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

September 16-17, 2003

Final Meeting-30 Highlights

U.S. Department of Labor
200 Constitution Avenue, N.W., Rm 4437-B,C,D
Washington, DC 20210

INTRODUCTION

The draft NAC/AEGL-29 meeting highlights were reviewed. There were no corrections or comments, and a motion was made by Loren Koller and seconded by John Hinz to accept the meeting highlights as presented. The motion passed unanimously by a voice vote. The final version of the NAC/AEGL-29 meeting highlights is attached (Appendix A) and was distributed to the NAC/AEGL by e-mail.

Ernie Falke discussed highlights of the July COT AEGL Subcommittee meeting. The COT subcommittee was concerned that the AEGL-2 and AEGL-3 values were very close for phosphine (less than a factor of 2), and questioned whether there should be a specific minimal difference between AEGL tiers because of the needs of emergency planners. It was pointed out that AEGL tiers for other chemicals, such as aniline, hydrogen cyanide and phosgene were also close together. George Rusch pointed out that in all of these cases the closeness of values reflects the exposure-response data (very steep concentration-response curve). After some discussion, the NAC felt that this closeness of values was appropriate and should be retained; doing otherwise would not reflect the toxicity of the chemical. Therefore, a comment will be added to the phosphine TSD acknowledging the closeness of the AEGL-2 and AEGL-3 values and explaining the basis of this closeness. Regarding the Level of Odor Awareness (LOA), the COT requested that the LOA methodology be published, either as an RIVM document or in the Journal of Inhalation Toxicology. Hopefully, this publication will precede the publication of any TSD that includes an LOA. The COT also requested that the following issues be addressed when the SOP is updated: RD_{50} and its use in developing AEGLs, benchmark dose approach, rounding and time-scaling, holding irritation concentrations stable across time, PBPK issues, modifying factor use, and time scaling vs. constant values for solvents (Attachment 1).

Ernie Falke distributed proposed chemical lists for NAC- 32, 33, 34, and 35 (March-December, 2004) and asked NAC members to volunteer to be chemical manager for these priority chemicals (Attachment 2).

A revised draft of language to be added to the SOP regarding use of occupational studies, prepared by John Morawetz, was reviewed. A motion was made by George Alexeeff and seconded by Richard Niemier to accept the revised language for inclusion into the SOP as presented. The motion passed unanimously by a voice vote (Attachment 3).

The highlights of the NAC/AEGL-30 meeting are summarized below along with the Meeting Agenda (Attachment 4) and the Attendee List (Attachment 5). The subject categories of the highlights do not necessarily follow the order listed in the NAC/AEGL-30 Agenda.

RESPONSES TO FEDERAL REGISTER COMMENTS ON THE PROPOSED AEGL VALUES

(A) Comments from the **Federal Register Notice** of July 18, 2003, on the proposed AEGL values for Phosphorus trichloride and Acetone cyanohydrin were received and discussed. The NAC/AEGL deliberation of these chemicals are briefly summarized as the following:

PHOSPHORUS TRICHLORIDE

Comments were received from John Morawetz regarding supporting data for AEGL-1. Human data from an abstract by Sassi (1952) were used as supporting information for AEGL-1 values. After discussion, it was agreed that it would be best to remove the Sassi report as support for AEGL-1 values due to ambiguities in the study report. A motion to move the chemical from proposed to interim status was made by John Morawetz and seconded by David Belluck. The motion was approved unanimously by the NAC/AEGL (Appendix B).

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ACETONE CYANOHYDRIN

Comments were received from John Morawetz and the Methacrylate Producers Association, Inc. Mr. Morawetz was concerned that descriptions of two occupational hydrogen cyanide studies (El Ghawabi et al., 1975, and Leeser, 1990) were in need of revision. The descriptions of these studies will be made consistent with the study descriptions in the hydrogen cyanide TSD. Mark Hamilton (?) made a presentation on behalf of the Methacrylate Producers Association, explaining that hydrogen cyanide (HCN) is the principal hazard from acetone cyanohydrin (ACN) exposure. The Association comments stated that ACN volatilizes rapidly and almost completely to HCN and that ACN itself is not detected during a release. Therefore, no separate AEGL values are needed for ACN. If separate values for ACN are derived, the Methacrylate Producers Association stated that there would be no justification for setting ACN values lower than HCN values. Peter Griem then responded to the comments (Attachment 6). After discussion, a motion was made by Ernest Falke and seconded by Richard Thomas to adopt HCN AEGL-2 and AEGL-3 values as AEGL-2 and AEGL-3 values for ACN; and to remove the MF of 2 from the ACN AEGL-1 values; and to raise the document to interim status. The motion was approved unanimously by the NAC/AEGL (Appendix C). This approach used ACN data to develop AEGL-1 values that are very similar to the HCN AEGL-1 values. A footnote will also be

added stating that these are nominal values for ACH and actual exposure may include acetone, HCN, and ACN. The interim values are presented in the table below.

Summary of Interim AEGL Values for Acetone Cyanohydrin [ppm]						
Classification	**10-minutes**	**30-minutes**	**1-hour**	**4-hour**	**8-hour**	**Endpoint (Reference)**
AEGL-1	2.2	2.2	1.7	1.1	0.70	Red nasal discharge in rats
AEGL-2	17	10	7.1	3.5	2.5	HCN AEGL-2 values adopted as ACN AEGL-2 values
AEGL-3	27	21	15	8.6	6.6	HCN AEGL-3 values adopted as ACN AEGL-3 values

(B). No comments were received regarding the **Federal Register Notice** of May 28, 2003, on the proposed AEGL values for Fluorine, Jet Fuel, Monochloroacetic acid, and Phosphorus oxychloride. Therefore, these chemicals were elevated to Interim status as indicated below.

FLUORINE

No comments were received regarding the **Federal Register Notice** of July 18, 2003. A motion to move the chemical from proposed to interim status was made by Richard Niemier and seconded by Richard Thomas. The motion was approved unanimously by the NAC/AEGL (Appendix D).

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JET FUEL

No comments were received regarding the **Federal Register Notices** of July 18, 2003. A motion to move the chemical from proposed to interim status was made by Richard Niemier and seconded by Richard Thomas. The motion was approved unanimously by the NAC/AEGL (Appendix E).

MONOCHLOROACETIC ACID

No comments were received regarding the **Federal Register Notices** of July 18, 2003. A motion to move the chemical from proposed to interim status was made by Richard Niemier and seconded by Richard Thomas. The motion was approved unanimously by the NAC/AEGL (Appendix F).

PHOSPHORUS OXYCHLORIDE

No comments were received regarding the **Federal Register Notices** of July 18, 2003. A motion to move the chemical from proposed to interim status was made by Richard Niemier and seconded by Richard Thomas. The motion was approved unanimously by the NAC/AEGL (Appendix G).

documentation as support. It was also requested that NAC members with supporting information send these data to Peter Griem.

Acrylic Acid (CAS No. 79-10-7)

Chemical Manager: Ernest Falke
Staff Scientist: Peter Griem, FOBIG

Dr. James McLaughlin, Chairman of the Basic Acrylic Monomer Manufacturers, Inc. (BAMM), provided additional data and a letter (Attachment 9) regarding the COT AEGL Subcommittee s comments on the acrylic acid TSD to assure that all information was considered. The letter had not been distributed to the NAC prior to the meeting. BAMMs major concerns were as follows: (1) An AEGL-1 value of 1.5 ppm is too low because RD$_{50}$ work suggests the irritation threshold to be at or above 6-8 ppm. The Renshaw study supports an AEGL-1 of 5-10 ppm and is consistent with international consensus; (2) AEGL-3 values are substantially too low and cannot be reconciled with current data, especially nose-only vapor exposures; and (3) LOA values are subject to abuse unless it is clearly stated that no health effects are implied.

Peter Griem discussed concerns expressed by the COT AEGL Subcommittee (Attachment 10). The COT AEGL Subcommittee s major concerns were as follows: (1) Use of a personal communication as the key study for AEGL-1; (2) Use of histological changes of the olfactory epithelium as the basis of AEGL-2; and (3) Use of an aerosol study instead of a vapor study and use of the MLE$_{01}$ instead of BMC$_{05}$ as the basis of AEGL-3. After much discussion, the AEGL-1 values were increased from 1.0 ppm at all time points to 1.5 ppm at all time points. Rationale for this approach is presented on page 8 of Attachment 10. AEGL-2 and AEGL-3 values were retained.

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REVIEW OF CHEMICAL WITH ISSUES FROM PREVIOUS MEETINGS

Vinyl Chloride (Cas No. 75-01-4)

Chemical Manager: Robert Benson
Staff Scientist: Fritz Kalberlah, FOBIG

Bob Benson, Chemical Manager, provided a brief update on the changes to the VC TSD. These changes included revision in the description of an occupational study, revision to the calculations of cancer risk in the appendix, including an additional appendix describing additional assessment of cancer incidence from occupational exposure, and addition of a table with the cancer calculations to the Executive Summary. There have been no changes in the AEGL values previously approved by the Committee. As the cancer calculations do not require a formal vote of

The proposed AEGL-3 was based on a 4-hour $BMDL_{05}$ of 3400 ppm in female rats (BASF, 1979). The TSD scientist suggested applying intraspecies and interspecies UFs of 3 each resulting in a total UF of 10. Time scaling using a chemical-specific, empirically derived n= 1.2 was proposed. Larry Gephart expressed concern over extrapolation from a 4-hour starting point to the 10-minute AEGL value. Concern was also expressed about extrapolation to 8-hours from the 4-hour starting point because toxicokinetic data for humans indicate very little or no increase at exposure times greater than 1 hour. A motion was made by Bob Snyder and seconded by Ernest Falke to accept the AEGL-3 values of 1900 ppm for 10- and 30-minutes, 1100 ppm for 1-hour, and 340 ppm 4-, and 8-hours. The motion passed (YES: 18; NO: 0; ABSTAIN: 0) (Appendix I).

The proposed LOA of 0.54 ppm was unanimously by a show of hands.

Summary of AEGL Values for Styrene						
Classification	**10-minute**	**30-minute**	**1-hour**	**4-hour**	**8-hour**	**Endpoint (Referen**
AEGL 1	20 ppm 85 mg/m^3	20 ppm 85 mg/m^3	20 ppm 85 mg/m^3	20 ppm 85 mg/m^3	20 ppm 85 mg/m^3	NOAEL for irritation (Seeber et al., 2002)
AEGL 2	230 ppm 980 mg/m^3	160 ppm 680 mg/m^3	130 ppm 550 mg/m^3	130 ppm 550 mg/m^3	130 ppm 550 mg/m^3	CNS effects - human (Stewart et al. 1968)
AEGL 3	1900 ppm 8090 mg/m^3	1900 ppm 8090 mg/m^3	1100 ppm 4690 mg/m^3	340 ppm 1450 mg/m^3	340 ppm 1450 mg/m^3	$BMDL_{05}$ in female rats (BASF, 1979)

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PROPANE
CAS Reg. No.74-98-6

Chemical Manager: Larry Gephart
Staff Scientist: P. J. M. Bos, RIVM, The Netherlands

The chemical review on propane was presented by Peter Bos (Attachment 12). The proposed AEGL-1 values were based on no effects in humans exposed to 10,000 propane for 10 minutes (Patty and Yant, 1929). An intraspecies UF of 1 was proposed because of the very steep concentration-response curve (for butane) implying little interindividual variability. Time scaling using n= 3 was proposed for extrapolation to 30-minutes and 1-hour, and it was proposed that the 1-hour value be adopted as both the 4- and 8-hour AEGL-1 values because steady-state is reached within 30 minutes. Proposed AEGL-1 values for propane were 10,000 ppm for 10-min, 6900 ppm for 30-min, and 5500 ppm for 1-, 4-, and 8-hours.

The proposed AEGL-2 values are based on a NOEL for cardiac sensitization in dogs at 50,000 ppm (Reinhardt et al., 1971). An intraspecies UF of 3 was proposed to protect sensitive individuals, and an interspecies UF of 1 was proposed because the dog is an optimized supersensitive model for humans. The value of 17,000 ppm was applied across all time points because cardiac sensitization is a concentration-related threshold effect.

30 minutes. Proposed AEGL-1 values for butane were 10,000 ppm for 10-min, 6900 ppm for 30-min, and 5500 ppm for 1-, 4-, and 8-hours.

The proposed AEGL-2 values were based on a dazed appearance (but able to walk) in guinea pigs exposed to 50,000-56,000 ppm for 2 hours (Nuckolls, 1929). A total UF of 3 was proposed and considered sufficient because effects were due to butane and, thus, no large differences in kinetics would be expected and a higher UF would yield AEGL-2 values close to AEGL-1 values. Time scaling using n= 3 was proposed for extrapolation to 10- and 30-minutes and 1-hour, and it was proposed that the 2-hour point of departure value be adopted as both the 4- and 8-hour AEGL-2 values because steady-state is reached within 30 minutes. Proposed AEGL-2 values for butane were 38,200 ppm for 10-min, 26,500 ppm for 30-min, 21,000 ppm for 1-hour, and 16,700 ppm for 4- and 8-hours.

The proposed AEGL-3 values were based on a calculated 2-hour LC_{01} of 160,000 ppm (Shugaev, 1969). A total UF of 3 was proposed and considered sufficient because effects were due to butane and, thus, no large differences in kinetics would be expected, the steep concentration-response curve suggested small interindividual variability, and the most sensitive species was used. Time scaling using n= 3 was proposed for extrapolation to 10- and 30-minutes and 1-hour, and it was proposed that the 2-hour point of departure value be adopted as both the 4- and 8-hour AEGL-2 values because steady-state is reached within 30 minutes. Proposed AEGL-3 values for butane were 122,000 ppm for 10-min, 85,000 ppm for 30-min, 67,000 ppm for 1-hour, and 53,000 ppm for 4-, and 8-hours.

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After some discussion, a motion was made by John Hinz and seconded by George Rodgers to accept the AEGL-1 values as proposed, to accept AEGL-2 values of 25,000 ppm for 10-minutes and 17,000 ppm for 30-min, 1-, 4-, and 8-hours, and to accept AEGL-3 values of 76,000 ppm for 10-minutes and 53,000 ppm for 30-min, 1-, 4-, and 8-hours. The points of departure utilized for the AEGL-2 and AEGL-3 values are those described above. However, instead of scaling across time for the 30-min and 1-hr values, the 2-hr point of departures (with the UF of 3 applied) were held constant for the 30-min, 1-, 4-, and 8-hr time points, and time scaling using n=3 was applied to derive the 10-min AEGL-2 and AEGL-3 values because steady-state is reached within 30-minutes, but not within 10-minutes. The motion passed (YES: 17; NO: 1; ABSTAIN: 1) (Appendix K).

Summary of AEGL Values for Butane						
Classification	**10-minute**	**30-minute**	**1-hour**	**4-hour**	**8-hour**	**Endpoint (Referen**
AEGL 1	10,000 ppm* 4200 mg/m^3	6900 ppm* 2900 mg/m^3	5500 ppm* 2300 mg/m^3	5500 ppm* 2300 mg/m^3	5500 ppm* 2300 mg/m^3	NOEL in humans (Patty and Yant, 1929)
AEGL 2	See below[1]	See below[1]	See below[1]	See below[1]	See below[1]	dazed appearance (but able to walk) in guinea pigs (Nuckolls, 1929)

when extrapolating to 10- and 30-min were proposed. Proposed AEGL-3 values were 1.1 ppm for 10-min, 0.73 ppm for 30-min, 0.58 ppm for 1-hour, 0.15 ppm for 4-hr, and 0.073 ppm for 8-hr.

Discussion included the selection of the exponent, n, for scaling across time values. LC_{50}s derived in rats of 64 ppm for an 1-hour duration (Hein, 1969) and of 32 ppm for a 4-hour exposure (Kennedy and Graepel, 1991) support the equation $C^2 \times t = k$. A similar time relationship was observed within mice, for which LC_{50} values of 98 ppm and 54 ppm were reported for an 1-hour and a 4-hour exposure, respectively (Hein, 1969; Rodkina et al. 1986). Discussion also involved selection of the key study for AEGL-3 derivation; it was suggested that the highest non-lethal concentration of 49 ppm (rats, 1-h exposure) be used for the derivation of the AEGL-3 values.

A motion was made by Loren Koller and Seconded by Ernest Falke to adopt AEGL-1 values of 0.035 ppm for 10- and 30-min, 0.024 ppm for 1-hr, 0.012 ppm for 4-hr and 0.0087 ppm for 8-hr; AEGL-2 values of 0.17 ppm for 10- and 30-min, 0.12 ppm for 1-hr, 0.061 ppm for 4-hr and 0.043 ppm for 8-hr; and AEGL-3 values of 12 ppm for 10- min, 6.9 ppm for 30-min, 4.9 ppm for 1-hr, 2.5 ppm for 4-hr and 1.7 ppm for 8-hr. These AEGL-1 and AGEL-2 values were based on the key studies/point of departure and UFs described in the proposals above; however, time scaling used n=2. These AEGL-3 values were based on the highest concentration causing no deaths in rats (49 ppm. 1hr), a total UF of 10, and time scaling using n = 2. The three AEGL tiers were balloted separately. The motion passed for AEGL-1 and AEGL-2 (YES: 19; NO: 0; ABSTAIN: 1) (Appendix L). The motion did not pass for AEGL-3 (YES: 6; NO: 8; ABSTAIN: 1) (Appendix L).

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A motion was then made by Richard Thomas and seconded by Richard Niemier to adopt AEGL-3 values of 4.0 ppm for 10- min, 2.3 ppm for 30-min, 1.8 ppm for 1-hr, 0.82 ppm for 4-hr and 0.58 ppm for 8-hr. These AEGL-3 values were based on the highest concentration causing no deaths in rats (49 ppm for 1hr), a total UF of 30 (intra =3, inter =10 because the rat is not the most sensitive species), and time scaling using n = 2. The motion passed (YES: 19; NO: 0; ABSTAIN: 1) (Appendix L).

Summary of AEGL Values for Dimethylsulfate						
Classification	**10-minute**	**30-minute**	**1-hour**	**4-hour**	**8-hour**	**Endpoint (Referen**
AEGL 1	0.035 ppm 0.18 mg/m^3	0.035 ppm 0.18mg/m^3	0.024 ppm 0.12 mg/m^3	0.012 ppm 0.062 mg/m^3	0.0087 ppm 0.045 mg/m^3	nasal cell proliferation in rat (Frame et al., 1993)
AEGL 2	0.17 ppm 0.88 mg/m^3	0.17 ppm 0.88 mg/m^3	0.12 ppm 0.62 mg/m^3	0.061 ppm 0.32 mg/m^3	0.043 ppm 0.22 mg/m^3	breathing problems rat, mouse, hamster (Schlogel, 1972)
AEGL 3	4.0 ppm 21 mg/m^3	2.3 ppm 12 mg/m^3	1.6 ppm 8.3 mg/m^3	0.82 ppm 4.3 mg/m^3	0.58 ppm 3.0 mg/m^3	Concentration causing no death in rats (Hein, 1969)

SOME HIGHLIGHTS FROM NAS-12

- Discussion of format of NAS reviews to have more consistency, closure, and eliminate contradictory comments.
- Phosphine- AEGL-2 and -3 seem to be too close and less than a factor of 2. Question is whether there should be at least a certain difference between AEGL tiers. Other chemicals also have small ratiosBut phosgene, HCN and aniline also have small ratios.
  - What do emergency planners need? Caveats? Discussion?
  - Science vs policy derivation?

ATTACHMENT 1

PROPOSED AEGL VALUES FOR PHOSPHINE						
Classification	10-min	30-min	1-hour	4-hour	8-hour	Endpoint (Reference)
AEGL-1 (Nondisabling)	NR	NR	NR	NR	NR	Appropriate data not available
AEGL-2 (Disabling)	4.0 ppm (5.6 mg/m³)	4.0 ppm (5.6 mg/m³)	2.0 ppm (2.8 mg/m³)	0.50 ppm (0.71 mg/m³)	0.25 ppm (0.35 mg/m³)	Red mucoid nasal discharge in rats exposed to 10 ppm phosphine for 6 hr (Newton et al., 1993)
AEGL-3 (Lethality)	7.2 ppm (10 mg/m³)	7.2 ppm (10 mg/m³)	3.6 ppm (5.1 mg/m³)	0.90 ppm (1.3 mg/m³)	0.45 ppm (0.63 mg/m³)	Concentration causing no death in rats exposed to 18 ppm phosphine for 6 hr (Newton, 1991)

Summary of Proposed AEGL Values for Phosgene [ppm (mg/m³)]						
Classification	10-minute	30-minute	1-hour	4-hour	8-hour	Endpoint (Reference)
AEGL-1 (Nondisabling)	NA	NA	NA	NA	NA	NA
AEGL-2 (Disabling)	0.60 (2.5)	0.60 (2.5)	0.30 (1.2)	0.08 (0.33)	0.04 (0.16)	Chemical pneumonia rats (Gross et al., 1965)
AEGL-3 (Lethal)	3.6 (15)	1.5 (6.2)	0.75 (3.1)	0.20 (0.82)	0.09 (0.34)	Highest concentration causing no mortality in the rat after a 30-minute or 10-minute exposure (Zwart et al., 1990)

Summary Table of AEGL Values for Hydrogen Cyanide [ppm (mg/m³)]						
Classification	10-Minute	30-Minute	1-Hour	4-Hour	8-Hour	Endpoint (Reference)
AEGL-1[a] (Nondisabling)	2.5 (2.8)	2.5 (2.8)	2.0 (2.2)	1.3 (1.4)	1.0 (1.1)	No adverse health effects - humans (Hardy et al. 1950; Grabois 1954; Maehly and Swensson 1970; Lesser et al. 1990); mild central nervous system effects - humans (El Ghawabi et al. 1975)
AEGL-2 (Disabling)	17 (19)	10 (11)	7.1 (7.8)	3.5 (3.9)	2.5 (2.8)	Slight central nervous system depression - monkey (Purser 1984)
AEGL-3[b] (Lethal)	27 (30)	21 (23)	15 (17)	8.6 (9.7)	6.6 (7.3)	Lethality (LC_{01}) - rat (E.I. du Pont de Nemours 1981

[a]The bitter almond odor of HCN may be noticeable to some individuals at the AEGL-1.
[b]Values for different timepoints were based on separate experimental values closest to the timepoint of interest.

SUMMARY TABLE OF AEGL VALUES FOR ANILINE[a] [ppm (mg/m³)]						
Classification	10-Minute	30-Minute	1-Hour	4-Hour	8-Hour	Endpoint (Reference)
AEGL-1[b] (Nondisabling)	48 (182)	16 (61)	8.0 (30)	2.0 (7.6)	1.0 (3.8)	22% Methemoglobin - cyanosis (Kim and Carlson, 1986)
AEGL-2 (Disabling)	72 (274)	24 (91)	12 (46)	3.0 (11)	1.5 (5.7)	41% Methemoglobin - lethargy (Kim and Carlson, 1986)
AEGL-3 (Lethal)	120 (456)	40 (152)	20 (76)	5.0 (19)	2.5 (9.5)	>70% Methemoglobin - lethality (extrapolated from data of Kim and Carlson, 1986)

[a]Cutaneous absorption of the neat material may occur, adding to the systemic toxicity.
[b]The aromatic, amine-like odor of aniline will be noticeable by most individuals at these concentrations.

- LOA
  - The ideal would be for The Netherlands to publish the in depth LOA approach as an RIVM document which could be cited. A short version would be used for an SOP revision. Alternatively, John Gardner could publish it quickly in the J Inhalation Toxicology. The consensus seemed to be that the LOA should be published and the NAC/AEGL Committee should continue to develop LOAs. Hopefully this would be done before the first LOA chemical is published. Otherwise LOAs might be dropped.
- Other Comments
  - What lessons have we learned across the compounds considered to date.
- Some SOP Update issues
  - RD50 and its use in developing AEGLs
  - More detailed category plot legend and description.
  - Benchmark dose approach needs more information
  - Time scaling rounding - when do we do it and how
  - Irritants - when do we hold concentrations stable across time
  - PBPK issues - when is it appropriate? What basic elements are required
  - When should time scaling be used for solvents and when should it be held constant
  - The possible use of Categorical Regression was mentioned.
  - How and when will we use Modifying Factors

NAC-32 March 2004

ATTACHMENT 2

CAS-NO	ChemicalName	PlanningByActivity	Status	Author	Chemical Manager
75-07-0	Acetaldehyde	NAC-32 Mar04-New NHSRC Chemical	Planning	ORNL	
141-32-2	Butyl acrylate	NAC-32 Mar04-New	Planning	ORNL	
78-95-5	Chloroacetone	NAC-32 Mar04-New NHSRC Chemical	Planning	ORNL	
106-93-4	Dibromoethane	NAC-32 Mar04-New NHSRC Chemical	Planning	ORNL	
674-82-8	Diketene	NAC-32 Mar04-New NHSRC Chemical	Planning	ORNL	
140-88-5	Ethyl acrylate	NAC-32 Mar04-New	Planning	ORNL	
79-41-4	Methacrylic acid	NAC-32 Mar04-New	Planning	Germany	Benson
80-63-7	Methyl 2-chloroacrylate	NAC-32 Mar04-New	Planning	ORNL	
80-62-6	Methyl methacrylate	NAC-32 Mar04-New	Planning	Germany	Benson
109-99-9	Tetrahydrofuran	NAC-32 Mar04-New	Planning	Troxel	

NAC-33 June 04

CAS-NO	ChemicalName	PlanningByActivity	Status	Author	Chemical Manager
95-63-6	1,2,4-trimethyl benzene	NAC-33 Jun04 New	Planning	ORNL	
578-94-9	Adamsite	NAC-33 Jun04-New ORD HS	Planning	ORNL	
98-82-8	Cumene	NAC-33 Jun04 New	Planning	ORNL	
100-41-4	Ethyl benzene	NAC-33 Jun04 New	Planning	ORNL	
598-14-1	Ethyl dichloroarsine	NAC-33 Jun04-New ORD HS	Planning	ORNL	
541-25-3	Lewisite L-1 2-chlorovinyl c	NAC-33 Jun04-New ORD HS	Planning	ORNL	
40334-69-8	Lewisite L-2 bis(2-chlorovir	NAC-33 Jun04-New ORD HS	Planning	ORNL	
40334-70-1	Lewisite L-3 tris(2-chlorovi	NAC-33 Jun04-New ORD HS	Planning	ORNL	
108-67-8	Mesitylene	NAC-33 Jun04 New	Planning	ORNL	
593-89-5	Methyl dichloroarsine	NAC-33 Jun04-New ORD HS	Planning	ORNL	
696-28-6	Phenyl dichloroarsine	NAC-33 Jun04-New ORD HS	Planning	ORNL	

NAC-34 September 2004

CAS-NO	ChemicalName	PlanningByActivity	Status	Author	Chemical Manager
97-02-9	2,4-dinitroaniline	NAC-34 Sep04-New	Planning	ORNL	
92-52-4	Biphenyl	NAC-34 Sep04 New	Planning	ORNL	
538-07-8	bis(2-chloroethyl)amine (Ni	NAC-34 Sep04-New ORD HS	Planning	ORNL	
51-75-2	bis(2-chloroethylmethyl)am	NAC-34 Sep04-New ORD HS	Planning	ORNL	
124-40-3	Dimethylamine	NAC-34 Sep04-New	Planning	Russia	
75-04-7	Ethyl amine	NAC-34 Sep04-New	Planning	Russia	
7803-49-8	Hydroxylamine	NAC-34 Sep04-New	Planning	ORNL	
74-89-5	Methyl amine	NAC-34 Sep04-New	Planning	Russia	
75-50-3	Trimethylamine	NAC-34 Sep04-New	Planning	Russia	
555-77-1	tris(2-chloroethyl)amine (N	NAC-34 Sep04-New ORD HS	Planning	ORNL	

NAC-35 December 2004

CAS-NO	ChemicalName	PlanningByActivity	Status	Author	Chemical Manager
105-60-2	Caprolactam	NAC-35 Dec04-New	Planning		
1341-24-8	Chloroacetophenone	NAC-35 Dec04-New	Planning		
3173-53-3	Cyclohexyl isocyanate	NAC-35 Dec04-New	Planning		
684-16-2	Hexafluoro acetone	NAC-35 Dec04-New	Planning		
1634-04-4	Methyl t-butyl ether	NAC-35 Dec04-New	Planning		
538-07-8	Nitrogen mustard bis(2-chl	NAC-35 Dec04-New	Planning	ORNL	
51-75-2	Nitrogen mustard bis(2-chl	NAC-35 Dec04-New	Planning	ORNL	
555-77-1	Nitrogen mustard tris(2-chl	NAC-35 Dec04-New	Planning	ORNL	

ATTACHMENT 3

Revised version after AEGL–29 meeting, June, 2003

To incorporate these points in the SOP, the following language should be added to the SOP's Evaluation section.

