported by the human data. While it is true that only minor effects were noted in two human volunteers exposed to 160 ppm acetonitrile for 4 hours, a third (more sensitive) volunteer experienced minor effects at 40 ppm for 4-hours (this was the POD for AEGL-1 values). Due to his increased sensitivity, this volunteer was not exposed to the 160 ppm concentration. Therefore, it is quite possible that a more severe effect may have been noted if the sensitive individual had been tested at the higher concentration.

The interspecies UF of 10 is considered appropriate because rat data were used and the rat is not the most sensitive species. Rat data were utilized because they provide a much more robust data set over a wider concentration range than do the mouse data. Data currently in the TSD suggest that the mouse, rabbit, and guinea pig are much more sensitive than the rat, and this fact is also confirmed by results of the 4-hr mouse LC_{50} provided by the commenter.

COMMENT: Section II.5.3 Derivation of AEGL-2

Acetonitrile is somewhat unusual in that chronic exposures to animals below levels that produce lethality do not result in notable systemic effects. It is one of the very few compounds where doses for the chronic NTP rodent bioassays were based on mortality in 90-day studies, and there was no evidence of chronic toxicity in these state-of-the-art studies. A recent review of this topic by Dr. Ernest McConnell, DVM, is attached for your reference. This point is recognized by EPA in the current IRIS file for acetonitrile, which identifies lethality as the key endpoint for establishing the RfC value for acetonitrile. Given the absence of pulmonary effects in the NTP rodent bioassays of acetonitrile, and the earlier discussion of Dr. Robert Garman's review of the vascular changes noted in the Pozzani monkey study we disagree with the selection of slight pulmonary congestion in the Pozzani rat study as the key endpoint for establishing AEGL-2 values. Tissue handling and necropsy procedures, as well as the method of exsanguination are serious confounders for this endpoint. We believe that the absence of this finding in more recent well conducted studies raises sufficient concern for it to be discounted. The NTP study results suggest that both the AEGL-2 and AEGL-3 values are most appropriately based on mortality as the endpoint of concern.

RESPONSE: Given the procedural problems identified in the Pozzani monkey study and data from the NTP rodent studies, it is appropriate to reconsider the POD for AEGL-2 values. The statement by the commenter that "AEGL-2 values are most appropriately based on mortality" presents a challenge for the NAC, because the lethality endpoint is above the usual definition of AEGL-2. No clear AEGL-2 POD from an acute study is identified in the available literature. Therefore, it may be necessary to derive AEGL-2 values by taking one-third of the AEGL-3 values. (4-Hour rat lethality data suggest that curve is relatively steep: 3/12 mortality at 8000 ppm; 9/12 at 16,000 ppm; 12/12 at 32,000 ppm).

Possible AEGL-2 options are as follows. Any of these sets of AEGL-2 values are consistent with possible AEGL-1 and AEGL-3 values for acetonitrile, as well as values for the other nitriles in this TSD.

	10-min	30-min	1-hr	4-hr	8-hr	Endpoint
Current AEGL-2	310 ppm	310 ppm	230 ppm	130 ppm	100 ppm	POD = 4000 ppm; 4-hr Slight pulmonary congestion and hemorrhage in rats UF = 30 (Intra = 3; Inter = 10); n = 2.5
Possible Revision (Same POD and UF; revised 'n' value)	510 ppm	510 ppm	326 ppm	130 ppm	85 ppm	POD = 4000 ppm; 4-hr Slight pulmonary congestion and hemorrhage in rats UF = 30 (Intra = 3; Inter = 10); n = 1.55
Possible Revision (AEGL-3 Revision 4÷ 3)	***370 ppm***	***180 ppm***	***120 ppm***	***120 ppm***	***120 ppm***	***(AEGL-3 Revision 4÷ 3)***
Possible Revision "Other" AEGL-3÷ 3						"Other" AEGL-3÷ 3

COMMENT: Section II.6.3 Derivation of AEGL – 3

We recommend using an 'n' value of 1.550 for scaling across time points as explained earlier in our comments about 'Temporal Extrapolation'.

We are not entirely comfortable with the calculated 4-hr rat LC01 value of 8421 ppm presented in the draft document. Our concern is driven by several factors. First, other cited 4-hr rat experiments conducted at 8000 ppm produced much higher mortality (e.g. Union Carbide, 30%; Pozzani, 12.5%). Second, we calculated a 4- hr rat LD01 of 2,194 ppm based on all of the dose specific data presented in Tables II.2 and II.3 in the draft document.

Lastly and perhaps most importantly we are concerned about calculating LD values below the observable range of the underlying experiments. There are ample 4-hr and 8-hr rat data available to support LD calculations. The group sizes in these experiments ranged from 10 to 30 animals; accordingly LD05 calculations would be suitable from these data. We ran LD05 calculations using Dr. ten Berge's DoseResp software, which produced a 4-hr LD05 value of 4,112 ppm, and an 8-hr LD05 value of 3,301 ppm. Calculation of rat LD05 values in DoseResp using the dose specific data in Tables II.2 and II.3 for all exposure durations yielded the following results:

Minutes	LD_{05}
10	33,620 ppm
30	16,540 ppm
60	10,580 ppm
240	4,323 ppm
480	2,764 ppm

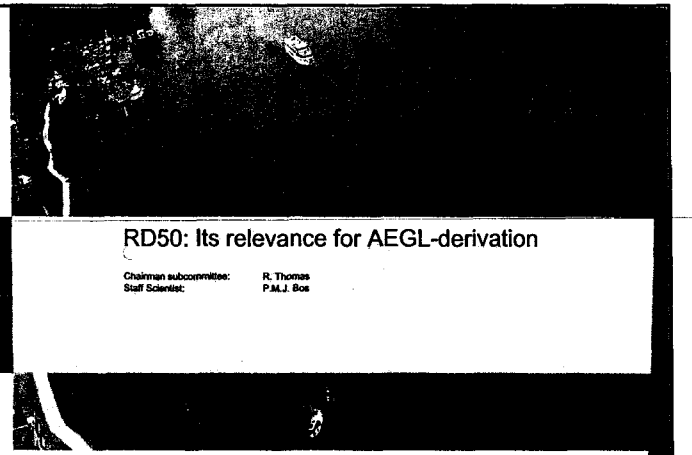
RESPONSE:

Possible AEGL-3 Options are as follows. Any of these sets of AEGL-3 values are consistent with possible AEGL-1 and AEGL-2 values for acetonitrile, as well as values for the other nitriles in this TSD.

	10-min	30-min	1-hr	4-hr	8-hr	Endpoint
Current AEGL-3	650 ppm	650 ppm	490 ppm	280 ppm	210 ppm	POD = 8421 ppm; 4-hr Rat LC_{01} UF = 30 (Intra = 3; Inter = 10) n = 2.5
Possible Revision-1 (Same POD and UF; revised 'n' value)	1100 ppm	1100 ppm	690 ppm	280 ppm	180 ppm	POD = 8421 ppm; 4-hr Rat LC_{01} UF = 30 (Intra = 3; Inter = 10) n = 1.55 Monsanto 1986
Possible Revision-2 (Rat LC_{01} POD from combined data)	280 ppm	280 ppm	180 ppm	73 ppm	47ppm	POD = 2194 ppm; 4-hr Rat LC_{01} (all data sets) UF = 30 (Intra = 3; Inter = 10) n = 1.55 *NOTE: The 4- and 8-hr values are inconsistent with human data (Pozzani)* 1959
Possible Revision-3 (Rat LC_{05} values from DoseResp)	1100 ppm	550 ppm	350 ppm	140 ppm	92 ppm	POD = Rat LC_{05} (all data sets- DoseResp) UF = 30 (Intra = 3; Inter = 10) *NOTE: The 4- and 8-hr values are inconsistent with human data (Pozzani)*

Suggestions

	10-min	30-min	1-hr	4-hr	8-hr	Endpoint
AEGL-1	**53 ppm**	**53 ppm**	**34 ppm**	**13 ppm**	**8.4 ppm**	**POD = 40 ppm; 4-hr Slight chest tightness and cooling sensation (1/3 human volunteers) UF =1; MF = 3 Time scaling: n = 1.55**
AEGL-2	**370 ppm**	**180 ppm**	**120 ppm**	**120 ppm**	**120 ppm**	**AEGL-3 ÷3**
AEGL-3	**1100 ppm**	**550 ppm**	**350 ppm**	**350 ppm**	**350 ppm**	**POD = Rat LC_{05} for 10-min, 30-min, 1-hr (all data sets- DoseResp) Adopt 1-hr as 4- and 8-hr value to be consistent with human data UF = 30 (Intra = 3; Inter = 10)**



RD50: Its relevance for AEGL-derivation

Chairman subcommittee: R. Thomas
Staff Scientist: P.M.J. Bos

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Aim

- The evaluation of the mouse bioassay (Alarie-test) for its use in AEGL-derivation
  - If yes: under what conditions
- The mouse bioassay addresses sensory irritation as mediated by trigeminal nerve stimulation
- The document is **not** meant to provide guidance on sensory irritation in general or to discuss other methods for the assessment of sensory irritation

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2

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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3

RD50: Historical overview

- Detailed review of sensory irritation by Alarie in 1973
  - Sensory irritant
  - Pulmonary irritant
  - Bronchoconstrictor
  - 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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4

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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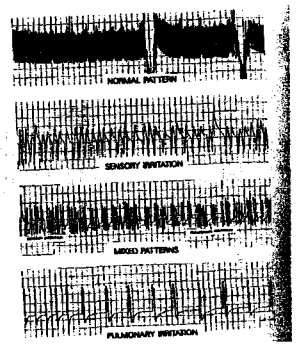
RD50: Methodology – Breathing patterns



Obtained from Alarie et al., 2000

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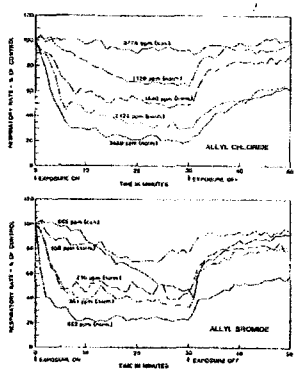
RD50: Methodology – Time-response curve



Obtained from Nielsen and Bakbo, 1985

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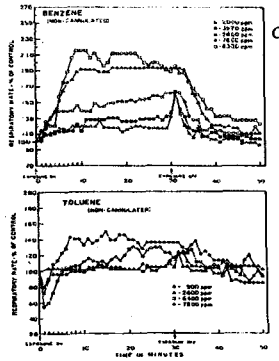
RD50: Methodology – Time-response curve



Obtained from Nielsen and Alarie, 1982

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RD50: Methodology – Log concentration-response curve

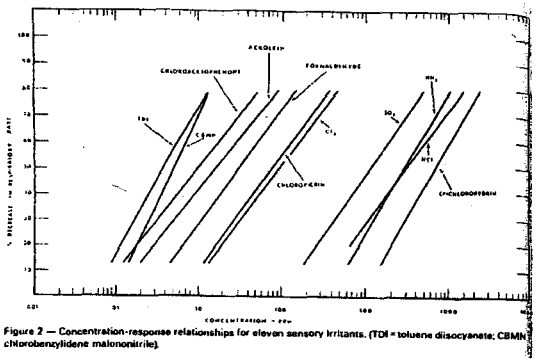

Figure 2 — Concentration-response relationships for eleven sensory irritants. (TDI = toluene diisocyanate; CBMN = chlorobenzylidene malononitrile).

Obtained from Kane et al., 1979

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RD50: Methodology – POD for risk assessment

- Alarie and colleagues
  - RD_{50}
  - 0.03 * RD_{50}
- Nielsen and colleagues
  - Broke down the factor of "0.03" in two components
    - 0.15 to extrapolate RD_{50} to RD_0
    - 0.2 as an uncertainty factor
  - Recommended Indoor Limit
    - RIL: RD50/133 (0.03 * (8/24) * (5/7) = 0.03/4)
- Basic starting point: "0.03 * RD_{50} is OEL"
  - Both RD_{50} and RD_0 to be used as starting point (Nielsen et al. 2007)

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RD50: Predictive power

- Human equivalent
  - A burning or stinging sensation in eyes, nose, or throat
- Validation of the bioassay (qualitative)
  - Alarie (1966; 1973): 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.
- 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)

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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
    - Perceived risk versus actual risk

RD50: Extrapolation to humans

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

RD50: Validation for extrapolation to humans

- Alarie (1966, 1973)
  - 51 substances tested
  - 1-min exposure of mice to $C^n t$ of (10 and) 40 min*mg/m^3
  - Humans exposed to $C^n t$ between 5 and 80 (1 and 50) min*mg/m^3
  - Animal response: "undefined significant" 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
    - "underclassification" in mice

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

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

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RD50: Comparison with TLVs

- Correlation of $R^2 = 0.78$
- Remarks:
  - 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)
    - Odor stimulation interferes in human data
    - TLVs have different levels of protection
    - 2006: 42 out of 89 TLVs are (intended to be) changed

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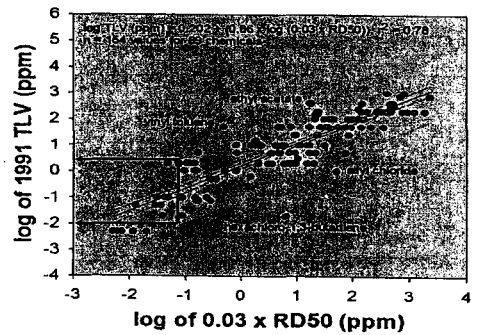
RD50: Comparison with TLVs



Obtained from Alarie et al., 2000

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RD50: Comparison with TLVs

- Correlation is not equal to association
- Most TLVs are not based on adequate human data
- Predictive range includes 2-3 orders of magnitude
  - AEGLs are predictive rather than protecting thresholds
- TLVs not suitable for calibration of RD_{50} values

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RD50: Comparison with TLVs

log TLV = 0.202 + 0.86*log(0.03*RD50)
= 0.202 + 0.86*log 0.03 + 0.86*log RD50
= 0.202 + (-1.310) + 0.86*log RD50
= -1.108 + 0.86*log RD50

*No basis for a specific relationship between the TLV and **0.03***RD50, but merely for a correlation between the TLV and any **a***RD50*

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RD50: Pungency thresholds *(Cometto-Muniz & colleagues)*

- 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

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RD50: Comparison with NPT

- Good agreement of eye irritation in normosmics and NPT in anosmics
  - both effects reflect trigeminus nerve stimulation

- Nasal Pungency Thresholds often are orders of magnitudes higher than odor thresholds
  - trigeminus versus olfactory stimulation

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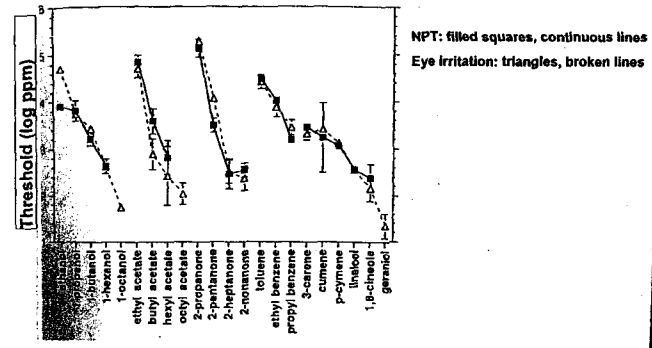
RD50: NPT versus eye irritation thresholds



Obtained from Cometto-Muniz, 2000

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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 against direct extrapolation of RD50s to humans
  - Additional human data on sensory irritation is needed

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Conclusions: Starting point

- At present quantitative determination of human equivalent from an RD_{50} is not possible
  - Different responses in mice and humans
  - Basic effect is similar: trigeminal nerve stimulation
- Alternative approach
  - Starting point: If a chemical has a potential for trigeminal nerve stimulation in mice it will also be capable to stimulate the trigeminal nerve in humans
  - Threshold to be defined:
    - Highest response level without an adverse health impact

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Conclusions: Threshold determination

- Bos et al. 1992:
  - RD_{10} based on maximum upper tolerance limit of 9.2% in OF_1 mice for respiratory rate reduction
- Alarie, 1998:
  - Just Detectable Effect of 12%
  - Responses <12% are considered ineffective and omitted from further analyses
  - ASTM: "Slight response" starts at 12%
- Threshold proposal: RD_{10}
  - Compare methemoglobinemia, FEV_1, carboxyhemoglobinemia

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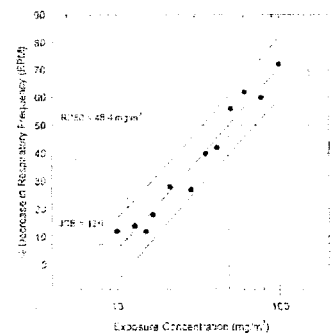
Threshold determination



Obtained from Alarie, 1998

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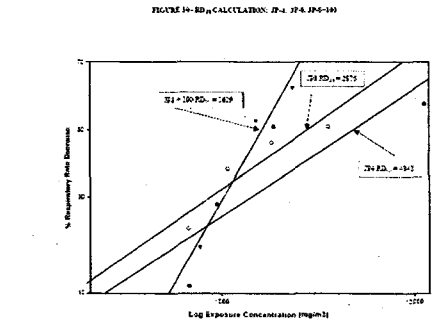
Threshold determination



JP4: closed circles

JP8: open circles

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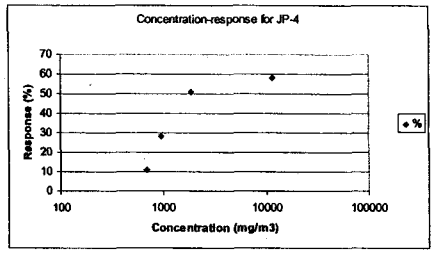
Threshold determination



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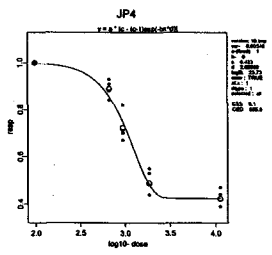
Threshold determination



DR-modeling:

RD_{50}: 1780 mg/m³

RD_{10}: 556 mg/m³

Linear regression:

RD_{50}: 4842 mg/m³

RD_{10}: appr. 250 mg/m³

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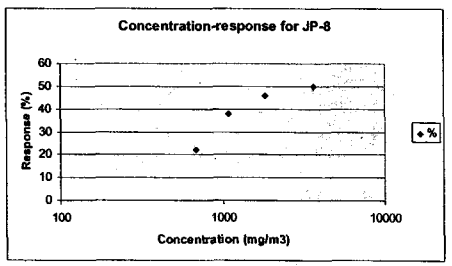
Threshold determination



