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

National Advisory Committee for Acute Exposure Guideline Levels for Hazardous Substances

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1060 Commerce Park Drive
Toxicology and Risk Analysis Section, Life Sciences Division
Oak Ridge National Laboratory
Oak Ridge, Tennessee 37830

NAC/AEGL-11

AGENDA

Monday, September 14, 1998

10:00 - 10:15 AM	Introductory remarks and approval of NAC/AEGL - 10 highlights (George Rusch, Roger Garrett and Paul Tobin)
10:15 - 11:45	Status Reports: • Revision of draft guideline for carcinogens (Richard Thomas) - 10 min. • Revision of draft guideline for anesthesia (George Rodgers) - 10 min. • Bromine testing (Larry Gephart) - 5 min. • Reference on Benchmark Dose approach from EPA (Bob Benson) - 5 min. • SOP report (Ernie Falke) - 60 min.
11:45 - 1:00 PM	**Lunch**
1:00 - 2:45	Revisit Draft AEGLs: • Hydrazine (Richard Thomas, Ernie Falke) - 45min. • Ethylene oxide (Kyle Blackman) - 45 min. • Carbon tetrachloride: issue of sensitive individuals for AEGL-3. Voting to decide to re-visit at this time or after Federal Register public comment (Bill Bress) - 15 min.
2:45 - 3:00	**Break**
3:00 - 5:30	Hydrogen Sulfide (Steve Barbee/Cheryl Bast)

Tuesday, September 15, 1998

8:00 - 8:15 AM	Propylene oxide: status report of industrial input for AEGL-1 values
8:15 - 9:30	Propylenimine (Mark McClanahan/Kowetha Davidson)
9:30 - 9:45	**Break**
9:45 - 12:00	Nitric oxides - NO, NO_2, N_2O_4 (Loren Koller/Carol Forsyth)
12:00 - 1:15 PM	**Lunch**
1:15 - 1:45	Nitric oxides (Continued)
1:45 - 3:15	Iron pentacarbonyl (Kyle Blackman/Bob Young)
3:15 - 3:30	**Break**
3:30 - 5:00	Furan (George Rodgers/Claudia Troxel)

Wednesday, September 16, 1998

8:00 - 10:30 AM	Isobutyronitrile, Methacrylonitrile, and Propionitrile (George Rodgers/Cheryl Bast)
10:30 - 10:45	**Break**
10:45 - 11:45	Piperidine (Mark McClanahan/ Kowetha Davidson)
11:45 - 12:00	NAS status report
12:00 - 12:30 PM	Administrative issues
12:30	Adjournment

NAC/AEGL meeting 11
Sept 14-16, 1998

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Bill Bress	ASTHO	802-863-7598
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Jim Deyo	Eastman Chem.	423-239-5625

Attachment 3

Standing Operating Procedures for the Developing

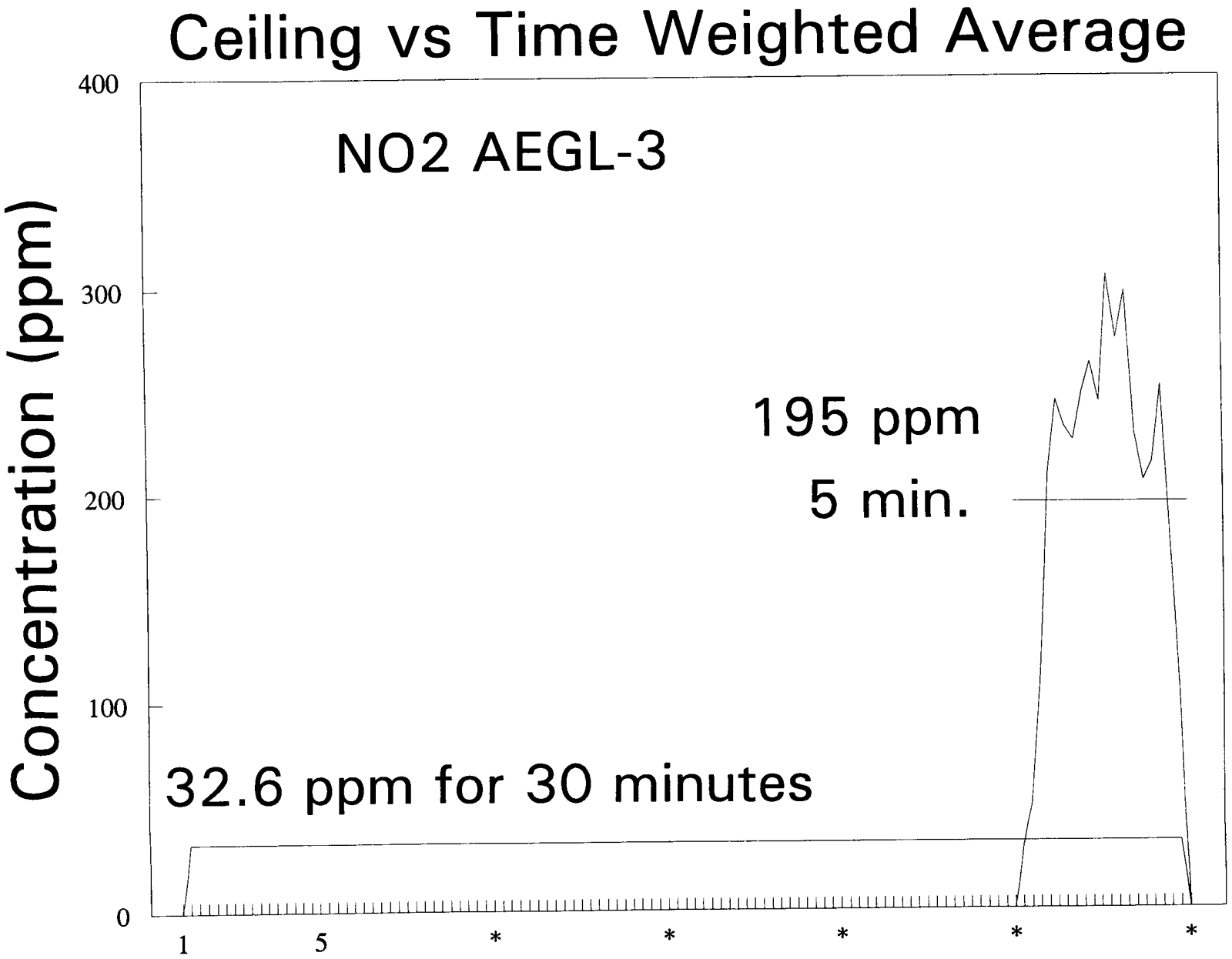
Acute Exposure Guideline Levels for Hazardous Chemicals

It is available at

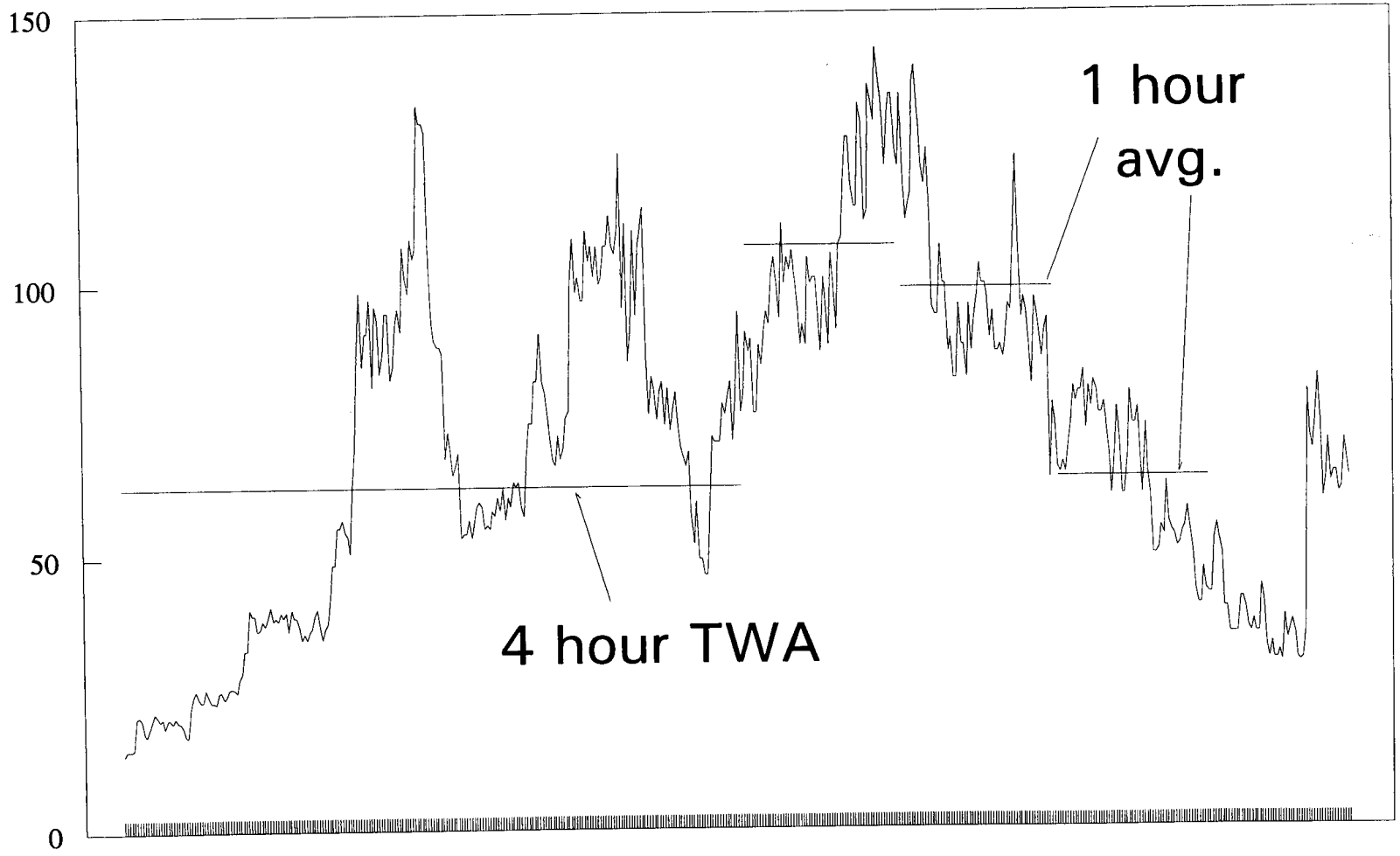
http://books.nap.edu/books/030907553X/html/index.html

CEILINGS

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 time period is determined (for example, 10 min.).

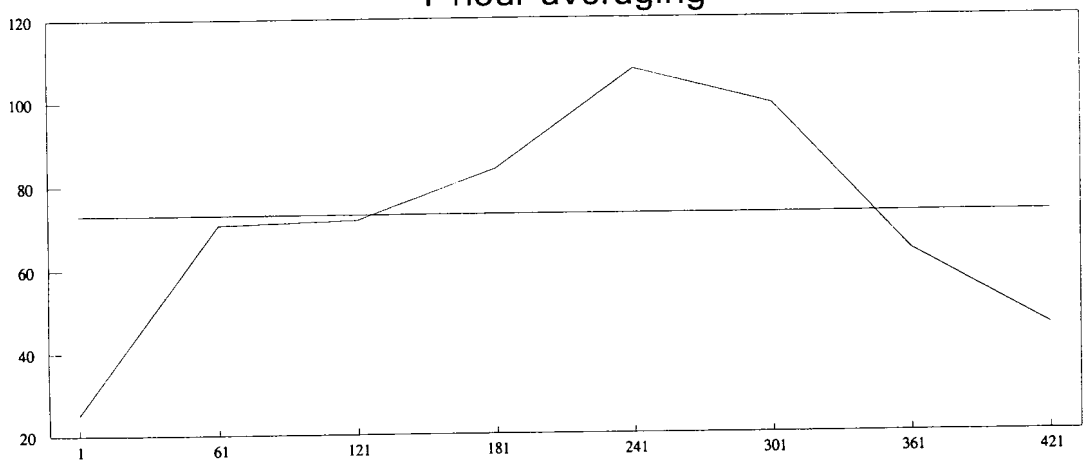

Ceiling vs Time Weighted Average
NO2 AEGL-3
Concentration (ppm)
400
300
200
100
0
195 ppm
5 min.
32.6 ppm for 30 minutes
1
5
*
*
*
*
*

Exposure variability



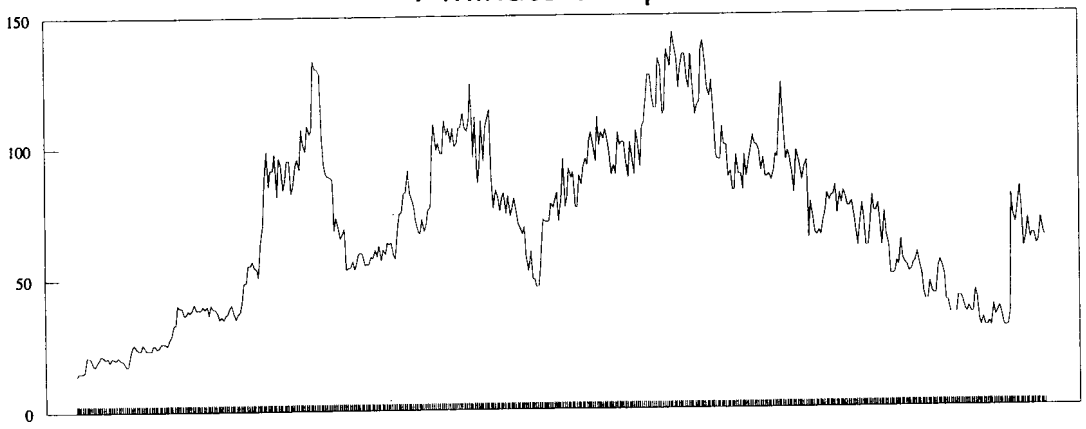
Exposure variability

1 hour averaging



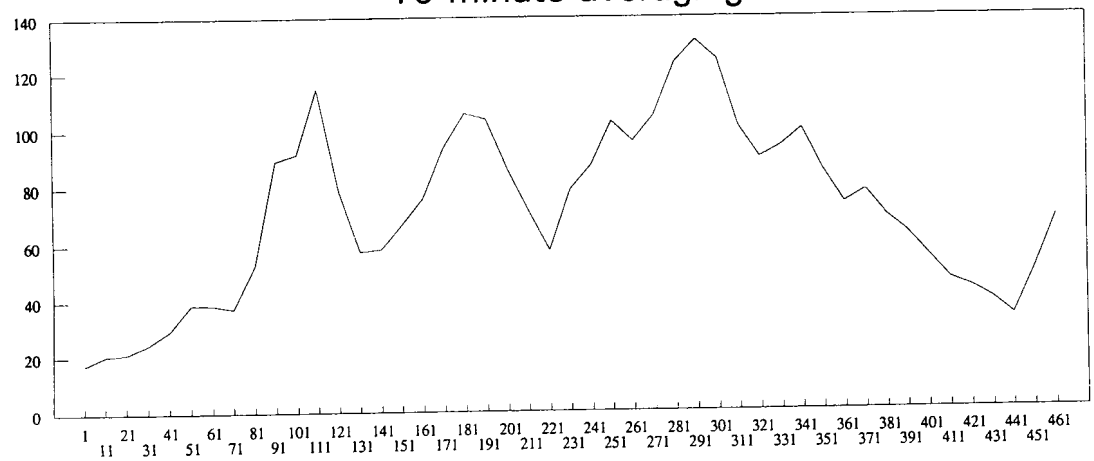
Exposure variability

1 minute samples



Exposure variability

10 minute averaging



REVISIT OF HYDRAZINE AEGL-2 AND AEGL-3

NAC/AEGL-11
Oak Ridge, TN
September 14-16, 1988

ORNL Staff Scientist: **Robert A.Young**
Chemical Manager: **Richard Thomas**

Attachment 5

REVISIT OF HYDRAZINE AEGL-2 AND AEGL-3

Issues

- **The regional gas dose methodology is not valid**

- **The determinant for AEGL-2 values (1-hr at 750 ppm) is inconsistent with the estimated lethality threshold (1-hr LC_{01} = 337ppm)**