In describing occupational studies all possible routes of entry and all contaminants should be listed.

1) All occupational monitoring results should clearly describe their measurement type (such as breathing zone, area/general workplace, bulk sample or theoretical calculation from bulk sample) and sampling time (instantaneous, short term, full shift).

2) Breathing zone samples are the preferred estimate of workers' exposures because it most accurately estimates the exposure that is inhaled by a worker. Breathing zone short term samples should be used primarily for the sampled time period.

3) General area, bulk samples and theoretical calculations from bulk samples are not usually accurate measurements of workers' exposures. They should not be utilized in the AEGL derivation sections unless there is substantial documentation on workers tasks and their relationship to these samples.

ATTACHMENT 4

National Advisory Committee for Acute Exposure Guideline Levels for Hazardous Substances

NAC/AEGL-30
September 16-18, 2003

US Department of Labor
200 Constitution Ave., N.W., Room 4437-B, C, D
Washington DC 20210

Metro: Judiciary Square (Red Line)

AGENDA

Tuesday, September 16, 2003

10:00 a..m.	Introductory remarks and approval of NAC/AEGL-29 Highlights (George Rusch, Ernie Falke, and Paul Tobin)
10:15	Review of July COT meeting (George Rusch, Ernie Falke, and Paul Tobin)
10:30	Review of Styrene (Mark McClanahan/Uwe Voss)
12:00 noon	Lunch
1:00	Revisit of Carbon monoxide- COT comments (George Rodgers/Peter Griem)
1:45	Revisit of Vinyl chloride (cancer assessment) (Bob Benson/Fritz Kalberlah)
3:00	Break
3:15	Revisit of Phenol- COT comments (Bob Snyder/ Peter Griem)
4:00	Discussion of Federal Register Public Comments (Acetone cyanohydrin, Bromine, Fluorine, Jet Fuel, Methyl ethyl ketone, Monochloroacetic acid, Phosphorus oxychloride, Phosphorus trichloride, Xylenes)
5:30	Adjourn for the day

Wednesday, September 17, 2003

8:00 a.m.	Review of Butane (Larry Gephart/Netherlands)
9:45	Break
10:00	Review of Propane (Larry Gephart/Netherlands)
12:00 noon	Lunch
1:00	Review of Aliphatic nitriles- Acetonitrile, Propionitrile, Isobutyronitrile, Chloroacetonitrile & Malononitrile (George Rodgers/Cheryl Bast)
3:00	Break
3:15	Review of Aliphatic Nitriles (con't.)
4:15	Revisit of Methanol- COT comments (Ernest Falke/Peter Griem)
5:00	Adjourn for the day

Thursday, September 18, 2003

8:00 a.m.	Review of Dimethyl sulfate (Bob Snyder/Susanne Gfatter/Fritz Kalberlah)
9:30	Revisit of Acrylic Acid- COT comments (Ernest Falke/Peter Griem)
10:15	Break
10:30	Occupational Exposure Estimates (John Morawetz)
10:50	Review of Hydrogen iodide (Mark McClanahan/Sylvia Talmage)
11:15	Review of Disulfur dichloride and Sulfur dichloride (Mark McClanahan/Kowetha Davidson)
11:45	Administrative matters
12:00 noon	Adjourn meeting

ATTENDANCE - PLEASE RETURN TO PAUL TOBIN
* 26 MEMBERS (13 = QUORUM) 18 PRESENT

NAC/AEGL Meeting 30: September 16-18, 2003

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

ATTACHMENT 5

NAC Member	AEGL1	AEGL2	AEGL3	LOA	NAC Member	AEGL1			
George Alexeeff	✓				Nancy Kim	X ABSENT			
Steven Barbee	X ABSENT				Loren Koller	✓			
Lynn Beasley	✓				Glenn Leach	X ~~ABSENT~~			
David Belluck	✓				Mark McClanahan	X ABSENT			
Robert Benson	✓				John Morawetz	✓			
Jonathan Borak	X ABSENT - plans to attend				Richard Niemeier	✓			
William Bress	✓				Marinelle Payton	X ABSENT plans to attend			
George Cushmac	✓				Zarena Post	X ABSENT			
Al Dietz	X ABSENT				George Rodgers	✓			
Ernest Falke	✓				George Rusch, Chair				
Larry Gephart	✓				Robert Snyder	✓			
John Hinz	✓				~~Thomas Sobotka~~	X RESIGNED			
Jim Holler	X ABSENT				~~Kenneth Still~~	X RESIGNED			
Thomas Hornshaw	✓				Richard Thomas	✓			
					Warren Jederberg	✓			
					TALLY				

PPM, (mg/m^3)	10 Min	30 Min	1 Hr	4 Hr	8 Hr
AEGL 1	, ( )	, ( )	, ( )	, ( )	, ( )
AEGL 2	, ( )	, ( )	, ( )	, ( )	, ( )
AEGL 3	, ( )	, ( )	, ( )	, ( )	, ( )
LOA					

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:** _____

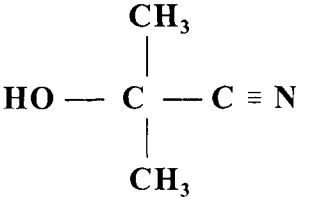
ATTACHMENT 6

Proposed AEGL values

for

ACETONE CYANOHYDRIN

(CAS Reg. No. 75-86-5)



Discussion of Public Comments

NAC/AEGL Meeting 30, September 16-18, 2003

FoBiG Staff Scientist:

Peter Griem

Chemical Manager in German Expert Group:

Rüdiger Bartsch

Industry Reviewer for German Expert Group:

Harald Müllerschön

Chemical Manager:

Larry Gephart

AEGL-1 VALUES				
10 minutes	30 minutes	1 hour	4 hours	8 hours
1.1 ppm	1.1 ppm	0.84 ppm	0.53 ppm	0.35 ppm

Reference: Monsanto Co., 1986. One-month inhalation toxicity of acetone cyanohydrin in male and female Sprague-Dawley rats with cover letter dated 04-25-86. Report No. BN-81-178, Monsanto Co., St. Louis, MO, USA.

Test Species/Strain/Number: rat / Sprague-Dawley / 10 female and 10 male per group

Exposure Route/Concentrations/Durations: Inhalation /59.6, 29.9, 9.2 (determinant for AEGL-1) and 0 ppm / 6 hours/day, 5 days/week for 4 weeks

Effects: During the first week of exposure, red nasal discharge (sign of local irritation of the upper respiratory tract) was reported in 4 animals of the 29.9-ppm group and in 2 animals of the 59.9-ppm group, but not in animals exposed to 9.2 ppm or in animals of the control group. No other effects.

Endpoint/Concentration/Rationale: Preferential deposition in the upper respiratory tract due to high water solubility. Red nasal discharge is probably caused by local tissue hypoxia leading to vasodilatation and subsequent extravasation of red blood cells (no histopathological findings). Effect is caused easily not only by locally acting chemicals, but also by stress, dry air or upper respiratory tract infections.

Derivation of AEGL-1 values was based on an exposure to 9.2 ppm for 6 hours, which did not result in irritative effects in rats (Monsanto Co., 1986a).

Uncertainty Factors/Rationale: Total uncertainty factor: 10

Interspecies: 3 - because LOEL for irritation in humans exposed to cyanide at the workplace is about 6-10 ppm cyanide (El Ghawabi et al., 1975), which is a factor of about 3 below the irritation threshold of acetone cyanohydrin in rats (about 30 ppm) and because a multiple exposure study was used for the derivation of AEGL values.

Intraspecies: 3 - because decomposition of acetone cyanohydrin does not involve enzyme-catalyzed steps and the binding to evolutionary conservative iron-containing proteins/enzymes, i.e., the target protein cytochrome c oxidase, is unlikely to differ substantially between individuals.

Modifying Factor: 2 - because of the lack of more adequate and supporting data for AEGL-1

Time Scaling: $C^n \times t = k$, using the default of n=3 for shorter and n=1 for longer exposure periods. For the 10-minute AEGL-1 the 30-minute value was applied because the derivation of AEGL values was based on a long experimental exposure period and no supporting studies using short exposure periods were available for characterizing the concentration-time-response relationship.

Data Quality and Support for AEGL Levels:

Since the effects of acetone cyanohydrin are due to the release of cyanide after rapid decomposition of acetone cyanohydrin, data on exposure of humans to cyanide can be used as supporting data. In humans occupationally exposed to cyanide, no adverse toxic effects have been found after exposure to concentrations up to 3 ppm (Leeser et al., 1993). It should be noted however, that due to lower water solubility, the deposition in the respiratory tract of hydrogen cyanide is probably different and red nasal discharge has not been described after exposure of rats to hydrogen cyanide.

AEGL-2 VALUES				
10 minutes	30 minutes	1 hour	4 hours	8 hours
6.8 ppm	6.8 ppm	5.4 ppm	3.4 ppm	2.2 ppm

Reference: Monsanto Co., 1986. One-month inhalation toxicity of acetone cyanohydrin in male and female Sprague-Dawley rats with cover letter dated 04-25-86. Report No. BN-81-178, Monsanto Co., St. Louis, MO, USA.

Test Species/Strain/Sex/Number: rat / Sprague-Dawley / 10 female and 10 male per group

Exposure Route/Concentrations/Durations: Inhalation /59.6, 29.9 (determinant for AEGL-2), 9.2 and 0 ppm / 6 hours/day, 5 days/week for 4 weeks

Effects: After the first exposure, in 4/20 animals respiratory distress, prostration, tremors/convulsions were observed and 3 of these animals died; no other deaths occurred after subsequent exposures. During the first week of exposure, red nasal discharge was reported in 4 animals of the 29.9-ppm group and in 2 animals of the 59.9-ppm group, but not in animals exposed to 9.2 ppm or in animals of the control group. No other effects were found.

Endpoint/Concentration/Rationale:

Derivation of AEGL-2 values was based on an exposure to 29.9 ppm for 6 hours. At this concentration, signs of irritation (red nasal discharge), but no respiratory distress were observed.

Uncertainty Factors/Rationale: Total uncertainty factor: 10

Interspecies: 3 - because repeated exposure of humans at the workplace (Blanc et al., 1985) to cyanide concentrations only about 3-fold lower than the lethality threshold of about 60 ppm acetone cyanohydrin in rats did not lead to life-threatening or irreversible health effects and because a multiple exposure study was used.

Intraspecies: 3 - because decomposition of acetone cyanohydrin does not involve enzyme-catalyzed steps and the binding to evolutionary conservative iron-containing proteins/enzymes, i.e., the target protein cytochrome c oxidase, is unlikely to differ substantially between individuals.

Time Scaling: $C^n \times t = k$, using the default of n=3 for shorter and n=1 for longer exposure periods. For the 10-minute AEGL-2 the 30-minute value was applied because the derivation of AEGL values was based on a long experimental exposure period and no supporting studies using short exposure periods were available for characterizing the concentration-time-response relationship

Data Quality and Support for AEGL Levels:

Since the effects of acetone cyanohydrin are caused by the release of cyanide after rapid decomposition of acetone cyanohydrin, data on exposure of humans to cyanide can be used as supporting data. Chronic occupational exposure to cyanide concentrations of about 6-10 or 15 ppm produced symptoms of eye irritation, headache, weakness, changes in taste and smell, irritation of the throat, vomiting and effort dyspnea (El Ghawabi et al., 1975; Blanc et al., 1985).

The derived values are further validated because on a molar basis they are similar to the AEGL-2 values for hydrogen cyanide (17, 10, 7.1, 3.5 and 2.5 ppm for 10 min, 30 min, 1 h, 4 h and 8 h, respectively) (Hydrogen Cyanide. Proposed Acute Exposure Guideline Levels. Technical Support Document, version of January 2000).

AEGL-3 VALUES				
10 minutes	30 minutes	1 hour	4 hours	8 hours
27 ppm	21 ppm	15 ppm	8.6 ppm	6.6 ppm

Reference: The AEGL-3 values for acetone cyanohydrin are set at the same values (on a ppm basis) as the AEGL-3 values for hydrogen cyanide (Hydrogen Cyanide. Proposed Acute Exposure Guideline Levels. Technical Support Document, version of January 2000).

Test Species/Strain/Sex/Number: not applicable

Exposure Route/Concentrations/Durations: not applicable

Effects: not applicable

Endpoint/Concentration/Rationale:

For the derivation of AEGL-3 values, it has to be taken into account that 1) acetone cyanohydrin decomposes spontaneously into hydrogen cyanide and acetone, 2) the decomposition of acetone cyanohydrin is accelerated by heat as well as by water, 3) the systemic toxic effects of acetone cyanohydrin are caused by free cyanide ions and 4) hydrogen cyanide has a far higher vapor pressure than acetone cyanohydrin. From these facts it can be concluded that with every exposure to acetone cyanohydrin a concomitant exposure to hydrogen cyanide will occur. It therefore seems reasonable to apply the AEGL-3 values (on a ppm basis) derived for hydrogen cyanide also to acetone cyanohydrin.

This procedure is supported by a very close similarity of acetone cyanohydrin and hydrogen cyanide regarding lethal effects in rats: Blank (1983) reported that 3 of 10 rats died after the first exposure to 68 ppm hydrogen cyanide, while the subsequent two exposures on the following days caused no additional deaths. This finding closely resembles that of Monsanto Co. (1986a) reporting death of 3 of 20 animals after the first exposure to 60 ppm acetone cyanohydrin (the actual exposure concentration on the first day might have been slightly higher than the average 59.6 ppm), while no additional deaths were found in the 19 subsequent exposures.

Uncertainty Factors/Rationale: not applicable

Time Scaling: not applicable

Data Quality and Support for the AEGL Levels:

Repeated exposure of rats to 57.7 ppm acetone cyanohydrin for 6 hours/day, 5 days/week for 3 months did not resulted in deaths (Monsanto Co., 1986b). Derivation of AEGL-3 values on the basis of this study, using a combined uncertainty factor of 10, would lead to very similar AEGL-3 values.

Comments from the Methacrylate Producers Association, Inc.

- ***MPA considers the derivation of AEGL values for ACH unnecessary and unwise***
  - ***because ACH is of concern only to the extent that it yields airborne HCN***
  - ***because monitoring only ACH levels in case of an accident could be misleading***
  - ***because monitoring for ACH would be impractical, while monitors for HCN exist***
  - ***because AEGL values for HCN have already been developed.***

Reply

- ACH is a different chemical than HCN having a different CAS number and showing other properties with regard to physico-chemical parameters.
- It cannot be assumed that in case of an accident all emergency responders will immediately know or will have enough chemistry knowledge to conclude that AEGL values for HCN have to be applied to ACH.
- Therefore, derivation of AEGL values for ACH is considered justified and necessary.

- ***MPA believes that there is no basis for setting any ACH AEGL level below the corresponding level for HCN. If ACH AEGLs need to be set at all, they should be set at the same ppm level as the final HCN levels.***

Reply

- ACH decomposes to HCN. The toxic effects after ACH exposure are caused by free cyanide.
- A mixed exposure to ACH and HCN will always occur in an accident with ACH.
- ACH, but not HCN, has been reported to induce red nasal discharge in rats. However, if at all, the irritative effects of ACH are not considered substantially greater than those of HCN. For HCN/cyanides, El Gawabi et al., 1975 and Blanc et al., 1985 reported eye and throat irritation in workers exposed to 6-15 ppm.
- Considering all the above factors, it seems plausible to apply the AEGL values derived for HCN also to ACH and use the ACH-specific data, which would lead to very similar AEGL values, as supportive evidence (as already done for AEGL-3).
- TSD should include a statement that in an accident air has to be monitored for both ACH and HCN.

AEGL Values for Acetone Cyanohydrin (proposed) and *HCN* (final)					
	10 minutes	**30 minutes**	**1 hour**	**4 hours**	**8 hours**
AEGL-1	1.1ppm *2.5 ppm*	1.1ppm *2.5 ppm*	0.84 ppm *2.0 ppm*	0.53ppm *1.3 ppm*	0.35ppm *1.1 ppm*
AEGL-2	6.8 ppm *17 ppm*	6.8 ppm *10 ppm*	5.4 ppm *7.1 ppm*	3.4 ppm *3.5 ppm*	2.5 ppm *2.5 ppm*
AEGL-3	27 ppm *27 ppm*	21 ppm *21 ppm*	15 ppm *15 ppm*	8.6 ppm *8.6 ppm*	6.6 ppm *6.6 ppm*

Comments from John Morawetz (ICWUC)

- ***The description of the El Ghawabi et al. (1975) study should be improved. The symptoms observed in the study demonstrate significant health effects and not a "LOEL for irritation".***

- ***In consequence the justification for the AEGL-1 interspecies UF has to be rewritten because the Ghawabi study is no longer a supportive argument for reducing the UF to 3. Rather, the study could be used to justify why a MF of 2 was considered necessary.***

Reply

- The description of the El Ghawabi et al. (1975) study in the ACH TSD should be made consistent with the study description in the HCN TSD. As suggested in the comment, the symptom incidence should be reported.

- The justification for the interspecies UF of 3 should be changed to:

  An interspecies UF of 3 was considered adequate for a locally acting substance and the derived AEGL values are supported by the study of Leeser (1990) that found no effect in workers exposed to a 8-hour mean geometric concentration of up to 1 ppm cyanide.

- ***The description of the measured personal exposures in the Leeser (1990) study should be improved. Rather than refering to the maximum of the measured concentration range ("up to 3 ppm"), reference should be made to the "8-hour mean geometric concentration of 1 ppm".***

Reply

- The description of the Leeser (1990) study should be made consistent with the study description in the HCN TSD. The geometric mean exposure concentration of 1 ppm reported in the Leeser study was, among other studies, used as a basis for AEGL-1 for HCN.

DERIVATION OF LOA

No reports on the odor threshold for ACH are available. Derivation of a LOA should not be recommended.

PHENOL

(CAS Reg. No. 108-95-2)

Discussion of NAS-COT Comments

NAC/AEGL Meeting 30, September 16-18, 2003

The AEGL document on phenol was reviewed by the Subcommittee on Acute Exposure Guideline Levels of the National Academy of Sciences Committee on Toxicology on January 27-29, 2003.

The subcommittee had about one hundred recommendations (many of which were of an editorial nature).

Major concerns were

(1) that COT felt that the all AEGL values were too conservative and that the ERPG values were far more consistent with the phenol toxicologic profile;

(2) the use of a NOAEL from a two-week animal study for derivation of AEGL-1;

(3) that AEGL-2 values were derived as a fraction of the AEGL-3 values;

(4) that COT questioned the validity of the AEGL-3 key study.

The COT subcommittee will reevaluate a revised phenol AEGL document after the NAC/AEGL committee responds to the concerns.

Comments on AEGL-1

COT: The AEGL-1 at 10 min to 1 hour is virtually identically with the occupational experience reported by Shamy et al (1994). What "notable discomfort" is associated with the 8-hour AEGL-1, which is less than half the current occupational limits?

Reply: AEGL-1 values are set in order to prevent notable discomfort in susceptible individuals. Thus, for derivation of AEGL-1 values the highest concentration is selected that does not elicit the symptoms or effects defined by the AEGL tier in question.

Comments on AEGL-1

COT: Data indicating the absence of histopathological effects in a 2-week animal study have been used to derive AEGL-1. It is important to look for data on the irritation/discomfort relating to phenol exposures and to use them for AEGL-1 derivation. The NAC should reconsider human data and review the basis for the occupational exposure values.

It would be more reasonable to use the apparent maximum no-effect vapor concentrations of Piotrowski (1971) and Ogata et al. (1986) as an AEGL-1. Humans were exposed to 5-6.5 ppm for as long as 8 hours without apparent ill effects. These exposures would very likely have been discontinued had the subjects experienced notable discomfort. Monkeys inhaling 5 ppm continuously for 90 days exhibited no adverse effects (Sandage, 1961).

Reply: The pharmacokinetic study of Piotrowski (1971) was not used because it did not report health effects, which was the reason for the COT to reject a similar study as keystudy for methanol AEGL-1 values (cf. COT methanol comments). No more relevant human data could be located in the literature

The Sandage (1961) study was not used because, apparently, exposure chambers did not allow observation of monkeys during the exposure and histopathology was performed on the lungs, but not on the upper respiratory tract.

The CMA (1998) (Hoffman et al. 2001) study is the only one fulfilling the SOP requirements for a key study and should therefore be retained.

The NAC/AEGL committee should discuss if the total UF can be reduced to 3 because the starting point was a NOAEL in a repeated study and the effect level was below that defined for AEGL-1. Moreover, the human experience support an exposure level of about 5 ppm for 8 hours. Since at low concentrations irritation is the predominant health effect, the exposure concentration should be flat lined.

Comments on AEGL-2

COT: The phenol AEGL-2 at 8 hours (7.7 ppm) said by NAC to be disabling and to impair one's ability to escape it not toxicologically different from the current occupational limits.

The proposed derivation of AEGL-2 based on reduction of the AEGL-3 is arbitrary. The approach could be acceptable only if relevant data are not available.

COT requests that NAC/AEGL committee to provide a proper justification for dividing AEGL-3 by a factor of 3 to derive an AEGL-2.

The AEGL-2 rationale does not mention the RD50 of 166 ppm. Generally, a 1-hour AEGL-2 can be about 1/5 of the RD50. Since the proposed value is about 1/10 of the RD50, the AEGL-2 could be higher.

Reply: The relevance of the RD50 for humans is unclear and is not considered an adequate basis for the derivation of AEGLs.

No study was located that would be an adequate basis for AEGL-2 derivation.

The German TE Group discussed the study of Brondeau et al. (1989) and considered it not adequate as a key study because no mention was made whether clinical effects were evaluated. Since no suitable data could be located, the SOP default procedure that AEGL-2 values to be derived as an AEGL-3 fraction, should be followed.

The NAC/AEGL committee should discuss the rationale for deriving AEGL-2 values as 1/3 of AEGL-3.

Comments on AEGL-3

COT: The use of the study of Flickinger (1976) as the basis for AEGL-3 is questionable, primarily due to the determination of the exposure concentration. The use of nominal concentrations of phenol should be avoided if other data exist that can be better relied upon.

In a liquid aerosol exposure, the rats would have been soaking wet with phenol. Thus, the exposure was the equivalent to a combined inhalation, dermal and oral study. Yet, there were no deaths. Therefore, the maximum non-lethal concentration for this study would have been significantly higher, probably at least a factor of two. It appears that the AEGL-3 levels could be increased substantially.

If it cannot be demonstrated that there is no statistically significant difference between vapor and aerosol inhalation toxicity, a clear explanation for why the particular aerosol concentration is both physically and biologically equivalent to the vapor concentration should be given.

The magnitude of the total uncertainty factor is not properly justified.

Reply: No other relevant studies with analytically determined exposure concentration were located for the derivation of AEGL-3. There are no vapor studies that would allow comparison of the toxicity of vapor and aerosol. However, due to its moderate vapor pressure at 20°C, formation of an aerosol due to condensation is considered likely after accidental release of hot phenol vapor. Therefore, the Flickinger (1976) study should be retained as the AEGL-3 basis.

The NAC/AEGL committee should discuss if the UF could be reduced to 3 because due to exposure to a liquid aerosol, dermal and oral exposure are considered likely in addition to inhalation exposure. Therefore, the total systemic dose was probably considerably higher than the systemic dose contributed by inhalation alone.

Phenol - AEGL-1

Keystudy: CMA, (1998)

Endpoint: In rats, exposure to 25 ppm for 6 h/d, 5 d/w for 2 weeks caused no clinical, hematological or histopathological effects

Scaling: $C^n \times t = k$ with default n = 3 for shorter and n = 1 for longer exposure periods

30-min value was applied to 10 min because no data are available for short-term human exposure to >5 ppm

Total uncertainty factor: 10

Interspecies: 3

because a multiple exposure study was used

Intraspecies: 3

toxicokinetic differences were considered limited for local irritation effects and a factor of 10 would have resulted in concentrations far below those used in pharmacokinetic studies

AEGL-1 Values for Phenol				
10 minutes	**30 minutes**	**1 hour**	**4 hours**	**8 hours**
5.7 ppm (22 mg/m³)	5.7 ppm (22 mg/m³)	4.5 ppm (17 mg/m³)	2.9 ppm (11 mg/m³)	1.9 ppm (7.3 mg/m³)

Supporting data:

- no effects in rhesus monkeys exposed continuously to 5 ppm for 90 days (Sandage, 1961)
- Piotrowski (1971) exposed subjects for 8 (-1) hours to up to 6.5 ppm and made no statement on health effects
- Shamy et al. (1994) made no statement on irritative effects in workers exposed to 5.4 ppm TWA

Phenol - Proposal for alternative AEGL-1

Keystudy: CMA, (1998)
Endpoint: In rats, exposure to 25 ppm for 6 h/d, 5 d/w for 2 weeks caused no clinical, hematological or histopathological effects

Scaling: At low exposure concentrations, irritation is the predominating health effect. Since irritation depends primarily on the exposure concentration and not on the exposure time, the same value was applied to all time periods.

Total uncertainty factor: 3

Interspecies: 1

The toxicokinetic component of the uncertainty factor was reduced to 1 because the local irritation effects of phenol depend primarily on the phenol concentration in inhaled air while toxicokinetic differences between species have only little influence. No data characterizing toxicodynamic differences between species were available. However, since the starting point for AEGL derivation was a NOAEL of a repeated exposure study, the effect level was below that defined for AEGL-1. Therefore, the interspecies factor was reduced to 1.

Intraspecies: 3

For local effects, the toxicokinetic differences between individuals are usually much smaller when compared to systemic effects. Therefore the toxicokinetic component of the uncertainty factor was reduced to 1 while the factor of 3 for the toxicodynamic component, reflecting a possible variability of the target-tissue response in the human population was retained.

Alternative AEGL-1 Values for Phenol				
10 minutes	**30 minutes**	**1 hour**	**4 hours**	**8 hours**
8.3 ppm (32 mg/m^3)	8.3 ppm (32 mg/m^3)	8.3 ppm (32 mg/m^3)	8.3 ppm (32 mg/m^3)	8.3 ppm (32 mg/m^3)

Supporting data: No reported human health effects at 6.5 ppm for 8 hours (Piotrowski, 1971) and 5.4 ppm at the workplace (Shamy et al., 1994)

Phenol - AEGL-2

Keystudy: not applicable

Endpoint: derived as fraction of AEGL-3

Scaling: not applicable

Divisor: 3

because a larger divisor would have resulted in an 8-hour concentration to which subjects have been exposed in a pharmacokinetic study and which was reported for workplaces

AEGL-2 Values for Phenol				
10 minutes	**30 minutes**	**1 hour**	**4 hours**	**8 hours**
20 ppm (77 mg/m³)	20 ppm (77 mg/m³)	16 ppm (61 mg/m³)	9.7 ppm (37 mg/m³)	7.7 ppm (30 mg/m³)

Supporting data:

- Shamy et al. (1994) reported slight effects on liver and blood parameters (increased serum transaminase activity, increased hemoglobin concentration, increased numbers of white blood cells) in workers exposed to 5.4 ppm TWA (mean time on job 13 years)
- similar values would be derived based on the NOAEL of 25 ppm for 6 h/d in rats (CMA, 1998) using a total UF of 3
-

Alternative AEGL-2 Values for Phenol				
10 minutes	**30 minutes**	**1 hour**	**4 hours**	**8 hours**
66 ppm (250 mg/m³)	66 ppm (250 mg/m³)	52 ppm (200 mg/m³)	33 ppm (130 mg/m³)	26 ppm (100 mg/m³)

Phenol - AEGL-3

Keystudy: Flickinger (1976)

Endpoint: No death of rats after 8-hour exposure to 900 mg/m³ phenol aerosol (234 ppm); prostration and tremors in 1/6 rats

Scaling: $C^n \times t = k$ with default n = 3 for shorter exposure periods

30-min value was applied to 10 min because no data are available for short-term exposure

Total uncertainty factor: 10

because this factor was considered adequate based on comparison with oral intoxication cases and because a higher factor of 30 would result in an exposure level for the 8-hour period, for which in pharmacokinetic studies no effects were mentioned. The total uncertainty factor of 10 was formally split up into an interspecies factor of 3 and an intraspecies factor of 3

Interspecies: **3**

Intraspecies: **3**

AEGL-3 Values for Phenol				
10 minutes	**30 minutes**	**1 hour**	**4 hours**	**8 hours**
59 ppm (230 mg/m³)	59 ppm (230 mg/m³)	47 ppm (180 mg/m³)	29 ppm (110 mg/m³)	23 ppm (88 mg/m³)

Supporting data:

- inhalation exposure in the key study (Flickinger, 1976) is equivalent to a total dose of 321 mg/kg, which is supported by oral toxicity data in rats
- AEGL-3 for 30 min, 1, 4 and 8 h correspond to 2.1, 3.2, 7.9 and 13 mg/kg, respectively, which is 8-48fold lower than the estimated dose (106-874 mg/kg) for lethal cases after oral and dermal exposure [*COT: comparison with bolus dose not adequate*].