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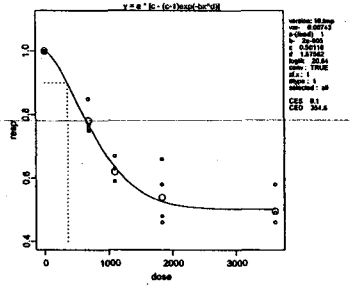
Threshold determination

JP8



DR-modeling:

RD_{50}: 2500 mg/m³

RD_{10}: 355 mg/m³

Linear regression:

RD_{50}: 2876 mg/m³

RD_{10}: appr. 150 mg/m³

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RD50: Toxicity profile

- Sensory irritation is in compliance with AEGL-1 definition
- Can sensory irritation be placed at the lower continuum of a toxicity profile?
- 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: 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
Ethyl benzene	9000			11,700 (4-h) 8000 (8-h)	rat
*Chloroformates**					
Methyl	52.4	1/4 at 50 ppm	mouse	88 (1-h) 47 (2-h)	rat mouse
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		

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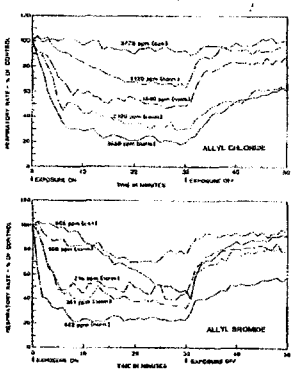
RD50: Time-extrapolation



Obtained from Nielsen and Bakbo, 1985

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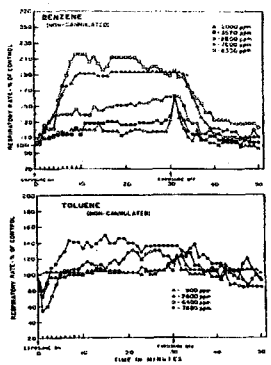
RD50: Time-extrapolation



Obtained from Nielsen and Alarie, 1982

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RD50: Time-extrapolation

- Shusterman et al. (2006) evaluated applicability of Haber's Law for human sensory irritation data
- Two human studies on ammonia, two on chlorine, one on formaldehyde
- Conclusions: limited data but
  - Effect of concentration on perceived stimulus is greater than duration
  - Plateau response or reversal of the time-effect
  - Time-extrapolation would require complex models
- Practical recommendation: similar AEGL-1 values for all time-points

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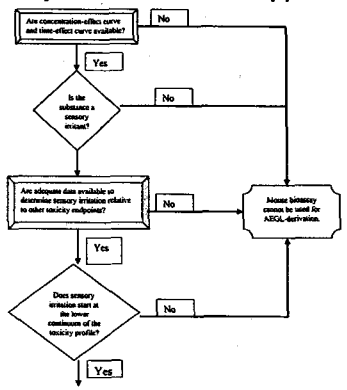
Mouse bioassay: Recommended approach



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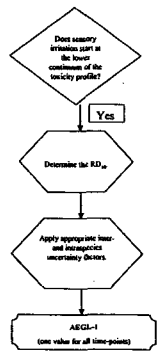
Mouse bioassay: Recommended approach



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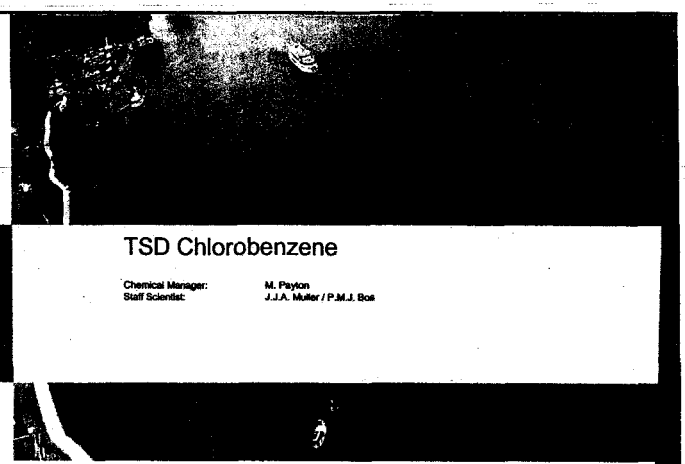

TSD Chlorobenzene

Chemical Manager: M. Payton
Staff Scientist: J.J.A. Muller / P.M.J. Bos

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Chlorobenzene: Use and Physical-chemical properties

- Use:
  - Solvent
  - Intermediate for chemcial synthesis (e.g. dyestuffs, pharmaceuticals)
- Physical-chemical properties
  - Molecular weight: 112.56
  - Colorless liquid
  - Water solubility: 500 mg/L
  - Boiling point: 132° C
  - Odor: aromatic, almond-like
    - Reported odor threshold: 0.2-1.8 ppm (insufficient for derivation of LOA)
  - Explosive: LEL=1.3%

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Chlorobenzene: Human data

- Case studies:
  - drowsiness, incoordination, unconsciousness
- Experimental: kinetic studies
  - Ogata et al. (1991)
    - Four male volunteers; 60 ppm for 7 hours (3+4)
    - disagreeable odor, drowsiness
    - headache, throbbing pain in the eyes, sore throat
    - decreased flicker fusion frequency
  - Knecht and Woitowitz (2000):
    - Eight volunteers (6 M, 2F); 10 ppm for 8h/d, 5d
    - no complaints

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Chlorobenzene: Animal lethality data

TABLE 2. Summary of Selected Relevant Acute Lethal Inhalation Data in Laboratory Animals

Species	Concentration (ppm)	Exposure Time	Effect[a]	Reference
rats (male)	2965	6 hours	LC_{50}	Bonnet *et al.* 1982
rats (or mice)	4400	2 hours	LC_{100}	Rozenbaum 1947 as cited by BUA 1990
cats	3700	7 hours	mortality	Flury and Zernik 1931
cats	8000	2 hours	mortality	Flury and Zernik 1931
rats	22000	3.5 hours	mortality in 2 out of 3	Anonymous, 1994
rats	9000	6 hours	mortality in 2 out of 3	Anonymous, 1994
mice (female)	1886	6 hours	LC_{50}	Bonnet *et al.* 1979
mice	7832 4070 2244	2 hours 2 hours 2 hours	LC_{84} LC_{50} LC_{16}	Sanotsky and Ulanova 1975 as cited by IRPTC 1988

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Chlorobenzene: Animal lethality data

TABLE 2. Summary of Selected Relevant Acute Lethal Inhalation Data in Laboratory Animals

Species	Concentration (ppm)	Exposure Time	Effect	Reference
rat (2-generation study)	450	6 h/d for 7 d/w up to 17 weeks	No mortality	Nair *et al.* 1984
pregnant rabbits	3000 1000	6 h/d for 13 days	Mortality No mortality	John *et al.* 1984
pregnant rats	3000 1000	6 h/d for 10 days	Mortality No mortality	John *et al.* 1984
Rats	248	7h/d; 5 d/w for 24 w	No mortality	Dilley 1977

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Chlorobenzene: Animal lethality data

- Bonnet *et al.* 1982
  - Rats: *Probit = -33 + 10.9 log C*
- Bonnet *et al.* 1979
  - Mice: *Probit = -17.06 + 6.734 log C*

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Chlorobenzene: Nonlethal animal data

TABLE 3. Summary of Selected Acute Nonlethal Inhalation Data in Laboratory Animals

Species	Concentration (ppm)	Exposure Time	Effect	Reference
rats (male)	1500 1000	8 h/d for 5 d	Reduction in auditary-evoked respons No effect	Frantik *et al.* 1994
rats (male)	611	4 hours	Shortening of the tonic extension of the hind limbs by 37.5% after electrical stimulation	Frantik *et al.* 1994
Cats	8000 2400-2900 1200 220-660	½ hour 2 hours 1 hour unknown several hours	Narcotic Mortality Unsteady movement, tremors, Clear narcotic effects Bearable for hours	Gotzmann 1904 as cited by Flury and Zernik 1931
mice (male)	1054	5 minutes	RD_{50} for sensory irritation	De Ceaurriz *et al.* 1981
mice	75	3 hours once or on 5 days	No effect on murine host defense	Aranyi *et al.* 1986
mice (female)	610	2 hours	Increase in velocity of the tonic extension of the hind limbs by 30% after electrical stimulation	Frantik *et al.* 1994
mice (male)	650	4 hours	Decrease in immobility in the "behavioral despair" swimming test by 2	De Ceaurriz *et al.* 1983

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Chlorobenzene: Developmental/reproduction

Developmental toxicity studies in rats and rabbits (John *et al.* 1984; Hayes *et al.* 1981).

- Preliminary study: 0, 300, 1000, 3000 ppm (6h/d, d6-15 (rats), d6-18 (rabbits))
  - 3000 ppm: severe toxicity, mortality
  - 1000 ppm: reduced body weight gain, organ weight changes, increased number of resorptions
  - 300 ppm: liver effects
- Main study: 0, 75, 210, 590 ppm
  - 590 ppm: maternal toxicity (reduced body weight gain; increased liver weights), no significant teratogenic effects
  - 210 ppm: NOAEL in rats, maternal toxicity in rabbits (increased liver weights), no significant teratogenic effects
- Two-generation study in rats *(Nair et al.* 1987)
- Chlorobenzene is not a developmental toxicant

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Chlorobenzene: available data

- Carcinogenicity
  - NTP gavage study in rats and mice: increase in the occurrence of neoplastic nodules of the liver in high dose group male rats only.

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Chlrorobenzene: Kinetics

- Kinetic studies in human volunteers
  - Main excretion products (urine): 4-chlorocatechol conjugates and 4-chlorophenylmercapturic acid
- PBPK-modeling
  - Human model only
  - Insufficient data to determine the appropriate dose-metric
  - Focused on main metabolite: 4-chlorocatechol
  - Too much uncertainty to be useful at the moment

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Chlorobenzene: AEGL-1

- No relevant animal data
- Human kinetic studies
  - Ogata et al. (1991)
    - Four male volunteers; 60 ppm for 7 hours (3+4)
    - disagreeable odor, drowsiness
    - headache, throbbing pain in the eyes, sore throat
    - decreased flicker fusion frequency
  - Knecht and Woitowitz (2000):
    - Eight volunteers (6 M, 2F); 10 ppm for 8h/d, 5d
    - no complaints

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Chlorobenzene: AEGL-1

- 8-hour exposure to 10 ppm as conservative POD
  (Knecht and Woitowitz (2000)
  - Interspecies UF: 1
  - Intraspecies UF: 1
    - Effects rather slight; possible odor interference
    - Repeated exposure (5 days)
  - Flatlining:
    - Irritation and CNS depression
    - Chlorobenzene levels in blood reach steady-state within one hour
- AEGL-1: 10 ppm for all time points

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Chlorobenzene: AEGL-2

- No relevant human data for AEGL-2
- Animal data adresses sub-AEGL-2 effects
  - 1000 ppm NOAEL for adverse auditory effects after repeated exposure
    - Relevance for single exposure difficult to assess
    - 1000 ppm higher than LC_{01} of 851 in mice
- No relevant POD for AEGL-2
  - AEGL-2 set as 1/3 AEGL-3
    - Lower levels not warranted (Ogata *et al.*, 1991)

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Chlorobenzene: AEGL-3

- No relevant human data
- Animal data only available from secondary sources or old and poorly described
- Bonnet et al.(1979): point of departure
  - 6-hour mouse LC_{50}: 1886 ppm (probit function)
  - 6-hour rat LC_{50}: 2965 ppm (probit function)
  - Mouse more susceptible: LC_{01} of 851 ppm chosen as POD

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Chlorobenzene: AEGL-3

- Point of departure: 6-h LC_{01} of 851 ppm
  - Interspecies UF: 1
    - Most susceptible species
    - Humans have already lower uptake than mice at similar concentrations
    - Higher UF not supported by human data (Ogata et al. 1991)
  - Intraspecies UF: 3
    - Relatively small interindividual variability for CNS-depression
  - Default values of n
    - n=1 for extrapolation to 480 min
    - n=3 for extrapolation to 30 min – 240 min
    - 10-min AEGL-3 = 30-min AEGL-3

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Chlorobenzene: AEGL-3

TABLE 6. AEGL-3 Values for Chlorobenzene

10-minute	30-minute	1-hour	4-hour	8-hour
650 ppm (3055 mg/m³)	650 ppm (3055 mg/m³)	520 ppm (2444 mg/m³)	320 ppm (1504 mg/m³)	210 ppm (987 mg/m³)

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Chlorobenzene: Summary of AEGL-values

TABLE 7. Summary of AEGL Values					
	Exposure Duration				
Classification	10-minute	30-minute	1-hour	4-hour	8-hour
AEGL-1 (Nondisabling)	10 ppm (47 mg/m³)	10 ppm (47 mg/m³)	10 ppm (47 mg/m³)	10 ppm (47 mg/m³)	10 ppm (47 mg/m³)
AEGL-2 (Disabling)	220 ppm (1034 mg/m³)	220 ppm (1034 mg/m³)	170 ppm (799 mg/m³)	110 ppm (517 mg/m³)	70 ppm (329 mg/m³)
AEGL-3 (Lethal)	650 ppm (3055 mg/m³)	650 ppm (3055 mg/m³)	520 ppm (2444 mg/m³)	320 ppm (1504 mg/m³)	210 ppm (987 mg/m³)

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Chlorobenzene: Additional data

- Additional data from Utah Biomedical Test Laboratory
  - 30-min whole body exposures of rats and guinea pigs (5 animals/sex/species)
  - 14-day observation before sacrifice
  - **2990 ppm**
    - slight eye and nasal irritation in rats and guinea pigs; none were judged to have impaired escape ability
  - **5850 ppm** (3950-7300)
    - Ataxia/narcosis in most rats, quick recovery; most animals were judged to have impaired escape ability
    - Narcosis in all guinea pigs; all animals judged to have impaired escape ability
  - **7970 ppm**
    - No deaths; ataxia within 10 min, narcosis within 15 min (guinea pigs) or 25 min (rats). All animals judged to have impaired escape ability

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Chlorobenzene: Alternative AEGL-2 values

- POD: 2990 ppm for 30 min (rats and guinea pigs)
  - Interspecies UF: 3
  - Intraspecies UF: 3
  - n=3 to 10 min exposure
  - n=1 to 60 min exposure
  - 4- and 8-h values equal to 1-h value
    - Chlorobenzene levels in blood reach steady-state within one hour
    - 4- (37 ppm) and 8-h value (19 ppm) would conflict with human data

TABLE. AEGL-2 Values for Chlorobenzene				
10-minute	30-minute	1-hour	4-hour	8-hour
430 ppm	300 ppm	150 ppm	150 ppm	150 ppm

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Chlorobenzene: Alternative 10-min AEGL-3 value

- No mortality in rats and guinea pigs after 30-min exposure to 7970 ppm
  - Interspecies UF: 3
  - Intraspecies UF: 3
  - n=3 to 10 min exposure
  - 10-min value of 1100 ppm

TABLE. AEGL-3 Values for Chlorobenzene				
10-minute	30-minute	1-hour	4-hour	8-hour
940 ppm	650 ppm	520 ppm	320 ppm	210 ppm

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Chlorobenzene: Alternative AEGL values

TABLE Summary of AEGL Values					
	Exposure Duration				
Classification	10-minute	30-minute	1-hour	4-hour	8-hour
AEGL-1 (Nondisabling)	10 ppm	10 ppm	10 ppm	10 ppm	10 ppm
AEGL-2 (Disabling)	*430 ppm*	*300 ppm*	*150 ppm*	*150 ppm*	*150 ppm*
AEGL-3 (Lethal)	*940 ppm*	650 ppm	520 ppm	320 ppm	210 ppm

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ATTACHMENT 6

#5

ACUTE EXPOSURE GUIDELINE LEVELS
for
TOLUENE

National Advisory Committee for AEGLs Meeting 42
March 20-22, 2007

ORNL Staff Scientist:
Sylvia S. Talmage

Chemical Manager:
George Woodall

Chemical Reviewer:
Marquea King

TOLUENE

Background:

The Draft TSD was written in 1999. At that time inter- and intrapspecies uncertainty factors of 3 and 3 were applied, and values were time scaled ($C^n \times t = k$) from the key study based on a mouse lethality study (n = 2). These values were unacceptable to the National Academy of Sciences (NAS) AEGL Subcommittee, and they suggested using available PBPK models and the rich data set of human and animal studies to develop more realistic values.

In the absence of modelers and modeling values, the TSD was re-written in 2002 with more realistic values. By 2004, Jim Dennison of CenturyEnvironmental and Claudia Troxel of the ORNL staff had completed a first draft of a White Paper on PBPK modeling that used toluene as an example chemical. At its January 2007 meeting, a revised White Paper received positive reviews by the NAS. Earlier, in 2006, AEGL values for xylenes, based on the same modeling technique, were accepted by the NAS.

TOLUENE AEGL VALUES

Classification	Exposure Duration				
	10-Minute	30-Minute	1-Hour	4-Hour	8-Hour
AEGL-1	200 ppm 200 ppm **200 ppm**	115 ppm 200 ppm **200 ppm**	82 ppm 200 ppm **200 ppm**	41 ppm 200 ppm **200 ppm**	29 ppm 200 ppm **200 ppm**
AEGL-2	600 ppm 990 ppm **1600 ppm**	267 ppm 570 ppm **780 ppm**	189 ppm 510 ppm **590 ppm**	94 ppm 510 ppm **410 ppm**	67 ppm 510 ppm **340 ppm**
AEGL-3	2000 ppm 7200 ppm **13,000 ppm**	897 ppm 4200 ppm **6100 ppm**	634 ppm 2900 ppm **4500 ppm**	317 ppm 1500 ppm **3000 ppm**	224 ppm 1500 ppm **2500 ppm**

TOLUENE - POINTS OF DEPARTURE

AEGL-1: Based on multiple clinical studies of exposure to 200 ppm for several hours. Some protocols included peak exposures to 300 ppm and exercise. Modeling was not used for the endpoint of sensory irritation/notable discomfort.

AEGL-2: Based a NOAEL for neurotoxicity in a clinical study following successive 20-minute exposures of 12 healthy male subjects to 100, 300, 500, and 700 ppm (Gamberale and Hultengren 1972). Blood concentrations were measured during this and other clinical studies.

AEGL-3: Based on a NOAEL for lethality following a 2-hour exposure of the rat to 6250 ppm (Mullin and Krivanek 1982).

