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National Advisory Committee (NAC)
for Acute Exposure Guideline Levels (AEGL) for Hazardous Substances
Final Meeting 3 Highlights
Green Room, 3rd Floor, Ariel Rios Building
1200 Pennsylvania Avenue, NW
Washington, D.C.
September 17-19, 1996

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INTRODUCTION

Dr. George Rusch, Chair, opened the meeting and welcomed the new members and participants including observers from the private sector to NAC AEGL meeting 3. The highlights of the meeting are noted below, and the meeting agenda (Attachment 1) and attendee list (Attachment 2) are attached.

The highlights of meeting 2 (August 5-7, 1996) were reviewed and approved with a minor change (Appendix A).

Dr. Roger Garrett welcomed the committee members and provided a brief overview of the NAC/AEGL program.

DISCUSSION OF TECHNICAL ISSUES

Single Exposure and Tumorigenic Responses
Dr. Edward Calabrese (University of Massachusetts School of Public Health) gave a presentation on a database that he has been compiling regarding increased tumorigenic responses following single exposures to chemicals. He noted that there are data showing tumorigenic responses to single low-dose exposures (e.g., 1/50, 1/75, 1/100 of the LD_{50}) (see Attachment 3). Several generic topics were mentioned, including the $B6C3F_1$ mouse issue and the importance of dose-rate vs cumulative dose and the timing of this with an endogenous promotion process. The database (developed in FoxPro) is a multiple field query format for single-exposure protocol data. Dr. Calabrese noted that: (1) only peer-reviewed data are used, (2) approximately 80 to 100 data sets per month are currently being entered, (3) only genuine single-exposure protocol (with no confounders) are selected, and (4) weight-of-evidence judgements are evaluated. He further noted that other factors are also critical (e.g., concurrent controls, descriptive vs hypothesis-testing statistics, and dosing protocol) in evaluating the data sets. In response to Committee questions, Dr. Calabrese noted that chemicals that were positive for single exposure tumor response were also positive in genotoxicity assays, and that the database includes therapeutic agents and not just chemicals of environmental importance. Dr. Calabrese emphasized that only a small percentage of the entries were for the inhalation exposure route, but that route-specific queries can be made in the database. He claimed not to have formulated any risk assessment strategies based on his data base. Dr. Calabrese offered the Committee access to the database.

Sensitive and Susceptible Subgroups
Dr. Jonathan Borak provided an overview (Attachment 4) on sensitive populations, including definitions of sensitivity and susceptibility for various groups (NRC Guidelines, AEGL definitions, NRC Science and Judgement, Commission on Risk Assessment). He also provided examples of such susceptible subgroups as infants, elderly, and individuals with coronary heart disease, liver disease, or asthma (Attachment 4). In summary Dr. Borak provided a list of seven recommendations upon which the Committee could base its considerations. Regarding the susceptibility of asthmatics, Dr. Borak noted that responses would likely be chemical specific and difficult to quantify. Additionally, he noted that exposure to levels of substances (e.g., nickel) that may sensitize should be within the purview of AEGLs but that hypersensitive responses (e.g., anaphylaxis) should not. There was a discussion followed by the Committee with agreement to establish a subcommittee to address the issue related to the susceptible and hypersusceptible populations. The subcommitte will include Drs. Borak (Chair), Koller, and Rodgers. A preliminary report will be presented in the December meeting.

AEGL Definitions
The AEGL definitions were reworded to be more "user friendly". Several issues arose including: (1) inclusion of a generic statement in the technical support documents preceding the definitions noting that AEGLs are derived for 30 min, 1 h, 4 h, and 8 h; (2) the relevance of "impaired escape", especially for 4- and 8-h time frames; (3) concern regarding the use of "susceptible"; (4) "overlap" of AEGL values (e.g., for HF, a 30-min AEGL-2 effect might be present at the 4-h time period for AEGL-3); and, (5) it was suggested that quotes might be placed around susceptible and hypersusceptible to emphasize that these terms are concepts defined in context. The final version of the AEGL definitions (Appendix B) was approved.

Time Frame for NAC/AEGL Processes and Products
A time line for document review was distributed by Dr. Rusch and reviewed by the Committee. Comments focused on the need for adequate review time. There were also comments regarding the need for adequate time to prepare the draft technical support documents. A need for a master list of chemicals was noted for inclusion in the *Federal Register*. It was also noted that priority chemicals (determined by storage or use) could be likely candidates for emergency-response potential (Attachment 5).

Uncertainty Factors (UFs)
Some considerations regarding uncertainty factor application were distributed by Dr. Rusch to the Committee. In the ensuing discussions, it was noted that the Committee should, as chartered, follow NAS guidelines. Several issues identified include: (1) what are the key judgments that justify the use of a UF less than the default of 10; (2) the Committee should track its use of UFs in a "living" document; and, (3) a subcommittee was formed to address UF issues (Attachment 6) and report the progress in the December meeting. The subcommittee includes Drs. Thomas (Chair), Alexeeff, Belluck, Falke, and Gephart.

Acute Inhalation Toxicity Study Protocol
Dr. Rusch requested comments about the distributed memo (Attachment 7) regarding the need for study protocol development for acute inhalation toxicity studies to fill data gaps identified by the NAC/AEGL.

REVIEW OF AEGL PRIORITY CHEMICALS

Hydrogen Fluoride, CAS Reg. No. 7664-39-3

Chemical Manager: Mr. Larry Gephart, Exxon Biomedical Sciences
Author: Dr. Sylvia Talmage, ORNL
Discussion focused on the need for a 10-min AEGL for HF. It was noted that this time frame (especially for compressed gases) would be appropriate for this chemical, especially for emergency planning purposes. Petroleum Environmental Research Forum will have an opportunity to comment when the proposed HF values are published in the *Federal Register*. It was the consensus of the Committee that a 10-min AEGL be derived for HF at the next meeting.

Ammonia, CAS Reg. No. 7664-41-7

Chemical Manager: Mr. Larry Gephart, Exxon Biomedical Sciences
Author: Dr. Kowetha Davidson, ORNL
Mr. Larry Gephart provided a summary of the revised ammonia AEGL document. Comments were received from International Institute of Ammonia Refrigeration indicating that they had not provided a response to the Committee because of time constraints and recent litigation. Dr. Robert Michaels of RamTrac indicated that he had requested that the ammonia industry submit data to the Committee; he also summarized alternate views regarding AEGLs for ammonia (Attachment 8). Some discussion focused on data-set selection for the ammonia AEGL. Ammonia was deferred to the December meeting. Mr. Gephart provided additional information and interpretations (Attachment 9) in response to Dr. Michaels.

Cyanogen Chloride (CK), CAS Reg. No. 506-77-4

Chemical Manager: Dr. Mark McClanahan, CDC
Author: Dr. Carol Forsyth, ORNL
Dr. Forsyth noted the acquisition of an additional reference as well as the difficulty in obtaining DoD data but noted cursory examination of some DoD data suggested that it would be of limited and questionable use for AEGL derivation. Dr. Forsyth explained that the AEGL-1 values were based on a 10-min LOAEL of 1 ppm and that 0.33 ppm be used for all time points. The proposed AEGL-2 values were based on tolerable irritation at 2 ppm and 0.66 ppm was initially proposed for all time points. No data were available for deriving AEGL-3 values (Attachment 10). Initially, concern was expressed that the conversion of CK to cyanide may require some type of pharmacokinetic analysis. However, the critical effect (pulmonary edema-induced lethality) did not support this concern. Furthermore, it was noted that additional data were not available. The Committee unanimously agreed that no AEGL-3 values be derived for CK until new information was available. For AEGL-1 and AEGL-2, the Committee decided (with one opposing vote) that consideration of these values be deferred until additional data become available. Actions recommended for cyanogen chloride were: (1) determine rationale for cyanogen chloride inclusion as an AEGL priority chemical; (2) attempt to retrieve DoD data; and (3) attempt to develop required data (via NAC/AEGL program or via manufacturers/industry). Derivation of AEGLs for cyanogen chloride was tabled indefinitely until additional data become available (Appendix C).

Nitric Acid, CAS Reg. No. 7697-37-2

Chemical Manager: Dr. Loren Koller, Orgeon State University
Author: Dr. Carol Forsyth, ORNL
Dr. Forsyth provided clarifications regarding the allergy and asthma studies in the technical support document and their categorization as hypersuceptible or susceptible. The limited human exposure data were also briefly reviewed (Attachment 11). For AEGL-1, it was noted that 0.25 ppm NO_2 was a NOAEL for exercising asthmatics. Discussion ensued regarding the possible relevance of NO_2 in deriving AEGLs for nitric acid. It was unanimously decided to accept 0.5 ppm as the AEGL-1 for nitric acid for all time points. Dr. Alexeeff noted that additional human exposure data were available in which a 1-h exposure of two individuals to 12 ppm resulted in notable irritation. Based on these data, NAC members suggested that the AEGL-2 values be 5, 4, 2.7, and 2.2 ppm for the 30-min, 1-h, 4-h, and 8-h periods, respectively (original draft document values were 30, 25, 17, and 14 ppm for these time frames). It was proposed that AEGL-2 values of 5, 4, 3, and 2 ppm be considered. Although the values were based on old data from only two exposed subjects, the data are consistent with more recent anecdotal, unpublished information, and the European MAK for nitric acid is based on these data. The Committee voted unanimously to adopt the proposed values but recommended that the data for NO_2 be evaluated to determine, in the December meeting, if it supports the AEGL-2 values for nitric acid. For AEGL-3, Dr. Koller suggested using the values based on red fuming nitric acid (15, 13, 8, and 7 ppm for 30-min, l-h, 4-h , and 8-h), respectively. These values were accepted by the Committee (Appendix D).