Phenol - Proposal for alternative AEGL-3

Keystudy: Flickinger (1976)

Endpoint: No death of rats after 8-hour exposure to 900 mg/m³ phenol aerosol (234 ppm); prostration and tremors in 1/6 rats

Scaling: $C^n \times t = k$ with default n = 3 for shorter exposure periods; the 30-min value was applied to 10 min.

Total uncertainty factor: 3

Interspecies: 1

A reduced interspecies uncertainty factor of 3 was considered adequate because oral LD50 values for rabbits, rats and mice differed by no more than a factor of 2 and in cases of lethality in humans after phenol ingestion the lowest estimation of the ingested dose was not lower than 1/3 of the mean LD50 in animals.

Furthermore, exposure of rats to an liquid aerosol most likely resulted in additional dermal and oral exposure. Therefore, the total systemic dose was probably considerably higher than the systemic dose contributed by inhalation alone, which is supported by the fact that Brondeau et al. (1989) did not mention any clinical effects in rats exposed to a vapor at a comparable concentration (211 ppm for 4 hours). Therefore, the interspecies factor was reduced to 1.

Intraspecies: 3

because the study of Baker et al. (1978) that investigated health effects in members of 45 families (including children and elderly), that were exposed to phenol through contaminated drinking water for several weeks, did not did not indicate that symptom incidence or symptom severity was higher in any specific subpopulation. Moreover, newborns and infants were not considered more susceptible than adults because of their smaller metabolic capacity to form toxic phenol metabolites (cf. Section 4.4.2.).

cont'd.

Alternative AEGL-3 Values for Phenol				
10 minutes	**30 minutes**	**1 hour**	**4 hours**	**8 hours**
200 ppm (750 mg/m³)	200 ppm (750 mg/m³)	160 ppm (600 mg/m³)	98 ppm (380 mg/m³)	78 ppm (300 mg/m³)

Supporting data:

- AEGL-3 for 30 min, 1, 4 and 8 h correspond to an inhaled dose of 6.7, 11, 27 and 42 mg/kg, respectively, which is lower than the estimated ingested dose (10-240 mg/kg/d) reported by Baker et al (1978) for people exposed to phenol for several weeks through contaminated drinking water (only mild gastrointestinal symptoms)

Phenol - DERIVATION OF LOA

Two Level 1 odor studies are available:

Odor detection threshold for phenol: 0.016 ppm (TNO, 1988)

The concentration (C) leading to an odor intensity (I) of distinct odor detection (I=3) is derived using the Fechner function:

$$I = kw * \log (C / OT50) + 0.5$$

For the Fechner coefficient, the default of kw = 2.33 will be used due to the lack of chemical-specific data:

$3 = 2.33 * \log (C / 0.11) + 0.5$ which can be rearranged to

$\log (C / 0.11) = (3 - 0.5) / 2.33$

$= 1.07$ and results in

$C = (10^{1.07}) * 0.016$

$= 11.8 * 0.016$

$= 0.19$ ppm

Field correction factor: adjustment for distraction (4-fold increase of odor threshold and peak exposure (3-fold reduction for concentration peaks over mean concentration): 4 / 3 = 1.33

LOA = 0.19 ppm * 1.33

= 0.25 ppm

The LOA for phenol is 0.25 ppm.

CARBON MONOXIDE

(CAS Reg. No. 630-08-0)

Discussion of NAS-COT Comments

NAC/AEGL Meeting 30, September 16-18, 2003

The AEGL document on carbon monoxide was reviewed by the Subcommittee on Acute Exposure Guideline Levels of the National Academy of Sciences Committee on Toxicology on January 27-29, 2003.

The subcommittee had about one hundred recommendations (many of which were of an editorial nature).

Major concerns were

(1) that COT felt that AEGL-2 and AEGL-3 values were conservative;

(2) the justification for 4% COHb as a starting point for AEGL-2 derivation;

(3) the validity of the AEGL-3 key studies.

The COT subcommittee will reevaluate a revised carbon monoxide AEGL document after the NAC/AEGL committee responds to the concerns.

Comments on AEGL-1

COT: Although it might be possible to establish an AEGL-1 on frontal headache or nausea and vomiting, the Subcommittee concurs with NAC that the NR designation is appropriate.

Reply: None, no action necessary.

Comments on AEGL-2

COT: The ST-segment change and angina criteria used for the AEGL-2 is reasonable and the uncertainty value of 1 is fine. The authors feel that an inter-species value of 1 would account for all sensitive species and provide supporting data for infants. However pregnant females and the elderly are also sensitive species and might not be covered by this factor.

There was concern about the conservative nature of the AEGL 2 values and questions regarding the justification for the low values even though the are in the same range as other reference standards. It was suggested that this documentation be reviewed by an expert cardiologist with ER experience.

Reply: The discussion should state more clearly that other susceptible subgroups (pregnant and children) will not experience serious long-lasting or disabling effects at 4% COHb.

Retain 4% as COHb level for AEGL-2 derivation. At this level, the most susceptible subgroup showed clinically significant myocardial ischemia. Although no data are available on effects of higher COHb in this group, it can be assumed that higher exposure may lead to the inability to escape due to severe chest pain or more serious effects.

The NAC/AEGL committee should discuss whether the alveolar ventilation rate of 13.2 l/min (23 m^3/day) used for the CFK model calculations are adequate for cardiac patients or whether a lower mean activity level than for normal healthy adults can be assumed. In this case the alveolar ventilation rate could be changed to 6.0 l/min, the value originally used by Coburn and Stewart and coworkers and also used for derivation of ERPG values.

Comments on AEGL-3

COT: Using cardiac patients for AEGL-2 values and normal humans for AEGL-3 values is comparing different subgroups because the individuals with impaired cardiac function would likely be more susceptible than normal individuals to myocardial infarction, although the papers by Dahms et al. and Ebisuno et al. do not seem to support that hypothesis.

The AEGL-3 is based on the papers by Chiodi et al. and Haldane using normal subjects and it seems that the total uncertainty factor of 3 may be too low. The NAS was also concerned that the Haldane study was old and there was only one subject.

There was concern about the conservative nature of the AEGL 3 values and questions regarding the justification for the low values even though they were in the same range as other reference standards.

Given the wealth of data on CO, it is hard to believe that there aren't more current studies that could be used to derive the AEGL values.

Reply: Use of data on a susceptible subpopulation for AEGL-2 and data on healthy humans is not considered inconsistent when the intraspecies factor is set accordingly.

Some experimental exposure studies can be reported additionally to support a starting point of 40% for healthy subjects:

- Kizakevich 2000 (no cardiac effects in healthy subjects 20% COHb)
- Nielson et al. 1971 (no effects reported after repeated exposure of 2 subjects to 25-33% COHb)
- Burney et al. 1982 (poisoning incident at school with no life-threatening effects at mean COHb of 21% (max. 30%))

An UF of 3 (i.e. a starting point of 15 % COHb) can be supported by a discussion of effects reported in susceptible subpopulations (15-20% as lowest COHb for myocardial infarction in CAD patients, 22 % as lowest for stillbirths).

Carbon monoxide - AEGL-2

Keystudy: Allred et al. (1989a; b; 1991); Sheps et al. (1990; 1991)

Endpoint: At 4 % [COHb], a reduced time to ST-segment depression in the electrocardiogram and a reduced time to the onset of angina pectoris during physical exercise were found. At 5.3 % [COHb], but not at 3.7 %, a increased frequency of exercise-induced arrhythmia was found.

AEGL-2 values were derived on a [COHb] of 4 %

Mathematical model (incl. time scaling):

The CFK model was used to calculate CO exposure concentrations that would result in a [COHb] of 4 % at the end of relevant exposure periods

Total uncertainty factor: 1

Intraspecies: 1

because the values are based on observations in the most sensitive human subpopulation (CAD patients)

AEGL-2 Values for CO				
10 minutes	**30 minutes**	**1 hour**	**4 hours**	**8 hours**
420 ppm (480 mg/m³)	150 ppm (170 mg/m³)	83 ppm (95 mg/m³)	33 ppm (38 mg/m³)	27 ppm (31 mg/m³)

AEGL-2 Values for CO					
	10 min	**30 min**	**1 hour**	**4 hours**	**8 hours**
4 % COHb in cardiac patients at Va 13,200 ml/min (23 m^3/day)	420 ppm	150 ppm	83 ppm	33 ppm	27 ppm
COHb in adults at Va 17,700 ml/min (10 m^3/8-h shift)	4.6 %	4.6 %	4.5 %	4.3 %	4.2 %
COHb in 20 kg 5-yr child at Va 3580 ml/min	5.2 %	5.2 %	5.1 %	4.7 %	4.5 %
COHb in 3.5 kg newborn at Va 1250 ml/min	5.5 %	5.5 %	5.5 %	5.0 %	4.7 %

Alternative AEGL-2 Values for CO					
	10 min	**30 min**	**1 hour**	**4 hours**	**8 hours**
4 % COHb in cardiac patients at Va 6000 ml/min	730 ppm	260 ppm	140 ppm	44 ppm	31 ppm
COHb in adults at Va 13,200 ml/min (23 m^3/day)	6.4 %	6.4 %	6.4 %	5.3 %	4.7 %
COHb in adults at Va 17,700 ml/min (10 m^3/8-h shift)	7.4 %	7.4 %	7.3 %	5.6 %	4.8 %
COHb in 20 kg 5-yr child at Va 3580 ml/min	8.4 %	8.4 %	8.2 %	6.1 %	5.1 %
COHb in 3.5 kg newborn at Va 1250 ml/min	9.0 %	8.9 %	8.6 %	6.3 %	5.2 %

Carbon monoxide - AEGL-3

Keystudy: Chiodi et al. (1941); Haldane (1895)

Endpoint: Exposure of healthy subjects to sufficient concentration-time combinations to reach levels of about 40 to 56% [COHb] did not result in severe or lift-threatening effects. At this level of CO exposure, Haldane described symptoms including hyperpnea, confusion of mind, dim vision and unsteady/inability to walk. A [COHb] of 40% was used as starting point

Mathematical model (incl. time scaling):

The CFK model was used to calculate CO exposure concentrations that would result in a [COHb] of 40% at the end of relevant exposure periods

Total uncertainty factor: 3

Intraspecies: 3

because a factor of 10 would have resulted in exposure concentrations sometimes found in homes and the environment and because the derived values (corresponding to a [COHb] of about 15%) are supported by information on effects in more susceptible subpopulations, such as myocardial infarction and stillbirths

AEGL-3 Values for CO				
10 minutes	**30 minutes**	**1 hour**	**4 hours**	**8 hours**
1700 ppm (1900 mg/m^3)	600 ppm (690 mg/m^3)	330 ppm (380 mg/m^3)	150 ppm (170 mg/m^3)	130 ppm (150 mg/m^3)

AEGL-3 Values for CO					
	10 min	**30 min**	**1 hour**	**4 hours**	**8 hours**
40 % COHb in adults at Va 13,200 ml/min (23 m^3/day) applying UF=3	1700 ppm	600 ppm	330 ppm	150 ppm	130 ppm
Cardiac patients at Va 6,000 ml/min	8.4 %	8.6 %	9.0 %	12.3 %	15.1 %
COHb in 20 kg 5-yr child at Va 3580 ml/min	18.6 %	18.5 %	18.2 %	18.4 %	17.8 %
COHb in 3.5 kg newborn at Va 1250 ml/min	19.8 %	19.5 %	18.9 %	18.0 %	17.0 %

Carbon monoxide - DERIVATION OF LOA

Since carbon monoxide is odorless, no LOA can be derived.

ATTACHMENT 9

BASIC ACRYLIC MONOMER MANUFACTURERS, INC.
941 Rhonda Place S.E., Leesburg, VA 20175
Office (703) 669-5688 ■ Fax (703) 669-5689 ■ ehunt@adelphia.net

September 12, 2003
VIA E-MAIL

Mr. Paul S. Tobin
Designated Federal Officer
Office of Prevention, Pesticides,
and Toxic Substances
1200 Pennsylvania Avenue, N.W.
Washington, D.C. 20460

Subject: Acute Exposure Guideline Levels for Acrylic Acid

Dear Mr. Tobin:

The Basic Acrylic Monomer Manufacturers, Inc. (BAMM) appreciates this opportunity to provide input on the Acute Exposure Guideline Levels for Acrylic Acid (CAS No. 79-10-7).[1] We have received this week a copy of a fifteen page paper giving proposed responses to the comments of the National Academy of Science's Committee on Toxicology (COT) on the draft Technical Support Document for acrylic acid.[2] This letter offers a few observations for consideration by the National Advisory Committee (NAC) at your upcoming meeting. In addition, BAMM's Chairman, Dr. James E. McLaughlin, will be attending your meeting and will be available to provide more information on this subject or answer any questions the Committee may have on acrylic acid.

1. *AEGL-1*

The COT commented that it did not seem appropriate to use a personal communication (Renshaw, 1988) as the key study for AEGL development. The Discussion Paper (p. 2) responds that the Renshaw data was provided by Dr. McLaughlin and cited in the ERPG documentation.

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[1] BAMM's members are ATOFINA Chemicals, Inc., BASF Corporation, Celanese Ltd., The Dow Chemical Company and Rohm and Haas Company.

[2] We will refer to this paper as "Discussion Paper." We recognize that it does not necessarily represent the views of the NAC as a whole.

To prevent any misunderstanding, we wish to make clear that BAMM provided the Renshaw data in response to a request from the NAC. Dr. Renshaw is of course a highly respected scientist and we believe that his data has some significance for the process here, but we did not intend to endorse the Renshaw personal communication as the sole basis for establishing AEGL-1 levels.

Nor do we think it significant that the Renshaw personal communication was cited in the ERPG documentation. The data was not used as a basis for setting any ERPG level. The ERPG-1 level was based on odor thresholds and not a discomfort level as is required for AEGL-1. The ERPG documentation did observe, however, that a one-hour exposure to 2 ppm acrylic acid "may cause very mild transient eye irritation." Given that AEGL-1 is supposed to mark the level at which the general population could experience "notable discomfort," this conclusion weighs strongly in favor of setting AEGL-1 above 2 ppm.

BAMM has also provided you with other data that we believe would be a more appropriate basis for setting the AEGL-1 level than the Renshaw personal communication. In April, Dr. McLaughlin provided a copy of an abstract reporting RD_{50} results for acrylic acid. As we noted then, researchers have identified a relatively strong correlation between the RD_{50} level for mice and the level that causes sensory irritation in humans. *See* Alarie, Y., "Dose Response Analysis in Animal Studies: Prediction of Human Responses," *Environ. Health Perspect.* 42:9-13 (1981). As applied to acrylic acid, the Alarie research indicates that no irritation should be experienced by humans at approximately 6.8 ppm acrylic acid (*i.e.*, one percent of the 685 RD_{50} for mice).

Renshaw's findings confirm that the general relationship identified by Alarie is valid for acrylic acid in that his data show no evidence of significant irritation below 6.8 ppm. This value would also be more consistent with the outcome of recent evaluations in other nations, who have adopted 8-hour occupational exposure levels ranging from 2-10 ppm and values as high as 20 ppm for short-term occupational exposures.

2. ***AEGL-2***

The COT sought a more explicit and transparent discussion of the uncertainty factors applied in the case of AEGL-2. We believe that the italicized language on page 11 of the Discussion Paper addresses this criticism satisfactorily.

3. ***AEGL-3***

The COT questioned whether it was appropriate to base the AEGL-3 value on an aerosol exposure study rather than a vapor study. The COT also asked for an explanation as to why the AEGL-3 values were not derived on the basis of the benchmark concentration approach recommended in the Standing Operating Procedures.

BAMM agrees with the Discussion Paper (p. 5) that some mishaps involving acrylic acid could lead to exposures in the form of aerosol as well as vapor. We also agree that the benchmark concentration approach using BMC05 is not appropriate here and would yield unjustifiably low values.

Despite our agreement on these points, we nevertheless believe that the AEGL-3 values are far too low. As we have pointed out before, there are several well-conducted studies finding no life-threatening effects from repeated exposures to acrylic acid levels that are substantially higher than the proposed AEGL-3 levels. For example, the currently proposed 8-hour level is 58 ppm, yet Klimisch *et al.* found no deaths among rats exposed to concentrations as high as 450 ppm for 6 hours per day for ten consecutive days. The Discussion Paper (p. 6) actually cites some of the same studies to explain why it would be inappropriate to use BMC05 to set the AEGL-3 level, but the MLE01 value is subject to the same critique.

We believe that one reason for the unreasonably low AEGL-3 values is the unjustified reliance on "whole-body" exposures from Hagan & Emmons (1988). In that experiment, the whole-body exposures led to a much higher effective dose of acrylic acid than humans would receive at comparable concentrations. The increased dose results from both dermal absorption and ingestion of deposited materials via preening. Significantly, Hagan & Emmons found no lethality at the highest levels of nose-only exposure tested (up to 3850 ppm for 30 minutes, 3882 ppm for 60 minutes, and 3992 ppm for 120 minutes) while "whole-body" exposures produced some deaths for aerosol concentrations as low as 3452 ppm for 30 minutes, 2713 ppm for 60 minutes, and 2363 ppm for 120 minutes. We believe this factor merits thorough consideration and discussion.[3]

Another reason for the unjustifiably low AEGL-3 values is the interspecies uncertainty factor. The factors justifying an interspecies uncertainty factor of 1 for AEGL-2 (Discussion Paper, p. 11) are equally applicable to AEGL-3. Indeed, the discussion of the interspecies uncertainty factor for AEGL-3 (Discussion Paper, p. 14) so clearly parallels the AEGL-2 discussion that the choice of 3 rather than 1 is baffling. It should be noted in this context that the COT found the interspecies uncertainty factor for AEGL-2 to be "conservative." Ninth Interim Report at 12.

4. ***LOA***

The last page of the Discussion Paper (p. 15) shows the derivation of an LOA for acrylic acid. To the best of our knowledge, there is no discussion of this subject in the Standing Operating Procedures nor in the prior Technical Support Document. We are not aware of any

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[3] The COT inquired about the difference between whole-body and nose-only exposures. See Ninth Interim Report at p. 11. However, the Discussion Paper does not mention this subject, much less justify the current reliance on whole-body exposures.

official explanation of the purpose or function of this level, nor of the methodology used to derive it. Certainly the methodology is not as widely recognized as the Alarie relationships discussed above. Since any level sanctioned by the NAC AEGL Committee will likely have important real-world consequences, this information vacuum is a matter of serious concern to BAMM and its members. The same lack of information also makes misuse of these values by others more likely. We believe that it is inappropriate to adopt such values before their purpose and the methodology for deriving them have been fully explained.

5. ***Conclusion***

Although we agree with some of the responses to the COT and its criticisms, BAMM believes that the NAC's work on this chemical requires serious reconsideration. Both AEGL-1 and AEGL-3 are significantly out of line with the scientific data and the results of similar assessments around the world. We urge the NAC to take the time necessary to reach a scientifically credible result for this important chemical.

If you would like any additional information concerning acrylic acid, please do not hesitate to contact me at (703) 669-5688. BAMM would be happy to provide whatever material we can to support your efforts in this endeavor.

Sincerely yours,

Elizabeth Hunt

Elizabeth Hunt
Executive Director

cc: Ernest Falke

Acrylic Acid

(CAS No. 79-10-7)

Discussion of NAS-COT Comments

NAC/AEGL Meeting 30, September 16-18, 2003

The AEGL document on acrylic acid was reviewed by the Subcommittee on Acute Exposure Guideline Levels of the National Academy of Sciences Committee on Toxicology on January 27-29, 2003.

The subcommittee had several recommendations (many of which were of an editorial nature).

Major concerns involved

(1) use of a personal communication as key study for AEGL-1;

(2) use of histological changes of the olfactory epithelium as AEGL-2 endpoint, and

(3) use of an aerosol study instead of a vapor study and use of the MLE01 instead of BMC05 as basis for derivation of AEGL-3.

The COT subcommittee will reevaluate a revised acrylic acid AEGL document after the NAC/AEGL committee responds to the concerns.

Comments on AEGL-1

COT: It does not seem appropriate to use a personal communication (Renshaw, 1988) as key study. One cannot tell the nature or extent of the communication (e.g., verbal, internal memo, or report with data). The reviewers need to evaluate this documentation.

A stronger argument needs to be made for UF=1 because workers are not considered a sensitive subpopulation. The lack of irritation in some workers exposed to higher concentrations could be the result of acclimatization and does not support the conclusion that the workers experiencing irritation were more susceptible.

Reply: The Renshaw data consists of a 3-page letter to AIHA and was provided by Jim McLaughlin (Rohm & Haas). It was also cited in the ERPG documentation. The fax was provided to the NAS-COT together with the other key studies.

No better study of irritation effects in humans is available. Therefore, the Renshaw data are considered valuable in the derivation of AEGLs although it does not conform completely to a standard of detailed methodology, data analysis and results reported.

The measurements using personal sampling were considered more relevant for AEGL derivation because they directly reflect breathing zone concentrations. People exposed to a certain area concentration could have received a much higher local exposure at their specific location.

It is suggested to use the lowest personal monitoring exposure of 4.5 ppm for 30 minutes as a starting point. A UF=3 is suggested for intraspecies toxicodynamic differences.

The lack of irritation at similar concentrations reported for "veteran chemical workers" can most likely be attributed to acclimatization.

Comments on AEGL-2

COT: The Subcommittee is not convinced that histological changes in the olfactory epithelium is the most appropriate endpoint for AEGL-2. The AEGL seems conservative given the relatively subtle changes. COT raises the question whether the olfactory epithelium has the capacity to repair/regenerate.

Reply: Regeneration of the olfactory epithelium will be incomplete if olfactory stem cells are damaged. It is not clear whether this was the case in the rat and monkey studies. Loss of olfactory epithelium could decrease the individuals sensitivity to odor (increase odor thresholds and reduce the number of different odors that can be recognized).

The NAC/AEGL committee should discuss the relevance of this effect with regard to the AEGL-2 definition as the level above which irreversible or other serious, long-lasting adverse health effects, or an impaired ability to escape, could be experienced.

The use animal studies reporting clinical symptoms of irritation could be discussed as an alternative basis for AEGL derivation.

Comments on AEGL-2

COT: UF needs additional explanation. It needs to be explicit and transparent as to what the toxicokinetic and toxicodynamic components for each UF are and why they are or are not included.

The interspecies UF=1 is appropriate, although conservative because of the higher tissue dose in rats compared to humans.

The toxicodynamic across species - at least monkeys and rats - appear the same.

It is not clear why a UF=3 for the toxicokinetic component of the intraspecies UF is retained and why the argument of local vs. systemic effects is not applied here.

Since a UF=1 is used for toxicodynamics the authors are apparently assuming that there is no variability in target-tissue response in the human population.

Reply: The COT criticism is due to an misunderstanding. For the intraspecies UF a toxicokinetic component of 1 and a toxicodynamic component of 3 should be applied. Revision of the wording should clarify the UF justification.

Comments on AEGL-3

COT: The concentration applied as vapor versus aerosol has a significant impact. Due to the high water solubility one would expect local effects on the upper respiratory tract (olfactory epithelium) in the vapor state. The aerosol could be delivered to the deep lung and therefore could be more toxic than vapor.

What is the likely form of an acute airborne exposure to the general public? It would seem that even if an aerosol was formed, it would quickly convert to vapor due to the relatively high vapor pressure. If that is the case, AEGL based on vapor is more relevant.

Reply: Exposure of the population to an acrylic acid aerosol cannot be excluded. Even if acrylic acid is not released as an aerosol during the accident, but as a (hot) vapor, it seems feasible that an aerosol is formed due to condensation of the hot vapor and due to the high water solubility of acrylic acid. Therefore, the aerosol study should be retained as the AEGL-3 basis.

Comments on AEGL-3

COT: A stronger argument has to be made for using MLE01 instead of BMC05 (as suggested in SOP)

Reply: For probit calculations, the software of ten Berge was used. This program uses data for all exposure times and exposure concentrations together to calculate not only MLE50, MLE01 and BMC05 values for the time periods experimentally tested, but also extrapolates to other time periods.

For the MLE01 the program provides the same values that would be obtained when a time scaling exponent n would be calculated from the MLE50 for 30 min, 1 and 2 hours. However, since at each time period the range of tested concentrations covered only a factor of 2 with considerable variation of lethality within groups, BMC05 confidence intervall become broad, esp. at 120 min for which data suggested a very steep dose-response. Moreover, the confidence interval becomes broader when BMC05 values are calculated for time periods outside of the experimental range.

Thus, for the 8-hour period a MLE01 of 579 ppm, but a BMC05 of 196 ppm is calculated. The latter is considered overly conservative for AEGL-3 derivation because in repeated exposure studies rats did not die and did not show life-threatening symptoms at 223 ppm (Miller et al., 1981), 300 ppm (Gage, 1970) and 439 ppm (Klimisch and Hellwig, 1991) for 6 hours.

For this reason, the MLE01 values are retained for AEGL-3 derivation.

This procedure is also in line with the SOP that states "Because of uncertainties that may be associated with extrapolations beyond the experimental data, the estimated values are compared with the empirical data. Estimated values that conflict with empirical data will generally not be used."

Comments on AEGL-3

COT: It is required that the rationale for each UF of 3 leading to a final UF of 10 to be clarified. The intraspecies UF needs to be better explained.

Reply: The wording for the UF rationale should be improved.

Acrylic Acid - AEGL-1

Keystudy: Renshaw (1988)

Endpoint: Eye irritation was noted after exposure to concentrations of 4.5 - 23 ppm for 16 - 30 minutes (other workers exposed to the same concentration for up to 1.5 hours did not report any symptoms) and that slight eye irritation was experienced after exposure to 0.3 - 1.6 ppm for 30 minutes to 2.5 hours. The mean of the latter concentration range, 1.0 ppm, was used for AEGL derivation.

Time scaling: Since very slight irritative effects depend primarily on the actual exposure concentration and not much on exposure time, it was considered adequate to use the same exposure concentration for all exposure durations between 10 minutes and 8 hours

Total uncertainty factor: 1

Interspecies: not applicable

Intraspecies: 1

because a) irritative effects described by Renshaw (1988) were very weak and increased only slowly with increasing exposure concentration, i.e. still tolerable eye irritation was noted after exposure to 4.5 - 23 ppm for 16 - 30 minutes; b) other workers exposed to the same concentrations (4.5 - 23 ppm) for up to 1.5 hours did not report any symptoms might indicate that the effects were observed in sensitive individuals; c) for local effects the toxicokinetic differences between individuals are much smaller compared to systemic effects.

AEGL-1 Values for Acrylic Acid				
10 minutes	**30 minutes**	**1 hour**	**4 hours**	**8 hours**
1.0 ppm 3.0 mg/m^3	1.0 ppm 3.0 mg/m^3	1.0 ppm 3.0 mg/m^3	1.0 ppm 3.0 mg/m^3	1.0 ppm 3.0 mg/m^3

Support: Lomax et al. (1994): 5 ppm for 6 h/d (2 weeks) in mice was the NOEL for histological changes

Acrylic Acid - Proposal for alternative AEGL-1

Keystudy: Renshaw (1988)

Endpoint: Eye irritation was noted after exposure to concentrations of 4.5 - 23 ppm for 30 minutes (exposure determined by personal sampling). The lower end of this range was used for AEGL derivation.

Time scaling: Since very slight irritative effects depend primarily on the actual exposure concentration and not much on exposure time, it was considered adequate to use the same exposure concentration for all exposure durations between 10 minutes and 8 hours

Total uncertainty factor: 3

Interspecies: not applicable

Intraspecies: 3

For local effects, the toxicokinetic differences between individuals are usually much smaller when compared to systemic effects. Therefore the toxicokinetic component of the uncertainty factor was reduced to 1 while the factor of 3 for the toxicodynamic component, reflecting a possible variability of the target-tissue response in the human population, was retained.

AEGL-1 Values for Acrylic Acid				
10 minutes	**30 minutes**	**1 hour**	**4 hours**	**8 hours**
1.5 ppm 4.5 mg/m^3	1.5 ppm 4.5 mg/m^3	1.5 ppm 4.5 mg/m^3	1.5 ppm 4.5 mg/m^3	1.5 ppm 4.5 mg/m^3

Support: Lomax et al. (1994): 5 ppm for 6 h/d (2 weeks) in mice was the NOEL for histological changes;

Acrylic Acid - AEGL-2

Keystudy: Frederick et al. (1998); Rohm and Haas Co. (1995); Harkema (2001); Harkema et al. (1997)

Endpoint: Single exposure of monkeys and rats to 75 ppm acrylic acid for 3 and 6 hours resulted in histopathological changes (olfactory epithelial cell degeneration, sustentacular cell necrosis). The basis for the AEGL-2 derivation is supported by the observation that 77 ppm was the NOEL for blepharospasm (involuntary eyelid closure) in rabbits (Neeper-Bradley et al., 1997).