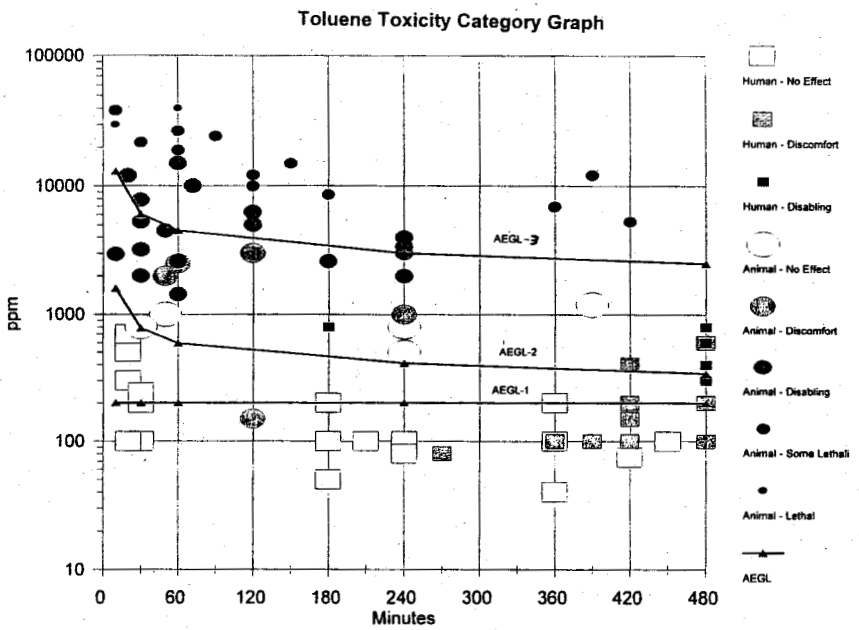
TOLUENE - MODELING

The concentration of the parent chemical toluene in the brain, as reflected by the concentration in the blood, determines the neurotoxic effect. It is assumed that this concentration would be the same in rodents and humans.

A validated PBPK model for rats was used, i.e., rat data sets were tested in the model. The model was scaled to human parameters and validated with the human data sets.

AEGL-2: the concentration in the venous blood (Cv, the internal dose) following the successive 20-minute exposures to toluene (a NOAEL for neurotoxicity) was provided in the key study (Gamberale and Hultengren 1972). The actual exposures were equivalent to a 20-minute exposure to 1000 ppm. An intraspecies uncertainty factor of 1 was applied because the effect was judged to be considerably below the threshold for narcosis. Furthermore, larger uncertainty factors would lower the values below the AEGL-1. PBPK modeling was used to determine the equivalent exposure concentration that yields the dose metric at each AEGL exposure duration.

AEGL-3: the rat model was used to determine the internal dose metric for the rat at the 2-hour NOAEL for lethality of 6250 ppm (Mullin and Krivanek 1982). The model was scaled to human parameters and, based on a minimum alveolar concentration range of 2-3 for volatile anesthetics in humans, an intraspecies uncertainty factor of 3 was applied to the dose metric. The PBPK model was used to determine the human values for the relevant exposure durations.



AEGL VALUES FOR XYLENES

Classification	Exposure Duration				
	10-Minute	30-Minute	1-Hour	4-Hour	8-Hour
AEGL-1	130 ppm	130 ppm	130 ppm	130 ppm	130 ppm
AEGL-2	1100 ppm	590 ppm	400 ppm	400 ppm	400 ppm
AEGL-3	3300 ppm	1700 ppm	1100 ppm	1100 ppm	1100 ppm

ATTACHMENT 7

ACUTE EXPOSURE GUIDELINE LEVELS FOR BROMINE CHLORIDE (BrCl)

National Advisory Committee for AEGLs Meeting
March 20-22, 2007

ORNL Staff Scientist:
Sylvia S. Talmage

Chemical Manager:
George Cushmac

Chemical Reviewers:
Alan Becker
Daniel Sudakin

BROMINE CHLORIDE

Mixture of bromine and chlorine (BrCl), about 40% undissociated.

Used as a water-treatment biocide and in fire-retardant chemicals, pharmaceuticals, brominated liquids, agricultural chemicals, dyes, and bleaching agents

Production data not located.
Production of bromine - several hundred thousand tons/year

Human Studies
No data

Animal Studies
A single lethality study with the rat was located (Dow Chemical Co. 1977).
Measured concentrations of 20, 40, 80, 120 ppm
Exposure duration 7 hours
Respective mortalities of 0/6, 0/6, 1/6, 5/6

BROMINE CHLORIDE

Toxicity predicted to be between that of chlorine and bromine

Chlorine: 1-hour highest non-lethal value for rat of 200-300 ppm (multiple studies)
Time-scaled 7-hour value would be 75-100 ppm
Bromine: Reliable data not available
Data on toxicity relative to chlorine available for mouse:
Chlorine is 1.3 to 2-fold more toxic than bromine

Relative Toxicities of Chlorine and Bromine to the Mouse

Chemical	30-Minute LC_{50}	Reference
Chlorine	203 127	Bitron and Aharonson 1978 Schlagbauer and Henschler 1967
Bromine	424 174	Bitron and Aharonson 1978 Schlagbauer and Henschler 1967

Fluorine: 1-hour highest non-lethal value for rat of 140 ppm (Keplinger and Suissa 1968)
Time-scaled 7-hour value would be 64-70 ppm

BROMINE CHLORIDE

Relative toxicity: Fluorine > chlorine > bromine
Atomic weights: 19, 35.5, 80, respectively

Water solubility: Bromine is more water soluble than chlorine;
more readily scrubbed in the upper respiratory tract
Chlorine: 0.092 moles/L
Bromine: 0.214 moles/L
Fluorine: reacts with water

BROMINE CHLORIDE

AEGL-1:

In the absence of data that meets the definition of an AEGL-1, the AEGL-1 values for bromine chloride was set equal to the AEGL-1 values for chlorine.

The AEGL-1 value for chlorine of 0.5 ppm for all exposure durations was based on a NOAEL for irritation in a well-conducted 8-hour clinical study (two 4-hour exposures with a break between) that included a sensitive individual (Rotman et al. 1983). There were several support studies with many individuals. Because a sensitive individual was included, an intraspecies uncertainty factor of 1 was applied. The value was not time-scaled because there is adaptation to the slight irritation that defines the AEGL-1.

AEGL-1 Values for Bromine Chloride				
10 minutes	**30 minutes**	**1 hour**	**4 hours**	**8 hours**
0.50 ppm	0.50 ppm	0.5 ppm	0.50 ppm	0.50 ppm

BROMINE CHLORIDE

AEGL-3:

Point of Departure:

Consider the 7-hour 80 ppm value the threshold for lethality. The single death was delayed, occurring 3 days after the exposure.

Uncertainty factors:

The 80 ppm value was divided by inter- and intraspecies uncertainty factors of 3 each for a total of 10. Uncertainty factors of 3 each are generally applied to direct-acting irritants.

Time-scaling:

In the absence of empirical data, the default values of n = 3 and n = 1 were used for time-scaling to shorter and longer exposure durations, respectively.

Alternative points of departure:

Threshold for lethality of 70 ppm

No mortality at 40 ppm

BROMINE CHLORIDE

Point of departure: 7-hour exposure to 80 ppm

AEGL-3 Values for Bromine Chloride				
10 minutes	**30 minutes**	**1 hour**	**4 hours**	**8 hours**
19 ppm	19 ppm	15 ppm	9.6 ppm	7.0 ppm

Point of departure: 7-hour exposure to 70 ppm

AEGL-3 Values for Bromine Chloride				
10 minutes	**30 minutes**	**1 hour**	**4 hours**	**8 hours**
17 ppm	17 ppm	13 ppm	8.4 ppm	6.1 ppm

Point of departure: 7-hour exposure to 40 ppm

AEGL-3 Values for Bromine Chloride				
10 minutes	**30 minutes**	**1 hour**	**4 hours**	**8 hours**
9.6 ppm	9.6 ppm	7.7 ppm	4.8 ppm	3.5 ppm

AEGL-2:

Divide the AEGL-3 values by 3

Point of departure: 7-hour exposure to 80 ppm

AEGL-2 Values for Bromine Chloride				
10 minutes	**30 minutes**	**1 hour**	**4 hours**	**8 hours**
6.3 ppm	6.3 ppm	5.0 ppm	3.2 ppm	2.3 ppm

Point of departure: 7-hour exposure to 70 ppm

AEGL-2 Values for Bromine Chloride				
10 minutes	**30 minutes**	**1 hour**	**4 hours**	**8 hours**
5.7 ppm	5.7 ppm	4.3 ppm	2.8 ppm	2.0 ppm

Point of departure: 7-hour exposure to 40 ppm

AEGL-2 Values for Bromine Chloride				
10 minutes	**30 minutes**	**1 hour**	**4 hours**	**8 hours**
3.2 ppm	3.2 ppm	2.6 ppm	1.6 ppm	1.2 ppm

PROPOSED BROMINE CHLORIDE AEGLs

Classification	Exposure Duration				
	10-Minute	30-Minute	1-Hour	4-Hour	8-Hour
AEGL-1	0.50 ppm	0.50 ppm	0.50 ppm	0.50 ppm	0.50 ppm
AEGL-2 (POD 80 ppm)	6.3 ppm	6.3 ppm	5.0 ppm	3.2 ppm	2.3 ppm
AEGL-3 (POD 80 ppm)	19 ppm	19 ppm	15 ppm	9.6 ppm	7.0 ppm

FINAL CHLORINE AEGLs

Classification	Exposure Duration				
	10-Minute	30-Minute	1-Hour	4-Hour	8-Hour
AEGL-1	0.50 ppm	0.50 ppm	0.50 ppm	0.50 ppm	0.50 ppm
AEGL-2	2.8 ppm	2.8 ppm	2.0 ppm	1.0 ppm	0.70 ppm
AEGL-3	50 ppm	28 ppm	20 ppm	10 ppm	7.1 ppm

#6

ATTACHMENT 8

ACUTE EXPOSURE GUIDELINE LEVELS FOR BORON TRIBROMIDE (BBr_3)

National Advisory Committee for AEGLs Meeting
March 20-22, 2007

ORNL Staff Scientist:
Sylvia S. Talmage

Chemical Manager:
Bob Benson

Chemical Reviewers:
Marc Baril
Calvin Willhite

BORON TRIBROMIDE

Colorless, fuming liquid

Important industrial chemical, but no data on production were located

Hydrolysis in the presence of moisture is considered rapid,
but no relevant information on the hydrolysis half-life was located
Hydrolysis yields three moles of hydrogen bromide and one mole of boric acid

Mechanism of action: irritation, likely due to hydrogen bromide breakdown product
Inhalation toxicity of boric acid in the mouse (Krystofiak and Schaper 1996):
300 mg/m^3 for 3 hours (~120 ppm): <20% decrease in respiratory rate
sensory irritation, no pulmonary effects

Human Studies:
No data.

Animal Studies:
No data.

Comparison of LC_{50} Data - Hydrogen Halides and Boron Trihalides

Hydrogen chloride and boron trichloride:
1-hour LC_{50} values in the rat (Vernot et al. 1977)
Hydrogen chloride: 3124 ppm (males)
Boron trichloride: 2541 ppm (males)
4418 ppm (females)
Similar pathological findings

Hydrogen fluoride and boron trifluoride:
1-hour LC_{50} in rats:
Hydrogen fluoride: 966-1300 ppm (NAS 2004)
4-hour LC_{50} for boron trifluoride in male and female rats (Rusch et al. 1986)
1.21 mg/L (~435 ppm); tested as dihydrate
Time scaled to 1 hour = 690-1740 ppm (n = 3 to 1)
2 ppm for 13 weeks: no toxic response
Boron trifluoride also rapidly reacts with moisture

Relative toxicity of hydrogen halides: HF > HCl ≥ HBr (Stavert et al. 1991)
Relative toxicity if boron trihalides: $BF_3 > BCl_3$ ..... > BBr_3 ?

Boron trihalides more toxic than/similar in toxicity to hydrogen halides....

BORON TRIBROMIDE

In absence of empirical data, the AEGLs were based on the breakdown product, hydrogen bromide.

Hydrogen Bromide AEGL Values					
Classification	Exposure Duration				
	10-minute	30-minute	1-hour	4-hour	8-hour
AEGL-1	1 ppm	1 ppm	1 ppm	1 ppm	1 ppm
AEGL-2	100 ppm	43 ppm	22 ppm	11 ppm	11 ppm
AEGL-3	740 ppm	250 ppm	120 ppm	31 ppm	31 ppm

AEGL-1: based on a NOAEL for notable discomfort (3 ppm) in a study with six human volunteers exposed to 2, 3, 4, 5, or 6 ppm HBr for several minutes (Connecticut State Department of Health 1955). An intraspecies uncertainty factor of 3 was applied.
AEGL-2: Analogy with HCl (1300 ppm for 30 minutes; Stavert et al. 1991); however, mortality in rats exposed to HBr at this concentration/duration was 8%.
AEGL-3: Based on 1-hour $BMCL_{05}$ of HBr in rats of 1239 ppm (MacEwen and Vernot 1972). Based on the mechanism of direct-acting irritation, UFs of 3 and 3 for a total of 10 were applied. Because HBr is well scrubbed in the upper respiratory tract, the 8-hour AEGL-2 and AEGL-3 values were set equal to the respective 4-hour values.

BORON TRIBROMIDE

Boron tribromide hydrolyzes into three moles of hydrogen bromide
Hydrogen bromide considered the toxic breakdown product

AEGL-1: In the absence of empirical data, the AEGL-1 for boron tribromide was derived by dividing the AEGL-1 for hydrogen bromide by 3. For both hydrogen bromide and boron tribromide, the same value was used across all exposure durations because there is adaptation to the slight irritation defined by the AEGL-1.

AEGL-1 Values for Boron Tribromide				
10 minutes	**30 minutes**	**1 hour**	**4 hours**	**8 hours**
0.33 ppm	0.33 ppm	0.33 ppm	0.33 ppm	0.33 ppm

BORON TRIBROMIDE

AEGL-2:

In the absence of empirical data and because the value for hydrogen bromide is two chemicals removed from boron tribromide, the AEGL-2 for boron tribromide was based on one-third of the hydrogen bromide AEGL-3 (according to SOP guidelines for chemicals with steep dose-response curves).

AEGL-2 Values for Boron Tribromide				
10 minutes	**30 minutes**	**1 hour**	**4 hours**	**8 hours**
83 ppm	28 ppm	13 ppm	3.3 ppm	3.3 ppm

BORON TRIBROMIDE

AEGL-3: In the absence of empirical data and based on the breakdown of boron tribromide into three moles of hydrogen bromide, the AEGL-3 values for boron tribromide were set at one-third of the hydrogen bromide AEGL-3 values.

AEGL-3 Values for Boron Tribromide				
10 minutes	**30 minutes**	**1 hour**	**4 hours**	**8 hours**
250 ppm	83 ppm	40 ppm	10 ppm	10 ppm

PROPOSED BORON TRIBROMIDE AEGLs

Classification	Exposure Duration				
	10-Minute	**30-Minute**	**1-Hour**	**4-Hour**	**8-Hour**
AEGL-1	0.33 ppm	0.33 ppm	0.33 ppm	0.33 ppm	0.33 ppm
AEGL-2	83 ppm	28 ppm	13 ppm	3.3 ppm	3.3 ppm
AEGL-3	250 ppm	83 ppm	40 ppm	10 ppm	10 ppm

ATTACHMENT 9

ACUTE EXPOSURE GUIDELINE LEVELS (AEGLs) FOR DIKETENE

NAC/AEGL-42
March 20-22, 2007
Irvine, CA

ORNL Staff Scientist: Kowetha Davidson

Chemical Manager: Bob Benson

Chemical Reviewers: John Hinz and Dieter Heinz

AEGL-1 VALUES: DIKETENE				
10 minute	30 minute	1 hour	4 hour	8 hour
0.019 ppm	0.019 ppm	0.019 ppm	0.019 ppm	0.019 ppm

Species: Human
Concentration: 0.58 ppm
Time: 1 minute
Endpoint: Mild eye, nose, and throat irritation (occupational)
Reference: Danishevskii, 1948; 1951 (cited in Fel'dman, 1967)

Time Scaling:

One-minute POD scaled to 10-min using $c^n \times t = k$, where the exponent, n, is the conservative default of 1.

30-min, 1-hr, 4-hr, and 8-hr values held constant across time because minor irritation does not vary greatly over time.

Uncertainty Factors:

Interspecies = 1: Human data

Intraspecies = 3: Direct-acting irritant

Mechanism of Toxicity

Direct-acting Irritant

Data Set

Very Sparse

AEGL-2 VALUES: DIKETENE				
10 minute	30 minute	1 hour	4 hour	8 hour
12 ppm	8.0 ppm	6.3 ppm	1.6 ppm	0.80 ppm

Endpoint:

Three-fold reduction of AEGL-3 values. Estimated threshold for the inability to escape.

(Although rats exposed to 250 ppm for 1-hr exhibited severe irritation, this concentration is >the POD for AEGL-3)

AEGL-3 VALUES: DIKETENE				
10 minute	30 minute	1 hour	4 hour	8 hour
35 ppm	24 ppm	19 ppm	4.8 ppm	2.4 ppm

Species: Rat
Concentration: 190 ppm
Time: 1 hour
Endpoint: $BMCL_{05}$
Reference: Katz, 1987

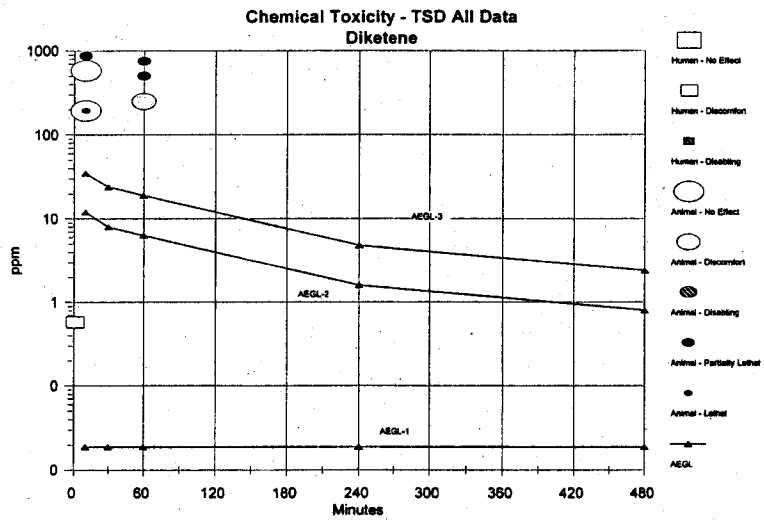
Time Scaling: $c^n \times t = k$, where the exponent, n, is the conservative default of 1 (4-hr and 8-hr) or 3 (10-min and 30-min).