SUMMARY OF PROPOSED AEGL VALUES FOR NITRIC ACID					
Classification	30-min	1-hour	4-hour	8-hour	Endpoint
AEGL-1	0.5 ppm 1.3 mg/m^3	0.5 ppm 1.3 mg/m^3	0.5 ppm 1.3 mg/m^3	0.5 ppm 1.3 mg/m^3	Minor irritation in humans
AEGL-2	5 ppm 12.9 mg/m^3	4 ppm 10.3 mg/m^3	3 ppm 7.7 mg/m^3	2 ppm 5.2 mg/m^3	Notable irritation, respiratory effects in humans
AEGL-3	15 ppm 38.7 mg/m^3	13 ppm 33.5 mg/m^3	8 ppm 20.6 mg/m^3	7 ppm 18.1 mg/m^3	Approximate LD_0 in rats

Hydrogen Cyanide, CAS Reg. No. 74-90-8

Chemical Manager: Dr. George Rodgers, AAPCC
Author: Dr. James Norris, ORNL
A data overview was presented by Dr. Rodgers (Attachment 12). It was noted that the steep dose-response curve may impact the validity of defining AEGLs for all three levels of concern. Dr. Norris presented specifics regarding data and derivation of AEGLs for hydrogen cyanide. He noted that for AEGL-3, data from a study using monkeys was used to validate a probit analysis equation originally derived by ten Berge et al. (1986) for scaling HCN exposures (Attachment 13). Dr. Neill Krivanek (DuPont/Haskell Laboratory) noted that the probit equation may not be valid beyond 1-h durations and that the AEGL-3 should be re-evaluated (Attachment 14). He agreed that an AEGL-1 may not be appropriate and that data are available for deriving an AEGL-2. It was Committee consensus that insufficient data were available for deriving AEGL-1 values. For AEGL-

3, Dr. Krivanek recommended 30, 25, 20, and 10 ppm for the 30-min, l-h, 4-h, and 8-h time points. He noted that the AEGL-2 may be based upon the i.v. study data of Wexler et al. (1947). Dr. Alexeeff stated that the Purser study noted EKG alterations at 60 ppm and that the above values should be reduced by a UF of 3. Dr. Barbee suggested that the Wexler data could be used and proposed AEGL-3 values of 20, 10, 6, and 3 ppm, respectively. Discussions ensued regarding intra- and interspecific variability in rhodanese activity and the robustness of the data sets. A polling of the Committee indicated that there was no consensus on the above values. Mr. Gephart felt that the original ORNL values were defensible because they were based on human experience but that the 4- and 8-h values should be similar because occupational exposures to 10 ppm have been shown to be nonlethal. Based on the Wexler i.v. data and several assumptions, Dr. Barbee proposed AEGL-3 values of 20, 14, 7, and 5 ppm for the 30-min, l-h, 4-h, and 8-hr time points. These proposed values were accepted by a majority vote. There was Committee consensus to attempt to derive AEGL-2 values for HCN. It was suggested that the AEGL-3 values be used as a reference point for this derivation. Dr. Alexeeff suggested that the original ORNL values adjusted by a UF of 3 be used (i.e., 9, 6, 3, and 2 ppm). Dr. Rodgers, in turn, suggested that the Wexler i.v. data adjusted by a UF of 3 be used for the 30-min AEGL-3 (i.e., 7 ppm). Dr. Alexeeff suggested that the AEGL-3 values, reduced three-fold to adjust for nonlethal effect, be used in conjunction with Dr. Rodgers proposal of 7 ppm for 30-min (i.e., 7, 5, 2, and 2 ppm, respectively). Dr. Krivanek cautioned that AEGLs should not be equivalent to normal CN^- blood levels. Dr. Borak suggested that for this AEGL determination, the Committee should err on the less conservative side because HCN releases will not be pressurized releases and that safety planning will have built-in safety factors. A divisor of 3 could then be used to reduce the AEGL-3 values to AEGL-2 values. A vote on the 7, 5, 2, and 2 ppm AEGL-2 values indicated majority disapproval. Dr. Thomas proposed that the AEGL-3 values divided by 2 be used as AEGL-2 (i.e., 10, 7, 4, and 3 ppm). The Committee accepted the proposed values (with 3 negative votes) (Appendix E).

SUMMARY OF PROPOSED AEGL VALUES FOR HYDROGEN CYANIDE

Classification	30-min	1-hour	4-hour	8-hour	Endpoint
AEGL-1	-	-	-	-	Not verifiable, insufficient data
AEGL-2*	10 ppm 11 mg/m³	7 ppm 8 mg/m³	4 ppm 4 mg/m³	3 ppm 3 mg/m³	Cardiac effects in humans (adjusted from AEGL-3)
AEGL-3*	20 ppm 22 mg/m³	14 ppm 15 mg/m³	7 ppm 8 mg/m³	5 ppm 6 mg/m³	Cardiac effects in humans

*Regarding the AEGL values for hydrogen cyanide, Dr. Steve Barbee noted that the Wexler et al. (1974) data should have been used to derive the AEGL-2 values instead of the AEGL-3 values. This change will not affect the selected concentrations and will be reflected in the issuance of the final draft report to be circulated for public comment.

1,2-Dichloroethylene, CAS Reg. No. 540-59-0 (mixture); 156-59-2 (*cis*), 156-60-5 (*trans*)

Chemical Manager: Dr. Ernest Falke, U.S. EPA
Author: Dr. Cheryl Bast, ORNL
Dr. Falke presented an overview of the title chemical (Attachment 15), and Dr. Bast presented the AEGL values and their respective derivation rationale (Attachment 16). The values as presented were accepted by the Committee with two dissenting votes (one regarding inadequate accounting of uncertainty and the other indicating that improper linking of UFs resulted in overly conservative values) (Appendix F).

SUMMARY OF PROPOSED AEGL VALUES FOR 1,2 DICHLOROETHYLENE

Classification	30-min	1-hour	4-hour	8-hour	Endpoint
AEGL-1	19 ppm 75 mg/m³	13 ppm 53 mg/m³	7 ppm 26 mg/m³	5 ppm 19 mg/m³	No effect level - human exposure
AEGL-2	56 ppm 224 mg/m³	40 ppm 160 mg/m³	20 ppm 80 mg/m³	14 ppm 56 mg/m³	Slight dizziness - human
AEGL-3	200 ppm 800 mg/m³	141 ppm 564 mg/m³	71 ppm 284 mg/m³	50 ppm 200 mg/m³	Fibrous swelling and hyperemia of cardiac muscle with poorly maintained striation - rat

Methyl Mercaptan, CAS Reg. No. 7783-06-4

Chemical Manager: Dr. Doan Hansen, Brookhaven National Laboratory
Author: Dr. James Norris, ORNL
In a revisit of methyl mercaptan, Dr. Norris provided a recap of the status of AEGL-3 values from the August 5-7, 1996, meeting (Attachment 17). The AEGL-2 values were based on shallow breathing/hypoactivity in mice. Alternatively, the AEGL-2 could also be based upon shallow breathing only. The Committee decided that the shallow-breathing/hypoactivity data should drive the AEGL-2. Dr. Hansen proposed that 0.5 ppm be considered for all AEGL-1 time points

(Attachment 18). The proposal was accepted by the Committee. The AEGL-2 and AEGL-3 proposed values were accepted in the previous (August 5-7, 1996) meeting. However, Mr. Gephart noted the AEGL-2 values may be overly conservative because there were no effects in the Tansy reports in rodents subjected to repeated exposures to 50 ppm. Following some discussion, it was suggested to change the AEGL-2 values from 3, 2, 1, and 1 (for 30-min, 1-h, 4-h, and 8-h, respectively) to 7, 5, 3, and 2 ppm. The Committee agreed to accept these values (Appendix G).

SUMMARY OF PROPOSED AEGL VALUES FOR METHYL MERCAPTAN					
Classification	30-min	1-hour	4-hour	8-hour	Endpoint
AEGL-1	0.5 ppm 1 mg/m^3	0.5 ppm 1 mg/m^3	0.5 ppm 1 mg/m^3	0.5 ppm 1 mg/m^3	Based relative to TLV
AEGL-2	8 ppm 16 mg/m^3	6 ppm 12 mg/m^3	3 ppm 6 mg/m^3	2 ppm 4 mg/m^3	Shallow breathing and hypoactivity in mice (Elf Atochem, 1996)
AEGL-3	34 ppm 67 mg/m^3	25 ppm 49 mg/m^3	13 ppm 26 mg/m^3	10 ppm 20 mg/m^3	Highest non-lethality in rats (Tansy et al., 1981) (n=2.2)

Arsine, CAS Reg. No. 7784-42-1

Chemical Manager: Dr. Richard Thomas, I.C.E.H.
Author: Dr. Robert Young, ORNL
Dr. Thomas provided an overview of salient information regarding arsine and the effects of acute exposures to this chemical (Attachment 19). Dr. Young provided a summary of AEGL values and their respective key studies and effects (Attachment 20). Because of the extreme toxicity of arsine and the fact that toxic effects to arsine exposure have been known to occur in the absence of odor, Dr. Thomas proposed that all AEGL-1 values be 0.1 ppm. The proposal was accepted by the Committee. Dr. Young noted that AEGLs derived using human equivalent dosimetric adjustments gave values that were considerably higher than those derived without dosimetric adjustment. It was the consensus of the Committee that such an adjustment was not warranted. Because of the extremely steep exposure-response curve for arsine, it was suggested that the AEGL-3 values be further reduced and based on a concentration that was not lethal to rats. This resulted in AEGL values somewhat lower than those proposed in the draft technical support document; 0.7, 0.5, 0.25, 0.18 ppm vs 2, 1, 0.7, and 0.5 ppm for the 30-min 1-h, 4-h, and 8-h periods, respectively. The adjusted values were approved by the Committee. AEGL-2 values were similarly altered based on exposures that did not produce potentially serious effects in rats. The adjusted and approved values were 0.24, 0.17, 0.08, and 0.06 ppm vs 2, 1, 0.7, and 0.5 ppm for the 30-min, 1-h, 4-h, and 8-h time exposures, respectively (Appendix H).

SUMMARY OF PROPOSED AEGL VALUES FOR ARSINE					
Classification	30-min	1-hour	4-hour	8-hour	Endpoint
AEGL-1	0.1 ppm 0.3 mg/m^3	0.1 ppm 0.3 mg/m^3	0.1 ppm 0.3 mg/m^3	0.1 ppm 0.3 mg/m^3	No effect level for hematological alterations in mice (Blair et al., 1990)
AEGL-2	0.24 ppm 0.8 mg/m^3	0.17 ppm 0.5 mg/m^3	0.1 ppm 0.3 mg/m^3	0.1 ppm 0.3 mg/m^3	No effect level for physiologically relevant hematological changes in mice (Peterson and Bhattacharrya, 1985)
AEGL-3	0.7 ppm 2.2 mg/m^3	0.5 ppm 1.6 mg/m^3	0.25 ppm 0.8 mg/m^3	0.18 ppm 0.6 mg/m^3	No effect level for lethality in mice (Peterson and Bhattacharrya, 1985)

Dimethyldichlorosilane, CAS Reg. No. 75-78-5

Chemical Manager: Dr. Ernest Falke, U.S. EPA
Author: Dr. Cheryl Bast, ORNL
Dr. Falke presented an overview of the title chemical (Attachment 21), and Dr. Bast followed with a more detailed account of AEGL derivations and key data (Attachment 22). The use of the mouse RD_{50} was considered to be applicable for derivation of the AEGL-1 for dimethyldichlorosilane. The AEGL-1 proposed values based on 0.01 x RD_{50} (1 ppm, 0.75 ppm, 0.4 ppm, and 0.3 ppm for 30-min, 1-h, 4-h, and 8-h periods, respectively) were unanimously accepted by the Committee. Dr. Falke proposed that the AEGL-2 values (0.1 x RD_{50}) as derived in the draft technical support document be accepted. The Committee accepted the values following rounding of the values to 10, 7, 4, and 3 ppm. The Committee agreed that 1/3 of the rat LC_{50} would be an acceptable estimate of the rat lethality threshold for this chemical. Dr. Garrett mentioned that the NAC guidelines indicate that human data should be preferentially considered. AEGL-3 values of 37, 26, 13, and 9 ppm were proposed for 30-min, 1-h, 4-h, and 8-h periods, respectively. The proposed values were accepted unanimously (Appendix I).