Time scaling: $C^n \times t = k$ with default n = 3 for shorter and n = 1 for longer exposure periods. 30-min value was applied to 10 min.

Total uncertainty factor: 3

Interspecies: 1

because single inhalation exposure of monkeys resulted in similar olfactory lesions than in rats (Rohm and Haas Co., 1995; Harkema, 2001; Harkema et al., 1997) and because the deposited concentration of acrylic acid on the olfactory epithelium is about two- to threefold higher in rats than in humans (Frederick et al., 1998).

Intraspecies: 3

The intraspecies uncertainty factor is used to compensate for both, toxicokinetic and toxicodynamic differences between species [*should be individuals*]. For local effects, the toxicokinetic differences between individuals are usually much smaller when compared to systemic effects. Therefore, a reduced uncertainty factor of 3 was applied for intraspecies variability.

AEGL-2 Values for Acrylic Acid				
10 minutes	**30 minutes**	**1 hour**	**4 hours**	**8 hours**
100 ppm 300 mg/m^3	100 ppm 300 mg/m^3	68 ppm 200 mg/m^3	31 ppm 94 mg/m^3	21 ppm 64 mg/m^3

AEGL-2 - Justification of UF

Interspecies: 1

Old: because single inhalation exposure of monkeys resulted in similar olfactory lesions than in rats (Rohm and Haas Co., 1995; Harkema, 2001; Harkema et al., 1997) and because the deposited concentration of acrylic acid on the olfactory epithelium is about two- to threefold higher in rats than in humans (Frederick et al., 1998).

New: ***The toxicokinetic component of the uncertainty factor was reduced to 1 because the deposited concentration of acrylic acid on the olfactory epithelium is about two- to threefold higher in rats than in humans (Frederick et al., 1998). The toxicodynamic component of the uncertainty factor was reduced to 1 because single inhalation exposure of monkeys resulted in similar olfactory lesions than in rats (Rohm and Haas Co., 1995; Harkema, 2001; Harkema et al., 1997)***

Intraspecies: 3

Old: The intraspecies uncertainty factor is used to compensate for both, toxicokinetic and toxicodynamic differences between species. For local effects, the toxicokinetic differences between individuals are usually much smaller when compared to systemic effects. Therefore, a reduced uncertainty factor of 3 was applied for intraspecies variability.

New: ***For local effects, the toxicokinetic differences between individuals are usually much smaller when compared to systemic effects. Therefore the toxicokinetic component of the uncertainty factor was reduced to 1 while the factor of 3 for the toxicodynamic component, reflecting a possible variability of the target-tissue response in the human population is retained.***

TABLE 9: IRRITATIVE EFFECTS IN ANIMALS				
Sp.	Conc. (ppm)	Exposure duration	Effect	Reference
rabbit	129, 245, 227	6 h/d; gd10-22 gd6-18	perinasal and perioral wetness, blepharospasm in 8/8 animals; after first and subsequent exposures	Neeper-Bradley et al., 1997
rabbit	61, 77	6 h/d; gd10-22 gd6-18	perinasal wetness in some animals after the last exposure, no perioral wetness or blepharospasm	Neeper-Bradley et al., 1997
rabbit	34	6 h/d; gd10-22	no signs of irritation (perinasal/perioral wetness or blepharospasm)	Neeper-Bradley et al., 1997
rat	218, 356, 439	6 h/d; gd 6-15	considerable discharge from eyes and nose, eyelid closure, restless behavior with snout wiping; after first and subsequent exposures	Klimisch and Hellwig, 1991
rat	300	6 h/d; 4 d	some nose irritation, lethargy	Gage, 1970
rat	223	6 h/d; 5 d/w, 2 w	scratching at the nose as sign of irritation	Miller et al., 1981
rat	114	6 h/d; gd 6-15	no signs of irritation	Klimisch and Hellwig, 1991
rat	80	6 h/d; 4 d	no signs of irritation	Gage, 1970
rat	74	6 h/d; 5 d/w, 2 w	no signs of irritation	Miller et al., 1981
mouse	223	6 h/d; 5 d/w, 2 w	scratching at the nose as sign of irritation	Miller et al., 1981
mouse	75	6 h/d; 5 d/w, 13 w	no signs of irritation	Miller et al., 1981

Acrylic Acid - AEGL-3

Keystudy: Hagan and Emmons (1988)

Endpoint: Lethality in rats after single inhalation exposure to acrylic acid aerosol. MLE_{01} values were calculated using Probit analysis.

Time scaling: $C^{1.8} \times t = k$ (n = 1.8) for shorter and longer exposure periods;
n was derived by Probit analysis from the data by Hagan and Emmons (1988)

Total uncertainty factor: 10

Interspecies: 3

because the mechanism of action of lethal effects, which involves local tissue destruction in the lung by a direct-acting toxicant with limited influences of metabolism, detoxification and elimination, is unlikely to differ between species.

Intraspecies: 3

The intraspecies uncertainty factor is used to compensate for both, toxicokinetic and toxicodynamic differences between species [*should be individuals*]. For local effects, the toxicokinetic differences between individuals are usually much smaller when compared to systemic effects.

AEGL-3 Values for Acrylic Acid				
10 minutes	**30 minutes**	**1 hour**	**4 hours**	**8 hours**
480 ppm 1400 mg/m^3	260 ppm 780 mg/m^3	180 ppm 540 mg/m^3	85 ppm 260 mg/m^3	58 ppm 170 mg/m^3

AEGL-3 - Justification of UF

Interspecies: 3

Old: because the mechanism of action of lethal effects, which involves local tissue destruction in the lung by a direct-acting toxicant with limited influences of metabolism, detoxification and elimination, is unlikely to differ between species.

New: Published interspecies comparisons are focused on the upper respiratory tract at lower doses. No definitive data for the involvement of the lung at higher doses are available. Acrylic acid causes lethal effects by local tissue destruction in the lung with limited influence of systemic distribution, metabolism and elimination. Therefore, the toxicokinetic differences are considered smaller than for other chemicals that require systemic distribution and metabolism. Also the toxicodynamic variability is considered to be limited because acrylic acid causes cell necrosis by reducing the pH and destroying mitochondria, which are unlikely to be influenced by species-specific differences. Overall these arguments support a reduced interspecies uncertainty factor of 3.

Intraspecies: 3

Old: The intraspecies uncertainty factor is used to compensate for both, toxicokinetic and toxicodynamic differences between species [*should be individuals*]. For local effects, the toxicokinetic differences between individuals are usually much smaller when compared to systemic effects.

New: Acrylic acid causes lethal effects by local tissue destruction in the lung with limited influence of systemic distribution, metabolism and elimination. Therefore, the toxicokinetic differences are considered smaller than for other chemicals that require systemic distribution and metabolism, although there might be some difference between babies and adults based upon projections from breathing rates, lung capacity, etc. Also the toxicodynamic variability is considered to be limited because acrylic acid causes cell necrosis by reducing the pH and destroying mitochondria, which are unlikely to be influenced by interindividual differences. Overall these arguments support a reduced intraspecies uncertainty factor of 3.

Acrylic Acid - DERIVATION OF LOA

Study: Hellman and Small (1974)

Odor detection threshold for acrylic acid:	0.094 ppm
Odor detection threshold for n-butanol:	0.3 ppm
OT_{50}: OT(AA) * 0.04 ppm /OT(n-butanol):	0.013 ppm

The concentration (C) leading to an odor intensity (I) of distinct odor detection (I=3) is derived using the Fechner function:

$$I = kw * \log (C / OT50) + 0.5$$

For the Fechner coefficient, the default of kw = 2.33 will be used due to the lack of chemical-specific data:

$3 = 2.33 * \log (C / 0.11) + 0.5$ which can be rearranged to

$\log (C / 0.11) = (3 - 0.5) / 2.33$

$= 1.07$ and results in

$C = (10^{1.07}) * 0.013$

$= 11.8 * 0.013$

$= 0.15$ ppm

Field correction factor: adjustment for distraction (4-fold increase of odor threshold and peak exposure (3-fold reduction for concentration peaks over mean concentration): 4 / 3 = 1.33

LOA = 0.15 ppm * 1.33

= 0.20 ppm

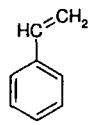
The LOA for acrylic acid is 0.20 ppm.

Acute Exposure Guideline Levels (AEGLs)

for

Styrene

(CAS Reg. No. 100-42-5)



NAC/AEGL-30, September 16-18, 2003

Washington, DC

Scientists (Toxicological Consultants):

Jens-Uwe Voss

Chemical Manager in German Expert Group:

Hans-Uwe Wolf

Chemical Reviewer for German Expert Group:

Rudolf Jäckh

Chemical Manager USA:

Loren Koller

Styrene **Properties**

- colorless or slightly yellow liquid
- odor pungent, slightly sweetish, plasticy;

  wide range of odor detection thresholds

  n-butanol corrected mean value (3 studies):
  0.0345 ppm (van Doorn et al. 2002)
- high vapor pressure, low flash point,lower range of explosive limits in air: 1.1 %:
  → fire and explosion hazard.

Production and Use

- catalytic ethylation of benzene with ethene to ethylbenzene followed by dehydrogenation of ethylbenzene to styrene
- co-product in synthesis of propene oxide from ethylbenzene and propene via ethylbenzene hydroperoxide, cleavage into propene oxide and 1-phenylethanol that is dehydrated to styrene
- worldwide production (1998): ~ 18 million tonnes
- production of polymers (polystyrene, copolymers) for e.g. paints, coatings, synthetic rubbers, polyesters

Toxicity mechanisms and health concerns

- acute exposure:
  - irritation of eyes and mucous membranes,
  - CNS-depression;
- repeated exposure:
  - neurotoxicity (hearing, color vision),
  - developmental effects, mutagenicity, carcinogenicity.

Human Data (see also Table 2 in TSD draft)

Summary of acute non-lethal effects in controlled humans studies

Conc. (ppm)	Exposure duration	No. subj	Effects, remarks	References
800	4 h	2	Immediate eye and throat irritation; CNS-effects: listlessness, drowsiness, impairment of balance, decreased ability in steadiness test; muscular weakness, unsteadiness, inertia, depression	Carpenter et al. 1944
≥ 600	n. r.	n. r.	Strong eye and nasal irritation; CNS-effects not reported	Wolf et al. 1956
~ 500 – 800 ~ 300 – 400	1 – 2 min	5	Previously unexposed subjects: Intolerable irritation Lacrymation, irritation of nasopharynx	Götell et al. 1972
376	≤ 15 min ≤ 1 hour	5	Eye and nasal irritation CNS-effects: decrements in tests on coordination and manual dexterity; nausea, headache, feeling of inebriation	Stewart et al. 1968
350 250	30 min 30 min	12	(Exposure via mouthpiece to avoid irritation) Reaction time in tests ↑ No effect	Oltramare and Hultengren 1974
216	1 h	3	Nasal irritation, no CNS-effects	Stewart et al. 1968
200	1 h	6	Eye irritation; Slight difficulties in balance performance ? Large variation of data	Oltramare et al. 1974
125	1 – 7.5 h	2 – 4	Irritation, headache, no effects in equilibrium and cognitive testing	Hake et al. 1983
117	2 h	1	Strong odor, no subjective or objective signs of illness	Stewart et al. 1968
99	2 x 3.5 h	6	Mild eye/throat irritation; intermittent difficulties in Romberg test, but no subjective symptoms or signs of CNS-effects at the end	Stewart et al. 1968

Summary of acute non-lethal effects in controlled humans studies

Conc. (ppm)	Exposure duration	No. subj	Effects, remarks	References
87 – 139	1 h	10	No effects in vestibulo-oculomotor tests except enhanced maximum speed of saccade during exposure	Ödkvist et al. 1982
99	≤ 100 min	4	No changes in performance tests; no changes in EEG	Pierce et al. 1998
100 50	1 – 3 h	6	Subjective symptoms of CNS-effects increased in rating score: Headaches, sleepiness, nausea, fatigue, ↓ concentration, malaise Headaches, fatigue, poor concentration	Oltramare et al. 1974
50 + peak 100	6 h (4 x 15 min peak)	42	No effects on subjective signs or performance in tests	Vyskocil et al. 2002
0.5 + peak 40 20	4 h 3 h	4	Odor, annoyance ↑ with concentration, marginal ↑ for irritation; rating for irritation verbally labelled as "hardly at all"	Seeber et al. 2002
11 – 66	≥ 4 a	52	Cross-sectional study of workers and age- & sex-matched controls: No difference in ability to detect 20 different standard aromas	Dalton et al. 2003
47 – 59	1 – 16 a	11	Cross-sectional study of male workers and matched (age, smoking) controls: No difference in morphology of nasal mucosa	Ödkvist et al. 1985

Animal Data (see also Tables 3 & 4 TSD draft)

Summary of lethality data for animals after acute inhalation exposure

Species (strain, sex)	Conc. (ppm)	Exp. Dur.	Effect, remarks	Reference
Rat and guinea pig (n.d.)	10 000	1 h	LC 0 (highest attainable vapor concentration?)	Spencer et al. 1942
		3 h	LC 100 (including delayed deaths)	
	5 000	3 h	LC 0	
		8 h	LC 100	
Rat	2500	8 h	LC 0	
		21 h	LC 100	
Guinea pig		6 h	LC 0	
		14 h	LC 100	
Rat (f, m, CD)	1500	6 h, rep.	0/20 died during subchronic exposure	Cruzan et al. 1997b
	1000	6 h, rep.	0/70 died during chronic exposure	Cruzan et al. 1998
Monkey (n.d.; f, m)	1300	7 – 8 h	0/4 died after repeated exposures over 7 (m) / 12 (f) months	Spencer et al. 1942
Mouse (f, OF 1)	1600	4 h	LC 50 (including delayed deaths)	BASF 1979a
(f, m, NMRI)	2429	6 h	LC 50 (including delayed deaths)	Bonnet et al. 1979b
(m, B6C3F1)	250	6 h	4/39 died after one exposure	Sumner et al. 1997
(m, CD-1)	250	6 h	0/39 died after one exposure	
(nd)	4914	2 h	LC 50 (including delayed deaths? Error in report?)	Shugaev 1969

Summary of lethality data for animals after acute inhalation exposure

Species (strain, sex)	Conc. (ppm)	Exp. Dur.	Effect, remarks	Reference
Rat (f, m, SD)	6410	4 h	LC 50 (including delayed deaths)	BASF 1979b
(f, SD)	7769	4 h	LC 0 (only immediate deaths, highest attainable vapor conc.)	Lundberg et al. 1986
(n.d.)	2761	4 h	LC 50 (including delayed deaths? Error in report?)	Shugaev 1969
(n. d.)	2700	4 h	LC 50 (abstract only)	Jaeger et al. 1974
(m, SD)	4618	6 h	LC50 (including delayed deaths)	Bonnet et al. 1982a

Benchmark calculations on lethality data for rats (BASF 1979b) (BMDS 1.3.2, US-EPA)

Sex	Model	BMD05	BMDL05	BMD01	LC50	Remark
Male	Weibull	4895 ppm	4121 ppm	4026 ppm	6688 ppm	
	Gamma	4250 ppm	3832 ppm	3513 ppm	6455 ppm	
	Logprobit	4884 ppm	4213 ppm	4344 ppm	6477 ppm	LC 50 (BASF): 6480 ppm
Female	Logprobit	4221ppm	**3409 ppm**	3571 ppm	6317 ppm	LC 50 (BASF): 6310 ppm
	Gamma	4153 ppm	3273 ppm	3417 ppm	6366 ppm	
	Weibull	3769 ppm	2817 ppm	2673 ppm	6525 ppm	
Male and female	Weibull	4269 ppm	3671 ppm	3244 ppm	6621 ppm	
	Gamma	4222 ppm	3863 ppm	3490 ppm	6411 ppm	
	Logprobit	4551 ppm	4036 ppm	3950 ppm	6405 ppm	LC 50 (BASF): 6410 ppm

Summary of acute non-lethal effects in animals after inhalation

Species	Conc. (ppm)	Exp. duration	Effect	Ref.
Rat	2000 ppm	5 hours	Loss of consciousness in "many of the test animals"	Withey and Collins 1979
Rat	1730 ppm	1 hour	Inability to suppress nystagmus	Niklasson et al. 1993
Rat	1500 ppm 500 ppm	6 hours	Reduced attention, sensory irritation Sensory irritation at start of exposure	Jarry et al. 2002
Rat	"4-hour LC_{50}" (2760 ppm)	1 hour	State of deep narcosis	Shugaev 1969
Mouse	549 ppm	4 hours	50 % decrease in immobility time in behavioral "despair swimming" test	de Ceaurriz et al. 1983
Mouse	156 ppm	3 minutes	RD_{50}	Alarie 1973
Mouse	586 ppm	5 minutes	RD_{50}	de Ceaurriz et al. 1981
Mouse	980 ppm	10 minutes	RD_{50}	Bos et al. 1992
Mouse	1420 ppm 2983 ppm 3766 ppm	4 hours	Staggered gait Apathy Narcosis	BASF 1979a

Concentration of styrene in blood of humans and rats

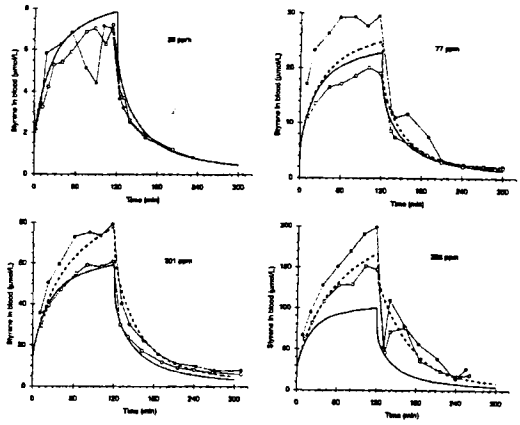
Humans

Exp. time	Conc. in air (ppm)	Conc. in blood (mg/L)	Remarks
55 min 1 h 55 min 3 h 30 min	51.4 116.7 116.7 99	0.2 – 0.7 (vb) 1.7 (vb) 2.7 (vb) 0.9 – 1.4 (vb)	Exposure at rest
30 min 1 h 2 h	69	1.8 (ab) 2.1 2.2	50 W exercise
30 min	154	~ 2 (ab) ~ 6 ~ 9 ~ 16	Exposure at rest 50 W exercise 100 W exercise 150 W exercise
2 h	69	1.6 (ab)	50 W exercise
2 h	26 77 201 386	~ 0.7/ 0.7 (acb) ~ 2/ 3.1 ~ 6.2/ 8.3 ~ 15/ 21	50 W exercise
6 h	80	0.92 (vb)	Exposure at rest

ab: arterial blood; acb: arterialized capillary blood; vb: venous blood; wb: whole blood; m/f: values for males/females;
2: approximate concentration, calculated from values presented as brain concentration relative to blood in original reference.

Rats

Exp. time	Conc. in air (ppm)	Conc. in blood (mg/L)	Remarks
5 h	45 520 1274 2800	< 2 (vb) ~ 43 ~ 149 ~ 198	Values estimated from graph
5 h	54 470 1018 1522 2144 2240	0.65 (vb)/ 0.2 (brain)[2] 31.8 / 43 65.3 / 76 72.8 / 105 173.7 / 302 135.5 / 256	
2 h	520 1274 2850	~ 24 ~ 73 ~ 100	Values estimated from graph
6 h	80 1200	1.0 (wb) 63	
6 h	50 200 500 1000	0.43/ 0.29 (m/f) 2.8/ 1.95 12.5/ 9.5 33.2/ 29.7	Values determined in week 95 of chronic study



Above: Observed (circles) and simulated concentrations of Styrene in arterialized capillary blood of humans

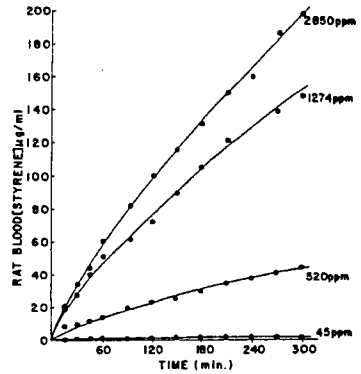
2 volunteers, 2 hours of exposure, light exercise (50 W).
Continuous line: PBPK model simulation with a linear model (nonsaturable metabolism in liver);
broken line: same model with saturable metabolism.
Graph from Löf and Johanson (1993).

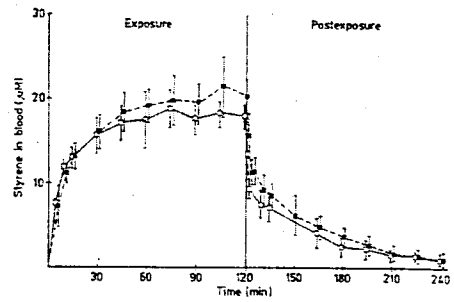
Lower right: Styrene concentration in arterial blood of humans during and after exposure to 69 ppm styrene in air

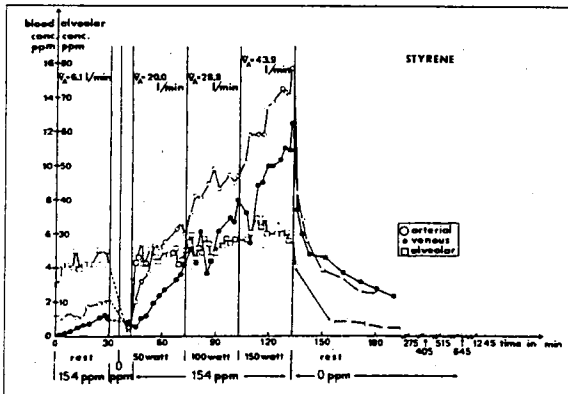
5 human volunteers; 2-hour exposure; light exercise (50 W), 69 ppm styrene (open symbols) or mixture of 70 ppm styrene and 520 ppm acetone (closed symbols), 1 μM = 104 μg/l (Graph from Wigaeus et al. 1984).

Upper right: Styrene concentration in blood of rats during a 5-hour exposure

Styrene was determined in blood from jugular vein. Graph from Withey and Collins 1979.







Above: Concentration of styrene in arterial and venous blood and in alveolar air in one subject during and after exposure to 154 ppm at different work loads (Astrand 1975).

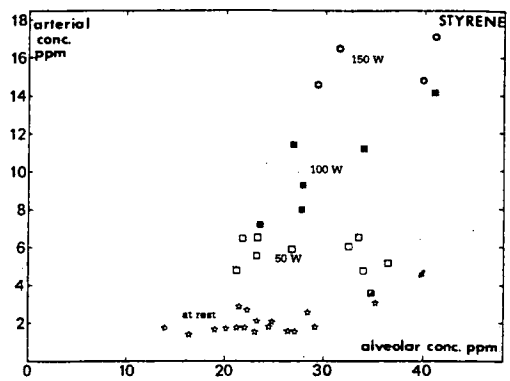


Fig. 9. Relation between the concentration of styrene in arterial blood and alveolar air after 30 min of exposure at rest and during work. Each symbol stands for one exposure period, i.e., a subject is represented by more than one symbol. Symbols: ○ rest, 50 ppm; ● 50 W, 50 ppm; ☆ rest, 150 ppm; □ 50 W, 150 ppm; ■ 100 W, 150 ppm; △ 100 W, 150 ppm, 80 min; ○ 150 W, 150 ppm; ✱ rest, 150 ppm + CO_2; ▲ 50 W, 150 ppm + CO_2; ◪ rest, 250 ppm; ✱ rest, 250 ppm. (50 = 0.210 mg/l 150 ppm = 0.630 mg/l; 250 ppm = 1.050 mg/l; 350 ppm = 1.470 mg/l) Note the wide scatter, e.g., an alveolar concentration from 5 up to 30 ppm can correspond to the same arterial concentration of 1 ppm.

Right: Concentration of styrene in arterial blood and alveolar air after 30 minutes of exposure to 150 ppm at different work loads (Astrand 1975).

Table 1. Alveolar and arterial concentrations after 30 min of exposure, as the percentages of the concentrations in inspiratory air, and the quotients between these concentrations. Exposure was made to toluene, methylchloroform, styrene, white spirit, methylene chloride, and trichloroethylene during rest and exercise. Mean values for 15 to 20 subjects are given at rest and during 50-W exercise and for 4 to 5 subjects during 100- and 150-W exercise. 150 W was always preceded by 100 W, and 100 W always by 50 W, without any pause between the exposure periods.

Solvent [a] (concentration in inspiratory air) mg/l	Rest			50 W			100 W			150 W		
	Alv. conc. %	Arter. conc. %	Quot.	Alv. conc. %	Arter. conc. %	Quot.	Alv. conc. %	Arter. conc. %	Quot.	Alv. conc. %	Arter. conc. %	Quot.
Toluene 0.375; 0.750	20	270	15	35	620	20	—	—	—	45[b]	720[b]	15[b]
Methylchloroform 1.357; 1.900	50	240	5	70	355	5	85	385	5	85	405	5
Styrene 0.210; 0.630	15	260	15	20	970	50	20	1840	85	25	2525	105
Aliphatic white spirit 1.038; 2.075	25	165	5	50	365	10	55	490	10	60	665	10
Aromatic white spirit 0.212; 0.425	15	120	10	20	435	25	20	800	40	30	1370	50
Methylene chloride 0.870; 1.740	30	290	9	55	600	11	65	770	12	70	850	12
Trichloroethylene 0.537; 1.074	25	215	10	45	350	10	50	700	15	60	840	15

[a] Two different concentrations were studied.
[b] Two subjects.

(Data from Astrand 1975)

AEGL-1

Key studies: Seeber et al. (2002)

Endpoint: NOAEL for irritation **20 ppm**

Scaling: one value for all time points since local effect, accommodation, complaints about discomfort at higher concentrations not reported to increase during several hours of exposure

Total uncertainty factor: 1

Intraspecies: 1

20 ppm as NOAEL for local effects, effects weak at higher concentrations.

AEGL-1 Values for ~~Acetone~~ Styrene

10 minutes	30 minutes	1 hour	4 hours	8 hours
20 ppm (85 mg/m³)	20 ppm (85 mg/m³)	20 ppm (85 mg/m³)	20 ppm (85 mg/m³)	20 ppm (85 mg/m³)

Remark: AEGL-1 is above odor recognition threshold; odor has warning properties.

AEGL-2

Key study: Stewart et al. (1968)

Endpoint: CNS-effects in humans during and after exposure to 376 ppm for 1 h.
NOAEL: 376 ppm, 1 h.

Scaling: $C^n \times t = k$ with n=3 for shorter periods of time; 1-hour AEGL-2 = 4-hour and 8-hour AEGL-2 since toxicokinetic data for humans indicate no or at most very little increase at exposure times > 1 hour.

Total uncertainty factor: 3

Interspecies: 1

Intraspecies: 3

Toxicokinetic data for human indicate severalfold higher blood level at heavy exercise, but a) high exercise level cannot be maintained for hours and b) endpoint is considered below level of CNS-depression that could impair escape.

AEGL-2 Values for Styrene

10 minutes	30 minutes	1 hour	4 hours	8 hours
230 ppm (980 mg/m³)	160 ppm (680 mg/m³)	130 ppm (550 mg/m³)	130 ppm (550 mg/m³)	130 ppm (550 mg/m³)

AEGL-3

Key studies: BASF (1979b)

Endpoint: $BMDL_{05}$ in female rats (4-hour exposure): 3400 ppm

Scaling: $C^n \times t = k$ with ~~with n=3 (default) for shorter periods of time and~~ n=1.2 (derived from 4-hour and 6-hour LC_{50}) for longer periods of time

Total uncertainty factor: 10

Interspecies: 3

Intraspecies: 3

Toxicokinetic data for humans indicate markedly higher blood levels of styrene at exercise (see above, derivation of AEGL-2).

AEGL-3 Values for Styrene

10 minutes	30 minutes	1 hour	4 hours	8 hours
4800 ppm* (20,450 mg/m³)	1900 ppm* (8090 mg/m³)	1100 ppm (4690 mg/m³)	340 ppm (1450 mg/m³)	190 ppm (810 mg/m³)

*: The lower explosive limit (LEL) of styrene in air is 1.1 %. Values marked with * are higher than 1/10 of the LEL. Therefore, safety considerations against hazard of explosion must be taken into account.