Interim AEGL Values for Hydrazine

PROPOSED AEGL VALUES FOR HYDRAZINE					
Classification	**30-min**	**1-hour**	**4-hour**	**8-hour**	**Endpoint**
AEGL-1	**0.1 ppm**	**0.1 ppm**	**0.1 ppm**	**0.1 ppm**	**Eye and facial irritation in monkeys (House, 1964)[a]**
AEGL-2	**8 ppm**	**6 ppm**	**3 ppm**	**2 ppm**	**Nasal lesions (Latendresse et al., 1995)**
AEGL-3	**47 ppm**	**33 ppm**	**17 ppm**	**12 ppm**	**Lethality in rats (HRC, 1993)**

The Regional Gas Dose Methodology is Not Valid

- **Assumptions implicit in methodology may not be valid or have not been verified**
  - **100% absorption**
  - **uniform distribution throughout region of concern**
  - **many components not validated or unknown; necessitates default to unity**

- **Not used for other AEGL determinations - consistency issue**

Response: Regional gas dose methodology rescinded

Determinant for AEGL-2 Values Inconsistent with Estimated Lethality Threshold

- **1-hr exposure to 750 ppm induced nasal lesions (determinant for AEGL-2)**

- **1-hr estimated lethality threshold: LC_{01} = 337 ppm (determinant for AEGL-3)**

Response: **Use one-third reduction of 1-hr LC_{50} (3,192 ppm) as determinant for AEGL-3 (1,064 ppm)**

Revision of AEGL-2

- **Endpoint:** **Nasal lesions in rats exposed for 1 hr to 750 ppm (Latrendesse et al., 1995); 10 exposures did not cause lethality**

- **UF:** **10 for interspecies variability (unchanged)**
  3 for intraspecies variability (unchanged)

- **Time scaling:** **$n = 2$ (data unavailable for empirical derivation)**

Revised AEGL-2 Values for Hydrazine

Classification	30-min	1-hour	4-hour	8-hour	Endpoint
AEGL-2	35.56 ppm (8 ppm)	25.0 ppm (6 ppm)	12.5 ppm (3 ppm)	8.8 ppm (2 ppm)	Nasal lesions (Latendresse et al., 1995)

(previous AEGL-2 values)

Revision of AEGL-3

- **Endpoint:** **Estimated lethality threshold (one third reduction of 1-hr LC_{50} (3,192 ppm/3 = 1,064 ppm) - consistent with Latendresse et al. data**

- **UF:** **10 for interspecies variability (unchanged) 3 for intraspecies variability (unchanged)**

- **Time scaling:** ***n*** **= 2 (data unavailable for empirical derivation)**

Revised AEGL-3 Values for Hydrazine

Classification	30-min	1-hour	4-hour	8-hour	Endpoint
AEGL-3	50.13 ppm (47 ppm)	35.47 ppm (33 ppm)	17.73 ppm (17 ppm)	12.54 ppm (12 ppm)	Estimated lethality threshold (HRC, 1993)

(previous AEGL-2 values)

Revised AEGL Values for Hydrazine

- **Revised values more accurately reflect known steep exposure-response relationship**
- **Methodology consistent with other AEGL derivations**
- **Adjustment of AEGL-2 to protect human health ?**

Revised AEGL-2 Values for Hydrazine					
Classification	30-min	1-hour	4-hour	8-hour	Endpoint
AEGL-2	35.56 ppm (8 ppm)	25.0 ppm (6 ppm)	12.5 ppm (3 ppm)	8.8 ppm (2 ppm)	Nasal lesions (Latendresse et al., 1995)

(previous AEGL-2 values)

Revised AEGL-3 Values for Hydrazine					
Classification	30-min	1-hour	4-hour	8-hour	Endpoint
AEGL-3	50.13 ppm (47 ppm)	35.47 ppm (33 ppm)	17.73 ppm (17 ppm)	12.54 ppm (12 ppm)	Estimated lethality threshold (HRC, 1993)

(previous AEGL-2 values)

ACUTE EXPOSURE GUIDELINE LELELS (AEGLs) FOR ETHYLENE OXIDE

RE-ASSESSMENT OF DATA APPLICABLE TO AEGL-2

ORNL STAFF SCIENTIST
CHEMICAL MANAGER

KOWETHA A. DAVIDSON
KYLE BLACKMAN

Attachment 6

REASONS FOR RE-ASSESSMENT

The study used to derive AEGL-2 resulted in dead implants (dominant lethality) in addition to the CNS effects.

If genetic toxicity should be considered in evaluation of AEGL-2 exposure levels, then the mouse studies by Sega (1988, 1991) should be considered also.

Determine which studies are appropriate for deriving AEGL-2 values

SUMMARY OF NONLETHAL EFFECTS OF ETHYLENE OXIDE IN HUMANS

Concentration		Exposure duration	Effects	Reference
ppm	mg/m^3			
3349	24028	10 sec	definitely irritating to nasal passages	Walker and Greeson, 1932
670	4806	not reported	slightly irritating to nasal passages, acetic acid-like odor	Walker and Greeson, 1932
700	1260	30 min	odor, headache, gastrointestinal effects, eye and upper respiratory tract irritation, pruritus, muscle weakness, dizziness, hemolysis	Deleixhe et al., 1986; Laurent, 1988
700	≥1260	4 h/day for 4 days	coughing, shortness of breath, wheezing, slight peripheral neuropathy, immunological asthma	Deschamps et al., 1992
kcursions 700	≥1260	2 weeks to 2 months	eye and mucous membrane irritation, difficult swallowing, headache, gastrointestinal effects, lethargy, fatigue, problems with memory and thinking, major motor seizures, peripheral neuropathy	Gross e al., 1979
500	900	2 to 5 min	gastrointestinal effects, unconsciousness, apnea, muscle twitching, malaise, incoordination for up to 1 week	Salinas et al., 1981
t reported	not reported	4 months to 1½ years	eye irritation, headaches, smelling of fumes, distal axonal neuropathy	Finelli et al., 1983
23 to 0.56 m (TWA); cursions of or 77 ppm	0.4 to 1mg/m^3; 19.8 to 139.6 mg/m^3	chronic	sweet-like odor, headache, dizziness, irritation of mucous membranes, gastrointestinal effects, fatigue, nervousness	Zey et al., 1994

SUMMARY OF NONLETHAL EFFECTS OF ETHYLENE OXIDE IN HUMANS (CONTINUED)

Concentration		Exposure duration	Effects	Reference
ppm	mg/m^3			
eak = 23.5 otal up to 10.7 verage 3.4	42.3 19.3 6.1	up to 1 min up to 11.75 min not reported	odor, headache, skin and eye irritation, dry mouth, sore throat, runny nose, shortness or breath, nausea, numbness in fingers, drowsiness	Bryant et al., 1989
.1 to 0.5 ppm 3-h TWA); eak 250 ppm; to 10 ppm 20 min daily)	0.18 to 0.9 (TWA); 450 9 to 18	during pregnancy	increased risk of spontaneous abortion[a]	Hemminki et al., 1982
ot reported	not reported	any duration during pregnancy	increased risk of spontaneous abortion, preterm birth, or postterm birth[a]	Rowland et al., 1996

he number of limitations and weaknesses of these studies preclude attributing effects to ethylene oxide.

DEVELOPMENTAL AND REPRODUCTIVE EFFECTS OF ETHYLENE OXIDE VAPOR

Species	Exposure	Effect	Reference
Rat	0, 10, 33, 100 ppm, 6 h/day, gd 6-15	33 ppm – NOEL 100 ppm – mild retarded growth of fetus	Snellings et al., 1982a
Rat	0, 50, 125, 250 ppm, 6 h/day, gd 6-15	50 ppm – LOEL for growth retardation 125 ppm – growth retardation of fetus 250 – more severe growth retardation	BRRC, 1993
Rat	0, 150 ppm, 7 h/day, 5 d/wk, premating, gd 7-16, or 1-16	growth retardation of fetus regardless of stage of exposure	Hackett, 1982
Rat	0, 400, 800, 1200 ppm, 0.5 h/day, gd 6-15	no effects on the fetus at any concentration	Saillenfait et al., 1996
Rat	0, 200, 400, 800, 1200 ppm, 0.5 h, 3 times per day, gd 6-15	800 ppm – fetal growth retardation 1200 ppm – maternal effects and fetal growth retardation	Saillenfait et al., 1996
Mouse	0, 1200 ppm, 1½ h, gd 1	fetal deaths, hydrops, and other malformations	Rutledge and Generoso, 1989
Mouse	0, 200, 400 ppm, 6 h/day, 5, 15, or 25 exposures	200 ppm: abnormal spermatozoa 400 ppm: abnormal spermatozoa	Ribeiro et al., 1987

DEVELOPMENTAL AND REPRODUCTIVE EFFECTS OF ETHYLENE OXIDE VAPOR (continued)

Rat	0, 10, 33, 100 ppm, 6 h/day, 1-generation reproduction	33 ppm – NOEL 100 ppm – reproductive and fetal effects	Snellings et al., 1982b
Rat, males	0, 50, 100, 250 ppm, 6 h/day, subchronic	50 ppm – abnormal sperm, teratic type 100 ppm – abnormal sperm, teratic type 250 ppm – abnormal sperm, testicular degeneration	Mori et al., 1991
Rabbits	0, 150 ppm, 7 h/day, gd 7-19 or 1-19	no developmental effects	Hackett et al., 1982

GENOTOXIC EFFECTS OF INHALED ETHYLENE OXIDE ON GERM CELLS IN MALE RODENTS

Species/Strain	Assay	Experimental Protocol	c × t	Results	Reference
Rat/Long-Evans	Dominant lethality[a]	1,000 ppm for 4 h; mated with females weekly for 10 weeks	4,000 ppm•h	Positive: increase in dead implants per pregnancy (wks 2, 3, 5) and dead implants per total implants (wks 1, 2, 3, 5)	Embree et al., 1977
Mouse/ (C3H × B110)F_1	DNA strand breaks and UDS	450 ppm for 4 h, 900 ppm for 2 h, or 1,800 ppm for 1 h	1,800 ppm•h	Positive: DNA strand breaks and UDS; exposure-rate effect: 1800 ppm>900 ppm>450 ppm	Sega et al., 1988
Mouse/ (C3H × B110)F_1	DNA alkylation of sperm and hemoglobin	75 ppm for 4 h, 150 ppm for 2 h, or 300 ppm for 1 h	300 ppm•h	DNA alkylation of epididymal and vas sperm and hemoglobin	Sega et al., 1991
Mouse/ (101 × C3HF_1)	Dominant lethality[b]	255 ppm, 6 h/day, 5 d/wk for 2 or 11 wks	15,300 ppm•h or 84,150 ppm•h	Positive: dominant lethals produced after 2 (39%) and 11 weeks (55%)	Generoso et al., 1983
Mouse/(C3H × 101)F_1	Dominant lethality	control, 300, 400, or 500 ppm, 6 h/d for 4 d	7,200 ppm•h, 9,600 ppm•h, 12,000 ppm•h	Positive: exposure-related increase; 4, 27, and 62% dominant lethals	Generoso et al., 1986

GENOTOXIC EFFECTS OF INHALED ETHYLENE OXIDE ON GERM CELLS IN MALE RODENTS (CONTINUED)

pecies/Strain	Assay	Experimental Protocol	c × t	Results	Reference
louse/ C3H × 101)F_1	Dominant lethality	control, 300 ppm for 6 h/d, 600 ppm for 3 h/d, or 1,200 ppm for 1.5 h/d for 4 d	1,800 ppm•h	Positive: exposure-rate increase; 11, 32, and 64% dominant lethals	Generoso et al., 1986
ouse/ C3H × 101)F_1	Dominant lethality	control, 165, 204, 250, or 300 ppm 6 h/d, 5 d/wk for 6 wks, then 7 d/wk for 2.5 wks.	47,025 - 85,500 ppm•h	Positive: dose-related increase; 6-8, 13-14, 23-24, and 45-60% dominant lethals	Generoso et al., 1990
ouse/(C3H × 01)F_1	Heritable translocation	control, 165, 204, 250, or 300 ppm 6 h/d, 5 d/wk for 6 wks, then 7 d/wk for 2.5 wks.	47,025 - 85,500 ppm•h	Positive: dose-related increase; 0.05, 2.80, 5.09, 10.84, and 25.53% translocation carriers in combined female strains	Generoso et al., 1990

efined as the number of dead implants per total implants.
efined as the average no. living embryos in experimental group/average no. for controls.
)S = unscheduled DNA synthesis

Attachment 7

PROPOSED AEGL VALUES FOR HYDROGEN SULFIDE

Chemical Manager: Steve Barbee
ORNL Staff Scientist: Cheryl Bast

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)

AEGL-2 FOR HYDROGEN SULFIDE (ppm [mg/m^3])				
AEGL Level	30-min	1-hr	4-hr	8-hr
AEGL-2	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	30-min	1-hr	4-hr	8-hr
AEGL-3	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)

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)**

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**
ERPG-2: **30 ppm**
ERPG-3: **100 ppm**

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

Responses to Questions on Human Experience Data from June 8, 1998 CMA Presentation

Susan D. Ripple, MS, CIH
CMA Propylene Oxide Panel
September 1998

Use of Human Data

- Inconsistent use of human exposure data in Draft 2 Propylene Oxide AEGL proposal document
- Guidance from NAS and AIHA on use of both human exposure data and animal toxicity data which is available
- Application of human data to Propylene Oxide AEGLs with newly released sample and task duration information

Conflicting Use of Human Data
Draft 2 PO AEGL Proposal

Discussion of human data for:

- AEGL-1: cited and used
- AEGL-2: cited, but not used
- AEGL-3: cited, but not used

Additional Human Exposure Information

- Defined sampling duration for Facility 1 Environmental Health survey (~3 hours)
- Defined typical drumming operation duration (7 hours)
- Defined sample analysis method for Facility 1 (gas phase chromatography)

General Question

Q: Is there information in the original report on the sampling and analysis methods available for review from facilities reported?

A: Analytical lab databooks of each company supporting the reports show QC techniques were routinely used.

- Techniques included standard curves, lab and field blanks and spikes, and analytical error determinations for each sample set analyzed.

Facility 3 Data*

Table Two. Summary of results of personal exposure monitoring for PO during plant operations in 1975.

Job Classifications	No. of Samples	Propylene Oxide		
		Concentration Ranges (ppm)	Mean[1] Job Class Concentration (ppm) Mean:	95% UCL:
Maintenance Personnel (Pipefitters, Boilermakers, Machinists, Electrician)	8	14.9 - 18.9	17.4	18.30
Laboratory Personnel (sampling)	2	30.2 - 31.8	31.0	36.05
Engineer	1	30.2	30.2	----
Foremen	4	16.1 - 23.8	20.58	24.49
Operators	11	13.2 - 23.3	18.69	20.31

[1] Calculated arithmetic mean and 95% upper confidence level for the associated job class

*Supplied to AEGL Committee in PO Panel comments November 1997

AEGL-1 Q&A
Facility 3:

Q: What was the design of the Facility 3 study that evaluated the potential exposures of a variety of job classes during 1975?

A: Comprehensive industrial hygiene survey:

- Part of the company's "total environmental health program" to perform "routine annual monitoring" of a variety of chemicals used in the facility
- Job classes were identified and monitored by *homogenous exposure groups* rather than job titles based on a qualitative exposure assessment
- Monitoring performed to quantitatively assess exposure was based on the combination of tasks performed by the individuals

AEGL-1 Q&A
Facility 3:

Q: Are there job descriptions available which describe the various tasks that the workers did?

How do you know these job titles/classes were homogenous exposure groups?

A: Program for Facility 3 in 1975 extensively describes the basis for the homogenous exposure groups (complete with job descriptions)

Personnel with similar job tasks were grouped into the homogenous exposure groups with an attached list of chemicals of potential exposure and the qualitative "degree of exposure" documented

AEGL-1 Q&A
Facility 3:

Q: Was the survey done to identify worker complaints or to gather baseline monitoring data, or done because workers had complained?

A: There is no mention of complaints by workers in the report, and further investigation into medical records did not reveal worker complaints.