Uncertainty Factors:

Interspecies = 3: Direct-acting irritant

Intraspecies = 3: Direct-acting irritant

Extant Standards and Guidelines for Diketene					
Guideline	Exposure Duration				
	10 minute	30 minute	1 hour	4 hour	8 hour
AEGL-1	0.019 ppm	0.019 ppm	0.019 ppm	0.019 ppm	0.019 ppm
AEGL-2	12 ppm	8.0 ppm	6.3 ppm	1.6 ppm	0.80 ppm
AEGL-3	35 ppm	24 ppm	19 ppm	4.8 ppm	2.4 ppm
ERPG-1 (AIHA)			1 ppm		
ERPG-2 (AIHA)			5 ppm		
ERPG-3 (AIHA)			~~17 ppm~~ 20 ppm		



ATTACHMENT 10

ACUTE EXPOSURE GUIDELINE LEVELS (AEGLs)
FOR
SILICON TETRAFLUORIDE
7783-61-1

NAC/AEGL-42
March 20-22, 2007
Irvine, CA

ORNL Staff Scientist: Cheryl Bast

Chemical Manager: Ernest Falke

Chemical Reviewers: George Rusch and Paul Tobin

AEGL-1 VALUES: SILICON TETRAFLUORIDE				
10 minute	30 minute	1 hour	4 hour	8 hour
0.30 ppm	0.30 ppm	0.30 ppm	0.30 ppm	0.30 ppm

Species: Rat
Concentration: 0.30 ppm
Time: 6 hr/day, 5 days/week for 4 weeks
Endpoint: Irritation during and after each exposure
Reference: IRI, 1988

Time Scaling: AEGL values held constant across time because minor irritation does not vary greatly over time.

Uncertainty Factors:

Interspecies = NA

Intraspecies = NA

Irritation did not increase in severity throughout a 4-week study and partially resolved between exposures

Mechanism of Toxicity: Irritant

Data Set: Sparse

Cannot use Hydrogen Fluoride Molar Equivalence Approach

AEGL-2 VALUES: SILICON TETRAFLUORIDE				
10 minute	30 minute	1 hour	4 hour	8 hour
19 ppm	13 ppm	10 ppm	2.6 ppm	1.3 ppm

Endpoint: Three-fold reduction of AEGL-3 values.

Approach justified by steep concentration-response curve

60% mortality in rats exposed to 100 ppm and 100% mortality at 150 ppm; 6 hours/day for up to 5 days (IRI, 1988)

Values considered protective

Rats exposed to 3.0 or 15 ppm for 6 hours/day, 5 days/week for 4 weeks showed signs of irritation during and after each exposure, and nasal, bone, and tooth pathology at the end of the study period (IRI, 1988)

AEGL-3 VALUES: SILICON TETRAFLUORIDE				
10 minute	30 minute	1 hour	4 hour	8 hour
56 ppm	39 ppm	31 ppm	7.7 ppm	3.8 ppm

Species: Rat
Concentration: 307 ppm
Time: 1 hour
Endpoint: Estimated lethality threshold (⅛ the LC_{50} of 922 ppm)
Reference: Scheel et al., 1968

POD justified by steep concentration-response curve

60% mortality in rats exposed to 100 ppm and 100% mortality at 150 ppm; 6 hours/day for up to 5 days (IRI, 1988)

Time Scaling: $c^n \times t = k$, where the exponent, n, is the conservative default of 1 (4-hr and 8-hr) or 3 (10-min and 30-min).

Uncertainty Factors:
Interspecies = 3: Direct-acting irritant
Intraspecies = 3: Direct-acting irritant

No MF for sparse database because values derived with a total adjustment of 10 would range from 19 ppm at 10-min to 1.3 ppm at 8-hrs.

No mortality in rats exposed to 3.0 or 15 ppm 6/hr day, 5 days/week for 4 weeks

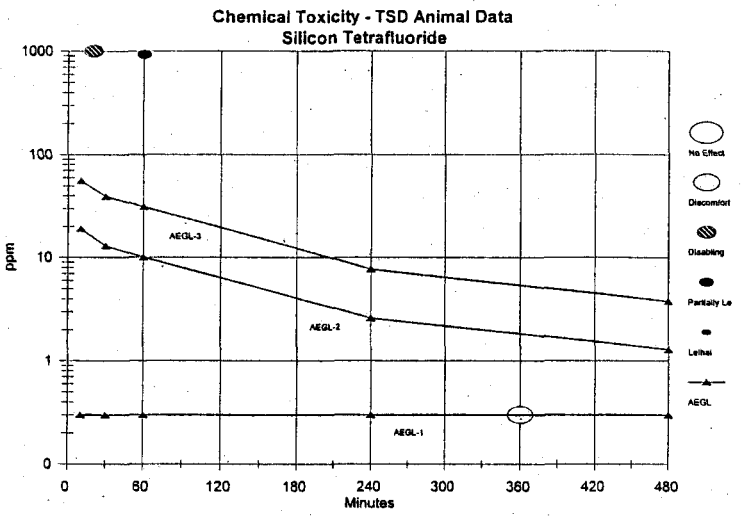
Support for Proposed AEGL-3 values:

POD: 1000 ppm for 20 min (rats)- Severe irritation , respiratory difficulty, lethargy, no mortality (Gage, 1970)

Same time scaling and UF application.

10 minute	*30 minute*	*1 hour*	*4 hour*	*8 hour*
125 ppm	*66 ppm*	*33 ppm*	*8.2 ppm*	*4.1 ppm*

There are no other standards or guidelines for silicon tetrafluodride!



ATTACHMENT 11

ACUTE EXPOSURE GUIDELINE LEVELS
ACRYLONITRILE

NAC/AEGL-42

March, 2007
Irvine, CA

ORNL Staff Scientist:
Robert Young

Chemical Manager:
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Chemical Reviewers:
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ACRYLONITRILE - HUMAN EXPOSURE DATA

- **16-100 ppm for 20-45 min (Wilson et al., 1948): headache, nasal & ocular irritation, irritability, nervousness; concurrent exposure to other polymerizes ??**
- **> 5 ppm - 20 ppm (Sakurai and Kusumoto, 1972; Sakurai et al., 1978): headache, fatigue, nausea, insomnia in occupational setting; questionable monitoring**
- **4.6 ppm for 8 hrs (Jakubowski et al., 1987): no effect among 6 informed volunteer subjects**

ACRYLONITRILE - ANIMAL LETHALITY DATA

- **Data in multiple species**
  - **monkeys, rats, cats, dogs, rabbits, guinea pigs**
  - **dog most sensitive**
  - **multiple exposure durations for several species**
  - **rat data set most robust**

ACRYLONITRILE - ANIMAL LETHALITY DATA

Toxicity of AN vapor in rats exposed for 0.5 to 8 hours (Dudley and Neal, 1942).

Exposure (hrs)	Exposure Conc. (ppm)	Mortality During Exposure	Total Mortality	Effects*
0.5	2445	0	0	marked; slight residual effects to 24 hrs
	1490	0	0	marked; no residual effects in 24 hrs
	1270	0	0	marked; no residual effects in 24 hrs
	665	0	0	moderate transitory effects
1	2445	0	13/16	deaths in 4 hrs; slight effects at 24 hrs in survivors
	1490	0	4/16	deaths in 4 hrs; slight effects at 24 hrs in survivors
	1270	0	0	marked effects; slight effects at 24 hrs; normal at 48 hrs
	665	0	0	marked transitory effects
2	1260	0	16/16	fatal; deaths within 4 hrs
	595	0	6	marked transitory effects
	305	0	0	slight transitory effects
4	635	8/16	16/16	fatal
	315	4/16	5/16	marked; no effects in survivors at 24 hrs
	130	0	0	slight transitory effects
8	320	15/16	15/16	fatal
	270	7/16	7/16	marked; no effects in survivors at 24 hrs
	210	1/16	1/16	marked transitory effects
	135	0	0	moderate transitory effects
	90	0	0	slight discomfort

ACRYLONITRILE - ANIMAL LETHALITY DATA

Lethal response of rats exposed to AN at various exposure concentration/durations (Appel et al., 1981).		
Exposure conc. (ppm)	**Exposure duration (min)**	**Mortality ratio**
650	180	1/3
950	120	1/3
1100	120	3/3
1600	30	0/3
2600	30	1/3
3000	30	6/6
2400	10	0/3

ACRYLONITRILE - ANIMAL LETHALITY DATA

Lethality in rats following nose-only inhalation exposure to AN for 4 hours (WIL Res. Labs, 2005)					
Exposure Conc. (ppm)	**Mortality During Exposure**		**Total Mortality**		**Comments**
	M	**F**	**M**	**F**	
539	0	0	0	0	
775	0	0	0	0	
871	0	0	1	3	deaths at 0 to 1 day postexposure
1006	1	1	3	4	2 (♂), 3 (♀) at 0 to 1 day postexposure
1181	4	3	5	4	1 (♂), 1 (♀) at 0 to 1 day postexposure

ACRYLONITRILE - ANIMAL LETHALITY DATA

Toxicity of AN vapor in dogs exposed for 4 hours (Dudley and Neal, 1942).		
Exposure Conc. (ppm)	Gender	Effects
30	F	slight salivation by end of exposure period; no other effects
	F	slight salivation by end of exposure period; no other effects
	F	slight salivation by end of exposure period; no other effects
	F	slight salivation by end of exposure period; no other effects
65	F	severe salivation; weak by end of exposure
	F	coma by end of exposure; died at 8 hrs
100	M	Severe salivation during exposure; full recovery within 24 hrs
	F	Convulsions at 2.5 hrs; coma by end of exposure; partial paralysis of hind legs for 3 days
	F	Convulsions at 2.5 hrs; coma by end of exposure; full recovery within 48 hrs
110	F	coma at end of exposure; dead at 4.5 hrs
	M	coma at end of exposure; dead at 3 days
	F	coma at end of exposure; food refusal for 10 days; slowly recovered
165	F	convulsions at 2 hrs; dead at 3 hrs of exposure
	M	coma from end of exposure to death at 4 hrs.

ACRYLONITRILE - ANIMAL DATA (NONLETHAL)

- Monkeys
  - No toxicity in rhesus monkeys exposed to 56 ppm, 4 hrs/day, 5 days/wk for 4 weeks (Dudley et al., 1942)
  - Rhesus monkeys (Dudley and Neal, 1942)
    - 65 ppm, 4 hrs - no effect
    - 90 ppm, 4 hrs - slight redness of face and genitals, slight increase in respiratory rate

- Rats
  - Dudley and Neal, 1942
    - 0.5 hrs, 2440 ppm: slight to moderate transitory effects
    - 1 hr, 1270 ppm: slight to moderate transitory effects
    - 2 hrs, 305 ppm: slight transitory effects
    - 4 hrs, 130 ppm: slight transitory effects
    - 8 hrs, 135 ppm: slight to moderate transitory effects
  - Appel et al., 1981
    - 10 min, 2400 ppm: no deaths
    - 0.5 hrs, 1600 ppm: no deaths
  - WIL Research Laboratories, 2005
    - 4 hrs, 775 ppm: no deaths

ACRYLONITRILE - ANIMAL DATA (NONLETHAL)

- Dogs (Dudley and Neal, 1942)
  - 6 hrs, 25-50 ppm: alterations in body temperature (Haskell Labs, 1942)
  - 1.75 hrs, 225 ppm: transient cardiovascular effects, signs of irritation, vomiting, incoordination (Haskell Labs, 1942)
  - 4 hrs, 30 ppm: salivation (Dudley and Neal, 1942)
  - 4 hrs, 65 ppm: weakness and coma with recovery (Dudley and Neal, 1942)
  - 4 hrs, 100 ppm: convulsions with recovery (Dudley and Neal, 1942)

- Rabbits (Dudley and Neal, 1942)
  - 135 ppm, 4 hrs: slight to marked transitory effects

ACRYLONITRILE - ANIMAL DATA (NONLETHAL)

Nonlethal Toxicity of AN in Laboratory Species			
Species	Exposure Concentration	Exposure duration	Effects
Monkey	56 ppm	4 hrs/d, 5 days/wk, 4 wks	no toxicity (Dudley et al., 1942)
	65 ppm	4 hrs	no significant effects (Dudley and Neal, 1942)
	90 ppm	4 hrs	no significant effects (Dudley and Neal, 1942)
Dog	25-50 ppm	6 hrs	transient alterations in body temp. (Haskell Labs, 1942)
	225 ppm	1.75 hrs	transient cardiovascular effects, irritation, vomiting, incoordination (Haskell Labs, 1942)
	30 ppm	4 hrs	salivation (Dudley and Neal, 1942)
	65 ppm	4 hrs	weakness, coma, recovery (Dudley and Neal, 1942)
	100 ppm	4 hrs	convulsions, recovery (Dudley and Neal, 1942)
Cat	100 ppm	4 hrs	salivation, reddened skin (Dudley and Neal, 1942)
	275 ppm	4 hrs	marked salivation, signs of pain (Dudley and Neal, 1942)
Rat	100 ppm	4 hrs/day, 5 days/wk, 8 wks	slight lethargy (Dudley et al., 1942)
	100 ppm	5 hrs/day, 5 days	histological alterations (Bhooma et al., 1992)
	539 ppm	4 hrs (nose-only)	no significant effects (WIL Res. Labs (2005)
	775 ppm	4 hrs (nose-only	ataxia, labored breathing, hyperactivity (WIL Res. Labs (2005)
	2445 ppm	0.5 hrs	marked but reversible effects (Dudley and Neal, 1942)
	1270 ppm	1 hr	marked but reversible effects (Dudley and Neal, 1942)
	1600 ppm	1 hrs	no lethality (Appel et al., 1981)
	2400 ppm	0.17 hrs	no lethality (Appel et al., 1981)
	130 ppm	4 hrs	slight transitory effects (Dudley and Neal, 1942)
	135 ppm	8 hrs	moderate transitory effects (Dudley and Neal, 1942)

ACRYLONITRILE - ANIMAL DATA (NONLETHAL)

Nonlethal Toxicity of AN in Laboratory Species			
Species	Exposure Concentration	Exposure duration	Effects
Guinea pig	100-265 ppm	4 hrs	slight or no effect (Dudley and Neal, 1942)
Cat	100 ppm 275 ppm 56 ppm	4 hrs 4 hrs 4 hrs/d, 5 d/wk, 8 wks	salivation and slight transient effects (Dudley and Neal, 1942) marked effects; no deaths (Dudley and Neal, 1942) notable effects (vomiting, lethargy, weakness) 1 of 4 died (Dudley and Neal, 1942)
Rabbit	100-135 ppm 100 ppm	4 hrs 4 hrs/d, 5 d/wk, 8 wks	slight to marked transitory effects (Dudley and Neal, 1942) lethargic and listless, no weight gain (Dudley and Neal, 1942)

ACRYLONITRILE TOXICITY

- Teratogenic effect in rats (Murray et al., 1978)
  - possible teratogenic effect in offspring of rats exposed to 80 ppm, 6 hrs/day on g.d. 6-15
  - 40 ppm, 6 hrs/day NOAEL

- Developmental toxicity in rats (Saillenfait et al., 1993)
  - reduced fetal weight; ≥25 ppm, 6 hrs/day, g.d. 6-20
  - 12 ppm NOAEL

- Genotoxicity
  - equivocal: generally positive in *in vitro* and negative in *in vivo* studies

- Carcinogenicity
  - carcinogenic in rats following chronic exposure (80 ppm)
  - epidemiologic data inadequate
  - Category 2b (possibly carcinogenic to humans) (IARC, 1999)

ACRYLONITRILE TOXICITY

- Species Variability
  - qualitatively similar effects
  - dog most sensitive
  - metabolism may account for some variability

- Susceptible populations
  - variability in oxidative metabolism

- Metabolism & disposition
  - readily absorbed and distributed
  - excretion primarily via the urine
  - toxicity directly related to metabolism
    - epoxidation to 2-cyanoethylene oxide (CEO)
    - conjugation with glutathione
    - cyanide end-product
  - evidence that parent compound may be instrumental in clonic convulsions

ACRYLONITRILE AEGL-1

AEGL-1 Values for Acrylonitrile				
10-min	30-min	1-hr	4-hr	8-hr
52 ppm	19 ppm	10 ppm	2.9 ppm	1.5 ppm

Critical effect/POD: No-effect level in male human volunteer subjects exposed to 4.6 ppm AN for 8 hours (Jakubowski et al., 1987).

Uncertainty factors: Total uncertainty adjustment of 10.

Interspecies: UF = 3; a non-human primate is considered a more relevant model than rodents, dogs or cats.

Intraspecies: UF = 3; the effects associated with acute AN exposure are not likely to vary greatly among individuals; metabolism is not likely to be instrumental in initial minor effects resulting from low-level exposure.

Modifying factor: none applied

Time scaling: empirically derived n of 1.1

ACRYLONITRILE AEGL-2

AEGL-2 Values for Acrylonitrile				
10-min	30-min	1-hr	4-hr	8-hr
160 ppm	60 ppm	32 ppm	9 ppm	4.8 ppm

Critical effect/POD: Redness of face and genitals, slight weakness, slight increase in respiratory rate in rhesus monkeys exposed for 4 hours to 90 ppm AN. Effects were transient and resolved within 12 hours post exposure (Dudley and Neal, 1942). Support: Sakurai et al. (1978) - headache, fatigue, nausea, and insomnia upon initial occupational exposure to AN in excess of 5 ppm; Wilson et al. (1948) - occupational exposure to 16-100 ppm for 20-45 minutes produced transient dull headaches, nasal and ocular irritation, discomfort in the chest, nervousness and irritability.

Uncertainty factors: Total uncertainty adjustment of 10.
Interspecies: UF = 3; a non-human primate is considered a more relevant model than rodents, dogs or cats; occupational exposure data as support
Intraspecies: UF = 3; the effects associated with acute AN exposure are not likely to vary greatly among individuals; metabolism is not likely to be instrumental in initial minor effects resulting from low-level exposure

Modifying factor: none
Time scaling: empirically derived *n* of 1.1 was applied.

ACRYLONITRILE AEGL-3

AEGL-3 Values for Acrylonitrile				
10-min	30-min	1-hr	4-hr	8-hr
430 ppm	160 ppm	100 ppm	35 ppm	19 ppm

Critical effect/POD: Estimated lethality threshold (30-minute, 1-hr, 2-hr,4-hr, and 8-hr $BMCL_{05}$ values are 1578.0, 1024.4, 491.3, 179.5 and 185.8 ppm, respectively) for rats exposed to various concentrations of AN for 30 minutes, 1, 2, 4, or 8 hours. The 4-hr value was not used due to inconsistency with values of the other durations. The 4-hour AEGL was time-scaled using the 8-hour $BMCL_{05}$. (Dudley and Neal, 1942; Appel et al., 1981a)

Uncertainty factors: Total uncertainty adjustment of 10.
Interspecies: UF = 3; Although the dog appears to be the most sensitive species, the overall database for rats is more robust thereby justifying use of the rat data. PBPK model simulations (Kedderis and Fennell, 1996; Sweeney et al., 2003) indicated that predicted blood and brain concentrations of AN and the metabolite CEO (2-cyanoethylene oxide) were similar in rats and humans exposed to AN by inhalation. A factor of 3 is considered sufficient to account for possible toxicodynamic/metabolism differences
Intraspecies: UF = 3; For effects resulting from a single acute exposure, an intraspecies uncertainty factor of 3 is sufficient for accounting for variability in metabolism-mediated effects. Additional uncertainty factor application would result in incompatible AEGL-3 and AEGL-2 values.

