NATIONAL ADVISORY COMMITTEE (NAC)
FOR ACUTE EXPOSURE GUIDELINE LEVELS (AEGLs)
FOR HAZARDOUS SUBSTANCES

Final Meeting 12 Highlights
Governor's House Hotel
1615 Rhode Island Avenue
Washington, D.C.

December 7-9, 1998

INTRODUCTION

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

Roger Garrett (Program Director) reported on his meeting in Europe with the Organisation for Economic Co-Operation and Development (OECD) which represents 21 nations. There is potential interest by OECD in adopting AEGL values. An observer sent by Germany, Dr. Ursula Stephan of the Hazardous Incident Commission, was welcomed by the NAC. OECD may send observers to future meetings. In further discussion, it was decided to solicit data from and use the expertise of OECD members before completion of the Technical Support Documents. However, the documents would not be sent out before adoption of values by the NAC. Roger will seek a contact person for getting information. There is a possibility of a more definitive presentation of the AEGL project to the OECD in June 1999.

Roger Garrett and Ernest Falke reported on the presentations of the Standing Operating Procedures (SOPs) and the first eight AEGLs to the National Academy of Sciences/Committee on Toxicology, Subcommittee for AEGLs. Although a formal response has not been received, the initial response from the Academy members concerning the SOPs, Technical Support Documents (TSDs), and methodology in general was positive, even where the Academy's approach to setting guidelines differed. The Academy noted that the SOP document went further than previous guideline documents. The TSDs were complimented and the response to time-scaling was especially positive. The next 10 chemicals have been sent to the Academy for their consideration. Ernie Falke noted the need to document the rationale for the uncertainty factors of 3 and 10 in the SOP. The discussion of the cancer endpoint needs additional work, but the risk of 10^{-4} is acceptable. Susceptible populations also need to be further defined in regard to the interspecies uncertainty factor issue.

Concerning additional funding, Paul Tobin and Richard Niemeier discussed the NIOSH National Occupational Research Agenda (NORA), a partnership between government, industry, and academia which funds special risk assessment projects. Paul Tobin has contacted the chairman of the NORA committee. The question arose as to whether or not a federal agency can submit a proposal. A discussion ensued concerning developmental/reproductive toxicity and the lack of human data.

Bill Pepelko said that his office is looking at differences in sensitivity between children and adults. Paul Tobin reported that interim TSDs will be accessible on the EPA Web site. The NAC/AEGL

Meeting 11 highlights were reviewed and accepted unanimously following minor revisions (Appendix A).

TECHNICAL DISCUSSIONS

Definition of Ceiling Values. Problems with the definition of ceiling values were brought up by John Morawetz. Specifically, the present definition would allow multiple exposures to higher values within the longer term exposure durations. John illustrated his concern with examples of the variability of exposure concentrations during industrial monitoring and/or an accidental release (Attachment 3). If a time-weighted average is used, higher-than-ceiling values may occur during an incident. Additional language to clarify the definition of ceiling value was proposed by George Rusch. Two solutions were suggested: (1) define each point on the line connecting the four exposure durations as a ceiling, with the 30-min value flatlined to the ordinate, and (2) use the line as a continuum with concentrations for exposure durations other than the four defined times read off the line. One committee member suggested clarifying the definition of ceiling value by adding a graph to each TSD. Bob Snyder pointed out that it is important to consider the mechanism of action for each chemical.

Action Item: Ernie Falke will write up a definition of ceiling value for the SOPs document and present it to the NAC/AEGL at the next meeting.

Definition of AEGL-1 Level. The disconnect between the definition of an AEGL-1 (generally a sensory response) and the AEGL-2 and -3 (health responses) was discussed. The endpoint for the AEGL-1 has been chemical-specific and/or dependent on the data, with a hierarchical or decision tree used for: sensory irritation, biochemical response, no effect, and odor. Discussion revolved around combining all endpoints into the definition; e.g., uncertainty in the use of a NOAEL, addition of the odor threshold to the summary table, the relationship between odor and discomfort, and anxiety, and the influence of the "quality" of the odor. It was noted that several members of the National Academy of Sciences committee recommended development of an AEGL-1 even in the absence of data or when odor is above the effect level. The OECD agrees with establishment of an AEGL-1 level in the absence of data.

Action Item: Ernie Falke will compile the data on the AEGL-1 endpoints used up to this point and report back at the next meeting.

Categorical Regression. Judy Strickland of the National Center for Environmental Assessment (NCEA/USEPA) started her discussion with an overview of the development of Acute Reference Exposures (ARE). The ARE are airborne concentrations that are unlikely to cause adverse effects in a sensitive human subpopulation during intermittent exposure or a single continuous exposure of <24 hr. The ARE support implementation of the Clean Air Act Amendments, Section 112. Depending on the available data, ARE will be developed by one of three approaches: the NOAEL approach, categorical regression, or the benchmark concentration. All three methods require dosimetric adjustment (the default is 1); categorical regression does not require a duration adjustment. Judy presented schematics of the categorical regression approach (Attachment 4) in which health effects are divided into severity categories and plotted graphically with the ordinate as log concentration and the abscissa as log exposure duration. Parallel lines that separate the severity categories are then generated. All available data is used in this approach. The line defining a 10% probability of an adverse effect with 95% confidence limits is used as the endpoint. Ernest Falke pointed out that a 10% response may be too large; whereas application of several uncertainty factors may be too conservative. The EPA

Science Advisory Board reviewed the categorical regression model, agreeing with several concepts (categorizing of data, use of all data, graphical representation) and questioning several points (appropriateness of parallelism of probability-response curves for all severity categories, judging severity categories across various target organs and species, reliability of the confidence limits, and the scaling factor). The NCEA has replied to these comments as well as those that addressed the NOAEL and Benchmark approach. It was noted by a NAC/AEGL member that the regression line may be an excellent source for estimating time scaling. Judy went on to illustrate the use of categorical regression with the hydrogen sulfide data. Her ARE values were similar to the AEGL-1 values originally proposed in the TSD (Attachment 5).

AEGL PRIORITY CHEMICALS

Propionitrile, CAS No. 107-12-0

Chemical Manager: Dr. George Rogers, University of Louisville, AAPCC
Author: Dr. Cheryl Bast, ORNL

George Rogers explained the mechanism of action of the nitriles which is based on the metabolic release of hydrogen cyanide. Cheryl Bast reviewed the data on methacrylonitrile and isobutylnitrile which were presented at the last meeting, noting the relative toxicities of these two chemicals to that of propionitrile. Cheryl then summarized the data for propionitrile (Attachment 6).

The proposed AEGL-3 values for propionitrile were based a 4-hr no-effect level for death in rats. This value of 690 ppm was divided by an interspecies uncertainty factor of 10 because the rat is not the most sensitive species and by an intraspecies uncertainty factor of 3 as effects appear to be due to cyanide and observations of human occupational exposures as well as toxicity to adult and neonatal mice suggest little individual variation. The value of *n* of 2.6 was based on that for cyanide in a lethality study with rats over exposure durations of 5, 15, 30, and 60 min. It was moved by Richard Niemeier and seconded by John Hinz to accept the values of 51, 39, 23, and 18 ppm for the 30-min and 1-, 4-, and 8-hr exposure durations, respectively. The motion passed unanimously (Appendix B).

Following discussion of two relevant studies, a human exposure and a developmental study with the rat, the proposed AEGL-2 was based on the human accidental exposure to 33.8 ppm for 2 hr which resulted in headache, nausea, and dizziness. The 33.8 ppm value was first divided by intraspecies and modifying factors of 3 each for a total of 10 resulting in time-scaled values of 5.8, 4.4, 2.6, and 2.0 ppm. A motion was made by George Alexeeff and seconded by Jonathan Borak to accept these values; the motion did not pass [YES: 8, NO: 14, ABSTAIN: 0]. Further discussion centered on the application of a modifying factor. To be consistent with the AEGL-3 and because the mechanism of action is based on the release of cyanide, an intraspecies uncertainty factor of 3 was applied. Because of uncertainty in the data, a modifying factor of 2 was also applied. It was moved by Loren Koller and seconded by Steven Barbee to accept the values of 9.6, 7.4, 4.3, and 3.3 ppm for the 30-min and 1, 4, and 8-hr exposure durations. The motion was accepted by the NAC/AEGL [YES: 17, NO: 5, ABSTAIN: 0] (Appendix B). Because of a lack of data, AEGL-1 values were not derived (moved, Loren Koller; seconded, Mark McClanahan). The motion passed unanimously (Appendix B).

SUMMARY OF PROPOSED AEGL VALUES FOR PROPIONITRILE					
Classification	**30-Min**	**1-Hr**	**4-Hr**	**8-Hr**	**Endpoint**
AEGL-1	ID	ID	ID	ID	
AEGL-2	9.6 ppm (22 mg/m^3)	7.4 ppm (17 mg/m^3)	4.3 ppm (9.8 mg/m^3)	3.3 ppm (7.6 mg/m^3)	Headache, nausea, and dizziness in human subject
AEGL-3	51 ppm (120 mg/m^3)	39 ppm (89 mg/m^3)	23 ppm (53 mg/m^3)	18 ppm (41 mg/m^3)	NOEL for death, rat

ID = Insufficient data.

Cyclohexylamine, CAS No. 108-91-8

Chemical Manager: Dr. Mark McClanahan, Centers for Disease Control and Prevention
Author: Dr. Sylvia Milanez, ORNL

Following discussion of the available data and presentation by Sylvia Milanez (Attachment 7), the discussion centered around relative species sensitivities, suitable endpoints for each AEGL level, and the deficiencies in the database. The AEGL-3 was based on the 4-hr exposure of rats to 567 ppm which was the threshold value for lethality. The value was adjusted by an interspecies uncertainty factor of 10 because there was insufficient data to determine the most sensitive animal species. Because one of two rats that died at the next higher dose had lung hemorrhage/edema, cyclohexylamine was determined to be a respiratory irritant. An intraspecies uncertainty factor of 3 was used because the mechanism of action for direct irritation by a strong base is not expected to differ among individuals. Scaling across time was based on $n = 2$. It was moved by Richard Niemeier and seconded by Bob Benson to accept the resulting values of 53, 38, 19, and 13 ppm for the 30-min, 1-, 4-, and 8-hr exposure durations, respectively. The motion passed [YES: 21, NO: 3, ABSTAIN: 0] (Appendix C).

Following a lengthy discussion on uncertainty and modifying factors and several votes, it was decided to base the AEGL-2 values on the no-effect concentration of 150 ppm for corneal opacity in rats and guinea pigs. An earlier vote included time-scaled values of 18, 13, 6.3, and 4.5 ppm based on an estimated no-effect level of 189 ppm (4 hrs) for corneal opacity in the rat with a combined uncertainty factor of 30 as for the AEGL-3 above. The motion did not pass [YES: 15, NO: 10, ABSTAIN: 0]. Although exposures to 150 ppm were repeated, the 7-hr exposure duration from the first day was chosen as the exposure time. An intraspecies uncertainty factor of 3 (cyclohexylamine is a direct acting irritant; effects are not expected to differ among individuals), an interspecies uncertainty factor of 3 (the endpoint of corneal opacity is not likely to differ greatly among species), and a modifying factor of 2 (to account for a deficient database) were applied (for a total uncertainty/modifying factor of 20); time scaling was based on $n = 2$. The NAC noted that the AEGL-2 values may cause respiratory irritation in humans. It was moved by Doan Hanson and seconded by Bob Benson to accept the resulting values of 28, 20, 9.9, and 7.0 ppm for the 30-min and 1-, 4-, and 8-hr exposure durations, respectively. The motion passed [YES: 17, NO: 7, ABSTAIN: 0] (Appendix C). It was noted by the committee that different modifying factors were applied to the AEGL-2 and AEGL-3.

The AEGL-1 was based on the LOAEL value for irritation of 54.2 ppm during a 4-hr exposure of rats

to cyclohexylamine. This value was divided by 3 to attain a NOAEL (and mild or no respiratory irritation) and by interspecies and intraspecies uncertainty factors of 3 and 3 (total 10) because cyclohexylamine is a direct-acting irritant and its effects are not likely to vary greatly among humans or between species. The resulting value of 1.8 was flatlined across all AEGL time intervals. A motion to accept this value was proposed by Steve Barbee and seconded by Bill Pepelko. The motion passed [YES: 23, NO: 1, ABSTAIN: 0] (Appendix C). The 1.8 ppm value is supported by a <20% depression in respiratory rate during exposure to
4 ppm in an RD_{50} study with the mouse.

SUMMARY OF PROPOSED AEGL VALUES FOR CYCLOHEXYLAMINE					
Classification	**30-Min**	**1-Hr**	**4-Hr**	**8-Hr**	**Endpoint**
AEGL-1	1.8 ppm (7.3 mg/m^3)	1.8 ppm (7.3 mg/m^3)	1.8 ppm (7.3 mg/m^3)	1.8 ppm (7.3 mg/m^3)	NOAEL or mild respiratory irritation, rat
AEGL-2	28 ppm (114 mg/m^3)	20 ppm (81 mg/m^3)	9.9 ppm (40 mg/m^3)	7.0 ppm (28 mg/m^3)	NOAEL for corneal opacity, rat. May cause respiratory irritation in humans.
AEGL-3	53 ppm (217 mg/m^3)	38 ppm (153 mg/m^3)	19 ppm (77 mg/m^3)	13 ppm (54 mg/m^3)	Threshold for lethality, rat

Hydrogen sulfide, CAS No. 7783-06-4

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

Following an introduction by Steven Barbee, Cheryl Bast presented an overview of the human and animal data and the relatively high value of *n* based on several of the data sets (Attachment 8). NAC/AEGL discussions centered primarily on sources of odor, odor detection, and at what concentration the odor becomes objectionable. It was noted that human deaths have occurred, primarily in enclosed spaces. The AEGL-3 was based on a 1-hr exposure concentration of 504 ppm which was a NOEL for death in rats. This value was adjusted by an interspecies uncertainty factor of 3 (the rat is only slightly less sensitive than the mouse and the rat showed the best dose response) and an intraspecies uncertainty factor of 3 (the mechanism of action of hydrogen sulfide is well known and will not differ greatly among individuals. A value of *n* of 4.36, derived from combined rat lethality data for periods of 10 mins to 6 hr was used to scale the values across time. The resulting concentrations for the 10- and 30-min and 1-, 4-, and 8-hr exposure durations were 76, 60, 50, 37, and 31 ppm, respectively. Following a motion by Mark McClanahan which was seconded by Loren Koller, the values were accepted unanimously (Appendix D).

The AEGL-2 was based on a 4-hr exposure of rats to 200 ppm which resulted in perivascular edema and increased protein and LDH in lavage fluid. This value was divided by inter- and intraspecies uncertainty factors of 3 each and scaled across time as for the AEGL-3 above. It was moved by Loren Koller and seconded by Ernie Falke to accept the resulting values of 42, 32, 28, 20, and 17 ppm for the

10- and 30-min and 1-, 4-, and 8-hr exposure durations, respectively. The motion carried [YES: 24, NO: 1, ABSTAIN: 0] (Appendix D). References from the ACGIH and WHO reports will be provided for discussion at the next meeting.

For the AEGL-1, Cheryl presented data on a no-effect level in exercising asthmatics exposed to hydrogen sulfide. The discussion for the AEGL-1 again centered around objectionable odor and data from hot springs and hog farms was cited by committee members. It was suggested that the endpoint of uncomfortable or objectionable odor could be used as an AEGL-1 endpoint. George Alexeeff cited data indicating that 5 times the odor threshold of 0.03 ppm (0.15 ppm) is objectionable to humans. It was moved by Larry Gephart and seconded by Dave Belluck that the 0.15 ppm concentration, flatlined across time, be accepted as the AEGL-1. The motion passed unanimously (Appendix D).

In addition to providing a reference from the ACGIH document, the committee asked that the primary reference cited by George Alexeeff on objectionable odor be provided at the next meeting. The committee also noted that the same odor problem exists with methyl mercaptan and suggested revisiting this chemical at the next meeting.

SUMMARY OF PROPOSED AEGL VALUES FOR HYDROGEN SULFIDE

Classification	10-Min	30-Min	1-Hr	4-Hr	8-Hr	Endpoint
AEGL-1	Not derived	0.15 ppm (0.21 mg/m^3)	0.15 ppm (0.21 mg/m^3)	0.15 ppm (0.21 mg/m^3)	0.15 ppm (0.21 mg/m^3)	Objectionable odor, humans
AEGL-2	42 ppm (59 mg/m^3)	32 ppm (45 mg/m^3)	28 ppm (39 mg/m^3)	20 ppm (28 mg/m^3)	17 ppm (24 mg/m^3)	Lung edema, rat
AEGL-3	76 ppm (106 mg/m^3)	60 ppm (85 mg/m^3)	50 ppm (71 mg/m^3)	37 ppm (52 mg/m^3)	31 ppm (44 mg/m^3)	NOEL for death, rat

1,1,1,2-Tetrafluoroethane (HFC-134a), CAS No. 811-97-2

Chemical Manager: Dr. George Rusch, AlliedSignal, Inc.
Author: Dr. Sylvia Talmage, ORNL

George Rusch is the NAC/AEGL Chair and Chemical Managers (CM) for HFC-134a and HCFC-141b. He opened the discussion on these chemicals with remarks to delineate his technical contributions and his NAC/AEGL responsibility. George is the Director of Risk Assessment and Toxicology of AlliedSignal, Inc. In this capacity he is in charge of AlliedSignal's testing program for replacements for chloroflurocarbons and also has served as chair of the International Program for Alternative Fluorocarbon Toxicity Testing. George contributes his technical expertise to the preparation of AEGL documents. He led the technical discussion sessions in dual roles as a Chair and as a CM. He abstained from voting on all levels of toxicity values derived from NAC/AEGL deliveries. Then, George proceeded to provided an overview of the protocol of the cardiac sensitization test with beagle dogs and the mechanism of action of chemically-induced heart arrhythmias (Attachment 9). Sylvia Talmage presented data on the first of

two halocarbons that are being considered for replacement of chlorofluorocarbons. She presented an overview of the available data, noting the richness of the database, and the development of the draft values for this chemical (Attachment 10). The AEGL-1 was based on a study with human subjects in which exposures to concentrations up to 8000 ppm for 1 hr resulted in no effects. Because this concentration is so far below concentrations showing any effects in animal studies (81,000 ppm was a no-effect concentration), the value was adjusted by an intraspecies uncertainty factor of 1. Because blood concentrations approached equilibrium by 55 min of exposure, no greater effects are anticipated at longer exposure intervals and the value of 8000 ppm was flatlined across time. There was one motion with individual votes for each AEGL level that the values be accepted. George Rogers moved and Kyle Blackman seconded the motion. The motion for the AEGL-1 passed [YES: 23, NO: 1, ABSTAIN: 2] (Appendix E). It was suggested that a statement indicating that in regard to the 10-min cardiac sensitization test, the dog is no more sensitive after 8 hr of exposure to halocarbons be added to the TSD.

The AEGL-2 was based on the no-effect concentration of 40,000 ppm in a cardiac sensitization test with beagle dogs in which the doses of epinephrine were individualized to each dog. Because the dog is a good model for the human in this test, an interspecies uncertainty factor of 1 was applied. Because the test is optimized with administration of greater than a physiological dose of epinephrine and differences among individuals are not anticipated, the value was adjusted by an intraspecies uncertainty factor of 3. Because exposure durations do not influence the results of the test, the resulting value of 13,000 ppm was flatlined across time. It was noted that other endpoints, such as the threshold for narcosis of 200,000 ppm in several animal species, when divided by inter- and intraspecies uncertainty factors of 3 each, would result in a higher value for the AEGL-2. The value for the AEGL-2 passed unanimously, with George Rusch abstaining (Appendix E).

The AEGL-3 value was based on a concentration of 80,000 ppm which resulted in a marked response in two of six dogs in the cardiac sensitization test. The next higher dose of 160,000 ppm resulted in convulsions in one of four dogs. Using the same reasoning as for the AEGL-2 above, the value of 27,000 ppm (80,000 ppm/3) was proposed for all AEGL-3 exposure durations. The value for the AEGL-3 passed [YES: 25, NO: 0, ABSTAIN: 1] (Appendix E). It was pointed out that other endpoints, such as the threshold for lethality of 359,000 ppm in an animal study, would, when divided by inter- and intraspecies uncertainty factors of 3 each, result in a higher value for the AEGL-3.

SUMMARY OF PROPOSED AEGL VALUES FOR 1,1,1,2-TETRAFLUOROETHANE

Classification	30-Min	1-Hr	4-Hr	8-Hr	Endpoint
AEGL-1	8000 ppm (34,000 mg/m^3)	8000 ppm (34,000 mg/m^3)	8000 ppm (34,000 mg/m^3)	8000 ppm (34,000 mg/m^3)	No effects, humans (Emmen and Hoogendijk, 1998)

AEGL-2	13,000 ppm (55,250 mg/m^3)	13,000 ppm (55,250 mg/m^3)	13,000 ppm (55,250 mg/m^3)	13,000 ppm (55,250 mg/m^3)	No effect in cardiac sensitization test with dogs (Hardy et al., 1991)
AEGL-3	27,000 ppm (114,750 mg/m^3)	27,000 ppm (114,750 mg/m^3)	27,000 ppm (114,750 mg/m^3)	27,000 ppm (114,750 mg/m^3)	Marked response in cardiac sensitization test with dogs (Hardy et al., 1991)

1,1-Dichloro-1-fluoroethane (HCFC-141b), CAS No. 1717-00-6

Chemical Manager: Dr. George Rusch, AlliedSignal, Inc.
Author: Dr. Sylvia Talmage, ORNL

Sylvia Talmage reviewed the data and noted corrections in the results of the dog sensitization test made necessary by receipt of primary references from a chemical company (Attachment 11). It was noted that HCFC-141b is more toxic than HFC-134a and takes longer to reach equilibrium in the blood than HFC-134a. The AEGL-1 was based on a 4-hr no-effect concentration of 1000 ppm in a study with exercising human subjects. Because no individual differences were noted in the study and because this concentration is far below the highest no-effect concentration in animal studies of 30,000 ppm, it was adjusted by an intraspecies uncertainty factor of 1. Because blood concentrations in this same study approached equilibrium by 145 min and effects are thought to be determined by blood concentrations, the value of 1000 ppm was flatlined across all AEGL-1 time periods. It was moved by Mark McClanahan and seconded by Richard Niemeier to accept all AEGL values. The motion passed with individual values for the AEGL-1 of YES: 21, NO: 0, ABSTAIN: 2 (Appendix F). This value is supported by the NOEL value of 2600 ppm in a cardiac sensitization test with the beagle dog.

The AEGL-2 was based on a concentration of 5200 ppm which caused a marked response in one of ten beagle dogs in one of two cardiac sensitization tests. A single high dose of epinephrine was administered to each dog in this study (8 µg/kg), i.e., doses were not individualized for each dog. Because the dog is a good model for the human in this test, an interspecies uncertainty factor of 1 was applied. Because the test is optimized with administration of greater than a physiological dose of epinephrine and great differences among individuals are not anticipated, the value was adjusted by an intraspecies uncertainty factor of 3. Because exposure durations do not influence the results of the test, the resulting value of 1700 ppm was flatlined across time. The previously made motion to accept the AEGL values by Mark McClanahan and seconded by Richard Niemeier passed with individual votes for the AEGL-2 [YES: 22, NO: 0, ABSTAIN: 1] (Appendix F). George Rogers pointed out that in the human study this chemical does not reach equilibrium in the blood within the 10-min test time period used in the cardiac sensitization test. It was also noted that other endpoints, such as the threshold for narcosis of 30,000 ppm in mice when divided by inter- and intraspecies uncertainty factors of 3 each would result in a higher value for the AEGL-2.

The AEGL-3 value was based on a concentration of 9000 ppm which resulted in a marked response in one of two dogs in a cardiac sensitization test. In this study, the highest nonlethal concentration was 19,000 ppm; however in an earlier cardiac sensitization test, one of ten dogs exposed to 10,000 ppm died. Therefore, 9000 ppm was considered the threshold for lethality. Using the same reasoning as for the AEGL-2 above, the value of 9000 ppm was divided by 3 and flatlined for all AEGL-2 exposure

durations. The previously made motion by Mark McClanahan which was seconded by Richard Niemeier to accept the proposed values passed with individual votes for the AEGL-3 [YES: 22, NO: 0, ABSTAIN: 1] (Appendix F). It was pointed out that other endpoints, such as the highest nonlethal concentration in the absence of an exogenous dose of epinephrine of 45,781 ppm in an animal study, would, when divided by inter- and intraspecies uncertainty factors of 3 each, result in a higher value for the AEGL-3.

SUMMARY OF PROPOSED AEGL VALUES FOR 1,1-DICHLORO-1-FLUOROETHANE					
Classification	**30-Min**	**1-Hr**	**4-Hr**	**8-Hr**	**Endpoint**
AEGL-1	1000 ppm (4850 mg/m^3)	1000 ppm (4850 mg/m^3)	1000 ppm (4850 mg/m^3)	1000 ppm (4850 mg/m^3)	No effects, humans (Utell et al., 1997)
AEGL-2	1700 ppm (8245 mg/m^3)	1700 ppm (8245 mg/m^3)	1700 ppm (8245 mg/m^3)	1700 ppm (8245 mg/m^3)	Marked response, cardiac sensitization test, dogs (1/10)
AEGL-3	3000 ppm (14,550 mg/m^3)	3000 ppm (14,550 mg/m^3)	3000 ppm (14,550 mg/m^3)	3000 ppm (14,550 mg/m^3)	Highest nonlethal concentration, cardiac sensitization test, dogs (Hardy et al., 1989a)

Ethylene Oxide, CAS NO. 75-21-8

Chemical Manager: Dr. Kyle Blackman, FEMA
Author: Dr. Kowetha Davidson, ORNL

Kyle Blackman reported that ethylene oxide will be revisited at the next meeting. Bill Snellings of Union Carbide Corporation, who was present at the meeting, will look for more data.

Piperidine, CAS No. 110-89-4

Chemical Manager: Dr. Mark McClanahan, Centers for Disease Control and Prevention
Author: Dr. Kowetha Davidson, ORNL

The chemical information was summarized by Mark McClanahan who noted the paucity of data for lethality and time scaling. Only an AEGL-1 had been proposed in the draft TSD. The Committee discussed the available lethality data and considered the data adequate to derive an AEGL-3. The Committee based the AEGL-3 on a reported 4-hr LC_{50} of 1723 ppm for the mouse (Attachment 12). This value was divided by 3 to attain a nonlethal concentration and then adjusted by an interspecies

uncertainty factor of 10 because there is only one data set and an intraspecies uncertainty factor of 3 because it is a strong primary irritant and there would be little intraspecies variation. The value of $n = 2$ was used for time scaling. The resulting AEGL-3 values of 54, 38, 19, and 14 ppm for the 30-min and 1-, 4-, and 8-hr time periods were accepted by the Committee (motion by Richard Niemeier, seconded by Larry Gephart [YES: 19, NO: 4, ABSTAIN: 0] (Appendix G). It was noted that the LC_{50} value on which the AEGL-3 is based was reported in a secondary source. Data that might be considered for development of an AEGL-2 were also reported in a secondary source. Further discussion on this chemical was tabled until requisition of possible primary references can be attempted.