AEGL-1 Q&A
Facility 3:

Q: Was 31.8 ppm above the level of irritation or odor threshold?

A: NIOSH odor threshold of PO ranges between 10 and 199 ppm
- The highest exposure concentration measured was 31.8 ppm (lab personnel during sampling) in this survey, which is above the lowest odor threshold but in the low end of the range.
- One could assume that most workers would recognize that PO was present in the environment.

- The OEL for PO was 100 ppm in 1975, well above the highest personal exposure measured in this survey.

AEGL-1 Q&A
Facility 3:

Q: Is 31.8 ppm a harmful level, yet not reported because it was not an OSHA recordable/reportable?

A: The report does not mention worker complaints,
- review of the medical records for this facility during this time period made no mention of complaints during routine medical surveys and physical exams regarding the work environment

"Facility 1" Human Exposure Data[1] during Drumming Operations*
(revised June 8, 1998)

Sample No.	Activity Description	Sampling Duration (min)	PO Concentration (ppm)*
1	Breathing zone of operator during drumming of PO; overhead heater fan turned on	177	380
2	Same location as Sample #1 but overhead heater fan turned off for about 5 minutes	171	1520
3	Same as Sample #2	124	1310
4	Same as Sample #2 & #3	121	525
5	Same location as samples #1 - #4, but heater fan had been turned back on and had been running about five minutes	135	392
6	Same as Sample #5	116	460

[1] Submitted November 1997 by CMA PO Panel to AEGL Committee
* Typical drumming operation duration = 7 hours

AEGL-2 & -3 Questions

Facility 1:

Q: Were the sampling and analytical methods used a NIOSH method?

What was the reliability of that method?

A: NIOSH was not in existence at the time this report was written (1968)

- The "accepted" collection method at that time and used for this data set was Saran® bags and analysis by vapor phase chromatography, using gas-tight syringes for injection into the chromatograph

AEGL- 2 & -3 Questions

Facility 1:

Q: How many people performed "Drumming Operations" in Facility 1?

A: 7

Q: How many shifts were there drumming, and how many shifts were monitored?

A: Drumming occurred only on the "day shift" (batch operation)

Q: How many people were actually monitored?

A: 7 monitored / 8 exposed during monitorin (including hygienist)

AEGL-2 & -3 Questions

Facility 1:

Q: Were hygienists in the sampling zone during the monitoring period?

A: The industrial hygienist was in the drumming booth during the monitoring period, and commented on the 'raw data form':

a) "odor was quite obvious but not objectionable",

b) "pronounced odor, non-objectionable", and

c) "General area in drumming room, about 10 feet from drumming station, odor was detectable but faint"

AEGL-2 & -3 Questions

Facility 1:

Q: Did all workers complain of eye irritation, or do we know which personnel complained of eye irritation?

How many people complained of eye irritation that were monitored?

How were the symptoms / complaints reported and measured *(e.g., slight, severe, etc.)*?

A: The report does not identify which or how many workers occasionally complained of eye irritation in the facility. The survey was done at the request of facility supervision as a result of a more comprehensive survey of all aspects of safety in the area.

AEGL-2 & -3 Questions

Facility 1:

Q: Is there a description of the protocol for heater fan operation (ON/OFF) during the sampling period and during normal operations (ambient temperatures during the time of eye irritation complaints?)

A:Overhead heating fans normally controlled by thermostat in the drumming booth for worker comfort

Testing protocol in the drumming booth:

- with the heater fans on (started sampling about 5 minutes after fans turned on)
- heater fans off (waited about 5 min to start sampling after fans turned off)

"Facility 1" Human Exposure Data[1] during Drumming Operations*

(revised June 8, 1998)

Sample No.	Activity Description	Sampling Duration (min)	PO Concentration (ppm)*
1	Breathing zone of operator during drumming of PO; overhead heater fan turned on	177	380
2	Same location as Sample #1 but overhead heater fan turned off for about 5 minutes	171	1520
3	Same as Sample #2	124	1310
4	Same as Sample #2 & #3	121	525
5	Same location as samples #1 - #4, but heater fan had been turned back on and had been running about five minutes	135	392
6	Same as Sample #5	116	460

[1] Submitted November 1997 by CMA PO Panel to AEGL Committee

* Typical drumming operation duration = 7 hours

Human Data Available for Consideration in Development of PO AEGL-2

- Using "Facility 1" data[1], human exposures between **380** and 1,500 ppm (3-hour sample time)[2] during drumming operations were associated with an AEGL-2 type endpoint of eye irritation

Proposed AEGL-2 Value based on Human Exposure Data:

  - based on 380 ppm for 2.95 hours sample time, ($C^n \times t = k$ where n=1.2, and UF of 3 for intraspecies variability) a 1-hour AEGL-2 of **312 ppm** is supported by the human data

[1]Previously submitted as comments by CMA PO Panel on November 19, 1997
[2] New information submitted by CMA PO Panel on June 8, 1998

"Facility 1" Human Exposure Data[1] during Drumming Operations*

(revised June 8, 1998)

Sample No.	Activity Description	Sampling Duration (min)	PO Concentration (ppm)*
1	Breathing zone of operator during drumming of PO; overhead heater fan turned on	177	380
2	Same location as Sample #1 but overhead heater fan turned off for about 5 minutes	171	1520
3	Same as Sample #2	124	1310
4	Same as Sample #2 & #3	121	525
5	Same location as samples #1 - #4, but heater fan had been turned back on and had been running about five minutes	135	392
6	Same as Sample #5	116	460

[1] Submitted November 1997 by CMA PO Panel to AEGL Committee
* Typical drumming operation duration = 7 hours

Human Data Available for Consideration in Developing PO AEGL-3

- Using "Facility 1" data[1], human exposures up to **1,520 ppm** for 2.85 hours sample time[2], during drumming operations, were not associated with lethality
  - minimum NOEL for lethality in humans = 1520 ppm for 2 .85 hours

Proposed AEGL-3 Value based on Human Exposure Data:

–based on 1520 ppm for 2.85 hours sample time, (C^n x t = k where n=1.2, and UF of 3 for intraspecies variability) a 1-hour AEGL-3 of **1,213 ppm** is supported by the human data

[1]Previously submitted as comments by CMA PO Panel on November 19, 1997
[2] New information submitted by CMA PO Panel on June 8, 1998

Summary

- We have shown you new information which clarifies the human exposure data submitted in November 1997
- Given that human data are to be used, and human exposure data is available, AEGLs should use this data
- Answered questions about human data presented June 8, 1998

ACUTE EXPOSURE GUIDELINE LEVELS for PROPYLENIMINE (PI)

ORNL Staff Scientist: Kowetha Davidson
Chemical Manager: Mark McClanahan
Secondary Reviewers: Nancy Kim

NAC/AEGL Meeting, September 14-16, 1998
Oak Ridge, Tennessee

PHYSICAL/CHEMICAL CHARACTERISTICS OF PI

- CAS No.: 75-55-8
- Chem. form.: $CH_3CH_2CH_2NH$
- Mol. Wt.: 57.11
- Phys. State: colorless oily or mobile liquid
- Vap. Pres: 112 mmHg@20°C
- Density: 0.8039-0.8070@25/25°C
- Solubility: miscible or soluble in water
- Odor: ammonia-like or fishy

USES

- Modify latex surface coating to improve adhesion
- Modify bonding properties of textiles, paper and dyes
- Photography
- Pharmaceutical industries
- Gelatins
- Organic synthesis

HUMAN TOXICITY

- No lethality data
- No primary data on nonlethal effects
- Nonlethal effects considered to be similar to those of ethylenimine (EI)
- EI causes skin, eye, and respiratory tract irritation, nausea, vomiting, headache, dizziness, and shortness of breath
- Effects of EI are delayed

ANIMAL TOXICITY

- Lethality Data
  - No LC_{50} data
  - 500 ppm for 240 min lethal to 5/6 rats
  - 500 ppm for 60, 120, or 240 min lethal to 1/6, 3/5, or 6/6 guinea pits
  - Toxic manifestations of PI are considered similar to those of EI: extreme respiratory difficulty, prostration, death, microscopic lesions in lungs and kidneys

ANIMAL TOXICITY

- Nonlethal Toxicity
  - No death occurred in groups of 5 or 6 rats exposed to 500 ppm for 5-120 minutes.
  - No deaths occurred in groups of 5 guinea pigs exposed to 500 ppm for 5-30 minutes.
- Carcinogenicity:
  - Oral adm. of PI to rats for 28 or 60 weeks caused increase in overall tumor incidence.
  - IARC classification - 2B (sufficient evidence)

DERIVATION OF AEGLS

- Data for PI are not available for deriving AEGL values.
- PI is structurally similar to EI.
- Relative toxicity approach was used to derive AEGL values for PI.

RELATIVE TOXICITY OF PI AND EI

Route	Species	PI	EI	Rel. Tox. (EI/PI)
Inhal.	Rat	500 ppm for 240 min: 5/6 deaths	500 ppm for 30 min: 5/6 deaths	8
	G.P.	500 ppm for 240 min: 6/6 deaths	500 ppm for 60 min: 6/6 deaths	4
	G.P.	500 ppm for 60 min: 1/6 deaths	100 ppm for 60 min: 1/6 deaths	5
Skin	G.P.	LD_{50}: 0.043 mL/kg bw	LD_{50}: 0.014 mL/kg bw	3

AEGL-1 VALUES for PROPYLENIMINE

- Neither odor not irritation thresholds are known for PI.
- The odor of EI is similar to that of ammonia, and the AEGL-2 values for 4 and 8 hours are less than odor detection level of 2 ppm.
- Therefore, no AEGL-1 values were approved for EI and, none are proposed for PI.

APPROVED AEGL-2 VALUES FOR EI AND PROPOSED VALUES FOR PI

Chemical	30 min	1 hour	4 hours	8 hours
Ethylenimine	9.8 ppm	4.6 ppm	1.0 ppm	0.47 ppm
Propylenimine	39 ppm	18 ppm	4.0 ppm	1.9 ppm

APPROVED AEGL-3 VALUES FOR EI AND PROPOSED VALUES FOR PI

Chemical	30 min	1 hour	4 hours	8 hours
Ethylenimine	18 ppm	9.8 ppm	2.8 ppm	1.5 ppm
Propylenimine	72 ppm	39 ppm	11 ppm	6.0 ppm

PROPOSED AEGL VALUES FOR PROPYLENIMINE[a,b]

Class.	30 min	1 h	4 h	8 h	Endpoint (Ref.)
AEGL-1	No values derived for AEGL-1				
AEGL-2	39 ppm (91 mg/m³)	18 ppm (42 mg/m³)	4.0 ppm (9.3 mg/m³)	1.9 ppm (4.4 mg/m³)	Respir. difficulty (Carpenter et al., 1948)
AEGL-3	72 ppm (168 mg/m³)	39 ppm (91 mg/m³)	11 ppm (26 mg/m³)	6.0 ppm (14 mg/m³)	Lethality (Carpenter et al., 1948)

[a]AEGL-2 and -3 values do not take into consideration the potential cancer risk due to inhalation exposure to propylenimine.
[b]Effects including lethality, irritation to eyes, and irritation to the respiratory tract may be delayed until after exposure.

EXOGENOUS SOURCES OF NO AND NO_2

Auto exhaust

Electric utilities

Industrial boilers

Gas stoves

Unvented space heaters

Kerosene heaters

Wood stoves

Tobacco products

TOXICITY OF NO

Methemoglobin formation

Conversion to NO_2

TOXICITY OF NO_2

Irritation

Pulmonary edema

Late onset bronchiolitis fibrosa obliterans

Silo Filler's disease

ATMOSPHERIC REACTIONS

$2NO + O_2 \rightarrow 2NO_2$
(minor at ambient temp)

$NO + O_3 \rightarrow NO_2 + O_2$

$NO + HO_2\cdot \rightarrow NO_2 + HO\cdot$

$NO + RO_2\cdot \rightarrow NO_2 + RO\cdot$

$NO_2 + HO\cdot \rightarrow HNO_3$

$2NO_2 \rightleftharpoons N_2O_4$

- temperature dependent
- favors NO_2 production

Calculated Time to Reach 5 ppm NO_2	
NO conc. in 20% O_2	**Time**
80 ppm	3 min
20 ppm	>1 hr

Source: Foubert et al., 1992

INDUSTRIAL USES OF NITRIC OXIDE

Intermediate in production of nitric acid from ammonia

Bleaching of rayon

Stabilizer for propylene and methyl ether

Formation of nitrosyl carbonyls

ENDOGENOUS ACTIONS OF NO

Regulator of functions of cardiovascular, immune, and nervous systems

Relaxation of vascular smooth muscle

THERAPEUTIC USES OF NITRIC OXIDE

ARDS

Persistent pulmonary hypertension of the newborn

Pulmonary hypertension
- congenital heart disease
- diaphragmatic hernia
- thoracic organ transplantation
- idiopathic
- COPD

SIGNS AND SYMPTOMS IN HUMANS ASSOCIATED WITH METHEMOGLOBIN CONCENTRATIONS	
Methemoglobin Concentration (%)	**Signs and Symptoms**
1.1	Normal level
1-15	None
15-20	Clinical cyanosis (chocolate brown blood); no hypoxic symptoms
30	Fatigue; recovery without treatment
20-45	Anxiety, exertional dyspnea, weakness, fatigue, dizziness, lethargy, headache, syncope, tachycardia
45-55	Decreased level of consciousness
55-70, ~60	Hypoxic symptoms: semistupor, lethargy, seizures, coma, bradycardia, cardiac arrhythmias
>70	Heart failure from hypoxia; high incidence of mortality
>85	Lethal

Sources: Kiese, 1974; Seger, 1992

SUMMARY OF HUMAN DATA FOR NO EXPOSURE

Concentration	Duration	Effects	Ref.
??	2 min	cyanosis; delayed pulmonary edema; death	Clutton-Brock, 1967
80 ppm	26 hr	40% metHb; human infant	Nakajima et al., 1997
10-80 ppm	10 min - 24 hr	decreased PAP in infants and children	(several)
80 ppm	6-108 hr	<10% metHb; organ transplantation and pulmonary hypertension	Adatia et al., 1994; Wessel et al., 1994
80 ppm	8 hr	11.9% metHb - PPHN	Davidson et al., 1998
80 ppm	10 min	modulation of methacholine-induced bronchoconstriction; increased airway conductance in asthmatics	Högman et al., 1993a
0.5-40 ppm	20 min-48 hr	therapeutic reduction of pulmonary artery pressure in ARDS patients	Manktelow et al., 1997; Troncy et al., 1997b

SUMMARY OF ANIMAL DATA FOR NO EXPOSURE

NONLETHAL DATA

Concentration	Duration	Species - Effects	Ref.
80, 160, 320 ppm	6 hr	dogs - 3, 6.6, 24% metHb	Wilhelm et al., 1998
40-80 ppm	≤ 40 min	dogs - decreased PAP in canine model of lung injury	Channick et al., Romand et al., Putensen et al., 1994; Zwissler et al., 1995; Chen et al., Hopkins et al., 1997
100 ppm	40 hr	rats - no evidence of lung injury	Garat et al., 1997
500-1500 ppm	5-30 min	rats - no evidence of lung injury	Stavert and Lehnert, 1990
20 ppm	6 hr	rabbit - decreased PAP in model of lung injury	Nishina et al., 1997
10-80 ppm	≤ 30 min	pigs - decreased PAP in model of lung injury	Goldstein et al., Hillman et al., 1997; Shah et al., Nelin et al., 1994
1000 ppm	15 min	pig - 20% metHb	Nelin et al., 1994
5-80 ppm	≤ 3 hr	sheep - decreased PAP in model of lung injury	Frostell et al., 1991; DeMarco et al., 1996
512 ppm	20 min	sheep - 11% metHb	Dyar et al., 1993

SUMMARY OF ANIMAL DATA FOR NO EXPOSURE

LETHALITY DATA

Concentration	Duration	Species - Effects	Ref.
5000 ppm 20,000 ppm	25 min 7-50 min	dogs - death; metHb; pulmonary edema due to NO_2	Greenbaum et al., 1967
640 ppm	6 hr	dogs - death; 78% metHb	Mihalko et al., 1998; Wilhelm et al., 1998
1000 ppm	30 min	rats - 11/20 died; cyanosis	Stavert and Lehnert, 1990

Proposed AEGL-1 for Nitric Oxide

Key studies: Adatia et al., 1994; Wessel et al., 1994; Davidson et al., 1998

Toxicity endpoint: ~10% metHb after therapeutic use of 80 ppm for 6-108 hrs

Scaling: none

Uncertainty factors: none

Proposed AEGL-1 Values for Nitric Oxide (ppm [mg/m^3])				
AEGL level	30-min	1-hr	4-hr	8-hr
AEGL-1	80 [100]	80 [100]	80 [100]	80 [100]

Supporting data:

Exposure: dog - 320 ppm for 6 hr caused 24% metHb (Wilhelm et al., 1998)

Scaling: $C^n \times t = k$; $n = 2$

UF: 10

1-hr AEGL-1 = 78 ppm

Proposed AEGL-2 for NO

No relevant human data.