ACRYLONITRILE AEGL-3

AEGL-3 Values for Acrylonitrile				
10-min	30-min	1-hr	4-hr	8-hr
430 ppm	160 ppm	100 ppm	35 ppm	19 ppm

Time scaling: For the 30-minute, 1-hr and 8-hr AEGL-3 values the 1-hr and 8-hr rat $BMCL_{05}$ values were simply adjusted by the total uncertainty factor product of 10. The 10-minute value was derived by time-scaling from the 30-minute rat $BMCL_{05}$:

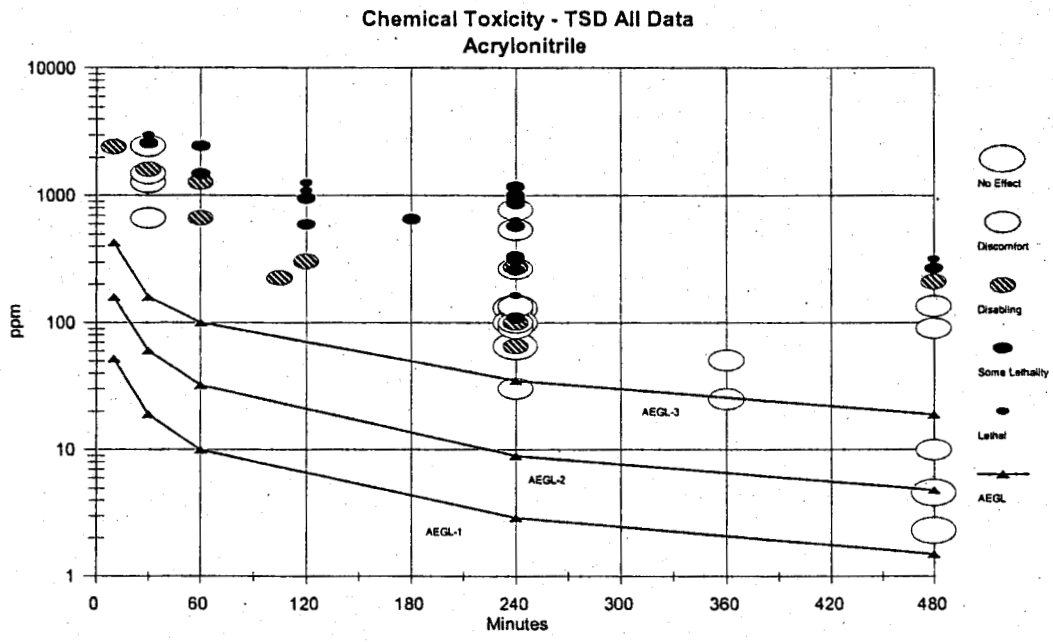
$$(1578\ ppm)^{1.1} \times 1\ hr = 1647.7\ ppm^{1.1} \cdot hrs$$

The 4-hr value was derived by scaling from the 8-hr rat $BMCL_{05}$ (the 8- hr $BMCL_{05}$ was considered more appropriate that the 2-hr value because it was derived from data for five dose groups rather than three):

$$(185.8\ ppm)^{1.1} \times 8\ hrs = 2506.3\ ppm^{1.1} \cdot hrs$$

Summary of AEGL Values for Acrylonitrile (AN)						
Classification	10-min	30-min	1-hour	4-hour	8-hour	Endpoint (Reference)
AEGL-1	52 ppm	19 ppm	10 ppm	2.9 ppm	1.5 ppm	No effect in volunteer human subjects exposed to 4.6 ppm for 8 hrs; UF=1x3;; n=1.1 (Jakubowski et al., 1987)
AEGL-2	160 ppm	60 ppm	32 ppm	9 ppm	4.8 ppm	Minor transient effects in rhesus monkeys exposed for 4 hrs to 90 ppm; UF=3x3; n=1.1 (Dudley and Neal, 1942)
AEGL-3	430 ppm	160 ppm	100 ppm	35 ppm	19 ppm	30-min, 1-hr, and 8-hr, $BMCL_{05}$ lethality threshold estimates in rats; UF=3x3; n=1.1 (Appel et al., 1981a; Dudley and Neal, 1942)

ACRYLONITRILE CATEGORY PLOT



ATTACHMENT 12

ACUTE EXPOSURE GUIDELINE LEVELS
OXYGEN DIFLUORIDE

NAC/AEGL-42

March, 2007
Irvine, CA

ORNL Staff Scientist:
Robert Young

Chemical Manager:
Iris Camacho

Chemical Reviewers:
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Henry Anderson

OXYGEN DIFLUORIDE - HUMAN EXPOSURE DATA

- **No lethality data**
- **0.5 ppm for several hours: respiratory tract irritation, pulmonary hemorrhage and edema (Deichmann and Gerarde, 1969)**
- **ppb levels: intractable headaches (LaBelle et al., 1945)**

OXYGEN DIFLUORIDE TOXICITY

- Species Variability
  - ~17-fold difference among 4 species
  - toxicity (lethality) inversely proportional to size

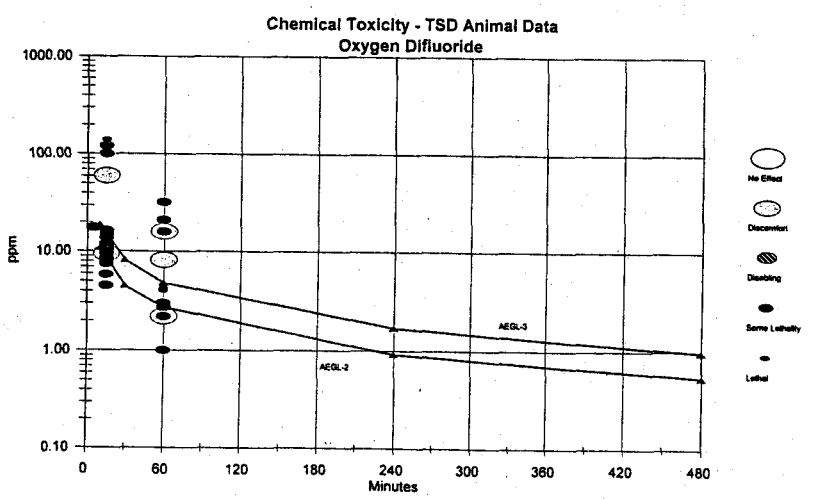
- Oxygen difluoride is of greater toxicity than other fluorinated compounds
  - $OF_2 > ClF_5 > ClF_3 > HF$

OXYGEN DIFLUORIDE AEGL-1

Not recommended; insufficient data

OXYGEN DIFLUORIDE AEGL VALUES

Summary of AEGL Values for Oxygen Difluoride (ppm)						
Classification	10-min	30-min	1-hr	4-hr	8-hr	POD (Reference)
AEGL-1	NR	NR	NR	NR	NR	not recommended; insufficient data
AEGL-2	4.3	1.6	0.83	0.24	0.13	1/3 of AEGL-3
AEGL-3	13	4.7	2.5	0.71	0.38	Est. lethality threshold (1-hr $BMCL_{05}$ of 7.48 ppm) in rhesus monkeys (Davis, 1971); UF = 3 x 3; n = 1.1



NAC/AEGL Meeting 42: March 20-22, 2007

Appendix A

Chemical: MINUTES NAC/AEGL 41 **CAS Reg. No.:**

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

Chemical Manager: **Staff Scientist:**

NAC Member	AEGL1	AEGL2	AEGL3	LOA	NAC Member	AEGL1	AEGL 2	AEGL3	LOA
Henry Anderson					Warren Jederberg				
Steven Barbee					Glenn Leach				
Marc Baril					Richard Niemeier				
Lynn Beasley					Marinelle Payton				
Alan Becker					Susan Ripple				
Robert Benson					George Rodgers				
George Cushmac					Marc Ruijten				
Ernest Falke					George Rusch, Chair				
Alfred Feldt					Daniel Sudakin				
Roberta Grant					Richard Thomas				
Dieter Heinz					Calvin Willhite				
John Hinz					George Woodall				
Jim Holler									
					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.

Approved unanimously.

NR= Not Recommended due to_____

AEGL 1 **Motion by:** R Thomas **Second by:** D Heinz
AEGL 2 **Motion by:**_____ **Second by:**_____
AEGL 3 **Motion by:**_____ **Second by:**_____
LOA **Motion by:**_____ **Second by:**_____

Approved by Chair: _____ **DFO:** Paul S. Tobin **Date:** 3/20/07

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

December 12-14, 2006

Meeting-41 Highlights

Hilton-Old Town/Alexandria
1767 King Street
Alexandria, VA 22314

INTRODUCTION

Chairman George Rusch welcomed the committee, and thanked Drs. Marc Ruijten and Wil ten Berge for conducting a workshop on the DoseResp software. The workshop was held prior to the NAC meeting (December 11, 2006) and was well attended by both NAC members and ORNL staff. The increased familiarity with the software and methods should help with future AEGL value development. George Rusch informed the committee that Dr. Elaine Krueger, NAC member representing the Massachusetts Department of Health, died as a result of cancer. Paul Tobin then read a summary of Dr. Krueger's professional background, and a moment of silence followed. Martha Steele will be the Massachusetts Department of Health representative on the NAC starting in June, 2006.

The draft NAC/AEGL-40 meeting highlights were reviewed. A motion was made by Henry Anderson and seconded by Dieter Heinz to accept the minutes as written. The motion passed unanimously by a show of hands (Appendix A). The final version of the NAC/AEGL-40 meeting highlights is attached (Appendix B).

The highlights of the NAC/AEGL-41 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-41 Agenda.

REVIEW of FEDERAL REGISTER-09 COMMENTS

Forty seven chemicals were included in the FR09 publication. Those not receiving comments are elevated to interim status. Chemicals elevated to interim status include:

Acetaldehyde (75-07-0), Benzonitrile (100-47-0), Bromine pentafluoride (7789-30-2), Bromine trifluoride (7787-71-5), Butadiene (106-99-0), Butane (106-97-8), Chlorine pentafluoride (13637–63–3), Chloroacetaldehye (107–20–0), Chloroacetone (78–95–5), Chloroacetyl chloride (79–04–9), Cumene (98–82–8), Dichloroacetyl chloride (79–36–7), Dimethyl sulfate (77–78–1), Disulfur dichloride (10025–67–9), Ethyl mercaptan (75–08–1), Hexane (110–54–3), Hydrogen bromide (10035–10–6), Hydrogen iodide (10034–85–2), Hydrogen selenide (7783–07–5), Lewisite L-1 (541–25–3), Lewisite L-2 (40334–69–8), Lewisite L-3 (40334–70–1), Methacrylonitrile (126–98–7), Methyl bromide (74–83–9), Methyl chloride (74–87–3), Methylene chloride (75–09–2), Oleum (8014–95–7), Piperidine (110–89–4), Propane (74–98–6), Propionaldehyde (123–38–6), Sulfur trioxide (7446–11–9), Sulfuric acid (7664–93–9), and Vinyl chloride (75–01–4).

Comments received will be discussed at the current meeting with the exception of five aliphatic nitriles which will be discussed at NAC-42 (March, 2007). Ernie Falke announced that there are a total of 285 priority chemicals. There are approximately 100 chemicals that still need to be addressed by the NAC. Several of these chemicals will be addressed by chemical class, and production/use information will be obtained to determine if it is prudent to address all remaining chemicals.

Ethyl Acrylate (CAS No. 140-88-5)
Butyl Acrylate (CAS No. 141-32-2)

Staff Scientist: Carol Wood, ORNL
Chemical Manager: George Woodall, U.S. EPA/ Ursula Gundert-Remy, Germany

Comments were received from the Basic Acrylic Monomers Manufacturers, Inc. (BAMM). Comments stated that the proposed AEGL values are scientifically appropriate and fully protective of human health. A motion was made by Richard Thomas and seconded by George Rodgers to elevate ethyl acrylate (Appendix C) and butyl acrylate (Appendix D) to interim status. The motion passed unanimously by a show of hands.

Formaldehyde (CAS No. 50-00-0)

Staff Scientist: Sylvia Talmage, ORNL
Chemical Manager: George Rodgers

Comments received from the Formaldehyde Council were reviewed by Sylvia Talmage (Attachment 3). The comments stated that the AEGL values represent the lower end of reasonable values. Discussion focused on AEGL-1 (value of 0.9 ppm at all time points implies a level of precision not supported by the data) and AEGL-3 values (possibility of revising time scaling). After a thorough discussion, a motion was made by Marc Ruijten and seconded by Richard Niemeier to elevate the formaldehyde AEGL values to interim. The motion carried unanimously (YES: 21; NO: 0; ABSTAIN: 0) (APPENDIX E).

Titanium Tetrachloride (CAS No. 7550-88-3)

Staff Scientist: Claudia Troxel, CMTox
Chemical Manager: Jim Holler, ATSDR

Claudia Troxel reviewed Comments from Lyondell Chemical Company (Attachment 4). Comments suggested having NR for AEGL-1 values because the proposed AEGL-2 values should be adequately protective for the AEGL-1 endpoint. Proposed AEGL-1 values were based on a no-effect-level in a 4-week repeated-exposure rat study. Discussion focused on the possibility of deriving AEGL-1 values by molar equivalence analogy to hydrogen chloride (i.e. one mole of titanium tetrachloride will yield 4 moles of HCl upon complete hydrolysis). However, this approach was not adopted because titanium tetrachloride may be more than 4-fold as toxic as hydrogen chloride. A motion was made by George Woodall and seconded by Ernest Falke to adopt NR for AEGL-1 values due to insufficient data. The motion passed by a show of hands (YES: 20; NO: 0; ABSTAIN: 1) (APPENDIX F). A motion was then made by John Hinz and seconded by Jim Holler to elevate proposed AEGL-2 and AEGL-3 values and NR for AEGL-1 to interim status. The motion passed by a show of hands (YES: 20; NO: 0; ABSTAIN: 1) (APPENDIX F).

Benzene (CAS No. 71-43-2)

Staff Scientist: Marcel vanRaaij, RIVM
Chemical Manager: Robert Snyder, Rutgers Univ.

Marc Ruijten reviewed the benzene comments on behalf of Marcel vanRaaij (Attachment 5). Comments were received from John Morawetz. Several editorial comments will be incorporated into the document. Technical comments focused on occupational studies used in a weight-of-evidence approach for AEGL-3 derivation; Mr. Morawetz had made similar comments at the June, 2003, NAC meeting, and these issues were discussed at that time. A motion was made by Ernest Falke and seconded by Bob Benson to elevate the proposed benzene AEGL values to interim status. The motion passed (YES19; NO: 0; ABSTAIN: 1) (APPENDIX G).

Methacrylic Acid (CAS No. 79-41-4)

Staff Scientist: Fritz Kalberlah, FOBIG
Chemical Manager: Robert Benson, U.S. EPA

Chemical manager Bob Benson presented comments on methacrylic acid from the Methacrylate Producers Association (MPA) (Attachment 6). MPA was in general agreement with the proposed AEGL values. A motion was made by George Rodgers and seconded by Richard Niemeier to elevate the proposed AEGL values for methacrylic acid to interim status. The motion passed unanimously by a show of hands (APPENDIX H).

Methyl Methacrylate (CAS No. 80-62-6)

Staff Scientist: Fritz Kalberlah, FOBIG
Chemical Manager: Robert Benson, U.S. EPA

Chemical manager Bob Benson presented comments on methyl methacrylate from the Methacrylate Producers Association (MPA) (Attachment 6). The MPA was in general agreement with the proposed AEGL-1 values. A motion was made by George Rodgers and seconded by Richard Niemeier to elevate the AEGL-1 values from proposed to interim status. The motion passed unanimously (YES 20; NO: 0; ABSTAIN: 0) (Appendix I). MPA commented that the AEGL-2 was too low because there were no serious effects noted in humans at concentrations above 300 ppm; MPA suggested deriving AEGL-2 values by dividing the AEGL-3 values by 3. After discussion, the NAC found no valid reason to reject high quality animal studies and adopt a default procedure. A motion was made by Richard Thomas and seconded by John Hinz to elevate the proposed AEGL-2 values to interim status. The motion passed unanimously (YES 20; NO: 0; ABSTAIN: 0) (Appendix I). MPA commented that the proposed AEGL-3 values were too low as a result of the BMD from the Tansy study (POD for proposed AEGL-3) being too low compared to other animal data. The MPA suggested reducing the uncertainty factor. After extensive discussion and consideration of six options/approaches (Attachment 6), a motion was made by Dieter Heinz and seconded by Bob Benson to adopt AEGL-3 values of 720 ppm for 10- and 30-minutes, 570 ppm for 1 hour, 360 ppm for 4-hours, and 180 ppm for 8-hours based on a BMCL05 of 3613 ppm for a single 6-hr rat exposure from the combined data of Tansy et al., (1980) and NTP (1986). The total uncertainty factor is 10, and time scaling used the default n values of 1 or 3. The motion passed unanimously (YES 20; NO: 0; ABSTAIN: 0) (Appendix I). The motion passed unanimously (YES 20; NO: 0; ABSTAIN: 0) (Appendix H).

Summary of AEGL-3 Values for Methyl Methacrylate

Classification	10-minute	30-minute	1-hour	4-hour	8-hour	Endpoint (Reference)
AEGL–2	720 ppm	720 ppm	570 ppm	360 ppm	180 ppm	4-hr BMCL05 in rats (Tansy et al., 1980; NTP, 1986)

Styrene (CAS No. 80-62-6)

Staff Scientist: Jens-Uwe Voss, Chemrisk, Germany
Chemical Manager: Lynn Beasley, U.S. EPA

Ernest Falke presented comments on styrene from the Styrene Information and Research Center (SIRC) (Attachment 7). None of the comments will affect the AEGL values; however,

incorporation of the comments will provide a more complete TSD. A motion was made by George Woodall and seconded by John Hinz to elevate the proposed AEGL values for styrene to interim status. The motion passed unanimously by a show of hands (YES 20; NO: 0; ABSTAIN: 0) (Appendix J). George Woodall is the IRIS chemical manager for styrene, and will help with the TSD revision.

REVIEW of COT COMMENTS

Allyl Alcohol (CAS No. 107-18-6)

Staff Scientist: Claudia Troxel, CMTox
Chemical Manager: Bob Benson, U.S. EPA

Bob Benson, the new chemical manager for allyl alcohol, made a few introductory remarks about the history of this TSD. He had recently been named the Chemical Manager as the previous chemical manager was no longer on the committee. The NAC had many previous discussions about the allyl alcohol. In previous action, the NAC had developed interim AEGL values. The TSD was returned to the NAC to respond to comments from the COT Committee.