SUMMARY OF PROPOSED AEGL VALUES FOR PIPERIDINE					
Classification	**30-Min**	**1-Hr**	**4-Hr**	**8-Hr**	**Endpoint**
AEGL-3	54 ppm (186 mg/m^3)	38 ppm (131 mg/m^3)	19 ppm (66 mg/m^3)	14 ppm (48 mg/m^3)	Threshold for lethality, mouse

Furan, CAS No. 110-00-9

Chemical Manager: Dr. George Rogers, University of Louisville (AAPCC)
Author: Dr. Claudia M. Troxel, ORNL

Claudia Troxel opened the discussion with a resolution of the conflicting data in mouse and rat LC_{50} studies, noting that the mouse data should be discredited based on the probability of insufficient oxygen in the closed system in which they were tested (Attachment 13). Claudia further discussed the sparse database, uncertainty factors, relative species metabolism, and mechanism of action of this chemical. The proposed AEGL-2 and -3 values were based on the 1-hr threshold for adverse effects and the threshold for lethality (highest NOEL for death) of 1014 and 2851 ppm, respectively. These values were adjusted by an interspecies uncertainty factor of 10 (although the simulated absorbed dose in the liver in humans is lower than in mice and rats, the relative species sensitivity to the reactive metabolite is unknown, and the liver was the only organ investigated), an intraspecies uncertainty factor of 3 (inter-individual variations in the activating enzyme are not predicted to be a factor in bioactivation), and by a modifying factor of 3 (sparse data set: only one study in one species). The value of $n = 2$ was used for time scaling. The proposed AEGL-2 and AEGL-3 values for the 30-min and 1-, 4-, and 8-hr time periods were 40, 29, 14, and 10 ppm and 14, 10, 5.1, and 3.6 ppm, respectively. A motion was made by Robert Snyder and seconded by Richard Thomas to accept the AEGL-2 and AEGL-3 values. The motion for both levels was accepted [YES: 19; NO: 5, ABSTAIN: 0] (Appendix H). The Committee unanimously agreed not to set AEGL-1 levels because of insufficient data.

SUMMARY OF PROPOSED AEGL VALUES FOR FURAN					
Classification	**30-Min**	**1-Hr**	**4-Hr**	**8-Hr**	**Endpoint**
AEGL-1	ID	ID	ID	ID	

AEGL-2	14 ppm (39 mg/m^3)	10 ppm (28 mg/m^3)	5.1 ppm (14 mg/m^3)	3.6 ppm (10 mg/m^3)	Threshold for adverse effects, rat
AEGL-3	40 ppm (110 mg/m^3)	29 ppm (81 mg/m^3)	14 ppm (39 mg/m^3)	10 ppm (28 mg/m^3)	Threshold for lethality, rat

ID = Insufficient data.

Propylene Oxide, CAS No. 75-56-9

Chemical Manager: Dr. Jim Holler, ATSDR
Author: Dr. Claudia M. Troxel, ORNL

Following a review of the history of propylene oxide presentations, human data (the data from environmental health surveys made available by the CMA) and pertinent animal data (Attachment 14) were discussed by Claudia. James Swenberg (University of North Carolina) discussed the formation of DNA adducts in the nasal tissues, tissue partition coefficients for various species, and cell proliferation of rats exposed to 500 ppm, 6 hr/day for 5 days/week (Attachment 15). Additionally, based on toxicokinetics, lethality, and pharmacokinetic modeling, the mouse is predicted to be more sensitive than humans. Therefore, there is no need for an interspecies uncertainty factor if using the mouse data for AEGL derivations. Dr. Larry Andrews of the CMA Propylene Oxide Panel expressed concern that the AEGL-3 values do not correlate with the human data (Attachment 16).

The environmental health surveys made available by the CMA were judged satisfactory by the Committee to derive all three AEGL levels. The AEGL-3 was based on the highest documented nonlethal exposure concentration of 1520 ppm for 171 min. This value was adjusted by an uncertainty factor of 3 for intraspecies differences (the mechanism of action, irritation, is not expected to differ among individuals) and by a modifying factor of 2 for a limited database (1 sample measurement from one worker; old survey) and time scaled using an *n* of 1.2 based on ethylene oxide. A motion to accept the resulting values of 1100, 610, 190, and 110 ppm for the 30-min and 1-, 4-, and 8-hr time periods was made by Jim Holler and seconded by Larry Gephart. The motion passed [YES: 19, NO: 4, ABSTAIN: 0] (Appendix I).

The AEGL-2 was based on the average of AEGL-2 values derived using four propylene oxide exposure concentrations measured in the breathing zone of three workers (see table below). At these concentrations, a strong odor with undefined irritation was reported. The AEGL-2 values were divided by an intraspecies uncertainty factor of 3 and scaled to the relevant time periods using $n = 1.2$.

EXPOSURE CONCENTRATIONS OF PROPYLENE OXIDE (ppm) MEASURED IN 3 WORKERS DURING ENVIRONMENTAL HEALTH SURVEY					
Concentration/Time	**UF/MF**	**30-Min**	**1-Hr**	**4-Hr**	**8-Hr**
380 ppm for 177 min.	3	560	310	98	55
525 ppm for 121 min.	3	560	310	99	56

392 ppm for 135 min.	3	460	260	81	45
460 ppm for 116 min.	3	470	270	84	47
Average	3	510	290	91	51

A motion to accept the resulting values of 510, 290, 91, and 51 ppm for the 30-min and 1-, 4-, and 8-hr time periods was made by Bill Bress and seconded by Loren Koller. The motion was unanimously passed (Appendix I).

The AEGL-1 was based on the highest 8-hr time-weighted concentration of 31.8 ppm (2 samples from 2 workers; 78 employees potentially exposed to 13.2 to 31.8 ppm). This value was divided by an intraspecies uncertainty factor of 3 (the mechanism of action, irritation, is not expected to differ among individuals) and scaled to the relevant time periods using the value of $n = 1.2$ which is based on ethylene oxide. A motion to accept the resulting values of 110, 60, 19, and 11 ppm for the 30-min and 1-, 4-, and 8-hr time periods was made by George Rogers and seconded by Richard Thomas. The motion passed [YES: 14, NO: 5, ABSTAIN: 0] (Appendix I).

SUMMARY OF PROPOSED AEGL VALUES FOR PROPYLENE OXIDE					
Classification	**30-Min**	**1-Hr**	**4-Hr**	**8-Hr**	**Endpoint**
AEGL-1	110 ppm (260 mg/m^3)	60 ppm (140 mg/m^3)	19 ppm (45 mg/m^3)	11 ppm (26 mg/m^3)	No effects, humans
AEGL-2	510 ppm (1200 mg/m^3)	290 ppm (690 mg/m^3)	91 ppm (220 mg/m^3)	51 ppm (120 mg/m^3)	Strong odor, irritation in monitoring study, humans
AEGL-3	1100 ppm (2600 mg/m^3)	610 ppm (1400 mg/m^3)	190 ppm (450 mg/m^3)	110 ppm (260 mg/m^3)	Highest nonlethal concentration, humans

ADMINISTRATIVE ISSUES

Times and places for the next meeting were discussed. Several options for the March meeting were prioritized with the highest priority being given to a meeting in New Orleans to precede the Society of Toxicology meeting of March 14-18.

Suggested future meetings:
March 11-12, 1999, New Orleans, LA
or March 3-5, Washington, DC
June 14-16, 1999, Washington, DC
September 14-16, 1999, Washington, DC
December 6-8, 1999, Washington, DC

George Rusch expressed appreciation for a productive meeting.

This report was prepared by Drs. Sylvia Talmage and Po-Yung Lu, ORNL.

LIST OF ATTACHMENTS

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

1. NAC/AEGL Meeting No. 12 Agenda
2. NAC/AEGL Meeting No. 12 Attendee List

3. Examples of "ceiling value" interpretations - John Morawetz
4. Use of Categorical Regression to Determine c x t Relationship for Hydrogen Sulfide - Judy A. Strickland
5. Comparison of ARE and AEGL values of Hydrogen sulfide - Judy Strickland
6. Data analysis of Propionitrile - Cheryl Bast
7. Data analysis of Cyclohexylamine - Sylvia Milanez
8. Data analysis of Hydrogen sulfide - Cheryl Bast
9. Overview of HCFC - George Rusch
10. Data analysis of HFC-134a - Sylvia Talmage
11. Data analysis of HCFC-141b - Sylvia Talmage
12. Data analysis of Piperidine - Kowetha Davidson/Mark McClanaham
13. Data analysis of Furan - Claudia M. Troxel
14. Data analysis of Propylene oxide - Claudia Troxel
15. Data analysis of Propylene oxide (DNA adducts) - James Swenberg
16. Data analysis of Propylene oxide - Larry Andrews

LIST OF APPENDICES

A. Approved NAC/AEGL-11 Meeting Highlights
B. Ballot for Propionitrile
C. Ballot for Cyclohexylamine
D. Ballot for Hydrogen sulfide
E. Ballot for HFC -134a
F. Ballot for HCFC 141b
G. Ballot for Piperidine
H. Ballot for Furan
I. Ballot for Propylene oxide

Attachment 1

National Advisory Committee for Acute Exposure Guideline Levels for Hazardous Substances

NAC/AEGL-12

The Governor's House
1615 Rhode Island Ave., N. W. , Washington, D.C. 20036
Phone: 202-296-2100

AGENDA

Monday, December 7, 1998

10:00 - 10:15 AM	Introductory remarks and approval of NAC/AEGL-11 Highlights (George Rusch, Roger Garrett, and Paul Tobin)
10:15 - 12:00	Status Reports • Extrapolation/interpretation of "ceiling" values (John Morawetz, Larry Gephart, George Rusch) -30 min. • Discussion of AEGL-1 Level - 45 min. • Report on NAS/COT-AEGL Subcommittee -15 min. • SOP Progress Report (Ernie Falke) -15 min.
12:00 - 1:00 PM	**Lunch**
1:00 - 2:15	Propionitrile (George Rogers/Cheryl Bast)
2:15 - 2:30	**Break**
2:30 - 4:00	Cyclohexylamine (Mark McClanahan/Sylvia Milanez)
4:00 - 5:00	HFC 134a & HCFC 141b (George Rusch/Sylvia Talmage)

Tuesday, December 8, 1998

8:00 - 10:30 AM	HFC 134a & HCFC 141b (continued)
10:30 - 10:45	**Break**
10:45 - 12:00	Hydrogen sulfide (Steve Barbee/Cheryl Bast)
12:00 - 1:00 PM	**Lunch**
1:00 - 2:15	Hydrogen sulfide (continued)
2:15 - 3:15	Piperidine (Mark McClanahan/Kowetha Davidson)
3:15 - 3:30	**Break**
3:30- 4:15	Furan (Claudia Troxel/George Rodgers)
4:15 - 4:30	Status of Jet Fuel (JP-4, -5, -7, and -8) (Sylvia Talmage)
4:30 - 5:00	Ethylene oxide (Kyle Blackman/Kowetha Davidson)

Wednesday, December 9, 1998

8:00 - 9:00 AM	Use of Categorical Regression to Determine c x t Relationship for Hydrogen Sulfide (Judy Strickland)
9:00 - 9:30	Hydrogen sulfide (continued)
9:30 - 10:30	Overviews of Sulfur trioxide, Sulfuric acid, and Oleum (Tom Hornshaw/Cheryl Bast)
10:30 - 10:45	**Break**
10:45 - 12:30 PM	Propylene oxide (Jim Holler/Claudia Troxel) and Industrial presentations (Larry Andrews/James Swenberg)
12:30 - 1:00	Administrative issues, future meetings
1:00	Adjourn

Attachment 2

Dec 7-9, 1998

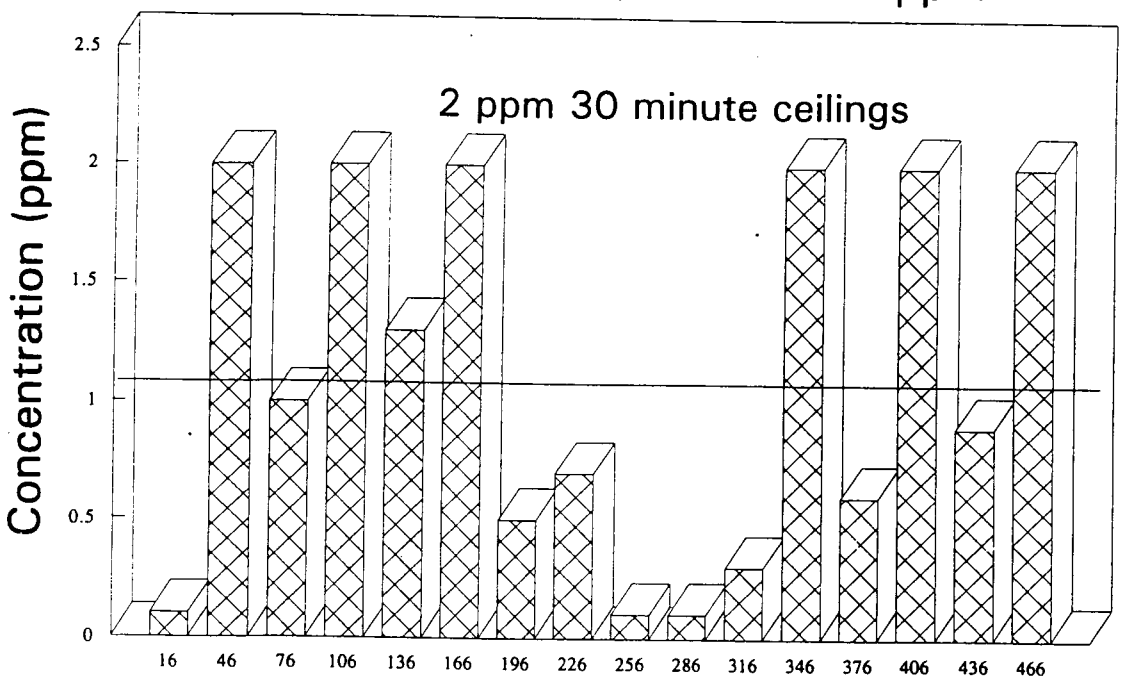
NAC/AEGL-12 meeting

Name	Affiliation	Phone No.
Po-Zyung Lu	ORNL	(423) 574-7587
Glenn Leach	U.S. Army CHPPM	410-436-2176
Kenneth R. Still	US NAVY-NHRC/TD	937-255-6058 x 202
Pamela Dalton	Monell Chemical Senses Ctr	215-898-5595
George Alexeeff	Cal/EPA	(510) 622-3202
Bill Pepelko	US EPA NCEA	202 564 3309
Loren D. Koller	Oregon State University	541 737 5547
Richard D. Thomas	Intercet, Ltd	703 734-1454
Bill Brese	ASTHO	802-863-7598
Dodd Hansen	BNL DOE	516 344-7535
Robert Benson	EPA Region 8	303-312-7070
Dale Bellew	MPCA	612-296-7874
Kyle Blackman	FEMA	202-646-4676
Roger Garrett	EPA	202-260-4302
George Rusch	Allied Signal	973-455-3672
Paul Tobin	EPA	202 260-1736
Ernest V. Falke	EPA	202 260-3433
John P. Hinz	USAF	(210) 536-6136
Surender Ahir	OSHA	202-693-9020
Rick Niemeier	NIOSH	(513) 533-8388
George Cushmac	DOT	202-366-4493
George Rodgers	AAPCC	502-852-8626
Nancy Kim	NYS DOH	518-458-6435
Tom Hornshaw	Ill EPA	217-785-0830
Steven Barbee	Olin Corp/AIHA	203-495-8550 x 5435
Jim Holler	ATSDR	404-639-6309
Lynn Beasley	EPA/OERR (Superfund)	703.603.9086

Name	Affiliation	Phone No.
Larry Gephart	Exxon Biomedical	732 873-6319
MARK A McCLANAHAN	CDC/NCEH	770-488-7297
NICOLE LAVEDAS	ENVIRON Corp.	703/516-2300
Kathleen Sidwell	IIAR	202/857-1110
Rick Beach	CTE Engineers.	703-204-6345
Sylvia Milanez	ORNL	423-576-2964
Susan Ripple	CMA-PO Panel	517-837-2290
Sylvia Talmage	ORNL	423/576-7758
Cheryl Bast	ORNL	423-574-7581
Thomas Sobotka	FDA	(301) 594-5881
Sara Thurin Rollin	BNA-Bureau of Env. News	(202) 452-4584
Ursula Stephan	FRG	0049/345/550673
Robert Snyder	Rutgers U.	732-445-3720
JONATHAN BORSTEL	ACOEM	203-777-6611
John Moramudz	ICMC	513-621-8883
Susan Snider	Am. Forest & Paper Assoc.	202-463-2589
John Festa	"	202-463-2582
Larry Andrews	Lyondell Chem	610-359-4876
Jim Swenberg	UNC	919-966-6139
Judy Strickland	US EPA	919 541 4930

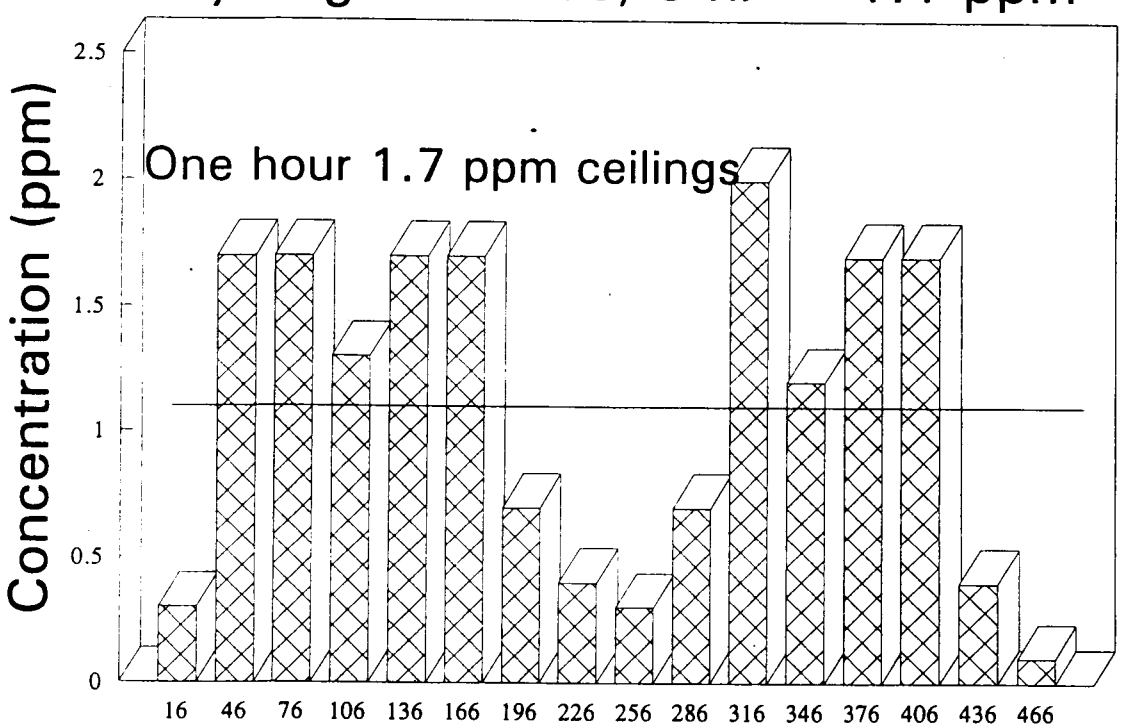
30 minute ceiling

Hydrogen Sulfide; 8 hr = 1.1 ppm



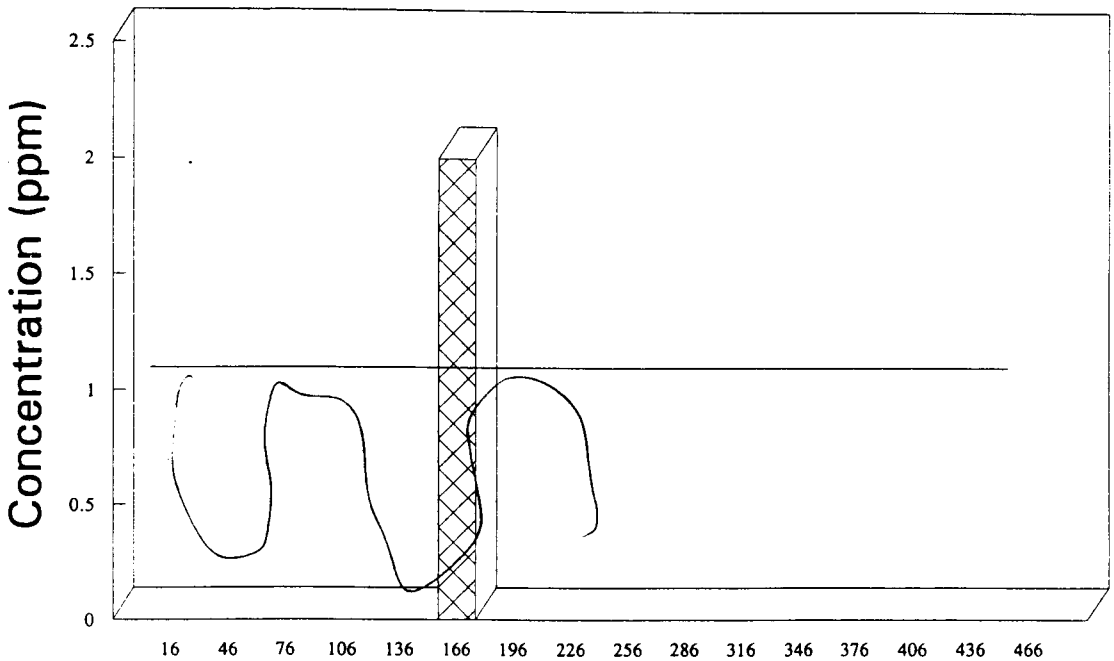
One hour ceiling

Hydrogen Sulfide; 8 hr = 1.1 ppm



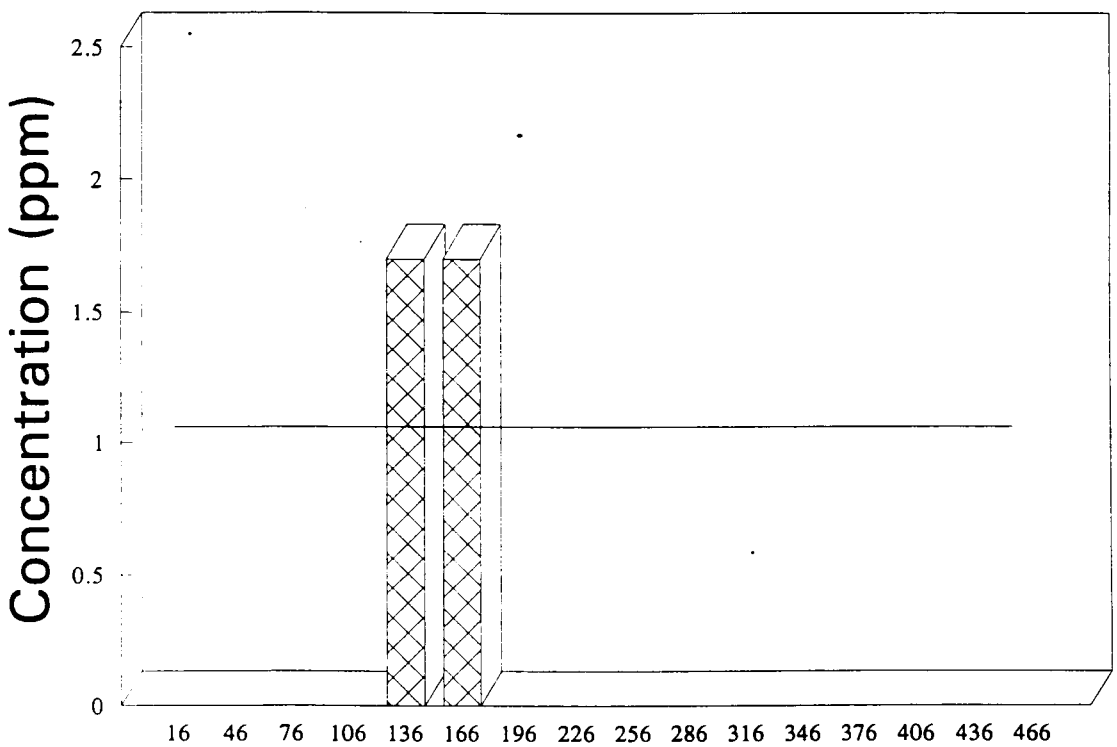
30 minute ceiling - 2 ppm

Hydrogen Sulfide; 8 hr ≐ 1.1 ppm



One hour ceiling - 1.7 ppm .

Hydrogen Sulfide; 8 hr = 1.1 ppm



Rationale for setting AEGLs as Ceilings

1) **Ceilings do not allow peak exposures that have been demonstrated to produce toxic effects.**

2) **Ceilings are consistent with the methodology of the vast majority of animal experiments.**

3) **Ceilings are consistent with the methodology of human experiments.**

4) **A ceiling definition is consistent with the 1993 Guidelines for Developing Community Emergency Exposure Levels for Hazardous Substances published by the Committee on Toxicology of the National Resource Council has language that might be useful.**

   "A ceiling is a concentration of a substance that should never be exceeded (page 2)"

5) **Without a definition of the 4 and 8 hour limits as ceilings, multiple 30 minute and one hour exposures would be allowed. This is inconsistent with the animal and human data used by this committee to set the 30 minute and one hour recommended levels.**

6) **Without a definition of the 4 and 8 hour limits as ceilings, an exposure at the 30 minute or one hour recommended levels would be allowed for a time period longer than the defined length of 30 minutes or 1 hour. This is inconsistent with the animal and human data used by this committee to set the 30 minute and one hour recommended levels.**

Definition and Applicability of AEGL time periods

Extrapolation below the shortest time period

The language distributed at the September Oak Ridge meeting was:

> "In this context, a ceiling level not to be exceeded is the AEGL value with the shortest (least) averaging time. For most chemicals, this will be the 30 minute value, unless a shorter period is determined (for example 10 minutes)."

Additional language proposed by George Rusch:

> "Frequently, exposure to a high level of a substance for a short time period can cause a toxic effect far more serious than exposure to a lower level for a longer period of time. In fact, while exposure to a chemical at a given level for 30 minutes might only result in a minimal toxic response, exposure to twice that level for 15 minutes could be lethal.

Applicability of appropriate AEGL time period

Discussed by working group of John Morawetz, Larry Gephart, John Hinz, Paul Tobin

> "The only exposure time period that should be used is the one that most closely matches the duration pertinent to realistic scenarios for hazardous substance accidents."

> reference: 1993 Guidelines for Developing Community Emergency Exposure Levels for Hazardous Substances; Committee on Toxicology of the National Resource Council, page 20

Additional language proposed by George Rusch:

> "For exposures of intermediate time periods, other than those specified in the AEGL guidelines, one should take the two values on each side of the desired time period and extrapolate to the given time using $C^n x$ where n is the exponent for the line connecting the two points on each side of the selected time period. Alternatively, the concentration can be estimated graphically.