SUMMARY OF PROPOSED AEGL VALUES FOR DIMETHYLDICHLOROSILANE					
Classification	30-min	1-hour	4-hour	8-hour	Endpoint
AEGL-1	1 ppm 6 mg/m^3	0.75 ppm 4 mg/m^3	0.4 ppm 2 mg/m^3	0.3 ppm 1 mg/m^3	0.01 RD_{50} - mouse
AEGL-2	10 ppm 55 mg/m^3	7 ppm 40 mg/m^3	4 ppm 19 mg/m^3	3 ppm 14 mg/m^3	0.1 RD_{50} - mouse
AEGL-3	37 ppm 195 mg/m^3	26 ppm 138 mg/m^3	13 ppm 69 mg/m^3	9 ppm 49 mg/m^3	0.33 x LC_{50} - rat

ADMINISTRATIVE MATTERS

Dr. Belluck distributed suggestions regarding format adjustments for data summarization in the technical support documents (Attachment 23). It was noted that the next list of priority chemicals will be made available within a few weeks. The high quality of the draft technical support documents and the need for adequate preparation time were noted.

Tentative schedules for the next three meetings were noted: December 16-18, 1996; March 11-13, 1997, or March 24-26, 1997; and June 9-11, 1997.

December Meeting
Agenda items include:
1. Report on sensitive-population issues
2. Uncertainty/safety factor report
3. Report on acute inhalation toxicity study protocol
4. 10-min AEGL for HF
5. Finalization of ammonia document
6. Discussions regarding:
    -Dr. Belluck's document format suggestions
    -Summary of NO_2 research
    -Dr. Falke's "living" document - compilation of rationale for AEGL values
7. New chemicals for future meetings (Attachment 24)

Meeting minutes were prepared by Drs. Robert Young and Po-Yung Lu, ORNL.

Table of Contents of Attachments

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

Table of Contents of Appendices

National Advisory Committee for AEGLs for Hazardous Substances

September 17-19, 1996

Agenda

SEPTEMBER 17, 1996

10-10:15	Introduction and Approval of Aug 5-7 Minutes
10:15-11:00	Carcinogenic Compounds Presentation (Ed Calabrese)
11-11:30	Carcinogenic Compounds Discussion
11:30-12:00	Sensitive subpopulations (J. Borak)
12:00-1:00	Lunch
1:00-2:30	Uncertainty factors (G. Rusch)
2:30-3:15	Hydrogen fluoride
3:15-3:30	Break
3:30-4:00	Ammonia
4:00-5:00	Cyanogen chloride

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8:45-9:45	Methyl mercaptan
9:45-10:30	Hydrogen cyanide
10:30-10:45	Break
10:45-12:00	Hydrogen cyanide
12:00-1:00	Lunch
1:00-3:00	Nitric acid
3:00-3:15	Break
3:15-4:45	1,2-Dichloroethylene

SEPTEMBER 19, 1996

8:30-9:00	Administrative Matters
9:00-10:30	Arsine
10:30-12:00	Dimethyldichlorosilane

NAC, AEGL #3   9/17-19/96

Name	Affilation
EUGENE NGAI	SOLKATRONIC CHEMICAL
Kathleen Bailor	IIAR
Leo Bernstein	CTRAPS
Mead Strilaud	PMP
Robert Michaels	RAM TRAC Corp (Schenectady, NY)
William J. Brock	DuPont
Sally L. Benjamin	Risk Writers Ltd.
Nancy Nickel	Reporter- Pesticide & Toxic Chemical News
Louis Conjo	Versar, Inc.
BARRY HOOBERMAN	ENVIRON CORP.
Po-Yung Lu	ORNL
John P Hinz	U.S. Air Force Brooks AFB
Loren D. Koller	Oregon State University
Bill Bress	ASTHO
George Alexeeff	Cal/EPA
George Rodgers	AAPCC
Larry Gephart	Exxon Biomedical
JONATHAN BORAK	ACOEM
Richard Thomas	ICEH
Ernest V. Falke	US Environmental Protection Agency
ROGER GARRETT	USEPA
RICK NIEMEIER	NIOSH
George Rusch	Allied Signal
Paul S. Tobin	EPA
Kyle Blackman	FEMA
DAVID BELLUCK	MPCA
STEVEN BARBEE	OLIN CORP
Lynn Beasley	USEPA - Superfund
MARK A McCLANAHAN	CDC/NCEH

GEORGE CUSHMAC   USDOT/RSPA
   JIM HOLLER   ATSDR
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Doan Hansen   USDOE / BNL

Selection Criteria:
    Study: HISTOLOGY=Yes and GROUPS>7 and INT_SACR=Yes **ATTACHMENT 3**
==
Citation:01021   1
    Authors:Driver, H.E., White, I.N.H., and Butler, W.H.
    Title:Dose-Response Relationship in Chemical Carcinogenesis: Renal
        Mesenchymal Tumours Induced in the Rat by Single Dose
        Dimethylnitrosamine
    Journal:British Journal of Experimental Pathology 68:133-143
          1987
    ---Chemical Information For Study 0102101   CAS No.:62-75-9
    Chemical:DIMETHYLNITROSAMINE
    Class:NITROSAMINE
    -----Study No.:0102101
    Outcome: POS   Single Exp.:Y   Dose Frac: N   Interim Sacrifice: Y
    Duration: 104   Analysis:D   Histology:Y   Sex:M
    Groups: 9   Animal: FISCHER 344 RATS
    Ctl Grp:Concurrent Veh.   Pos. Ctl: N   Ctl Resp Ratio:0/50
    Exp Pd: WEANLING   Exp Rte: IP   TD50: NC
    ------------------- Study Comments-----------------------
    ><TREATMENT LEVELS:After weaning the rats were placed on a diet of
    pure sucrose for 3 days, then administered 2, 5, 10, 15, 20, 25, 30,
    40, or 50 mg/kg DMN in saline and placed on pelleted MRC Diet 41B.

    ><INTERIM SACRIFICE:

    ><TISSUES:Mainly the kidney, but the livers, lungs, and any other
    organ with visible abnormalities were also examined.

    ><PATHOLOGY:All rats were sacrificed using CO2. Animals were
    autopsied and organs were prepared for routine histology. Kidneys
    were also stained with alcian blue with a neutral red counterstain.
    Others were stained with 9-aminoacridine followed by propidium iodine
    and examined under fluorescence according to the technique of Steven
    et al (1985, Eur. J. Biochem 130:335-339) to identify cells expressing
    guanidinobenzoatase.

    ><DOSE-RESPONSE RELATIONSHIP:None of 50 controls developed kidney
    tumors. None of 38 treated with 2 mg/kg, 1 of 80 (1%) treated with 5
    mg/kg, 2 of 68 (3%) treated with 10 mg/kg, 8 of 25 (32%) treated with
    15 mg/kg, 7 of 8 (87%) treated with 20 mg/kg, all 16 treated with 25
    mg/kg, all 10 treated with 30 mg/kg, all 14 treated with 40 mg/kg, and
    all 12 treated with 50 mg/kg developed kidney tumors in either one or
    both kidneys.

    ><STATISTICAL ANALYSIS:

    ><COMMENTS:Renal mesenchymal tumors never occur spontaneously in this
    rat. The dose response curve is sigmoidal in nature. In this article
    the authors also examined the time course of tumor development by
    sacrificing animals treated with 40 mg/kg DMN at 1, 3, 6, 8, 10, 12,
    or 16 weeks, but since the authors provided insufficient information
    to this study it is not reported here. The authors also examined the
    dose response of foci by sacrificing animals at 3 weeks. The dose
    response for foci is linear.

    ----------Group No: 0102101001
    Number of subjects: . 38   Transgenic? N
    Dose Administration: 2.000 mg/kg
    Respiratory: Liver: Kidney:- Pancreas: Skin: Mammary: Colon:

Nervous: Reproductive: Stomach: Blood: Other: Total:

Response Ratio:0/38   Percent LD50: Unknown

----------Group No: 0102101002

Number of subjects: 80   Transgenic? N

Dose Administration: 5.000 mg/kg

Respiratory: Liver: Kidney:+ Pancreas: Skin: Mammary: Colon:

Nervous: Reproductive: Stomach: Blood: Other: Total:

Response Ratio:1/80   Percent LD50: Unknown

      --------------Tumor Id:0102101002

    Organ: KIDNEY   Response Ratio:1/80

    Tumor type:mesenchymal tumor

----------Group No: 0102101003

Number of subjects: 68   Transgenic? N

Dose Administration: 10.000 mg/kg

Respiratory: Liver: Kidney:+ Pancreas: Skin: Mammary: Colon:

Nervous: Reproductive: Stomach: Blood: Other: Total:

Response Ratio:2/68   Percent LD50: Unknown

      --------------Tumor Id:0102101003

    Organ: KIDNEY   Response Ratio:2/68

    Tumor type:mesenchymal tumor

----------Group No: 0102101004

Number of subjects: 25   Transgenic? N

Dose Administration: 15.000 mg/kg

Respiratory: Liver: Kidney:+ Pancreas: Skin: Mammary: Colon:

Nervous: Reproductive: Stomach: Blood: Other: Total:

Response Ratio:8/25   Percent LD50: Unknown

      --------------Tumor Id:0102101004

    Organ: KIDNEY   Response Ratio:8/25

    Tumor type:mesenchymal tumor

      --------------Tumor Id:0102101004

    Organ: KIDNEY   Response Ratio:3/25

    Tumor type:epithelial tumor

----------Group No: 0102101005

Number of subjects: 8   Transgenic? N

Dose Administration: 20.000 mg/kg

Respiratory: Liver: Kidney:+ Pancreas: Skin: Mammary: Colon:

Nervous: Reproductive: Stomach: Blood: Other: Total:

Response Ratio:7/8   Percent LD50: Unknown

      --------------Tumor Id:0102101005

    Organ: KIDNEY   Response Ratio:7/8

    Tumor type:mesenchymal tumor

      --------------Tumor Id:0102101005

    Organ: KIDNEY   Response Ratio:4/8

    Tumor type:epithelial tumor

----------Group No: 0102101006

Number of subjects: 16   Transgenic? N

Dose Administration: 25.000 mg/kg

Respiratory: Liver: Kidney:+ Pancreas: Skin: Mammary: Colon:

Nervous: Reproductive: Stomach: Blood: Other: Total:

Response Ratio:16/16   Percent LD50: Unknown

      --------------Tumor Id:0102101006

    Organ: KIDNEY   Response Ratio:16/16

    Tumor type:mesenchymal tumor

      --------------Tumor Id:0102101006

    Organ: KIDNEY   Response Ratio:2/16

    Tumor type:epithelial tumor

----------Group No: 0102101007

Number of subjects: 10   Transgenic? N

Dose Administration: 30.000 mg/kg

Respiratory: Liver: Kidney:+ Pancreas: Skin: Mammary: Colon:

Nervous: Reproductive: Stomach: Blood: Other: Total:

Response Ratio:10/10   Percent LD50: Unknown

      --------------Tumor Id:0102101007

    Organ: KIDNEY   Response Ratio:10/10

    Tumor type:mesenchymal tumor

      --------------Tumor Id:0102101007

```
                    Tumor type:epithelial tumor
          ----------Group No: 0102101008
Number of subjects:      14      Transgenic? N
Dose Administration:    40.000 mg/kg
Respiratory:    Liver:      Kidney:+ Pancreas:    Skin:    Mammary:   Colon:
Nervous:       Reproductive:    Stomach:        Blood:    Other:     Total:
Response Ratio:14/14                    Percent LD50: Unknown
         ---------------Tumor Id:0102101008
      Organ: KIDNEY                      Response Ratio:14/14
      Tumor type:mesenchymal tumor
         ---------------Tumor Id:0102101008
      Organ: KIDNEY                      Response Ratio:4/14
      Tumor type:epithelial tumor
          ----------Group No: 0102101009
Number of subjects:      12      Transgenic? N
Dose Administration:    50.000 mg/kg
Respiratory:    Liver:      Kidney:+ Pancreas:    Skin:    Mammary: .Colon:
Nervous:       Reproductive:    Stomach:        Blood:    Other:     Total:
Response Ratio:12/12                    Percent LD50: Unknown
         ---------------Tumor Id:0102101009
      Organ: KIDNEY                      Response Ratio:12/12
      Tumor type:mesenchymal tumor
         ---------------Tumor Id:0102101009
      Organ: KIDNEY                      Response Ratio:3/12
      Tumor type:epithelial tumor
```

Body Weight: Animals will, at a minimum, be weighed on Days -1, 0, 1, 2, 4, 7, 10 and 14 where Day 0 is designated as the day of exposure.