980 680 540 340 170

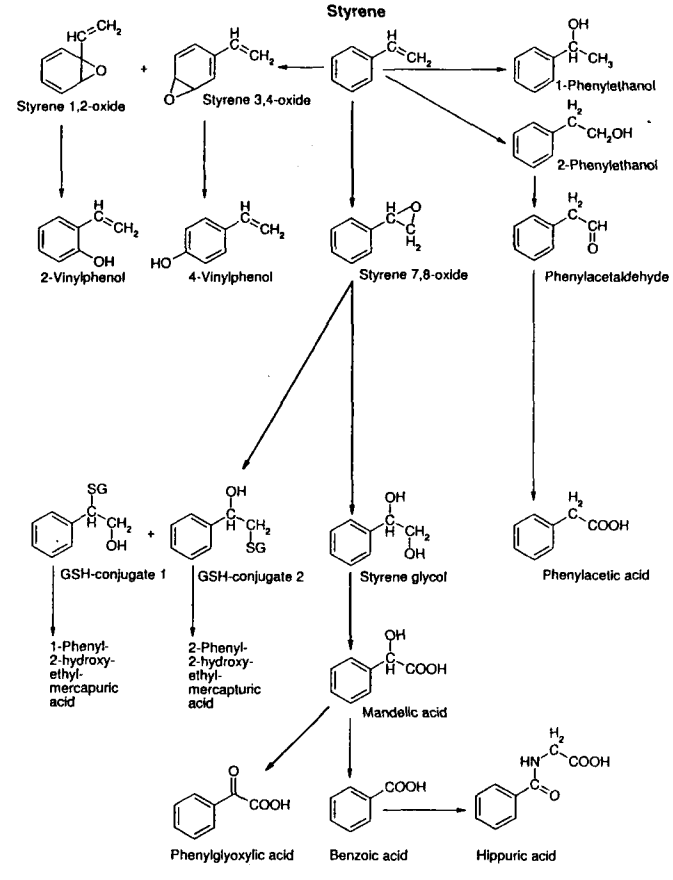
Level of Distinct Odor Awareness (LOA)

LOA Concentration above which it is predicted that more than half of the exposed population will experience at least a distinct odor intensity, about 10% of the population will experience a strong odor intensity. LOA derivation follows the guidance given in Van Doorn et al. (2002).

Van Doorn et al. (2002):

- calculated an n-butanol corrected mean odor threshold of 0.0345 ppm for styrene.
- The concentration (C) leading to an odor intensity (I) of distinct odor awareness (I=3) is derived using the Fechner function:
  $I = k_w * \log (C / OT_{50}) + 0.5$.
- For the Fechner coefficient, the default of k_w = 2.33 will be used due to the lack of chemical-specific data:
  $3 = 2.33 * \log (C / 0.0345) + 0.5$;
  $C = 0.41$ ppm.
- The resulting concentration is multiplied by an empirical field correction factor. It takes into account that in everyday life factors such as age, gender, sleep, smoking, upper airway infections and allergy as well as distraction, increase the odor detection threshold by a factor of 4. In addition, it takes into account that odor perception is very fast (about 5 seconds) which leads to the perception of concentration peaks. Based on the current knowledge, a factor of 1/3 is applied to adjust for peak exposure. Adjustment for distraction and peak exposure lead to a correction factor of 4 : 3 = 1.33.

LOA = 0.41 ppm * 1.33 = **0.54 ppm styrene.**



Metabolism: Qualitatively similar in rats, mice, and humans; quantitative differences in importance of individual pathways.

September 17, 2003

TSD Propane

Chemical Manager: L.A. Gephart
Staff Scientist: P.M.J. Bos

Propane: Uses

ATTACHMENT 12

- Production of LPG
- Manufacturing of e.g. ethylene and propylene
- Aerosol propellant
- Refrigerant solvent and extractant in deasphalting and degreasing of crude oils

Propane: Physical-chemical properties

- Molecular weight: 44.11
- Colorless gas
- Water solubility: 65 mg/L
- Boiling point: -42.1 °C
- Odor: odorless when pure
- Flammability: extremely flammable gas
- LEL: 2.3%

Propane: Case reports

- Causes
  - Abuse (including autoerotic fatalities)
  - Suicide attempts
- Effects
  - asphyxia
  - frothy material in upper airways and oral cavity
  - hemorrhages in epicardium and pleural spaces
  - cerebral and pulmonary congestion and edema

Propane: Case reports

- No adequate exposure estimation
- In case of abuse:
  - repeated exposure
  - possible exposure to other substances
- Data not suitable for AEGL-setting

Propane: Experimental human data

- *Stewart et al. (1977)*
  - Eight volunteers; 20-22 years-of-age
  - Exposure to 250 ppm or 500 ppm (1, 2, and 8 hours) or 1000 ppm (1, 2, 10 min, 8 h/d for 9 d)
  - No effects on clinical parameters, neurological and neurobehavioral tests, EEG, VER, spirometry, ECG.

Propane: Experimental human data

- *Patty and Yant (1929)*
  - Aim: odor intensity and physiological response
  - 3-6 volunteers; 20-30 years-of-age
  - Continuous exposure up to 50,000 ppm (> 6 min)
  - Intermittent exposure up to 100,000 ppm (few minutes)
    no effects at 10,000 ppm for 10 min
    no irritation but "distinct vertigo" at 100,000 ppm (2 min)
  - Basis for AEGL-1

Propane: Animal data

- No adequate acute lethality data
  - 15-min LC_{50} in rats > 250,000 ppm
- Study on CNS depression in guinea pigs.
  - *Nuckolls (1933)*
  - *Clark and Tinston (1982) (supportive)*
- Studies on cardiac sensitization with monkeys, dogs, mice, but mostly under anesthetic conditions and or oxygen suppletion.
  - *Reinhardt et al. (1971);*
  - *Clark and Tinston (1982) (supportive)*

Propane: Animal data

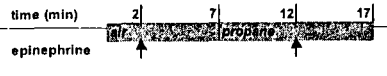
- CNS depression *(Clark and Tinston 1982)*
  - 10 min EC_{50} of 280,000 ppm in rats (n=6 per concentration)
    (note: oxygen suppletion above 250,000 ppm)
- CNS depression *(Nuckolls 1933)*
  - Groups of 3 guinea pigs
  - Exposure duration: 5, 30, 60, or 120 min
  - Exposure concentrations:
    ~~low exposure: 22,000 - 29,000 ppm~~
    high exposure: 47,000 - 55,000 ppm

Propane: Animal data

- CNS depression *(Nuckolls 1933)*
  - Results low exposure group (22,000 - 29,000 ppm)
    occasional chewing movements and irregular breathing
  - Results high exposure group (47,000 - 55,000 ppm)
    occasional tremors within 5 min
    occasional effects: irregular breathing, retching,
    "dazed appearance" but able to walk
    no increase in severity with continuing exposure
    all animals showed rapid recovery after exposure
    no histopathological changes in one animal at 7 days
    ~~postexposure~~

Propane: Animal data

- Cardiac sensitization *(Reinhardt et al. 1971)*
  - Experimental setting



  - Male beagle dogs exposed to 50,000 ppm (n=6), 100,000 ppm (n=12) or 200,000 ppm (n=12)
  - Response: multiple consecutive ventricular beats or cardiac arrest

Propane: Animal data

- Cardiac sensitization *(Reinhardt et al. 1971)*
  - Result (animals with marked response):
    0/6 at 50,000 ppm
    2/12 at 100,000 ppm
    7/12 at 200,000 ppm (one death)
  - Basis for AEGL-2 (50,000 ppm) and AEGL-3 (100,000 ppm)
- EC_{50}: 180,000 ppm *(Clark and Tinston 1982)*
  - Supportive study

Propane: Kinetic data

- Rapidly reached steady-state blood concentrations
  - Comparable propane concentrations in blood sampled at 15-min prior to the end of a 1-, 2-, and 8-hour exposure to 250 or 500 ppm
  - Butane: steady-state pulmonary uptake within 30 min
  - Relatively insoluble gases (like propane) reach rapid uptake equilibrium

Propane: AEGL-1

- *Patty and Yant (1929)*
  - No effects at 10,000 ppm for 10 min
  - No irritation but "distinct vertigo" at 100,000 ppm (2 min)
  - UF = 1

    very steep concentration-response curve (butane) thus small interindividual variation

    10,000 ppm is a conservative starting point compared to 100,000 ppm (no effects at 1000 ppm 8 h/d for 9 days)

    agreement with butane

    realistic values

Propane: Estimation of *n*

CNS depression in mice exposed to butane (Stoughton and Lamson 1936)

Species	Concentration (ppm)	Exposure Time	Effect	Reference
Mice	130,000 ppm	2 hours	Light anesthesia within 25 min	Stoughton and Lamson 1936
Mice	220,000 ppm	2 hours	Light anesthesia within 1 min Complete anesthesia within 15 min	Stoughton and Lamson 1936
Mice	270,000 ppm	2 hours	Complete anesthesia within 4 min	Stoughton and Lamson 1936
Mice	310,000 ppm	2 hours	Complete anesthesia within 3 min	Stoughton and Lamson 1936

Based on "complete anesthesia": n>4.

Propane: AEGL-1

- *Patty and Yant (1929)*
  - n=3 (based on butane data) for time extrapolation to 30 and 60 min
  - flatlining from 1- to 4- and 8-hour exposures because of steady-state reached within 30 min

TABLE 2. AEGL-1 Values for Propane

10-minute	30-minute	1-hour	4-hour	8-hour
10,000 ppm* (5550 mg/m³)	6900 ppm* (3830 mg/m³)	5500 ppm* (3050 mg/m³)	5500 ppm* (3050 mg/m³)	5500 ppm* (3050 mg/m³)

* The AEGL-1 value is higher than 10% of the lower explosive limit of propane in air (LEL = 2.3 % (23,000 ppm)). Therefore, safety considerations against hazard of explosion must be taken into account.

Propane: AEGL-2

- Cardiac sensitization *(Reinhardt et al 1971)*
  - No effects at 50,000 ppm
    (response in 2/12 dogs at 100,000 ppm)
  - Rapid steady-state blood level
  - Analogous to HFC-134a
    interspecies UF = 1 (dog is an optimized supersensitive model for humans)
    intraspecies UF = 3 to protect sensitive individuals
    one value for all AEGL-2 time points because cardiac sensitization is a concentration-related threshold effect

Propane: AEGL-2

TABLE 3. AEGL-2 Values for Propane

10-minute	30-minute	1-hour	4-hour	8-hour
See below*	See below*	See below*	See below*	See below*

* The AEGL-2 value is higher than 50% of the lower explosive limit of propane in air (LEL = 2.3 % (23,000 ppm)). Therefore, extreme safety considerations against hazard of explosion must be taken into account.
The calculated AEGL-2 values are similar for all time periods: 17,000 ppm (9450 mg/m^3).

Propane: AEGL-3

- Cardiac sensitization *(Reinhardt et al 1971)*
  - No deaths at 100,000 ppm
    (1/12 deaths at 200,000 ppm)
  - UF = 3 (similar to AEGL-2)
  - time extrapolation similar to AEGL-2

TABLE 4. AEGL-3 Values for Propane

10-minute	30-minute	1-hour	4-hour	8-hour
See below*	See below*	See below*	See below*	See below*

* The AEGL-3 value is higher than 50% of the lower explosive limit of propane in air (LEL = 2.3 % (23,000 ppm)). Therefore, extreme safety considerations against hazard of explosion must be taken into account.
The calculated AEGL-3 values are similar for all time periods: 33,000 ppm (18,300 mg/m^3).

Propane: Summary of AEGL-values

TABLE 5. Summary of AEGL Values

Classification	Exposure Duration				
	10-minute	30-minute	1-hour	4-hour	8-hour
AEGL-1 (Nondisabling)	10,000 ppm* (5550 mg/m^3)	6900 ppm* (3830 mg/m^3)	5500 ppm* (3050 mg/m^3)	5500 ppm* (3050 mg/m^3)	5500 ppm* (3050 mg/m^3)
AEGL-2 (Disabling)	See below¶	See below¶	See below¶	See below¶	See below¶
AEGL-3 (Lethal)	See below§	See below§	See below§	See below§	See below§

* The AEGL-1 value is higher than 10% of the lower explosive limit of propane in air (LEL = 2.3 % (23,000 ppm)). Therefore, safety considerations against hazard of explosion must be taken into account.
¶ The AEGL-2 value is higher than 50% of the lower explosive limit of propane in air (LEL = 2.3 % (23,000 ppm)). Therefore, extreme safety considerations against hazard of explosion must be taken into account.
The calculated AEGL-2 values are similar for all time periods: 17,000 ppm (9450 mg/m^3).
§ The AEGL-3 value is higher than 50% of the lower explosive limit of propane in air (LEL = 2.3 % (23,000 ppm)). Therefore, extreme safety considerations against hazard of explosion must be taken into account.
The calculated AEGL-3 values are similar for all time periods: 33,000 ppm (18,300 mg/m^3).

ATTACHMENT 13

September 17, 2003

TSD Butane

Chemical Manager: L.A. Gephart
Staff Scientist: P.M.J. Bos

Butane: Uses

- Production of LPG
- Manufacturing of e.g. ethylene and 1,3-butadiene
- Aerosol propellant
- Blending of gasoline or motor fuel
- Refrigerant solvent and extractant in deasphalting and degreasing of crude oils
- Cigarette lighter fuel

Butane: Physical-chemical properties

- Molecular weight: 58.14
- Colorless gas
- Water solubility: 61 mg/L
- Boiling point: -0.5 °C
- Odor: odorless when pure
- Flammability: extremely flammable gas
- LEL: 1.9%

Butane: Case reports

- Causes
  - Mainly abuse
- Effects
  - Severe encephalopathy (hemiparesis, disintegration)
  - Cardiac effects (tachycardia, ventricular fibrillation)
  - Pulmonary edema

Butane: Case reports

- No adequate exposure estimation
- In case of abuse:
  - repeated exposure
  - possible exposure to other substances
- Data not suitable for AEGL-setting

Butane: Case reports

- Teratogenic effects
  - accident at gestation week 27
    absence of cerebral hemispheres
    thalamus, brainstem, and cerebellum were present
    caused by intra-uterine anoxia
  - suicide attempt at gestation week 30
    spontaneous labor at 36 weeks; infant died after 11 hours
    decreased brain seize (about 1/3 of normal weight)

Butane: Experimental human data

- *Patty and Yant (1929)*
  - Aim: odor intensity and physiological response
  - 3-6 volunteers; 20-30 years-of-age
  - Continuous exposure up to 50,000 ppm (> 10 min)
  - Intermittent exposure up to 100,000 ppm (few minutes)
    no symptoms except drowsiness at 10,000 ppm for 10 min
    no information about effects at higher concentrations
  - Basis for AEGL-1

Butane: Animal data

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

Species	Concentration (ppm)	Exposure Time	Effect[a]	Reference
Rat	227,000 278,000 333,000	4 hours	LC_{16} LC_{50} LC_{84}	Shugaev 1969
Mouse	224,000 287,000 363,000	2 hours	LC_{16} LC_{50} LC_{84}	Shugaev 1969
Mouse	130,000	2 hours	0/6 deaths	Stoughton and Lamson 1936
Mouse	220,000	2 hours	0/10 deaths	Stoughton and Lamson 1936
Mouse	270,000	2 hours	4/10 deaths	Stoughton and Lamson 1936
Mouse	310,000	2 hours	6/10 deaths	Stoughton and Lamson 1936

Note: Stoughton and Lamson data are probably initial concentrations.

Butane: Animal data

- No adequate data on cardiac sensitization
  - limited data with anesthetized dogs
- CNS depression *(Stoughton and Lamson 1936)*
  - probably initial concentrations
- CNS depression *(Nuckolls 1933)*
  - Groups of 3 guinea pigs
  - Exposure duration: 5, 30, 60, or 120 min
  - Exposure concentrations:
    low exposure: 21,000 - 28,000 ppm
    high exposure: 50,000 - 56,000 ppm

Butane: Animal data

TABLE 3. Summary of Nonlethal Inhalation Data in Laboratory Animals

Species	Concentration (ppm)	Exposure Time	Effect	Reference
Guinea pigs	21,000-28,000 ppm	Up to 2 hours	Increased respiration rate Increased sniffing and chewing behavior	Nuckolls 1933
Guinea pigs	50,000-56,000 ppm	Up to 2 hours	Increased respiration rate Increased reaching and chewing behavior Dazed appearance	Nuckolls 1933
Mice	130,000 ppm	2 hours	Light anesthesia within 25 min	Stoughton and Lamson 1936
Mice	220,000 ppm	2 hours	Light anesthesia within 1 min Complete anesthesia within 15 min	Stoughton and Lamson 1936
Mice	270,000 ppm	2 hours	Complete anesthesia within 4 min	Stoughton and Lamson 1936
Mice	310,000 ppm	2 hours	Complete anesthesia within 3 min	Stoughton and Lamson 1936

Note: Stoughton and Lamson data are probably initial concentrations (n>4 based on "complete anesthesia").
Nuckolls: basis for AEGL-2

Butane: kinetic data

- Rapidly reached steady-state blood concentrations
  - Steady-state pulmonary uptake within 30 min
  - Propane: comparable concentrations in blood sampled at 15-min prior to the end of a 1-, 2-, and 8-hour exposure to 250 or 500 ppm
  - Relatively insoluble gases (like butane) reach rapid uptake equilibrium

Butane: AEGL-1

- *Patty and Yant (1929)*
  - No effects but some drowsiness at 10,000 ppm for 10 min
  - No irritation up to 100,000 ppm (few min)
  - UF = 1
    very steep concentration-response curve thus small interindividual variation
    apparently no significant effects reported at a few min exposure to 100,000 ppm
    realistic values

Butane: AEGL-1

- *Patty and Yant (1929)*
  - n=3 (based on data) for time extrapolation to 30 and 60 min
  - flatlining from 1- to 4- and 8-hour exposures because of steady-state reached within 30 min

TABLE 4. AEGL-1 Values for Butane

10-minute	30-minute	1-hour	4-hour	8-hour
10,000 ppm* (4200 mg/m³)	6900 ppm* (2900 mg/m³)	5500 ppm* (2300 mg/m³)	5500 ppm* (2300 mg/m³)	5500 ppm* (2300 mg/m³)

* The AEGL-1 value is higher than 10% of the lower explosive limit of butane in air (LEL = 1.9 % (19,000 ppm)). Therefore, safety considerations against hazard of explosion must be taken into account.

Butane: AEGL-2

- *Nuckolls 1929*
  - starting point:
    - 2-hour exposure of guinea pigs to 50,000 - 56,000 ppm
    - effects: dazed appearance but able to walk
  - total UF = 3
    - effects considered to be due to butane, therefore, no large differences in kinetics expected
    - higher UF would lead to AEGL-2 values close to AEGL-1 values
  - n=3 (supported by data) for time extrapolation to 10, 30, and 60 min
  - flatlining from 2- to 4- and 8-hour exposures because of steady-state reached within 30 min

Butane: AEGL-2

TABLE 5. AEGL-2 Values for Butane

10-minute	30-minute	1-hour	4-hour	8-hour
See below*	See below*	See below*	See below*	See below*

* The AEGL-2 value is higher than 50% of the lower explosive limit of butane in air (LEL = 1.9 % (19,000 ppm)). Therefore, extreme safety considerations against hazard of explosion must be taken into account.

The calculated AEGL-2 values are:
10-min: 38,200 ppm (16,100 mg/m³);
30-min: 26,500 ppm (11,200 mg/m³);
1-hour: 21,000 ppm (8900 mg/m³);
4-hour: 16,700 ppm (7000 mg/m³);
8-hour: 16,700 ppm (7000 mg/m³).

Butane: AEGL-3

- Mortality *(Shugaev 1969)*
  - 2-hour LC_{50} in mice: 287,000 ppm (brain concentration: 7.5 µg/g)
  - calculated 2-h LC_{01}: 160,000 ppm
  - 4-hour LC_{50} in rats: 278,000 ppm (brain concentration: 7.8 µg/g)
  - calculated 4-h LC_{01}: 172,000 ppm

Butane: AEGL-3

- total UF = 3
  - effects considered to be due to butane, therefore, no large differences in kinetics expected
  - steep concentration-response curve thus small interindividual variation
  - relative susceptible species used
  - higher UF would lead to AEGL-2 values close to AEGL-1 values
- n=3 (supported by data) for time extrapolation to 10, 30, and 60 min
- flatlining from 2- to 4- and 8-hour exposures because of steady-state reached within 30 min

Butane: AEGL-3

TABLE 6. AEGL-3 Values for Butane

10-minute	30-minute	1-hour	4-hour	8-hour
See below*	See below*	See below*	See below*	See below*

* The AEGL-3 value is higher than 50% of the lower explosive limit of butane in air (LEL = 1.9 % (19,000 ppm)). Therefore, extreme safety considerations against hazard of explosion must be taken into account.

The calculated AEGL-3 values are:
10-min: 122,00 ppm (52,000 mg/m^3);
30-min: 85,000 ppm (36,000 mg/m^3);
1-hour: 67,000 ppm (28,000 mg/m^3);
4-hour: 53,000 ppm (23,000 mg/m^3);
8-hour: 53,000 ppm (23,000 mg/m^3).

The values for the shorter exposure periods are supported by the data from Patty and Yant (1925) who reported that exposure to slowly increasing concentrations up to 50,000 ppm (total exposure duration at least 10 min) and a short exposure (possibly a few minutes) to 100,000 ppm on the same day did not result in serious complaints (Patty and Yant 1929).

Butane: Summary of AEGL-values

TABLE 7. Summary of AEGL Values

Classification	Exposure Duration				
	10-minute	30-minute	1-hour	4-hour	8-hour
AEGL-1 (Nondisabling)	10,000 ppm* (4200 mg/m^3)	6900 ppm* (2900 mg/m^3)	5500 ppm	5500 ppm	5500 ppm
AEGL-2 (Disabling)	38,200 ppm	26,500 ppm	21,000 ppm	16,700 ppm	16,700 ppm
AEGL-3 (Lethal)	122,000 ppm	85,000 ppm	67,000 ppm	53,000 ppm	53,000 ppm

* The AEGL-1 value is higher than 10% of the lower explosive limit of butane in air (LEL = 1.9 % (19,000 ppm)). Therefore, safety considerations against hazard of explosion must be taken into account.

¶ The AEGL-2 values are higher than 50% of the lower explosive limit of butane in air (LEL = 1.9 % (19,000 ppm)). Therefore, extreme safety considerations against hazard of explosion must be taken into account.

§ The AEGL-3 values are higher than 50% of the lower explosive limit of butane in air (LEL = 1.9 % (19,000 ppm)). Therefore, extreme safety considerations against hazard of explosion must be taken into account.

ATTACHMENT 14

Acute Exposure Guideline Levels (AEGLs)

for

Dimethyl Sulfate

(CAS Reg. No. 77-78-1)

NAC/AEGL-30 meeting
Sept 16-18, 2003
Washington

Staff Scientist:
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US Chemical Manager:
Robert Snyder
(EOHS, Environmental and Occupational Health Sciences Institute)

Propert

- colorless oily liquid
- slight onion-like odor
- no quantitative data on odor recognition
- hydrolyzes readily to monomethyl sulfate, methanol, and sulfuric acid

Production and use

- used as methylating agent
- used in production of methyl esters, ethers and amines in the dye, agricultural, surfactant, and perfumery industry

Exposure

- DMS is used within enclosed plants
- Exposure can occur during maintenance, filling, unloading, spillage, or accidental release
- Exposure occurs mainly via inhalation pathway

Toxicity mechanism and concerns

- Primary effects are irritation of eyes and respiratory tract
- followed by lesions in bronchi and lung
- Local effects in the foreground for lethal and non-lethal intoxication
- Alarm signs absent due to the anesthetic effect on mucosa
- Latency period

Interspecies variability

- moderate species differences
- very similar lesions in various species

Intraspecies variability

- no major toxicokinetic differences
- unspecific irritating and corrosive action

Data relevant for AEGL-1

Human

No scientific human data are available to derive an AEGL-1.

Animal

- Frame et al. (1993; abstract publication) — repeated exposure on rats for 6 hours/d (2 weeks, 10 exposures)

  Changes in nasal cell proliferation at 0.1 ppm:
  Labeling index slightly depressed in respiratory epithelium
  Labeling index increased in olfactory epithelium

  Erosion, ulceration, atrophy of respiratory and olfactory epithelia at 0.7 ppm and 1.5 ppm

- Schlögel (1972) — single 6-hour exposure on rats, mice, and golden hamster

  Closed or half-closed eyes after 20 minutes exposure to 0.5 ppm, breathing problems and asthmatic-like breathing sounds after 6 hours.
  Aggravated breathing problems, conjunctivitis, sensitivity to light at 2 ppm.

AEGL-1

Key study: Frame et al. (1993; abstract publication)

Endpoint: Altered nasal cell proliferation in rats from repeated exposure to 0.1 ppm for 10 exposures of 6 hours each.

Time scaling: $C^3 \times t$ for extrapolation to 4 hours, 1 hour, 30 minutes
$C^1 \times t$ for extrapolation to 8 hours
The 10-min AEGL-1 was set at the same concentration as the 30-min AEGL-1

Total uncertainty factor: 10

Interspecies: 3

- moderate species differences
- very similar lesions in various species
- repeated exposure

Intraspecies: 3

- no major toxicokinetic differences
- unspecific irritating and corrosive action

AEGL-1 Values for Dimethyl Sulfate [ppm (mg/m³)]*)				
10-minute	30-minute	1-hour	4-hour	8-hour
0.023 ppm (0.12 mg/m³)	0.023 ppm (0.12 mg/m³)	0.018 ppm (0.093 mg/m³)	0.011 ppm (0.057 mg/m³)	0.0075 ppm (0.039 mg/m³)

*) Relevant skin uptake and sensitizing properties of DMS may not be excluded. DMS is a methylating and mutagenic substance, classified as suspected human carcinogen.

Data relevant for AEGL-2

Human

No scientific human data are available to derive an AEGL-2.

Animal

- Schlögel (1972) 6-hour exposure on rats, mice, hamster

  Closed or half-closed eyes after 20 minutes exposure to **0.5 ppm**, breathing problems and asthmatic-like breathing sounds after 6 hours. Aggravated breathing problems, conjunctivitis, sensitivity to light at **2 ppm**.
  After repeated exposure to **0.5 ppm** or **2 ppm** a higher incidence of inflammation of lungs are reported.

- Frame et al. (1993) repeated exposure on rats 6 hours/d (2 weeks, 10 exposures)

  Ulceration, atrophy of respiratory and olfactory epithelia at **0.7 ppm** and **1.5 ppm**

- Alvarez et al. (1997) repeated exposure on rats 6 hours/d (2 weeks, 10 exposures)

  Significantly reduced body weight gain between day 7 and day 17 of gestation at **0.7 ppm** or **1.5 ppm**.

- Hein (1969) 1-hour exposure on rats, mice, guinea pigs

  Closed eyes within all species during exposure to **10 ppm**, additionally lacrimation, salivation in guinea pigs, corneal injuries several hours after cessation. Occasionally hemorrhagic lung zones, pulmonary congestion, emphysema, and edema. Demucosation of trachea and bronchi at histopathology.

AEGL-2

Key study: Schlögel (1972)

Endpoint: Breathing difficulties and asthmatic-like breathing sounds at 0.5 ppm for 6 hours in rats, mice and golden hamsters.

Time scaling: $C^3 \times t$ for extrapolation to 4 hours, 1 hour, 30 minutes
$C^1 \times t$ for extrapolation to 8 hours
The 10-min AEGL-2 was set at the same concentration as the 30-min AEGL-2

Total uncertainty factor: 10

Interspecies: 3

- moderate species differences
- very similar lesions in various species

Intraspecies: 3

- no major toxicokinetic differences
- unspecific irritating and corrosive action

AEGL-2 Values for Dimethyl Sulfate [ppm (mg/m³)]*)				
10-minute	30-minute	1-hour	4-hour	8-hour
0.11 ppm (0.57 mg/m³)	0.11 ppm (0.57 mg/m³)	0.091 ppm (0.47 mg/m³)	0.057 ppm (0.29 mg/m³)	0.038 ppm (0.19 mg/m³)

*) Relevant skin uptake and sensitizing properties of DMS may not be excluded. DMS is a methylating and mutagenic substance, classified as suspected human carcinogen.

Data relevant for AEGL-3

Human

No scientific human data are available to derive an AEGL-3.

Animal

Hein (1969) 1-hour exposure on rats, mice, hamsters, and guinea pigs

Dyspnea at exposure.
Lung emphysema, hemorrhage, hyperemia, edema at necropsy.
Inflation of stomach and small intestine.