Use of Categorical Regression to Determine c x t Relationship for Hydrogen Sulfide

Judy A. Strickland
National Center for Environmental Assessment
U.S. Environmental Protection Agency

Acute Reference Exposure Methodology

- *Methods for Exposure-Response Analysis for Acute Inhalation Exposure to Chemicals, Development of the Acute Reference* Exposure EPA/600/R-98/051
- *CatReg Software User Manual* EPA/600/R-98/052
- *CatReg Software Documentation* EPA/600/R-98/053

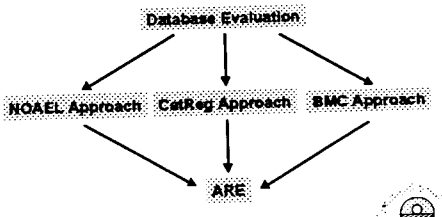
ARE Definition

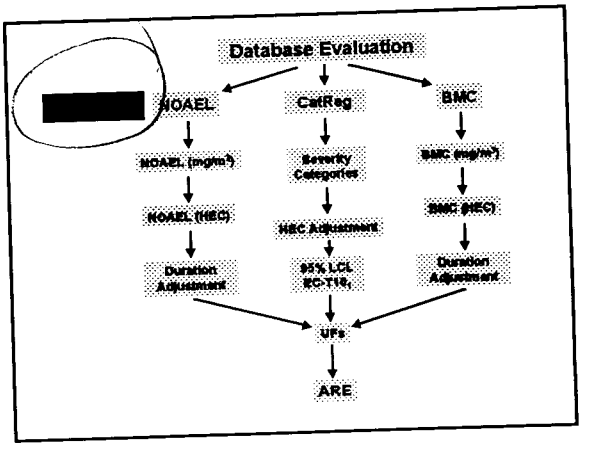
- Exposure--concentration and duration--that is not likely to cause adverse effects in a sensitive human subpopulation exposed on an intermittent basis
- Single continuous exposure for < 24 hours

Purpose

- Develop airborne levels unlikely to cause adverse effects during short-term exposures
- Support implementation of the CAAA (Section 112) by providing means for risk assessment for accidental or routine short-term exposures

Overview of ARE Derivation





Categorical Regression

- Group effect data into severity categories
  - No adverse (0)
  - Adverse (1)
  - Lethal (2)
- Calculate probability-response (severity) relationship for concentration and duration
- 10% probability ≥ Adverse effects = 90% probability No observed adverse effects

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CatReg Model

$$Pr(Y \geq s \mid C,T) = H\{\alpha_s + \beta_1 f_1(C) + \beta_2 f_2(T)\}$$

s = Response as severity category
0, No observed adverse effect
1, Adverse effect
2, Lethal effect

C = Concentration
T = Exposure duration

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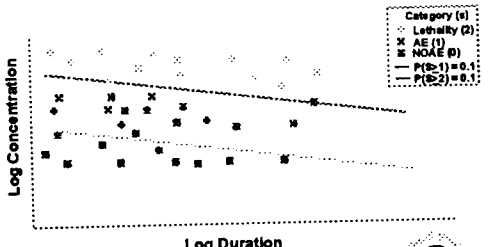
Categorical Regression Schematic



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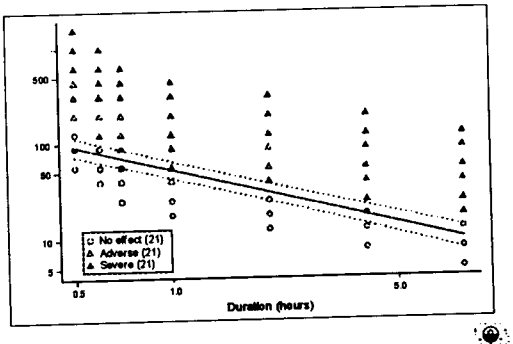
EC_{10} Line (Adverse Effects) with 95% Confidence Bounds



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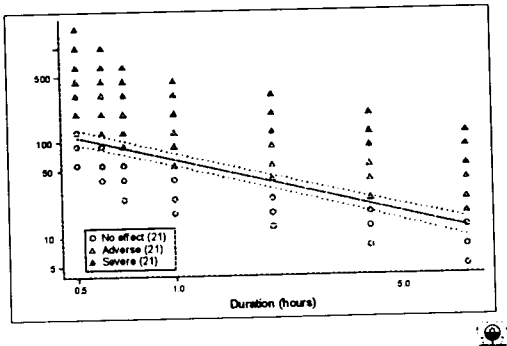
EC_{50} Line (Adverse Effects) with 95% Confidence Bounds



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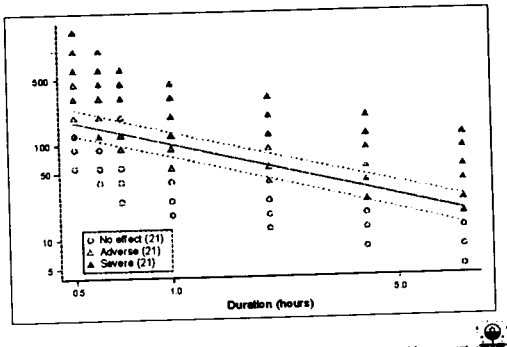
EC_{90} Line (Adverse Effects) with 95% Confidence Bounds



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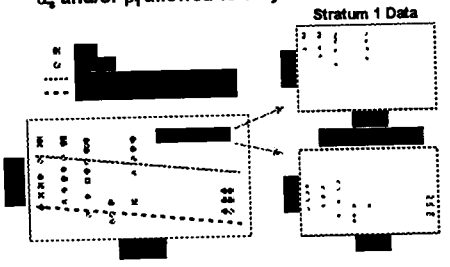
Stratified Model

$$\Pr(Y \geq s \mid C,T) = H\{\alpha_s + \beta_1 f_1(C) + \beta_2 f_2(T)\}$$

α_s and/or β_1 allowed to vary between strata



SAB Review

- NOAEL
- BMC
- Dosimetry
- c x t
- Categorical regression

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c x t

- Duration adjustments
  - BMC and NOAEL approaches
    - Use c x t for short durations to long durations
    - Use same concentration from long durations to short durations
    - Interpolate when more than one duration is available
  - Categorical regression approach
    - Does not apply

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Categorical Regression

- Parallelism of probability-response curves for all severity categories
- Judging severity category across various target organs, species
- Unreliable confidence limits
- Scaling factor

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Next Steps

- Remove restriction of parallelism
- Statistical consultations
- Develop guidance for determining severity
- Other applications for categorical regression
- Finalize documents this FY

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Categorical Regression for Hydrogen Sulfide

- 14 Studies, 199 data points
- Humans, rats, mice
- Respiratory, metabolic, clinical signs, death
- 5 min - 6 h
- Continuous, incidence

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Categorical Regression for Hydrogen Sulfide

- 3 severity categories
  - No-observed-adverse effect
  - Adverse effect
  - Lethal effect

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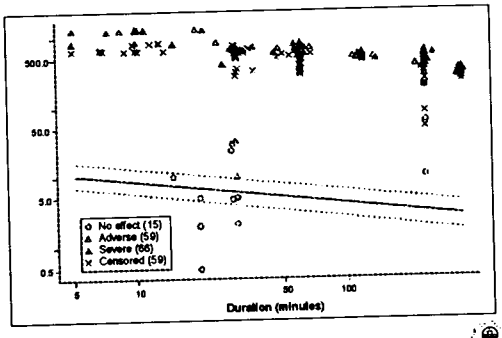
H_2S EC_{10} (Adverse Effects) with 95% Confidence Bounds



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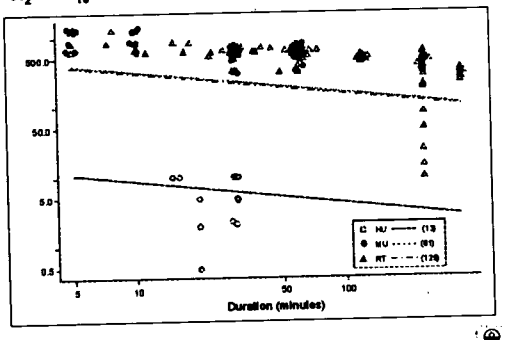
H_2S EC_{10} Common Slope Lines Stratified by Species



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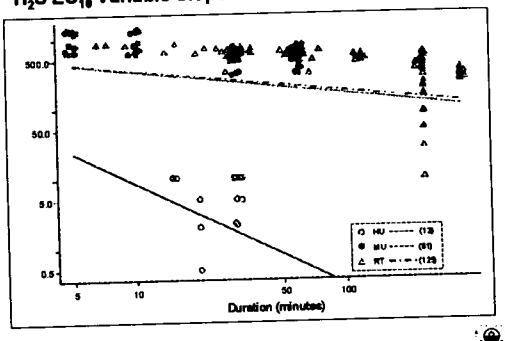
H_2S EC_{10} Variable Slope Lines Stratified by Species



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ARE Derivation for Hydrogen Sulfide (10% Probability ≥ Adverse effects)

Time	EC10 (ppm)	95% LCL (ppm)	ARE (ppm)
5 min	10.5	7.1	0.7
10 min	8.5	5.7	0.6
30 min	5.9	3.9	0.4
1 hr	4.8	3.1	0.3
2 hr	3.8	2.5	0.2
4 hr	3.1	2.0	0.2
6 hr	2.7	1.7	0.2

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Comparison of Hydrogen Sulfide ARE to Other Values

Exposure Duration	ARE (ppm)	AEGL-1 (ppm)	REL (ppm)	ERPG-1 (ppm)
30 min	0.4	2		
1 h	0.3	1.7	0.1	0.1
4 h	0.2	1.2		
8 h		1.1		

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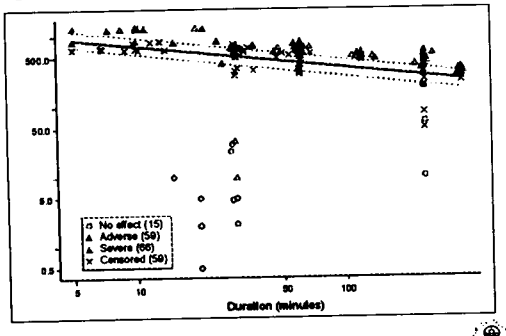
H_2S EC_{10} Line (Lethality) with 95% Confidence Bounds



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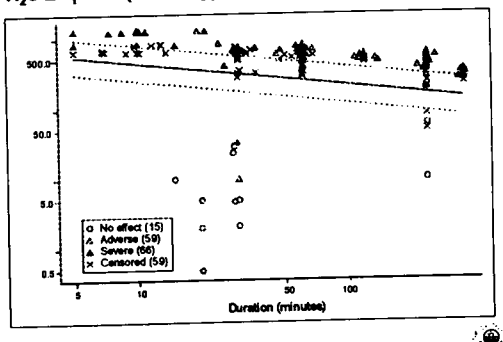
H_2S EC_1 Line (Lethality) with 95% Confidence Bounds



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Probability of Lethal Effects

Duration	10% Lethality		1% Lethality	
	EC10 (ppm)	95% LCL (ppm)	EC10 (ppm)	95% LCL (ppm)
5 min	914.8	701.2	557.1	311.5
10 min	737.4	573.0	449.0	251.2
30 min	514.7	403.0	313.5	174.2
1 hr	414.9	323.1	252.7	139.2
2 hr	334.4	257.2	203.6	111.0
4 hr	269.6	203.6	164.2	88.2
6 hr	233.5	188.0	142.2	75.6

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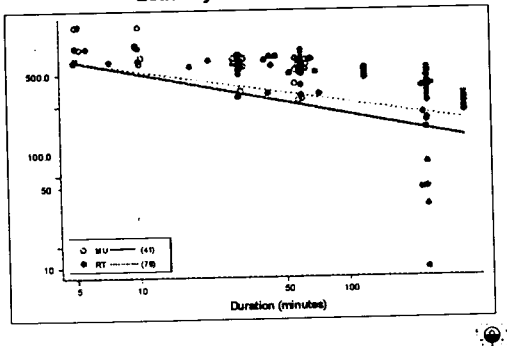
Slope Analysis for Adverse vs Lethal Effects

- To identify slopes/n's
  - No-observed-adverse effect + Adverse effect
    - Calculate 10% Probability Adverse Effects
  - Adverse effect + Lethal effect
    - Calculate 10% Probability Lethal Effects

H_2S (Adverse Effects) EC_{10} Lines Variable Slope Lethality Data Removed



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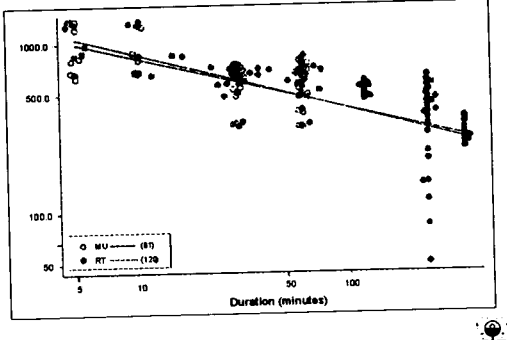
H_2S (Lethal Effects) EC_{10} Lines Variable Slope No Observed Effect Data Removed



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c x t Slopes for Adverse & Lethal Effects

	Rats & Mice	Rats	Mice
Adverse Effects Slope n	 -0.27 3.7	 -0.27 3.7	 -0.36 2.8
Lethality Slope n	 -0.31 3.2	 -0.29 3.3	 -0.64 3.1

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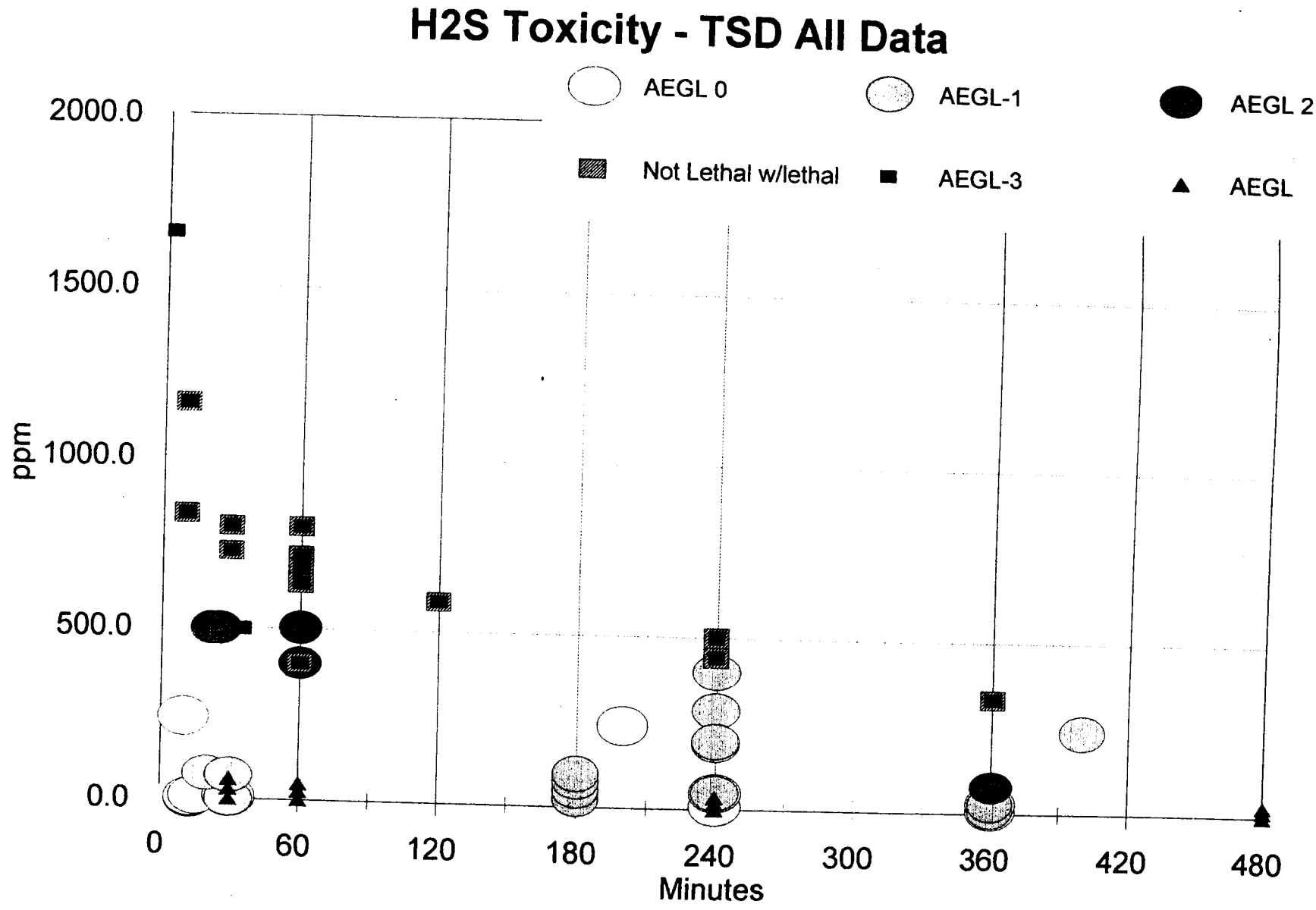
Duration Extrapolations with Various n's

n	1hr	8 hr
2.8	0.3	0.14
3.1	0.3	0.15
3.2	0.3	0.16
3.3	0.3	0.16
3.7	0.3	0.17



Attachment 5

Attachment 6

PROPOSED AEGL VALUES:

PROPIONITRILE

Chemical Manager: George Rodgers
ORNL Staff Scientist: Cheryl Bast

NITRILES: GENERAL ISSUES

- Acute toxicity likely due to metabolic release of cyanide
- Rat appears to be more resistant to lethal effects of methacrylonitrile than mice, guinea pigs, or rabbits

Summary of Proposed AEGL Values for Isobutyronitrile					
	30-min	1-hr	4-hr	8-hr	Endpoint (Reference)
AEGL-1	ID	ID	ID	ID	Insufficient data to derive AEGL-1 values
AEGL-2	8.7 ppm	6.6 ppm	3.9 ppm	3.0 ppm	No-effect-level in rat developmental toxicity study 100 ppm, 6 hr/day, 5 days/week, days 6-20 of gestation. Values calculated from single 6 hr. exposure. (Saillenfait et al., 1993)
AEGL-3	26 ppm	20 ppm	12 ppm	9.0 ppm	Estimated NOEL for death in rats. 1-hr. $LC_{50} \div 3$ (1800 ppm÷3=600 ppm) (Kodak, 1996)

Uncertainty factors:

Intraspecies = 3: effects appear to be due to cyanide and human accidental and occupational exposure to HCN suggest little intraindividual variability

Interspecies = 10: the rat is not the most sensitive species

Time scaling:

C^n x t = k where n = 2.6, value is for hydrogen cyanide (NAC/AEGL, 1997) based on cyanide rat lethality data. The n value for hydrogen cyanide was utilized for time scaling for isobutryonitrile since much of the acute toxicity appears to be due to hydrogen cyanide and data were insufficient for deriving

Summary of Proposed AEGL Values for Methacrylonitrile					
	30-min	1-hr	4-hr	8-hr	Endpoint (Reference)
AEGL-1	ID	ID	ID	ID	Insufficient data to derive AEGL-1 values
AEGL-2	1.5 ppm	1.1 ppm	0.7 ppm	0.5 ppm	One-third reduction in AEGL-3 values
AEGL-3	4.5 ppm	3.4 ppm	2.0 ppm	1.5 ppm	NOEL for death in mice. 19.6 ppm for 4 hr. (Pozzani et al., 1968)

Uncertainty factors:

Intraspecies = 3: effects appear to be due to cyanide and human accidental and occupational exposure to HCN suggest little intraindividual variability

Interspecies = 3: the mouse is the most sensitive species

Time scaling:
$C^n \times t = k$ where n = 2.6, value is for hydrogen cyanide (NAC/AEGL, 1997) based on cyanide rat lethality data. The n value for hydrogen cyanide was utilized for time scaling for isobutryonitrile since much of the acute toxicity appears to be due to hydrogen cyanide and data were insufficient for deriving an n value for the nitrile itself.

Summary of Proposed AEGL Values for Propionitrile					
Classification	30-min	1-hr	4-hr	8-hr	Endpoint (Reference)
AEGL-1 (Nondisabling)	ID	ID	ID	ID	Insufficient data to derive AEGL-1 values
AEGL-2 (Disabling)	ID	ID	ID	ID	Insufficient data to derive AEGL-2 values
AEGL-3 (Lethality)	51 ppm (120 mg/m^3)	39 ppm (89 mg/m^3)	23 ppm (53 mg/m^3)	18 ppm (41 mg/m^3)	No-effect-level for death in rats (Younger Labs, 1978)

NIOSH TWA: 6 ppm (14 mg/m^3)

ACUTE EXPOSURE GUIDELINES FOR PROPIONITRILE (CAS NO. 107-12-0)

AEGL-3 VALUES			
30 minutes	1 hour	4 hours	8 hours
51 ppm	39 ppm	23 ppm	18 ppm

Reference: Younger Labs. 1978. Initial Submission: Toxicological Investigation of Propionitrile with Cover Letter dated 081992. OTS0546148.

Test Species/Strain/Sex/Number: Sprague-Dawley rats/ 5 males and 5 females/ concentration

Exposure Route/Concentrations/Durations: Rats/Inhalation: 690, 1100, 1700, 2800, 4400, or 6900 ppm/4 hours

Endpoint/Concentration/Rationale: NOEL for death of 690 ppm was determinant for AEGL-3

Uncertainty Factors/Rationale:
Total uncertainty factor: 30
Interspecies: 10- the rat is not the most sensitive species
Intraspecies: 3- effects appear to be due to cyanide and human accidental and occupational exposure to cyanide suggest little intraindividual variability

Modifying Factor: none

Animal to Human Dosimetric Adjustment: Insufficient data

Time Scaling: $C^n \times t = k$ where $n = 2.6$, value is for hydrogen cyanide (NAC/AEGL, 1997) based on cyanide rat lethality data. The n value for hydrogen cyanide was utilized for time scaling for propionitrile since much of the acute toxicity appears to be due to hydrogen cyanide and data were insufficient for deriving an n value for the nitrile itself. Data point used for AEGL-3 derivation was 4 hours. Other time points were based on extrapolation.

Confidence and Support for AEGL values: Confidence is low due to the sparse data base.

POSSIBLE AEGL-2 STUDY

- **Developmental Rat (Saillenfait et al., 1993)**

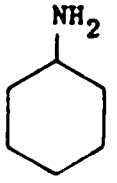
  0, 50, 100, 150, or 200 ppm for 6 hr/day on days 6-20 of gestation

  Maternal death, increase in nonsurviving implants and embryonic resorptions, and decreased fetal weights at 200 ppm.

Possible AEGL-2 Values for Propionitrile								
30-min	1-hr	4-hr	8-hr	UF	Concentration	Time	Endpoint	Reference
13 ppm	10 ppm	5.8 ppm	4.4 ppm	Inter: 10 Intra: 3	150 ppm	6-hr.	No effects	Saillenfait et al., 1993
51 ppm	*39 ppm*	*23 ppm*	*18 ppm*	*Proposed AEGL-3 Values*				

Attachment 7

ACUTE EXPOSURE GUIDELINE LEVELS (AEGLs) FOR CYCLOHEXYLAMINE



ORNL Staff Scientist: Sylvia Milanez
Chemical Manager: Mark McClanahan
Chemical Reviewers: Nancy Kim and Richard Niemeier

AEGL-1

Key study: Watrous and Schulz (1950). Exposure to 4-10 ppm cyclohexylamine "caused no symptoms of any kind," but exposure to higher but not measured levels for ≤ 1 ½ hours caused headache, rapid heartbeats, vomiting, and eye, nose and throat irritation. Theoretical exposure to 4 ppm for 2 hours is used for AEGL-1 calculations (odor detection threshold is 2.6 ppm).

Toxicity endpoint: Odor detection; threshold for sensory irritation, nausea.

Scaling: $C^2 \times t = k$ (ten Berge et al., 1986) default - no data to estimate n
$(4\ ppm)^2\ (2\ hrs) = k = 32$ ppm-hrs

UF: 3 for intraspecies (cyclohexylamine is an irritant and its effect should not vary greatly among humans; metabolism not likely a factor)

AEGL-1 Values for Cyclohexylamine			
30 minutes	**1 hour**	**4 hours**	**8 hours**
2.7 ppm [11 mg/m^3]	2.7 ppm [11 mg/m^3]	2.7 ppm [11 mg/m^3]	2.7 ppm [11 mg/m^3]

Supporting Evidence for Cyclohexylamine AEGL-1 Values

Bio/dynamics, 1990: Many rats (40-60%) exposed to 54.2 ppm for 4 hours had labored breathing ½ hour into the exposure, by 1 hour 70-90% of the rats had partially closed eyes, 10-30% also had red nasal discharge.
Use ½-hour exposure for derivation, $C^2 \times t = k$ for scaling, UF = 10 (3 X 3)

Gagnaire et al., 1989: Mouse RD_{50} = 51 ppm
Nielsen and Yamagiwa, 1989: Mouse RD_{50} = 27 ppm
Exposure to 0.1 x RD_{50} for "hours-days" ⇒ "some sensory irritation"
Exposure to 0.01 x RD_{50}" for "days" ⇒ no sensory irritation (Alarie, 1981).
Use 8 hour exp. for derivation, $C^2 \times t = k$ for scaling, UF = 3 (intraspecies)

Alternate AEGL-1 values for cyclohexylamine (ppm)						
30 min	**1 hr**	**4 hrs**	**8 hrs**	**UF**	**Endpoint (Reference)**	
5.4	3.8	1.9	1.4	10	Eye and respiratory irritation; ½ -hour exposure to 54.2 ppm (Bio/dynamics,1990)	
0.68 6.8	0.48 4.8	0.24 2.4	0.17 1.7	3 3	*8-hr exp. to:* 0.01 x RD_{50} 0.1 x RD_{50}	RD_{50} = 51 ppm (Gagnaire et al,1989)
0.36 3.6	0.25 2.5	0.13 1.3	0.09 0.90	3 3	*8-hr exp. to:* 0.01 x RD_{50} 0.1 x RD_{50}	RD_{50} = 27 ppm (Nielsen & Yamagiwa, 1989)
2.6	2.6	2.6	2.6	-	Human odor detection (Amoore and Hautala, 1983)	
2.7*	**2.7***	**2.7***	**2.7***	3	**Threshold for sensory irritation, nausea (Watrous and Schultz, 1950)**	

*Proposed AEGL-1 values

Cyclohexylamine acute inhalation exposure animal studies					
Single exposure studies					
Species	Exposure time	Conc. (ppm)	Time of death	Morta-lity	Comments (Reference)
Rat	6 hrs 6 hrs	1000 12,000	-- 48 hrs	0/3 2/3	Nominal conc.; obs. time?) (Eastman Kodak, 1984)
Rat	4 hrs 4 hrs ≤ 2 hrs	4000 8000 ~15,000	-- ? --	0/6 6/6 0/6	Nominal concs; time of death at 8000 ppm not given (Smyth, et al. 1969)
Rat	4 hrs 4 hrs 4 hrs	54.2 567 >542**	-- -- Day 2	0/10 0/10 2/10	Analytical concs.; **highest conc. also cont. 612 mg/m^3 aerosol(Bio/dynamics,1990)
Rat	not given (2-7 hrs ?)	443 1059 1847 2833	-- Death on days 7-14	0/? LC_{Lo} LC_{50} LC_{100}	Exposure time, # animals per dose, and time of death were not given. LC_{50} was calculated by the study author using Pershin's formula. (Lomonova, 1965)
Mouse	not given (2-7 hrs ?)	12.3 24.6 264 1059	-- Death on days 1-5	0/? LC_{Lo} LC_{50} LC_{100}	
Mouse	30 min	355	--	0/4	75% lower resp. rate; 20' obs. (Nielsen and Y.,1989)
Multiple-exposure studies					
Rat	2 h/d x2mo 4 h/d x5mo	172 24.6	2 mo. 4 mo.	3/6 1/20	Death towards end of 2 mo Death during 4th month (Lomonova, 1965)
Rat	7hrs/day x 10 d.	150 800 1200	? (10d) 24 hrs 7 hrs	1/5 ?/5‡ 4/5‡	No. rats/dose not given; may be 5. ‡ indicated it was unclear if this was the total for the 10-day obs. period or if other animals died after the given time of death (Watrous and Scultz, 1950)
Guinea pig	7hrs/day x 10 d.	150 800 1200	? (10d) 14 hrs 7 hrs	3/5 2/5‡ 5/5	
Rabbit	7hrs/day x 10 d.	150 800 1200			

AEGL-2 and AEGL-3

Key study: Bio/dynamics, 1990. Rats (5/sex/dose) exposed for 4 hours to 567 ppm cyclohexylamine had labored breathing, gasping, tremors, and irreversible ocular lesions. At the next higher conc. (542 ppm + 612 mg/m^3 aerosol) rats had similar or more severe effects; 2/10 died.

Toxicity endpoint:

AEGL-2: 189 ppm [i.e., 1/3(567 ppm)] is estimated threshold for irreversible ocular lesions and serious respiratory effects.