Food and Water Consumption: Will be measured at weekly intervals during the 14-day post-exposure observation period.

Organ Weights: Organ weights for at least the lungs, liver, kidney, brain and gonads will be measured on animals surviving to the fourteen day sacrifice. .

Histopathological Examination: Will not normally be conducted on the animals in this study. However, if the nature of the test substance is such that a specific mode of toxic action is probable, histopathological examination of the organs potentially involved should be considered.

Pulmonary Function: When the compound being evaluated is an irritant, tests will be conducted on 2 additional animals per sex per level from the highest two non-lethal levels from each of two time intervals. Measurements will be conducted 24 hours post-exposure. Evaluations for pulmonary resistance, functional residual capacity, quasistatic pressure-volume curves, maximal forced exhalations, and single breath carbon monoxide diffusing capacity may be included.

Complete Blood Counts: Would not normally be included, but should be considered for test substances which may effect the bone marrow or blood. These measurements would normally be conducted at the end of the 14-day observation period and this would not identify subtle, reversible effects. If conducted, these measurements should be run on all animals.

Clinical Chemistry: Measurements again would not normally be included, but should be considered for test materials that can have an effect on an organ system which would result in a change in one or more serum chemistry parameters. These measurements would normally be conducted at the end of the 14-day observation period and thus would not identify subtle reversible effects. - If conducted, these measurements should be run on all animals.

Other Tests: Such other tests as may help in understanding the toxic or pharmacokinetic action of the test sample should be considered.

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"DEFINITIONS": SENSITIVITY and SUSCEPTIBILITY

AEGL Definitions: "... including susceptible but excluding hypersusceptible individuals ..."

NRC Guidelines: "Although CEELs are designed to protect "sensitive" individuals, some hypersusceptible individuals might not be protected ..."

"Criteria recommended by EPA should be considered when examining studies to identify sensitive or hypersusceptible individuals"

(see EPA: Interim Methods for Development of Inhalation Reference Concentrations, 1990)

"DEFINITIONS": SENSITIVITY and SUSCEPTIBILITY

NRC Science and Judgment:

"... it appears that some of the individual determinants of susceptibility are distributed bimodally ... other determinants seem to be distributed more or less continuously and unimodally ..."

"... in terms of the bimodal type of variation, with a normal majority and a hypersusceptible minority ... that model might be appropriate for noncarcinogenic effects (e.g., normal vs asthmatic response to SO_2), but it ignores a major class of variability vis-a-vis cancer ... "

(NRC: Science and Judgment in Risk Assessment, 1994)

"DEFINITIONS": SENSITIVITY and SUSCEPTIBILITY

Commission on Risk Assessment:

"Genetic, nutritional, metabolic and other differences make some segments of a population more <u>susceptible</u> than others ... <u>Susceptibility</u> ... depends on the <u>sensitivity</u> of a person's response to different doses. <u>Susceptibility</u> is influenced by many factors ..."

> age and sex
> genetic variation in metabolism ...
> genetic variation in response at site of action ...
> ethnic origin and ethnic practices
> socioeconomic status
> geographic location
> lifestyle factors (e.g., tobacco, EtOH, diet, exercise) ...

"Dose-response relationships are chemical-specific and depend on modes of action; people are not <u>hypersusceptible</u> to all kinds of exposures".
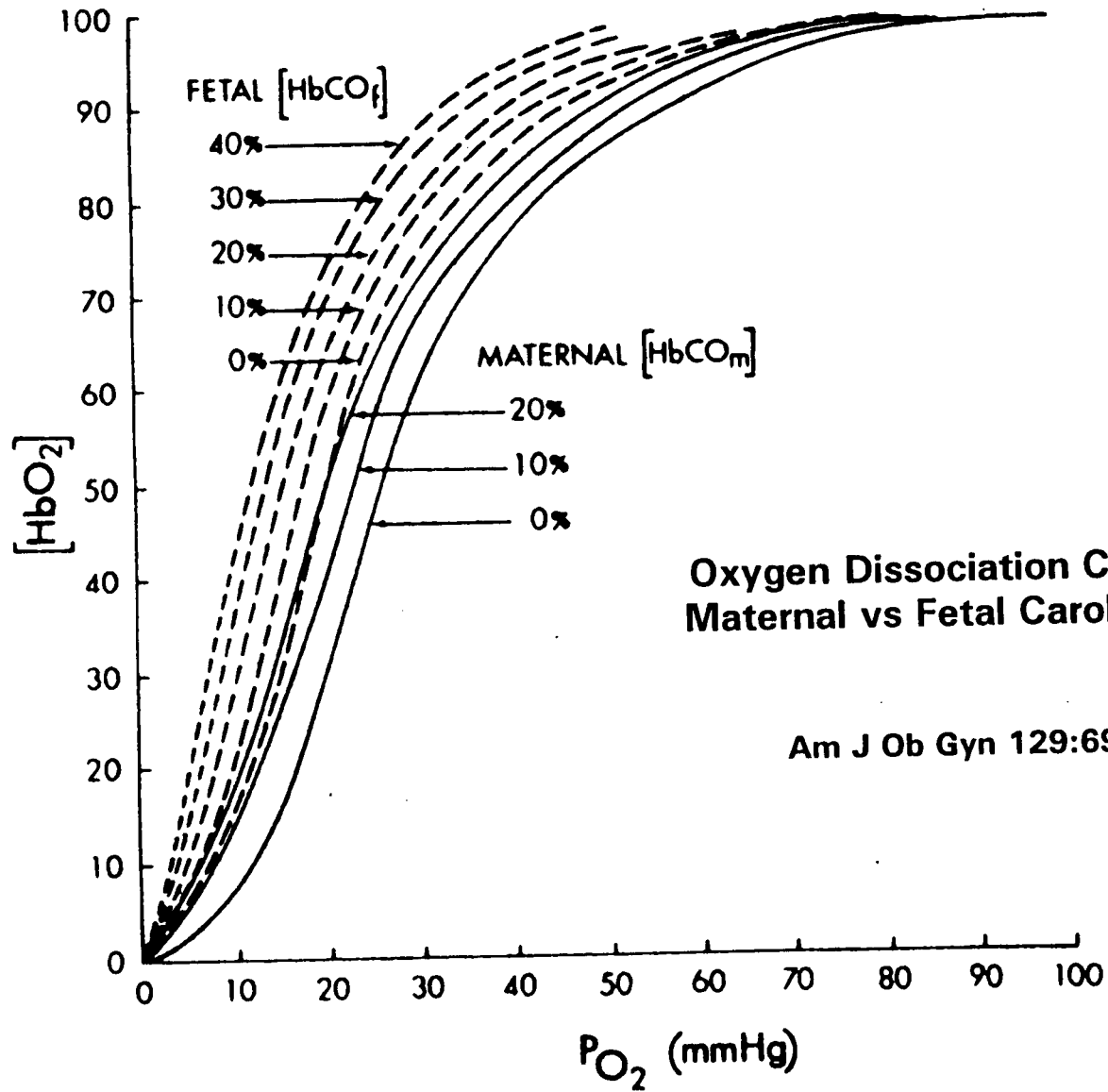
Oxygen Dissociation Curves:
Maternal vs Fetal Caroboxyhemoglobin

Am J Ob Gyn 129:69, 1977

Examples of "Susceptibility Subgroups"

"Susceptibility Subgroup"	Prevalence	Model Toxicants
Embryos and Fetuses (Maternal Exposure)	~21/1000	CO / Methylene Chloride Lead, Organic Mercury Solvents (EtOH) Furans, DES PCBs (?)
Breast-Fed Babies (Maternal Exposure)		Chlorinated Hydrocarbons Furans, PCBs (?)
Infants (1-4 years)	~70/1000	Lead Nitrates Tobacco Smoke
Elderly		Ozone, SO_2, NO_x, PM_{10} Cadmium (Post-Menopause)
Chronic Bronchitis	~50/1000	Ozone, SO_2, NO_x, PM_{10} Respiratory Irritants
Asthma	~50/1000	Ozone, SO_2, NO_x, PM_{10} Respiratory Irritants
Coronary Artery Disease	~32/1000	CO / Methylene Chloride CFCs Chlorinated Hydrocarbons
Liver Disease	~20/1000	Solvents (EtOH, CCl_4) PCBs (?) Acetaminophen
Iron Deficiency		Lead
Sulfite-Oxidase Deficit		SO_2, Sulfites California Wines (!!)
Hyperthyroidism		Alkylating Agents Oxidant Gases

JB'S RECOMMENDATIONS: SENSITIVITY and SUSCEPTIBILITY

1. SENSITIVE = SUSCEPTIBLE

    but, "sensitive" sounds like "allergic" = "hypersusceptible"
    therefore, SUSCEPTIBLE is the preferred term

2. SUSCEPTIBILITY entails observable, physiological processes

3. SUSCEPTIBILITY reflects dose-response relationships unique to a
    chemical (e.g., SO_2) or class of chemicals (e.g., acid aerosols)

4. HYPERSUSCEPTIBLE = IDIOSYNCRATIC

5. HYPERSUSCEPTIBILITY reflects discontinuous distributions of
    biological function and non-standard dose-responses relationships

6. Within SUSCEPTIBLE populations, at any given time there may be
    some who are transiently HYPERSUSCEPTIBLE (e.g., asthmatics
    during asthma attacks)

7. If possible, protection of SUSCEPTIBLE populations should be
    based on empirical data derived from well-defined populations
    characterized by independent physiological parameters

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Morristown, NJ 07962-1139

DRAFT

ATTACHMENT 5

DATE: August 21, 1996

TO: NAC AEGL Committee

FROM: George M. Rusch

SUBJECT: **Time Line for Document Review**

We have all expressed concern regarding the time available between our initial receipt of the AEGL documents and the meeting at which they are scheduled for review. This has lead to lengthy discussions on several points which might otherwise have been addressed prior to the meeting.

While having two reviewers plus a chemical manager, will help greatly to address many of the questions that have come up during our meeting, it would still be advantageous to have the documents earlier for review.

I would like to propose the following time line, which can be discussed during our September meeting.

- Notice and chemical list published in Federal Register: 60 Days Prior to Meeting.

- Proposed agenda, draft documents and key reference lists mailed to Committee: 60 Days Prior to Meeting.

- Comments from Reviewers and other interested Committee members sent to Chemical Manager: 40 Days Prior to Meeting.