Rats: LC_{50} for 1 hour:	**64 ppm**
Mice: LC_{50} for 1 hour:	**98 ppm**
Hamsters: LC_{50} for 1 hour:	**56 ppm**
Guinea pigs: LC_{50} for 1 hour:	**32 ppm**

Calculated $BMCL_{05}$ (1 hour) :

Rats:	**32 ppm**	(log Probit)
Mice:	**44 ppm**	(log Probit)
Hamster:	**12.6 ppm**	(multistage)
Guinea pigs:	**5.8 ppm**	(Quantal quadratic)

Guinea pigs LC_x (1 hour) :

LC_{100}	**71 ppm**
LC_{60}	**40 ppm**
LC_{90}	**33 ppm**
LC_0	**10 ppm**

AEGL-3

Key study: Hein (1969)

Endpoint: Lethality after 1-hour exposure in guinea pigs. Calculation of $BMCL_{05}$ with 5.8 ppm

Time scaling: $C^3 \times t$ for extrapolation to 10 and 30 minutes
$C^1 \times t$ for extrapolation to 4 and 8 hours

Total uncertainty factor: 10

Interspecies: 3

- moderate species differences
- very similar lesions in various species

Intraspecies: 3

- no major toxicokinetic differences
- unspecific irritating and corrosive action

AEGL-3 Values for Dimethyl Sulfate [ppm (mg/m³)] *)				
10-minute	30-minute	1-hour	4-hour	8-hour
1.1 ppm (5.4 mg/m³)	0.73 ppm (3.8 mg/m³)	0.58 ppm (3 mg/m³)	0.15 ppm (0.77 mg/m³)	0.073 ppm (0.38 mg/m³)

*) Relevant skin uptake and sensitizing properties of DMS may not be excluded. DMS is a methylating and mutagenic substance, classified as suspected human carcinogen.

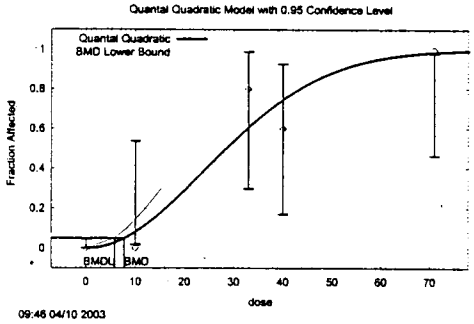
Summary of AEGL Values [ppm (mg/m³)]					
Classification	Exposure Duration				
Reference	10-minute	30-minute	1-hour	4-hour	8-hour
AEGL-1 (Nondisabling)	0.023 ppm	0.023 ppm	0.018 ppm	0.011 ppm	0.0075 ppm
Frame et al. (1993)	(0.12 mg/m³)	(0.12 mg/m³)	(0.094 mg/m³)	(0.057 mg/m³)	(0.039 mg/m³)
AEGL-2 (Disabling)	0.11 ppm	0.11 ppm	0.091 ppm	0.057 ppm	0.038 ppm
Schlögel (1972)	(0.57 mg/m³)	(0.57 mg/m³)	(0.47 mg/m³)	(0.30 mg/m³)	(0.20 mg/m³)
AEGL-3 (Lethal)	1.1 ppm	0.73 ppm	0.58 ppm	0.15 ppm	0.073 ppm
Hein (1969)	(5.7 mg/m³)	(3.8 mg/m³)	(3.0 mg/m³)	(0.78 mg/m³)	(0.38 mg/m³)

Benchmark Calculations

$BMCL_{05}$ for guinea pigs (lethality)

BMC = 7.73348

BMCL = 5.81184



We assumed that no mortality would occur at background concentrations (mortality 0 at dose 0 ppm).

All other models (Weibul, logistic, gamma, multistage, probit) resulted in poorer fits and/or less degrees of freedom and were rejected.

Carcinogenicity Assessment

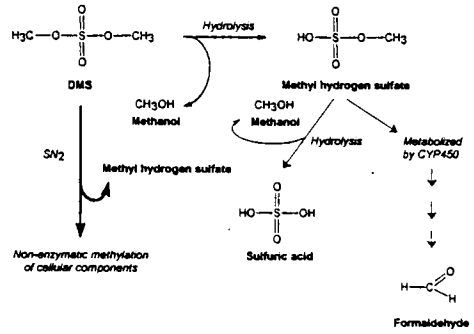
- methylating potency
  reacts with nucleophilic groups of nucleic acids
  acts as a directly genotoxic agent
- malignant tumors of lung and nose observed by Schlögel (1972) in rats, mice and golden hamsters at **0.5 ppm, 2 ppm and sublethal concentration** (only in rats; **34 ppm**).
  Highest incidence in 2 ppm - group
  No dose-effect relationship

  Incidence of malignant tumor in rats / mice / hamsters:

	0.5 ppm	2 ppm	Sublethal
lung	1 / 1 / 0	0 / 3 / 1	1 / 0 / 0
nose	2 / 0 / 0	6 / 0 / 0	1 / 0 / 0

- ECB (2002): carcinogenic activity attributable to the exposure to DMS per unit concentration, expressed as I_{conc} = **2.2 mg/m³** *)
- Concentration of DMS that would cause a theoretical excess cancer risk of 10^{-4} was calculated as **411 µg/m³** for an 8-hour exposure.
- Calculations uncertain due to the missing dose-response relationship.
- Cytotoxic effects (irritant effects in target tissues) observed by Schlögel (1972) might have influenced cancer incidence.
- The 10^{-4} risk level is above AEGL-2 for 8-hour exposure.

*) I_{conc} = Carcinogenic activity for life span exposure per unit air concentration



Main Pathways for the Methylation of DMS
(most relevant pathways are illustrated by thick arrows).

ATTACHMENT 15

ACUTE EXPOSURE GUIDELINE LEVELS (AEGLs) FOR SELECTED ALIPHATIC NITRILES

Acetonitrile
Isobutyronitrile
Propionitrile
Chloroacetonitrile
Malononitrile

NAC/AEGL-30
September 16-18, 2003
Washington, DC

ORNL Staff Scientist: Cheryl Bast

Chemical Manager: George Rodgers

Chemical Reviewers: Ernest Falke and George Rusch

Mechanism of Toxicity

Metabolic release of cyanide via cytochrome P450 hydroxylation

Structure Activity Relationships

Acute toxicity dependent on ability to undergo cytochrome P450 mediated hydroxylation, on the carbon alpha to the cyano group (α-carbon).

The hydroxylation is a radical-based reaction.

Acute toxicity of nitriles is related to the structural features that influence α-carbon radical stability.

Generally, the nitriles that are metabolized most quickly or easily at the carbon atom alpha to the cyano group (α-carbon) are more toxic than nitriles metabolized more slowly at the α-carbon.

Thus, the toxicity pattern, in decreasing order, with regard to the type of α-carbon radical formed following α-hydrogen abstraction is benzylic≈3°>2°>1°.

The presence of a hydroxy or a substituted or unsubstituted amino group on the α-carbon increases toxicity, and the presence of these moieties at other carbon positions decreases acute toxicity.

Acetonitrile	$CH_3C{\equiv}N$	**1° α-carbon**
Propionitrile	$CH_3CH_2C{\equiv}N$	**2° α-carbon**
Isobutyronitrile	$(CH_3)_2CHC{\equiv}N$	**3° α-carbon**

Chloroacetonitrile $ClCH_2C{\equiv}N$

More toxic than acetonitrile because Cl promotes cyanohydrin formation, and therefore, radical formation at the α-carbon

Malononitrile $N{\equiv}CCH_2C{\equiv}N$

Support from Experimental Data on Title Nitriles:

Rate of cyanide production in *in vitro* male rat studies (Dahl and Waruszewski, 1987; 1989)

Ethmoturbinate Microsomes:

aceto- ≈ acrylo- < propio- ~ butyro- ~ isobutyro- ~ succino- ~ benzyl cyanide.

Maxilloturbinate Microsomes:

aceto- < propio- < isobutyro- ~ succino- < butyro- < benzyl cyanide < acrylonitrile.

Hepatic Microsomes:

succino < aceto- < propio- ~ butyro- < isobutyro- < acrylo- < benzyl cyanide.

Hepatic and blood cyanide levels following oral administration of 1 LD_{50} to male rats (Ahmed and Farooqui, 1982):

malononitrile > propionitrile> potassium cyanide> butyronitrile> acrylonitrile> allylcyanide>> fumaronitrile> acetonitrile.

Brain cyanide levels following oral administration of 1 LD_{50} to male rats (Ahmed and Farooqui, 1982):

potassium cyanide> malononitrile > propionitrile> butyronitrile> acrylonitrile> allylcyanide>> fumaronitrile> acetonitrile.

Hepatic and brain cytochrome c oxidase levels were decreased. Decreases corresponded to measured cyanide levels.

	Mouse i.p. LD_{50}	Reference
Acetonitrile	521 mg/kg	Yoshikawa, 1968
Chloroacetonitrile	100 mg/kg	Lewis, 1996
Propionitrile	34 mg/kg	Yoshikawa, 1968
Isobutyronitrile	25 mg/kg	Zeller et al., 1969
Malononitrile	13 mg/kg	Jones and Israel, 1970
	Ratio of mouse i.p. LD_{50} values	
Acetonitrile/Chloroacetonitrile	5.21	
Acetonitrile/Propionitrile	15	
Acetonitrile/Isobutyronitrile	21	
Acetonitrile/Malononitrile	40	

Jones, G.N. and Israel, M.S. 1970. Mechanism of toxicity of injected CS gas. Nature 228: 1315-1317.

Lewis, R.J. 1996. Sax's Dangerous Properties of Industrial Materials. 9th ed. Van Nostrand Reinhold: New York.

Yoshikawa, H. 1968. Toxicity of nitrile compounds. 1. Aliphatic nitriles. Medicine and Biology 77:1-4.

Zeller, H.V., Hoffmann, H.T., Thiess, A.M., and Hey, W. 1969. Toxicity of Nitriles. Zentralbl Arbeitsmed Arbeitsschutz. 19: 225-238.

AEGL-1 VALUES: ACETONITRILE				
10 minute	30 minute	1 hour	4 hour	8 hour
40 ppm	40 ppm	40 ppm	40 ppm	40 ppm

Species: Human (3 male)
Concentration: 40 ppm
Time: 4 hours
Endpoint: Slight chest tightness, cooling sensation in lungs (1/3)
Reference: Pozzani et al., 1959

Time Scaling: Concentration 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 more severe than those defined by AEGL-1.

Uncertainty Factors:

Interspecies = 1 Subjects were human

Intraspecies = 1 Considered sufficient because:

Mild effect is considered to have occurred in a sensitive subject because no symptoms were reported by two other subjects exposed to this same regimen and no effects were noted at 80 ppm for 4 hours in these same two subjects.

AEGL-2 VALUES: ACETONITRILE				
10 minute	30 minute	1 hour	4 hour	8 hour
310 ppm	310 ppm	230 ppm	130 ppm	100 ppm

Species: Rat (12/sex/group)
Concentration: 4000 ppm
Time: 4 hours
Endpoint: Slight pulmonary congestion or hemorrhage
Reference: Pozzani et al., 1959

Time Scaling: $c^n \times t = k$, where n= 2.5 (derived from rat lethality data ranging from 15 minutes to 8 hours exposure duration). The 30-minute AEGL-2 was also adopted as the 10-minute value

Uncertainty Factors:

Interspecies = 10 The rat is not the most sensitive species

Intraspecies = 3 Considered sufficient because:

Human accidental and occupational exposures indicate that there are individual differences in sensitivity to HCN but the magnitude of these differences does not appear to be great (NRC, 2002)

Values derived with a total default uncertainty factor (of 10 x 10) would range from 33 to 100 ppm, which are below the range of the 40 to 160 ppm concentrations causing only minor effects in humans (Pozzani et al., 1959).

Total UF = 30

AEGL-3 VALUES: ACETONITRILE				
10 minute	30 minute	1 hour	4 hour	8 hour
650 ppm	650 ppm	490 ppm	280 ppm	213 ppm

Species: Rat (10/males/group)
Concentration: 8421 ppm
Time: 4 hours
Endpoint: Calculated LC_{01}
Reference: Monsanto, 1986

Time Scaling: $c^n \times t = k$, where n= 2.5 (derived from rat lethality data ranging from 15 minutes to 8 hours exposure duration). The 30-minute AEGL-3 was also adopted as the 10-minute value

Uncertainty Factors:

Interspecies = 10 The rat is not the most sensitive species

Intraspecies = 3 Considered sufficient because:

Human accidental and occupational exposures indicate that there are individual differences in sensitivity to HCN but the magnitude of these differences does not appear to be great (NRC, 2002)

Values derived with a total default uncertainty factor (of 10 x 10) would be inconsistent with the available data (163 ppm for 1-hr, 93 ppm for 4-hr, and 71 ppm for 8-hr; values in the range of the 40 to 160 ppm concentrations causing only minor effects in humans (Pozzani et al., 1959).

Total UF = 30

ACETONITRILE

Guideline	Exposure Duration				
	10-Minute	30-Minute	1-Hour	4-Hour	8-Hour
AEGL-1	40 ppm	40 ppm	40 ppm	40 ppm	40 ppm
AEGL-2	310 ppm	310 ppm	230 ppm	130 ppm	100 ppm
AEGL-3	650 ppm	650 ppm	490 ppm	280 ppm	213 ppm
NIOSH IDLH	500 ppm				
NIOSH REL-TWA					20 ppm
OSHA PEL-TWA					40 ppm
ACGIH TLV-TWA					20 ppm
OSHA PEL-STEL	40 ppm				
German MAK					20 ppm
Dutch MAC					40 ppm
Swedish OEL-LLV					30 ppm
Swedish OEL-STV	60 ppm				

AEGL-1 VALUES: ISOBUTYRONITRILE				
10 minute	30 minute	1 hour	4 hour	8 hour
0.95 ppm	0.95 ppm	0.95 ppm	0.95 ppm	0.95 ppm

Endpoint: Derived by analogy to acetonitrile AEGL-1 values. Mouse i.p. LD_{50} data suggest that isobutyronitrile is approximately 21 times more toxic than acetonitrile. Therefore, the acetonitrile AEGL-1 values were divided by 21 to approximate AEGL-1 values for isobutyronitrile.

Reference: Analogy to Aectonitrile.

Modifying Factor: 2

Applied because the data suggesting that isobutyronitrile is 21 times more toxic than acetonitrile are very limited, and thus, the value cannot be predicted with great precision.

Rationale for Approach:

In the absence of inhalation data, the i.p. route is considered the most appropriate for approximating inhalation toxicity values.

Both routes involve potentially rapid absorption through a semipermeable membrane (peritoneal membrane and alveolar membrane).

Rate of availability (in descending order) for the different routes of administration are: intraveneous, inhalation, intraperitoneal, subcutaneous, intramuscular, intradermal, oral, and topical.

AEGL-2 VALUES: ISOBUTYRONITRILE				
10 minute	30 minute	1 hour	4 hour	8 hour
33 ppm	23 ppm	18 ppm	11 ppm	7.5 ppm

Species: Rat (21/pregnant females/group)
Concentration: 100 ppm
Time: 6 hours (6 hr/day, gestation days 6-20)
Endpoint: NOEL for maternal and developmental effects
Reference: Saillenfait et al., 1993

Time Scaling: $C^n \times t = k$, where $n = 3$ or $n = 1$. The 30-minute AEGL-2 would normally be adopted as the 10-minute value when starting with a 6-hour point-of-departure; however, the approach taken here assumes a single 6-hour exposure when, in fact, the exposure was repeated over several days.

Uncertainty Factors:

Interspecies = 3 10 would typically be applied because the rat is not the most sensitive species. However, use of the full uncertainty factor of 10, would yield AEGL-2 values that are not consistent with the available data. AEGL-2 values would be 11 ppm for 10-minutes, 7.6 ppm for 30-minutes, 6.1 ppm for 1-hour, 3.8 ppm for 4-hours, and 2.5 ppm for 8-hours. An exposure of a "few minutes" to estimated concentrations of 20-25 ppm isobutyronitrile during an industrial spill did not produce symptoms of cyanide poisoning in humans (AIHA, 1992).

Intraspecies = 3 Considered sufficient because:

Human accidental and occupational exposures indicate that there are individual differences in sensitivity to HCN but the magnitude of these differences does not appear to be great (NRC, 2002)

AEGL-3 VALUES: ISOBUTYRONITRILE				
10 minute	30 minute	1 hour	4 hour	8 hour
123 ppm	85 ppm	68 ppm	17 ppm	8.5 ppm

Species: Rat (5/sex/group)
Concentration: 677 ppm
Time: 1 hour
Endpoint: Calculated LC_{01}
Reference: Eastman Kodak Company, 1986a

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

Uncertainty Factors:

Interspecies = 3 10 would typically be applied because the rat is not the most sensitive species. However, use of the full uncertainty factor of 10, would yield AEGL-3 values that are not consistent with the available data. AEGL-3 values would be 41 ppm for 10-minutes, 26 ppm for 30-minutes, 22 ppm for 1-hour, 5.6 ppm for 4-hours, and 2.8 ppm for 8-hours. However, an exposure of a "few minutes" to estimated concentrations of 20-25 ppm isobutyronitrile during an industrial spill did not produce symptoms of cyanide poisoning in humans (AIHA, 1992).

Intraspecies = 3 Considered sufficient because:

Human accidental and occupational exposures indicate that there are individual differences in sensitivity to HCN but the magnitude of these differences does not appear to be great (NRC, 2002)

Total UF = 10

EXTANT STANDARDS AND GUIDELINES FOR ISOBUTYRONITRILE					
Guideline	Exposure Duration				
	10 minutes	30 minutes	1 hour	4 hours	8 hours
AEGL-1	*0.95 ppm*	*0.95 ppm*	*0.95 ppm*	*0.95 ppm*	*0.95 ppm*
AEGL-2	33 ppm	23 ppm	18 ppm	11 ppm	7.5 ppm
AEGL-3	123 ppm	85 ppm	68 ppm	17 ppm	8.5 ppm
ERPG-1(AIHA)	-	-	10 ppm	-	-
ERPG-2 (AIHA)	-	-	50 ppm	-	-
ERPG-3 (AIHA)	-	-	200 ppm	-	-
REL-TWA (NIOSH)	-	-	-	-	8 ppm

AEGL-1 VALUES: PROPIONITRILE				
10 minute	30 minute	1 hour	4 hour	8 hour
1.3 ppm	1.3 ppm	1.3 ppm	1.3 ppm	1.3 ppm

Endpoint: Derived by analogy to acetonitrile AEGL-1 values. Mouse i.p. LD_{50} data suggest that propionitrile is approximately 15 times more toxic than acetonitrile. Therefore, the acetonitrile AEGL-1 values were divided by 15 to approximate AEGL-1 values for propionitrile.

Reference: Analogy to Aectonitrile.

Modifying Factor: 2

Applied because the data suggesting that propionitrile is 15 times more toxic than acetonitrile are very limited, and thus, the value cannot be predicted with great precision.

Rationale for Approach:

In the absence of inhalation data, the i.p. route is considered the most appropriate for approximating inhalation toxicity values.

Both routes involve potentially rapid absorption through a semipermeable membrane (peritoneal membrane and alveolar membrane).

Rate of availability (in descending order) for the different routes of administration are: intraveneous, inhalation, intraperitoneal, subcutaneous, intramuscular, intradermal, oral, and topical.

AEGL-2 VALUES: PROPIONITRILE				
10 minute	30 minute	1 hour	4 hour	8 hour
18 ppm	18 ppm	14 ppm	5.7 ppm	2.8 ppm

Species: Human (2 male)
Concentration: 33.8 ppm
Time: 2 hours
Endpoint: Headache, nausea, vomiting, dizziness, confusion (1 of 2)
Reference: Scolnick et al., 1993

Time Scaling: $C^n \times t = k$, where an $n = 3$ applied to extrapolate to the 30-minute and 1-hour time periods, and an $n = 1$ will to extrapolate to the 4- and 8-hour time periods, to provide AEGL values that would be protective of human health (NRC, 2001). The 30-minute AEGL-2 value is also adopted as the 10-minute value

Uncertainty Factors:

Interspecies = 1 Subjects were human

Intraspecies = 3 Considered sufficient because:

human accidental and occupational exposures indicate that there are individual differences in sensitivity to HCN (the metabolically-liberated toxicant) but the magnitude of these differences does not appear to be great (NRC, 2002)

Support for Proposed values:

Maternal and fetal no-effect-level of 150 ppm in rats exposed 6 hours/day on days 6-15 of gestation, total uncertainty factor of 30 (10 for interspecies and 3 for intraspecies), and time scaling using *n* values of 1 or 3, values of 11 ppm, 11 ppm, 9.1 ppm, 5.7 ppm, and 3.8 ppm are obtained for the 10-min, 30-min, 1-hr, 4-hr, and 8-hr time points, respectively. These values, derived assuming a single 6 hour exposure from repeated exposure data, are in the same range as the proposed AEGL-2 values, suggesting that the proposed values will be protective of human health

AEGL-3 VALUES: PROPIONITRILE				
10 minute	30 minute	1 hour	4 hour	8 hour
46 ppm	46 ppm	37 ppm	23 ppm	12 ppm

Species: Rat (5/sex/group)
Concentration: 690 ppm
Time: 4 hours
Endpoint: Highest conncentration causing no death
Reference: Younger Labs, 1978

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

Uncertainty Factors:

Interspecies = 10 The rat is not the most sensitive species.

Intraspecies = 3 Considered sufficient because:

Human accidental and occupational exposures indicate that there are individual differences in sensitivity to HCN but the magnitude of these differences does not appear to be great (NRC, 2002)

Total UF = 30

EXTANT STANDARDS AND GUIDELINES FOR PROPIONITRILE					
Guideline	Exposure Duration				
	10 minutes	30 minutes	1 hour	4 hours	8 hours
AEGL-1	1.3 ppm	1.3 ppm	1.3 ppm	1.3 ppm	1.3 ppm
AEGL-2	18 ppm	18 ppm	14 ppm	5.7 ppm	2.8 ppm
AEGL-3	46 ppm	46 ppm	37 ppm	23 ppm	12 ppm
REL-TWA (NIOSH)	-	-	-	-	6 ppm

Chloroacetonitrile					
Classification	10-minute	30-minute	1-hour	4-hour	8-hour
AEGL-1	7.8 ppm	7.8 ppm	7.8 ppm	7.8 ppm	7.8 ppm
AEGL-2	60 ppm	60 ppm	44 ppm	25 ppm	19 ppm
AEGL-3	125 ppm	125 ppm	94 ppm	54 ppm	41 ppm

Endpoint: Derived by analogy to acetonitrile AEGL values. Mouse i.p. LD_{50} data suggest that chloroacetonitrile is approximately 5.2 times more toxic than acetonitrile. Therefore, the acetonitrile AEGL values were divided by 5.2 to approximate AEGL values for propionitrile.

Reference: Analogy to Aectonitrile.

Modifying Factor: NA

None applied because although the data suggesting that chloroacetonitrile is 5.2 times more toxic than acetonitrile are limited, little data variability are expected over the 5.2-fold extrapolation.

Rationale for Approach:

In the absence of inhalation data, the i.p. route is considered the most appropriate for approximating inhalation toxicity values.

Both routes involve potentially rapid absorption through a semipermeable membrane (peritoneal membrane and alveolar membrane).

Rate of availability (in descending order) for the different routes of administration are: intraveneous, inhalation, intraperitoneal, subcutaneous, intramuscular, intradermal, oral, and topical.

Malononitrile					
Classification	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	2.6 ppm	2.6 ppm	1.9 ppm	1.1 ppm	0.83 ppm
AEGL-3	5.3 ppm	5.3 ppm	4.0 ppm	2.3 ppm	1.8 ppm

Endpoint: Derived by analogy to acetonitrile AEGL values. Mouse i.p. LD_{50} data suggest that malononitrile is approximately 40 times more toxic than acetonitrile. Therefore, the acetonitrile AEGL values were divided by 40 to approximate AEGL values for malononitrile.

Reference: Analogy to Aectonitrile.

Modifying Factor: 3

Applied because the data suggesting that malononitrile is 40 times more toxic than acetonitrile are very limited, and thus, the value cannot be predicted with great precision.

Rationale for Approach:

In the absence of inhalation data, the i.p. route is considered the most appropriate for approximating inhalation toxicity values.

Both routes involve potentially rapid absorption through a semipermeable membrane (peritoneal membrane and alveolar membrane).

Rate of availability (in descending order) for the different routes of administration are: intraveneous, inhalation, intraperitoneal, subcutaneous, intramuscular, intradermal, oral, and topical.

EXTANT STANDARDS AND GUIDELINES FOR MALONONITRILE					
Guideline	Exposure Duration				
	10 minutes	30 minutes	1 hour	4 hours	8 hours
AEGL-1	0.33 ppm	0.33 ppm	0.33 ppm	0.33 ppm	0.33 ppm
AEGL-2	2.6 ppm	2.6 ppm	1.9 ppm	1.1 ppm	0.83 ppm
AEGL-3	5.3 ppm	5.3 ppm	4.0 ppm	2.3 ppm	1.8 ppm
REL-TWA (NIOSH)	-	-	-	-	3 ppm

	AEGL-1				
	10-min	30-min	1-hr	4-hr	8-hr
Acetonitrile	40 ppm	40 ppm	40 ppm	40 ppm	40 ppm
Chloroacetonitrile	7.8 ppm	7.8 ppm	7.8 ppm	7.8 ppm	7.8 ppm
Propionitrile	1.3 ppm	1.3 ppm	1.3 ppm	1.3 ppm	1.3 ppm
Isobutyronitrile	0.95 ppm	0.95 ppm	0.95 ppm	0.95 ppm	0.95 ppm
Malononitrile	0.33 ppm	0.33 ppm	0.33 ppm	0.33 ppm	0.33 ppm

	AEGL-1				
	10-min	30-min	1-hr	4-hr	8-hr
Acetonitrile					
Chloroacetonitrile					
Propionitrile					
Isobutyronitrile					
Malononitrile					

	AEGL-1				
	10-min	30-min	1-hr	4-hr	8-hr
Acetonitrile					
Chloroacetonitrile					
Propionitrile					
Isobutyronitrile					
Malononitrile					

	AEGL-2				
	10-min	**30-min**	**1-hr**	**4-hr**	**8-hr**
Acetonitrile	**310 ppm**	**310 ppm**	**230 ppm**	**130 ppm**	**100 ppm**
Chloroacetonitrile	**60 ppm**	**60 ppm**	**44 ppm**	**25 ppm**	**19 ppm**
Propionitrile	***18 ppm***	***18 ppm***	***14 ppm***	***5.7 ppm***	***2.8 ppm***
Isobutyronitrile	***33 ppm***	***23 ppm***	***18 ppm***	***11 ppm***	***7.5 ppm***
Malononitrile	**2.6 ppm**	**2.6 ppm**	**1.9 ppm**	**1.1 ppm**	**0.83 ppm**

	AEGL-2				
	10-min	**30-min**	**1-hr**	**4-hr**	**8-hr**
Acetonitrile					
Chloroacetonitrile					
Propionitrile					
Isobutyronitrile					
Malononitrile					

	AEGL-2				
	10-min	**30-min**	**1-hr**	**4-hr**	**8-hr**
Acetonitrile					
Chloroacetonitrile					
Propionitrile					
Isobutyronitrile					
Malononitrile					

	AEGL-3				
	10-min	**30-min**	**1-hr**	**4-hr**	**8-hr**
Acetonitrile	**650 ppm**	**650 ppm**	**490 ppm**	**280 ppm**	**213 ppm**
Chloroacetonitrile	**125 ppm**	**125 ppm**	**94 ppm**	**54 ppm**	**41 ppm**
Propionitrile	***46 ppm***	***46 ppm***	***37 ppm***	**23 ppm**	**12 ppm**
Isobutyronitrile	***123 ppm***	***85 ppm***	***68 ppm***	**17 ppm**	**8.5 ppm**
Malononitrile	**5.3 ppm**	**5.3 ppm**	**4.0 ppm**	**2.3 ppm**	**1.8 ppm**

	AEGL-3				
	10-min	**30-min**	**1-hr**	**4-hr**	**8-hr**
Acetonitrile					
Chloroacetonitrile					
Propionitrile					
Isobutyronitrile					
Malononitrile					

	AEGL-3				
	10-min	**30-min**	**1-hr**	**4-hr**	**8-hr**
Acetonitrile					
Chloroacetonitrile					
Propionitrile					
Isobutyronitrile					
Malononitrile					

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

June 17-19, 2003

Final Meeting-29 Highlights

U.S. Department of Labor
200 Constitution Avenue, N.W., Rm 3437-B.C.D
Washington, DC 20210

INTRODUCTION

George Rusch, NAC/AEGL Chair, and Ernie Falke, EPA Representative, began the meeting with a tribute to Roger Garrett. Among many other projects with which Roger was associated, his involvement in the successful AEGL program may be his most lasting legacy. George Rusch handed out mini-posters, copies of posters of final AEGLs presented by ORNL staff at the 42nd Annual Meeting of the Society of Toxicology in Salt Lake City. Paul Tobin, EPA Designated Project Officer, updated the Committee on the status of the EPA internet site. It was also mentioned that files of draft documents of AEGL chemicals are available for review by committee members on the non-public ORNL web site prior to NAC meetings. Federal Register Notice 7 is now at the EPA Assistant Administrator's Office, and should be signed shortly. In response to the USEPA concern on human studies, Ernie Falke had previously noted that the Standing Operation Procedures (SOPs) already has a statement addressing the use of human data. George Rusch mentioned the availability of electronic Organization of Economic Development (OECD) data on high production chemicals. Warren W. Jederberg is Navy's nomination to replace Kenneth Still (who has taken a new position as Director, Fleet Safety and Occupational Health for the U.S. Pacific Fleet).