No relevant animal data.

Possible AEGL-3 Derivation for NO

Key study: Nakajima et al., 1997

Toxicity endpoint: 40% metHb after 26 hours of 80 ppm

Scaling: $c^n \times t = k$, $n = 2$

Uncertainty factors: none

AEGL-3 Values:

30 min	1 hr	4 hr	8 hr
577 ppm	408 ppm	204 ppm	144 ppm

Problems:

extrapolation from long time period to relatively short time period

not supported by animal data

30 min and 1-hr too high as compared to estimated rat LC_0 of 333 ppm

11% metHb in sheep after exposure to 512 ppm, 20 min

20% metHb in pigs after exposure to 1000 ppm, 15 min

not supported by human data

~10% metHb after therapeutic use of 80 ppm for 6-108 hrs

concentration-response data not available

saturation kinetics of rhodanese unknown

Possible AEGL-3 Derivation for NO

Key study: Stavert and Lehnert, 1990

Toxicity endpoint: 11/20 rats died after exposure to 1000 ppm for 30 min; approximate LC_0 is 333 ppm

Scaling: $c^n \times t = k$, $n = 2$

Uncertainty factors: none

AEGL-3 Values:

30 min	1 hr	4 hr	8 hr
333 ppm	235 ppm	118 ppm	83 ppm

Problems:

no uncertainty factors applied

4- and 8-hr approach therapeutic concentration

concentration-response data not available

saturation kinetics of rhodanese unknown

species variability unknown

Possible AEGL-3 Values for Nitric Oxide (ppm [mg/m^3])				
30-min	1-hr	4-hr	8-hr	Endpoint (Ref.)
577 [721]	408 [510]	204 [255]	144 [180]	40% metHb after 80 ppm for 26 hr (Nakajima et al., 1997)
333 [416]	235 [294]	118 [148]	83 [104]	estimated LC_0 (Stavert and Lehnert, 1990)

RECOMMENDATIONS

- Propose AEGL-1, -2, and -3 values for NO_2
- Propose AEGL-1 values for NO
- Add NO_2 Executive Summary as an appendix to the NO TSD
- Include in the NO TSD that NO_2 is also of concern, but exact amount is impossible to predict

Effects in humans from acute exposure to NO_2	
Concentration (ppm)	**Effect**
0.4	approximate odor threshold
15-25	respiratory and nasal irritation
25-75	reversible pneumonia and bronchiolitis
150-300+	fatal bronchiolitis and bronchopneumonia

From NRC, 1977.

Effects of NO_2 in Healthy Subjects

Concentration	Duration	Effects	Reference
0.18 - 1.5 ppm	0.5 - 3 hrs	none	(several)
2 ppm	3 or 4 hr	none	Hackney et al., 1978; Devlin et al., 1992
3 ppm	2 hr	none	Goings et al., 1989
2.3 ppm	5 hr	none	Rasmussen et al., 1992
4 ppm	75 min	none	Linn and Hackney 1983
5 ppm	2 hr	37% mean decrease in airway resistance; 6/11 responded	von Nieding et al., 1979
30 ppm	2 hr	burning sensation in nose, chest; cough, dyspnea, sputum	NRC, 1977
90 ppm	40 min	pulmonary edema	Norwood et al., 1966

Experimental Studies with NO_2 in Asthmatic Subjects

Concentration	Duration	Effects	Reference
0.12	up to 1 hr	none	Koenig et al., 1985, 1987
0.3 - 1 ppm	up to 4 hr	none	(several)
0.6 ppm	75 min	none	Roger et al., 1990
4 ppm	75 min	none	Linn and Hackney, 1984
0.5 ppm	2 hr	slight irritation in 7/13	Kerr et al., 1978
0.3 ppm	4 hr	slight reductions in FEV_1 and specific airway conductance	Bauer et al., 1985

Proposed AEGL-1 for Nitrogen Dioxide

Key studies: Linn and Hackney, 1983; 1984

Toxicity endpoint: no effects in asthmatics exposed to 4 ppm for 75 minutes

Scaling: $C^n \times t = k$, where n = 3.5

Uncertainty factors: none

Proposed AEGL-1 Values for Nitrogen Dioxide (ppm [mg/m^3])				
AEGL level	30-min	1-hr	4-hr	8-hr
AEGL-1	5.2 [9.8]	4.3 [8.0]	2.9 [5.4]	2.4 [4.4]

Supporting data:

Exposure: monkey - 10 ppm for 2 hr caused mild irritation (Henry et al., 1969)

UF: 3 for sensitive subpopulations

	30-min	1-hr	4-hr	8-hr
AEGL-1	5.0 ppm	4.1 ppm	2.7 ppm	2.1 ppm

Proposed AEGL-2 for Nitrogen Dioxide

Key study: NRC, 1977

Toxicity endpoint: burning sensation in the nose and chest, cough, dyspnea, and sputum production in volunteers exposed to 30 ppm for 120 min

Scaling: $C^n \times t = k$, where n = 3.5

Uncertainty factors: 3 for sensitive populations

Proposed AEGL-2 Values for Nitrogen Dioxide (ppm [mg/m^3])				
AEGL level	30-min	1-hr	4-hr	8-hr
AEGL-2	14.9 [28.0]	12.2 [22.9]	8.2 [15.4]	6.7 [12.6]

Supporting data:

Exposure: no effects in coal miners exposed to peak concentrations of 14 ppm (Robertson et al., 1984)

Proposed AEGL-3 for Nitrogen Dioxide

Key study: Norwood et al., 1966

Toxicity endpoint: pulmonary edema in a welder exposed to 90 ppm for 40 min

Scaling: $C^n \times t = k$, where n = 3.5

Uncertainty factors: 3 for sensitive populations

Proposed AEGL-3 Values for Nitrogen Dioxide (ppm [mg/m^3])				
AEGL level	30-min	1-hr	4-hr	8-hr
AEGL-3	32.6 [61.2]	26.7 [50.2]	18.0 [33.8]	14.7 [27.6]

Supporting data:

Exposure: monkey - 50 ppm for 2 hr caused marked irritation, no deaths (Henry et al., 1969)

UF: 3 for sensitive subpopulations

	30-min	1-hr	4-hr	8-hr
AEGL-3	24.8 ppm	20.3 ppm	13.7 ppm	11.2 ppm

DRAFT ACUTE EXPOSURE GUIDELINE LEVELS
FOR
IRON PENTACARBONYL

NAC/AEGL-11
Oak Ridge, TN
September 14-16, 1988

ORNL Staff Scientist: **Robert A.Young**
Chemical Manager: **Kyle Blackman**
Chemical Reviewers: **Richard Niemeier**
Glenn Leach

Attachment 11

Study on the Inhalation Toxicity of Eisenpentacarbonyl as a Vapor in Rats - 28 Day Test (BASF, 1995)

- 5 male and 5 female Wistar rats/group
- infrared spectroscopy analysis of chamber concentrations
- Exposure protocol: 6 hrs/day up to 28 days; whole-body exposure

Test Group	Exposure conc. in ppm (analytical)
0	clean air control
4	0.1 (0.1±0.01)
E	0.3 (0.3 ±0.01)
1	1 (1.00±0.02)
2	3 (2.91±0.01)
3	10 (9.85)

Results (BASF, 1995)

- **Lethality**
  - **No deaths in Groups 0 (control), 4 (0.1 ppm), E (0.3 ppm) and 1 (1 ppm) at any time during 28-day exposure period**
  - **50% lethality (dead or killed in moribund state) in Group 2 (2.91 ppm) following only two exposures; deaths occurred within 4 days of last exposure (one death after first exposure)**
  - **100% lethality (dead or killed in moribund state) in Group 3 (10 ppm) after one exposure; deaths occurred within by 3 days of following exposure**

- **Clinical signs**
  - **No clinical signs in Groups 0 (control), 4 (0.1 ppm) , E (0.3 ppm) and 1 (1 ppm)**
  - **Group 2 (2.91 ppm): surviving rats exhibited piloerection and hyperventilation up to 9 days postexposure; resolved thereafter**
  - **Group 3 (10 ppm): prior to death exhibited labored respiration, blood on nostrils, piloerection, hunched posture**

Results (BASF, 1995)

- **Histopathology**

  - **lungs: interstitial and perivascular edema, congestion, hemorrhage and dilation of alveolar capillaries in Group 3 (10 incidences) and Group 2 (7 incidences)**

  - **spleen: atrophy of lymphoid tissue in Group 3 (6 incidences) and Group 2 (2 incidences)**

  - **no additional remarkable findings**

Acute Inhalation Toxicity Study of Iron Pentacarbonyl in Rats (Biodynamics, 1988)

- 5 male and 5 female Sprague-Dawley rats/group
- Colorimetric analysis
- Exposure protocol: single 4-hr whole-body exposure; 14-day observation period

Test Group	Exposure conc. in ppm (analytical)
I	0
IV	7.5 (5.2)
V	24 (17)
III	38 (28)
II	80 (60)

Results (Biodynamics, 1988)

- **Lethality**

Test Group	Mortality		
	Male	Female	Total
I (control)	0/5	0/5	0/10
IV (5.2 ppm)	0/5	0/5	0/10
V (17 ppm)	5/5	5/5	10/10
III (28 ppm)	5/5	5/5	10/10
II (60 ppm)	5/5	5/5	10/10

- **Deaths occurred 1-8 days postexposure**

- **4-hr LC_{50} = 10.42 ppm (sexes combined) (95% c.i.: 8.5-13 ppm)**
  4-hr LC_{16} = 6.99 ppm (sexes combined)
  4-hr lethality threshold ≈5.2 ppm (2.2% lethality, estimated from exposure-response plot provided in study)

Results (Biodynamics, 1988)

- **Clinical observations**
  - **labored breathing, hypoactivity, lacrimation, nasal discharge during exposure (17, 28, and 60 ppm groups)**
  - **control and 5.2 ppm group exhibited "minimal responses"; recovery within a few days**
  - **continuous body weight loss in 17, 28, and 60 ppm groups**

- **Neurological tests**
  - **reduced muscle tone, toe-pinch, righting, and startle reflexes attenuated in 60-ppm group; controls and 5.2-ppm group comparable**

- **Carboxyhemoglobin**
  - **exposure-related increase in COHb) for three highest exposures (11.6% for 60 ppm at 1 hour postexposure); 5.2 ppm group exhibited slight elevation relative to controls; COHb declining by 4 hrs postexposure**

- **Gross pathology**
  - **rats that died prior to scheduled termination:**
    - **signs of pulmonary edema**
    - **red discoloration in various tissues (? treatment related ?)**

Toxicity Study of Iron Pentacarbonyl (Sunderman et al., 1959)

- 20 Swiss albino mice or 12-18 Wistar rats/group
- Analytical methods: Not specified
- Exposure protocol: single 30-min whole-body exposure; 5-day observation period
- Mice

	Mortality ratios	
Exposure conc.	3 days	5 days
204 ppm	5/20	5/20
270 ppm	8/20	9/20
387 ppm	15/20	17/20
470 ppm	16/20	20/20

- 30-min LC_{50} = 285 ppm

Sunderman et al., 1959

- **Antidote studies in mice:**
  - **30-minute exposure of mice to 390 ppm as positive controls for six experimental (antidote) groups**

	Mortality ratios	
Exposure conc.	3 days	5 days
390 ppm	50/60	54/60

Sunderman et al., 1959

- **Rats**

Exposure conc.	Mortality ratios 3 days	5 days
86 ppm	1/12	11/12
118 ppm	3/12	6/12
160 ppm	12/18	13/18
195 ppm	12/18	15/18
244 ppm	11/12	11/12

- **30-min LC_{50} = 188 ppm**

- **No clinical observations, gross pathology, or histopathology in the Sunderman et al. report**

ISSUES

- **Selection of determinants for AEGL values**

AEGL-3

- **5.2 ppm (Biodynamics, 1988) estimated 4-hr lethality threshold; actual exposure at this level caused no deaths in rats; 4-hr LC_{16} = 6.99 ppm**
- **2.91 ppm (6 hrs) caused death in 1 of 10 rats; 50% mortality after two 6-hr exposures (BASF, 1995)**

AEGL-2

- **2.91 ppm (6 hrs) may be too close to lethality threshold to use as a determinant for AEGL-2**
- **1 ppm (6 hrs) resulted in no significant effects (BASF, 1995)**

AEGL-1

- **1 ppm (6 hrs) produced no notable signs of toxicity**
- **meaningful and valid determinant for AEGL-1 ??**

ISSUES

- **Value of '*n*' for temporal extrapolation**

  - **available data suggest port-of-entry irritation (i.e., pulmonary damage) as cause of death; $n = 1$**

  - **if n=2, a 4-hr exposure to 5.2 ppm caused no effect (Biodynamics, 1988) but two 6-hr exposures at 2.91 ppm caused 50% mortality (BASF, 1995) (both, however, provide similar Ct values of 108 ppm·hrs)**

- **Uncertainty factor application**

  - **data suggest that mechanism is port-of-entry irritation (pulmonary damage); individual variability likely to be less than an order-of-magnitude (individual variability UF=3)**

  - **exposure-response data in only two species (interspecies UF=10)**

AEGL-1

- endpoints consistent with AEGL-1 not defined

- exposures that produce clinical signs are at or very near those that cause severe effects and lethality

- ? validity/practicality of an AEGL-1 ?

ACUTE EXPOSURE GUIDELINES FOR IRON PENTACARBONYL
(CAS NO. 13463-40-6)

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

Reference: NA
Test Species/Strain/Number: NA
Exposure Route/Concentrations/Durations: NA
Toxicity Endpoint: data unavailable for defining AEGL-1 specific endpoints
Time Scaling: NA
Concentration/Time Selection/Rationale: NA
Uncertainty Factors/Rationale : NA
Modifying Factor: NA
Animal-to-Human Dosimetric Adjustments: NA
Comments: NA

ACUTE EXPOSURE GUIDELINES FOR IRON PENTACARBONYL
(CAS NO. 13463-40-6)

AEGL-2 VALUES			
30 minutes	1 hour	4 hours	8 hours
0.35 ppm	0.17 ppm	0.044 ppm	0.022 ppm

Reference: BASF. 1995. Study on the inhalation toxicity of eisenpentacarbonyl as a vapor in rats - 28 day test. BASF Dept. of Toxicology. EPA/OTS Doc # 89-950000244.

Test Species/Strain/Number: Rat/Wistar/5 males and 5 females per exposure group

Exposure Route/Concentrations/Durations: 6 hr inhalation exposure

Test Group	Exposure conc. in ppm (analytical)
0	clean air control
4	0.1 (0.1±0.01)
E	0.3 (0.3 ±0.01)
1	1 (1.00±0.02)
2	3 (2.91±0.01) (determinant for AEGL-2)
3	10 (9.85)

Toxicity Endpoint: severe pulmonary damage; 10% mortality after one 6-hr exposure; 50% mortality following two 6-hr exposures

Time Scaling: $C^n \times t = k$, where $n = 1$. The concentration-exposure time relationship for many irritant and systemically acting vapors and gases may be described by $C^n \times t = k$, where the exponent n ranges from 1 to 3.5 (ten Berge et al., 1986). Available data suggest a near linear response which is consistent with the contact irritant, port-of-entry effects observed for iron pentacarbonyl.