AEGL-3: 567 ppm is lethality threshold

Scaling: $C^2 \times t = k$ (ten Berge et al., 1986) default - no data to estimate n

$(189\ ppm)^2\ (4\ hrs) = k = 142{,}884$ ppm-hrs

$(567\ ppm)^2\ (4\ hrs) = k = 1{,}285{,}956$ ppm-hrs

UF: 30: 3 for sensitive humans

10 for interspecies (rat was not most sensitive species)

AEGL-2 and AEGL-3 values for cyclohexylamine				
Level	**30 minute**	**1 hour**	**4 hours**	**8 hours**
AEGL-2	18 ppm [62 mg/m^3]	13 ppm [44 mg/m^3]	6.3 ppm [22 mg/m^3]	4.5 ppm [16 mg/m^3]
AEGL-3	53 ppm [217 mg/m^3]	38 ppm [153 mg/m^3]	19 ppm [77 mg/m^3]	13 ppm [54 mg/m^3]

COMPOSITION OF AEROSOL IN BIO/DYNAMICS (1990) STUDY

Observations & Background Information:

- No aerosol component seen during empty chamber trials
- Cyclohexylamine saturated vapor conc. is ~14,000 ppm (~57 mg/L)
- Airflow in 100 L chamber was ~21 Lpm; should have been ~ 100 Lpm
- Chambers of Group I and II became cloudy by 1-2 hours into exposure
- Group I and II rats had wet fur and yellow ano-genital stains
- Extra desiccation of group II and III chamber removed most aerosol

Conclusion:

- ***Water vapor in air, mostly from urine, condensed to form WATER AEROSOL (droplets) in which cyclohexylamine is dissolved***

Group	Nominal conc. (mg/L)	Analytic vapor conc. (mg/L)	Aerosol conc.** (mg/L)	Effects (summary)
I	8.8	2.2 (542 ppm)	0.612	Group I: 2/10 die; breathing difficulties, corneal lesions, red/brown nasal discharge or stains on face, yellow ano-genital stains, wet fur
II	6.4	2.3 (567 ppm)	0.00018	
III	0.57	0.22 (54.2 ppm)	0.015	Labored breathing, eye irritation, mucoid or red/brown nasal discharge

**Note that the aerosol concentration cannot be converted to ppm!!

TABLE 3: Exposure and post-exposure observations in rats administered cyclohexylamine vapor[1] (5 m, 5 f per dose) (Bio/dynamics, Inc., 1990)

Observation	Hours into exposure						Days or hours post-exposure[2]			
	¼	½	¾	1	2	4	½-2 h	2-7 d	8-14d	15-22d
GROUP I (542 ppm+612mg/m³ aerosol)										
Lacrimation	1-3	10	10				3	1	-	1
Mucoid nasal discharge	-	1-3	7-9	Clouding or			-	-	-	-
Red nasal discharge(w/d)	-	-	-	residual			3	5	1	-
Dried brown m. on face	-	-	-	build-up			-	4	4	3
Labored breathing	1-3	7-9	7-9	inside the			10	9	2	7
Gasping	-	-	-	chamber			7	5	1	2
Rales: moist or dry	-	-	-				6	9	5	7
Eyes closed	10	10	10				-	1	-	-
Coarse tremors	-	-	-				6	1	-	-
Corneal opacity	-	-	-				2	7	8	7
Corneal irreg. or ulcer.	-	-	-				9	1	-	-
Yellow ano-genital stains	-	-	-				2	7	2	1
Alopecia	-	-	-				-	-	2	3
Decreased activity	-	-	-				10	1	-	-
Wet fur	-	-	-				9	-	-	-
GROUP II (567 ppm)										
Lacrimation	-	1-3	1-3	1-3			5	2	2	2
Chromodacryorrhea	-	-	-	-	Resid.		2	-	-	-
Mucoid nasal discharge	-	1-3	1-3	1-3	build-up		-	3	-	-
Red nasal discharge(w/d)	-	-	-	-	inside		7	5	2	1
Dried brown m. on face	-	-	-	-	the		8	9	9	1
Labored breathing	1-3	4-6	4-6	4-6	chamber		10	1	7	-
Gasping	-	1-3	1-3	1-3			2	2	-	-
Rales: moist or dry	-	-	-	-			10	10	10	9
Eyes partially closed	10	10	10	10			-	-	-	-
Coarse tremors	-	-	-	-			2	-	-	-
Corneal opacity	-	-	-	-			-	9	10	10
Corneal irreg. or ulcer.	-	-	-	-			-	2	10	10
Yellow ano-genital stains	-	-	-	-			9	9	5	-
Wet fur	-	-	-	-			5	-	-	-
GROUP III (54.2 ppm)										
Lacrimation	-	-	-	-	-	-	4	1	-	
Chromodacryorrhea	-	-	-	-	-	-	2	-	-	
Mucoid nasal discharge	-	-	-	-	-	-	3	1	-	all sacri-
Red nasal discharge(w/d)	-	-	-	1-3	1-3	1-3	2	4	3	ficed on
Dried brown/red on face	-	-	-	-	-	-	10	-	-	day 15
Labored breathing	1-3	4-6	7-9	7-9	10	10	-	-	-	
Eyes partially closed	-	-	-	7-9	10	10	-	-	-	

Supporting Evidence for Cyclohexylamine AEGL-2 Values

Lomonova, 1965. 2-month (2 hrs/day at 172 ppm) study. Decreased blood hemoglobin and RBC count after 10 days (the first test point), progressing to severe hemolysis, vascular effects, and lung inflammation by end of 2 months. A single 2-hour exposure was used for AEGL-2 derivation as the threshold of causing hematological changes and/or vascular lesions. Use $C^2 \times t = k$ for scaling, UF = 30: 3 for intraspecies, 10 for interspecies (rat was not most sensitive animal species).

Potential alternate AEGL-2 values for cyclohexylamine (ppm)					
30 min	**1 hr**	**4 hrs**	**8 hrs**	**UF**	**Endpoint (Reference)**
18*	**13***	**6.3***	**4.5***	**30**	**Threshold for irreversible ocular lesions; severe resp. effects (Bio/dynamics, 1990)**
11	8.1	4.1	2.9	30	Threshold for vascular and hemolytic changes (Lomonova, 1965)

*Proposed AEGL-2 values

Supporting Evidence for Cyclohexylamine AEGL-3 Values

Scaling for all studies was: $C^2 \times t = k$ (ten Berge et al., 1986) (default because there were no data to estimate n)

Alternate AEGL-3 values for Cyclohexylamine (ppm)						
30 min	**1 hr**	**4 hrs**	**8 hrs**	**UF**	**Endpoint (Reference)**	
56	40	20	14	10	Rat, guinea pig - 10 exp. to 150 ppm (7 hrs/day) caused 1/5 and 3/5 deaths (none early); use one 7-hr exposure (Watrous and Schultz, 1950).	
36	25	13	8.9	10	Mice exposed 30 min to 355 ppm had 0/4 mort. but had 75% dec. in breathing rate. (Nielsen and Yam., 1989).	
41-77	29-54	14-27	10-19	30	Rat: 1/3(LC_{50})= 616 ppm	Lethality thresholds. Exposure time not given; values calc. for 2-7 hrs. (Lomonova, 1965)
30-55	21-39	10-20	7.4-14	30	"max. tolerated" conc. = 443 ppm	
18-33	12-23	6.2-12	4.4-8.2	10	Mouse:1/3(LC_{50})=88ppm	
2.5-4.6	1.7-3.3	0.87-1.6	0.62-1.2	10	"max. tolerated" conc. = 12.3 ppm	
53*	**38***	**19***	**13***	**30**	**Rat lethality threshold (4-hr exp. to 567 ppm) (Bio/dynamics, 1990)**	

*Proposed AEGL-3 values

SUMMARY OF AEGL VALUES FOR Cyclohexylamine					
Classification	**30 minute**	**1 hour**	**4 hours**	**8 hours**	**Endpoint (Reference)**
AEGL-1	2.7 ppm [11 mg/m^3]	2.7 ppm [11 mg/m^3]	2.7 ppm [11 mg/m^3]	2.7 ppm [11 mg/m^3]	Sensory irritation and nausea in humans (Watrous and Schultz, 1950)
AEGL-2	18 ppm [72 mg/m^3]	13 ppm [51 mg/m^3]	6.3 ppm [26 mg/m^3]	4.5 ppm [18 mg/m^3]	Irreversible ocular lesions marked respiratory effects (Bio/dynamics, Inc.,1990)
AEGL-3	53 ppm [217 mg/m^3]	38 ppm [153 mg/m^3]	19 ppm [77 mg/m^3]	13 ppm [54 mg/m^3]	Lethality threshold in rats (Bio/dynamics,Inc.,1990).

Attachment 8

PROPOSED AEGL VALUES FOR HYDROGEN SULFIDE

CHEMICAL MANAGER: STEVEN BARBEE
ORNL STAFF SCIENTIST: CHERYL BAST

NAC/AEGL MEETING 12
DECEMBER 7-9, 1998
WASHINGTON, DC

Summary of Proposed AEGL Values for Hydrogen Sulfide					
Classification	30-min	1-hr	4-hr	8-hr	Endpoint (Reference)
AEGL-1 (Nondisabling)	2.0 ppm (2.8 mg/m^3)	1.7 ppm (2.4 mg/m^3)	1.2 ppm (1.7 mg/m^3)	1.1 ppm (1.5 mg/m^3)	Headache, increased Raw in asthmatic humans (Jappinen et al., 1990)
AEGL-2 (Disabling)	32 ppm (45 mg/m^3)	28 ppm (39 mg/m^3)	20 ppm (28 mg/m^3)	17 ppm (24 mg/m^3)	Perivascular edema and increased protein and LDH in lavage fluid in rats (Green et al., 1991; Khan et al., 1991)
AEGL-3 (Lethality)	60 ppm (85 mg/m^3)	50 ppm (71 mg/m^3)	37 ppm (52 mg/m^3)	31 ppm (44 mg/m^3)	1-hour no-effect-level for death in rats (MacEwen and Vernot, 1972)

AEGL-1 FOR HYDROGEN SULFIDE (ppm [mg/m^3])				
AEGL Level	30-min	1-hr	4-hr	8-hr
AEGL-1	2.0 [2.8]	1.7 [2.4]	1.2 [1.7]	1.1 [1.5]

Species: Human- asthmatic
Concentration: 2 ppm
Time: 30 min.
Endpoint: Headache in 3/10 and increased Raw in 2/10 subjects with no significant effects on FVC, FEV_1, or FEF
Reference: Jappinen et al., 1990

n = 4.36

Uncertainty Factor = none

Interspecies = NA. Subjects were human
Intraspecies = NA. Subjects were sensitive population (asthmatic)

Supporting Data (Bambhani et al.):

No adverse effects observed in humans exposed to H_2S while exercising to exhaustion.

5 ppm for 30 minutes
10 ppm for 15 minutes

AEGL-2 FOR HYDROGEN SULFIDE (ppm [mg/m^3])					
AEGL Level	*10-min*	30-min	1-hr	4-hr	8-hr
AEGL-2	*42 [59]*	32 [45]	28 [39]	20 [28]	17 [24]

Species: Rat
Concentration: 200 ppm
Time: 4 hr.
Endpoint: Perivascular edema and increased protein and LDH in lavage fluid in rats
References: Green et al., 1991; Khan et al., 1991

n = 4.36

Uncertainty Factor: 3 x 3 =10

Interspecies = 3 (Rat and mouse lethality data suggest little species variability)
Intraspecies = 3 (Rat data suggest little strain variability)

AEGL-3 FOR HYDROGEN SULFIDE (ppm [mg/m^3])					
AEGL Level	*10-min*	30-min	1-hr	4-hr	8-hr
AEGL-3	*76 [106]*	60 [85]	50 [71]	37 [52]	31 [44]

Species: Rat
Concentration: 504 ppm
Time: 1 hour
Endpoint: No-effect-level for death
Reference: MacEwen and Vernot, 1972

n = 4.36

Uncertainty Factor = 3 x 3 = 10

Interspecies = 3 (Rat and mouse lethality data suggest little species variability)
Intraspecies = 3 (Rat data suggest little strain variability)

Supporting Data (Toxigenics, 1983a):

No deaths in rats exposed to 80 ppm H_2S for 6 hr/day, 5 days/week, for 90 days.

Classification	30-min	1-hr	4-hr	8-hr	Endpoint (Reference)
AEGL-1 (Nondisabling)	2.0 ppm (2.8 mg/m^3)	1.7 ppm (2.4 mg/m^3)	1.2 ppm (1.7 mg/m^3)	1.1 ppm (1.5 mg/m^3)	Headache, increased Raw in asthmatic humans (Jappinen et al., 1990)
AEGL-2 (Disabling)	32 ppm (45 mg/m^3)	28 ppm (39 mg/m^3)	20 ppm (28 mg/m^3)	17 ppm (24 mg/m^3)	Perivascular edema and increased protein and LDH in lavage fluid in rats (Green et al., 1991; Khan et al., 1991)
AEGL-3 (Lethality)	60 ppm (85 mg/m^3)	50 ppm (71 mg/m^3)	37 ppm (52 mg/m^3)	31 ppm (44 mg/m^3)	1-hour no-effect-level for death in rats (MacEwen and Vernot, 1972)

ACGIH TLV-TWA: 10 ppm
ACGIH TLV-STEL: 15 ppm

NIOSH IDLH: 100 ppm
NIOSH REL- 10 min. ceiling 10 ppm

OSHA PEL-TWA: 20 ppm
PEL- 10 min. peak: 50 ppm

ERPG-1: 0.1 ppm (Based on objectionable odor)
ERPG-2: 30 ppm
ERPG-3: 100 ppm

NAS EEGL- 10 min. 50 ppm
NAS EEGL- 24-hr. 10 ppm

Cardiac Sensitization

- Phenomena where exposure of the heart to a substance renders it hypersensitive to the effects of adrenaline.
- This can result in the development of rapid, irregular heart beat, tachycardia and death.

Early Observations

- First reported in 1911 – 1913 by Levy using chloroform with adrenaline
- 1967-1968 – Abusive "sniffing" (more accurately described as deep breathing) of aerosol products (fry-pan lubricant, hair spray, deodorant, cocktail glass chiller) resulted in 65 deaths.

Study Design

Dogs are trained to stand in a sling and fitted with a face mask.

Dogs are given injections of adrenaline via the cephalic vein at doses of
4 – 12 μg/kg.* This determines the maximum dose that does not induce arrhythmia.

After a few days at rest, the evaluation is conducted.

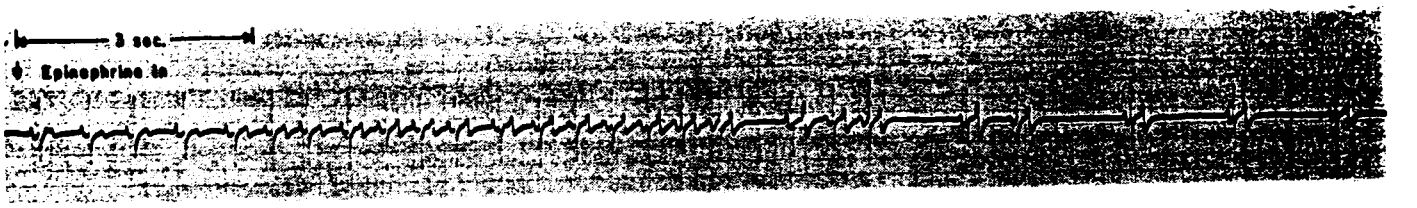
- The dog is placed in the sling, fitted with EKG leads, etc., allowed to become used to the apparatus.
- The mask is placed on the dog and he is exposed to air.
- After 2 minutes, the dog is given an injection of adrenaline at the previously determined dose.
- If no arrhythmias develop within 5 minutes, the test compound exposure is initiated.
- Five minutesinto the test compound exposure, a second injection of adrenaline if administered.
- Dog is observed for five minutes while being exposed to test compound.
- Exposure is concluded.

*** 8 μg/kg is approximately 10 times the level of adrenaline seen in humans at times of stress**

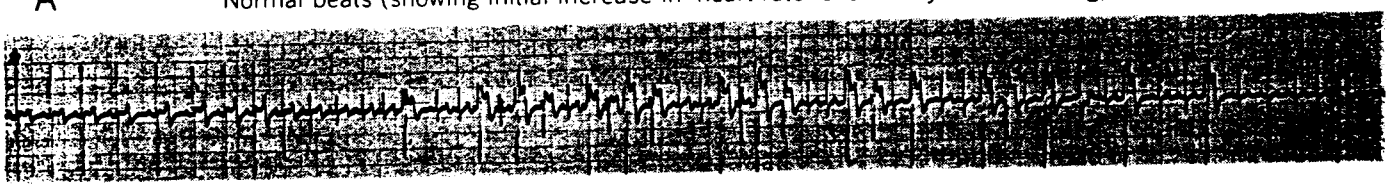
Cardiac Sensitization Test

AIR	0 Min: Start – 2 Min: Administer epinephrine[a] – – – –
AIR AND COMPOUND	7 Min: Administer test chemical – – – – 12 Min: Administer epinephrine (challenge injection) – – – – 17 Min: Stop administration of chemical. End experiment.

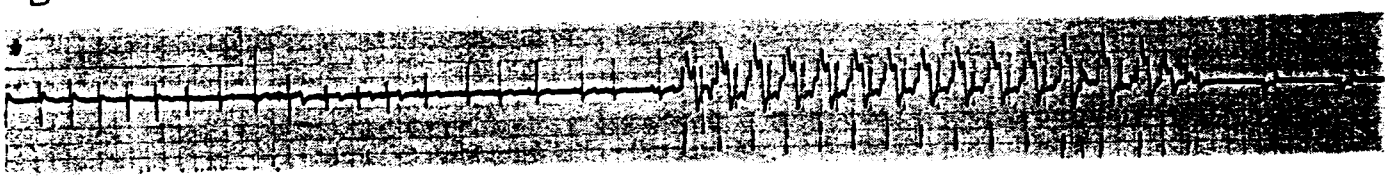
Protocol for cardiac sensitization.



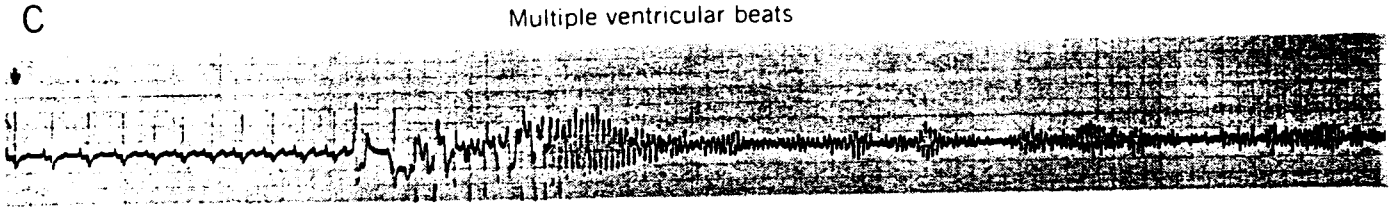
A Normal beats (showing initial increase in heart rate followed by reflex slowing)



B Isolated abnormal beats



C Multiple ventricular beats



D Multiple ventricular beats preceding ventricular fibrillation

Examples of electrocardiographic patterns recorded following challenge injection of epinephrine.

Sensitivity of Protocol

CFC 113

Threshold for response in dogs with adrenaline	5,000 ppm
Threshold for response in dogs w/o adrenaline with loud, startling noise or electric shock	> 12,000 ppm
Threshold for response in dogs w/o adrenaline on treadmill	> 20,000 ppm
Threshold for response in monkeys w/o adrenaline	> 50,000 ppm
Threshold for response in mice w/o adrenaline	> 100,000 ppm

Compounds Tested for Cardiac Sensitization Properties

Those Considered Most Acute

Benzene
Heptane
Chloroform
Trichloroethylene

Those Considered Intermediate in Potency

Carbon tetrachloride
Halothane (or Fluothane)

Those Considered Weak Sensitizing Agents or Where Data Make Classification Difficult

Methyl chloride
Methylene chloride
Ethyl chloride
Ethylene chloride
Propyl chloride
Ethane
Propane
Propylene
n-Butane
Acetylene
Spiropentane
Trifluorochlor-ethylene
Monochlorodifluoroethylene

Isopropyl chloride
Primary butyl chloride
Secondary butyl chloride
Isobutyl chloride
Tertiary butyl chloride
Isobutane
Cis- or **trans-**butene-2
Cyclobutene
Cyclobutane
Vinyl chloride
Isopropenyl chloride
Trichloromonofluoroethylene
Cis-dichloroethylene

Methyl bromide
Ethyl bromide
Methyl iodide
Ethyl iodide

Cyclopentane
Isopentane
2,2,-dimethyl-butane

Methyl chyclobutane

Trans-dichloroethylene

Compounds Which Did Not Cause Sensitization

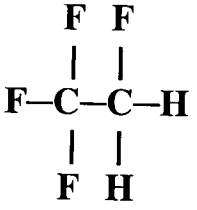
Ethylene
Tetrafluoroethylene
Ethylene oxide
Alcohol (very weak)

Difluoroethylene
Propylene oxide
Acetone (very weak)

s:\toxdoc\gmr\decnac

Attachment 10

ACUTE EXPOSURE GUIDELINE LEVELS (AEGLs)
FOR
HFC-134a



NAC/AEGL-12 Meeting

December 1998

ORNL Staff Scientist:
Sylvia S. Talmage

Chemical Managers:
George Rusch

Chemical Reviewers:
Robert Benson
Kenneth Still

HFC-134a

Introduction

Substitutes for chlorofluorocarbons (CFCs) which are considered responsible for ozone depletion and global warming are being developed under the Programme for Alternative Fluorocarbon Toxicity Testing (PAFT).

HFC-134a is used/being considered for use in:

- mobile air conditioning
- rigid foam insulation and packaging
- medical aerosols

Primarily as a replacement for CFC-12 (CF_2Cl_2)
has 0.1 the global warming potential of CFC-12

Production: estimated at ~175,000 tons/year

HFC-134a

Toxicity

Available inhalation data:

- Study with human volunteers
- Acute studies with the monkey, dog, rat, mouse
- Subchronic and chronic studies with the rat
- Reproductive study with the rat
- Developmental studies with the rat and rabbit
- Cardiac sensitization studies with dogs
- Genotoxicity studies
- Carcinogenicity with the rat

HFC-134a

Toxicity

Human study (Emmen and Hoogendijk, 1998)

Inhalation of 0, 1000, 2000, 4000, or 8000 ppm: 1 hour

No effects:

blood pressure
heart rate and rhythm (EKG)
lung function: peak expiratory flow
clinical chemistry
hematology parameters
blood concentrations approached equilibrium

HFC-134a

Toxicity

Animal studies

Lethality (LC_{50}, rat):

15 minutes: 800,000 ppm (Collins, 1984)

30 minutes: 750,000 ppm (Rissolo and Zapp, 1967)

4 hours: 500,000 ppm (Collins, 1984)

Non-lethal toxicity:

rapid narcosis (several species): 500,000 ppm
(Shulman and Sadove, 1967)

threshold/rapid narcosis: ~200,000
(Collins, 1984; Silber and Kennedy, 1979)

no effect (4 hours, rat): 81,000 ppm
(Silber and Kennedy, 1979)

HFC-134a

Toxicity

Animal studies

Subchronic, chronic (carcinogenicity) studies (rat)

14 or 28 days for 6 hours/day, 5 days/week
(Silber and Kennedy, 1979)

10,000 ppm: no effect
50,000 ppm: interstitial pneumonitis, no other effects
100,000 ppm: interstitial pneumonitis, no other effects

28 days for 6 hours/day, 5 days/week
(Riley et al., 1979)

1000, 10,000, 50,000 ppm: organ weight changes, not toxicologically significant

104 weeks for 6 hours/day, 5 days/week
(Hext and Dobrzanski, 1993; Collins et al., 1995)

2500, 10,000, 50,000 ppm:
no effects other than increased gonad weight and increased incidence of benign testicular Leydig-cell tumors in male rats in the 50,000 ppm group

HFC-134a

Toxicity

Animal studies

Reproductive studies (rat)

28 days for 6 hours/day, 5 days/week
(Riley et al., 1979)

50,000 ppm: reduced gonad weight,
not toxicologically significant

90 days for 6 hours/day, 5 days/seek
(Hext, 1989; Collins et al., 1995)

50,000 ppm: no effects

HFC-134a

Toxicity

Animal studies

Developmental studies

Rat, gestation days 6-15, 6 hours/day
(Lu and Staples, 1981)

30,000 ppm: no effects
100,000 ppm: maternal toxicity
300,000 ppm: fetal toxicity

Rat, gestation days 6-15, 6 hours/day
(Hodge et al., 1979)

10,000 ppm: no effect
50,000 ppm: fetal toxicity

Rabbit, gestation days 6-18, 6 hours/day
(Wickramaratne, 1989a,b)

10,000 ppm: maternal toxicity (weight gain)
10,000 ppm: fetal toxicity

NO TERATOGENIC EFFECTS IN RATS OR RABBITS

Toxicity

Animal studies

Cardiac sensitization

Cardiac Sensitization in Dogs Administered Exogenous Epinephrine[a]			
Concentration (ppm)	**Exposure Time**	**Response[b]**	**Reference**
50,000 75,000 100,000	10 minutes 10 minutes 10 minutes	no response marked response (2/10) marked response (1/4); death (1/4)	Mullin and Hartgrove, 1979
40,000 80,000 160,000 320,000	10 minutes 10 minutes 10 minutes 10 minutes	no response (6/6) marked response (2/6) convulsions (1/4) marked response (2/3); convulsions (1/3)	Hardy et al., 1991

[a]Animals were administered an intravenous dose of epinephrine of 8 μg/kg (Mullin and Hartgrove, 1979) or individualized doses of 2, 4 or 8 μg/kg (Hardy et al., 1991).
[b]A marked response is considered an effect; number of animals affected/number of animals tested in parenthesis.

HFC-134a

Disposition and Metabolism

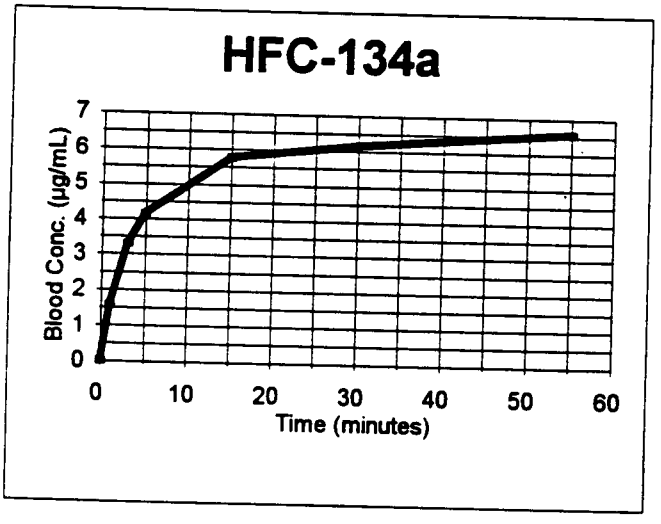
Animal studies: Rapid absorption. For many halocarbons, blood concentrations reach equilibrium in ~15 minutes (NRC/COT/SRTAC).

Human study: Blood concentrations appeared to be reaching equilibrium at 55 minutes (Emmen and Hoogendijk, 1998).

Minimal metabolism (0.34-0.40%)
metabolite is trifluoroacetic acid

Rapidly excreted as the unchanged parent compound; small amounts retained in organs

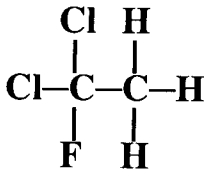
Time (minutes)	Blood Conc. (µg/mL)
0	0.01
1	1.57
3	3.30
5	4.14
15	5.77
30	6.16
55	6.57



Blood concentrations of HFC-134a in humans exposed to 8000 ppm for 1 hour

Attachment 11

ACUTE EXPOSURE GUIDELINE LEVELS (AEGLs)
FOR
HCFC-141b



NAC/AEGL-12 Meeting

December 1998

ORNL Staff Scientist:
Sylvia S. Talmage

Chemical Managers:
George Rusch

Chemical Reviewers:
Robert Benson
Kenneth Still

HCFC-141b

Introduction

Substitutes for chlorofluorocarbons (CFCs) which are considered responsible for ozone depletion and global warming are being developed under the Programme for Alternative Fluorocarbon Toxicity Testing (PAFT).