The draft NAC/AEGL-28 meeting highlights were reviewed. One change - a clarification of the basis for the AEGL-1 for formaldehyde - was suggested by George Alexeeff. Bob Benson volunteered to clarify the basis/effect for the AEGL-1. A motion was made by Loren Koller and seconded by Bob Benson to accept the meeting highlights as presented with the aforementioned revision. The motion passed unanimously by voice vote. The final version of the NAC/AEGL-28 meeting highlights is attached (Appendix A) and was distributed to the NAC/AEGL by e-mail. At this time Paul Tobin passed out information sheets to be filled out by the chemical managers (assuming they are not making the presentation) and to be used for writing up the meeting minutes (Attachment 1). Ernie Falke promised to send a WAV file covering the discussion of the chemical of interest to each chemical manager.

Ernie Falke discussed the status of chemicals that will be considered at the NAC-30 and -31 meetings (Attachment 2). A possible change in the process by which Proposed AEGLs are announced in the Federal Register was discussed. Proposed AEGL chemicals could be listed in the Federal Register with a notice to go to the EPA web site to view the actual values as well as the technical support documents. A discussion among Ernie and several NAC members addressed the listing of several chemicals with low production data but that appear on lists of potential terrorist chemicals.

The highlights of the NAC/AEGL-29 meeting are summarized below along with the Meeting Agenda (Attachment 3) and the Attendee List (Attachment 4). The subject categories of the highlights do not necessarily follow the order listed in the NAC/AEGL-29 Agenda.

TECHNICAL ISSUE DISCUSSIONS

Revisit of Fundamental Principles of Industrial Hygiene
John Morawetz

John Morawetz discussed the five points to be considered in evaluation of occupational studies (Attachment 5). These points are under consideration for addition to the SOPs. John stressed the need for personal sampling data in using human studies to set AEGL values and the need to always associate an exposure level with a sampling time. He reiterated the problems associated with other types of monitoring data including the different types of occupational samples, variability in sampling time, variability in exposures in the work environment, and the different types of collection devices. Although there was general agreement with all five statements suggested by John, there was further discussion on rearranging and/or combining points. These included moving point 2 to point 1, combining points 1 and 4, and omitting point 5. There should also be inclusion of the statement that other routes of exposure (other than inhalation) are recognized. Richard Niemeier reported that the Health Hazard Evaluation program has a monitoring data base, but it is not easily searchable. George Rusch recommended that the committee vote on this issue electronically before the next meeting.

Industrial Hygiene/Emergency Planning Considerations in AEGL Development
Edward Bishop (NRC/COT AEGL Subcommittee)

Ed Bishop, an industrial hygienist, environmental engineer, member of the National Academy of Sciences Subcommittee on AEGLs, and lead COT reviewer for the nerve agent AEGLs, presented his address to the Chemical Stockpile Emergency Preparedness Program (CSEPP) National Preparedness Workshop entitled, "AEGLs and CSEPP." The Workshop was held in Mobile, AL, on June 24-26, 2003. The CSEPP, jointly managed and supported by FEMA and the Department of the Army, provides technical and training support for chemical warfare agent emergency preparedness in the states where agent stockpiles are located. During a short introductory

discussion of industrial hygiene considerations, Ed stressed the necessity for rigorous evaluation of occupational monitoring data. He noted that exposure assessments from exposure reconstructions are generally poor. For emergency planning, planners first consider hazard vs toxicity. For example, for high-production volume chemicals, the first question should be, "is there a hazard?" Extremely hazardous chemicals are considered first. Transport and storage of chemicals also need to be considered. For emergency planners, the AEGL-1 is considered a notification level, not an evacuation level (evacuations have their own risk). For the AEGL-2, which is an evacuation or shelter-in-place level, mitigations should be considered ahead of time. These include storage of insufficient quantities to reach an AEGL-2 level, implementation of a public risk communication program, and issuance of evacuation or shelter-in-place procedures. As an example of risk communication, Ed discussed his role as a National Academy of Sciences member in communicating the safety of the AEGL-1 for nerve agents that are stored at the Anniston, AL, depot. Ed pointed out that the final adjustment factors for VX AEGLs were those recommended by the COT and were reductions of those originally recommended by the NAC. The talk was followed by a discussion among Ed, John Morawetz, and other NAC members concerning evaluation of industrial hygiene studies. There appeared to be a general consensus among participants concerning the definition of an adequate monitoring study.

Derivation of an Uncertainty Factor for NOAEL to LOAEL Extrapolation
George Alexeeff

George Alexeeff discussed his findings on extrapolation from LOAELs to NOAELs for mild health effects (Attachment 6). This work is published in *Regulatory Toxicology and Pharmacology* 36:96-195 (2002). The results are based on 40 hazardous air pollutants (88 data sets). George listed the signs and symptoms identified with mild health effects. Ratios of LOAELS to NOAELs ranged from 1.1 to 13.8 (median 2.0). The 95th percentile was 6.3. Results were not affected by species, group size, exposure duration, or endpoint. Paul Tobin pointed out that thresholds for AEGLs are neither NOAELs or LOAELs but somewhere in between; using either NOAEls or LOAELS reduced by certain factors may be conservative. With approval of the NAC/AEGL a description of George's findings along with how the NAC/AEGL will use this information will be placed in the SOPs.

Categorizing the Signs and Symptoms at the AEGL and Sub-AEGL
George Alexeeff

George Alexeeff passed out summary sheets of effects used as endpoints at the sub-AEGL-1, AEGL-1, and AEGL-2 levels (Attachment 7). These descriptors will be added to the USEPA web site.

AEGL Application in Emergency Planning
Robert Snyder

Robert Snyder demonstrated an Emergency Response Center program that integrates AEGL levels with chemical release modeling data over time. This program identifies the time and distance at which AEGL concentrations are reached downwind following a release. The model can be specific for geographic areas/cities in that vulnerable sites (schools, hospitals) and sites of emergency responders can be mapped. A chlorine release was used as an example of both emergency planning and an educational tool. A question arose concerning the use of averaging AEGL concentrations across time intervals vs using the specific time intervals set by the NAC.

Relevance of Developmental Endpoints
Marcel van Raaij

Marcel van Raaij stressed that developmental toxicity is a relevant endpoint for setting AEGL values. He evaluated data for single day vs multiple exposures (i.e. regular guideline based developmental studies) in order to determine which effects observed in regular guideline based studies were relevant or useful for setting acute health limits. Comparisons were made for a specific species-substance-route-effect combination. Endpoints of interest were: maternal toxicity, resorptions, fetal body weight, and malformations. For most endpoints, higher doses were required for single exposure studies to get the same effect as from a repeat dose.

It was indicated that general maternal toxicity in regular guideline studies is not a good indicator for acute effects. Resorptions can be induced in single dose studies with similar doses (or slightly higher) than those used in repeated dose studies. Fetal body weight analysis showed variable data. For some substance-species-route combination there was no difference in the NOAEL/LOAEL values between single and repeated doses while for others a substantial difference was observed (NOAEL/LOAEL about 4-5 fold higher in single dose studies). This requires a case-by-case evaluation taking into account also other developmental effects. For malformations, a similar pictures was found (no difference for some, substantial difference for others). By default, it was proposed to consider malformations as relevant endpoints for acute limit setting, unless information was available to indicate the contrary. The full report of this investigation can be downloaded from the RIVM-website (www.rivm.nl).

Review of Criteria Document of Simple Asphyxiants
Marcel van Raaij (Author)
Jonathan Borak (Chemical Manager)
George Rusch and George Rodgers (Chemical Managers)

Marcel presented highlights from his paper on simple asphyxiants (Attachment 8). The purpose is to develop criteria for handling hypoxia within the scope of AEGLs. So, the document is intended to serve as a guideline for handling the effect of asphyxia rather than handling asphyxiants per se. Discussion covered starting points, physiological response to hypoxia, susceptible populations including individuals with obstructive pulmonary and cardiovascular diseases and individuals with reduced oxygen transport capacity. Comments on susceptible populations were made (e.g. sickle cell anemia). Endpoints for hypoxia could be correlated with the arterial saturation level.

Data for effects at different levels of arterial oxygen saturation were taken from high altitude physiology, air travel, and experimental observations on patients with coronary or pulmonary diseases. Levels of 80% (190,000 ppm) and 65% arterial oxygen saturation (330,000 ppm) were suggested for the AEGL-2 and -3, respectively. No AEGL-1 was proposed. It was agreed that comments could be sent to the author before August 2003. The description of the clinical part of the document should be edited and additional attention should be paid to the 10-minute interval.

REVIEW of PRIORITY CHEMICALS

Revisit of Nickel Carbonyl AEGL-2
(CAS No. 13463-39-3)

Chemical Manager: Ernie Falke, EPA
Staff Scientist: Bob Young, ORNL

In response to concerns expressed by the COT AEGL Subcommittee, the AEGL-2 for nickel carbonyl was revisited for the second time (Attachment 9). Following earlier derivations, the COT stated that death or unknown health status of dams at the concentrations chosen as the points of departure for the AEGL-2 (1998: 8.4 ppm for the hamster, Sunderman et al. 1980; and 2002: 11 ppm for the rat Sunderman et al. 1979) precluded the contention that nickel carbonyl is a developmental toxicant (developmental toxicity was originally chosen as the AEGL-2 endpoint). Because dams died or their health status was unknown at concentrations that caused malformations, the COT stated that the data do not support the contention that nickel is a selective developmental toxin. A discussion of malformations as a toxicant endpoint as well as the relative sensitivity of the rat, mouse, and hamster for the endpoint of developmental toxicity ensued. The NAC tended to accept malformations as an AEGL endpoint. A suggestion for reducing the AEGL-3 value by 3 in order to derive an AEGL-2 value was also entertained. However, the NAC chose to use the available data rather than dividing the AEGL-3 by 3. It was moved by Bob Benson and seconded by Tom Hornshaw to use 2.17 ppm, a 30-minute non-lethal value for the mouse, the most sensitive species in lethality studies, as the point of departure for the AEGL-2. This value was divided by inter- and intraspecies uncertainty factors of 3 each for a total of 10 and a modifying factor of 3. In the absence of time-scaling data, the default n values of 3 and 1 had previously been established. The resulting values for the 10-minute through 8-hour exposure durations are 0.10, 0.72, 0.036, 0.0090, and 0.0045 ppm, respectively. The motion passed (YES: 13; NO: 3; ABSTAIN: 0) (Appendix B). The AEGL-3 values will be retained. Justification for not using the hamster data needs to be added to the TSD.

Benzene
CAS Reg. No.71-43-2

Chemical Manager: Robert Snyder,
Staff Scientist: Marcel van Raaij, RIVM, The Netherlands

The chemical revisit/review on benzene was presented by Marcel van Raaij (Attachment 10). The AEGL-1 values of benzene had been accepted at the NAC-27 meeting in December 2002. The endpoint for the AEGL-1 was absence of CNS effects in humans exposed to 110 ppm for 2 h; there were several support studies. AEGL-1 values were 127, 73, 52, 18, and 9 ppm for 10 minutes, 30 minutes, 1 hour, 4 hours, and 8 hours respectively.

Marcel discussed studies relevant to derivation of AEGL-2 and AEGL-3 values, noting the lack of clinical studies compared with toluene. Therefore, an animal neurobehavioral study with the rat (Molnar et al. 1986) was suggested for the AEGL-2, and the same study with the endpoint of no deaths (Molnar et al. 1986) was suggested for the AEGL-3. The various indications from (old) occupational and some case studies, with exposures over 1000 ppm, was suggested to serve as a back-ground framework, although caveats are present with most of these studies. At this point there was a lengthy discussion of the quality of the monitoring studies, and how the information from these studies might be used or interpreted. In particular the usefulness of area sampling values (from historic literature) for human exposure was discussed. John Morawetz moved to remove the study of Greenberg et al. (1926, 1939) from the derivation section because the exposure duration was only 20 minutes and involved an area sample. The motion was seconded by George Alexeeff. The motion failed (YES: 7; NO: 9; ABSTAIN: 0) (Appendix C). In addition, Morawetz made comments on the description of studies by Midzenski et al. (1992) and Wong (2002), especially with respect to the derivation sections. John Hinz and George Alexeeff proposed to shorten the description of the monitoring studies in derivation sections and to refer back to the primary study summaries. After considerable discussion it was decided that reference to the human studies (which are not inconsistent with the AEGL values) in the derivation sections for AEGL-2 and AEGL-3 will be reduced as possible, and if referenced, their limitations would be clearly described in order to provide the same message in the derivation sections as in the primary study summaries.

At this point, John Hinz moved and Bill Bress seconded AEGL-2 values of 2000, 1100, 800, 400, and 200 ppm based on a 4-hour no-effect level for adverse locomotor depression (CNS-related effect) of 4000 ppm with the rat. Inter- and intraspecies uncertainty factors of 3 each for a total of 10 were applied. These uncertainty factors are adequate as higher values do not comply with the (limited) human experience (occupational exposures above 1000 ppm), and CNS depression does not vary by more than a factor of 2-3 in the human population. In addition, higher uncertainty factors would provide AEGL-values that do not match the values of toluene and xylene. Time scaling was based on n values of 2 for shorter exposure durations and 1 for longer exposure durations. The data of von Oettingen had shown that a value of 3 for the shorter exposure durations was too conservative. The motion passed (YES: 14; NO: 2; ABSTAIN: 1) (Appendix D).

A motion was made by John Hinz and seconded by Mark McClanahan to accept AEGL-3 values of 9700, 5600, 4000, 2000, and 990 ppm based on no deaths in rats exposed to 5900 ppm for 4 hours (Molnar et al. 1986). Inter- and intraspecies uncertainty factors of 1 (based on allometric arguments as evidenced by the data on toluene), and 3 (see above), respectively, were applied.

Time scaling utilized n values of 2 and 1 as for the AEGL-2 above. The AEGL-values are supported by Svirbely et al. (1943). In addition, the (high) values for the 10 and 30 minutes are supported by a range of animal data. The motion passed (YES: 15: NO: 1; ABSTAIN: 1) (Appendix D).

Summary of AEGL Values for Benzene						
Classification	**10-minute**	**30-minute**	**1-hour**	**4-hour**	**8-hour**	**Endpoint (Reference)**
AEGL–1	127 ppm	73 ppm	52 ppm	18 ppm	9 ppm	Derived earlier
AEGL–2	2000 ppm	1100 ppm	800 ppm	400 ppm	200 ppm	NOAEL, CNS effects - rat (Molnar et al. 1986)
AEGL–3	9700 ppm	5600 ppm	4000 ppm	2000 ppm	990 ppm	NOAEL for mortality in rats (Molnar et al. 1986)

Chlorine Pentafluoride
CAS No. 13637-63-3

Staff Scientist: Sylvia Talmage, ORNL
Chemical manager: Bill Bress, ASTHO

Sylvia Talmage reviewed the data base on chlorine pentafluoride, a strong oxidizing chemical once proposed for use as a rocket fuel (Attachment 11). Only animal data were available. The AEGL-3 was based on the highest 1-hour non-lethal value of 80 ppm for the rat (Darmer et al. 1972). The calculated $BMCL_{05}$ was the same value (81 ppm). The rat data were used because they provided the best dose-response relationship and because group sizes were larger for the rat than for the monkey or dog. The 80 ppm was adjusted by interspecies and intraspecies uncertainty factors of 3 each for a total of 10. Time scaling was based on the same rat lethality data which covered exposure durations from 15 minutes to 1 hour. The time-scaled exponent (n) was 2. It was moved by John Hinz and seconded by Steve Barbee to accept AEGL-3 values of 20, 11, 8, 4, and 2.8 ppm for the 10-minute through 8-hour exposure durations. The motion passed unanimously (YES: 17; NO: 0; Abstain: 0) (Appendix E).

The proposed AEGL-2 was based on a series of studies with monkeys, dogs, rats, and mice (MacEwen and Vernot 1972, 1973). Exposures were to 5 or 10 ppm for 60 minutes, 20 ppm for 30 minutes, and 30 ppm for 10 minutes. Following discussion of which series of studies to use, it was decided to use the higher value of 10 ppm at the 60-minute exposure and the respective values at the 10 and 30-minute exposures. Each of these concentrations was adjusted by interspecies and intraspecies uncertainty factors of 3 each for a total of 10. The 4- and 8-hour values were extrapolated from the 1-hour value. It was moved by John Hinz and seconded by Bob Snyder to accept AEGL-2 values of 3, 2, 1, 0.5, and 0.36 ppm for the 10-minute through 8-hour exposure durations. The motion passed (YES: 14; NO: 1; ABSTAIN: 1) (Appendix E).

The proposed AEGL-1 value was based on a NOAEL for signs of irritation in the rat (MacEwen and Vernot 1973). The TSD author suggested dividing this value by interspecies and intraspecies uncertainty factors of 10 and 3, respectively, in order to obtain a value consistent with the breakdown product, HF (AEGL-1 = 1 ppm) and the related chemical, ClF_3 (AEGL-1 = 0.12 ppm). The NAC agreed with the 3 ppm concentration, but adjusted by intraspecies and interspecies uncertainty factors of 3 each for a total of 10. The resulting 0.3 ppm was used across all exposure durations because there is adaptation to the slight irritation that defines the AEGL-1. The motion passed (YES: 13; NO: 4; ABSTAIN: 0) (Appendix E). It was noted that the 8-hour AEGL-1 of 0.3 ppm is essentially the same value as the 8-hour AEGL-2 of 0.36 ppm.

Summary of AEGL Values for Chlorine Pentafluoride						
Classification	**10-minute**	**30-minute**	**1-hour**	**4-hour**	**8-hour**	**Endpoint (Reference)**
AEGL-1	0.30 ppm	0.30 ppm	0.30 ppm	0.30 ppm	0.30 ppm	No signs of sensory irritation - rat (MacEwen and Vernot 1973)
AEGL-2	3.0 ppm	2.0 ppm	1.0 ppm	0.50 ppm	0.36 ppm	Lacrimation, salivation - monkey, rat, mouse (MacEwen and Vernot 1972)
AEGL-3	20 ppm	11 ppm	8.0 ppm	4.0 ppm	2.8 ppm	Highest non-lethal value, $BMCL_{05}$ - rat (Darmer et al. 1972)

Bromine pentafluoride
CAS No. 7789-30-2

Staff Scientist: Sylvia Talmage, ORNL
Chemical Manager: Bill Bress, ASTHO

Sylvia Talmage described the data base for bromine pentafluoride (Attachment 12). The data base consisted of a single lethality study with the rat, conducted at two concentrations (Dost et al. 1968, 1970). The AEGL-3 was based on the highest non-lethal value in this study, 500 ppm for 40 minutes. This concentration was divided by inter- and intraspecies uncertainty factors of 3 each for a total of 10 and time scaled using the default values for n of 3 for shorter time intervals and 1 for longer time intervals. In the absence of conflicting data, a total uncertainty factor of 10 for irritants has been acceptable to the NAC and the COT. It was moved by Bob Benson and seconded by John Hinz to accept the resulting values of 79, 55, 33, 8.3 and 4.2 ppm for the 10-minute through 8-hour exposure durations, respectively. The motion passed unanimously (YES: 16; NO: 0; ABSTAIN 0) (Appendix F).

In the absence of data for the AEGL-2, the values for chlorine pentafluoride were used. These values are acceptable as bromine pentafluoride has been shown to be less reactive and slightly less toxic than chlorine pentafluoride. Tom Hornshaw moved and Bill Bress seconded the motion that AEGL-2 values of 3.0, 2.0, 1.0, 0.50, and 0.36 ppm be accepted. The motion passed unanimously (YES: 16; NO: 0; ABSTAIN: 0) (Appendix F).

It was decided that, in the absence of data, the AEGL-1 values for bromine pentafluoride would not be set equal to the AEGL-1 values for chlorine pentafluoride. It was moved by George Alexeeff and seconded by Nancy Kim to use NR (not recommended) for the AEGL-1 due to the absence of data. The motion passed (YES: 12; NO: 3; ABSTAIN: 2) (Appendix F). It was then moved and seconded by Richard Niemeier and Loren Koller, respectively, to add a notation below the summary table that emergency responders may refer to chlorine pentafluoride or chlorine trifluoride for AEGL-1 values. The motion did not pass (YES: 6; NO: 7; ABSTAIN: 4) (Appendix F). The NAC noted that if this chemical becomes important to some agency, it would be beneficial to have additional testing done to improve the precision of the data.

Summary of AEGL Values for Bromine Pentafluoride						
Classification	**10-minute**	**30-minute**	**1-hour**	**4-hour**	**8-hour**	**Endpoint (Reference)**
AEGL-1	NR[a]	NR	NR	NR	NR	
AEGL-2	3.0 ppm	2.0 ppm	1.0 ppm	0.50 ppm	0.36 ppm	Based on analogy with chlorine pentafluoride
AEGL-3	79 ppm	55 ppm	33 ppm	8.3 ppm	4.2 ppm	Highest non-lethal value - rat (Dost et al. 1970)

NR: AEGL-1 values are not recommended due to the lack of data.

Nitric acid
CAS No. 7697-37-2

Staff Scientist: Carol Wood, ORNL
Chemical Manager: Loren Koller, OSU (retired)

Carol Wood reviewed the history of and data for nitric acid (Attachment 13). Values had been adopted in 1997, but the key studies for the AEGL-2 and AEGL-3 were questionable. At the present meeting, an additional study (DuPont 1987) was made available. This study was a nose-only exposure of rats to >70% respirable particles of nitric acid; nitrogen dioxide was monitored and not detected. The AEGL-3 was based on the 1-hour LC_{01}, calculated from the LC_{50} study by log-probit analysis. The resulting 1-hour LC_{01} of 919 ppm was used to derive AEGL-3 values. Values were scaled using the equation $C^n \times t = k$ where n ranges from 0.8 to 3.5 (ten Berge et al. 1986). In the absence of an empirically derived, chemical-specific exponent, scaling was performed using n = 3 for extrapolating to the 10- and 30-minute time points and n = 1 for the 4- and 8-hour time points. An total uncertainty factor of 10 was used including a 3 for interspecies

extrapolation and 3 for intraspecies extrapolation. It was moved by Loren Koller and seconded by Richard Niemeier to accept values of 170, 120, 92, 23, and 11 ppm for the 10-minute through 8-hour exposure durations, respectively. The motion passed (YES: 12; NO: 3; ABSTAIN: 1) (Appendix G). Ernie Falke stated that the above scenario is not realistic and that nitric acid will convert to nitrogen dioxide. Therefore, the values should defer to nitrogen dioxide.

The same study (DuPont 1987) served as the basis for the AEGL-2. Discussion centered around options for the point of departure: one-third of the AEGL-3, the non-lethal value of 470 ppm, or a lower, no-effect value of 260 ppm. A concern over the presence of ulcers on the noses of confined rats was answered by a telephone call to Dave Kelly, author of the DuPont study (the ulcers were an artifact of the exposure method). The accepted point of departure was a 1-hour exposure of rats to 470 ppm which resulted in transient body weight loss 1-2 days post-exposure. In the absence of an empirically derived, chemical-specific exponent, scaling was performed using n = 3 for extrapolating to the 10- and 30-minute time points and n = 1 for the 4- and 8-hour time points. A total uncertainty factor of 10 was used including a 3 for interspecies extrapolation and 3 for intraspecies extrapolation. In addition, a modifying factor of 2 was applied because clinical observations were not well described, a concentration-response could not be determined for nonlethal effects, and clear evidence of AEGL-2 effects was not available in the study. As supporting evidence, no effects or cancer were observed in rats exposed to 19 ppm 6 hr/day every other day for a total of 6 exposures followed by observation for 22 months. It was moved by Steve Barbee and seconded by Bob Snyder (with the provision that the NAC sees the final document) to accept values of 43, 30, 24, 6, and 3 ppm for the 10-minute through 8-hour exposure durations, respectively. The motion passed (YES: 12; NO: 2; ABSTAIN: 0) (Appendix G).

For the AEGL-1, a 30-minute through 8-hour value of 0.53 ppm had been adopted previously. The highest NOAEL in humans of 1.6 ppm for 10 minutes was used to derive AEGL-1 values. An uncertainty factor of 3 was applied to account for sensitive populations since both human and animal data suggest that asthmatics may be especially sensitive to acidic atmospheres. Extrapolations were not performed because this was based on a no-effect level and because irritation is generally concentration dependent but not time dependent. It was moved by Bob Benson and seconded by McClanahan to adopt the same value for the 10-minute exposure duration. The motion passed unanimously by a show of hands.

Summary of AEGL Values for Nitric Acid

Classification	10-minute	30-minute	1-hour	4-hour	8-hour	Endpoint (Reference)
AEGL-1	0.5 ppm	0.5 ppm	0.5 ppm	0.5 ppm	0.5 ppm	NOAEL for irritation - humans
AEGL-2	43 ppm	30 ppm	24 ppm	6 ppm	3 ppm	Transient weight loss - rat (DuPont 1987)
AEGL-3	170 ppm	120 ppm	92 ppm	23 ppm	11 ppm	LC_{01} - rat (DuPont 1987)

Hydrogen Selenide
CAS No. 7783-07-5

Staff Scientist: Carol Wood, ORNL
Chemical manager: Robert Snyder, Rutgers University/EOHSI

Carol Wood presented the data on hydrogen selenide (Attachment 14). The AEGL-3 was based on an estimated LC_{01} of 66 ppm obtained by a log-probit analysis of data from a 1-hour LC_{50} study in Wistar rats (Zwart and Arts 1989). Values were scaled using the equation $C^n \times t = k$ where n ranges from 0.8 to 3.5 (ten Berge et al. 1986). A value of n = 2 was calculated by Zwart and Arts (1989) from a probit analysis of lethality data in the rat. A total uncertainty factor of 30 was applied which includes 3 to account for sensitive individuals and 10 for interspecies extrapolation. The intraspecies uncertainty factor of 3 is considered sufficient due to the relatively steep concentration-response relationship with regard to lethality in rats, suggesting little individual variability. An interspecies UF of 10 is needed because data were available in only two species and the limited data available indicate that the rat is not the most sensitive. Bob Benson moved and Steve Barbee seconded the motion to accept the AEGL-3 values for the 10-minute through 8-hour exposure durations of 5.4, 3.1, 2.2, 1.1, and 0.78 ppm, respectively. The motion passed (YES: 14; NO: 1; ABSTAIN: 0) (Appendix H).

Because no data with appropriate endpoints were found, the AEGL-2 was derived by dividing the AEGL-3 by 3. The motion was made by Ernie Falke and seconded by Richard Niemeier to accept values of 1.8, 1.0, 0.73, 0.37, and 0.26 ppm. The motion passed (YES: 12; NO: 3; ABSTAIN: 1) (Appendix H).

An AEGL-1 was not recommended because no data with the appropriate endpoints were found. The motion was made by Mark McClanahan and seconded by Steve Barbee to not recommend an AEGL-1. The motion passed with a show of hands.

Summary of AEGL Values for Hydrogen Selenide						
Classification	**10-minute**	**30-minute**	**1-hour**	**4-hour**	**8-hour**	**Endpoint (Reference)**
AEGL–1	NR[a]	NR	NR	NR	NR	
AEGL–2	1.8	1.0	0.73	0.37	0.26	One-third of the AEGL-3
AEGL–3	5.4	3.1	2.2	1.1	0.78	1-hour LC_{01} - mouse (Zwart and Arts 1989)

NR: AEGL-1 values are not recommended due to the lack of data.

Methyl thiocyanate
CAS No.

Staff Scientist: Carol Wood, ORNL
Chemical Manager:

Carol Wood noted the lack of data for methyl thiocyanate, other than an intraperitoneal injection study with mice (Attachment 15). Two options were presented: (1) values should not be recommended (NR), or (2) adopt HCN values, based on the breakdown of methyl thiocyanate to HCN. However, there was no data on relative potency. It was moved by Ernie Falke and seconded by Loren Koller to not adopt values. The motion passed (YES: 12; NO: 1; ABSTAIN: 1) (Appendix I). The chemical will not be forwarded to the National Academy of Sciences.

Bromine trifluoride
CAS No. 7787-71-5)

Staff Scientist: Sylvia Talmage, ORNL
Chemical Manager: Bill Bress, ASTHO

In the absence of any data, Sylvia Talmage proposed using the AEGL values for the chemical analogue, chlorine trifluoride (Attachment 16). Information on chemical reactivity and toxicity shows that bromine fluorides are less reactive and less toxic than chlorine fluorides. Therefore, using the chlorine trifluoride values, which are based on empirical data, would be conservative. The chlorine trifluoride values were based on studies with rats and dogs in which slight irritation (Horn and Weir 1956), severe irritation (Horn and Weir 1955), and the LC_{01} for the mouse (MacEwen and Vernot 1970), were endpoints for the AEGL-1, -2, and -3, respectively. It was moved by Ernie Falke and seconded by Mark McClanahan to adopt the chlorine trifluoride values for bromine trifluoride. The motion passed (YES: 14; NO: 1; ABSTAIN: 0) (Appendix J). The values appear in the table below. The NAC suggested adding a caveat to the TSD to the effect that, if the chemical becomes important, additional testing be done.