Concentration/Time Selection/Rationale: The 6-hr exposure to 2.91 ppm was considered an estimate of the lethality threshold. In the absence of exposure-response data for AEGL-2 effects, this exposure was reduced 3-fold as an estimate of a threshold for a serious but nonlethal exposure.

Uncertainty Factors/Rationale

Total Uncertainty Factor: 30

Interspecies: 10 to account for data deficiencies in species variability in the toxic response to iron carbonyl and for possible variability in metabolism and disposition

Intraspecies: 3 to account for possible individual variability in the sensitivity to iron pentacarbonyl-induced toxicity; a reduced UF is justified by the steep exposure-response relationship and because the toxicity appears the function of contact irritation at the port of entry

Modifying Factor: 3 to estimate a threshold for a serious but nonlethal response from data indicative of a lethality threshold.
Animal-to-Human Dosimetric Adjustments: none
Comments: The AEGL-2 values are based upon assumptions regarding the exposure-response relationship. Definitive data were unavailable that described effects consistent with AEGL-2 definition.

ACUTE EXPOSURE GUIDELINES FOR IRON PENTACARBONYL
(CAS NO. 13463-40-6)

AEGL-3 VALUES			
30 minutes	1 hour	4 hours	8 hours
1.16 ppm	0.58 ppm	0.16 ppm	0.073 ppm

Reference: BASF. 1995. Study on the inhalation toxicity of eisenpentacarbonyl as a vapor in rats - 28 day test. BASF Dept. of Toxicology. EPA/OTS Doc # 89-950000244.

Test Species/Strain/Number: Rat/Wistar/5 males and 5 females per exposure group

Exposure Route/Concentrations/Durations: 6 hr inhalation exposure

Test Group	Exposure conc. in ppm (analytical)
0	clean air control
4	0.1 (0.1±0.01)
E	0.3 (0.3 ±0.01)
1	1 (1.00±0.02)
2	3 (2.91±0.01) (determinant for AEGL-3)
3	10 (9.85)

Toxicity Endpoint: 10% mortality after one 6-hr exposure; 50% mortality following two 6-hr exposures

Time Scaling: $C^n \times t = k$, where $n = 1$. The concentration-exposure time relationship for many irritant and systemically acting vapors and gases may be described by $C^n \times t = k$, where the exponent n ranges from 1 to 3.5 (ten Berge et al., 1986). Available data suggest a near linear response which is consistent with the contact irritant, port-of-entry effects observed for iron pentacarbonyl.

Concentration/Time Selection/Rationale: The 6-hr exposure to 2.91 ppm was considered an estimate of the lethality threshold due to the lethality response. An independent study (Biodynamics, 1988) provided a 4-hr LC_{50} of 10.42 ppm (sexes combined) (95% c.i.: 8.5-13 ppm), 4-hr LC_{16} of 6.99 ppm (sexes combined), and a 4-hr lethality threshold ≈5.2 ppm (2.2% lethality, estimated from exposure-response plot provided in study). The 6-hr exposure to 2.91 ppm appears to be a defensible estimate of the lethality threshold.

Uncertainty Factors/Rationale:	
Total Uncertainty Factor:	**30**
Interspecies:	**10 to account for data deficiencies in species variability in the toxic response to iron carbonyl and for possible variability in metabolism and disposition**
Intraspecies:	**3 to account for possible individual variability in the sensitivity to iron pentacarbonyl-induced toxicity; a reduced UF is justified by the steep exposure-response relationship and because the toxicity appears the function of contact irritation at the port of entry**
Modifying Factor: none	
Animal-to-Human Dosimetric Adjustments: none	
Comments: The AEGL-3 values have been developed based upon an estimate of the lethality threshold as determined by data available from a well-conducted GLP study.	

Attachment 12

FURAN AEGLs

George Rodgers
Claudia M. Troxel

FURAN

- **PROPERTIES**
  - Colorless, highly flammable liquid
  - Low boiling and flash point
  - High vapor pressure
    - Daylight: react with hydroxyl radicals
      - $t_{1/2}$ of 2-6 hours; 9.5 hours
    - Nighttime: react with nitrate radicals
      - $t_{1/2}$ of ½ hour

- **PRODUCTION/USE**
  - Decarbonylation of furfural
  - Intermediate in production of:
    - tetrahydrofuran, pyrrole, and thiophene; lacquers and solvents for resins; pharmaceuticals; agricultural chemicals; stabilizers

- **AVAILABLE DATA**
  - No human data
  - Animal toxicity data limited to lethality and pharmacokinetic data

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 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

Egle and Gochberg. (1979) Respiratory retention and acute toxicity of furan.

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

No information regarding the sex of animals, individual vapor concentrations, method of vapor analysis, period of observation following exposure

Toxicity signs in mice that died during the 1-hour exposure: hypoactivity for 5-15 minutes, followed by labored breathing and death.

Gross findings: pulmonary inflammation and fluid accumulation

1-hour (static) LC_{50} = 42 ppm

Stasenkova, K.P., and Kochetkova, T.A., and Schirskaya, V.A. (1967) Furan Toxicity.

and

Stasenkova, K.P., and Kochetkova, T.A. (1968) Comparative evaluation of toxicity of furane family compounds.

General Comments:

Scientific papers at this time were not peer reviewed

About this time, use of units changed over?

LC_{50} = 0.04 μmol/L = 1.0 ppm

calculated from text = 1030 ppm (mg/L in text)

Many inconsistencies in the studies - use of species not clear; different durations given for same studies

General protocol:

Exposures were static.

Furan vapor concentrations in exposure chambers measured by furan reaction with para nitrophenyl diazonine: leads to formation of yellow complex [sensitivity: 0.01 mg furan in volume of 5 mL]

Mortality Rate of Furan in White Mice (and Rats?)					
Concentrations (ppm)				Total # animals	Lethality
Target	Measured during Exp.				
	15 min	30 min	120 min		
5400	3600	3600	2900	10	10
3600	2700	2500	2500	10	10
2700	1800	1800	1600	10	10
1800	1100	1100	900	10	6 [a]
1100	720	720	540	10	1 [b]
720	540	470	470	10	0
360	290	180	180	10	0

[a] All animals died on the 1st day
[b] Died on 1st or 2nd day

2-hour (static) LC_{50} = 1030 ppm

Clinical Signs of Mice (and Rats?) Exposed Statically to Furan for 2-hours		
Conc. (ppm)	Time (min.)	Effect
1800, 2700, and 3600	2-3	eye and upper respiratory tract irritation (w/ liquid discharge from nose
	5-10	increased respiration, asthma slowed motion, muscular weakness impaired motor activity (shaky walk)
	15-20	lateral body position observed head tremor hind extremity convulsions
	30-40	all animals were dead
1100 to 1400 (?)		same clinical signs - developed at slower rate, more weakly manifested
	20	lateral body position observed
		6 dead (by day 1 post-exposure)

Clinical Signs of Mice (and Rats?) Exposed Statically to Furan for 2-hours (con't)		
Conc. (ppm)	Time	Effect
540, 720	post-exp.	Development of Narcotic Signs: no response to touching lacked defensive (needle prick) and corneal reflexes muscular weakness and motor incoordination signs disappeared in a day; behavior of experimental **rats and mice** did not differ from controls
		1 animal dead (day 1 or 2 post-exposure)
290		no clinical signs reported

Microscopic Observations in White Mice (and Rats?) Exposed Statically to Furan for 2-Hours	
Animals	Observation
dead animals [720, 1100, 1800, 2700, and 3600 ppm]	hemorrhages in lungs, liver, spleen, heart diffuse lung edema
lower concentrations [290 and 540]	bloody internal organs brain: perivascular, pericellular edema weakly manifested catarrhal bronchitis in lungs

SUMMARY OF ACUTE LETHAL INHALATION DATA IN LABORATORY ANIMALS			
Species	Time (h)	LC_{50} (ppm)	Reference
Mouse	1	42	Egle and Gochberg, 1979
Mouse ?	2	1030	Stasenkova and Kochetkova, 1967
Rat	1		Terrill et al., 1989
male		3398	
female		3550	
combined		3464	

GENERAL NOTES:

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

Metabolism

mice> humans >rats

Predicted absorbed dose:

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

SUMMARY OF ALTERNATIVE AEGL-3 DERIVATIONS (ppm)					
Endpoint/Rationale/Reference	**UF**	**30 m**	**1 h**	**4 h**	**8 h**
MOUSE: ⅓ the 1-hour LC_{50} of 42 ppm = 14 ppm [Egle and Gochberg, 1979]	10	0.66	0.47	0.23	0.16
MOUSE?: ⅓ the 2-hour LC_{50} of 1030 ppm = 340 ppm [Stasenkova and Kochetkova, 1967]	10	68	48	24	17
	30	23	16	8.0	5.7
	100	6.8	4.8	2.4	1.7
MOUSE?: Highest "NOEL" for lethality for 2-hour exposure = 540 ppm [Stasenkova and Kochetkova, 1967]	10	110	76	38	27
	30	36	25	13	9
	100	11	7.6	3.8	2.7
General Comments: Time scaling : $C^n \times t = k$ where n = 2 ("default")					

SUMMARY OF ALTERNATIVE AEGL-3 DERIVATIONS (ppm)					
Endpoint/Rationale/Reference	**UF**	**30 m**	**1 h**	**4 h**	**8 h**
RAT: ⅓ the 1-hour LC_{50} of 3464 ppm = 1155 ppm [Terrill et al., 1989]	30	54	39	19	14
	100	16	12	5.8	4.1
RAT: Highest "NOEL" for lethality for 1-hour exposure = 2851 ppm [Terrill et al., 1989]	30	120	95	48	34
	100	37	29	14	10
General Comments: Time scaling : $C^n \times t = k$ where n = 2 ("default")					

AEGL-3 (ppm)			
30 minutes	1 hour	4 hours	8 hours
0.66	0.47	0.23	0.16

- **Reference:** Egle and Gochberg. (1979). Respiratory retention and acute toxicity of furan.

- 3 or 4 Swiss mice/exposure group

- **Concentration/Time Selection/Rationale:**
  ⅓ the 1-hour LC_{50} of 42 ppm is 14 ppm

- **Uncertainty Factors/Rationale:**
  Total uncertainty factor: 10
  - Interspecies: 3 - species to species extrapolation; mouse appears to be sensitive
  - Intraspecies: 3 to protect sensitive individuals: the mechanism of toxicity not expected to vary significantly between individuals

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

AEGL-3 (ppm)				
UF	30 min	1 hour	4 hours	8 hours
30	54	39	19	14
100	**16**	**12**	**5.8**	**4.1**

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

- 5 Sprague Dawley rats/sex/group

- **Concentration/Time Selection/Rationale:**
  ⅓ the 1-hour LC_{50} of 3464 ppm = 1155 ppm

- **Uncertainty Factors/Rationale:**
  Total uncertainty factor: 100
  Interspecies: 10 - species to species extrapolation; rat not the most sensitive species
  Intraspecies: 10 to protect sensitive individuals

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

AEGL-3 (ppm)				
UF	30 min	1 hour	4 hours	8 hours
30	120	95	48	34
100	**37**	**29**	**14**	**10**

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

- 5 Sprague Dawley rats/sex/group

- **Concentration/Time Selection/Rationale:**
  Highest "NOEL" for lethality for 1-hour exposure = 2851 ppm

- **Uncertainty Factors/Rationale:**
  Total uncertainty factor: 100
  Interspecies: 10 - species to species extrapolation; rat not the most sensitive species
  Intraspecies: 10 to protect sensitive individuals

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

AEGL-3 (ppm)				
UF	30 minutes	1 hour	4 hours	8 hours
10	68	48	24	17
30	23	16	8.0	5.7
100	6.8	4.8	2.4	1.7

- **Reference:** Stasenkova, K.P., and Kochetkova, T.A., and Schirskaya, V.A. (1967) Furan Toxicity.

- 10 White mice and rats(?)/group

- **Concentration/Time Selection/Rationale:**
  ⅓ the 2-hour LC_{50} of 1030 ppm = 340 ppm

- **Uncertainty Factors/Rationale:**
  at least 100

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

AEGL-3 (ppm)				
UF	30 minutes	1 hour	4 hours	8 hours
10	110	76	38	27
30	36	25	13	9
100	11	7.6	3.8	2.7

- **Reference:** Stasenkova, K.P., and Kochetkova, T.A., and Schirskaya, V.A. (1967) Furan Toxicity.

- 10 White mice and rats(?)/group

- **Concentration/Time Selection/Rationale:**
  Highest "NOEL" for lethality for 2-hour exposure = 540 ppm

- **Uncertainty Factors/Rationale:**
  at least 100

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

Attachment 13

PROPOSED AEGL VALUES:

METHACRYLONITRILE, PROPIONITRILE, AND ISOBUTYRONITRILE

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
- Lack of metabolism data in humans: Are humans more like rats or other species?
- Discrepancy between NIOSH TWA values and proposed AEGL values.
- Discrepancy between proposed propionitrile AEGL values and proposed methacrylonitrile and isobutyronitrile AEGL values

METHACRYLONITRILE

Summary of Proposed AEGL Values for Methacrylonitrile					
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)	2.7 ppm (7.4 mg/m^3)	2.0 ppm (5.5 mg/m^3)	1.2 ppm (3.3 mg/m^3)	0.92 ppm (2.5 mg/m^3)	Estimated 4-hr no-effect-level for death in mice (Pozzani et al., 1968)

NIOSH TWA: 1 ppm (2.5 mg/m^3)

ACUTE EXPOSURE GUIDELINES FOR METHACRYLONITRILE (CAS NO. 126-98-7)

AEGL-3 VALUES			
30 minutes	1 hour	4 hours	8 hours
2.7 ppm	2.0 ppm	1.2 ppm	0.92 ppm

Reference:Pozzani et al. 1968. The mammalian toxicity of methacrylonitrile. Am. Ind. Hyg. Assoc. J. 29: 202-210.