Claudia Troxel discussed the comments from the COT (Attachment 8). The COT had comments on the derivation of values for each AEGL level. With regard to AEGL-3, the COT did not agree with the use of the adjustment factor or the modifying factor. In addition COT recommended that the value of n be derived from the lethality data. With regard to AEGL-1 and AEGL-2, the COT did not agree with the proposed values being set at the same level for all time points based on the occurrence of irritation from a 5 minute exposure. The COT recommended that the NAC consider the systemic toxicity to the liver and kidney from longer term exposure. Claudia Troxel discussed the values obtained taking into account the COT comments. After considerable discussion amongst the NAC with no clear resolution at hand because of some conflicting data, the industry observer (Dr. Marcy Banton, Lyondell Chemical) stated that her company was the sole US manufacturer of allyl alcohol and that she would ask Lyondell Chemical to conduct additional studies to resolve some of the conflicting data. The NAC enthusiastically accepted the offer and deferred action on the chemical until Dr. Banton has a decision about additional testing.

Carbon Disulfide (CAS No. 75-15-0)

Staff Scientist: Jens-Uwe Voss, Chemrisk, Germany
Chemical Manager: George Woodall, U.S. EPA

Chemical manager George Woodall reviewed the COT comments on carbon disulfide (Attachment 9). The COT agreed with the AEGL-2 and AEGL-3 values and recommended no changes. The COT commented that the discussion of sensitive subgroups should be expanded in the TSD and that the UF of 10 should be reduced to 3. Persons consuming alcohol are not a sensitive subpopulation, and an uncertainty factor of 3 should be sufficient to protect atypical metabolizers. After deliberation, a motion was made by John Hinz and seconded by Bob Benson to reduce the UF from 10 to 3 and to accept AEGL-1 values of 17 ppm for 10- and 30-min, 13 ppm for 1-hr, 8.4 ppm for 4-hr, and 6.7 ppm for 8-hr. The point-of-departure (increase in blood acetaldehyde in humans with moderate intake of alcohol) and time scaling remain unchanged. The motion passed unanimously by a show of hands (YES 20; NO: 0; ABSTAIN: 0) (Appendix K).

Summary of AEGL-1 Values for Carbon Disulfide						
Classification	**10-minute**	**30-minute**	**1-hour**	**4-hour**	**8-hour**	**Endpoint (Reference)**
AEGL–1	17 ppm	17 ppm	13 ppm	8.4 ppm	6.7 ppm	Increase in blood acetaldehyde in humans with moderate intake of alcohol (Freundt et al., 1976)

Phosphorus Trichloride (CAS No. 7719-12-2)

Staff Scientist: Bob Young, ORNL
Chemical Manager: Tom Hornshaw, Illinois

Bob Young reviewed the data set for phosphorus trichloride (Attachment 10) and explained that even though AEGL-1 values were based on a NOAEL for irritation in rats (3.4 ppm, 6 hr/day, 5 days/week for 4 weeks), the values had been scaled across time. In order to be consistent with the SOP, these AEGL-1 values should be held constant across time. A motion was made by Bob Benson and seconded by Ernest Falke to adopt AEGL-1 values of 0.34 ppm for all time periods. The point-of-departure and uncertainty factor of 10 remain unchanged. The motion passed unanimously by a show of hands (YES 20; NO: 0; ABSTAIN: 0) (Appendix L).

Summary of AEGL-1 Values for Phosphorus Trichloride						
Classification	**10-minute**	**30-minute**	**1-hour**	**4-hour**	**8-hour**	**Endpoint (Reference)**
AEGL–1	0.34 ppm	0.34 ppm	0.34 ppm	0.34 ppm	0.34 ppm	NOAEL for irritation in rats exposed to 3.4 ppm, 6 hr/day, 5 days/week for 4 weeks (Hazleton, 1983)

Sulfur Dioxide (CAS No. 7446-09-5)

Staff Scientist: Cheryl Bast, ORNL
Chemical Manager: George Woodall, U.S. EPA

The COT subcommittee commented that the AEGL-1 and AEGL-2 values for sulfur dioxide were appropriate. However, the AEGL-3 values were too high, especially at the 10-min, 30-min, and 1-hr time points.

The interim AEGL-3 values (42 ppm for 10-min, 32 ppm for 30-min, 27 ppm for 1-hr, 19 ppm for 4-hr, and 16 ppm for 8-hr) were based on a rat 4-hr $BMCL_{05}$ of 573 ppm (Cohen et al, 1973) (Attachment 11). An uncertainty factor of 10 was applied for intraspecies extrapolation due to the wide variability in response to SO_2 exposure between healthy and asthmatic humans. An uncertainty factor of 3 was applied for interspecies variability. Data were not sufficient to ascertain whether a maximal response to SO_2 for a lethal endpoint is obtained within 10 minutes. Therefore, time scaling was utilized in the derivation of AEGL-3 values. The 4-hour experimental value was scaled to the 10- and 30-minute, and 1-, and 8-hour time points, using $c^n \times t = k$.

The COT suggested using the concentration causing no deaths and a moderate Sraw response in guinea pigs (200 ppm for 1 hour) (Amdur, 1959) as the point-of departure for AEGL-3 values. An interspecies uncertainty factor of 10 would be applied because data suggest that the guinea pig is approximately 10-times less sensitive than an asthmatic human. An intraspecies uncertainty factor of 1 would be applied because the interspecies UF of 10 already accounts for extrapolation to a sensitive human subpopulation (asthmatics). Because role of exposure duration to the magnitude of SO_2-induced bronchoconstriction in asthmatics appears to decrease with extended exposure and data suggest that a major portion of the SO_2-induced bronchoconstriction occurs within 10-minutes and increases minimally or resolves beyond 10-minutes of exposure, AEGL-3 values for SO_2 will be held constant across all time points. This approach yields values of 20 ppm at all time points.

After much deliberation, it was the consensus of the NAC that the decrease in airway resistance was not an appropriate endpoint for AEGL-3. However the NAC also recognized that because asthmatics are highly sensitive to sulfur dioxide for short time periods, time scaling may not be appropriate.

A motion was made by George Rodgers and seconded by Henry Anderson to retain the point-of-departure (rat 4-hr $BMCL_{05}$) and uncertainty factors (Intraspecies = 10, Interspecies = 3) as in the interim TSD. However, because data are not sufficient to ascertain whether a maximal response to SO_2 for a lethal endpoint is obtained within 10 minutes, time scaling will be utilized in the derivation of AEGL-3 values. Data were unavailable for an empirical derivation of *n* for sulfur dioxide. Therefore, an *n* of 3 was applied to extrapolate to the 1-hour time period, and *n* of 1 was used for extrapolation to the 8-hour time period to provide AEGL values that would be protective of human health. The 1-hour AEGL-3 value was also adopted as 10-minute and 30-minute values because asthmatic humans are highly sensitive to sulfur dioxide at short time periods. The motion passed (YES 17; NO: 1; ABSTAIN: 1) (Appendix M).

Summary of AEGL-3 Values for Sulfur Dioxide						
Classification	**10-minute**	**30-minute**	**1-hour**	**4-hour**	**8-hour**	**Endpoint (Reference)**
AEGL–1	30 ppm	30 ppm	30 ppm	19 ppm	9.6 ppm	4-hr BMCL05 in rats (Cohen et al., 1973)

N, N-Dimethylformamide (CAS No. 68-12-2)

Staff Scientist: Claudia Troxel, CMTox
Chemical Manager: George Woodall, U.S. EPA

N, N-Dimethylformamide will be postponed to a future NAC meeting due to outstanding issues.

REVIEW of PRIORITY CHEMICALS

Ethyl benzene (CAS No. 100-41-4)

Staff Scientist: Carol Wood, ORNL
Chemical Manager: John Hinz, U.S. Air Force

Carol Wood summarized the data in the TSD (Attachment 12). Proposed AEGL-1 values (27 ppm for 10- and 30-min, 21 ppm for 1-hr, 13 ppm for 4-hr, and 6.7 ppm for 8-hr) were based on an increase in motor activity and no-effect-level for asymptomatic non-clinical effects in rats exposed to 400 ppm for 4 hours (Molnar et al., 1986). Time scaling was accomplished using the default values of n =1 or n = 3; and an interspecies UF of 3 was proposed because clinical signs and systemic effects were consistent between species. An intraspecies UF of 10 was proposed because the mechanism of systemic toxicity is unknown. Proposed AEGL-2 values (38 ppm for 10- and 30-min, 30 ppm for 1-hr, 19 ppm for 4-hr, and 13 ppm for 8-hr) were based on decreased weight gain in the absence of clinical signs in weanling rats exposed to 500 ppm for 6 hours (Stump, 2003). Uncertainty factor application and time scaling were as described for AEGL-1. Proposed AEGL-3 values (76 ppm for 10- and 30-min, 61 ppm for 1-hr, 38 ppm for 4-hr, and 25 ppm for 8-hr) were based an approximate threshold for death in weanling rats (Stump, 2003). Uncertainty factor application and time scaling were as described for AEGL-1. Carol then discussed the possibility of using PBPK modeling to derive AEGL values for ethyl benzene (Attachment 13). Paul Tobin noted that there is a need to reference the Xylene TSD, AEGL values and animal test data, since commercial Xylene contains a significant percentage of Ethyl benzene and the AEGLs should be consistent with both compounds. After discussion, the NAC decided to defer ethyl benzene until the PBPK modeling data become available. Dr. Marcy Banton, an industry observer from Lyondell Chemical, offered assistance with the PBPK effort.

Carbonyl Fluoride (CAS No. 353-50-4)

AEGL-41

Staff Scientist: Sylvia Talmage, ORNL
Chemical Manager: Iris Camacho, U.S. EPA

Sylvia Talmage reviewed the database for carbonyl fluoride (Attachment 14); no draft TSD was presented. However, input from the NAC was requested as how to proceed with the limited and conflicting data set. The main issue focuses on whether inhaled carbonyl fluoride hydrolyzes to carbon dioxide and two moles of hydrogen fluoride in the moist respiratory tract, or does some carbonyl fluoride penetrate into the lungs. If hydrolysis is essentially complete, then carbonyl fluoride AEGL values should be one-half the HF AEGL values; however, this may not be the case. The NAC suggested searching for chemical modeling data to determine the hydrolysis rate and also determine if phosgene data might be useful. This chemical will be discussed at a future meeting.

Methacrylaldehyde (CAS No.78-85-3)

Staff Scientist: Tom Marshall, ORNL
Chemical Manager: Susan Ripple, Dow Chemical

Tom Marshall presented an overview of the TSD for methacrylaldehyde and the derivation of the draft AEGL values (Attachment 15). Proposed AEGL-1 values for 10-min, 30-min, and 1-hr (0.10 ppm) were based on a NOAEL for eye irritation in healthy humans (0.3 ppm for 20 min); whereas the proposed 4- and 8-hr AEGL-1 values (0.07 ppm) were based on a NOAEL for increased blink frequency in healthy humans (0.2 ppm for 20 min) (Nojgaard et al., 2005). An intraspecies UF of 3 was proposed because the mechanism is direct contact irritation. Proposed AEGL-2 values (2.8 ppm for 10- and 30-min, 2.2 ppm for 1-hr, 1.4 ppm for 4-hr, and 0.8 ppm for 8-hr) were derived by dividing the AEGL-3 values by 3; this approach was supported by a steep concentration-response curve. Proposed AEGL-3 values (8.3 ppm for 10- and 30-min, 6.6 ppm for 1-hr, 4.2 ppm for 4-hr, and 2.1 ppm for 8-hr) were based on an estimated 4-hr lethality threshold in rats (⅓ the LC_{50} of 125 ppm = 41.7 ppm) (Carpenter et al., 1949). Uncertainty factors of 3 each were proposed for inter- and intraspecies extrapolation because the mechanism of toxicity is direct acting irritation. Time scaling was accomplished using the default values of n =1 or n = 3. Discussion of the AEGL-1 values focused on whether to use the subjective (NOAEL for irritation) or objective (blink frequency) as the point-of-departure. A motion was made by Marc Ruijten and seconded by Dieter Heinz to adopt an AEGL-1 value of 0.2 ppm for all time points. The point-of-departure is the increase in blink frequency in healthy human subjects exposed to 0.2 ppm for 20 minutes. No uncertainty factor was applied because the POD is below effects defined by AEGL-1. The motion passed (YES 14; NO: 0; ABSTAIN: 4) (Appendix N). Concern was expressed regarding the Carpenter et al. (1949) data (proposed as the POD for AEGL-3) because concentrations were not measured. A motion was made by Ernest Falke and seconded by Marc Baril to accept AEGL-3 values of 5.9 ppm for 10- and 30-min, 4.7 ppm for 1-hr, 2.9 ppm for 4-hr, and 1.9 ppm for 8-hr. The POD is ⅓ of the 90% lethal level

in rats exposed to 77 ppm for 6 hours (⅓ x 77 ppm = 25.7 ppm) (Coombs et al., 1992). This POD is supported by a repeated-exposure study showing no lethality at 19 ppm. Uncertainty factors of 3 each were applied for inter- and intraspecies extrapolation because the mechanism of toxicity is direct acting irritation. Time scaling was accomplished using the default values of n =1 or n = 3. The motion passed (YES 17; NO: 0; ABSTAIN: 1) (Appendix N). A motion was then made by Marc Ruijten and seconded by Bob Benson to accept AEGL-2 values of 3.5 ppm for 10- and 30-min, 2.8 ppm for 1-hr, 1.8 ppm for 4-hr, and 1.1 ppm for 8-hr based on signs of irritation noted on the first day of exposure in rats repeatedly exposed to 15.3 ppm, 6 hr/day for 4 weeks. The use of a repeated exposure study was warranted because the only other alternative was to divide AEGL-3 values by 3. The derived AEGL-2 values are slightly higher than one-third the AEGL-3 values and are supported by comparison with the acrolein values. The motion passed (YES 18; NO: 0; ABSTAIN: 1) (Appendix N).

Summary of AEGL Values for Methacrylaldehyde						
Classification	**10-minute**	**30-minute**	**1-hour**	**4-hour**	**8-hour**	**Endpoint (Reference)**
AEGL–1	0.20 ppm	0.20 ppm	0.20 ppm	0.20 ppm	0.20 ppm	NOAEL for increased blink frequency in humans (Nojgaard et al.,2005)
AEGL–2	3.5 ppm	3.5 ppm	2.8 ppm	1.8 ppm	1.1 ppm	Irritation in rats (Coombs et al. 1992)
AEGL–3	5.9 ppm	5.9 ppm	4.7ppm	2.9 ppm	1.9 ppm	One-third 90% Rat lethality level (Coombs et al. 1994)

Methyl Vinyl Ketone (CAS No. 98-94-4)

Staff Scientist: Tom Marshall, ORNL
Chemical Manager: Jim Holler, ATSDR

Tom Marshall presented a summary of the available data and an overview of the development of proposed AEGL value for Methyl Vinyl Ketone (MVK) (Attachment 16). Proposed AEGL-1 values (0.05 ppm for all time points) were based on a NOAEL for nasal cavity lesions in rats and mice exposed to 0.5 ppm MVK, 6 hours/day, 5 days/week for 12 exposures (Morgan et al., 2000). Uncertainty factors of 3 each were proposed for inter- and intraspecies variability because MVK is a direct-acting irritant. Values were held constant at all time points. Proposed AEGL-2 values (0.66 ppm for 10-min, 0.46 ppm for 30-min, 0.36 ppm for 1-hr, 0.23 ppm for 4-hr, and 0.15 ppm for 8-hr) were based on a NOAEL for lung lesions (nasal cavity necrosis was present) in rats and mice exposed to 2 ppm MVK 6 hours/day, 5 days/week for 12 exposures (Morgan et al., 2000). Inter- and

intraspecies uncertainty factors of 3 each were proposed because the mechanism of action is irritation. Time scaling was performed using the $C^n x\ t = k$ equation, where the values of n were the defaults of 1 or 3. Time scaling to the 10-minute value was considered appropriate because the POD was from a repeated-exposure study. Proposed AEGL-3 values (1.3 ppm for 10-min, 0.92 ppm for 30-min, 0.73 ppm for 1-hr, 0.46 ppm for 4-hr, and 0.30 ppm for 8-hr) were based on rat and mouse lethality data. There were no deaths in rats or mice exposed to 4 ppm for 12 days (Morgan et al., 2000), and there was 20% mortality in rats after 8 days of exposure to 3.9 ppm (Eastman Kodak, 1992). Inter- and intraspecies uncertainty factors of 3 each were proposed because the mechanism of action is irritation. Time scaling was performed using the $C^n x\ t = k$ equation, where the values of n were the defaults of 1 or 3. Time scaling to the 10-minute value was considered appropriate because the POD was from a repeated-exposure study. A motion was made by Steve Barbee and seconded by Calvin Willhite to accept an AEGL-1 value of 0.17 ppm at all time points. The POD was as proposed. A UF of 3 will be applied for intraspecies variability; however, no interspecies uncertainty factor is considered necessary since similar NOAELs were obtained in multiple species (rat, mouse, guinea pig, rabbit) in two separate studies. The motion passed (YES: 15; NO: 1; ABSTAIN: 3) (APPENDIX O). A motion was made by Richard Niemeier and seconded by John Hinz to accept AEGL-2 values of 1.5 ppm, 1.5 ppm, 1.2 ppm, 0.76 ppm, and 0.50 ppm for 10 min, 30 min, 1, 4, and 8 hrs, respectively. The POD is as proposed, and UF application is as for AEGL-1. Time scaling uses the default n values of 1 or 3; and the 30-min value is adopted as the 10-min value. The motion passed (YES: 18; NO: 0; ABSTAIN: 1) (APPENDIX O). A motion was made by Calvin Willhite and seconded by Susan Ripple to accept AEGL-3 values of 3.1 ppm for 10- and 30-min, 2.4 ppm for 1-hr, 1.5 ppm for 4-hr, and 1.0 ppm for 8-hr. The POD is as proposed, UF application is as for AEGL-1 and AEGL-2 values and time scaling is consistent with the AEGL-2 approach. The motion passed (YES: 19; NO: 0; ABSTAIN: 0) (APPENDIX O).