Summary of AEGL Values for Bromine Trifluoride						
Classification	**10-minute**	**30-minute**	**1-hour**	**4-hour**	**8-hour**	**Endpoint (Reference)**
AEGL–1	0.12 ppm	0.12 ppm	0.12 ppm	0.12 ppm	0.12 ppm	Analogy with chlorine trifluoride
AEGL–2	6.20 ppm	6.2 ppm	3.1 ppm	0.77 ppm	0.39 ppm	Analogy with chlorine trifluoride
AEGL–3	81 ppm	27 ppm	14 ppm	3.4 ppm	1.7 ppm	Analogy with chlorine trifluoride

Revisit of Formaldehyde AEGL-1 and Time-Scaling of AEGL-3
CAS No. 50-00-0

Chemical Manager: Mark McClanahan

Staff Scientist: Sylvia Talmage, ORNL

The AEGL-1 value of 0.41 ppm, passed at the NAC-28 meeting, was reconsidered because the study on which the value was based was flawed (Attachment 17). Sylvia Talmage pointed out that not only did the study authors find irritation at levels not irritating in approximately 20 other well-conducted clinical studies, but the authors did not take analytical measurements. Following review of the clinical studies, there was a debate as to the perception of mild vs moderate irritation. Sylvia Talmage suggested using 3 ppm for the AEGL-1, based on an average irritation score of mild in over 100 subjects. It was moved by Bob Benson and seconded by Steve Barbee to use the NOAEL for slight irritation of 0.9 ppm for the AEGL-1. This was the highest exposure of subjects whose eyes were sensitive to formaldehyde at which the subjects' "responses were not significantly different from clean air" (Bender et al. 1983). At 1 ppm there was slight to moderate eye irritation. Exposures were eye-only for 6 minutes. The 0.9 ppm was used across all exposure durations. The motion passed (YES: 11; NO: 3; ABSTAIN: 0) (Appendix K).

At the NAC-28 meeting, time scaling for the AEGL-3 was based on two LC_{50} values for the rat. The value of n was 3.9. In the meantime, another LC_{50} study was located. Sylvia Talmage presented graphs of the n values using the rat and mouse data separately and combined. The value of n ranged from 1.4 (mouse data) to 2.4 (rat data). However, based on the age of the studies and flaws in most of the studies, the default n values of 3 and 1 appeared appropriate. The point of departure remained the same, a 4-hour non-lethal value of 350 ppm for the rat (Nagorny et al. 1979). The adjusted 10-minute to 8-hour values were 100, 70, 56, 35, and 35 ppm, respectively (the 8-hour value was set equal to the 4-hour value because formaldehyde is well scrubbed in the nasal passages). It was moved by Mark McClanahan and seconded by Ernie Falke to accept the adjusted values. The motion passed (YES: 11; NO: 1; ABSTAIN: 2) (Appendix K).

Administrative Matters

The site and time of the next meeting, NAC/AEGL-30, will be September 16-18, 2003 in Washington, D.C. The date for NAC/AEGL-31 has been set tentatively as December 10-12, 2003 in San Antonio, Texas. John Hinz will provide more details on the December meeting.

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

LIST OF ATTACHMENTS

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

Attachment 1. Chemical Manager sheet
Attachment 2. Status update of chemicals to be considered at the NAC-30 and -31
Attachment 3. NAC/AEGL-29 Meeting Agenda
Attachment 4. NAC/AEGL-29 Attendee List
Attachment 5. Revised Proposal for Evaluation of Occupational Monitoring Studies for inclusion in TSDs
Attachment 6. Evaluation of Data for LOAEL to NOAEL Extrapolation
Attachment 7. Categorizing the Signs and Symptoms at the AEGL sub-1, 1, and 2 Levels
Attachment 8. Criteria for Simple Asphyxiants
Attachment 9. Data Analysis of Nickel Carbonyl
Attachment 10. Data Analysis of Benzene
Attachment 11. Data Analysis of Chlorine Pentafluoride
Attachment 12. Data Analysis of Bromine Pentafluoride
Attachment 13. Data Analysis of Nitric Acid
Attachment 14. Data Analysis of Hydrogen Selenide
Attachment 15. Data Analysis of Methyl Thiocyanate
Attachment 16. Data Analysis of Bromine Trifluoride
Attachment 17. Data Analysis of Formaldehyde

LIST OF APPENDICES

Appendix A. Revised meeting highlights of NAC/AEGL-28
Appendix B. Ballot for nickel carbonyl
Appendix C. Ballot for omitting human studies in benzene derivation
Appendix D. Ballot for benzene
Appendix E. Ballot for chlorine pentafluoride
Appendix F. Ballot for bromine pentafluoride
Appendix G. Ballot for nitric acid
Appendix H. Ballot for hydrogen selenide
Appendix I. Ballot for methyl thiocyanate
Appendix J. Ballot for bromine trifluoride
Appendix K. Ballot for formaldehyde

NAC/AEGL Meeting 30: September 16-18, 2003

Chemical: PHOSPHORUS TRICHLORIDE **CAS Reg. No.:**

NAC Member	AEGL1	AEGL2	AEGL3	LOA	NAC Member	AEGL1	AEGL 2	AEGL3	LOA
George Alexeeff					Nancy Kim				
Steven Barbee					Loren Koller				
Lynn Beasley					Glenn Leach				
David Belluck					Mark McClanahan				
Robert Benson					John Morawetz				
Jonathan Borak					Richard Niemeier				
William Bress					Marinelle Payton				
George Cushmac					Zarena Post				
Al Dietz					George Rodgers				
Ernest Falke					George Rusch, Chair				
Larry Gephart					Robert Snyder				
John Hinz					Thomas Sobotka				
Jim Holler					Kenneth Still				
Thomas Hornshaw					Richard Thomas				
					TALLY				

Raise to Interim - UNANIMOUS

PPM, (mg/m^3)	10 Min	30 Min	1 Hr	4 Hr	8 Hr
AEGL 1	, ( )	, ( )	, ( )	, ( )	, ( )
AEGL 2	, ( )	, ( )	, ( )	, ( )	, ( )
AEGL 3	, ( )	, ( )	, ( )	, ( )	, ( )
LOA					

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:** 9/16/03

NAC/AEGL Meeting 30: September 16-18, 2003

Chemical: ACETONE CYANOHYDRIN **CAS Reg. No.:**

NAC Member	AEGL1	AEGL2	AEGL3	LOA	NAC Member	AEGL1	AEGL 2	AEGL3	LOA
George Alexeeff	A	→	→		Nancy Kim	A	→		
Steven Barbee	A				Loren Koller	Y			
Lynn Beasley	Y				Glenn Leach	Y			
David Belluck	Y				Mark McClanahan	A			
Robert Benson	Y				John Morawetz	Y			
Jonathan Borak	Y				Richard Niemeier	Y			
William Bress	Y				Marinelle Payton	Y			
George Cushmac	Y				Zarena Post	A			
Al Dietz	A				George Rodgers	Y			
Ernest Falke	Y				George Rusch, Chair	Y			
Larry Gephart	Y				Robert Snyder	Y			
John Hinz	Y				~~Thomas Sobotka~~				
Jim Holler	Y				~~Kenneth Still~~				
Thomas Hornshaw	Y				Richard Thomas	Y			
					TALLY	20/20			

Raise to Interim

PPM, (mg/m³)	10 Min	30 Min	1 Hr	4 Hr	8 Hr
AEGL 1	~~2.5~~ 2.2 ( )	~~2.5~~ 2.2 , ( )	~~2.0~~ 1.7 , ( )	~~1.3~~ 1.1 , ( )	~~1.1~~ 0.70 , ( )
AEGL 2	17 , ( )	10 , ( )	7.1 , ( )	3.5 , ( )	2.5 , ( )
AEGL 3	37 , ( )	21 , ( )	15 , ( )	8.6 , ( )	6.6 , ( )
LOA					

AEGL 1 Motion by: Falke **Second by:** 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:** 9/17/03

NAC/AEGL Meeting 30: September 16-18, 2003

Chemical: FLUORINE JET FUEL 8 MONOCHLOROACETIC ACID PHOSPHORUS OXYCHLORIDE **CAS Reg. No.:**

NAC Member	AEGL1	AEGL2	AEGL3	LOA	NAC Member	AEGL1	AEGL 2	AEGL3	LOA
George Alexeeff	P				Nancy Kim	P			
Steven Barbee	A				Loren Koller	YYYY			
Lynn Beasley	A				Glenn Leach	YYYY			
David Belluck	YYYY				Mark McClanahan	A			
Robert Benson	YYYY				John Morawetz	YYYY			
Jonathan Borak	A				Richard Niemeier	YYYY			
William Bress	YYYY				Marinelle Payton	A			
George Cushmac	YYYY				Zarena Post	A			
Al Dietz	A				George Rodgers	YYYY			
Ernest Falke	YYYY				George Rusch, Chair	AYYY			
Larry Gephart	YYYY				Robert Snyder	YYYY			
John Hinz	YYYY				Thomas Sobotka				
Jim Holler	A				Kenneth Still	YYYY			
Thomas Hornshaw	YYYY				Richard Thomas				
					TALLY				

Fluorine Jet Fuel 8, Mono-Chloroacetic Acid, Phosphorus Oxychloride

PPM, (mg/m³)	10 Min	30 Min	1 Hr	4 Hr	8 Hr
AEGL 1	,( )	,( )	,( )	,( )	,( )
AEGL 2	,( )	,( )	,( )	,( )	,( )
AEGL 3	,( )	,( )	,( )	,( )	,( )
LOA					

→ INTERIM

AEGL 1 Motion by: Niemeier **Second by:** Thomas

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

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

LOA Motion by: _____ **Second by:** _____

Approved by Chair: [signature] **DFO:** [signature] **Date:** 9/16/03

NAC/AEGL Meeting 30: September 16-18, 2003

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

NAC Member	AEGL1	AEGL2	AEGL3	LOA	NAC Member	AEGL1	AEGL 2	AEGL3	LOA
George Alexeeff	N				Nancy Kim	A			
Steven Barbee	A				Loren Koller	Y			
Lynn Beasley	A				Glenn Leach	A			
David Belluck	N				Mark McClanahan	A			
Robert Benson	P				John Morawetz	N			
Jonathan Borak	A				Richard Niemeier	Y			
William Bress	N				Marinelle Payton	A			
George Cushmac	N				Zarena Post	A			
Al Dietz	A				George Rodgers	Y			
Ernest Falke	Y				George Rusch, Chair	P			
Larry Gephart	Y				Robert Snyder	Y			
John Hinz	N				Thomas Sobotka	—			
Jim Holler	A				Kenneth Still	—			
Thomas Hornshaw	N				Richard Thomas	N			
					TALLY	6/14			

PPM, (mg/m^3)	10 Min	30 Min	1 Hr	4 Hr	8 Hr
AEGL 1	8.3, (32)	8.3, (32)	8.3, (32)	8.3, (32)	8.3, (32)
AEGL 2	66, (250)	66, (250)	53, (200)	33, (130)	26, (100)
AEGL 3	200, (750)	200, (750)	160, (600)	98, (380)	78, (300)
LOA					

Express as mg/m3

AEGL 1 Motion by: Rodgers **Second by:** Niemeier

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:** 9/16/03

NAC/AEGL Meeting 30: September 16-18, 2003

Chemical: STYRENE **CAS Reg. No.:** 100-42-5

NAC Member	AEGL1	AEGL2	AEGL3	LOA	NAC Member	AEGL1	AEGL 2	AEGL3	LOA
George Alexeeff	Y	N	Y		Nancy Kim	A	A	A	
Steven Barbee	A	A	A		Loren Koller	Y	Y	Y	
Lynn Beasley	Y	Y	Y		Glenn Leach	Y	Y	Y	
David Belluck	A	A	Y		Mark McClanahan	A	A	A	
Robert Benson	P	Y	Y		John Morawetz	Y	N	Y	
Jonathan Borak	A	A	A		Richard Niemeier	Y	Y	Y	
William Bress	Y	Y	Y		Marinelle Payton	A	A	A	
George Cushmac	Y	Y	Y		Zarena Post	A	A	A	
Al Dietz	A	A	A		George Rodgers	Y	Y	Y	
Ernest Falke	Y	Y	Y		George Rusch, Chair	Y	Y	Y	
Larry Gephart	Y	Y	Y		Robert Snyder	N	Y	Y	
John Hinz	Y	N	Y		Thomas Sobotka				
Jim Holler	A	A	A		Kenneth Still				
Thomas Hornshaw	Y	P	Y		Richard Thomas	A	Y	Y	
					TALLY	14/15	13/15	18/18	

PPM, (mg/m^3)	10 Min	30 Min	1 Hr	4 Hr	8 Hr
AEGL 1	20, ( )	20, ( )	20, ( )	20, ( )	20, ( )
AEGL 2	230, ( )	160, ( )	130, ( )	130, ( )	130, ( )
AEGL 3	1900 ( )	1900, ( )	1100 ( )	340, ( )	340, ( )
LOA	0.54 ppm - UNANIMOUS				

AEGL 1 Motion by: Rodgers **Second by:** Niemeier

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

AEGL 3 Motion by: Snyder **Second by:** Falke

LOA Motion by: _____ **Second by:** _____

Approved by Chair: [signature] **DFO:** Paul S. Tobin **Date:** 9/16/03

NAC/AEGL Meeting 30: September 16-18, 2003

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

NAC Member	AEGL1	AEGL2	AEGL3	LOA	NAC Member	AEGL1	AEGL 2	AEGL3	LOA
George Alexeeff	A				Nancy Kim	A			
Steven Barbee	A				Loren Koller	Y			
Lynn Beasley	Y				Glenn Leach	Y			
David Belluck	Y				Mark McClanahan	A			
Robert Benson	Y				John Morawetz	N			
Jonathan Borak	Y				Richard Niemeier	Y			
William Bress	Y				Marinelle Payton	Y			
George Cushmac	Y				Zarena Post	A			
Al Dietz	A				George Rodgers	Y			
Ernest Falke	Y				George Rusch, Chair	Y			
Larry Gephart	Y				Robert Snyder	Y			
John Hinz	Y				~~Thomas Sobotka~~				
Jim Holler	A				~~Kenneth Still~~				
Thomas Hornshaw	Y				Richard Thomas	A			
					TALLY				

PPM, (mg/m³)	10 Min	30 Min	1 Hr	4 Hr	8 Hr
AEGL 1	10,000 ,( )	6900 ,( )	5500 ,( )	5500 ,( )	5500 ,( )
AEGL 2 *	SEE BELOW 17,000)	,( )	,( )	,( )	,( )
AEGL 3 †	SEE BELOW 33,000)	,( )	,( )	,( )	,( )
LOA					

* Above 50% LEL → NOT IN TABLE † > LEL

AEGL 1 Motion by: Koller **Second by:** Hinz

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:** 9/17/03

NAC/AEGL Meeting 30: September 16-18, 2003

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

NAC Member	AEGL1	AEGL2	AEGL3	LOA	NAC Member	AEGL1	AEGL 2	AEGL3	LOA
George Alexeeff	A				Nancy Kim	A			
Steven Barbee	A				Loren Koller	Y			
Lynn Beasley	Y				Glenn Leach	Y			
David Belluck	Y				Mark McClanahan	A			
Robert Benson	Y				John Morawetz	N			
Jonathan Borak	Y				Richard Niemeier	Y			
William Bress	Y				Marinelle Payton	Y			
George Cushmac	Y				Zarena Post	A			
~~Al Dietz~~	~~A~~				George Rodgers	Y			
Ernest Falke	Y				George Rusch, Chair	Y			
Larry Gephart	Y				Robert Snyder	Y			
John Hinz	Y				~~Thomas Sobotka~~	~~A~~			
Jim Holler	P				~~Kenneth Still~~				
Thomas Hornshaw	Y				Richard Thomas	A			
					TALLY				

PPM, (mg/m³)	10 Min	30 Min	1 Hr	4 Hr	8 Hr
AEGL 1	10,000 ,( )	6900 ,( )	5500 ,( )	5500 ,( )	5500 ,( )
AEGL 2	25,000 ,( )	17,000 ,( )	17,000 ,( )	17,000 ,( )	17,000 ,( )
AEGL 3	76,000 ,( )	53,000 ,( )	53,000 ,( )	53,000 ,( )	53,000 ,( )
LOA					

> 50% LEL (LEL = 19,000) > 100% LEL

AEGL 1 **Motion by:** HINZ **Second by:** RODGER

AEGL 2 **Motion by:** ↓ **Second by:** ↓

AEGL 3 **Motion by:** ↓ **Second by:** ↓

LOA **Motion by:** _____ **Second by:** _____

Approved by Chair: [signature] **DFO:** [signature] **Date:** 9/17/03

NAC/AEGL Meeting 30: September 16-18, 2003

Chemical: DIMETHYL SULFATE **CAS Reg. No.:**

NAC Member	AEGL1	AEGL2	*AEGL3	LOA	NAC Member	AEGL1	AEGL 2	AEGL3	LOA
George Alexeeff	A		A		Nancy Kim	A		A	
Steven Barbee	A		A		Loren Koller	Y	Y	Y Y	
Lynn Beasley	Y	Y	Y Y		Glenn Leach	Y	Y	P Y	
David Belluck	Y	Y	Y Y		Mark McClanahan	A		A	
Robert Benson	Y	Y	P Y		John Morawetz	Y	Y	N Y	
Jonathan Borak	Y	Y	P Y		Richard Niemeier	Y	Y	N Y	
William Bress	Y	Y	N Y		Marinelle Payton	Y	Y	Y Y	
George Cushmac	Y	Y	P Y		Zarena Post	A		A	
Al Dietz	A		A		George Rodgers	Y	Y	N Y	
Ernest Falke	Y	Y	N Y		George Rusch, Chair	Y	Y	N Y	
Larry Gephart	Y	Y	N Y		Robert Snyder	Y	Y	Y Y	
John Hinz	P	P	P P		~~Thomas Sobotka~~				
Jim Holler	Y	Y	Y Y		~~Kenneth Still~~				
Thomas Hornshaw	Y	Y	N Y		Richard Thomas	Y	Y	N Y	
					TALLY	19/19	19/19	*6/15 DOESN'T PASS	19/19 #

PPM, (mg/m³)	10 Min	30 Min	1 Hr	4 Hr	8 Hr
AEGL 1	0.035 ,( )	0.035 ,( )	0.024 ,( )	0.012 ,( )	0.0087 ,( )
AEGL 2	0.17 ,( )	0.17 ,( )	0.12 ,( )	0.061 ,( )	0.043 ,( )
AEGL 3	*12 7.0 ,( )	6.9 2.3 ,( )	4.9 1.8 ,( )	2.5 0.82 ,( )	1.7 0.58 ,( )
LOA					

AEGL 1 Motion by: Koller **Second by:** Falke

AEGL 2 Motion by: ↓ **Second by:** ↓

AEGL 3 Motion by: * # Thomas **Second by:** * # Niemeier

LOA Motion by: **Second by:**

Approved by Chair: _____ **DFO:** Paula S. Tobin **Date:** 9/17/03

NAC/AEGL Meeting 30: September 16-18, 2003

Chemical: ACETONITRILE ≠ **CAS Reg. No.:**

NAC Member	AEGL1	AEGL2	AEGL3	LOA	NAC Member	AEGL1	AEGL 2	AEGL3	LOA
George Alexeeff	A		A		Nancy Kim	A	A	A	
Steven Barbee	A		A		Loren Koller	Y	Y	Y N	
Lynn Beasley	Y	Y	Y Y		Glenn Leach	Y	Y	Y Y	
David Belluck	N	Y	Y Y		Mark McClanahan	A	A	A	
Robert Benson	N	N	N Y		John Morawetz	N	P	Y Y	
Jonathan Borak	N	Y	Y Y		Richard Niemeier	N	Y	Y Y	
William Bress	N	Y	Y Y		Marinelle Payton	N	Y	Y Y	
George Cushmac	N	Y	Y Y		Zarena Post	A	A	A A	
~~Al Dietz~~					George Rodgers	Y	Y	Y Y	
Ernest Falke	Y	N	N Y		George Rusch, Chair	P	Y	Y Y	
Larry Gephart	N	Y	Y Y		Robert Snyder	Y	Y	Y Y	
John Hinz	P	Y	Y Y		~~Thomas Sobotka~~				
Jim Holler	P	Y	Y Y		~~Kenneth Still~~				
Thomas Hornshaw	N	P	P Y		Richard Thomas	Y	Y	Y Y	
					TALLY	7/17	16/18	~~16/18~~ 17/19	

≠ 19/20

PPM, (mg/m³)	10 Min	30 Min	1 Hr	4 Hr	8 Hr
AEGL 1	~~40~~ ≠13, ( )	~~40~~ ≠13, ( )	~~40~~ ≠13, ( )	~~40~~ ≠13, ( )	~~40~~ ≠13, ( )
AEGL 2	310, ( )	310, ( )	230, ( )	130, ( )	100, ( )
AEGL 3	650, ( )	650, ( )	490, ( )	280, ( )	210, ( )
LOA					

AEGL 1 **Motion by:** Rodgers Benson ≠ **Second by:** Hinz ≠ Morawetz

AEGL 2 **Motion by:** ↓ **Second by:** ↓

AEGL 3 **Motion by:** ↓ **Second by:** ↓

LOA **Motion by:** _____ **Second by:** _____

Approved by Chair: [signature] **DFO:** [signature] **Date:** 9/17/03

NAC/AEGL Meeting 30: September 16-18, 2003

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

NAC Member	AEGL1	AEGL2	AEGL3	LOA	NAC Member	AEGL1	AEGL 2	AEGL3	LOA
George Alexeeff	A	A	A		Nancy Kim	A	A	A	
Steven Barbee	A	A	A		Loren Koller	A	A	A	
Lynn Beasley	Y	Y	Y		Glenn Leach	Y	Y	Y	
David Belluck	Y	N	N		Mark McClanahan	A			
Robert Benson	Y	Y	Y		John Morawetz	Y	N	N	
Jonathan Borak	Y	Y	Y		Richard Niemeier	Y	Y	Y	
William Bress	Y	Y	Y		Marinelle Payton	Y	Y	Y	
George Cushmac	Y	Y	Y		Zarena Post	A	A	A	
~~Al Dietz~~					George Rodgers	N	Y	Y	
Ernest Falke	Y	Y	Y		George Rusch, Chair	Y	Y	Y	
Larry Gephart	Y	Y	Y		Robert Snyder	Y	Y	Y	
John Hinz	Y	Y	Y		~~Thomas Sobotka~~				
Jim Holler	Y	Y	Y		~~Kenneth Still~~				
Thomas Hornshaw	Y	N	N		Richard Thomas	A	A	A	
					TALLY	17/18	15/18	15/18	

PPM, (mg/m^3)	10 Min	30 Min	1 Hr	4 Hr	8 Hr
AEGL 1	NR, ( )	NR, ( )	NR, ( )	NR, ( )	NR, ( )
AEGL 2	33, ( )	23, ( )	18, ( )	11, ( )	7.5, ( )
AEGL 3	120, ( )	85, ( )	68, ( )	17, ( )	8.5, ( )
LOA					

AEGL 1 **Motion by:** Falke **Second by:** Hinz

AEGL 2 **Motion by:** ↓ **Second by:** ↓

AEGL 3 **Motion by:** ↓ **Second by:** ↓

LOA **Motion by:** _____ **Second by:** _____

Approved by Chair: [signature] **DFO:** [signature] **Date:** 9/17/03

NAC/AEGL Meeting 30: September 16-18, 2003

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

NAC Member	AEGL1	AEGL2	AEGL3	LOA	NAC Member	AEGL1	AEGL 2	AEGL3	LOA
George Alexeeff	A	A	A		Nancy Kim	A	A	A	
Steven Barbee	A	A	A		Loren Koller	A	A	A	
Lynn Beasley	Y	Y	Y		Glenn Leach	Y	Y	Y	
David Belluck	Y	Y	Y		Mark McClanahan	A	A	A	
Robert Benson	Y	Y	Y		John Morawetz	Y	Y	Y	
Jonathan Borak	Y	Y	Y		Richard Niemeier	Y	Y	Y	
William Bress	Y	Y	Y		Marinelle Payton	Y	Y	Y	
George Cushmac	Y	Y	Y		Zarena Post	A	A	A	
~~Al Dietz~~	A				George Rodgers	Y	Y	Y	
Ernest Falke	Y	Y	Y		George Rusch, Chair	Y	Y	Y	
Larry Gephart	Y	Y	Y		Robert Snyder	Y	N	Y	
John Hinz	A	A	P		~~Thomas Sobotka~~				
Jim Holler	Y	Y	Y		~~Kenneth Still~~				
Thomas Hornshaw	Y	Y	Y		Richard Thomas	A	A	A	
					TALLY	17/17	16/17	17/17	

PPM, (mg/m^3)	10 Min	30 Min	1 Hr	4 Hr	8 Hr
AEGL 1	NR, ( )	NR, ( )	NR, ( )	NR, ( )	NR, ( )
AEGL 2	~~18~~ 9.0, ( )	~~18~~ 9.0, ( )	~~18~~ 7.0, ( )	~~5.7~~ 2.9, ( )	~~2.8~~ 1.4, ( )
AEGL 3	46, ( )	46, ( )	37, ( )	23, ( )	12, ( )
LOA					

AEGL 1 **Motion by:** Morawetz **Second by:** Benson

AEGL 2 **Motion by:** Morawetz **Second by:** Benson

AEGL 3 **Motion by:** Benson **Second by:** Rodgers

LOA **Motion by:** _____ **Second by:** _____

Approved by Chair: [signature] **DFO:** [signature] **Date:** 9/17/03

NAC/AEGL Meeting 30: September 16-18, 2003

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

NAC Member	AEGL1	AEGL2	AEGL3	LOA	NAC Member	AEGL1	AEGL 2	AEGL3	LOA
George Alexeeff	A				Nancy Kim	A			
Steven Barbee	A				Loren Koller	A			
Lynn Beasley	Y				Glenn Leach	Y			
David Belluck	P				Mark McClanahan	A			
Robert Benson	Y				John Morawetz	Y			
Jonathan Borak	P				Richard Niemeier	Y			
William Bress	N				Marinelle Payton	A			
George Cushmac	Y				Zarena Post	A			
~~Al Dietz~~					George Rodgers	Y			
Ernest Falke	Y				George Rusch, Chair	Y			
Larry Gephart	Y				Robert Snyder	P			
John Hinz	A				~~Thomas Sobotka~~				
Jim Holler	Y				~~Kenneth Still~~				
Thomas Hornshaw	Y				Richard Thomas	A			
					TALLY	12/13			

PPM, (mg/m^3)	10 Min	30 Min	1 Hr	4 Hr	8 Hr
AEGL 1	NR, ( )	NR, ( )	NR, ( )	NR, ( )	NR, ( )
AEGL 2	31, ( )	31, ( )	23, ( )	13, ( )	10, ( )
AEGL 3	65, ( )	65, ( )	49, ( )	28, ( )	21, ( )
LOA					

1/16 ACETONITRILE

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:** Paul S. Tobin **Date:** 9/17/03

NAC/AEGL Meeting 30: September 16-18, 2003

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

NAC Member	AEGL1	AEGL2	AEGL3	LOA	NAC Member	AEGL1	AEGL 2	AEGL3	LOA
George Alexeeff	A				Nancy Kim	A			
Steven Barbee	A				Loren Koller	A			
Lynn Beasley	Y				Glenn Leach	Y			
David Belluck	Y				Mark McClanahan	A			
Robert Benson	Y				John Morawetz	Y			
Jonathan Borak	Y				Richard Niemeier	A			
William Bress	Y	P	P		Marinelle Payton	A			
George Cushmac	Y				Zarena Post				
~~Al Dietz~~					George Rodgers	Y			
Ernest Falke	Y				George Rusch, Chair	Y			
Larry Gephart	Y				Robert Snyder	Y			
John Hinz	A				~~Thomas Sobotka~~				
Jim Holler	Y				~~Kenneth Still~~				
Thomas Hornshaw	Y				Richard Thomas	A			
					TALLY	15/15			

PPM, (mg/m^3)	10 Min	30 Min	1 Hr	4 Hr	8 Hr
AEGL 1	NR, ( )	NR, ( )	NR, ( )	NR, ( )	NR, ( )
AEGL 2	4.8, ( )	4.8, ( )	3.5, ( )	2.0, ( )	1.5, ( )
AEGL 3	10, ( )	10, ( )	7.5, ( )	4.3, ( )	3.2, ( )
LOA					

1/65 ACETONITRILE

AEGL 1 Motion by: Benson **Second by:** 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. Tikkanen **Date:** 9/19/03