Test Species/Strain/Sex/Number: A/J mice/ 6 males/concentration

Exposure Route/Concentrations/Durations: Mice/Inhalation: Unspecified concentrations/4 hours

Endpoint/Concentration/Rationale: Estimated NOEL for death of ⅓ x LC_{50} (36 ppm x ⅓ = 12 ppm) was determinant for AEGL-3

Uncertainty Factors/Rationale:
Total uncertainty factor: 10
Interspecies: 3- the mouse is 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 methacrylonitrile 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-1 STUDY (Pozzani et al., 1968)

HUMAN RESPONSE TO ONE MINUTE EXPOSURES TO METHACRYLONITRILE

Concentration	24 ppm	14 ppm	7 ppm	2 ppm	0 ppm
Number of subject inhalations	18	17	17	18	18
Incidence of odor detection, %	89	88	47	0	0
Incidence of throat irritation, %	22	0	0	0	0
Incidence of eye irritation, %	17	0	0	0	0
Incidence of nose irritation, %	6	0	0	0	0

HUMAN RESPONSE (INCIDENCE/9 SUBJECTS)- 2 PPM FOR 10 MINUTES

Time (min.)	Odor Detection	Eye Irritation	Tears	Nose Irritation	Throat Irritation
1	4	2	1	0	0
2	4	1	0	0	1
3	3	0	0	0	1
4	0	0	0	0	0
5	0	0	0	0	0
6	0	0	0	0	0
7	0	0	0	2	0
8	0	1	0	1	0
9	0	0	0	0	0
10	0	0	0	0	0

HUMAN RESPONSE (INCIDENCE/7 SUBJECTS)- 14 PPM FOR 10 MINUTES

Time (min.)	Odor Detection	Eye Irritation	Tears	Nose Irritation	Throat Irritation
1	7	0	0	0	1
2	6	1	0	0	0
3	1	1	0	0	0
4	0	1	0	0	0
5	0	1	0	0	0
6	0	1	0	0	1
7	0	1	0	1	0
8	0	1	0	1	0
9	0	1	0	1	0
10	0	0	1	0	0

POSSIBLE AGEL-2 STUDIES

- Repeated-Dose Rat (Pozzani et al., 1968)

  0, 19.3, 52.6, or 109.3 ppm for 7 hours/day, 5 days/week, for 91 days

  Deaths observed at 52.6 and 109.3 ppm

  No treatment-related effects at 19.3 ppm

- Repeated-Dose Dog (Pozzani et al., 1968)

  0, 3.2, 8.8, or 13.5 ppm for 7 hours/day, 5 days/week, for 90 days

  Convulsions and loss of hindlimb control at 13.5 ppm after 39 days

  Transient SGOT and SGPT elevation at 8.8 ppm after 21 days

  No treatment-related effects at 3.2 ppm

- Developmental Rat (Saillenfait et al., 1993)

  0, 12, 25, 50, or 100 ppm for 6 hr/day on days 6-20 of gestation

  Decreased fetal weights at 25, 50, and 100 ppm

Possible AEGL-2 Values for Methacrylonitrile								
30-min	1-hr	4-hr	8-hr	UF	Concentration	Time	Endpoint	Reference
1.7 ppm	1.4 ppm	0.79 ppm	0.61 ppm	Inter: 10 Intra: 3	19.3 ppm	7-hr.	Rat NOEL	Pozzani et al., 1968
2.4 ppm	1.8 ppm	1.1 ppm	0.84 ppm	Inter: 3 Intra: 3	8.8 ppm	7-hr.	Increased dog liver enzymes	Pozzani et al., 1968
2.2 ppm	1.7 ppm	0.97 ppm	0.75 ppm	Inter: 10 Intra: 3	25 ppm	6-hr.	5% decrease in fetal weight	Saillenfait et al., 1993
2.7 ppm	*2.0 ppm*	*1.2 ppm*	*0.92 ppm*	*Proposed AEGL-3 Values*				

METHACRYLONITRILE: ANIMAL LETHALITY

Species	Sex	Endpoint	Concentration	Comments	Reference
Rat	F	4-hr. LC_{50}	700 ppm	Loss of consciousness but no deaths at 176 ppm within 3 hr.	Pozzani et al., 1968
Rat	F	4-hr. LC_{50}	496 ppm	Loss of consciousness and one death preceded by convulsions at 176 ppm within 3 hr.	Pozzani et al., 1968
Rat	M	4-hr. LC_{50}	440 ppm	Irregular respiration, tremors, and convulsions at 625 ppm.	DuPont, 1968a
Rat	M	4-hr. LC_{50}	328 ppm	Loss of consciousness but no deaths at 176 ppm within 3 hr.	Pozzani et al., 1968
Guinea pig	M	4-hr. LC_{50}	88 ppm	52.5 ppm caused no symptoms.	Pozzani et al., 1968
Rabbit	M	4-hr. LC_{50}	37 ppm	19.7 ppm caused no symptoms.	Pozzani et al., 1968
Mouse	M	4-hr. LC_{50}	36 ppm	19.7 ppm caused no symptoms.	Pozzani et al., 1968
Dog	F	7-hr.	53 ppm	Vomiting, convulsions, unconsciousness within 7 hr. Death occurred overnight.	Pozzani et al., 1968
Dog	F	3- or 7-hr.	106 ppm	Vomiting, diarrhea, and convulsions prior to death.	Pozzani et al., 1968
Dog	F	7 hr.	87.5 ppm	Vomiting, convulsions, unconsciousness prior to death. No effects were observed at 40 ppm.	DuPont, 1968b

PROPIONITRILE

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., 199**
51 ppm	*39 ppm*	*23 ppm*	*18 ppm*	*Proposed AEGL-3 Values*				

PROPIONITRILE: ANIMAL LETHALITY

Species	Sex	Endpoint	Concentration	Comments
Rat	M/F	4-hr. $\mathbf{LC_{50}}$	1441 ppm	NOEL for death= 690 ppm. Salivation, lethargy, weakness, convulsions, tremors, collapse, and death were observed during exposure.
Rat	M	6/6 animals dead 1.25 hr exposure	39,325 ppm	Hemorrhagic lungs and gastrointestinal inflammation observed at necropsy.
Mouse	M	1-hr. $\mathbf{LC_{50}}$	163 ppm	Dyspnea, tachypnea, gasping, tremors, convulsions, and corneal opacity observed 30-300 minutes following initial contact with propionitrile. All mice exposed to 400 ppm dead within 180 min.

ISOBUTYRONITRILE

Summary of Proposed AEGL Values for Isobutyronitrile					
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)	8.7 ppm (24 mg/m^3)	6.6 ppm (18 mg/m^3)	3.9 ppm (11 mg/m^3)	3.0 ppm (8.4 mg/m^3)	No-effect-level for death in rats (Saillenfait et al., 1993)

NIOSH TWA: 8 ppm (22 mg/m^3)

ISOBUTYRONITRILE DATA:

- Rat LCLo: 1000 ppm (no details available)

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

  0, 50, 100, 200, or 300 ppm for 6 hr/day on days 6-20 of gestation

  300 ppm: 3/21 maternal deaths
  Increase in nonsurviving implants and embryonic resorptions
  Decreased fetal weights (14-16%)
  Unilateral hydronephrosis

  200 ppm: 1/21 maternal deaths
  Decreased female fetal weight (8%)

  No treatment-related effects at lower concentrations.

ACUTE EXPOSURE GUIDELINES FOR ISOBUTYRONITRILE (CAS NO. 78-82-0)

AEGL-2 VALUES			
30 minutes	1 hour	4 hours	8 hours
8.7 ppm	6.6 ppm	3.9 ppm	3.0 ppm

Reference: Saillenfait, A.M., et al. 1993. Relative developmental toxicities of inhaled aliphatic mononitriles in rats. Fund. Appl. Toxicol. 20: 365-375.

Test Species/Strain/Sex/Number: Sprague-Dawley rats/ 21 pregnant females/concentration

Exposure Route/Concentrations/Durations: Rats/Inhalation/0, 50, 100, 200, or 300 ppm/6 hours/day on gestation days 6-20

Endpoint/Concentration/Rationale: NOEL for maternal death and developmental effects of 100 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 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. Data point used for AEGL-3 derivation was a single 6 hour exposure. Other time points were based on extrapolation.

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

LETHALITY DATA FOR RATS EXPOSED TO ISOBUTYRONITRILE

Concentration	Duration	Result	Reference
1200 ppm	1-hr. (Rats held 14 days)	1/10 deaths; lethargy	Eastman Kodak Company, 1986a.
1800 ppm	1-hr. (Rats held 14 days)	5/10 deaths; lethargy	
2700 ppm	1-hr. (Rats held 14 days)	8/10 deaths; narcosis	
1173 ppm	1-hr.	LC_{10}: male 1143 ppm female 1630 ppm	
1898 ppm	1-hr.	LC_{50}	
56,640 ppm	10-min.	0/3 deaths	Eastman Kodak Company, 1957
43,648 ppm	15-min.	4/4 deaths	
5465 ppm	89-min.	3/3 deaths	
1248-2709 ppm	1-hr.	6/12 deaths; significant differences in pulmonary function (due to pulmonary edema) in survivors	Eastman Kodak Company, 1986b

Eastman Kodak Company. 1957. Toxicity report: Isobutyronitrile. [Unpublished Data]. Eastman Kodak Company, Rochester, NY 14650.

Eastman Kodak Company. 1986a. Acute inhalation toxicity and one-hour LC10 value of isobutyronitrile in the rat. (Study No. TX-86-193) [Unpublished Data]. Eastman Kodak Company, Rochester, NY 14650.

Eastman Kodak Company. 1986b. Pulmonary function in animals exposed to isobutyronitrile by inhalation. (Study No. TX-86-240) [Unpublished Data]. Eastman Kodak Company, Rochester, NY 14650.

ALTERNATIVE AEGL-3 VALUES FOR ISOBUTYRONITRILE

AEGL-3 VALUES			
30 minutes	1 hour	4 hours	8 hours
26 ppm	20 ppm	12 ppm	9.0 ppm

Reference: Eastman Kodak Company. 1986a. Acute inhalation toxicity and one-hour LC10 value of isobutyronitrile in the rat. (Study No. TX-86-193) [Unpublished Data]. Eastman Kodak Company, Rochester, NY 14650.

Test Species/Strain/Sex/Number: rats

Exposure Route/Concentrations/Durations: Rats/Inhalation/ 1 hr.

Endpoint/Concentration/Rationale: Estimated NOEL for death (LC_{50} ÷3 ; 1800 ppm ÷ 3 = 600 ppm)

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 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. Data point used for AEGL-3 derivation was a single 1 hour exposure.

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

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

Attachment 14

COMMITTEE ON TOXICOLOGY

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September 15, 1998

ROSTER

Committee on Toxicology

SUBCOMMITTEE ON ACUTE EXPOSURE GUIDELINE LEVELS

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TENTATIVE SCHEDULE FOR PREPARATION OF DRAFT TECHNICAL SUPPORT DOCUMENTS (TSDs)

Preparation of Draft TSDs by ORNL

Attachment 15

1st Draft of TSDs Received by Chem. Mgr./Chem. Revs.
(2 weeks review)

Batch 1
4 Chemicals
10 wks prior to meeting

Batch 2
4 Chemicals
8wks prior to meeting

Principal Comments Received by ORNL from Chem. Mgr./Chem. Revs.
(1 week revision)

4 Chemicals
8 wks prior to meeting

4 Chemicals
6 wks prior to meeting

TSDs Received by Committee Members and Sent Comments to Chem. Mgr./ORNL
(3 weeks review)

4 Chemicals
7 wks prior to meeting

4 Chemicals
5 wks prior to meeting

Incorporate Final Comments Received by Chem. Mgr./ORNL
(2 weeks revision)

4 Chemicals
4 wks prior to meeting

4 Chemicals
2 wks prior to meeting

0 week

NAC/AEGL Meeting

0 week

AEGL DEVELOPMENT STATUS/TRACKING SHEET

First Draft of Technical Support Document

Chemical Name: _____

AEGL Devlopment Team

Author: _____

Chemical Manager (CM): _____

Chemical Reviewers (CRs): _____

Schedule Dates	Event	Actual Dates	Initials
_____	1st draft TSD completed and sent to CM/CRs ❒ E-mail ❒ Hardcody	_____	_____ Author
_____	CM/CRs review completed and received by author ❒ Oral ❒ Written ❒ No comment	_____	_____ Author

Send comments by telephone, fax, overnight or regular mail

NAC/AEGL COMMITTEE REVIEW STATUS/TRACKING SHEET

NAC/AEGL Committee Draft of Technical Support Document

Chemical Name: _____

AEGL Devlopment Team

Author: _____

Chemical Manager (CM): _____

Chemical Reviewers (CRs): _____

_____

Other Parties: _____

Schedule Dates	Event	Actual Dates	Initials
_____	Revision of TSD completed and sent to NAC/AEGL Committee ❒ E-mail ❒ Hardcopy	_____	_____ PYL
_____	Committee member review completed and comments sent to CM and author ❒ Oral ❒ Written ❒ No comment	_____	_____ NAC/AEGL Member
_____	Recommended revisions from CM received by author ❒ Oral ❒ Written ❒ No comment	_____	_____ Author

Send comments by telephone, fax, E-mail, overnight or regular mail, courier

Status of Development of AEGL Values

August, 1998

AEGL Chemical with Interim Status

1.	57-14-7	1,1-Dimethyl hydrazine
2.	60-34-4	Methyl hydrazine
3.	62-53-3	Aniline
4.	540-59-0	1,2-Dichloroethylene
5.	540-73-8	1,2-Dimethyl hydrazine
6.	7697-37-2	Nitric acid
7.	7782-41-4	Fluorine
8.	7782-50-5	Chlorine
9.	7784-42-1	Arsine
10.	7803-51-2	Phosphine

AEGL Values with Proposed Status

1.	56-23-5	Carbon tetrachloride
2.	67-66-3	Chloroform
3.	74-90-8	Hydrogen cyanide
4.	74-93-1	Methyl mercaptan
5.	75-21-8	Ethylene oxide
6.	75-44-5	Phosgene
7.	75-56-9	Propylene oxide
8.	75-78-5	Dimethyldichlorosilane
9.	75-79-6	Methyl trichlorosilane
10.	79-21-0	Peracetic acid
11.	91-08-7	Toluene 2,6-diisocyanate
12.	106-89-6	Epichlorohydrin
13.	107-02-8	Acrolein
14.	107-11-9	Allyl amine
15.	107-18-6	Allyl alcohol
16.	107-30-2	Chloromethyl methyl ether
17.	151-56-4	Ethyleneimine
18.	302-01-2	Hydrazine
19.	584-84-9	Toluene 2,4-diisocyanate
20.	4170-30-3	cis and trans-Crotonaldehyde
21.	7647-01-0	Hydrogen chloride
22.	7664-39-3	Hydrogen fluoride
23.	7664-41-7	Ammonia
24.	7790-91-2	Chlorine trifluoride
25.	10294-34-5	Boron trichloride
26.	13463-39-3	Nickel carbonyl
27.	19287-45-7	Diborane

AEGL Chemicals with Draft Status

1.	75-55-8	Propyleneimine
2.	78-82-0	Isobutyronitrile
3.	107-12-0	Propionitrile
4.	110-00-9	Furan
5.	110-89-4	Piperidine
6.	126-98-7	Methacrylonitrile
7.	7697-37-2	Nitric acid
8.	10102-43-9	Nitric oxide
9.	13463-40-6	Iron pentacarbonyl

Chemical in Holding Status

1.	79-22-1	Methyl chloroformate
2.	506-77-7	Cyanogen chloride
3.	814-68-6	Acrylyl chloride
4.	108-23-6	Isopropyl chloroformate
5.	109-61-5	Propyl chloroformate
6.	7784-34-1	Arsenic trichloride

Appendix A

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

Final Meeting 10 Highlights
Old Post Office, M09
1100 Pennsylvania Avenue
Washington, D.C.
June 8-11, 1998

INTRODUCTION

In opening remarks, Roger Garrett expressed appreciation for the productivity of the AEGL program on the occasion of its second anniversary. George Rusch (Chair) stated that approximately 52 chemicals to date have been addressed by the NAC/AEGL and that 12 published in the Federal Register are also being submitted to the National Academy of Science Committee of Toxicology (NAS/COT) for review. Roger Garrett indicated that the COT may meet in late July or early August for its initial review of these chemicals and the NAC/AEGL Standing Operating Procedures (SOP).

The highlights of the meeting are noted below, and the meeting agenda (Attachment 1) and attendee list (Attachment 2) are attached. Highlights of the NAC Meeting 9 (March 10-12,1998) were reviewed and approved with minor revision to the section on nickel carbonyl (Appendix A).

REPORTS FROM WORKING GROUPS AND GENERAL INTEREST ITEMS

Standing Operating Procedure (SOP) Working Group

Ernest Falke (EPA) led discussion on the draft SOP document that was distributed prior to the NAC meeting. He emphasized that any comments received during the discussion or by June 30, 1998, would be addressed in the revision of the document. Several comments of an editorial nature were also received. There was also discussion pertaining the use of the term "ceiling" in the AEGL definitions. It was agreed that Jonathan Borak, George Rodgers, and Doan Hansen would prepare definitions/guidelines for hypersusceptible populations for inclusion in the SOP document. Jonathan Borak also emphasized that AEGLs are planning tools and not for retrospective use. If needed, SOP-specific issues can be re-opened and addressed at future meetings.

General Interest Items

- Draft Guideline for Carcinogens

  Richard Thomas led discussion on the acute exposure/carcinogenesis issue (Attachment 3). Richard stated that views regarding the carcinogenic potential of acute exposures to toxicants are equivocal. Robert Snyder cautioned that extrapolation from long-term (e.g., 2-year bioassays) does not account for the critical time factor usually required for a carcinogenic response, and that extrapolation from cancer bioassays that use a Maximum-Tolerated Dose to an acute exposure may be precarious. Editorial suggestions were also provided that included a suggestion to move the last paragraph of the write-up (regarding the acute exposure issues) to the beginning, making for a more effective introduction to the issue. Following revision of the write-up, it will be recirculated among the NAC/AEGL.