HCFC-141b is used/being considered for use in:

rigid insulating foams
solvent, for cleaning

Primarily as a replacement for CFC-12 (CF_2Cl_2)

Production: estimated at ~100,000 tons/year

HCFC-141b

Toxicity

Available inhalation data:

- Study with human volunteers
- Acute studies with the rat, mouse
- Subchronic and chronic/carcinogenicity studies with the rat
- Neurotoxicity with the rat
- Reproductive study with the rat
- Developmental studies with the rat and rabbit
- Cardiac sensitization studies with dogs
- Genotoxicity studies

HCFC-141b

Toxicity

Human study (Utell et al., 1977)

Eight exercising subjects, ages 22-30 years

Inhalation of 0, 250, 500, 1000 ppm: 4 and 6 hours

No effects:

- subjective symptoms
- blood pressure
- heart rate and rhythm (EKG)
- lung function: spirometry
- clinical chemistry
- hematology parameters
- nasal lavage
- blood concentrations approached equilibrium
- neurotoxicity - 2 subjects

HCFC-141b

Toxicity

Animal studies

Lethality (LC_{50}, rat):

30 minutes (mouse): 80,000-100,000 ppm
(Davies et al., 1976; Vlachos, 1988)

4 hours (rat): ~60,000 ppm
Brock et al., 1995)

6 hours (rat): 56,700 ppm
Brock et al., 1995)

Non-lethal toxicity:

>30,000 ppm	prenarcotic signs (rat): >30,000 ppm (Hardy et al. 1989)
11,000 ppm-30,000 ppm	3, 6-hours, no-effect/minor biochemical change (mouse, rat) (Brock et al., 1995; Vlachos, 1988; Loizou et al., 1996)
41,000 ppm	6-hours, lethargy, tremors, hunched posture (Vlachos, 1988)

HCFC-141b

Toxicity

Animal studies

Subchronic, chronic (carcinogenicity) studies (rat)

10,000 ppm, 14 days for 6 hours/day, 5 days/week
no clinical signs; hematology, clinical chemistry changes
(Brock et al., 1995)

2000, 8000, 20,000 ppm, 90 days for 6 hours/day, 5 days/week (Brock et al., 1995)
20,000 ppm: reduced weight gain,
biochemical changes
organ weight changes
no gross or microscopic organ changes
8000 ppm: no effects

1500, 8000, or 20,000 ppm for 4 weeks (Hino et al., 1992)
20,000 ppm: biochemical, clinical chemistry changes
8,000 ppm: biochemical, clinical chemistry changes

1500, 5000, or 15,000 ppm, 104 weeks, 6 hours/day, 5 days/week (Millischer et al., 1995)
no clinical signs, changes in any group
5000 and 15,000 ppm: males, Leydig cell adenomas

HCFC-141b

Toxicity

Animal studies

Reproductive/Developmental studies

Rat, gestation days 6-15, 6 hours/day
(Rusch et al., 1995)

8000 ppm: no effects
20,000 ppm: maternal toxicity, fetotoxic

Rat, two-generation study
(Rusch et al., 1995)

2,000 ppm: no effect
10,000 ppm: no/minimal effects
20,000 ppm: decreased number of litters

Rabbit, gestation days 7-19, 6 hours/day
(Rusch et al., 1995)

1400 ppm: no effects
4200 ppm: no effect on fetus; maternal clinical signs
12,600 ppm: no effect on fetus; maternal clinical signs

NO TERATOGENIC EFFECTS IN RATS OR RABBITS

HCFC-141b

Toxicity

Animal studies

Neurotoxicity

0, 1500, 5000, or 15,000 ppm for 6 hours/day, 5 days/week for 16 weeks, examined postexposure - rat (Coombs et al., 1992)

no effects on:
- behavior
- motor activity
- grip strength
- pain response
- corneal reflex
- pinna reflex
- brain weight
- neural tissues

HCFC-141b

Toxicity

Animal studies

Cardiac sensitization with male beagle dogs

	Concentration	Response
Mullin (1977)	2600 ppm	no response (10/10)
	5200 ppm	marked response (1/10)
	10,000 ppm	death (1/10)
	21,600 ppm	death (2/2)
Hardy et al. 1989	9000 ppm	marked response ((1/2)
	12,000 ppm	no response (1/1)
	13,000 ppm	no response (1/1)
	14,000 ppm	marked response (1/2)
	15,000 ppm	marked response (1/2)
	18,000 ppm	marked response (2/2)
	19,000 ppm	marked response (1/2)
	20,000 ppm	death (1/1)

Doses of epinephrine were not adjusted for individual dogs.
8 μg/kg (Mullin, 1977)
10 μg/kg @ 1 μg/second (Hardy et al., 1989)

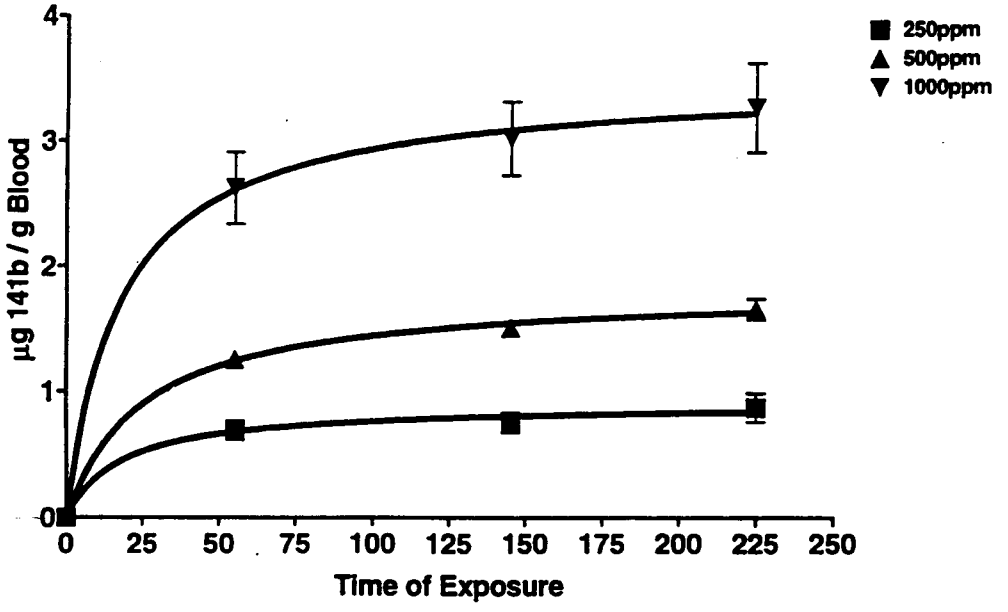
HCFC-141b

Disposition and Metabolism

Animal studies: Rapid absorption. For many halocarbons, blood concentrations reach equilibrium in ~15 minutes (NRC/COT/SRTAC).

Human study: Blood concentrations appeared to be reaching equilibrium at 145 minutes (Utell et al., 1997)

Minimal metabolism
<6% of dose (Loizou et al., 1996)
metabolite is 2,2-dichloro-2-fluoroethyl glucuronide



Blood concentrations of HCFC-141b in humans exposed to 250, 500, or 1000 ppm for 3.75 hours

ACUTE EXPOSURE GUIDELINE LEVELS for PIPERIDINE (PIP)

ORNL Staff Scientist: Kowetha Davidson
Chemical Manager: Mark McClanahan
Secondary Reviewers: Jim Holler
Thomas Hornshaw

NAC/AEGL Meeting, December 7-9, 1998
Washington, D.C.

PHYSICAL/CHEMICAL CHARACTERISTICS OF PIPERIDINE

- CAS No.: 110-89-4
- Chem. form.: $C_5H_{11}N$
- Mol. Wt.: 85.15
- Phys. State: colorless liquid
- Vap. Pres: 32.1 mmHg @ 25°C
- Vap. Density: 3.0 (air = 1)
- Density: 0.8622 @ 20°C
- Solubility: 1.6×10^6 mg/L H_{20} @ 20°C
- Odor: pungent pepper- or amine-like

USES

- Solvent, curing agent for rubber and epoxy resins
- Catalyst in silicone ester, intermediate in organic synthesis, wetting agent
- Manufacture of pharmaceuticals (analgesics, anesthetics, and germacides)
- Food additive

HUMAN TOXICITY

- Piperidine is corrosive because of its strong alkalinity
- No lethality data available
- Data for nonlethal effect
  - Odor threshold <2 ppm
  - Irritation threshold = 26 ppm; no data on subjects exposed or duration of exposure
  - Inhalation exposure associated with sore throat, coughing, labored breathing and dizziness (no details available)

ANIMAL TOXICITY

- Lethality Data
  - LC_{50} data: mouse,1723 ppm, 4-hour; guinea pig, 3444 ppm, 1-hour
  - 4000 ppm for 4 hours caused death of 6/6 rats;

ANIMAL TOXICITY

- Nonlethal Toxicity
  - 2000 ppm for 4 hours causes 0/6 deaths in rats
  - 0.58 ppm, 4 h/d, 5 d/wk, 4 mon. caused effects on blood vessels, respiration, and neural and muscular excitability after multiple exposures.
  - 2.9 ppm, 4 h/d, 5 d/wk, 4 mon. caused ↓RBC and WBC parameters, ↓ blood pressure, effects on liver and kidney function and testicular morphology, and effects at 0.58 ppm.

ANIMAL TOXICITY

- Other Effects
  - Developmental toxicity: inconsistent results regarding decreased fetal body weights
  - Carcinogenicity: negative in drinking water study using 0.9% PIP
  - Genetic toxicity: neg. in Salmonella and E.coli; positive in mouse lymphoma cells with S9
  - Skin: causes severe burns on contact

BASIS FOR DERIVING AEGL-1 VALUES

- The odor at 2 ppm was very pungent and could be tolerated for only a short period of time.
- This concentration is above the odor threshold.
- Therefore, the concentration of 2 ppm was reduced by a factor of 3 to estimate the odor threshold.
- The estimated odor threshold was flatlined across all exposure durations.

DERIVATION OF AEGL-1

30 min	1 hour	4 hours	8 hours
0.67 ppm	0.67 ppm	0.67 ppm	0.67 ppm

DERIVATION OF AEGL-2

- AEGL-2 values were not derived
- Data were not considered suitable
  - Irritation threshold is not consistent with the definition of AEGL-2
  - Conc. of PIP causing no deaths in rats exposed for 4 hours was not accompanied by description of clinical signs.
  - The repeat exposure study lacked details to adequately evaluate its usefulness; effects after a single exposure were not described.
  - Effects in developmental toxicity study could not be attributed to piperidine.
  - No data are available for time extrapolation.

DERIVATION OF AEGL-3

- AEGL-3 values were not derived
- Data were not considered suitable
  - No dose-response data on lethality were available
  - Stand-alone LC_{50} values are not considered adequate data for deriving AEGL values.
  - No data are available for time extrapolation.

PROPOSED AEGL VALUES FOR PIPERIDINE

Class	30 minutes	1 hour	4 hours	8 hours	Endpoint/Ref.
AEGL-1	0.67 ppm (2.3 mg/m^3)	0.67 ppm (2.3 mg/m^3)	0.67 ppm (2.3 mg/m^3)	0.67 ppm (2.3 mg/m^3)	Estimated odor threshold (Trochimowicz et al., 1994)
AEGL-2	Insufficient data, no values				
AEGL-3	Insufficient data, no values				

TABLE 2. SUMMARY OF INHALATION TOXICITY DATA IN LABORATORY ANIMALS

Species	Exposure Conditions	Effects	Reference
Mouse	2-h LC_{100}	LT_{50} = 80 min	Zayeva et al., 1968
Mouse	4 h	LC_{50} = 1723	AIHA, 1982
Rat	2000 ppm for 4 h	0/6 deaths	Smyth et al., 1962
	4000 ppm for 4 h	6/6 deaths	Smyth et al., 1962
	Conc. vapor for 15 min	6/6 deaths	Smyth et al., 1962
NR	NR	LC_{50} = 6500 mg/m^3 (1885 ppm)	Bazarova and Migoukina, 1975
Rat	2 mg/m^3 (0.58 ppm), 4 h/day, 5 d/wk for 4 mo	effects on blood vessels, respiration, neural and muscular excitability after multiple exposures	Bazarova, 1973
Rat	10 mg/m^3 (2.9 ppm), 4 h/day, 5 d/wk for 4 mo	effect on body wt., neural and muscular excitability, blood vessels, erythrocyte parameters, leukocytes, blood pressure, respiration, liver and kidney function, and testicular morphology	Bazarova, 1973

NR = not reported

TABLE 2. SUMMARY OF INHALATION TOXICITY DATA IN LABORATORY ANIMALS

Rabbit	2 or 10 mg/m^3 (0.58 or 2.9 ppm), 4 h/day, 5 d/wk for 4 mo	decreased arterial blood pressure at both concentrations	Bazarova, 1973
NR	20 mg/m^3 (5.8 ppm)	threshold for nervous system response	Bazarova and Migoukina, 1975
Guinea pig	1 hour	LC_{50} = 3444 ppm	AIHA, 1982

R = not reported

Attachment 13

FURAN AEGLs

George Rodgers
Claudia M. Troxel

Conflicting LC_{50} Values:

Egle and Gochberg (1979):
1-hour LC_{50} in mice = 42 ppm

Terrill et al. (1989):
1-hour LC_{50} in rats = 3464 ppm

Egle and Gochberg study unacceptable:

3 or 4 Swiss mice statically exposed to **10.5 - 350 ppm** furan for **1 hour**

Toxicity signs: hypoactivity for 5-15 minutes, followed by labored breathing and death; Gross findings: pulmonary inflammation and fluid accumulation

Garcia and James (1998):

4 mice in closed system for one hour breathe 9.6 L of air (4 mice x 40 mL/min x 60 min).

Exposure desiccator only 5.2 L

Therefore, one cannot be assured that the toxic effects observed were due solely to furan exposure.

Terrill et al. (1989) Acute inhalation toxicity of furan, 2 methylfuran, furfuryl alcohol, and furfural in the rat.

5 male or 5 female Sprague-Dawley rats/group, exposed to **1014, 2851, or 4049 ppm** for **1 hour**; sacrificed 14 days after exposure

Toxicity signs: respiratory distress, increased secretory response (degree at each concentration not provided)

Body weights decreased in mid- and high-concentration groups

No treatment-related gross lesions

MORTALITY RATE OF FURAN IN SPRAGUE-DAWLEY RATS		
Concentration (ppm)	Mortality rate	
	Male	Female
1014 ± 36.6	0/5	0/5
2851 ± 246.7	0/5	0/5
4049 ± 227.8	5/5	4/5

1-hour LC_{50} = 3464 ppm

GENERAL NOTES:

Comparing hepatocytes from rats, mice, humans (3):

Metabolism
mice> humans >rats

Predicted absorbed dose (the liver dose of the reactive metabolite):
highest: mice (10x) >rats (3.5x) >humans

Projected rate of liver perfusion with furan oxidation: Blood flow predicted to be limiting factor in biotransformation of furan

Furan metabolized by P450-2E1 that hepatic P450-2E1 concentrations would have to decrease almost 40-fold before bioactivation rate would decrease below blood flow limitation

Interindividual variations in human P450 2E1 levels not factor in bioactivation of furan

DERIVATION OF *n*

$C^n \times t = k$ where n = 2 (represent midpoint of reported values as referenced by ten Berge et al., 1986)

Total UF/Modifying Factor = 100

Interspecies UF : 10

Following simulated exposure to 10 ppm for 4 hours, the predicted absorbed dose of furan (mg/kg) in humans, and consequently the liver dose of the reactive metabolite cis-2-butene-1,4-dial, was 10 fold less than in mice and 3.5 fold lower than in rats. However, the differences between humans and rodents in sensitivity to the reactive metabolite is not known.

Interspecies UF : 3

Because blood flow is predicted to be the limiting factor in the bioactivation of furan, levels of the reactive intermediate will not be influenced by interindividual variations in the levels of cytochrome P450 2E1 (the bioactivating enzyme).

Modifying Factor : 3

Only one data set addressing furan toxicity following inhalation exposure

AEGL-2

- **Reference:** Terrill et al. (1989)

- 5 Sprague Dawley rats/sex/group

- **Concentration/Time Selection/Rationale:** Lowest exposure concentration of 1014 ppm for 1 hour. Although severity of clinical signs (respiratory distress, increased secretory response) not reported, this group did not exhibit decrease in b. w. like rats exposed to 2851 ppm or 4049 ppm.

- **Total uncertainty factor/Modifying Factor: 100**
  Interspecies UF: 10
  Intraspecies UF: 3
  Modifying factor: 3

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

AEGL-2 (ppm)				
Endpoint	30 m	1 h	4 h	8 h
1014 ppm	14	10	5.1	3.6
⅓ AEGL-3	13	9.7	4.7	3.3

AEGL-3 (ppm)			
30 min	1 hour	4 hours	8 hours
40	29	14	10

- **Reference:** Terrill et al. (1989).
- 5 Sprague Dawley rats/sex/group
- **Concentration/Time Selection/Rationale:** Highest nonlethal exposure concentration for 1-hour = 2851 ppm
- **Total uncertainty factor/Modifying Factor: 100**

  Interspecies UF: 10
  Intraspecies UF: 3
  Modifying factor: 3

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

SUMMARY OF AEGL VALUES (ppm)				
Endpoint	30 m	1 h	4 h	8 h
AEGL-2	14	10	5.1	3.6
AEGL-3	40	29	14	10

SMAC: Acute Lethality and Hepatotoxicity

The 1-h LC_{50} value of 3500 ppm (9,700 mg/m^3) of Terrill et al. (1989) was used to derive an AC value for hepatotoxicity. This was done to avoid setting an AC based on lethality. Data from oral exposures indicate that hepatotoxicity is the most likely effect at lower exposures. To extrapolate from the LC_{50} to a non-hepatotoxic concentration, the dose of furan retained by rats during the 1-h exposure was estimated and compared to the oral NOAEL as follows:

$$\text{Dose} = R \times LC_{50} \times V_{hr} = 0.9 \times 9{,}700 \text{ mg/m}^3 \times 0.01 \text{ m}^3\text{/hr} = 90 \text{ mg}$$

The V_{hr} was calculated from the minute volume of 0.16 l/m (Crosfill and Widdicombe, 1961) for 250 g rats and the respiratory retention, indicated by "R," was estimated from studies on dogs (Egle and Gochberg, 1979).

The single oral doses of furan that are considered "severely toxic" to the livers of male rats are those above 100 mg/kg (Wilson et al., 1992). The stated age of the rats dosed with furan was 10 w to 1 y, so the weight range was approximately 350 to 450 gm; hence, the 100 mg/kg dose averaged about 40 mg per rat. This seems consistent with the calculation above showing that the LC_{50} dose was about 90 mg/rat. Studies with the same strain of rat show that 8 mg/kg (about 3 mg/400 gm rat) given orally is a high NOAEL based on increased liver enzymes in serum (Wilson et al., 1992). Based on this comparison of the LC_{50} and oral

NOAEL, the factor needed to extrapolate from the LC_{50} to an inhalation NOAEL for hepatotoxicity is estimated to be 90mg/3mg = 30. The NRC Committee on Toxicology has discussed factors of 20 to 50 for extrapolation of an LC_{50} to a NOAEL for sublethal effects (Paulson, 1998), and the value of 30 for furan is within this expected range. The 1-hour AC to avoid hepatotoxicity was estimated as follows:

$$\textbf{1-hr AC} = 9{,}700\ \text{mg/m}^3 \times 1/30 \times 1/3 \times 1/10 = 11\ \text{mg/m}^3 = \mathbf{4\ ppm}$$

Besides the factor of 30 for extrapolation of the LC_{50} to a NOAEL, factors of 3 and 10 were used. The factor of 3 was applied for species extrapolation from rats to humans. The species factor was less than the usual factor of 10 because pharmacokinetic data indicate that, on a mg/kg body weight basis, humans have a lower rate of metabolism of inhaled furan vapors than do rats when exposed to 10 ppm (Kedderis and Held, 1996). The species extrapolation factor was not reduced to 1 because it was uncertain whether human liver would be more susceptible than rat liver to furan toxicity. A factor of 10 was applied due to inadequate data on the sub-lethal effects of inhaled furan vapors, lack of data on effects in humans by any route of exposure, and to be more consistent with the very low AC values calculated for exposure durations of 7-d, 30-d, and 180-d (see below). The NRC does not normally recommend the use of a factor for lack of data, however, the nature of the database for the toxicity of furan suggests the need for such a factor in this case.

SPACECRAFT MAXIMUM ALLOWABLE CONCENTRATIONS			
Duration	Concentration		Target Toxicity
	ppm	mg/m^3	
1-h	4	1.4	Hepatotoxicity
24-h	0.4	1	Hepatotoxicity
7-d	0.025	0.07	Carcinogenicity
30-d	0.025	0.07	Carcinogenicity
180-d	0.025	0.07	Carcinogenicity

AEGL-3 (ppm)				
Endpoint	30 m	1 h	4 h	8 h
2851 ppm	40	29	14	10
⅓ the 1-hour LC_{50} of 3464 ppm	16	12	5.8	4.1

Attachment 14

PROPYLENE OXIDE AEGLs

Jim Holler
Claudia M. Troxel

HISTORY OF PO AEGL

September 1997: Approved AEGL-2 and -3 values, voted NA for AEGL-1; CMA stated that human data available for AEGL-1

↓

June 1998: AEGL-1 levels proposed based on limited human data (from CMA). No vote. CMA presentations: 1) data for human exposure 2) input regarding animal toxicity

↓

September 1998: Presentations by CMA addressing committee questions posed during June 1998 meeting regarding human data

↓

December 1998: Propose AEGL-1 levels and revised AEGL-2 and -3 levels; based on revised CMA submissions

HUMAN DATA

- **NONLETHAL EFFECTS**

Case-report: worker exposed to high conc. of propylene oxide vapor for 10-15 min: eye and lung irritation, burning in chest, restlessness, headache, weakness, diarrhea, vomiting, unconsciousness

Odor threshold: Range of 10-200 ppm; odor is sweet, alcoholic in nature

Genotoxicity/Carcinogenicity: Inconclusive: good correlation between exposure and decreased DNA repair proficiency and hemoglobin adduction; no significant correlation between exposure and chromosomal aberrations or cancer

REFERENCE: CMA. 1998.

FACILITY 1:

Environmental health survey during PO drumming in 1968 in response to worker complaints of occasional eye irritation:

PO concentrations in worker breathing zone
Odor noted as strong during sampling, but "irritation not intolerable"

- Overhead heater fan turned on:
  380 ppm - 177 min
  392 ppm - 135 min
  460 ppm - 116 min

- Overhead heater fan turned off:
  525 ppm - 121 min
  1310 ppm - 124 min
  1520 ppm - 171 min

Work not ceased; no deaths in 30 potentially exposed workers within 5 months of sampling

CMA
FACILITY 2:

Environmental health survey during propylene glycol drumming in 1949:

- two 30-minute task samples taken over drums as they were being filled with polypropylene glycol: 348 and 913 ppm

- sample taken over opening to polypropylene glycol mixing tank during purging for 12 minutes: 28 ppm

- workers complained of eye irritation after about 2 weeks of steady operations

No deaths in 23 potentially exposed workers within 5 months of sampling

CMA

FACILITY 3:

Environmental health survey to determine personnel exposures to PO in 1975:

- Ambient air concentrations over three 8-hour shifts:

  None detected (<0.01 ppm) to 41.8 ppm

- Personnel exposure concentrations over the three 8-hour shifts:

  13.2 - 31.8 ppm PO

- No worker complaints of irritation noted in the report

No deaths in the 78 potentially exposed workers within 5 months of sampling

SUMMARY RESULTS OF PERSONAL EXPOSURE MONITORING IN 1975 (FACILITY 3)					
Job Class.	No. of Persons Monitored	No. of Samples	Propylene Oxide		
			Conc. Ranges (ppm)	Mean* Job Class Conc. (ppm)	
				Mean	95% UCL
Maintenance personnel	5	8	14.9 - 18.9	17.4	18.30
Laboratory personnel	2	2	30.2 - 31.8	31.0	36.05
Engineer	1	1	30.2	30.2	---
Foreman	2	4	16.1 - 23.8	20.58	24.49
Operators	6	11	13.2 - 23.3	18.69	20.31

*Cal. arithmetic mean and 95% upper confidence level for associated job class

ANIMAL DATA

SUMMARY OF NONLETHAL INHALATION DATA IN LABORATORY ANIMALS				
Species	Conc. (ppm)	Dur. (h)	Effects	References
Dog	1363	4	Highest concentration causing no mortality; Lacrimation, salivation, nasal discharge	Jacobson et al., 1956
Rat	2684	4	Highest concentration causing no mortality; Frequent movement and preening, nasal discharge, lacrimation, salivation, gasping	Jacobson et al., 1956
Rat	1277	4	No mortality; no clinical signs or gross pathology changes	NTP, 1985
Rat (M)	4050	4	Highest concentration causing no mortality; Lacrimation, eye irritation, sedation, piloerection, mucous discharge from nose and mouth, respiratory difficulty	Shell Oil Co., 1977
Rat (F)	3450	4	Highest concentration causing no mortality; Lacrimation, eye irritation, sedation, piloerection, mucous discharge from nose and mouth, respiratory difficulty	Shell Oil Co., 1977
Rat	600	6 hr/d, 5 d/wk	Transient restless behavior observed only during first 3 days of exposure, occasional salivation and piloerection noted	Dow Chemical Company, 1981
Rat	997	6 h/d, 10 d	Excessive lacrimation and eye irritation, sedation, piloerection, mucous discharge (frequently bloodstained), respiratory difficulty - All disappeared after 3 day of exposure	Shell Oil Company, 1977

SUMMARY OF NONLETHAL INHALATION DATA IN LABORATORY ANIMALS, cont.				
Species	Conc. (ppm)	Dur. (h)	Effects	References
Mouse (M)	859	4	Highest concentration causing no mortality; Dyspnea; no compound-related effects at gross necropsy	NTP, 1985
Mouse (F)	387 859	4 4	1/5 died (not treatment-related); dyspnea; no compound-related effects at gross necropsy No mortality; dyspnea; no compound-related effects at gross necropsy	NTP, 1985
Mouse	98.5 196 487	6 h/d, 5d/wk, 2wk	No-effects Dyspnea Dyspnea, hypoactive	NTP, 1985
Mouse	31, 63, 125, 250, 500	6 h/d, 5 d/wk, 13 wk	No mortalities except one in 125 ppm group; no gross or microscopic changes observed in any groups	NTP, 1985
Guinea pig	16,000 8000 4000 2000	0.5 1 2 7	Highest concentrations/longest durations not causing mortality; Signs of toxicity in all groups: eye and nasal irritation, breathing difficulty, drowsiness, weakness	Rowe et al., 1956

KEY STUDIES/SUPPORTING STUDIES

DOGS

- Jacobson et al., 1956. The toxicity of inhaled ethylene oxide and propylene oxide vapors.

  3 male, beagle dog/group exposed to **1363, 2005, 2030, or 2481 ppm** PO for **4 hours**

  Lacrimation, salivation and nasal discharge in all dogs

MALE DOGS EXPOSED TO PO FOR 4 HOURS		
Conc. (ppm)	Mortality (%)	Other Effects
1363	0/3 (0)	
2005	1/3 (33)	motor weakness
2030	2/3 (67)	motor weakness, pulmonary edema and congestion
2481	3/3 (100)	motor weakness, pulmonary edema and congestion

MICE

- NTP, 1985.