Summary of AEGL Values for Methyl Vinyl Ketone

Classification	10-minute	30-minute	1-hour	4-hour	8-hour	Endpoint (Reference)
AEGL–1	0.17 ppm	0.17 ppm	0.17 ppm	0.17 ppm	0.17 ppm	NOAEL for respiratory tract irritation (Morgan et al. 2000)
AEGL–2	1.5 ppm	1.5 ppm	1.2 ppm	0.76 ppm	0.50 ppm	LOAEL for respiratory tract irritation (Morgan et al. 2000)
AEGL–3	3.1 ppm	3.1 ppm	2.4 ppm	1.5 ppm	1.0 ppm	Lethality at 4 ppm (Eastman Kodak 1992; Morgan et al. 2000)

Mercury Vapor (CAS No. 7439-97-6)

Staff Scientist: Sylvia Talmage, ORNL
Chemical Manager: Marquea King, U.S. EPA

An overview of the available data and the derivation of draft AEGL values was provided by Sylvia Talmage (Attachment 17). AEGL-1 values were not recommended because mercury has no odor or warning properties. Proposed AEGL-2 values (6.1 mg/m^3 for 10-min, 4.2 mg/m^3 for 30-min, 3.4 mg/m^3 for 1-hr, 1.3 mg/m^3 for 4-hr, and 0.7 mg/m^3 for 8-hr) were based on the absence of lesions in pregnant rats exposed to 8 mg/m^3 for 2 hours (Morgan et al., 2001). An interspecies UF of 1 was proposed due to greater lung uptake and deposition in rodents because of higher respiratory rate and cardiac output, and incompatibility with monitoring data if a higher UF is applied. For example, reviews of past workplace exposure show that concentrations in the range of 0.4-2 mg/m^3 in industry have resulted in symptoms of mercury poisoning only after chronic exposure, and concentrations of 1.0-5.0 mg/m^3 were not unusual in mercury mining operations in the past (AIHA 2006). An intraspecies UF of 3 was proposed because infants are more susceptible than adults, but there is no evidence that the difference is greater than 3-fold. Time scaling used default n values of 1 or 3. Proposed AEGL-3 values (16 mg/m^3 for 10-min, 11 mg/m^3 for 30-min, 8.9 mg/m^3 for 1-hr, 2.2 mg/m^3 for 4-hr, and 2.2 mg/m^3 for 8-hr) were based on no clinical signs in rats exposed to 26.7 mg/m^3 for 1 hour; extending the exposure for one more hour resulted in 20/32 deaths (Livardjani et al., 1991). Therefore, the POD was considered an estimate of a lethality threshold. Uncertainty factors and time scaling were proposed as for AEGL-2 except that the 8-hour AEGL-3 was set equal to the 4-hour value because time scaling resulted in a value below occupational exposures. Discussion focused on the susceptibility of the fetus and whether the proposed interspecies UF of 3 is sufficient to protect the fetus. Calvin Willhite stated that summary reports suggest that for compounds known to be developmental toxicants (such as mercury) the UF of 3 is justified; however, definitive data are not available. Ernest Falke suggested using the reconstruction studies to support the UF of 3, and Henry Anderson pointed out that for the fetus, an acute exposure is actually a chronic exposure because the mercury accumulates. A motion was then made by George Woodall and seconded by Bob Benson to adopt AEGL-3 values as proposed, supporting the UF of 3 with the human reconstruction study (16 mg/m^3 for 2 hr resulted in severe health effects, but no mortality). More support for the increased rate of uptake in the rodent should also be included. The motion passed (YES: 12; NO: 4; ABSTAIN: 4) (APPENDIX P). A motion was then made by Bob Benson and seconded by Ernest Falke to adopt AEGL-2 values of 3.1 mg/m^3 for 10-min, 2.1 mg/m^3 for 30-min, 1.7 mg/m^3 for 1-hr, 0.67 mg/m^3 for 4-hr, and 0.33 mg/m^3 for 8-hr based on no fetal effects in rats exposed to 4 mg/m^3 for 2 hours/day for 10 days (Morgan et al., 2001). The 4 mg/m^3 was selected as the POD because the proposed 8 mg/m^3 is equivalent to ⅓ the LC_{50} (7-8 mg/m^3). Uncertainty factor application and time scaling were as proposed. The motion passed (YES: 11; NO: 3; ABSTAIN: 5) (APPENDIX P). A motion was then made by Ernest Falke and seconded by Jim Holler to not recommend AEGL-1 values. The motion passed unanimously by a show of hands (Appendix P).

Summary of AEGL Values for Mercury Vapor						
Classification	**10-minute**	**30-minute**	**1-hour**	**4-hour**	**8-hour**	**Endpoint (Reference)**
AEGL–1	NR	NR	NR	NR	NR	Lack of data on irritation effects
AEGL–2	3.1 mg/m^3	2.1 mg/m^3	1.7 mg/m^3	0.67 mg/m^3	0.33 mg/m^3	No fetal effects in rats (Morgan et al., 2001)
AEGL–3	16 mg/m^3	11 mg/m^3	8.9 mg/m^3	2.2 mg/m^3	2.2 mg/m^3	Estimated lethality threshold in rats (Livardjani et al., 1991)

Propargyl Alcohol (CAS No. 107-19-7)

Staff Scientist: Bob Young, ORNL
Chemical Manager: George Cushmac, U.S. DOT

Bob Young reviewed the data set for propargyl alcohol (Attachment 18). Proposed AEGL-1 values (2.5 ppm at all time points) were based on no effects on olfactory or respiratory epithelium following exposure of male mice at 25.3 ppm 6 hrs/day for up to 9 days (Zissu, 1995). Support was provided by a study from BASF (1992) showing no effects in rats exposed to 9.8 ppm for ten 6-hr exposures, and metaplasia of the olfactory mucosa at 50 ppm. An interspecies UF of 3 was proposed because of a similar exposure-response profile among several species, and an intraspecies UF of 3 was applied because effects are a result of direct-acting irritation and because the POD is based on a multiple-exposure regimen. Proposed AEGL-2 values (20 ppm for 10- and 30-min, 16 ppm for 1-hr, 10 ppm for 4-hr, and 6.6 ppm for 8-hr) were based on histological changes in respiratory tract epithelium of male mice exposed to 88 ppm, 6 hr/day for 4 days (Zissu, 1995). Support was provided by a study from BASF (1992) showing metaplasia of the olfactory mucosa but no clinical signs at 50 ppm. Uncertainty factors were proposed as for AEGL-1 values and time scaling used default n values of 1 or 3. Proposed AEGL-3 values (130 ppm for 10-min, 93 ppm for 30-min, 74 ppm for 1-hr, 29 ppm for 4-hr, and 15 ppm for 8-hr) were based on a 2-hr $BMCL_{05}$ of 584 ppm in mice (Stasenkova and Kochetkova, 1966). Uncertainty factor application and time scaling are as proposed for AEGL-2. After a short discussion, a motion was made by Marc Ruijtten and seconded by Richard Niemeier to accept AEGL-3 values as proposed. The motion passed (YES: 16; NO: 0; ABSTAIN: 1)

(APPENDIX Q). A motion was made by Marc Ruijten and seconded by Dieter Heinz to accept AEGL-2 values as proposed. The motion passed (YES: 16; NO: 0; ABSTAIN: 1) (APPENDIX Q). Finally, a motion was made by Susan Ripple and seconded by Dieter Heinz to accept AEGL-1 values as proposed. The motion passed (YES: 17; NO: 0; ABSTAIN: 0) (APPENDIX Q).

Summary of AEGL Values for Propargyl Alcohol						
Classification	**10-minute**	**30-minute**	**1-hour**	**4-hour**	**8-hour**	**Endpoint (Reference)**
AEGL–1	2.5 ppm	2.5 ppm	2.5 ppm	2.5 ppm	2.5 ppm	NOAEL for respiratory tract histopathology in mice (Zissu, 195)
AEGL–2	20 ppm	20 ppm	16 ppm	10 ppm	6.6 ppm	Olfactory and respiratory epithelial lesions in mice (Zissu, 1995)
AEGL–3	130 ppm	93 ppm	74 ppm	29 ppm	15 ppm	2-hr $BMCL_{05}$ in mice (Stasenkova and Kochetkova, 1966)

Selenium Hexafluoride (CAS No. 7783-79-1)

Staff Scientist: Cheryl Bast, ORNL
Chemical Manager: George Rusch, Honeywell

Cheryl Bast reviewed the data set for selenium hexafluoride (Attachment 19). Proposed AEGL-1 values (0.067 ppm for 10- and 30-min, 0.053 ppm for 1-hr, 0.033 ppm for 4-hr, and 0.017 ppm for 8-hr) were based on a NOEL for irritation in the guinea pig, rabbit, rats, and mice (1 ppm for 4-hours) (Kimmerle, 1960). Interspecies and intraspecies uncertainty factors of 3 each were proposed because selenium hexafluoride is highly irritating and corrosive, and much of the toxicity is likely caused by a direct chemical effect on the tissues; this type of port-of-entry effect is not expected to vary greatly between species or among individuals. Also, the limited data suggest that the guinea pig, rabbit, rat, and mouse are similarly sensitive to the acute effects of selenium hexafluoride, further supporting the interspecies UF of 3. A modifying factor of 3 was also proposed to account for potential enzymatic effects of the selenium moiety and the sparse database. Time scaling utilized the default n values of 1 and 3. Although AEGL-1 values might normally be held constant across all time points because minor irritation does not vary over time, time scaling was proposed for selenium hexafluoride AEGL-1 values to account for any potential enzymatic effects resulting from the selenium moiety. In the absence of empirical data, the proposed AEGL-3 values were divided by 3 to obtain proposed AEGL-2 values (0.11 ppm for 10- and 30-min, 0.087 ppm for 1-hr, 0.057 ppm for 4-hr, and 0.083 ppm for 8-hr) for selenium hexafluoride. This approach is

justified based on a steep concentration response curve (no effects in rabbit, guinea pig, rat, or mouse for 4-hour exposures at 1 ppm, difficulty breathing and pulmonary edema, but no mortality at 5 ppm, and 100% mortality at 10 ppm) (Kimmerle, 1960). Proposed AEGL-3 values (0.33 ppm for 10- and 30-min, 0.26 ppm for 1-hr, 0.17 ppm for 4-hr, and 0.083 ppm for 8-hr) were based on the highest concentration causing no mortality in the guinea pig, rabbit, rats, and mice (5 ppm for 4-hours) (Kimmerle, 1960). Time scaling and uncertainty factor application were as proposed for AEGL-1 values. After a discussion focusing on whether enough data existed to derive AEGL values for selenium hexafluoride, a motion was made by Marc Baril and seconded by Richard Niemeier to adopt AEGL-3 values as proposed except that the interspecies UF will be reduced from 3 to 1 because available data show no interspecies differences and the MF will increase from 3 to 10 because of the sparse data base and potential selenium effects (the intraspecies UF and resulting AEGL values remain the same). The motion passed (YES: 14; NO: 3; ABSTAIN: 0) (APPENDIX R). A motion was then made by Richard Niemeier and seconded by Dieter Heinz to accept AEGL-2 values as proposed. The motion passed (YES: 14; NO: 3; ABSTAIN: 0) (APPENDIX R). A motion was then made by Dieter Heinz and seconded by Susan Ripple to accept AEGL-1 values as proposed except that the interspecies UF will be reduced from 3 to 1 because available data show no interspecies differences and the MF will increase from 3 to 10 because of the sparse data base and potential selenium effects (the intraspecies UF and resulting AEGL values remain the same). The motion passed (YES: 13; NO: 4; ABSTAIN: 0) (APPENDIX R).

Summary of AEGL Values for Selenium Hexafluoride

Classification	10-minute	30-minute	1-hour	4-hour	8-hour	Endpoint (Reference)
AEGL–1	0.067 ppm	0.067 ppm	0.053 ppm	0.033 ppm	0.017 ppm	NOEL for irritation in rabbit, guinea pig, rats, and mice (Kimmerle, 1960)
AEGL–2	0.11 ppm	0.11 ppm	0.087 ppm	0.057 pm	0.028 ppm	One-third of the AEGL-3 values
AEGL–3	0.33 ppm	0.33 ppm	0.26 ppm	0.17 ppm	0.083 ppm	Highest concentration causing no mortality in rabbit, guinea pig, rats, and mice (Kimmerle, 1960)

Oxygen Difluoride (CAS No. 7783-41-7)

Staff Scientist: Bob Young, ORNL
Chemical Manager: Iris Camacho, U.S. EPA

The discussion of this chemical was postponed pending evaluation of new monkey data.

Thionyl Chloride (CAS No. 7719-09-7)

Staff Scientist: Jennifer Rayner, ORNL
Chemical Manager: Steve Barbee, Arch Chemical

Steve Barbee reviewed the data set for thionyl chloride (Attachment 20). Data are not available from human or animal studies to derive AEGL-1 values. Therefore, proposed AEGL-1 values are not recommended. Proposed AEGL-2 values (4.3 ppm for 10-min, 3.0 ppm for 30-min, 2.4 ppm for 1-hr, 0.59 ppm for 4-hr, and 0.30 ppm for 8-hr) were based on swollen noses and dyspnea, but no irreversible or incapacitating effects in rats exposed to 71 ppm thionyl chloride for one hour (Pauluhn 1987). A total uncertainty factor of 30 was proposed. A similar mechanism of action would be expected across species, therefore, an uncertainty factor of 3 was proposed for interspecies variability while a factor of 10 was proposed for intraspecies variability to account for sensitive populations. Thionyl chloride hydrolyzes into sulfur dioxide and hydrogen chloride. Asthmatics are more sensitive than healthy people to the effects of sulfur dioxide. Time scaling used default n values of 1 or 3. The proposed AEGL-3 values (25 ppm for 10-min, 17 ppm for 30-min, 14 ppm for 1-hr, 3.4 ppm for 4-hr, and 1.7 ppm for 8-hr) were based upon the highest concentration causing no lethality in rats exposed to thionyl chloride for one hour (Pauluhn 1987; Nachreiner 1993). A one hour exposure to 593 ppm produced 58% mortality (Nachreiner 1993), the next highest experimental concentration at which no mortality was observed (407 ppm, Pauluhn 1987) was used as the point of departure. This concentration is only slightly greater than the lethality threshold (371 ppm) reported in Nachreiner (1993). The same uncertainty factors and rationale and time scaling used for AEGL-2 were applied to AEGL-3 calculations. Discussion focused on why the HCl AEGL values are much higher than the proposed thionyl chloride values. The fact that HCl is well-scrubbed in the respiratory tract and thionyl chloride is not as well scrubbed may account for the difference. A statement to this effect should be added to the TSD. Another point of discussion involved the use of the highest experimental concentration causing no death, rather than the calculated $BMCL_{05}$, as the POD for AEGL-3. The experimental concentration was used because the calculated value provided a bad "model fit" (p value is 0.002 and should be >0.1). A motion was made by Richard Thomas and seconded by Ernest Falke to accept AEGL-1 values as proposed. The motion passed unanimously by a show of hands (Appendix S). A motion was then made by Marc Baril and seconded by Henry Anderson to accept AEGL-3 values as proposed. The motion passed (YES: 18; NO: 0; ABSTAIN: 0) (APPENDIX S). Finally, a motion was made by Susan Ripple and seconded by Dieter Heinz to accept AEGL-2 values as proposed. The motion passed (YES: 18; NO: 0; ABSTAIN: 0) (APPENDIX S).

Summary of AEGL Values for Thionyl Chloride						
Classification	**10-minute**	**30-minute**	**1-hour**	**4-hour**	**8-hour**	**Endpoint (Reference)**
AEGL–1	NR	NR	NR	NR	NR	Insufficient data
AEGL–2	4.3 ppm	3.0 ppm	2.4 ppm	0.59 ppm	0.30 ppm	Dyspnea (Pauluhn 1987)
AEGL-3	25 ppm	17 ppm	14 ppm	3.4 ppm	1.7 ppm	Threshold of lethality (Pauluhn 1987; Nachreiner 1993)

GENERAL ISSUES

DFO Award: Paul Tobin was the recipient of the FACA Distinguished Designated Federal Officer Award in recognition of his work with the NAC/AEGL.

Suggestion on TSD Review Process: Calvin Willhite suggested that a "TLV Model" be used in AEGL document review to help TSDs get through the NAC and COT subcommittee more efficiently. Specifically, he suggested that the AEGL development teams meet the first half day of the meeting to discuss the TSD and presentation. George Rusch suggested that this same type of meeting could occur by teleconference prior to the meeting. However, for NAC-42, a pilot break-out session could be held if the teleconferences did not work.

ADMINISTRATIVE MATTERS

The site and time of future meetings is as follows:

NAC/AEGL-42: March 20-22, 2007, Irvine, CA
NAC/AEGL-43: June 20-22, 2007, Rotterdam, Netherlands

All items in the agenda were discussed as thoroughly as the time permitted. The meeting highlights were prepared by Cheryl Bast and Robert Young, Oak Ridge National Laboratory, and Robert Benson, U.S. EPA, 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-41 Meeting Agenda
Attachment 2. NAC/AEGL-41 Attendee List
Attachment 3. Review of FR-09 comments for formaldehyde
Attachment 4. Review of FR-09 comments for titanium tetrachloride
Attachment 5. Review of FR-09 comments for benzene
Attachment 6. Review of FR-09 comments for methacrylic acid and methyl methacrylate
Attachment 7. Review of FR-09 comments for styrene
Attachment 8. Review of COT comments for allyl alcohol
Attachment 9. Review of COT comments for carbon disulfide
Attachment 10. Review of COT comments for phosphorus trichloride
Attachment 11. Review of COT comments for sulfur dioxide
Attachment 12: Data analysis for ethyl benzene
Attachment 13: PBPK modeling for ethyl benzene
Attachment 14: Data analysis for carbonyl fluoride
Attachment 15: Data analysis for methacrylaldehyde
Attachment 16: Data analysis for methyl vinyl ketone
Attachment 17: Data analysis for mercury vapor
Attachment 18: Data analysis for propargyl alcohol
Attachment 19: Data analysis for selenium hexafluoride
Attachment 20: Data analysis for thionyl chloride

LIST OF APPENDICES

Appendix A. Ballot for NAC-40 meeting summary
Appendix B. Final NAC-40 Meeting Highlights
Appendix C. Ballot for ethyl acrylate
Appendix D. Ballot for butyl acrylate
Appendix E. Ballot for formaldehyde
Appendix F. Ballot for titanium tetrachloride
Appendix G. Ballot for benzene
Appendix H. Ballot for methacrylic acid
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Appendix J. Ballot for styrene
Appendix K. Ballot for carbon disulfide
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Appendix N. Ballot for methacrylaldehyde
Appendix O. Ballot for methyl vinyl ketone
Appendix P. Ballot for mercury vapor
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Appendix R. Ballot for selenium hexafluoride
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Appendix T. Committee chairman certification of minutes

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Appendix C

Chemical: ACETONITRILE & ALIPHATIC NITRILES (ISOBUTYRONITRILE, PROPIONITRILE, CHLOROACETONITRILE, MALONONITRILE) **CAS Reg. No.:** (AEGL-2+3 only)

Action: Proposed____ **Interim** ✓ **Other**____

Chemical Manager: RODGERS (Based on Comments) **Staff Scientist:** BAST

NAC Member	AEGL1	AEGL2	AEGL3	LOA	NAC Member	AEGL1	AEGL 2	AEGL3	LOA
Henry Anderson	Y				Warren Jederberg	A →		→	
Steven Barbee	Y				Glenn Leach	A			
Marc Baril	Y				Richard Niemeier	Y			
Lynn Beasley	Y				Marinelle Payton	A	→	→	
Alan Becker	Y				Susan Ripple	Y			
Robert Benson	Y				George Rodgers	Y			
George Cushmac	Y				Marc Ruijten	Y			
Ernest Falke	~~Y~~				George Rusch, Chair	Y			
Alfred Feldt	Retd →	→			Daniel Sudakin	A	→	→	
Roberta Grant	Y				Richard Thomas	Y			
Dieter Heinz	Y				Calvin Willhite	Y			
John Hinz	A →	→			George Woodall	Y			
Jim Holler	Y								
					TALLY				
					PASS/ FAIL				

PPM, (mg/m^3)	10 Min	30 Min	1 Hr	4 Hr	8 Hr
AEGL 1	,( )	,( )	,( )	,( )	,( )
AEGL 2	,(490)	,(490)	,(320)	,(130)	,(86)
AEGL 3	,(1000)	,(1000)	,(670)	,(280)	,(180)
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.