- Draft Guideline for Anesthesia

  George Rodgers discussed the basic issue of anesthesia that would be relevant to AEGL derivation (Attachment 4). These included the relationship between blood:gas partition coefficients and rate of anesthesia induction, the Minimal Alveolar Concentration (MAC),and other factors affecting anesthesia (e.g., temperature, blood chemistry, lung pathology, age, etc.). He stated that children are known to be clinically more sensitive but that quantitative data are lacking. He also explained that the precise mechanism of anesthesia is still unknown.

- Bromine Testing

  Larry Gephart circulated a copy of the correspondence to Great Lakes Chemical Corporation indicating the need for additional acute exposure toxicity data for bromine (Attachment 5). Larry informed the NAC/AEGL that a panel of industry representatives indicated that testing may be done. Consequently, Larry recommended that the deliberations on bromine AEGLs be deferred until decisions on testing or the results of new tests become available.

- Benchmark Dose

  Robert Benson provided a summary of the Benchmark Dose (BMD) methodology emphasizing that one must assess the validity and quality of the biology/toxicology data prior to application of the BMD program (Attachment 6). Robert Snyder provided his conceptual application of BMD approach to AEGLs development (Attachment 7). He also stated that the NAS/COT is currently establishing guidelines for using the BMD and that the ED_{10} is being considered as the benchmark, providing that appropriate data are available. Additionally, the NAS/COT is also currently assessing the procedures for extrapolating to lower response levels and the application of uncertainty factors (specifically, a methodology that does not simply multiply factors and that incorporates the slope of the dose-response curve).

- Tests for Sensory Irritation

  Pam Dalton gave an excellent presentation on testing of volatile chemicals that are sensory irritants. Data were presented that addressed key questions: (1) Does odor have an effect on the response ?, (2) Is there adaptation to the response, and (3) Can expectation/beliefs about the chemical influence perception of odor and irritation? The results of tests have indicated that the answer to all of these questions is yes. In such testing, involvement of the trigeminal nerve was a criterion for irritation and the slope of the irritation response was much steeper than that for the odor response. It occurs above the odor threshold but below the irritation threshold (as determined by trigeminal activation). The annoyance response tended to be perceived irritation and was more closely related to odor than to true irritation. Currently, both subjective and objective methods are being used to evaluate irritation in humans. Physiologic and biochemical endpoints will also be investigated.

- Application of AEGLs to Air Release Dispersion Model

  The application of AEGL values (specifically AEGL-2 values) in a dispersion model was presented by Ken Steinberg (Attachment 8). The model incorporates elements such as release description

and meteorologic conditions and provides information on toxic cloud footprint, greatest cloud penetration,

and other factors allowing for analysis of the release scenario. For short duration releases, the lower AEGL time points (30 min and 1 hr) were used, while for longer duration release the longer time points (4 and 8 hrs) were used. Using the chlorine AEGL values, for a 60-second release scenario, it was found that downwind cloud penetration distance was greatest for the 10-min AEGL-2 and, as expected, was less for 2-, 3-, and 60-min AEGL-2. Modeling of a 5-min hydrogen fluoride release, however, produced unexpected results.

AEGL PRIORITY CHEMICALS

Propylene Oxide, CAS No. 75-56-9

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

Presentations were made on behalf of the CMA Propylene Oxide (PO) Panel. Larry Andrews made a presentation summarizing the CMA Propylene Oxide Panels' concerns regarding the application of the human and animal data in the derivation of the draft AEGLs for propylene oxide (Attachments 9 and 10). Additionally, the issues of mechanistic similarity/dissimilarity of propylene oxide and ethylene oxide, and the application of uncertainty factors were discussed. Alternate AEGL values were presented with summary remarks that human data should be used and, where possible, linked to the animal data. Susan Ripple discussed the human exposure and experience data for propylene oxide (Attachment 11). The presentation focused on the use of human data for the development of AEGL values and also upon newly released sample and task duration information. Cheryl Bast provided an overview of the current draft AEGL values for propylene oxide and the data sets used in their derivation. There was also discussion regarding the flat-lining of AEGL values across time periods when contact irritation was the endpoint of concern. In deliberations on other AEGL chemicals, flat-lining was shown to be appropriate. It was the consensus of the NAC/AEGL that further deliberations on propylene oxide be deferred to the September 1998 meeting pending receipt of company reports and review of the data.

Acrolein, CAS No. 107-02-8

Chemical Manager: Dr. Robert Snyder, Rutgers University
Author: Dr. Cheryl Bast, ORNL

An overview of the derivation of draft AEGLs for acrolein was presented by Cheryl Bast (Attachment 12). Following discussions of possible AEGL values, a motion was made (Steve Barbee, seconded by Loren Koller) to accept AEGL-2 values of 0.18 ppm for 30 min and 0.1 ppm for 1, 4, and 8 hrs. The values were based upon a 1-hr exposure to 0.3 ppm and a total uncertainty factor application of 3. In the absence of data for a 30-min exposure duration, the 1-hr exposure of 0.3 ppm was adjusted to 0.18 ppm by temporal scaling to attain the 30-min exposure value. The 4- and 8-hr values were then flat-lined based upon the 1-hr value of 0.1 ppm (0.3 ppm adjusted by a total UF of 3). These values were accepted [YES: 20; NO: 8]. A motion was made by Robert Benson to accept the AEGL-1 value as presented in the Technical Support Document. The motion, seconded by Richard Thomas, passed unanimously. Following discussion on the effect if varying the temporal extrapolation exponent, n, a motion was made by Robert Benson to accept the AEGL-3 values of 2.5, 1.4, 0.48, and 0.27 for 30-minute, 1, 4, and 8 hrs, respectively (UP = 10; n = 1.2).

The 30-min and 1-hr values were based upon a 1-hr NOEL of 14 ppm for lethality while the 4- and

8-hr AEGL-3 values were based upon a 4-hr NOEL of 4.8 ppm for lethality. The motion, seconded by George Rodgers, passed unanimously (Appendix B).

SUMMARY OF PROPOSED AEGL VALUES FOR ACROLEIN					
Classification	**30-min**	**1-hour**	**4-hour**	**8-hour**	**Endpoint**
AEGL-1	0.03 ppm 0.07 mg/m^3	0.03 ppm 0.07 mg/m^3	0.03 ppm 0.07 mg/m^3	0.03 ppm 0.07 mg/m^3	eye irritation, annoyance, discomfort in humans
AEGL-2	0.18 ppm 0.41 mg/^{3}	0.10 ppm 0.23 mg/m^3	0.10 ppm 0.23 mg/m^3	0.10 ppm 0.23 mg/m^3	10% decrease in respiratory rate in humans
AEGL-3	2.5 ppm 5.7 mg/m^3	1.4 ppm 3.2 mg/m^3	0.48 ppm 1.1 mg/m^3	0.27 ppm 0.62 mg/m^3	NOEL for death in rats

Peracetic acid, CAS No. 79-21-0

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

The issue of the chemical composition of peracetic acid (hydrogen peroxide, acetic acid and sulfuric acid) and the changeable nature of the relative concentrations of these component was considered to be a relevant issue of concern regarding the development of AEGL value for this chemical (Attachment 13). Following discussion on uncertainty factor application, the AEGL-3 values of 9.6 ppm, 4.8 ppm, 2.6 ppm, and 1.9 ppm were passed [YES: 24, NO: 1, ABSTAIN: 0]; motion made by Ernest Falke (seconded by George Rodgers) for the 30-min, 1-, 4-, and 8-hr time periods, respectively. The 30-min AEGL-3 values were based upon a 30-min. nonlethal exposure of 96 ppm, while the 1-hr value was based upon a 1-hr nonlethal exposure of 48 ppm. The 4-hr and 8-hr values were scaled from the 1-hr value using an exponent of 2.2. The AEGL-2 values were based upon an estimated irritation threshold in humans of 0.5 ppm, 1.5 ppm caused slight discomfort and 2 ppm induced severe irritation). An uncertainty factor of 3 (protection of sensitive individuals) was applied to the 1.5 ppm and the resulting 0.5 ppm value was proposed for all time periods. A motion made by Robert Snyder and seconded by George Rodgers to accept these values was approved [YES: 22, NO: 1, ABSTAIN: 0]. For the AEGL-1 values, discussion focused on 0.5 ppm causing mild discomfort in human subjects. Application of an uncertainty factor of 3 for protection of sensitive individuals resulted in proposed AEGL-1 values of 0.17 ppm for all time periods. Following a motion made by Larry Gephart (seconded by Thomas Hornshaw), these values were accepted by the NAC/AEGL [YES: 21, NO: 4, ABSTAIN: 0]. (Appendix C).

SUMMARY OF PROPOSED AEGL VALUES FOR PERACETIC ACID

Classification	30-min	1-hour	4-hour	8-hour	Endpoint
AEGL-1	0.17 ppm 0.53 mg/m^3	0.17 ppm 0.53 mg/m^3	0.17 ppm 0.53 mg/m^3	0.17ppm 0.53 mg/m^3	Threshold for irritation in human subjects
AEGL-2	0.50 ppm 1.6 mg/m^3	0.50 ppm 1.6 mg/m^3	0.50 ppm 1.6 mg/m^3	0.50 ppm 1.6 mg/m^3	1.5 ppm irritation threshold for humans; at 2 ppm effects were severe
AEGL-3	9.6 ppm 3.0 mg/m^3	4.8 ppm 15 mg/m^3	2.6 ppm 8.1 mg/m^3	1.9 ppm 5.9 mg/m^3	NOEL for lethality

Nitric oxide, CAS No. 10102-43-9

Chemical Manager: Dr. Loren Keller, Oregon State University
Author: Dr. Carol Forsyth, ORNL

Loren Koller explained that the development of AEGLs for nitric oxide is currently on hold awaiting new data that were presented at the 1998 Society of Toxicology Annual Meeting and that would be useful in developing AEGL-2 and AEGL-3 values (Attachment 14). The new data have not yet been transferred for use by the NAC/AEGL but should be available by the September meeting. The half-life of NO in atmospheric and kinetics were briefly discussed by Kyle Blackman (Attachment 15). The issue of conversion of NO to NO_2 is also being addressed as are the mechanisms of toxicity of these two compounds and their possible sources. Following a brief discussion, the following recommendations were made: (1) derive AEGL values for NO and NO_2, (2) add the executive summary for NO_2 as an appendix to the NO technical support document (TSD), and (3) note in the NO TSD, that NO_2 is of concern but exact exposure concentrations will be impossible to predict. If substantial changes are required in the TSDs, revised documents will be distributed in July pending availability of the new data.

Crotonaldehyde mixture CAS No. 4170-30-3 & *trans* isomer CAS No. 123-73-9

Chemical Manager: Dr. Doan Hansen, Brookhaven National Laboratory
Author: Dr. Sylvia Milanez, ORNL

Sylvia Milanez presented a summary of data available for crotonaldehyde and the derivation of the draft AEGLs (Attachment 16). Bob Benson motioned (second by Richard Niemeier) to accept the AEGL-1 values as proposed in the TSD (0.19 ppm for all time points, based upon irritation threshold). The motion carried unanimously [YES: 23, NO: 0, ABSTAIN: 0]. The draft AEGL-2 values proposed in the TSD were based upon the lowest exposure (expressed in the key study as a concentration x time product) resulting in pulmonary lesions in rats. (i.e., 8,000 ppm min). Although alternate AEGL values were proposed, the use of the Ct of 8,000 ppm-min as the threshold for bronchiolar lesions was accepted [YES: 19, NO: 2, ABSTAIN: 0] for determining the AEGL-2 values (motion made by Doan Hansen,second by Thomas Hornshaw). James A. Dego from Eastman Chemical Company indicated that use of the RD_{50} was not appropriate as an endpoint for AEGL-2. Following a brief discussion, Ernest Falke motioned (seconded by David Belluck) to accept the AEGL-3 values based upon time-specific data for the 30-min, 1- and 4-hr values, and that the 8-hr values be scaled from the 4-hr value (n = 1.2). The motion carried (YES: 20, NO: 1, ABSTAIN: 0] (Appendix D).

SUMMARY OF PROPOSED AEGL VALUES FOR CROTONALDEHYDE					
Classification	**30-min**	**1-hour**	**4-hour**	**8-hour**	**Endpoint**
AEGL-1	0.19 ppm 0.53 mg/m^3	0.19 ppm 0.53 mg/m^3	0.19 ppm 0.53 mg/m^3	0.19 ppm 0.53 mg/m^3	Irritation threshold
AEGL-2	8.9 ppm 2.5 mg/m^3	4.4 ppm 13 mg/m^3	1.1 ppm 3.2 mg/m^3	0.56 ppm 1.6 mg/m^3	Threshold for bronchiolar lesions, n=1 due to use of Ct (8000 ppm-min) rather than series of conc.-time values
AEGL-3	27 ppm 77 mg/m^3	14 ppm 40 mg/m^3	2.6 ppm 7.5 mg/m^3	1.5 ppm 4.2 mg/m^3	Lethality threshold in rats

Nickel carbonyl, CAS No. 13463-39-3

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

Although AEGL-1 values were deemed inappropriate and draft proposed AEGL-3 values for nickel carbonyl were approved by the NAC/AEGL at the December 1997 meeting (Meeting 8), time did not allow for addressing the data sets relevant to AEGL-2 values. Kyle Blackman opened the deliberations on nickel carbonyl by addressing salient issues regarding the degradation of the chemical in ambient conditions (Attachment 17). Robert Young provided an overview of the previous deliberations as well as data and issues concerning development of AEGL-2 values (Attachment 18). Sally Williams (INCO, Wales, UK) presented information (Attachment 19) on the use and properties of nickel carbonyl, stressing that it occurs only under strictly controlled conditions and that its use is restricted to only a few sites in the world aside from very small amounts occasionally produced in research laboratories. Additionally, she emphasized that monitoring of ambient nickel carbonyl levels is not currently feasible, and that development of AEGL values beyond 1 hr would be inappropriate due to the rapid degradation of the chemical. Following discussion of the developmental toxicity data, AEGL-2 values were approved [YES: 21, NO: 6, ABSTAIN: 2]; motion made by George Alexeeff, second by William Bress. It was also the consensus of the NAC/AEGL that 8-hr values for both AEGL-2 and AEGL-3 were inappropriate due to the properties of the chemical (Appendix E).

SUMMARY OF PROPOSED AEGL VALUES FOR NICKEL CARBONYL

Classification	30-min	1-hour	4-hour	8-hour	Endpoint
AEGL-1	NA	NA	NA	NA	Not appropriate; toxicity below odor threshold
AEGL-2	0.059 ppm 0.41 mg/m^3	0.042 ppm 0.29 mg/m^3	0.021 ppm 0.14 mg/m^3	NA	Developmental toxicity in hamsters; gestational exposure
AEGL-3	0.32 pm 2.2 mg/m^3	0.22 popm 1.5 mg/m^3	0.11 ppm 0.76 mg/m^3	NA	Estimated lethality threshold (LC_{01} of 3.17 ppm) in mice, UF=30; *n*=2

Hydrogen sulfide, CAS No. 7783-06-4

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

The deliberations on hydrogen sulfide were deferred to the next meeting following issues/concerns expressed by several NAC members (George Alexeeff, Calif. EPA: David Belluck, MN Pollution Control Agency; Zarena Post, TX Nat. Resource Conserv. Comm.) regarding assessments by their respective states.