Groups of 5 male and 5 female $B6C3F_1$ mice exposed to **0, 387, 859, 1102, 1277, or 2970 ppm** for **4 hours**

$B6C3F_1$ MICE EXPOSED TO PO FOR 4 HOURS			
Conc. (ppm)	Mortality (%)		Other Effects
	Males	Females	
387	0/5 (0)	1/5 (20)	dyspnea
859	0/5 (0)	0/5 (0)	dyspnea
1102	2/5 (40)	4/5 (80)	dyspnea
1277	2/5 (40)	5/5 (100)	dyspnea, sedation
2970	5/5 (100)	5/5 (100)	dyspnea, sedation, lacrimation

5 male or 5 female $B6C3F_1$ mice/group exposed to **0, 20.1, 47.2, 98.5, 196 or 487 ppm** PO for **6 h/d, 5 d/wk, for 2 wks.**

No mortalities

Dyspnea in 196 and 487 ppm groups, and 487 ppm groups were hypoactive

10 male and 10 female $B6C3F_1$ mice/group exposed to **0, 31, 63, 125, 250, or 500 ppm** PO for **6 h/d, 5 d/wk**, for **13 wks.**

No mortalities except 1 male 125-ppm mouse on Day 14

High-dose groups had lower body wts.; no gross or microscopic compound-related changes

SUMMARY OF 4-HOUR INHALATION LC_{50} DATA IN LABORATORY ANIMALS			
Species	Conc. (ppm)	LC_{50} - Method of Calculation	Reference
Dog	1941	Probit analysis (calc. for document: use with caution)	Jacobson et al., 1956
Rat	4000	Bliss-Finney method	Jacobson et al., 1956
Rat	3205	Probit analysis (calc. for document)	NTP, 1985
Rat	4197	Not given	Shell Oil Co., 1977
Mouse	1740	Bliss-Finney method	Jacobson et al., 1956
Mouse	1160	Probit analysis (calc. for document)	NTP, 1985

ISSUES

MECHANISM OF ACTION:

Support for Site of Entry Mechanism:

"Obligate nose breathers" (rats, mice) -

Acute exposure: dyspnea, gasping, mucous discharge from nose/mouth, distended stomach

Repeated exposure/chronic: upper respiratory tract lesions, such as rhinitis, and squamous metaplasia, hyperplasia, necrosis, and/or suppurative inflammation of upper respiratory tract epithelium

Dogs: congestion of tracheal mucosa and lungs, spotty alveolar edema, perivascular and peribronchial edema

Cancer: site of contact - intragastric administration: forestomach tumors; subcutaneous injections: sarcoma at injection site; inhalation: nasal cavity tumors

Systemic:

Neurotoxicity -

Dogs - motor weakness, vomiting

Rodents - drowsiness, sedation, weakness, incoordination, hypoactivity, ataxia, diarrhea, and transient restless behavior; Rats exhibited hindlimb ataxia, changes compatible with central-peripheral distal axonopathy (1500 ppm PO for 7 wks)

Case report - restlessness, headache, general weakness, diarrhea, vomiting

SPECIES DIFFERENCES:

Lethality - 4-hour LC_{50} (ppm)

mice (1160-1740) < dogs (1941) < rats (3205-4197)

Predicted airway tissue burden following 500 ppm PO exp:

Calculated Tissue Conc. of PO (mmol/L) at Steady State (exposure to 500 ppm)				
Tissue	Mouse	Human	Dog	Rat
Nasal resp. epithelium	0.92	0.85	0.7	0.57
Nasal olf. epithelium	0.92	0.84	Not done	0.34
Lung	0.19	0.13-0.19	0.17	0.13
Liver	0.07	0.06-0.12	0.05	0.038

In Vitro Metabolism:

Cytosolic lung and liver GST (Vmax/Km)-

mice > humans ≥ rats

Microsomal lung and liver epoxide hydrolase (Vmax/Km)-

humans > mice ≈ rats

Hemoglobin adduction (nmol HOPrOVal/g Hb):

high dose: dog (1.7) > rat (0.72) > mice (0.59)

low dose: dogs ≈ rats ≈ mice

Other:

Worker exposed to 1520 ppm for 2.85 hours - strong odor, irritation not intolerable, nonlethal

DERIVATION OF *n*

Use derived value of *n* for ethylene oxide because of similar mechanisms; ***n* = 1.2** (derived from rat 1- and 4-hour LC_{50} values)

- Direct alkylating agents that alkylate DNA and proteins
- Possess irritant properties
- Affect nervous system

INTRASPECIES UNCERTAINTY FACTOR:

3 - mechanism of toxicity, direct alkylation, would not be expected to differ between individuals, although potential polymorphism in the glutathione detoxification pathway for PO suggests there may be some potential for variability between individuals. Enzymatic metabolism of PO, however, is not limited to glutathione-S-transferase; epoxide hydrolase in human liver and lung subcellular fractions has also been shown to metabolize PO *in vitro*.

AEGL-1 (ppm)			
30 minutes	1 hour	4 hours	8 hours
110	60	19	11

- **Reference:** CMA. 1998. Chemical Manufacturers Association to National Advisory Committee, (NAC)/AEGLs, Human Experience with Propylene Oxide. Dated October 16, 1998.

- **Concentration/Time Selection/Rationale:**
  78 potentially exposed employees
  8-hr TWAs for PO determined from measured concentrations in breathing zone of workers over three 8-hr shifts ranged from 13.2 to 31.8 ppm. Highest 8-hr TWA of 31.8 ppm was used (2 samples from 2 workers).

- **Uncertainty Factors/Rationale:**
  Total uncertainty factor: NA (3)
  Interspecies: NA (1) - human data used
  Intraspecies: 3 - mechanism of toxicity, direct alkylation, would not be expected to differ between individuals

- **Time scaling:** $C^n \times t = k$ where $n = 1.2$; based on EO.

SUPPORTING DATA FOR AEGL-1

AEGL-1 (ppm)			
30 minutes	1 hour	4 hours	8 hours
160	84	24	13

- **Reference:** NTP. 1985. Toxicology and Carcinogenesis Studies of Propylene Oxide (CAS No. 75-56-9) in F344/N Rats and B6C3F$_1$ Mice (Inhalation Studies).

- **Concentration/Time Selection/Rationale:**
  Groups of 5 B6C3F$_1$ mice/sex
  Exposure to 98.1 ppm for 6 h/d, 5 d/wk for 2 wks: no-effect-level (no dyspnea)

- **Uncertainty Factors/Rationale:**
  Total uncertainty factor: NA (6)
  Interspecies: 2 - mouse most sensitive species tested: LC_{50} values for the different species tested (mice, dogs, and rats) differed at most by a factor of 3.5, with the mouse being the most sensitive and the rat being the least sensitive; available human data suggest that mice may be more sensitive than humans in their response to propylene oxide exposure
  Intraspecies: 3 - mechanism of toxicity, direct alkylation, would not be expected to differ between individuals

- **Time scaling:** $C^n \times t = k$ where $n = 1.2$; based on EO

SUMMARY OF AEGL-1 VALUES FOR PROPYLENE OXIDE (ppm)					
Endpoint	UF/ MF	30 m.	1 h	4 h	8 h
Key Study: CMA, 1998 Humans: 8-hour TWA of 31.8; NOEL	3	110	60	19	11
Supporting Study:					
NTP, 1985 Mouse: NOEL for dyspnea at 98.5 ppm for 6 hours	6	130	73	23	13

AEGL-2 (ppm)			
30 minutes	1 hour	4 hours	8 hours
360	200	65	36

- **Reference:** NTP. 1985.

- **Concentration/Time Selection/Rationale:**
  Groups of 5 $B6C3F_1$ mice/sex
  Exposure to 387 ppm for 4 hr resulted in dyspnea; no other effects noted

- **Uncertainty Factors/Rationale:**
  Total uncertainty factor: NA (6)
  Interspecies: 2 - mouse most sensitive species tested: LC_{50} values for the different species tested (mice, dogs, and rats) differed at most by a factor of 3.5, with the mouse being the most sensitive and the rat being the least sensitive; available human data suggest that mice may be more sensitive than humans in their response to propylene oxide exposure
  Intraspecies: 3 - mechanism of toxicity, direct alkylation, would not be expected to differ between individuals

- **Time scaling:** $C^n \times t = k$ where $n = 1.2$; based on EO.

SUPPORTING DATA FOR AEGL-2

- **Reference:** CMA. 1998.

- **Concentration/Time Selection/Rationale:**
  3 exposed employees
  Workers exposed to 380 ppm for 177 minutes, 525 ppm for 121 minutes, 392 ppm for 135 minutes, 460 ppm for 116 minutes: strong odor, irritation not intolerable

- **Uncertainty Factors/Rationale:**
  Total uncertainty factor: NA (3)
  Interspecies: NA (1) - human data used
  Intraspecies: 3 - mechanism of toxicity, direct alkylation, would not be expected to differ between individuals

- **Time scaling:** $C^n \times t = k$ where $n = 1.2$; based on EO.

SUMMARY OF AEGL-2 VALUES FOR PROPYLENE OXIDE (ppm)					
Endpoint	UF/ MF	30 m.	1 h	4 h	8 h
Key Study: NTP, 1985 Mouse: dyspnea at 387 ppm for 4 hours	6	360	200	65	36
Supporting Studies: CMA, 1998 Human: strong odor, undefined irritation					
380 ppm for 177 min.	3	560	310	98	55
525 ppm for 121 min.	3	560	310	99	56
392 ppm for 135 min.	3	460	260	81	45
460 ppm for 116 min.	3	470	270	84	47

AEGL-3 (ppm)			
30 minutes	1 hour	4 hours	8 hours
770	430	140	77

- **Reference:** Jacobson, K. H., et al. 1956. The toxicity of inhaled ethylene oxide and propylene oxide vapors.

- **Concentration/Time Selection/Rationale:**
  3 male beagle dogs/group
  Highest nonlethal exposure concentration 1363 ppm for 4 hr; exhibited lacrimation, salivation, nasal discharge, no motor weakness

- **Uncertainty/Modifying Factors/Rationale:**
  Total uncertainty/modifying factor: 10
  Interspecies: 3 - dog was not the most sensitive species tested, but data supports UF of 3: LC_{50} values for mice, dogs, and rats differed at most by a factor of 3.5, (mouse most sensitive); predicted airway and tissue burdens for mice, rats, dogs, and humans for nasal respiratory and olfactory epithelium, lung, and liver do not differ by more than 3.2; measured hemoglobin adduct levels following inhalation exposure in rats, mice, and dogs varied at most by a factor of 2.9.
  Intraspecies: 3 - mechanism of toxicity, direct alkylation, would not be expected to differ between individuals

- **Time scaling:** $C^n \times t = k$ where $n = 1.2$ based on EO

SUPPORTING DATA FOR AEGL-3

- **Reference:** CMA. 1998.

- **Concentration/Time Selection/Rationale:**
  1 worker exposed to 1520 ppm for 171 minutes; strong odor, irritation not intolerable

- **Uncertainty Factors/Rationale:**
  Total uncertainty factor: 3
  Interspecies: NA (1) - human data used
  Intraspecies: 3 - mechanism of toxicity, direct alkylation, would not be expected to differ between individuals

- **Modifying Factor/Rationale**
  2 - sparse data set: data from only one worker for one sampling period

- **Time scaling:** $C^n \times t = k$ where $n = 1.2$; based on EO.

SUPPORTING DATA FOR AEGL-3, cont.

- **Reference:** NTP. 1985.

- **Concentration/Time Selection/Rationale:**
  Groups of 5 $B6C3F_1$ mice/sex
  Highest nonlethal concentration in mice of 859 ppm for 4 hours; dyspnea observed

- **Uncertainty Factors/Rationale:**
  Total uncertainty factor: NA (6)
  Interspecies: 2 - mouse most sensitive species tested: LC_{50} values for the different species tested (mice, dogs, and rats) differed at most by a factor of 3.5, with the mouse being the most sensitive and the rat being the least sensitive; available human data suggest that mice may be more sensitive than humans in their response to propylene oxide exposure
  Intraspecies: 3 - mechanism of toxicity, direct alkylation, would not be expected to differ between individuals

- **Time scaling:** $C^n \times t = k$ where $n = 1.2$; based on EO.

SUMMARY OF AEGL-3 VALUES FOR PROPYLENE OXIDE (ppm)					
Endpoint	UF/ MF	30 m	1 h	4 h	8 h
Key Study: Jacobson et al, 1956 Dog: NOEL for lethality 1363 ppm for 4 hr	10	770	430	140	77
Supporting Studies:					
CMA, 1998 Human: Highest documented nonlethal exposure conc. 1520 ppm for 171 min	6	1100	610	190	110
NTP, 1985 Mouse: NOEL for lethality of 859 ppm for 4 hr	6	810	450	140	80

ACUTE EXPOSURE GUIDELINE LEVELS (AEGLS)

FOR

PROPYLENE OXIDE

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Attachment 15

DNA ADDUCT MEASUREMENT STUDY PROTOCOL

Animals

Adult male F344 rats

Exposure

0 and 500 ppm PO

Time

6 hours/day; 5 days/week; 4 weeks

Groups

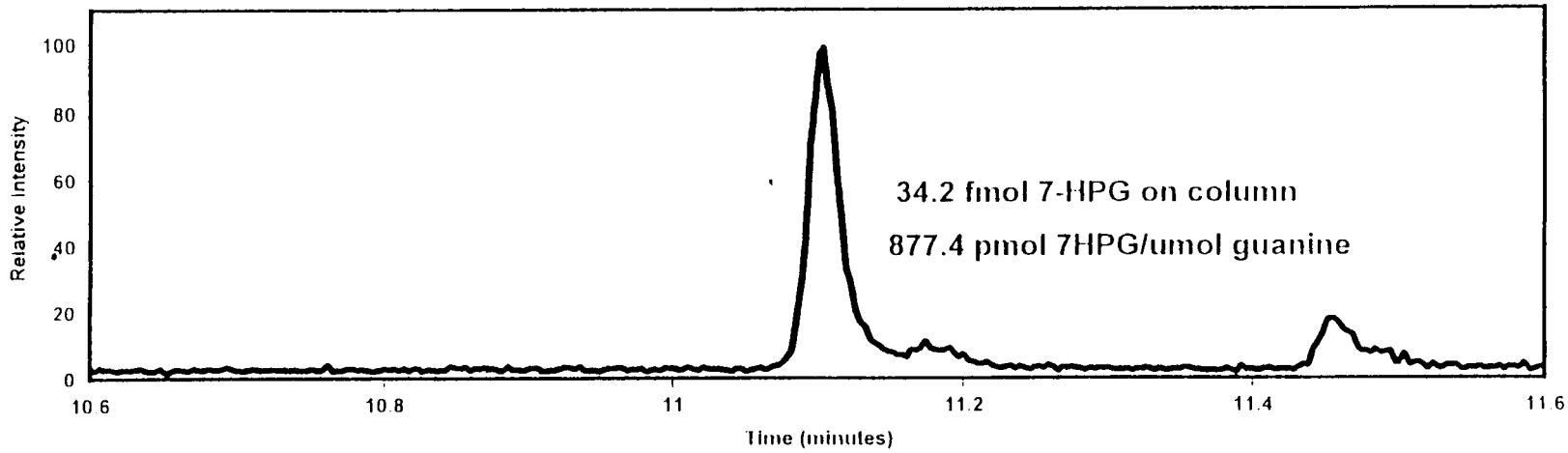
Exposed: 30 rats

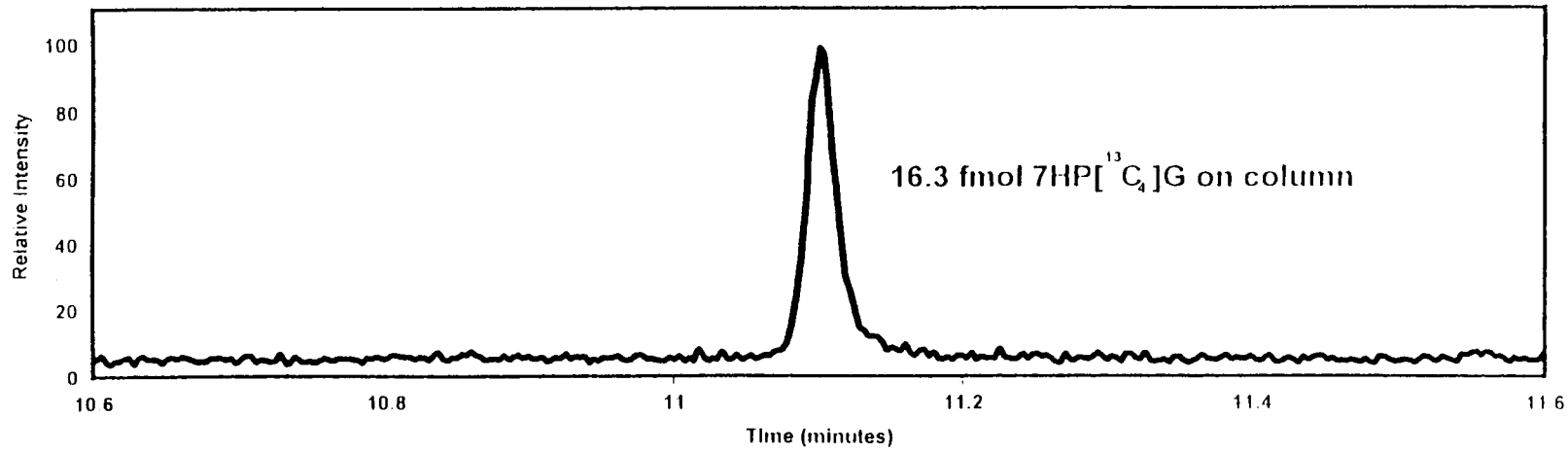
Exposed - Recovery: 10 rats

Control: 15 rats

Control Recovery: 5 rats

Representative Chromatogram of 7-HPG found in Nasal Respiratory Tissue DNA of a male rat exposed to 500 ppm PO for 20 days





Tissue distribution of 7-(2-hydroxypropyl)guanine DNA adducts in F344 rats exposed to 500 ppm PO for four weeks (6hr/day, 5 days/wk)

	GROUPS	
TISSUE	EXPOSED	EXPOSED-RECOVERY
Nasal Respiratory	835.4 ± 80.1 (n = 3)	592.7 ± 53.3 (n = 4)
Nasal Olfactory	396.8 ± 53.1 (n = 4)	296.5 ± 32.6 (n = 4)
Lung	69.8 ± 3.8 (n = 3)	51.5 ± 1.2 (n = 3)
Spleen	43.0 ± 3.8 (n = 3)	26.7 ± 1.0 (n = 3)
Liver	33.2 ± 6.1 (n = 8)	23.3 ± 1.4 (n = 6)
Testis	14.2 ± 0.7 (n = 3)	10.4 ± 0.1 (n = 3)

[a] mean ± std. dev.

n = number of animals

Table 1 Partition coefficients for matrix:air of PO for selected tissues of mouse, rat and human (37°C)

Tissue	Mouse	Rat	Human
Liver	60	50	53
Muscle	52	55	58
Fat	70	71	68
Blood	71	60	66

Table 4. Values predicted by means of a toxicokinetic model: average concentrations of PO at steady state in tissues of rats exposed to 500 ppm PO; concentration ratios tissue:air, together with DNA adducts resulting from 4 week exposures (6h/d, 5d/w) to 500 ppm PO

Tissue	Predicted PO concentration (mmol/l)	Predicted concentration ratio tissue:air	Predicted DNA adducts (pmol/μmol guanine)
Nasal respiratory epithelium	0.57	29	794
Nasal olfactory epithelium	0.34	17	544
Lung	0.13	6.5	147
Liver	0.038	1.9	44

Table 5. Calculated concentrations of propylene oxide (mmol/l) in diverse tissues of mouse, rat, dog and human exposed to 500 ppm propylene oxide at steady state.

Tissue	Mouse	Rat	Dog	Human
Nasal respiratory epithelium	0.92 *	0.57	0.7 * +	0.85 *
Nasal olfactory epithelium	0.92 *	0.34	not done	0.84 *
Lung	0.19	0.13	0.17 *	0.13-0.19
Liver	0.07	0.038	0.05 &	0.06-0.12

*reflecting the highest possible concentrations, since the data were not adjusted for PO elimination via metabolism

+ modeled for the nasal-pharyngeal region

& calculated using data from Segerbäck et al. (1994)

PROPYLENE OXIDE - CELL PROLIFERATION STUDIES

STUDY PROTOCOL

Animals

Adult male F344 rats: 6 rats/group

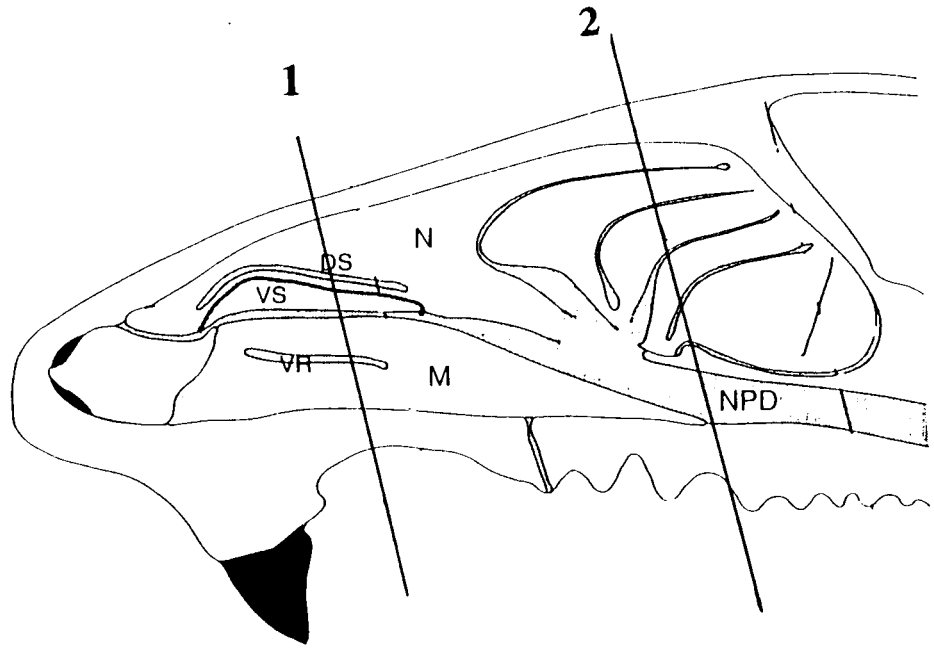
Exposure

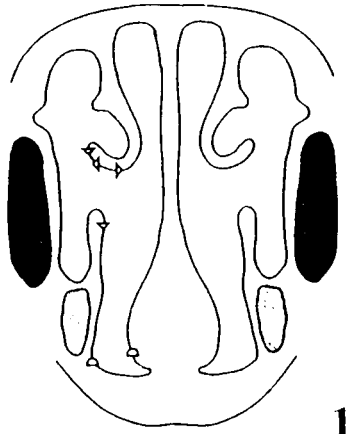
Route: Inhalation (6 hours/day)

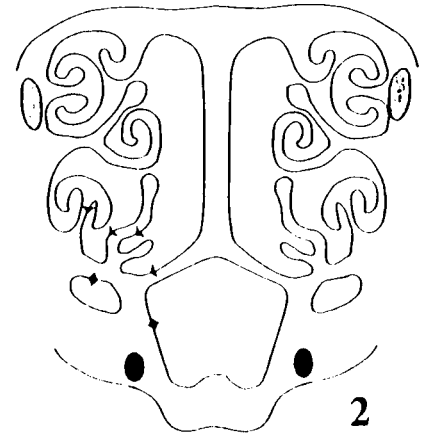
Length: 3 days

Doses: 0, 5, 25, 50, 300, 500 ppm

Midsaggital section of the nasal passages of a F344 rat. Straight vertical lines indicate section levels selected for transverse diagrams







Cell Proliferation in the Nasal Respiratory Epithelium and Nasopharyngeal Duct of F344 rats exposed to Propylene Oxide for 3 days (6hr/day)

Exposure Concentration (ppm)	Nasal Respiratory Epithelium	Nasopharyngeal Duct
0	3.5 ± 1.9	4.9 ± 1.1
5	3.7 ± 0.9	6.3 ± 1.8
25	4.1 ± 0.8	6.3 ± 1.7
50	2.6 ± 1.2	5.3 ± 2.9
300	10.9 ± 4.8 *	6.7 ± 1.7
500	20.0 ± 11.1 **	11.2 ± 7.5

Statistically different from control (Dunnett's test): * $p < 0.05$, ** $p < 0.01$

Table 1. Different exposure scenarios in which no treatment related mortality was observed together with equivalent exposure concentrations ($C_{Exp\ (8h)}$) calculated for an 8 h exposure using the relationship $C^{1.2} \times t = k$. (Citations of the references according to the NAC/Pro Draft 3: 11/98)

Species	Exposure	References	$C_{Exp\ (8h)}$
Dog	1363 ppm, 4 h	Jacobsen et al. (1956)	765 ppm
Rat	1277 ppm, 4 h	NTP (1985)	717 ppm
	2684 ppm 4 h	Jacobsen et al. (1956)	1506 ppm
	3450 ppm, 4 h	Shell Oil Company (1977)	1936 ppm
	2000 ppm 7 h	Rowe et al. (1956)	1789 ppm
Mouse	859 ppm, 4 h	NTP (1985)	482 ppm
Guinea pig	2000 ppm, 7 h	Rowe et al. (1956)	1789 ppm

The calculated concentrations ($C_{Exp\ (8h)}$) show that even the most sensitive species (mouse) can be exposed up to 480 ppm PO for 8 h without treatment related mortality.

Concentration-time courses of atmospheric propene oxide in closed exposure chambers each containing 5 male B6C3F1 mice

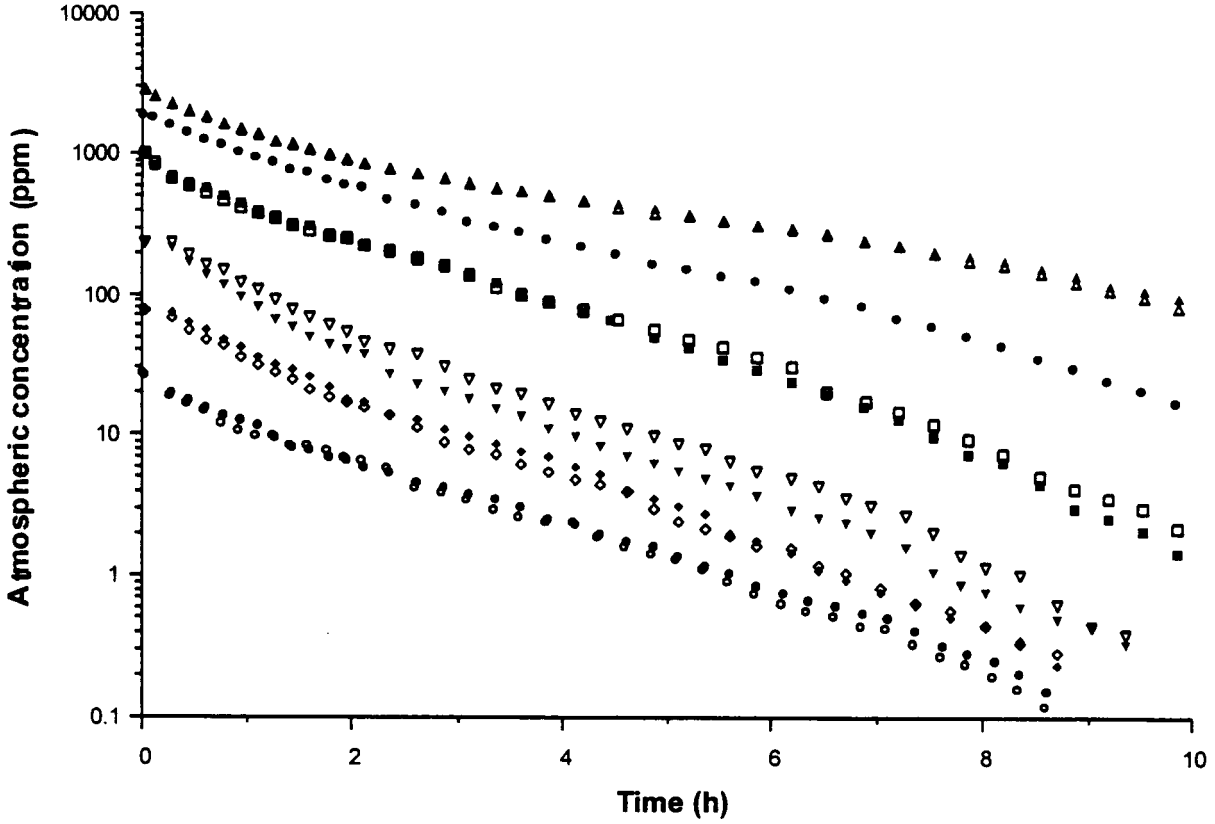


Table 2. Exposure parameters for inhalation experiments in which groups of male 5 B6C3F1 mice were exposed in closed chambers to defined initial concentrations of PO (Schmidbauer 1977). The exposure parameters are initial PO concentration in the closed chamber (C0; see Figure 1), exposure duration (texp), area under the curve (AUC) of the resulting concentration-time course of atmospheric PO, the equivalent constant average exposure concentrations ($C_{const.}$) and the equivalent constant average 8 h exposure concentration (C_{8h}).