- Revised Draft and Agenda sent to Committee and other interested parties: 20 Days Prior to Meeting.

Having the draft documents and agenda available 60 days before the meeting would give all interested parties, including members of the public, an opportunity to carefully review them; develop meaningful questions, and get responses well before the meeting. This should help us to focus our discussions during the meeting and review the documents more expeditiously.

Best regards,

GMR:rb

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AlliedSignal Inc.
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Morristown, NJ 07962-1139

ATTACHMENT 6

DRAFT

DATE: August 20, 1996

TO: NAC AEGL Committee

FROM: George M. Rusch

SUBJECT: **Application of Safety/Uncertainty Factors**

During our first two committee meetings, we have had a great deal of discussion on the topic of uncertainty factors or safety factors. I would, therefore, like to offer, for discussion, some suggestions as to how we could apply these factors. First, we need to consider that we are developing guidance levels for accidental exposures. As such, our values should approximate thresholds since there are consequences for being both too high and too low. Therefore, any adjustment to the data endpoints should be minimal. Extrapolations tend to lead to overly conservative conclusions when various uncertainties are multiplied leading to large denominators. In our current mission this could lead to the development of criteria for action levels that would be well below levels needed to indicate the proper response to a given situation.

This could lead to two negative courses of action: First, unnecessary responses (evacuation, overburdening of medical facilities, temporary disruption of life) could be mandated; second, our advice could be recognized as too conservative and be ignored, leaving the emergency responder without a meaningful reference. On the other hand, if we do not accurately apply the data we have, people could be inadvertently injured as a consequence of an exposure presumed to be safe. To the best of our ability, both outcomes must be avoided.

Below, I have attempted to identify some of the key uncertainties and suggest an approach for incorporating them into our AEGLs.

1.   Extrapolation from animals to man. Several factors should be considered:

    A.   Are we using a threshold, or a no-adverse-effect level?
    B.   Do we have information on a single species or multiple species? Is the data consistent across species?
    C.   Do we expect man to be uniquely more sensitive (or possibly less sensitive) than the test species?
    D.   Are we using a benchmark dose or maximum likelihood approach?
    E.   Is the endpoint accurately defined by our definition or is it a more or less serious effect? For example, if we are looking for AEGL-2, serious toxic effect but only have irritation, we may treat it one way, if the only information is lethality, we would treat it another way.

- For a start, if we have consistent data from more than one species that defines the no-adverse-effect level for the defined level (AEGL 1, 2 or 3) and we are using a maximum likelihood calculation - we should use an uncertainty factor of 10X.

- If we have the same data, but are using the Bench Mark Dose Level approach (at 0.01), we should use an uncertainty factor of 3X, since this approach already has a greater degree of confidences.

- If we are extrapolating from an appropriate serious effect level, we should increase the uncertainty factor 3X to approximate a no-adverse-effect-level.

- If the effect is of a less serious nature than that described by the appropriate AEGL definition, we should apply an 0.3X uncertainty factor.

- If we are using a long-term exposure study (4 or 13 weeks), we could apply an uncertainty factor of 0.3 since the threshold is conservative.

Thus, for a substance for which we have only limited data and are using a maximum likelihood estimate from the threshold for a serious effect, we would apply an uncertainty factor of 30. For a substance for which we have consistent data from more than one species and are using the benchmark dose approach from an endpoint of less severe than the appropriate AEGL definition, we would use an uncertainty factor of 0,.9 (3 X 0.3). The typical range for uncertainty factors for extrapolation from animals to man would, therefore, fall between 30 and 0.3.

The second area which has been discussed extensively is how to apply an uncertainty factor to include the more sensitive members of the population. Concurrent with that question is the question of what segment of the population are to be included? At present, it is virtually impossible to quantify this second endpoint since the slope of dose response lines will vary greatly. As a general approach, we should consider the application of either 1X, 3X or 10X to the value derived from either animal or human exposure modeling.

A 1X factor would relate to situations where it is unlikely that there will be a uniquely sensitive subpopulation. This conclusion might, for example, come from the results of some significant human exposure data. A 3X factor would be more appropriate for many materials that do not elicit sensitivity responses, for example, irritants. The 10X factor could be applied in cases where it is known that sensitive subpopulations exist and it is believed that a factor larger than 3 is needed for their protection.. A good example would be sulfite exposures.

As we go through our documents and are presented with these situations, we can begin to develop an improved insight to how these factors should be applied.

Your thoughts on this approach are critical to our success. Please send them to me, and consider discussing them at our next meeting.

Best regards,

/rb

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DATE: September 16, 1996

TO: AEGL Committee

FROM: George M. Rusch

SUBJECT: Acute Inhalation Toxicity Study Outline

This outline has been developed to list some of the experimental details to be considered when writing a protocol for a study being conducted to evaluate short term inhalation toxicity of a specific material. As endpoints will vary from case to case, some studies will include additional parameters and some may not need to include all parameters listed here. For an acute study, the primary goal is to assess the immediate effects associated with a single high level exposure and the reversibility of these effects. Therefore, the experimental approach will be different from that taken with repeat exposure studies seeking to define toxic endpoints.

Study Type: Acute Inhalation - Exposure Duration: Typically 1 hour, with some groups being exposed for 1/2, 4 and 8 hours.

Specie: Typical: Laboratory rat, but mouse guinea pig or hamster are also useful.

Group size: 5 male and 5 female

Number of Groups: For 1 hour exposures, 4 to 5 groups including an air exposed control (enough to define the LC_{50} or limit of toxicity); 2 to 3 groups at 1/2, 4 and 8 hours each.
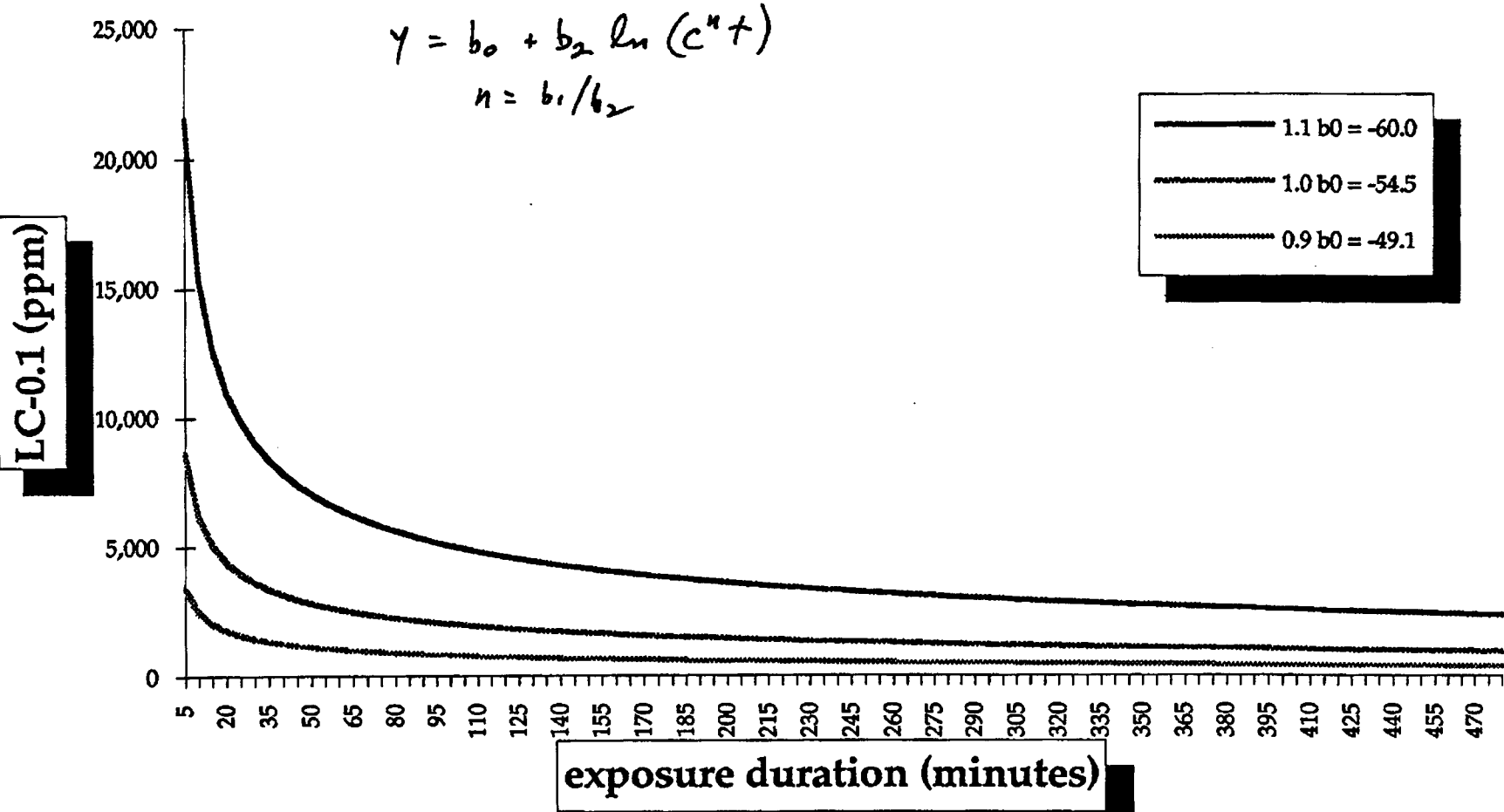
Exposure Level Monitoring: Shall be conducted by an appropriate analytical method and described clearly in the report.

Particle Size Measurement: Shall be conducted as appropriate for each specific compound.

Post-Exposure Observation Period: All survivors shall be held for a period of 14 days following the exposure.

Clinical Observations: All animals shall be observed during the exposure, hourly for 4 hours post-exposure on the day of exposure, and daily during the 14-day post-exposure observation period.