Chloroform, CAS No. 67-66-3

Chemical Manager: Dr. Stephen Barbee, Olin Corporation
Author: Dr. Robert Young, ORNL

Steve Barbee commented on the proposed draft AEGLs for chloroform and the assumptions used to derive them. Robert Young presented an overview of the draft values and the key data sets pertinent to each AEGL level (Attachment 20). Data consistent with AEGL-1 effects were unavailable. Limited data in humans indicated that no toxic effects were associated with exposures producing strong but not unpleasant odor. It was the consensus of the NAC/AEGL that AEGL-1 values for chloroform be considered inappropriate due to properties of the chemical [YES: 22, NO: 1, ABSTAIN: 0]. Motion by David Belluck (second by Richard Thomas) for the development of draft AEGL-2 values, the use of human data from older studies were originally used to estimate a narcosis threshold. However, following discussion of the available data and its relevance to the AEGL process, it was the consensus of the NAC/AEGL to use rodent developmental toxicity data as the basis for the AEGL-2. The total uncertainty factor was 3 for protection of sensitive populations. Due to greater sensitivity of rodents in metabolism and toxicity, no further adjustment by uncertainty factor application was warranted. A motion to accept the AEGL-2 values was made by Larry Gephart (second by Richard Thomas); the motion passed [YES: 20, NO: 3, ABSTAIN: 0]. The AEGL-3 values were based upon a lethality threshold estimated by a one-third reduction in a rat 4-hr LC50 (9780 ppm/3 = 3260 ppm). An uncertainty factor of 3 was applied

for protection of sensitive individuals. Based upon PB-PK modeling of metabolism/disposition of chloroform in rodents species, humans appear to be less sensitive to the toxic effects of chloroform. Data were unavailable for empirically deriving a scaling exponent (*n)* and, therefore, temporal extrapolation for all AEGL values utilized an default value for *n (n* = 2). The AEGL-3 values were accepted [YES: 22, NO: 1, ABSTAIN: 0] (motion by Steve Barbee, second by George Rodgers) (Appendix F).

SUMMARY OF PROPOSED AEGL VALUES FOR CHLOROFORM					
Classification	**30-min**	**1-hour**	**4-hour**	**8-hour**	**Endpoint**
AEGL-1	NA	NA	NA	NA	Not appliable due to properties of chemical
AEGL-2	120 ppm 584 mg/m^3	88 ppm 429 mg/m^3	44 ppm 214 mg/m^3	31 ppm 151 mg/m^3	Based on NOAEL for developmental effects in rats following gestational exposure to 100 ppm; UF=3
AEGL-3	920 ppm 4480 mg/m^3	650 ppm 3166 mg/m^3	330 ppm 1607 mg/m^3	230 ppm 1120 mg/m^3	Lethality threshold estimatead by ⅓ reduction in rat 4-hr LC_{50}; UF=3

Carbon tetrachloride, CAS No. 56-23-5

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

In response to concerns expressed by John Morawetz (ICWU), studies and issues pertaining to human lethality following acute exposure to carbon tetrachloride were discussed. Robert Young presented an overview of studies distributed to the NAC/AEGL by John Morawetz that focused on human lethality as well as studies addressing the issue of P-450 induction and its enhancement of carbon tetrachloride toxicity (Attachment 21) . Special focus was placed upon the Norwood et al. (1950) study as a possible driver for the AEGL-3 values because it identified an individual that would not have been protected by the current draft proposed AEGL-3 values accepted by the NAC/AEGL at the December 1997 meeting (Meeting 8). There was discussion regarding the reliability of the Norwood report and precision of the exposure data. There was also discussion on the effect of P-450 induction on lethality and nonlethal toxicity of carbon tetrachloride. Use of the Norwood et al. data as the primary driver for the AEGL-3 values would lower the AEGL-3 values somewhat (189 ppm, 143 ppm, 83 ppm, and 63 ppm for the 30 min, 1-, 4-, and 8-hr periods, respectively) relative to the draft proposed values of 230 ppm, 170 ppm, 99 ppm, and 75 ppm. It was decided that a poll of the NAC/AEGL would be taken at the next meeting to determine if the draft proposed AEGL-3 values should be retained or if they should be revised based upon the Norwood et al. report. The draft proposed AEGL values accepted at the December 1997 meeting are shown below.

SUMMARY OF PROPOSED AEGL VALUES FOR CARBON TETRACHLORIDE					
Classification	**30-min**	**1-hour**	**4-hour**	**8-hour**	**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
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 humans subjects (intolerable to one of four subjects)
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)

ADMINISTRATIVE ISSUES

Roger Garrett addressed issues regarding the time-line for document preparation, distribution, and review, and the overall responsibilities/function of the AEGL Development Team. He presented a potential schedule for preparation of draft TSDs (Attachment 22).

Plans for future NAC/AEGL meeting dates were discussed. The following are proposed meeting dates:

September 14-16, 1998, Oak Ridge, TN
December 7-9, 1998, Washington, DC
March 18-19, 1999, New Orleans, LA (after SOT)

These meeting highlights were prepared by Bob Young and Po-Yung Lu, Oak Ridge National Laboratory.

LIST OF ATTACHMENTS

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

1. NAC Meeting No. 10 Agenda
2. NAC Meeting No. 10 Attendee List
3. Draft Guideline for Carcinogens - Richard Thomas
4. Information of potential applications of anesthetic effects for AEGLs development - George Rodgers
5. Correspondence on Bromine testing - Larry Gephart
6. Bench Mark Dose Approach discussion I - Bob Benson
7. Bench Mark Dose Approach discussion II - Bob Snyder
8. Influence of toxicity averaging time on cloud penetration for accidental releases - Ken Steinberg
9. Comments of draft AEGL of Propylene oxide from Chemical Manufacturers Association
10. CMA Propylene Oxide Panel - Larry Andrews
11. Human Exposure & Experience to Propylene Oxide - Susan Ripple
12. Data analysis of Acrolein - Cheryl Bast
13. Data analysis of Peracetic acid - Kowetha Davison
14. Data analysis of NO_2- Loren Koller and Carol Forsyth
15. Data analysis of NO_2 in atmospheric air - Kyle Blackman
16. Data analysis of Crotonaldehyde mixture - Sylvia Milanez
17. Kinetics of Nickel carbonyl - Kyle Blackman
18. Data analysis of Nickel carbonyl - Bob Young
19. Comments of draft AEGL of Nickel carbonyl - Sally Williams
20. Data analysis of Chloroform - Bob Young
21. Data analysis of carbon tetrachloride - Bob Young
22. Schedule for draft AEGL preparation - Roger Garrett

LIST OF APPENDICES

A. Approved NAC-9 Meeting Highlights
B. Ballot for Acrolein
C. Ballot for Peracetic acid
D. Ballot for Crotonaldehyde mixture
E. Ballot for Nickel carbonyl
F. Ballot for Chloroform

Appendix B

Date of NAC/AEGL Meeting: ept. 14-16, 1998 **Chemical:** HYDRAZINE

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

NAC Member	AEGL 1	AEGL 2	AEGL3
Loren Koller		A	A
Glenn Leach	Absent	Absent	Absent
Mark A. McClanahan		Y	Y
John S. Morawetz		N	N
Deirdre L. Murphy	Absent	Absent	Absent
Richard W. Niemeier		Y	Y
William Pepelko		Y	Y
Zarena Post	Absent	Absent	Absent
George Rodgers		A	A
George Rusch, Chair		Y	Y
Bob Snyder		Y	Y
Thomas J. Sobotka	Absent	Absent	Absent
Kenneth Still		Y	Y
Patricia Ann Talcott	Absent	Absent	Absent
Richard Thomas	Absent	Absent	Absent
Thomas Tuccinardi/ ~~Doan Hansen~~		Y ~~Y~~	Y ~~Y~~
TALLY		~~19~~ 18/20	~~20~~ ~~21~~ 19/20 15 one

PPM, (mg/m³)	30 Min	60 Min	4 Hr	8Hr
AEGL 1	, ( )	, ( )	, ( )	, ( )
AEGL 2	18 , ( )	13 , ( )	6.2 , ( )	4.4 , ( )
AEGL 3	~~50~~ , ( )	35 , ( )	18 , ( )	13 , ( )

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

AEGL 2 Motion: Robert Snyder **Second:** Tom Hornshaw

AEGL 3 Motion: Doan Hansen **Second:** Steve Barbee

Approved by Chair: _____ **DFO:** Paul S. Tobin **Date:** 9/14/98

Date of NAC/AEGL Meeting: ept. 14-16, 1998 **Chemical:** ~~ETHYLENEIMINE~~ PROPYLENEIMINE Appendix C

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

NAC Member	AEGL 1	AEGL 2	AEGL3
Loren Koller	Y	Y	Y
Glenn Leach	Absent	Absent	Absent
Mark A. McClanahan	Y	N	N
John S. Morawetz	Y	Y	Y
Deirdre L. Murphy	Absent	Absent	Absent
Richard W. Niemeier	Y	Y	Y
William Pepelko	Y	Y	Y
Zarena Post	Absent	Absent	Absent
George Rodgers	A	A	A
George Rusch, Chair	Y	Y	Y
Bob Snyder	Y	Y	Y
Thomas J. Sobotka	Absent	Absent	Absent
Kenneth Still	Y	Y	Y
Patricia Ann Talcott	Absent	Absent	Absent
Richard Thomas	Absent	Absent	Absent
Thomas Tuccinardi/ ~~Doan Hansen~~	Y ~~Y~~	Y ~~Y~~	Y ~~Y~~
TALLY	20/20	18/20	19/20

PPM, (mg/m³)	30 Min	60 Min	4 Hr	8Hr
AEGL 1	N/A ,( )	N/A ,( )	N/A ,( )	N/A ,( )
AEGL 2	25 ,( )	11 ,( )	2.5 ,( )	1,2 ,( )
AEGL 3	50 ,( )	23 ,( )	5.1 ,( )	2.4 ,( )

AEGL 1 Motion: R. Benson **Second:** W. Pepelko

AEGL 2 Motion: W Bress **Second:** T. Hornshaw

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

Approved by Chair: [signature] **DFO:** Paul S. Tobin **Date:** 9/15/98

Date of NAC/AEGL Meeting: ept. 14-16, 1998 Chemical: NITROGEN DIOXIDE NO2 Appendix D

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

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

PPM, (mg/m³)	~~10 min~~	30 Min	60 Min	4 Hr	8Hr
AEGL 1		0.50 ,( )	0.50 ,( )	0.50 ,( )	0.50 ,( )
AEGL 2		15 ,( )	12 ,( )	8.2 ,( )	6.7 ,( )
AEGL 3	~~30~~	25 ,( )	20 ,( )	14 ,( )	11 ,( )

AEGL 1 Motion: Bob Benson Second: E. Falke

AEGL 2 Motion: Koller Second: W. Pepelko

AEGL 3 Motion: Hansen Second: M c Clanahan

Approved by Chair: [signature] DFO: Paul S. Price Date: 9/15/98

Appendix E

Date of NAC/AEGL Meeting: ept. 14-16, 1998 **Chemical:** * NITROGEN OXIDE

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

NAC Member	AEGL 1	AEGL 2	AEGL3
Loren Koller	Y		
Glenn Leach	Absent	Absent	Absent
Mark A. McClanahan	Y		
John S. Morawetz	Y		
Deirdre L. Murphy	Absent	Absent	Absent
Richard W. Niemeier	N		
William Pepelko	Y		
Zarena Post	Absent	Absent	Absent
George Rodgers	Y		
George Rusch, Chair	Y		
Bob Snyder	Y		
Thomas J. Sobotka	Absent	Absent	Absent
Kenneth Still	Y		
Patricia Ann Talcott	Absent	Absent	Absent
Richard Thomas	Absent	Absent	Absent
Thomas Tuccinardi/ ~~Doan Hansen~~	N N		
TALLY	16/20		

* A dept NO2 for NO with a note that short term exposures to 80 ppm for NO do not represent a hazard

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

AEGL 1 Motion: M. McClanahan **Second:** G. Rodgers

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

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

Approved by Chair: _____ **DFO:** _____ **Date:** 9/15/98

Fe(CO)5 Appendix F

Date of NAC/AEGL Meeting: ept. 14-16, 1998 **Chemical:** 13463-40-6 IRON PENTACARBONYL

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

PPM, (mg/m³)	30 Min	60 Min	4 Hr	8Hr
AEGL 1	*NR ,( )	NR ,( )	NR ,( )	NR ,( )
AEGL 2	0.35 ,( )	0,17 ,( )	0,044 ,( )	0,022 ,( )
AEGL 3	1.2 ,( )	0.58 ,( )	0.16 ,( )	~~0.093~~ ,( )

* NR - LACK OF DATA

AEGL 1 Motion: McCanahan **Second:** John Hinz

AEGL 2 Motion: M.Clanahan **Second:** Koller

AEGL 3 Motion: R. Benson **Second:** S. Barbee

Approved by Chair: _____ **DFO:** Paul S. Tobin **Date:** 9/15/98

$(CH_3)_2CH-C\equiv N$ Appendix G

Date of NAC/AEGL Meeting: ept. 14-16, 1998 **Chemical:** ISOBUTYRONITRILE

NAC Member	AEGL 1	AEGL 2	AEGL 3	NAC Member	AEGL 1	AEGL 2	AEGL3
George Alexeeff	Absent	Absent	Absent	Loren Koller	A	A	A
Steven Barbee	Y	Y	Y	Glenn Leach	Absent	Absent	Absent
Lynn Beasley	Y	Y	Y	Mark A. McClanahan	Y	Y	Y
David Belluck	A	A	A	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	Absent	Absent	Absent	William Pepelko	Y	Y	Y
William Bress	Y	Y	Y	Zarena Post	Absent	Absent	Absent
Luz Claudio	Absent	Absent	Absent	George Rodgers	Y	Y	Y
George Cushmac	Y	Y	Y	George Rusch, Chair	Y	Y	Y
Ernest Falke	A	A	A	Bob Snyder	Y	Y	Y
Larry Gephart	Y	P	N	Thomas J. Sobotka	Absent	Absent	Absent
John Hinz	Y	Y	Y	Kenneth Still	A	A	Y
Jim Holler	A	A	A	Patricia Ann Talcott	Absent	Absent	Absent
Thomas C. Hornshaw	Y	Y	Y	Richard Thomas	Absent	Absent	Absent
Benjamin A. Jackson	Absent	Absent	Absent	Thomas Tuccinardi/ Doan Hansen	Y A	Y A	Y A
Nancy K. Kim	Y	Y	Y				
				TALLY	16/18	17/18	18/19

PPM, (mg/m³)	30 Min	60 Min	4 Hr	8Hr
AEGL 1	NA ,( )	NA ,( )	NA ,( )	NA ,( )
AEGL 2	8.7 ,( )	6.6 ,( )	3.9 ,( )	3.0 ,( )
AEGL 3	26 ,( )	20 ,( )	12 ,( )	9.0 ,( )

AEGL 1 Motion: McClanahan **Second:** Bob Benson

AEGL 2 Motion: Bill Bress **Second:** R. Niemeier

AEGL 3 Motion: G. Rodgers **Second:** R. Snyder

Approved by Chair: [signature] **DFO:** Paul S. Tobin **Date:** 9/16/98

$CH_2=CH(CH_3)C\equiv N$
126-98-7

Date of NAC/AEGL Meeting: ept. 14-16, 1998 **Chemical:** METHACRYLONITRILE

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

NAC Member	AEGL 1	AEGL 2	AEGL3
Loren Koller	A	A	A
Glenn Leach	Absent	Absent	Absent
Mark A. McClanahan	Y	Y	Y
John S. Morawetz	Y	Y	P
Deirdre L. Murphy	Absent	Absent	Absent
Richard W. Niemeier	Y	Y	Y
William Pepelko	Y	Y	Y
Zarena Post	Absent	Absent	Absent
George Rodgers	Y	Y	N
George Rusch, Chair	Y	Y	Y
Bob Snyder	A	A	Y
Thomas J. Sobotka	Absent	Absent	Absent
Kenneth Still	A	A	A
Patricia Ann Talcott	Absent	Absent	Absent
Richard Thomas	Absent	Absent	Absent
Thomas Tuccinardi/ Doan Hansen	Y N	Y A	P A
TALLY	17/17	14/~~16~~ 17	14/~~18~~

PPM, (mg/m³)	30 Min	60 Min	4 Hr	8Hr
AEGL 1	NA ,( )	NA ,( )	NA ,( )	NA ,( )
AEGL 2	1.5 ,( )	1.1 ,( )	0.67 ,( )	0.50 ,( )
AEGL 3	~~4.0~~ 4.5 ,( )	~~3.0~~ 3.4 ,( )	~~1.9~~ 2.0 ,( )	~~1.5~~ 1.5 ,( )

AEGL 1 Motion: Rodgers **Second:** McClanahan

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

AEGL 3 Motion: B. Benson **Second:** M. McClanahan

Approved by Chair: [signature] **DFO:** Paul S. Tobin **Date:** 9/16/98