(Nitrile n to 1, 6)

NR= Not Recommended due to____

AEGL 1 Motion by: C Rodgers **Second by:** E Falke

AEGL 2 Motion by:____ **Second by:**____

AEGL 3 Motion by:____ **Second by:**____

LOA Motion by:____ **Second by:**____

Approved by Chair: [signature] **DFO:** Paul S. Tobin **Date:** 3/20/07

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Appendix D

Chemical: PROPIONITRILE / ISOBUTYRONITRILE **CAS Reg. No.:**

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

Chemical Manager: RODGERS Elevate to Interim **Staff Scientist:** BAST

NAC Member	AEGL1	AEGL2	AEGL3	LOA	NAC Member	AEGL1	AEGL 2	AEGL3	LOA
Henry Anderson					Warren Jederberg	A			
Steven Barbee					Glenn Leach	A			
Marc Baril					Richard Niemeier				
Lynn Beasley					Marinelle Payton	A			
Alan Becker					Susan Ripple				
Robert Benson		Y			George Rodgers		Y		
George Cushmac					Marc Ruijten				
Ernest Falke					George Rusch, Chair				
Alfred Feldt	Recused				Daniel Sudakin	A			
Roberta Grant					Richard Thomas				
Dieter Heinz					Calvin Willhite	Abstain	→	→	
John Hinz	A				George Woodall				
Jim Holler									
					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: Niemeier **Second by:** Heinz
AEGL 2 Motion by: Niemeier **Second by:** Heinz
AEGL 3 Motion by: Niemeier **Second by:** Heinz
LOA Motion by:_____ **Second by:**_____

Approved by Chair: [signature] **DFO:** Paul S. Tobin **Date:** 3/20/07

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Appendix E

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

Action: Proposed_____ **Interim** ✓ **Other**_____
Elevate to Interim

Chemical Manager: RODGERS **Staff Scientist:** BAST

NAC Member	AEGL1	AEGL2	AEGL3	LOA	NAC Member	AEGL1	AEGL 2	AEGL3	LOA
Henry Anderson					Warren Jederberg				
Steven Barbee					Glenn Leach				
Marc Baril					Richard Niemeier				
Lynn Beasley					Marinelle Payton				
Alan Becker					Susan Ripple				
Robert Benson					George Rodgers				
George Cushmac		X			Marc Ruijten				
Ernest Falke					George Rusch, Chair				
Alfred Feldt	Ret'd				Daniel Sudakin				
Roberta Grant					Richard Thomas				
Dieter Heinz					Calvin Willhite	Abstain	→	→	
John Hinz	A				George Woodall				
Jim Holler									
					TALLY				
					PASS/ FAIL				

PPM, (mg/m^3)	10 Min	30 Min	1 Hr	4 Hr	8 Hr
AEGL 1	,(NR)	,(NR)	,(NR)	,(NR)	,(NR)
AEGL 2	,(49)	,(49)	,(32)	,(13)	,(8.6)
AEGL 3	,(100)	,(100)	,(67)	,(28)	,(18)
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: R Niemeier **Second by:** D Heinz
AEGL 2 Motion by:_____ **Second by:**_____
AEGL 3 Motion by:_____ **Second by:**_____
LOA Motion by:_____ **Second by:**_____

Approved by Chair: [signature] **DFO:** Paul S. Tobin **Date:** 3/20/07

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Chemical: Malononitrile **CAS Reg. No.:** Appendix F

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

Chemical Manager: Rodgers Elevate to Interim **Staff Scientist:** BAST

NAC Member	AEGL1	AEGL2	AEGL3	LOA
Henry Anderson				
Steven Barbee				
Marc Baril				
Lynn Beasley				
Alan Becker				
Robert Benson				
George Cushmac				
Ernest Falke				
Alfred Feldt	Recb.			
Roberta Grant				
Dieter Heinz				
John Hinz	A			
Jim Holler				

NAC Member	AEGL1	AEGL 2	AEGL3	LOA
Warren Jederberg	A			
Glenn Leach	A			
Richard Niemeier				
Marinelle Payton	A			
Susan Ripple				
George Rodgers				
Marc Ruijten				
George Rusch, Chair				
Daniel Sudakin	A			
Richard Thomas				
Calvin Willhite	~~Withdrew~~ 6 stmin			
George Woodall				
TALLY				
PASS/ FAIL				

PPM, (mg/m³)	10 Min	30 Min	1 Hr	4 Hr	8 Hr
AEGL 1	,(NR)	,(NR)	,(NR)	,(NR)	,(NR)
AEGL 2	,(7,5)	,(7,5)	,(4,9)	,(2,0)	,(1,3)
AEGL 3	,(15)	,(15)	,(10)	,(4,3)	,(2,8)
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: H Anderson **Second by:** M Baril
AEGL 2 Motion by:_____ **Second by:**_____
AEGL 3 Motion by:_____ **Second by:**_____
LOA Motion by:_____ **Second by:**_____

Approved by Chair: [signature] **DFO:** [signature] **Date:** 3/20/07

NAC/AEGL Meeting 42: March 20-22, 2007

Chemical: CHLOROBENZENE **CAS Reg. No.:** Appendix G

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

Chemical Manager: PAYTON **Staff Scientist:** BOS

NAC Member	AEGL1	AEGL2	AEGL3	LOA
Henry Anderson	Y	→	→	
Steven Barbee	Y	→	→	
Marc Baril	Y	→	→	
Lynn Beasley	Y	→	→	
Alan Becker	Y	→	→	
Robert Benson	Y	→	→	
George Cushmac	Y	→	→	
Ernest Falke	Y	→	→	
Alfred Feldt	Rctd	Rctd	Rctd	
Roberta Grant	Y	→	→	
Dieter Heinz	Y	→	→	
John Hinz	A			
Jim Holler	Y	→	→	

NAC Member	AEGL1	AEGL 2	AEGL3	LOA
Warren Jederberg	A	A	A	
Glenn Leach	A	A	A	
Richard Niemeier	Y	→	→	
Marinelle Payton	AB	AB	AB	
Susan Ripple	Y	→	→	
George Rodgers	Y	→	→	
Marc Ruijten	Y	→	→	
George Rusch, Chair	Y	→	→	
Daniel Sudakin	A	A	A	
Richard Thomas	Y	→	→	
Calvin Willhite	Y	→	→	
George Woodall	Y	→	→	
TALLY				
PASS/ FAIL	19/19	19/19	19/19	

PPM, (mg/m^3)	10 Min	30 Min	1 Hr	4 Hr	8 Hr
AEGL 1	,(10)	,(10)	,(10)	,(10)	,(10)
AEGL 2	,(430)	,(300)	,(150)	,(150)	,(150)
AEGL 3	,(1100)	,(800)	,(400)	,(400)	,(400)
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:** FA
AEGL 2 Motion by:_____ **Second by:**_____
AEGL 3 Motion by:_____ **Second by:**_____
LOA Motion by:_____ **Second by:**_____

Approved by Chair: [signature] **DFO:** Paul S. Tobin **Date:** 3/20/07

NAC/AEGL Meeting 42: March 20-22, 2007

Chemical: TOLUENE **CAS Reg. No.:** Appendix H

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

Chemical Manager: **Staff Scientist:**

NAC Member	AEGL1	AEGL2	AEGL3	LOA
Henry Anderson	Y	Y	Y	
Steven Barbee	Y	Y	Y	
Marc Baril	Y	X	Y	
Lynn Beasley	Y	Y	Y	
Alan Becker	Y	Y	Y	
Robert Benson	Y	Y	Y	
George Cushmac	Y	Y	Y	
Ernest Falke	Y	Y	Y	
Alfred Feldt	A	A	A	
Roberta Grant	Y	Y	Y	
Dieter Heinz	Y	Y	Y	
John Hinz	A	A	A	
Jim Holler	Y	Y	Y	

NAC Member	AEGL1	AEGL 2	AEGL3	LOA
Warren Jederberg	A	A	A	
Glenn Leach	A	A	A	
Richard Niemeier	Y	Y	Y	
Marinelle Payton	A	A	A	
Susan Ripple	Y	Y	Y	
George Rodgers	Pass	Pass	Pass	
Marc Ruijten	Y	Y	Y	
George Rusch, Chair	Y	Y	Y	
Daniel Sudakin	A	A	A	
Richard Thomas	Y	Y	Y	
Calvin Willhite	Y	Y	Y	
George Woodall	Y	Y	Y	
TALLY	18/18	18/18	18/18	
PASS/ FAIL				

PPM, (mg/m^3)	10 Min	30 Min	1 Hr	4 Hr	8 Hr
AEGL 1	,(200)	,(200)	,(200)	,(200)	,(200)
AEGL 2	*,(3100)	,(*1600)	,(1200)	,(790)	,(650)
AEGL 3	**,(13000)	*,(6100)	*,(4500)	*,(3000)	*,(2500)
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:** Marc Ruijten **Second by:** R. Thomas
AEGL 2 **Motion by:** ↓ **Second by:** ↓
AEGL 3 **Motion by:** ↓ **Second by:** ↓
LOA **Motion by:** _____ **Second by:** _____

Approved by Chair: [signature] **DFO:** Paul S Tobin **Date:** 3/21/07

NAC/AEGL Meeting 42: March 20-22, 2007

Appendix I

Chemical: BROMINE CHLORIDE **CAS Reg. No.:**

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

Chemical Manager: **Staff Scientist:**

NAC Member	AEGL1	AEGL2	AEGL3	LOA
Henry Anderson	Y	Y	Y	
Steven Barbee	Y	Y	Y	
Marc Baril	Y	Y	Y	
Lynn Beasley	Y	Y	Y	
Alan Becker	Y	Y	Y	
Robert Benson	Y	Y	Y	
George Cushmac	Y	Y	Y	
Ernest Falke	Y	Y	Y	
Alfred Feldt	A	A	A	
Roberta Grant	Y	Y	Y	
Dieter Heinz	Y	Y	Y	
John Hinz	A	A	A	
Jim Holler	Y	Y	Y	

NAC Member	AEGL1	AEGL 2	AEGL3	LOA
Warren Jederberg	A	A	A	
Glenn Leach	A	A	A	
Richard Niemeier	Y	Y	Y	
Marinelle Payton	A	A	A	
Susan Ripple	Y	Y	Y	
George Rodgers	A	A	A	
Marc Ruijten	Y	Y	Y	
George Rusch, Chair	Y	Y	Y	
Daniel Sudakin	A	A	A	
Richard Thomas	Y	Y	Y	
Calvin Willhite	Y	Y	Y	
George Woodall	Y	Y	Y	
TALLY				
PASS/ FAIL				

PPM, (mg/m^3)	10 Min	30 Min	1 Hr	4 Hr	8 Hr
AEGL 1	,(0.5)	,(0.5)	,(0.5)	,(0.5)	,(0.5)
AEGL 2	,(3.2)	,(3.2)	,(2.5)	,(1.6)	,(1.2)
AEGL 3	,(9.5)	,(9.5)	,(7.6)	,(4.8)	,(3.5)
LOA					
* = ≥10% LEL					
** = ≥ 50% LEL					
*** = ≥100% LEL					

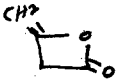
*Safety considerations against the hazard(s) of explosion(s) must be taken into account.
** and ***Extreme safety considerations against the hazard(s) of explosion(s) must be taken into account.

NR= Not Recommended due to _____

AEGL 1 Motion by: D. Heinz **Second by:** M. Wright BARIL
AEGL 2 Motion by: ↓ **Second by:** ↓
AEGL 3 Motion by: ↓ **Second by:** ↓
LOA Motion by: _____ **Second by:** _____

Approved by Chair: _____ **DFO:** Paul S. Tobin **Date:** 3/21/07

NAC/AEGL Meeting 42: March 20-22, 2007

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

Appendix J

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

Chemical Manager: BENSON **Staff Scientist:** BAST

NAC Member	AEGL1	AEGL2	AEGL3	LOA
Henry Anderson	Y			
Steven Barbee	Y			
Marc Baril	Y			
Lynn Beasley	Y			
Alan Becker	Y			
Robert Benson	Y			
George Cushmac	Y			
Ernest Falke	Y			
Alfred Feldt	Not			
Roberta Grant	Y			
Dieter Heinz	Y			
John Hinz	A			
Jim Holler	Y			

NAC Member	AEGL1	AEGL 2	AEGL3	LOA
Warren Jederberg	A			
Glenn Leach	A			
Richard Niemeier	Y			
Marinelle Payton	A			
Susan Ripple	Y			
George Rodgers	Y			
Marc Ruijten	Y			
George Rusch, Chair	Y			
Daniel Sudakin	A			
Richard Thomas	Y			
Calvin Willhite	Y			
George Woodall	Y			
TALLY	19/19			
PASS/ FAIL				

PPM, (mg/m^3)	10 Min	30 Min	1 Hr	4 Hr	8 Hr
AEGL 1	,(NR)	,(NR)	,(NR)	,(NR)	,(NR)
AEGL 2	~~,(12)~~ 11	~~,(8.0)~~ 7.7	~~,(6.3)~~ 6.0	~~,(1.6)~~ 1.5	~~,(0.80)~~ 0.77
AEGL 3	~~,(35)~~ 33	~~,(24)~~ 23	~~,(19)~~ 18	~~,(4.8)~~ 4.5	~~,(2.4)~~ 2.3
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 Lack of Data

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

Approved by Chair: [signature] **DFO:** [signature] **Date:** 3/20/07

NAC/AEGL Meeting 42: March 20-22, 2007

Chemical: ACRYLONITRILE **CAS Reg. No.:** Appendix K

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

Chemical Manager: **Staff Scientist:**

NAC Member	AEGL1	AEGL2	AEGL3	LOA
Henry Anderson	Y	Y	Y	
Steven Barbee	Y	Y	Y	
Marc Baril	Y	Y	Abstain	
Lynn Beasley	Y	Y	Y	
Alan Becker	Y	Y	Y	
Robert Benson	N	Y	Y	
George Cushmac	Y	Y	Y	
Ernest Falke	Y	Y	Y	
Alfred Feldt	A	A	A	
Roberta Grant	Y	Y	Y	
Dieter Heinz	Y	Y	Y	
John Hinz	A	A	A	
Jim Holler	Y	Y	Y	

NAC Member	AEGL1	AEGL 2	AEGL3	LOA
Warren Jederberg	A	A	A	
Glenn Leach	A	A	A	
Richard Niemeier	Y	Y	N	
Marinelle Payton	A	A	A	
Susan Ripple	Y	Y	N	
George Rodgers	Y	Y	Y	
Marc Ruijten	Y	Y	Y	
George Rusch, Chair	Y	Y	Y	
Daniel Sudakin	A	A	A	
Richard Thomas	Y	Y	Y	
Calvin Willhite	Y	Y	N	
George Woodall	Y	Y	N	
TALLY	18/19	19/19	14/19	
PASS/ FAIL				

PPM, (mg/m^3)	10 Min	30 Min	1 Hr	4 Hr	8 Hr
AEGL 1	,(4.6)	,(4.6)	,(4.6)	,(4.6)	,(4.6)
AEGL 2	,(290)	,(110)	,(57)	,(16)	,(8.6)
AEGL 3	,(480)	,(180)	,(100)	,(35)	,(19)
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:** R Thomas **Second by:** FALKE
AEGL 2 **Motion by:** RUIJTEN **Second by:** HEINZ
AEGL 3 **Motion by:** Falke **Second by:** Thomas
LOA **Motion by:** _____ **Second by:** _____

Approved by Chair: [signature] **DFO:** Paul S. Tobin **Date:** 3/21/07

NAC/AEGL Meeting 42: March 20-22, 2007

Appendix L

Chemical: OXYGEN DIFLUORIDE **CAS Reg. No.:**

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

Chemical Manager: IRIS CAMACHO **Staff Scientist:** BOB YOUNG

NAC Member	AEGL1	AEGL2	AEGL3	LOA	NAC Member	AEGL1	AEGL 2	AEGL3	LOA
Henry Anderson	Y	Y	Y		Warren Jederberg	A	A	A	
Steven Barbee	Y	Y	Y		Glenn Leach	A	A	A	
Marc Baril	Y	Y	Y		Richard Niemeier	Y	Y	Y	
Lynn Beasley	Y	Y	Y		Marinelle Payton	A	A	A	
Alan Becker	Y	Y			Susan Ripple	Y	Y	Y	
Robert Benson	Y	Y	Y		George Rodgers	Y	Y	Y	
George Cushmac	Y	Y			Marc Ruijten	Y	Y	Y	
Ernest Falke	Y	Y	Y		George Rusch, Chair	Y	Y	Y	
Alfred Feldt	A	A	A		Daniel Sudakin	A	A	A	
Roberta Grant	Y	Y	Y		Richard Thomas	Y	Y	Y	
Dieter Heinz	Y	Y	Y		Calvin Willhite	Y	Y	Y	
John Hinz	A	A	A		George Woodall	Y	Y	Y	
Jim Holler	Y	Y	Y						
					TALLY	19/19	19/19	19/19	
					PASS/ FAIL				

PPM, (mg/m^3)	10 Min	30 Min	1 Hr	4 Hr	8 Hr
AEGL 1	,(NR)	,(NR)	,(NR)	,(NR)	,(NR)
AEGL 2	,(4.3)	,(1.6)	,(0.83)	,(0.24)	,(0.13)
AEGL 3	,(13)	,(4.7)	,(2.5)	,(0.71)	,(0.38)
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: _____ **Second by:** _____
AEGL 2 Motion by: ↓ **Second by:** ↓
AEGL 3 Motion by: ↓ **Second by:** ↓
LOA Motion by: _____ **Second by:** _____

Approved by Chair: _____ **DFO:** _____ **Date:** 3/21/07