C0 (ppm)	Texp (h)	AUC (ppm*h)	C_{const} (ppm)	C_{8h} (ppm)
28	8.58	37	4	5
28	8.58	40	5	5
80	8.67	109	13	13
80	8.67	121	14	15
240	9.33	354	38	43
240	9.33	281	30	34
1019	9.83	1398	142	169
1031	9.83	1410	143	170
1900	9.83	3478	354	420
1900	9.83	3479	354	420
3000	9.83	6077	618	734
3000	9.83	6143	625	742

Table 3. Highest none lethal 8 h exposure concentrations in mice, rats, guinea pigs, dogs and humans.

Species	8 h PO Exposure concentration (ppm)
Human	643
Dog	765
Rat	1936
Mouse	742
Guinea pig	1789

Proposed Interspecies Uncertainty Factor is not Science-Based

1. The mouse is equally or more sensitive than humans.
    a. Mortality data
    b. Clinical signs
    c. Physiologically-based modeling
    d. Obligatory nose breather
    e. Science-based uncertainty factor should be 1

2. The dog is similar to humans.
    a. Clinical signs at 1363 ppm in dog and 1520 ppm in human
    b. Physiologically-based modeling
    c. Science-based uncertainty factor of 2 due to small number of animals

AEGL-3 Values for Propylene Oxide (ppm)

Endpoint	UF/MF	30 min.	1 hour	4 hours	8 hours	Reference
Key Study Human: Highest documented nonlethal exposure concentration [1520 ppm for 171 minutes]	6	1100	610	190	110	CMA, 1998a
Supporting Studies						
Mouse: NOEL for lethality [859 ppm for 4 hours]	3	1620	900	280	160	NTP, 1985
Dog: NOEL for lethality [859 ppm for 4 hours]	6	1280	716	233	128	Jacobson et al., 1956

REVIEW OF DRAFT 2 ACUTE EXPOSURE GUIDELINE LEVELS FOR PROPYLENE OXIDE

L. S. Andrews, Ph.D.
CMA Propylene Oxide Panel
December 9, 1998

Attachment 16

SUMMARY

Proposed AEGL Draft 3	Comment
AEGL-1	Appropriate Values
AEGL-2	Appropriate Values (Rat Data Set Preferred as Basis)
AEGL-3	Values are Intuitively Too Low

AEGL-3 Values Presented in Draft 3 are Intuitively Too Low

Classification	30-Minute	1-Hour	4-Hour	8-Hour
AEGL-3*	770	430	***140***	***77***

* Highest non-lethal exposure concentration in dogs : 1363ppm for 4-hours (Jacobson et. al. 1956)

Comments:

- Under OSHA PEL of ***100ppm*** which has been in effect since 1970 there have been no related mortalities from PO exposure. (OSHA Log 200; OSHA 29 CFR 1904.8)
- ACGIH had in effect a TLV of ***100ppm*** from 1959 to 1981 and a TLV of 20ppm from 1981 to present.
- Industry environmental health survey data show that workers have survived without serious adverse effect – ***1520ppm/2.85hr. (7hr. shift)*** and ***348-913ppm/30min)***. (Industry exposure data previously reviewed with Panel)

PROPOSED AEGL-3 VALUES FOR PO

SOURCE	30 Min.	1-Hour	4-Hour	8-Hour
Draft 3 [a]	770	430	140	77
PO Panel-Human Experience [b]	2161	1213	382	214
PO Panel – Rat Data [c]	2408	1351	426	239

[a] **Based on highest nonlethal exposure concentration in dogs: 1363ppm for 4 hours (Jacobson et al, 1956)**

[b] **Workers exposed to 1520ppm PO for 2.85 hours were without serious adverse effect (PO Panel, 1998)**

[c] **Based on lowest 4 hour concentration not causing lethality in rats (NTP, 1985).**

SELECTION OF STUDIES FOR CALCULATIONS OF AEGL-2 & AEGL-3 VALUES

- **Robust acute inhalation exposure database for rats**

  - **4 separate acute inhalation lethality studies**
  - **25 separate exposure groups**
  - **3 exposure groups of 4 hr. duration reported by 3 different investigators**

- **There are appropriate AEGL-2 and AEGL-3 data in the F344 rat (strain used for cancer bioassay and extensive toxicokinetic modeling/mechanistic studies)**

EXPLICIT UNCERTAINTY FACTOR OF 3 RECOMMENDED FOR AEGL – 2&3 CALCULATIONS

- Rodents, as obligate nose breathers, are more sensitive than humans to PO-induced upper respiratory tract damage: Interspecies uncertainty factor = 1.
- Differences in anatomy/physiology between rats and humans indicate that on a dose/unit target tissue surface area basis, rats experience a 40x greater dose than humans (3x based on min-vol/KBW).
- Toxicokinetic data (Filser) indicate that inhaled PO is rapidly biotransformed in mouse, rat and humans. There is no reason to assume humans to be more sensitive than rodents.
- Worker data support that humans are less sensitive than rodents.

AEGL – 3 CALCULATION

NTP (1985) reported a non-lethal dose for 4 hr. exposures to be 1277 ppm in the F 344 rat.

$(1277)^{1.2}$ x 4 hr. = 21345 = K
$(C)^{1.2}$ x 1 hr. = 21354
C = 4054 ppm C/3 = 1351ppm/1 hr.

<u>IMPLICIT SAFETY FACTORS:</u>

>2-fold by using NTP data (2684 ppm and 3450 ppm also reported as 4 hr. non-lethal levels)
3-fold higher dose based on min-vol/kg bw
40-fold higher dose based on dose/unit target tissue surface area

AEGL PANEL INFORMATION REQUEST

- Document Human Exposure Data
- Address Site-of-Action for Acute Toxicity of PO
- Address Issue of Obligate Nose Breathing -Human vs. Rodent
- Explicit Safety Factor Recommendations

UPPER RESPIRATORY TRACT IS SITE-OF-ACTION FOR ACUTE INHALATION TOXICITY OF PO

- **Based on PO's appreciable water solubility (33%) reactivity/damage to the upper respiratory tract is expected.**

- **Clinical signs of toxicity for acute inhalation exposure are consistent with damage to the upper respiratory tract including nasal obstruction.**
  - **dyspnea,**
  - **gasping,**
  - **nasal discharge (clear and bloody)**
  - **distended stomach at autopsy**

- **Clinical signs of acute toxicity are <u>not</u> indicative of deep lung damage-pulmonary edema; broncheoalveolar histopathology.**

- **Following chronic and subchronic inhalation exposure studies, histopathology of the upper respiratory tract was the only consistent toxicologic finding.**

RECOMMENDED AEGL VALUES FOR PO BASED ON RAT DATA (n = 1.2; explicit safety factor = 3)

	30 min	1 hr.	4 hr.	8 hr.
AEGL-2	397	223	70	39
AEGL-3	2408	1351	426	239

1896

AEGL VALUES DERIVED FOR PO BASED ON HUMAN EXPERIENCE (n=1.2; explicit safety factor = 3)

	30 min	1 hr.	4 hr.	8 hr.
AEGL-2	556	312	98	55
AEGL-3	2161	1213	382	214

AEGL-2 CALCULATION

Eldridge et al (1995) reported an increase in nasal respiratory epithelial cell proliferation and mild histopathology in male F344 rats exposed to 525 ppm PO vapors for 6 hr/day for 5 days. Minimal changes seen at 150 ppm.

$$(150)^{1.2} \times 6 \text{ hr.} = 2452 = K$$
$$C^{1.2} \times 1 \text{ hr.} = K$$
$$C = 668\text{ppm} \rightarrow C/3 = 223 \text{ ppm/1hr.}$$

Implicit Safety Factors:

5 days of exposure
3-fold higher dose based on min-vol/kg bw
40-fold higher dose based on dose/unit target tissue surface area

INFANTS ARE PREFERENTIAL (NOT OBLIGATE) NOSE BREATHERS

- Review and opinion offered by Paul L. Ogburn, Jr. M.D., Maternal-Fetal Medicine, Mayo Clinic. (included in submission to AEGL Panel).
- Bilateral Choanal Atresia is initially managed by mouth breathing through a "McGovern Nipple" (baby bottle nipple with tip cut off).
- Oral airway used by infants in response to experimental complete nasal occlusion.

RODENTS ARE OBLIGATE NOSE-BREATHERS

- Anatomical Foundation
- Epiglottis and Soft Palate are in Close Apposition
- Prevents Communication between Oral & Nasal Passages

* Haschek, Wm. And Rousseaux, CG. Handbook of Toxicologic Pathology pp. 763-765, 1991

Appendix A

NATIONAL ADVISORY COMMITTEE (NAC) FOR ACUTE EXPOSURE GUIDELINE LEVELS (AEGLS) FOR HAZARDOUS SUBSTANCES

Final Meeting 11 Highlights
Oak Ridge National Laboratory
1060 Commerce Park Drive, Oak Ridge, TN 37830

September 14-16, 1998

INTRODUCTION

George Rusch (NAC Chairman) opened the meeting and welcomed all participants. The meeting agenda (Attachment 1) and the attendee list (Attachment 2) are enclosed. Paul Tobin (DFO) stated that considerable progress had been made by the NAC/AEGL on the initial list of 85 priority chemicals. For future chemicals, an effort will be made to determine chemical-specific production volume, storage, and use information. Acquiring such information will assist the NAC/AEGL in deciding if AEGL values are warranted for title chemicals. Additionally, Paul Tobin requested that respective agencies and organizations provide information regarding how AEGLs are used and that the NAC representative of these agencies/organizations also attempt to obtain review/feedback on the Technical Support Documents (TSDs) and AEGL values from their respective agency/organization.

Roger Garrett (Program Director) briefly discussed the budget and the need to ensure uninterrupted funding to avoid possible breaks in work momentum and productivity. George Cushmac (U.S. DOT) suggested that a yearly report from the NAC to funding organizations would possibly inform such agencies of the NAC/AEGL activities and productivity record.

The NAC/AEGL Meeting 10 highlights were reviewed and accepted following minor revisions (Appendix A).

REPORTS FROM WORKING GROUPS AND GENERAL INTEREST ITEMS

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

Roger Garrett stated that the NAS/COT Subcommittee on Acute Exposure Guideline Levels has been assembled (Attachment 3) and that the first meeting is scheduled for October 15-16, 1998. It is expected that this first meeting will entail an overview of the NAC/AEGL, its Standing Operating Procedures and possibly initial presentation of the Interim AEGLs for 10 chemicals.

General Interest Items

- Draft Guideline for Carcinogens

Presentation and discussion were deferred until the next meeting.

- Draft Guideline for Anesthesia
  Presentation and discussion were deferred until the next meeting.

- Draft Guidelines for Sensitive Populations
  A draft document has been distributed to the NAC/AEGL. Comments should be directed to Ernie Falke in a timely fashion for incorporation into the Standing Operating Procedures. It was suggested that this effort should possibly address the topic of pharmacogenetics.

- Bromine Testing
  Larry Gephart (Exxon Biomedical Sciences) stated that the industries contacted had tests pending that would address comparative respiratory effects of chlorine and bromine (1- and 4-hr LC_{50} studies).

- Benchmark Dose (BMD)
  Robert Benson (U.S. EPA, Region VIII) circulated a publication (Attachment 3) resulting from the U.S. EPA Benchmark Dose Workshop. Questions were raised regarding the validity of the BMD methodology for acute exposures.

- Time-Dose Extrapolation Issues
  Issues pertaining to time-dose extrapolation and interpretation of AEGLs were raised by John Morawetz (International Chemical Workers Union) and Larry Gephart. Following discussion, a draft AEGL-specific definition of "ceiling" (Attachment 4) was provided that captured identified concerns.

  Action Item: The preceding issue of time-dose extrapolation and interpretation of "ceiling" will be an agenda item for the next NAC/AEGL meeting.

- Standing Operating Procedures (SOP)
  Ernie Falke (U.S. EPA, Chairman, SOP Working Group) provided an overview of SOP items that had been revised following input from NAC/AEGL members. These revisions included AEGL definitions (will include discussion of ceilings), deletion of Section 2.11 (rationale for AEGLs; this subsection was redundant with another), expanded acronyms in Appendix 1, and revision of the times scaling section. Ernie stated that any additional comments/suggestions on the SOPs should be submitted to him by 9/24/98.

AEGL PRIORITY CHEMICALS

Hydrazine, CAS No. 302-01-2

Chemical Manager: Dr. Richard Thomas, ICEH

Author: Dr. Robert A. Young, ORNL

In response to Federal Register comments, the AEGL-2 and AEGL-3 values for hydrazine were revised. Ernie Falke substituted for Richard Thomas (absent) as Chemical Manager. Ernie outlined the pertinent issues of the Federal Register comments and the need for the revision. Robert Young provided further details regarding the issues at hand: (1) rescinding of the regional gas dose methodology for human equivalent exposure adjustment, and (2) selection of a more defensible estimate of the lethality threshold (Attachment 5). The application of the regional gas dose methodology that was originally applied to the derivation of the hydrazine AEGL-2 and AEGL-3 values was withdrawn because (1) the methodology has not been validated, and (2) required the use of broad-reaching assumptions because its use is inconsistent with NAC/AEGL procedures to date. The original derivation of AEGL-3 values was based upon an LC_{01} as an estimate of the lethality threshold in rats for acute inhalation of hydrazine. This estimated value was inconsistent (too low) relative to a nonlethal exposure (used for AEGL-2) from a well-conducted study. A lethality threshold estimated by a one-third reduction in the LC_{50} was found to be more scientifically defensible because it was consistent with available data. The determinant for the revised AEGL-3 was 1,064 ppm (one-third of the 1-hr LC_{50} of 3,192 ppm as opposed to the original LC_{01} estimated of 337 ppm) from a rat study conducted by Huntington Research Corporation (same key study as original AEGL-3). The uncertainty factors remained unchanged (10 for species variability [this is likely to account for interspecies variability in dosimetry] and 3 for individual variability). For the AEGL-2, the determinant remained unchanged; nasal lesions in rats resulting from a 1-hr exposure to 750 ppm. Uncertainty factor application was 10 for interspecies variability, 3 for individual variability and an additional factor of 2 to account for a deficient data base regarding serious but nonlethal toxic responses. The revised AEGL values are shown below (original values are in parentheses) and remain very similar to the previous values: A motion was made by Doan Hansen, and seconded by Steve Barbee; the motion was accepted by NAC/AEGL [YES: 20, NO: 2, ABSTAIN: 0] (Appendix B). The revised AEGL-2 values, although approximately two-fold higher than the previous values, more accurately reflect the known steep exposure-response curve for hydrazine. Based upon the available data, the revised AEGL-2 values are considered to be protective of human health relative to AEGL-2 category effects. A motion was made by Bob Snyder and seconded by Tom Hornshaw to adopt the revised AEGL-2 values. The motion was accepted [YES:20, NO: 2, ABSTAIN: 0] (Appendix B). It was also the consensus of the NAC that notation be made that the 30-min concentration should be regarded as a ceiling that should not be exceeded.

SUMMARY OF REVISED AEGL VALUES FOR HYDRAZINE					
Classification	30-min	1-hr	4-hr	8-hr	Endpoint
AEGL-1	0.1 ppm	0.1 ppm	0.1 ppm	0.1 ppm	Not revised; based upon eye and facial irritation in monkeys
AEGL-2	18 ppm (8 ppm)[a]	13 ppm (6 ppm)	6.2 ppm (3 ppm)	4.4 ppm (2 ppm)	Nasal lesions in rats; includes UF of 2 for deficiencies in data specific for serious but nonlethal responses
AEGL-3	50 ppm (47 ppm)	35 ppm (33 ppm)	18 ppm (17 ppm)	13 ppm (12 ppm)	Estimated lethality threshold in rats (1/3 of 1-hr LC_{50}); 3,192 ppm/3 = 1,064 ppm

[a] ( ) = original values

Ethylene oxide, CAS No. 75-21-8

Chemical Manager: Dr. Kyle Blackman, FEMA
Author: Dr. Kowetha Davidson, ORNL

For the revisit of ethylene oxide, Kyle Blackman provided introductory remarks. Kowetha Davidson gave an overview of the data sets and outlined the revisit issue pertaining to evaluation of endpoints from the key study (neurotoxicity or dominant lethality) and their relevance to deriving AEGL-2 and AEGL-3 levels (Attachment 6). Bill Snellings (Union Carbide) explained a rationale for looking at the neurotoxic effects rather than the dominant lethality aspect of the study in questions. It was decided that the Federal Register comments as well as the rationale for the AEGL values be reviewed and that a decision will be made at the next meeting to determine if revisiting these issues is required.

Hydrogen sulfide, CAS No. 7783-06-4

Chemical Manager: Dr. Stephen Barbee, Olin Corporation
Author: Dr. Cheryl Bast, ORNL

Cheryl Bast provided an overview of available data (Attachment 7) and addressed the use of categorical regression methodology that had been suggested by an external reviewer as a possible methodology. The issues of nuisance odor and recurrent exposures were also briefly discussed (both of these being factors in the assessments by several states). A poll of the NAC/AEGL indicated a general consensus on the approach used for derivation of draft AEGL-2 and AEGL-3 values, and that most concern was focused on the AEGL-1 values. A poll of the NAC/AEGL also indicated a consensus for deriving 10-min AEGL values for AEGL-2 and AEGL-3 but for not for AEGL-1. The deliberations on hydrogen sulfide were again deferred in the absence of individuals (George Alexeeff, California EPA; David Belluck, Minnesota Pollution Control Agency; Zarena Post, Texas Nat. Resource Conserv. Comm.) previously expressing concerns regarding assessments by their respective states and NAC/AEGL assessments on this chemical. At least one NAC/AEGL member strongly objected to the extended deferment.

Carbon tetrachloride, CAS No. 56-23-5

Chemical Manager: Dr. William Bress, Vermont Dept. of Health
Author: Dr. Robert A. Young, ORNL

A brief revisit of the AEGL-3 values for carbon tetrachloride focused attention to the human case reports involving enhanced toxic responses to carbon tetrachloride in individuals also exposed to alcohol. The reports affirm such an interaction but, with the exception of a report by Norwood et al. (1950), the reports lacked quantitative information on exposure terms. The known alcohol-potentiated toxicity of carbon tetrachloride toxicity is clearly described in the TSD and an uncertainty factor of 10 for individual variability in toxic responses was applied in the derivation of the AEGLs. It was the consensus of the NAC that the anecdotal data reported by Norwood et al. (1950) was insufficient as a key study upon which to base the AEGL-3 values, and that the lethality data in animals and the overall data base indicated that the currently proposed AEGL-3 values were justified. The proposed AEGL values for carbon tetrachloride remain as shown.

SUMMARY OF PROPOSED AEGL VALUES FOR CARBON TETRACHLORIDE					
Classification	30-min	1-hr	4-hr	8-hr	Endpoint
AEGL-1	16 ppm 100.6 mg/m^3	12 ppm 75.5 mg/m^3	6.9 ppm 43.4 mg/m^3	5.2 ppm 32.7 mg/m^3	Nervousness, slight nausea in human subjects (Davis, 1934)
AEGL-2	90 ppm 566.1 mg/m^3	68 ppm 427.7 mg/m^3	39 ppm 245.3 mg/m^3	30 ppm 188.7 mg/m^3	Nausea, vomiting, headache in human subjects (intolerable to one of four subjects) (Davis 1934)
AEGL-3	230 ppm 1,446.7 mg/m^3	170 ppm 1,069.3 mg/m^3	99 ppm 622.7 mg/m^3	75 ppm 471.8 mg/m^3	Estimated lethality threshold (LC_{01} = 5,135.5 ppm) in rats (Adams et al.,1952; EPA-OTS, 1986)

Propylene Oxide, CAS No. 75-56-9

Chemical Manager: Dr. James Holler, ATSDR
Author: Dr. Claudia Troxel, ORNL

Presentations were made by Susan Ripple on behalf of the CMA Propylene Oxide (PO) Panel (Attachment 8). She provided responses to questions previously posed by the NAC/AEGL regarding human experience data originally presented by the CMA PO Panel. AEGL-2 and AEGL-3 values developed by the PO Panel and based upon human exposure data were presented. Discussions followed that revolved around the limited number of human subjects, uncertainty factor applications (intraspecies UF of 3 appropriate for extrapolation to larger populations), and the propylene oxide concentrations used as determinants for the AEGL values. Susan requested that the NAC/AEGL defer further deliberations until the next meeting at which time Larry Andrews (CMA PO Panel) will provide an interpretation of the animal data. It was decided that additional data or information that can be obtained be provided to the ORNL staff scientist and Chemical Manager by November 1, 1998. It was also requested that quality control/assurance information pertaining to the human exposure information presented by Susan Ripple be made available, if possible, to the NAC/AEGL. Further deliberations were deferred until the next NAC/AEGL meeting.

Propylenimine, CAS No. 75-55-8

Chemical Manager: Dr. Mark McClanahan, CDC
Author: Dr. Kowetha Davidson, ORNL

Mark McClanahan opened the presentation by noting the paucity of data and reference to ethylenimine. Kowetha Davidson provided an overview of the available data and how it related to that for ethylenimine (Attachment 9). For the AEGL-3 values, a lethality threshold was estimated from data on guinea pigs (30-minute exposure to 500 ppm, n=0.91, interspecies UF=3, intraspecies UF=3. A motion was made (Robert Snyder) and seconded (Richard Niemeier) to accept the values of 50, 23, 5.1, and 2.4 ppm for 30-min, 1-, 4-, and 8-hr as AEGL-3 values. The motion passed [YES: 19; NO: 1; ABSTAIN: 0].

In the absence of data specific for AEGL-2 type effects, the AEGL-2 values for propylenimine were derived by applying a relative potency factor of 5 and a modifying factor of 2 to the AEGL-2 values for ethylenimine. The resulting values of 25, 11, 25, and 1.2 for 30 min, 1-, 4-, and 8-hrs, respectively were accepted (motion by Bill Bress, seconded by Thomas Hornshaw [YES: 18; NO: 2; ABSTAIN: 0] (Appendix C). It was suggested that a skin notation be made regarding the toxicity of propylenimine and ethylenimine to the skin. It was the consensus of the NAC/AEGL that AEGL-1 values would not be meaningful and, therefore, not developed (Appendix C).

SUMMARY OF PROPOSED AEGL VALUES FOR PROPYLENIMINE					
Classification	30-min	1-hr	4-hr	8-hr	Endpoint
AEGL-1	NR	NR	NR	NR	Data not available
AEGL-2	25 ppm	11 ppm	2.5 ppm	1.2 ppm	Respiratory difficulty Carpenter et al., 1948
AEGL-3	50 ppm	23 ppm	5.1 ppm	2.4 ppm	Estimated lethality threshold

NR: not recommended

Nitrogen Oxides
Nitric oxide, CAS No. 10102-43-9
Nitrogen dioxide, CAS No. 10102-44-0

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

Carol Forsyth presented an overview of the available data (Attachment 10) and the development of the draft AEGL values for nitric oxide, noting that the data previously expected from industry (preliminary data were presented at the 1998 Society of Toxicology Annual Meeting, see NAC/AEGL Meeting 9 Highlights) was not received. Also reviewed was the prior NAC/AEGL decision that for the methemoglobinemia endpoint, a methemoglobin level of ≤20% was consistent with AEGL-1 and that ≥85% was consistent with AEGL-3. Previously, data were limited to developing only AEGL-1 values for nitric oxide (80 ppm for all time points based upon methemoglobin formation in compromised individuals). As per the consensus of the NAC/AEGL (Meeting No. 9), the toxicity of nitrogen dioxide was examined prior to further deliberations on nitric oxide.

For AEGL development, nitrogen dioxide was discussed first. A summary of human data was presented (≥150 ppm is fatal; ≤4 ppm produces no effect) and that pulmonary irritation and edema occurs at high exposures. For the AEGL-3 30-min, 1-, 4-, and 8-hr periods, values of 25, 20, 14, and 11 ppm were accepted (motion by Doan Hansen, seconded by mark McClanahan, with unanimous approval) (Appendix D) based upon marked irritation (but no deaths) in monkeys exposed for 2 hrs to 50 ppm (n=3.5; UF=3). Following discussion regarding the feasibility and need for 10-min values, it was the consensus of the NAC/AEGL that such values would be developed only if requested by industry and/or emergency planners.

Exposure of humans (120-min to 30 ppm) resulting in a burning sensation in the chest and nose, cough, dyspnea, and excessive production of sputum was used as the basis for the AEGL-2 values. The resulting AEGL-2 values (n=3.5, UF=3) of 14.9, 12.2, 8.2, and 6.7 ppm were accepted by the Committee (motion by Loren Koller, seconded by Bill Pepelko with unanimous approval) (Appendix D). Following brief discussions, AEGL-1 values were set at 0.5 ppm (there was evidence from available studies showing that some effects occurred at concentrations <1 ppm) (motion by Bob Benson, seconded by Ernie Falke with unanimous approval) (Appendix D).

At this time, the issue was raised regarding increased susceptibility to pathogens following pulmonary irritation. It was suggested that, where appropriate, mention be made that exposure to irritants that results in pulmonary or airway damage may increase susceptibility to respiratory tract infection. It was also noted that animal studies with respect to this effect differ from the human experience because humans would be treated while animals would not.

Discussion proceeded to nitric oxide with initial notes that nitric oxide is rapidly converted to nitrogen dioxide and that the major toxicity endpoint reported for nitric oxide is the formation of methemoglobin. Following considerable discussion regarding the nitric oxide-nitrogen dioxide conversion and the ramifications of this on the validity of developing AEGL values for nitric oxide, there was a proposal of the NAC/AEGL that no values be developed for nitric oxide and that the nitrogen dioxide values be used for emergency planning with a reference to the known conversion and that clinical data indicate that short-term exposure (time not specified) to 80 ppm nitric oxide is without significant effect (motion by Mark McClanahan, second by George Rodgers [YES: 16; NO: 4; ABSTAIN: 0] (Appendix E). It was also decided that separate TSDs would be prepared for nitric oxide and nitrogen dioxide but that the nitrogen dioxide TSD would be amended to the nitric oxide TSD.

SUMMARY OF PROPOSED AEGL VALUES FOR NITROGEN DIOXIDE*					
Classification	30-min	1-hr	4-hr	8-hr	Endpoint
AEGL-1	0.50 ppm	0.50 ppm	0.50 ppm	0.50 ppm	Minor irritation
AEGL-2	15 ppm	12 ppm	8.2 ppm	6.7 ppm	Burning in chest and nose, cough, dyspnea, excessive sputum in humans exposed to 30 ppm for 2 hrs.
AEGL-3	25 ppm	20 ppm	14 ppm	11 ppm	Marked irritation (no deaths) in monkeys exposed 50 ppm for 2 hrs.

*AEGLs for nitric oxide not recommended; use nitrogen dioxide values for planning but note that short-term exposure to 80 ppm nitric oxide is without clinical effects.