Human LC-0.1 for Ammonia: Sensitivity to Value of Ten Berge Regression Coefficient b0 for Mice

$$y = b_0 + b_2 \ln(c^n t)$$
$$n = b_1/b_2$$

Legend:
- 1.1 b0 = -60.0
- 1.0 b0 = -54.5
- 0.9 b0 = -49.1

Y-axis: LC-0.1 (ppm) — 0, 5,000, 10,000, 15,000, 20,000, 25,000

X-axis: exposure duration (minutes) — 5, 20, 35, 50, 65, 80, 95, 110, 125, 140, 155, 170, 185, 200, 215, 230, 245, 260, 275, 290, 305, 320, 335, 350, 365, 380, 395, 410, 425, 440, 455, 470
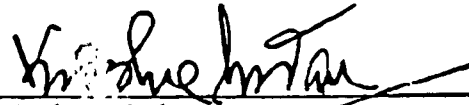
ATTACHMENT 9

GE Power Systems

Report on the Potchefstroom, South Africa Ammonia Incident
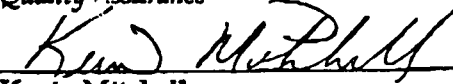
March 1996

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Krishr: Mudan
Quality Assurance

Kevin Mitchell
Project Manager

Figure 1   *The Potchefstroom Incident*
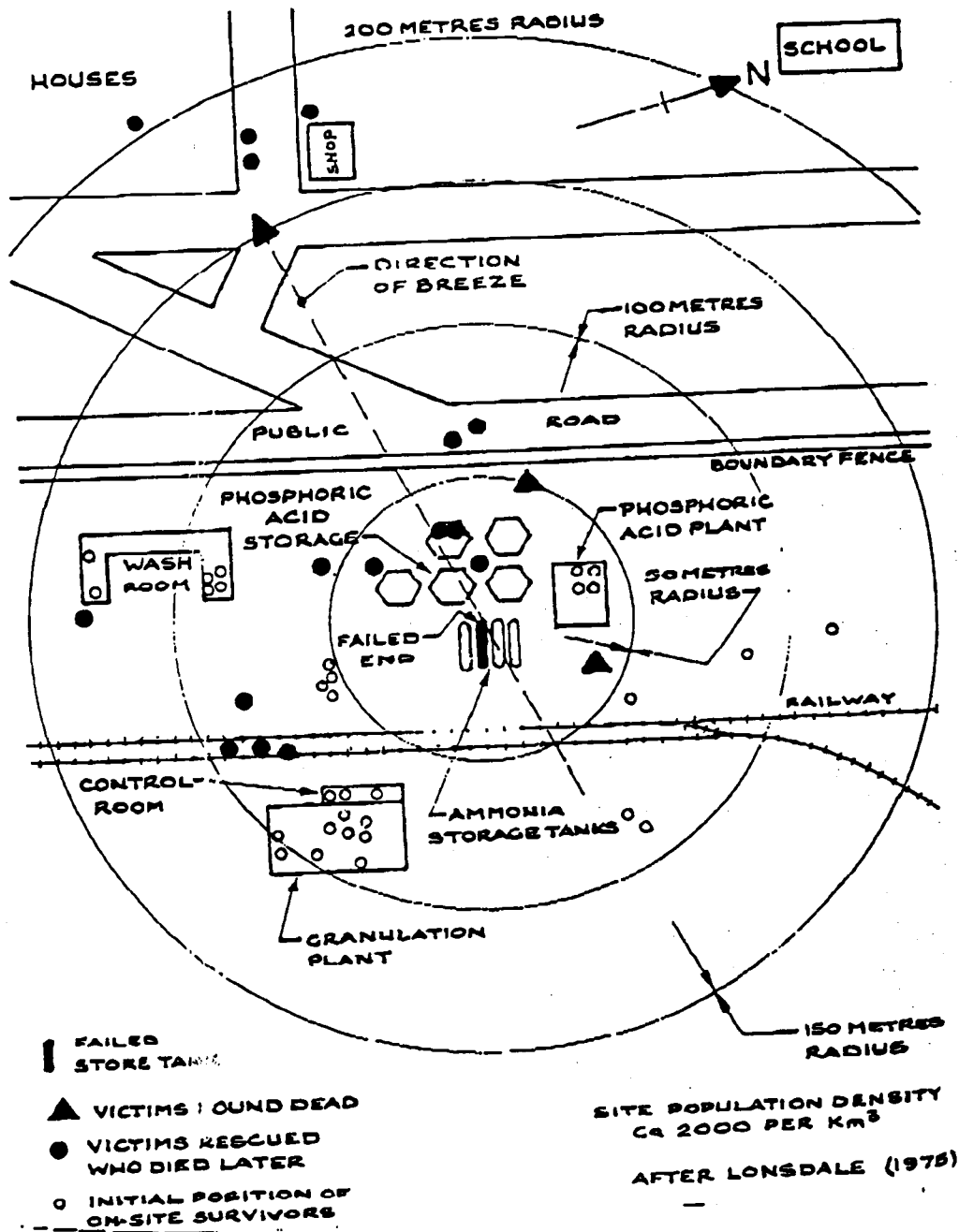
Source: Marshall, V.C., 1987

Figure 1. General layout of Potchefstroom plant.
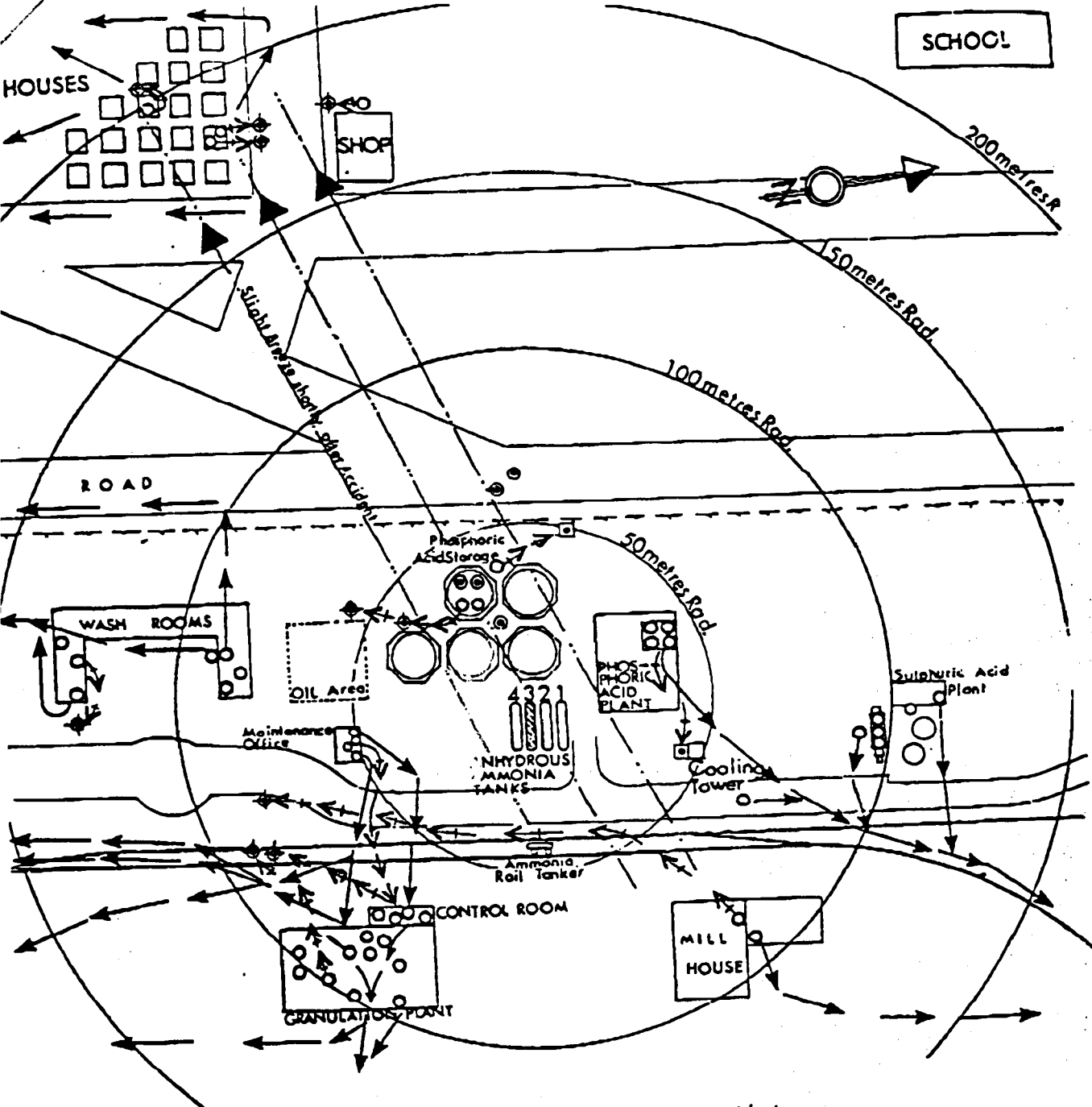
O   Positions where people were working or present at the time of the accident.

Routes followed by people who escaped.

Routes followed by people who died.

Positions of people who were found dead.

Positions where people who died to escape, were found injured and who subsequently died.

Positions, where people who could not escape, were found injured and who subsequently died.

Approximate direction of slight breeze that sprang up shortly after the accident.

Tank of which the West End failed.

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4.0   RESULTS OF THE ANALYSIS

The analysis indicates that the cloud rapidly developed within 30 seconds to encompass about 150 meters (490 feet) in both the upwind and downwind directions. During this initial expansion, the cloud concentration was estimated to be as high as 640,000 ppm and as low as 220,000 ppm (volumetric parts per million). Figure 2 indicates the cloud lingered in the immediate area of the failed tank (i.e., +/- 50 meters) for about 6 to 8 minutes. Personnel located in this area were estimated to be exposed to ammonia concentrations exceeding 50,000 ppm for the first two minutes. Thereafter, concentrations dropped below 10,000 ppm within the next 3 to 4 minutes. As stated above, six of the ten workers in this area died.   — *all survivors were inside*!

Within 100 meters (330 feet) of the tank, a maximum concentration of 360,000 ppm is estimated. Figure 3 indicates this area would have been subjected to concentrations exceeding 50,000 ppm for about 2 minutes, while concentrations would have exceeded 10,000 ppm for 5 to 6 minutes. Seven people within this effect zone were fatalities. Although 24 survivors were in this area at the time of the failure, some took refuge within the control room to minimize exposure.

The area 200 meters (660 feet) downwind of the tank was impacted within about one minute. Figure 4 indicates the maximum concentration at this location was estimated as 136,000 ppm. The concentration then dropped below 50,000 within the next minute and below 10,000 ppm within 4 to 5 minutes of exposure. Four fatally-wounded members of the public located in the township were estimated to be exposed to these concentrations.

At 250 meters (820 feet) and beyond no fatalities were observed. Serious injuries probably resulted in this effect radius, but the exact number was not reported. At 250 meters (820 feet) the initial, maximum concentration was estimated to be about 80,000 ppm. Figure 5 indicates that within the next 40 to 60 seconds the concentration dropped below 50,000 ppm. The population was estimated to be exposed to concentrations exceeding 10,000 ppm for no more than 4 to 5 minutes total.

Concentrations exceeding 5000 ppm were estimated to occur as far as 500 meters (1600 feet) downwind from the point of release. At such distances, exposure above 5,000 ppm would have been for no longer than 1 to 2 minutes.

5.0   *SUMMARY*

The concentration profile is summarized in Table 1 for the low wind speed option and Table 2 for the high wind speed option. The results of the analysis may be summarized as follows:

- Within a 50 meter radius (160 feet) the peak concentration was approximately 640,000 ppm. The total number of onsite workers exposed was ten. Six of these workers died, and four managed to escape the cloud and survive.

- At a 100 meter radius (330 feet) the peak concentration was approximately 360,000 ppm. An estimated 31 people were exposed. Seven fatalities were identified (including two members of the public). A total of 24 people survived, many by seeking shelter.

- At a 200 meter radius (660 feet) the peak concentration was approximately 136,000 ppm. An unknown number of people were exposed. Five fatalities were identified (including four members of the public).

- At 250 meters and beyond there were no fatalities. The peak concentration was approximately 80,000 ppm. An unknown number of people were exposed.

zone	# people	# dead/ #inside	# dead/# outside
1 (50 m)	10	2/6	4/4
2 (50-100 m)	31	0/16	7/15
3 (100-200 m)	?	0/?	5/?

TECHNICAL ISSUES - AMMONIA AEGL

ISSUE	ACTION/DISCUSSION	
Dispersion model (WHAZAN) used in Potchefstroom accident reconstruction published by Pedersen and Selig is outdated.	Added text and table from reconstruction performed using the HGSYSTEM model. Added description of the Potchfstromm accident to section 2.1.	*pg 5* *pg 38*
Concentration in case study by Mulder and Van Der Zalm inaccurately cited (reported as 10,000 ppm).	Text changed to indicate that concentrations were likely very high but unknown.	*pg 3*
Lethal effects data in animals should be assessed using additional extrapolation procedures (BD).	Added table of values derived using the BD procedure, provided by GA. *Also, included text on pg 37 and AEGL values using the BMD c HEC Adj, UF = 30, MF = 0.3*	*table 11*
No explanation provided on why data in mice were used to set AEGL-3 in section 5.2.	Text modified to indicate that data in both mice (Kapegian) and rats (Appleman) were considered as high quality studies appropriate for use as starting points in deriving AEGL-3.	*pg 31 added statement for the Beye*
Use of the HEC.	It is not clear how or if the HEC should be used, since ammonia is acting on more than one site in the respiratory tract (ET, TB, P) and the current HEC guidance document does not provide a way to address this. Also, ammonia does not clearly fall into a category 1 gas class, since under certain exposure conditions, some absorption of ammonia is occurring. Finally, equilibrium occurs at 500 ppm and use of the HEC above this level is likely invalid.	

TECHNICAL ISSUES - AMMONIA AEGL (CONT'D)

ISSUE	ACTION/DISCUSSION
Realistic ammonia accidental release scenarios indicate need for short term (e.g., 5-10 minute) AEGLs.	Draft 10 minute AEGL-3 and 2 values derived for consideration.
Final AEGL 3 values should be coherent with values derived using different data sets, including data from the Potchefstroom accident, the Houston accident, the opinions of Henderson and Haggard, Lehman, and Mulder and Van der Zalm, as well as the animal data (e.g., mice)	Agree on general principle of coherency. However, data from accident reconstruction's lack adequate information about exposure; opinions concerning exposure/effects from the early 1900's and late 1800's should not be considered as equal in "weight of evidence" evaluation as recently generated actual data.
Use of $LC_{0.1}$ already provides at least the degree of protection required of the AEGL, without further adjustment (i.e., use of 1/1000 accounts for sensitive individuals).	LC_1 (probability of 1/100) used as starting point, which is not viewed as ultra conservative; intra-species UF of 3 applied to account for sensitive/susceptible people.
AEGL 2 should be based on disabling or irreversible injury, not escape-impairing effects.	None. The AEGL 2 definition clearly indicates a need to consider escape-impairing effects.
Inaccurate wording of Silverman et al. citation in section 6.3 (500 ppm is intolerable).	Text modified to state that lacrimation and irritation of the nose and throat were observed.
Summary of human exposure study by Ferguson et al. not included in section 2.1.	Added summary.

CYANOGEN CHLORIDE - KEY REFERENCES

Flury, F. and Zernik, F. **1931**. Noxious Gases, Vapors, Mists, Smoke and Dust Particles, Springer Verlag, Berlin, pp. 350-354.

Prentiss, A.M. **1937**. Chemicals in War. A Treatise on Chemical Warfare, McGraw-Hill Book Co., Inc., New York, p. 175.

NDRC. **1946**. National Defense Research Committee. Hydrogen cyanide and cyanogen chloride. In: Preparation and Evaluation of Potential Chemical Warfare Agents. Summary Technical Report of Division 9, NDRC, vol. 1, part 1, chapter 2. Office of Scientific Research and Development, Vannevar Bush, Director. NDRC Chairman, James B. Conant; Division 9 Chief, W.R. Kirner. Washington, D.C. pp. 7-16.

Hartung, R. 1994. Cyanides and Nitriles. In: Patty's Industrial Hygiene and Toxicology, 4th ed. G.D. Clayton and F.E. Clayton, Eds. John Wiley and Sons, Inc., New York, pp. 3119-3172.

EFFECTS OF CYANOGEN CHLORIDE		
Concentration	**Duration**	**Effect**
1 [2.51]	?	minimum irritating
20 [50.2]	?	intolerable
159 [400]	10 minutes	probably fatal

Jacobs, M.B. 1942. War Gases: Their identification and decontamination. Interscience Publishers, New York.

TABLE 2. EFFECTS OF CYANOGEN CHLORIDE ON HUMANS		
Concentration (ppm [mg/m^3])	**Duration (min)**	**Response**
1 [2.51]	10	lowest irritant level
2 [5.02]	10	intolerable
20 [50.2]	1	intolerable
48 [120]	30	fatal
159 [399]	10	fatal

AEGL-1 VALUES FOR CYANOGEN CHLORIDE (ppm [mg/m³])				
AEGL level	30-min	1-hr	4-hr	8-hr
AEGL-1	0.33 [0.83]	0.33 [0.83]	0.33 [0.83]	0.33 [0.83]

LOAEL: 1 ppm (2.51 mg/m³) for 10-minutes

Endpoint: eye and respiratory irritation in humans

UF: 3 to account for sensitive individuals

Reference: Prentiss, 1937; Jacobs, 1942; Hartung, 1994

AEGL-2 VALUES FOR CYANOGEN CHLORIDE (ppm [mg/m³])				
AEGL level	30-min	1-hr	4-hr	8-hr
AEGL-2	0.66 [1.66]	0.66 [1.66]	0.66 [1.66]	0.66 [1.66]

Exposure: 2 ppm (2.51 mg/m³) for 10-minutes

Endpoint: intolerable irritation in humans

UF: 3 to account for sensitive individuals

Reference: Flury and Zernik, 1931; Hartung, 1994

AEGL-3 VALUES FOR CYANOGEN CHLORIDE (ppm [mg/m³])				
AEGL level	30-min	1-hr	4-hr	8-hr
AEGL-3				

Human data: 48 ppm for 30 minutes (Hartung, 1994)

159 ppm for 10 minutes (Prentiss, 1937; Jacobs, 1942; Hartung, 1994)

Summary of Proposed AEGL Values					
Classification	30-minute	1-hour	4-hour	8-hour	Endpoint (Reference)
AEGL-1	0.33 [0.83]	0.33 [0.83]	0.33 [0.83]	0.33 [0.83]	eye and respiratory irritation in humans (Prentiss, 1937)
AEGL-2	0.66 [1.66]	0.66 [1.66]	0.66 [1.66]	0.66 [1.66]	intolerable irritation in humans (Flury and Zernik, 1931)
AEGL-3	n/a	n/a	n/a	n/a	

ASTHMA

p. 4 Ostro, et al., 1991

clinic patients with history of airway obstruction reversible with a β-agonist bronchodilator

p. 5 Koenig, et al., 1989

9/9 had exercise-induced bronchospasm (>15% drop in FEV_1 after 6 min of exercise at 85% oxygen consumption)

5/9 had allergic asthma

ALLERGY

p. 9 Abraham, et al., 1982

bronchospasm in sheep in response to antigen challenge

TABLE 3-1.   PREVALENCE OF SUBGROUPS HYPERSUSCEPTIBLE TO EFFECTS OF COMMON POLLUTANTS[a]

Hyper-susceptible	Prevalence[b]	Chemicals[c]	Reference[c]
Embryo, fetus, neonate	pregnant women: 21/1000[d]	carcinogens, solvents, CO, mercury, lead, PCBs, pesticides	Rice, 1981; Kurzel Centrulo, 1981; Saxena et al., 1981
Young children	ages 1-4: 70/1000	hepatotoxins, PCBs, metals	Calabrese, 1981; Friberg et al., 1979
Lung disease	emphysema, asthma: 37/1000[e]	ozone, Cd, particulates, SO_2, NO_2	Holland et al., 1979; Redmond, 1981
Coronary heart disease	coronary heart disease: 16-27/1000[e]	chlorinated solvents, fluorocarbons	McCauley and Bull, 1980; Aviado, 1978
Liver disease	liver abnormalities: 20/1000[f]	carbon tetrachloride, PCBs, insecticides, carcinogens	Calabrese, 1978

[a]Source: Erdreich and Sonich, 1984.

[b]All estimates based on 1970 census.

[c]Representative samples of chemicals to which these individuals may be hyper-susceptible. Some evidence from animal studies only.

[d]Authors' estimate from 1970 census statistics data.

[e]Health Interview Survey (NCHS, 1970).

[f]Health Interview Survey (NCHS, 1975).

TABLE 2-4. PREVALENCE OF SUBGROUPS SUSCEPTIBLE TO EFFECTS OF COMMON POLLUTANTS

Susceptibility Subgroup	Population Prevalence	Chemicals[*],[a]	Reference
Embryo, fetus, neonate	Pregnant women: 21/1,000[b]	Carcinogens, solvents, CO, mercury, lead, PCBs, pesticides	Rice (1981), Kurzel and Cetrulo (1981), Saxena et al. (1981), U.S. Environmental Protection Agency (1986a, 1991)
Young children	Ages 1-4: 70/1,000[b]	Hepatotoxins, PCBs, metals, NO_2	Calabrese (1981), Friberg et al. (1979), U.S. Environmental Protection Agency (1993a)
Chronic obstructive pulmonary disease	Chronic bronchitis: 13,494,000 (5.4%)[c] Asthma: 12,375,000 (4.9%)[c] Emphysema: 1,915,000 (0.8%)[c]	O_3, Cd, particulate matter, SO_2, NO_2	Holland et al. (1979), Redmond (1981), U.S. Environmental Protection Agency (1982b; 1993a,b)
Circulatory conditions	Ischemic heart disease: 8,155,000 (3.2%)[c]	Chlorinated solvents, fluorocarbons, CO	McCauley and Bull (1980), Aviado (1978), U.S. Environmental Protection Agency (1991)
Liver disease	Liver abnormalities: 20/1,000[d]	Carbon tetrachloride, PCBs, insecticides, carcinogens	Calabrese (1978)

[*]Abbreviations:
CO = Carbon monoxide;
PCBs = Polychlorinated biphenyls;
O_3 = Ozone;

Cd = Cadmium;
SO_2 = Sulfur dioxide;
NO_2 = Nitrogen dioxide.

[a]Representative samples of chemicals to which these individuals may be susceptible. Some evidence from laboratory animal studies only.
[b]Estimates of Erdreich and Sonich-Mullin (1984) from 1970 census statistics data.
[c]Population base 251,448,000; estimate from U.S. Department of Health and Human Services (1992).
[d]Estimate of Erdreich and Sonich-Mullin (1984) from Health Interview Survey (National Center for Health Statistics, 1975).

Source: Adapted from Erdreich and Sonich-Mullin (1984).