Iron pentacarbonyl, CAS No. 13463-40-6

Chemical Manager: Dr. Kyle Blackman, FEMA
Author: Dr. Robert Young, ORNL

Kyle Blackman gave an overview of the physicochemical properties of iron pentacarbonyl and also stated that he had contacted the two companies known to produce the chemical but had received no response from them. Robert Young provided an overview the three data sets available for this chemical (Attachment 11). Two of the three data sets were from recent well-conducted studies in rats that provided adequate

information on experimental design and analytical techniques. However, the available studies all focused on lethal responses. Although indices of lethality and estimates of a lethality threshold were defined by these data, no information was available regarding effects consistent with AEGL-1 or AEGL-2 definitions. The available data allowed for exposure-time-response comparisons indicating linearity and, therefore, *n* =1 for C^n x t = k. Based upon clinical observations and histopathologic findings in rats, the mechanism of lethality appeared to be pulmonary damage. Results of these experiments showed that the lethality threshold for rats was approximately 5.2 ppm for a 4-hr exposure and that 28-day exposures to 1 ppm for 6 hrs/day resulted in no effects. However, examination of the data from 1995 BASF study revealed that one of ten rats exposed to 2.91 ppm for six hours died and that 50% mortality was observed after two 4-hr exposures to this concentration. Although, the remaining rats survived 28 consecutive exposures, this exposure was considered an estimate of a lethality threshold. This contention is supported by a notable latency (1-8 days) in the lethal response. The AEGL-3 values were, therefore, based upon the 6-hr exposure to 2.91 ppm. Because the mechanism of action appears to be a port-of-entry effect mediated by contact irritation and destruction of pulmonary membranes, the intraspecies uncertainty factor was set at 3 (the mechanism of action is not likely to vary considerably among individuals). Due to the uncertainties regarding interspecies variability in the toxic response to iron pentacarbonyl and the lack of human data, the uncertainty factor for interspecies variability remained at 10. The AEGL-3 values of 1.2, 0.58, 0.16 were accepted for the 30-min, 1-hr and 4-hr time frames, respectively (motion by Bob Benson, seconded by Steve Barbee with unanimous approval) (Appendix F). In the absence of data on serious but nonlethal effects of exposure to iron pentacarbonyl (the animal data provided only lethality

or no-effect responses), the AEGL-2 values were based upon a one-third reduction of the AEGL-3 values (i.e., MF of 3) as an estimate for a threshold for serious but nonlethal effects. Due to the exposure-response data suggesting little differentiation between no-effect levels and lethal exposures, this adjustment appeared defensible. The values of 0.35, 0.17, and 0.044 were accepted for the 30-min, 1-, and 4-hr time frames (motion by Mark McClanahan, seconded by Loren Koller [YES: 19; :NO: 2; ABSTAIN: 0] (Appendix F). Due to the physicochemical properties of iron pentacarbonyl, 8-hour AEGL values were considered inappropriate. No data were available regarding effects consistent with the AEGL-1 definition and no odor threshold data are available. Therefore, AEGL-1 values were not developed.

SUMMARY OF PROPOSED AEGL VALUES FOR IRON PENTACARBONYL					
Classification	30-min	1-hr	4-hr	8-hr	Endpoint
AEGL-1	ND	ND	ND	ND	No data
AEGL-2	0.35 ppm	0.17 ppm	0.044 ppm	NR	Estimate of exposure causing serious but nonlethal effects; based upon 1/3 reduction of AEGL-3 values.
AEGL-3	1.2 ppm	0.58 ppm	0.16 ppm	NR	Estimated rat lethality threshold of 2.91 ppm, 6-hr exposure (BASF, 1995)

NR: not recommended

Furan, CAS No. 110-00-9

Chemical Manager: Dr. George Rodgers, Univ. of Louisville, AAPCC
Author: Dr. Claudia Troxel, ORNL

George Rodgers provided production/use information about furan and also explained problems with the available data (i.e., human exposure data are limited and involve concurrent exposures to other chemicals). In addition to the problem exposure to complex mixtures, the human data are also very subjective in nature. The data do, however, suggest that central nervous system effects and irritation may be associated with the exposures. Claudia Troxel provided an overview of data during the meeting (Attachment 12). A National Academy of Sciences report and a report by the Bio/dynamics (HLS) were not available at the time the TSD was being prepared, will be obtained and reviewed. Deliberations on furan were deferred until after these reports are obtained and reviewed.

Nitriles
Isobutyronitrile, CAS No. 78-82-0
Methacrylonitrile, CAS No.126-98-7
Propionitrile, CAS No. 107-12-0

Chemical Manager: Dr. George Rodgers, Univ. of Louisville, AAPCC
Author: Dr. Cheryl Bast, ORNL

Following introductory remarks by George Rodgers, Cheryl Bast began an overview of isobutyronitrile by reviewing data received earlier that day from Dr. James Deyo of Eastman Kodak Co. (Attachment 13). These GLP studies provided data with which to derive AEGL-3 values that differed somewhat from those in the draft TSD. A motion was made by George Rodgers (second by Robert Snyder) to accept the new values of 26, 20, 12, and 9 ppm (UF=30; 10 for interspecies and 3 for intraspecies variability, n=2.6). The motion passed [YES: 18; NO: 1; ABSTAIN:0] (Appendix G). Bill Bress proposed (motioned; second by Richard Niemeier) that a no-effect level from a developmental toxicity study in rats be used as the basis for the AEGL-2 for isobutyronitrile resulting in AEGL-2 values of 8.7, 6.6, 3.9, and 3.0 ppm. The motion passed [YES: 17; NO: 1, ABSTAIN: 0) (Appendix G). Mark McClanahan made a motion (second by Robert Benson) that there was insufficient data to develop AEGL-1 values. The motion passed unanimously (Appendix G).

SUMMARY OF PROPOSED AEGL VALUES FOR ISOBUTYRONITRILE					
Classification	30-min	1-hr	4-hr	8-hr	Endpoint
AEGL-1	ND	ND	ND	ND	No data
AEGL-2	8.7 ppm	6.6 ppm	3.9 ppm	3.0 ppm	100 ppm exposure no effect in developmental toxicity study
AEGL-3	26 ppm	20 ppm	12 ppm	9 ppm	Estimated NOEL for death in rats; 1/3of the 1-hr LC_{50} (1800 ppm/3 = 600 ppm)

Cheryl Bast continued to review the available data for methacrylonitrile (Attachment 13). For AEGL-3 development, a Committee poll indicated that a 19.6 ppm exposure of mice (NOAEL for lethality) be used

as the determinant. A motion was made by Bob Benson (second by Mark McClanahan) to accept the values of 4.5, 3.4, 2.0, and 1.5 ppm (UF=3 for interspecies and 3 for intraspecies variability, n=2.6). The motion carried [YES: 14; NO: 4; ABSTAIN 0] (Appendix H). For AEGL-2 Cheryl Bast provided options suggested by NAC/AEGL members who provided review comments. These included using one-third of the AEGL-3 values and the use of data from a dog study where a 7-hr exposure to 13.5 ppm produced convulsions. A motion was made by Mark McClanahan, seconded by Richard Niemeier, to accept [YES: 14; NO: 3; ABSTAIN: 0] (Appendix H) the values generated by using one third of the AEGL-3 values (1.5., 1.1, 0.7, and 0.5 ppm) and to use the findings from the dog study as supporting data. A motion was made by George Rodgers (second by Mark McClanahan) that data were insufficient for deriving AEGL-1 values. The motion passed unanimously (Appendix H).

SUMMARY OF PROPOSED AEGL VALUES FOR METHACRYLONITRILE					
Classification	30-min	1-hr	4-hr	8-hr	Endpoint
AEGL-1	ND	ND	ND	ND	No data
AEGL-2	1.5 ppm	1.1 ppm	0.67 ppm	0.50 ppm	One-third reduction in AEGL-3 values
AEGL-3	4.5 ppm	3.4 ppm	2.0 ppm	1.5 ppm	NOEL for lethality in mice (19.6 ppm for 4 hrs)

Deliberations on propionitrile were deferred until the next meeting due to lack of time.

ADMINISTRATIVE ISSUES

Roger Garrett provided information regarding the NAS/COT meeting. The COT Subcommittee on Acute Exposure Guideline Levels has been formed (Attachment 14) and the first meeting scheduled for October 15-16, 1998. Roger stated that the agenda will likely include an overview of the NAC/AEGL SOP, its overall process and how it differs from the NRC (1993) approach on acute exposures. It is hoped that some of the first 10 (interim) AEGLs can be presented. It is likely that the COT review process will be an iterative effort to come to consensus on issue and will take several meetings. The application and justification of uncertainty factors and the derivation of the time scaling factor, n, will probably be key issues.

The status of invitations to other participants were discussed briefly (WHO, European Commission, etc.)

The preparation/review schedule for Technical Support Documents was again discussed. Several components of the document preparation/review process were emphasized including the need for uninterrupted funding to ensure timely development of draft AEGLs, and completion/distribution of the TSDs. A projected schedule for the aforementioned process (Attachment 15) as well as tracking sheets (Attachment 16) to monitor the process were distributed and discussed. Finally, Roger Garrett reported the status of the development of AEGL values since the project launched in 1996 (Attachment 17).

A poll of the NAC/AEGL indicated unanimous approval of ORNL as an annual meeting site.

Future meetings:

December 7-9, 1998, Washington, DC
March 18-19, 1999, New Orleans, LA (after SOT)

George Rusch expressed thanks and appreciation for a productive meeting and to ORNL as host of the meeting

This report was prepared by Drs. Robert Young and Po-Yung Lu, ORNL.

LIST OF ATTACHMENTS

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

1. NAC Meeting No. 11 Agenda
2. NAC Meeting No. 11 Attendee List
3. Draft SOP for NAS/COT
4. Draft definition of "ceiling" - John Morawetz/ Larry Gephart
5. Data analysis of Hydrazine - Bob Young
6. Data analysis of Ethylene oxide - Kowetha Davidson
7. Data analysis of Hydrogen sulfide - Cheryl Bast
8. Data analysis of Propylene oxide from CMA Propylene Oxide (PO) Panel - Susan Ripple
9. Data analysis of Propyleneimine - Kowetha Davidson
10. Data analysis of Nitrogen oxides - Carol Forsyth
11. Data analysis of Iron pentacarbonyl - Bob Young
12. Data analysis of Furan - Claudia Troxel
13. Data analysis of Nitriles - Cheryl Bast
14. COT roster of subcommittee on AEGLs - Roger Garrett
15. Projected schedule for AEGLs TSD preparation process - Roger Garrett
16. AEGLs tracking sheets - Roger Garrett
17. Status of development of AEGL values - Roger Garrett

LIST OF APPENDICES

A. Approved NAC-10 Meeting Highlights
B. Ballot for Hydrzine
C. Ballot for Propylenimine
D. Ballot for Nitrogen dioxide
E. Ballot for Nitrogen oxide
F. Ballot for Iron pentacarbonyl
G. Ballot for Isobutyronitrile
H. Ballot for Methyacrylonitrile

Date of NAC/AEGL Meeting: Dec. 7-9, 1998 **Chemical:** 107-12-0 PROPIONITRILE

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

NAC Member	AEGL 1	AEGL 2 (a)	AEGL 2 (b)	AEGL3
Loren Koller	Y	N	Y	Y
Glenn Leach	Y	N	Y	Y
Mark A. McClanahan	Y	N	N	Y
John S. Morawetz	A	A	A	A
Deirdre L. Murphy	Absent	Absent		Absent
Richard W. Niemeier	A	A	A	Y
William Pepelko	Y	N	Y	Y
Zarena Post	Absent	Absent		Absent
George Rodgers	Y	N	Y	Y
George Rusch, Chair	Y	Y	Y	Y
Bob Snyder	Y	P	P	A
Thomas J. Sobotka	Y	N	N	A
Kenneth Still	Y	N	Y	Y
Patricia Ann Talcott	Absent	Absent		Absent
Richard Thomas	A	A	A	A
Thomas Tuccinardi/ Doan Hansen	A Y	A Y	A Y	A Y
TALLY	23/23	8/22	17/22	23/23

PPM, (mg/m³)	30 Min	60 Min	4 Hr	8Hr
AEGL 1	NA* ,( )	NA ,( )	NA ,( )	NA ,( )
AEGL 2	(a) 5.8 (b) 9.6 ,( )	(a) 4.4 (b) 7.4 ,( )	(a) 2.6 (b) 4.3 ,( )	(a) 2.0 (b) 3.3 ,( )
AEGL 3	51 ,( )	39 ,( )	23 ,( )	18 ,( )

* INSUFFICIENT DATA
a VOTE DEFEATED
b VOTE PASSED

AEGL 1 Motion: M. McCLANAHAN **Second:** L. KOLLER

AEGL 2 Motion: (a) G. ALEXEEFF (b) L. KOLLER **Second:** (a) S. BARBEE (b) J. BORAK

AEGL 3 Motion: R. NIEMEIER **Second:** J. HINZ

Approved by Chair: [signature] **DFO:** Paul S. Tobin **Date:** 12/7/98

Date of NAC/AEGL Meeting: Dec. 7-9, 1998 **Chemical:** 108-91-8 CYCLOHEXYL AMINE

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

NAC Member	AEGL 1 (a)	AEGL 2 (a)	AEGL 2 (b)	AEGL3
Loren Koller	Y	Y	Y	Y
Glenn Leach	Y	Y	Y	Y
Mark A. McClanahan	Y	N	N	N
John S. Morawetz	N	A	N	A
Deirdre L. Murphy	Absent	Absent		Absent
Richard W. Niemeier	Y	Y	Y	Y
William Pepelko	Y	Y	N	Y
Zarena Post	Absent	Absent		Absent
George Rodgers	A	Y	Y	Y
George Rusch, Chair	Y	Y	Y	Y
Bob Snyder	Y	Y	Y	Y
Thomas J. Sobotka	A	N	A	Y
Kenneth Still	Y	Y	Y	Y
Patricia Ann Talcott	Absent	Absent		Absent
Richard Thomas	A	A	A	A
Thomas Tuccinardi/ Doan Hansen	A Y	A N	A Y	A Y
TALLY	23/24 (a)	(a) 15/25	(b) 17/24	21/24

PPM, (mg/m³)	30 Min	60 Min	4 Hr	8Hr
AEGL 1	~~5.4~~ 1.8, ( )	~~3.8~~ 1.8, ( )	~~1.9~~ 1.8, ( )	~~1.4~~ 1.8, ( )
AEGL 2	(a) 18 (b) ~~28~~, ( )	(a) 13 (b) ~~20~~, ( )	(a) 6.3 (b) 9.9, ( )	(a) 4.5 (b) 7.0, ( )
AEGL 3	53, ( )	38, ( )	19, ( )	13, ( )

(a) - DEFEATED (b) CARRIED/APPROVED (c) WITHDRAWN (D)

AEGL 1 Motion: (a) S. Barbee (b) D. Hansen (c) B. Bress **Second:** (a) B. Pepelko (b) R. Benson (c) L. Gephart

AEGL 2 Motion: (a) R. Niemeier **Second:** (a) R. Benson

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

Approved by Chair: [signature] **DFO:** Paul S. Tobin **Date:** 12/7/98

Date of NAC/AEGL Meeting: Dec. 7-9, 1998 **Chemical:** 7783-06-4 HYDROGEN SULFIDE

NAC Member	AEGL 1	AEGL 2	AEGL 3	NAC Member	AEGL 1	AEGL 2	AEGL3
George Alexeeff	Y	N	Y	Loren Koller	Y	Y	Y
Steven Barbee	Y	Y	Y	Glenn Leach	Y	Y	Y
Lynn Beasley	Y	Y	Y	Mark A. McClanahan	Y	Y	Y
David Belluck	Y	Y	Y	John S. Morawetz	Y	Y	Y
Robert Benson	Y	Y	Y	Deirdre L. Murphy	Absent	Absent	Absent
Kyle Blackman	Y	Y	Y	Richard W. Niemeier	Y	Y	Y
Jonathan Borak	Y	Y	Y	William Pepelko	Y	Y	Y
William Bress	Y	Y	Y	Zarena Post	Absent	Absent	Absent
Luz Claudio	A	A	A	George Rodgers	Y	Y	Y
George Cushmac	Y	Y	Y	George Rusch, Chair	Y	Y	Y
Ernest Falke	Y	Y	Y	Bob Snyder	Y	Y	Y
Larry Gephart	Y	Y	Y	Thomas J. Sobotka	A	A	A
John Hinz	Y	Y	Y	Kenneth Still	Y	Y	Y
Jim Holler	Y	Y	A	Patricia Ann Talcott	Absent	Absent	Absent
Thomas C. Hornshaw	P	Y	Y	Richard Thomas	A	A	A
Nancy Kim	Y	Y	Y	Thomas Tuccinardi/ Doan Hansen	A Y	A A	A X
				TALLY	25/25	24/25	25/25

PPM, (~~mg/m~~^{3})	10 min	30 Min	60 Min	4 Hr	8Hr
AEGL 1	0.15	0.15, ( )	0.15, ( )	0.15, ( )	0.15, ( )
AEGL 2	42	32, ( )	28, ( )	20, ( )	17, ( )
AEGL 3	76	60, ( )	50, ( )	37, ( )	31, ( )

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

AEGL 2 Motion: L. Koller **Second:** E. Falke

AEGL 3 Motion: M. McClanahan **Second:** L. Koller

Approved by Chair: [signature] **DFO:** [signature] **Date:** 12/8/98

811-97-2 Appendix E

Date of NAC/AEGL Meeting: Dec. 7-9, 1998 **Chemical:** HFC -134a

NAC Member	AEGL 1	AEGL 2	AEGL 3	NAC Member	AEGL 1	AEGL 2	AEGL3
George Alexeeff	A	A	A	Loren Koller	Y	Y	Y
Steven Barbee	Y	Y	Y	Glenn Leach	Y	Y	Y
Lynn Beasley	Y	Y	Y	Mark A. McClanahan	Y	Y	Y
David Belluck	Y	Y	Y	John S. Morawetz	Y	Y	Y
Robert Benson	N	Y	Y	Deirdre L. Murphy	Absent	Absent	Absent
Kyle Blackman	Y	Y	Y	Richard W. Niemeier	Y	Y	Y
Jonathan Borak	Y	Y	Y	William Pepelko	Y	Y	Y
William Bress	Y	Y	Y	Zarena Post	Absent	Absent	Absent
Luz Claudio	A	A	A	George Rodgers	Y	Y	Y
George Cushmac	Y	Y	Y	George Rusch, Chair	P	P	P
Ernest Falke	Y	Y	Y	Bob Snyder	Y	Y	Y
Larry Gephart	P	Y	Y	Thomas J. Sobotka	A	A	A
John Hinz	Y	Y	Y	Kenneth Still	Y	Y	Y
Jim Holler	Y	Y	Y	Patricia Ann Talcott	Absent	Absent	Absent
Thomas C. Hornshaw	Y	Y	Y	Richard Thomas	Y	Y	Y
Nancy Kim	Y	Y	Y	Thomas Tuccinardi/ Doan Hansen	A Y	A Y	A Y
				TALLY	23/24	24/24	24/24

PPM, (~~mg/m³~~)	30 Min	60 Min	4 Hr	8Hr
AEGL 1	8000 ,( )	8000 ,( )	8000 ,( )	8000 ,( )
AEGL 2	13,000 ,( )	13,000 ,( )	13,000 ,( )	13,000 ,( )
AEGL 3	27,000 ,( )	27,000 ,( )	27,000 ,( )	27,000 ,( )

AEGL 1 Motion: G. Rodgers **Second:** K. Blackman

AEGL 2 Motion: G. Rodgers **Second:** K. Blackman

AEGL 3 Motion: G. Rodgers **Second:** K. Blackman

Approved by Chair: [signature] **DFO:** Paul S. Tobin **Date:** 12/8/98

1717-00-6

Date of NAC/AEGL Meeting: Dec. 7-9, 1998 **Chemical:** HCFC 141 b

NAC Member	AEGL 1	AEGL 2	AEGL 3	NAC Member	AEGL 1	AEGL 2	AEGL3
George Alexeeff	A			Loren Koller	Y	Y	Y
Steven Barbee	Y	Y	Y	Glenn Leach	Y	Y	Y
Lynn Beasley	Y	Y	Y	Mark A. McClanahan	Y	Y	Y
David Belluck	Y	Y	Y	John S. Morawetz	N	Y	Y
Robert Benson	N	Y	Y	Deirdre L. Murphy	Absent	Absent	Absent
Kyle Blackman	Y	Y	Y	Richard W. Niemeier	Y	Y	Y
Jonathan Borak	Y	Y	Y	William Pepelko	A		
William Bress	Y	Y	Y	Zarena Post	Absent	Absent	Absent
Luz Claudio	A			George Rodgers	Y	Y	Y
George Cushmac	Y	Y	Y	George Rusch, Chair	P	P	P
Ernest Falke	Y	Y	Y	Bob Snyder	Y	Y	Y
Larry Gephart	P	Y	Y	Thomas J. Sobotka	A		
John Hinz	Y	Y	Y	Kenneth Still	Y	Y	Y
Jim Holler	Y	Y	Y	Patricia Ann Talcott	Absent	Absent	Absent
Thomas C. Hornshaw	Y	Y	Y	Richard Thomas	Y	Y	Y
Nancy Kim	Y	Y	Y	Thomas Tuccinardi/ Doan Hansen	A Y	Y	Y
				TALLY	21/25	24/25	24/25

PPM, (~~mg/m~~^{3})	30 Min	60 Min	4 Hr	8Hr
AEGL 1	1,000 ,( )	1,000 ,( )	1,000 ,( )	1,000 ,( )
AEGL 2	1,700 ,( )	1,700 ,( )	1,700 ,( )	1,700 ,( )
AEGL 3	3,000 ,( )	3,000 ,( )	3,000 ,( )	3,000 ,( )

AEGL 1 Motion: M. McClanahan **Second:** R. Niemeier

AEGL 2 Motion: M. McClanahan **Second:** R. Niemeier

AEGL 3 Motion: M. McClanahan **Second:** R. Niemeier

Approved by Chair: [signature] **DFO:** Paul S. Tobin **Date:** 12/8/98

Appendix G

110-89-4

Date of NAC/AEGL Meeting: Dec. 7-9, 1998 **Chemical:** PIPERIDINE

NAC Member	AEGL 1	AEGL 2	AEGL 3	NAC Member	AEGL 1	AEGL 2	AEGL3
George Alexeeff	A		A	Loren Koller			Y
Steven Barbee			Y	Glenn Leach			A
Lynn Beasley			Y	Mark A. McClanahan			Y
David Belluck			N	John S. Morawetz			N
Robert Benson			Y	Deirdre L. Murphy	Absent	Absent	Absent
Kyle Blackman			N	Richard W. Niemeier			Y
Jonathan Borak			A	William Pepelko			A
William Bress			Y	Zarena Post	Absent	Absent	Absent
Luz Claudio			A	George Rodgers			Y
George Cushmac			Y	George Rusch, Chair			Y
Ernest Falke			Y	Bob Snyder			Y
Larry Gephart			Y	Thomas J. Sobotka			A
John Hinz			Y	Kenneth Still			Y
Jim Holler			Y	Patricia Ann Talcott	Absent	Absent	Absent
Thomas C. Hornshaw			Y	Richard Thomas			Y
Nancy Kim			Y	Thomas Tuccinardi/ Doan Hansen			A N
				TALLY			19/23

PPM, (mg/m³)	30 Min	60 Min	4 Hr	8Hr
AEGL 1	,( )	,( )	,( )	,( )
AEGL 2	,( )	,( )	,( )	,( )
AEGL 3	54 ,( )	38 ,( )	19 ,( )	14 ,( )

OPTIONAL FORM 99 (7-90)

FAX TRANSMITTAL # of pages ▶ 1

To Po-Yung Lu From Paul Tobin

Dept./Agency 423 [redacted] 241-0397 Phone # 260-1736

Fax # Fax #

NSN 7540-01-317-7368 5099-101 GENERAL SERVICES ADMINISTRATION

AEGL 1 Motion:

AEGL 2 Motion:

AEGL 3 Motion: R. Niemeier **Second:** L. Gephart

Approved by Chair: _____ **DFO:** _____ **Date:** 12/8/98

110-00-9 Appendix H

Date of NAC/AEGL Meeting: Dec. 7-9, 1998 **Chemical:** FURAN

NAC Member	AEGL 1	AEGL 2	AEGL 3	NAC Member	AEGL 1	AEGL 2	AEGL3
George Alexeeff		A		Loren Koller		N	N
Steven Barbee		Y	Y	Glenn Leach		Y	Y
Lynn Beasley		Y	Y	Mark A. McClanahan		N	N
David Belluck		Y	Y	John S. Morawetz		Y	Y
Robert Benson		N	N	Deirdre L. Murphy	Absent	Absent	Absent
Kyle Blackman		Y	Y	Richard W. Niemeier		Y	Y
Jonathan Borak		A		William Pepelko		N	N
William Bress	UNANIMOUS	Y	Y	Zarena Post	Absent	Absent	Absent
Luz Claudio		A		George Rodgers	UNANIMOUS	Y	Y
George Cushmac		A		George Rusch, Chair		Y	Y
Ernest Falke		Y	Y	Bob Snyder		Y	Y
Larry Gephart		Y	Y	Thomas J. Sobotka		A	
John Hinz		Y	Y	Kenneth Still		Y	Y
Jim Holler		Y	Y	Patricia Ann Talcott	Absent	Absent	Absent
Thomas C. Hornshaw		Y	Y	Richard Thomas		Y	Y
Nancy Kim		Y	Y	Thomas Tuccinardi/ Doan Hansen		A N	N
				TALLY		19/24	19/24

PPM, ~~(mg/m³)~~	30 Min	60 Min	4 Hr	8Hr
AEGL 1	*NA ,( )	NA ,( )	NA ,( )	NA ,( )
AEGL 2	14 ,( )	10 ,( )	5.1 ,( )	3.6 ,( )
AEGL 3	40 ,( )	29 ,( )	14 ,( )	10 ,( )

* INSUFFICIENT DATA (UNANIMOUS BY COMMITTEE)

AEGL 1 Motion: _____ **Second:** _____

AEGL 2 Motion: R. Snyder **Second:** R. Thomas

AEGL 3 Motion: R. Snyder **Second:** R. Thomas

Approved by Chair: [signature] **DFO:** Paul S. Tobin **Date:** 12/9/98

Date of NAC/AEGL Meeting: Dec. 7-9, 1998 **Chemical:** 75-56-9 PROPYLENE OXIDE

NAC Member	AEGL 1	AEGL 2	AEGL 3	NAC Member	AEGL 1	AEGL 2	AEGL3
George Alexeeff	A	A	A	Loren Koller	A	Y	Y
Steven Barbee	Y	Y	Y	Glenn Leach	A	A	Y
Lynn Beasley	Y	Y	Y	Mark A. McClanahan	A	A	A
David Belluck	N	Y	Y	John S. Morawetz	N	Y	N
Robert Benson	Y	Y	Y	Deirdre L. Murphy	Absent	Absent	Absent
Kyle Blackman	Y	Y	Y	Richard W. Niemeier	N	Y	N
Jonathan Borak	A	A	A	William Pepelko	Y	Y	Y
William Bress	Y	Y	Y	Zarena Post	Absent	Absent	Absent
Luz Claudio	A	A	A	George Rodgers	Y	Y	Y
George Cushmac	A	A	A	George Rusch, Chair	Y	Y	Y
Ernest Falke	N	Y	Y	Bob Snyder	A	A	N
Larry Gephart	Y	Y	Y	Thomas J. Sobotka	A	A	A
John Hinz	P	Y	Y	Kenneth Still	Y	Y	Y
Jim Holler	Y	Y	Y	Patricia Ann Talcott	Absent	Absent	Absent
Thomas C. Hornshaw	Y	Y	Y	Richard Thomas	Y	Y	Y
Nancy Kim	N	Y	N	Thomas Tuccinardi/ Doan Hansen	A Y	A Y	A Y
				TALLY	14/19	21/21	19/23

')	30 Min	60 Min	4 Hr	8Hr
	110 ,( )	60 ,( )	19 ,( )	11 ,( )
	510 ,( )	290 ,( )	91 ,( )	51 ,( )
	1100 ,( )	610 ,( )	190 ,( )	110 ,( )

[otion: G. Rodgers Second: R. Thomas

[otion: W. BRESS Second: L. Koller

[otion: Holler Second: Gephart

--y Chair: _____ DFO: Paul S. Tobin Date: 12/9/98

OPTIONAL FORM 99 (7-90)

FAX TRANSMITTAL

# of pages ▶ 2

To Po-Yung Lu From Paul Tobin

Dept./Agency 433 Phone # 260-1236

Fax # 741-0397 Fax #

NSN 7540-01-317-7368 5099-101 GENERAL SERVICES ADMINIST