Summary of Relevant Human Data

Concentration	Duration	Population	Effect	Reference
0.05 ppm [0.14 mg/m^3]	40 min	asthmatic adolescents with exercise	NOAEL	Koenig, et al., 1989
1.6 ppm [4.13 mg/m^3]	10 minutes	healthy adults	NOAEL	Sackner and Ford, 1981
62 ppm [160 mg/m^3]	1 hour	healthy adult	slight irritation	Lehmann and Hasegawa, 1913
75 ppm [194 mg/m^3]	1 hour	healthy adult	cough with increased pulse and respiratory rates	Lehmann and Hasegawa, 1913

PROPOSED AEGL-1 VALUES

AEGL-1 Values for Nitric Acid (ppm [mg/m^3])				
AEGL level	30-min	1-hr	4-hr	8-hr
AEGL-1	1.2 [3.1]	0.96 [2.48]	0.65 [1.68]	0.53 [1.37]

Key study: Sackner and Ford, 1981

Exposure: 1.6 ppm [4.13 mg/m^3] for 10 minutes

Effect: NOAEL

UF: none

PROPOSED AEGL-2 VALUES

AEGL-2 Values for Nitric Acid (ppm [mg/m^3])				
AEGL level	30-min	1-hr	4-hr	8-hr
AEGL-2	30 [77.4]	25 [64.5]	17 [43.9]	14 [36.1]

Key study: Lehmann and Hasegawa, 1913

Exposure: 75 ppm [194 mg/m^3] for 1 hour

Effect: irritation with cough; increased pulse and respiratory rates

UF: 3
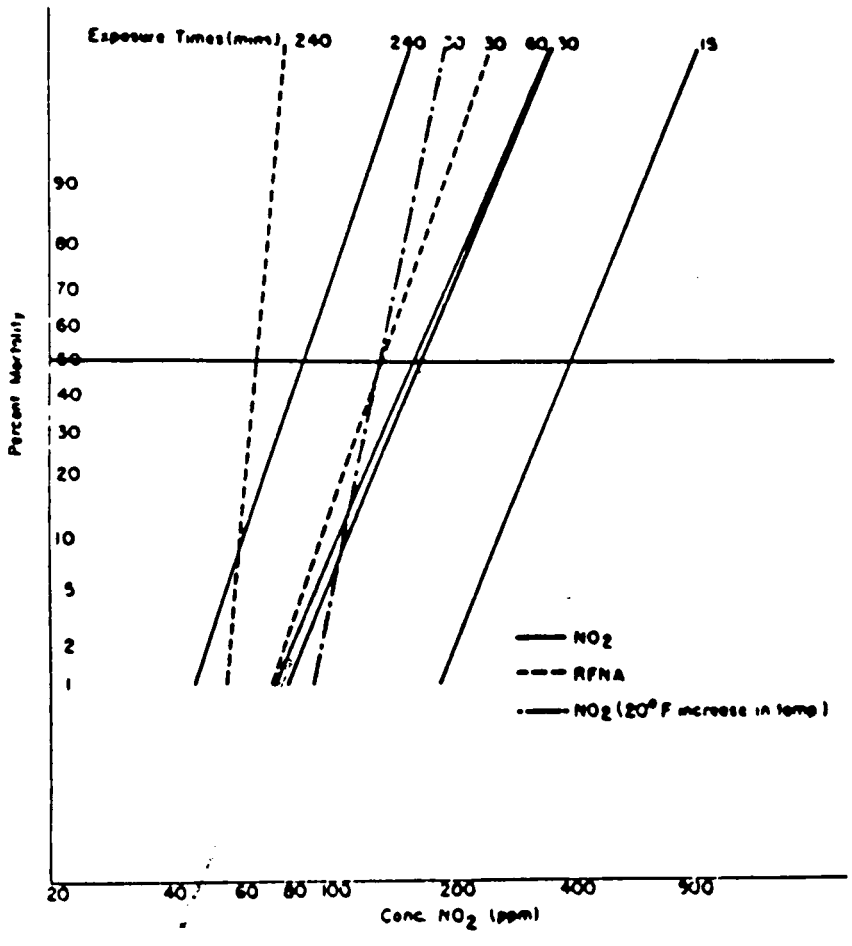
PROPOSED AEGL-3 VALUES

AEGL-3 Values for Nitric Acid (ppm [mg/m^3])				
AEGL level	30-min	1-hr	4-hr	8-hr
AEGL-3	34 [89]	28 [72]	29 [75]	24 [62]

Key study: Gray, et al., 1954

Exposure: 310 ppm [800 mg/m^3] for 30 minute

Effect: LC$_{50}$

Modifying factor: 0.33

UF: 3

Table 2: Non-Lethal Hydrogen Cyanide Exposure Concentrations in Humans

Responses	Exposure Concentration	
	mg/l	ppm
Tolerated for 0.5-1 hour without immediate or late effects	0.05-0.06	45-54
Slight symptoms after several hours	0.02-0.04	18-36

Source: Hartung (1994)

Table 3: Lethal Hydrogen Cyanide Exposure Concentrations in Humans		
Responses	Exposure Concentration	
	mg/l	ppm
Immediately fatal	0.3	270
Fatal after 10 minutes	0.2	181
Fatal after 30 minutes	0.15	135
Fatal after 0.5-1 hour or later, or dangerous to life	0.12-0.15	110-135

Source: Hartung (1994)

Table 4: LCt_{50} Estimates for Hydrogen Cyanide in Humans Calculated by the Moore-Gates Formula

Exposure Time (minutes)	Respiration Rate			
	25 Liters/minute		15 Liters/minute	
	Concentration (mg/m^3)	Ct Product‡ $[(mg/m^3)$ x min]	Concentration (mg/m^3)	Ct Product‡ $[(mg/m^3)$ x min]
0.5	8800	4400	14,400	7200
1	4400	4400	7590	7590
3	1500	4500	2610	7830
10	504	5040	860	8600
30	210	6300	360	10,800
60	140	8400	240	14,400

Source: McNamara, 1978.

Table 5: Non-Lethal Responses of Monkeys to Exposure Concentrations and Times			
Responses	Exposure Concentration		References
	mg/m³	ppm	
"Safe" indefinitely?	180	160	Barcroft (1931)
Fell down in 12 minutes	140	127	Flury and Zernik (1931)

Source: NIOSH (1976)

Table 14: Lethal Exposures of Dogs to Hydrogen Cyanide			
Exposure Concentration mg/m³ (ppm)	Exposure Time (minutes)	Ct Product [(mg/m³) x min]	Length of Survival
620 (563)	2	1240	16 hr
590 (535)	2	1180	16 hr
700 (635)	1.75	1225	20 hr

Source: Haymaker et al. (1952)

Table 23: LCt$_{50}$ Values and Lethal Exposure Concentrations [ppm x minutes] for Various Animals at Different Exposure Times

Animal	Minutes									
	0.5	0.75	1	2	3	5	10	30	35	60
Monkeys	§1466[1]		§1543[2]							
Sheep	§1308[1]									
Goats	§1180[2] §2136[1]			§1996[2] §1969[3]						
Pigs	§1579[1]									
Cats	§1338[1]		§771[2]	§1112[1]						
Dogs	§726[2] §726[1]		§635[2] §558[1]	‡1126[7] ‡1070[7] ‡1270[7]	§907[2]					
Rabbits	§820[1]	§1655[8]	§771[2] §889[1]			§1855[8]	§2904[2]		§6609[8]	
Guinea Pigs	§2269[2] §1916[1]		§1915[2]							
Rats	§726[2] §698[1]		§1406[2] §846[1] §1024[8]	§1996[2] §1987[4]	§1633[2]	§2420[9] §2235[8] §2515[10]		§4601[8]		§8567[8]
Mice	§408[5] §514[1]		§681[5] §827[1]	§1223[1] §1151[2] §1142[6]	§998[2]	§1615[10]	§2087[2] §668[1]	§4923[2] §4437[6] §4980[11]		

§LCt$_{50}$ value
‡Lethal exposure concentration
[1]Coon et al. (1943)
[2]Moore and Gates (1946)
[4]Silver et al. (1944b)
[5]Armstrong et al. (1923)
[6]Silver et al. (1941)
[8]Ballantyne (1983a)
[9]Vernot et al. (1977)
[10]Higgins et al. (1972)

Tidal Air (cc)	Exposure Concentration (mg/m³) [ppm]	Flow Rate (L/min)	Time of Inspiration (sec)	Time of Hold (sec)	Time in Lungs (sec)	Mean Percentage Retained (%)
450	0.5 [0.45]	18	1.5	0.5	2	58
450	4 [3.6]	18	1.5	0.5	2	58
450	20 [18.1]	18	1.5	0.5	2	59
450	4 [3.6]	18	1.5	0.5	2	58
1350	4 [3.6]	54	1.5	0.5	2	63
900	5 [4.54]	18	3.0	1	4	65

Table 24: Retention of Hydrogen Cyanide by Human Lungs at Different Physiological Parameters and Exposure Concentrations

Table 24: Retention of Hydrogen Cyanide by Human Lungs at Different Physiological Parameters and Exposure Concentrations						
450	4 [3.6]	18	1.5	2.5	4	73
1350	5 [4.54]	18	4.5	1.5	6	77
225	5 [4.54]	18	0.75	0.25	1	39
675	5 [4.54]	54	0.75	0.25	1	61

Source: Landahl and Herrmann, 1950

$$Y = b_0 + b_1 \ln c + b_2 \ln t, \quad \text{where } Y = \text{probit}$$

$$c = \text{exposure concentration}$$

$$t = \text{exposure time}$$

$$b_0, b_1, b_2 = \text{regression coefficients}$$

Table 27: Calculated Probit Values and Approximate Lethality Percentages Generated from the ten Berge Equation with Exposure Concentrations and Exposure Times for the Incapacitation and Lethality of Monkeys

Exposure Concentration		Exposure Time [minutes]	Ct Product [(mg/m³) x min]	Calcu-lated Probit Values	Approx-imate Lethality [%]	Toxicological Endpoint	Reference
ppm	mg/m³						
100	110.2	19	2094	2.97	~2	Incapacitation	Purser et al. (1984)
102	112.4	16	1798	2.86	~2	Incapacitation	Purser et al. (1984)
123	135.6	15	2034	3.10	~2	Incapacitation	Purser et al. (1984)
147	162	8	1296	2.86	~2	Incapacitation	Purser et al. (1984)
156	172	8	1376	2.95	~2	Incapacitation	Purser et al. (1984)
2933	3232	0.5	1616	5.23	~50	Lethality	Coon et al. (1943)
1543	1700	1.0	1700	4.81	~50	Lethality	Moore and Gates (1946)
127	140	12	1680	2.96	~2	Incapacitation	Flury and Zernik (1931)

Data presented in Table 27 suggest that the equation of ten Berge (1986) was validated for the exposure concentrations and times of incapacitated monkeys. This equation was used to determine the exposure concentrations for the 4 exposure times at a probit

value of 3 (~2% lethality) in Table 28. This probit value was chosen, because it is the lowest value typically presented on probit plotting graphs. The predicted lethality for humans should be zero, since humans appear to be less sensitive than monkeys.

Table 28: Approximate Incapacitation Exposure Concentrations Generated from the ten Berge Equation Using Different Exposure Times and a Probit Value of 3				
Exposure Concentration		Exposure Time (minutes)	Probit	Predicted Human Lethality (%)
(mg/m^3)	(ppm)			
88	80	30	3	0
61	54	60	3	0
29	26	240	3	0
20	18	480	3	0

Reduction of these values by application of an uncertainty factor of 3 was employed, because the mechanism of action of cyanide is specific to a physiologically important enzyme involved in oxidative phosphorylation. This enzyme is necessary for life, and any deviation from normal activity would result in death, as evident by the low lethal concentration of cyanide and by the steep exposure response curve of cyanide. The resulting proposed AEGL-3 values are shown in Table 29.

TABLE 29: Proposed AEGL-3 Values for Hydrogen Cyanide				
Classification	30-min	1-hr	4-hr	8-hr
AEGL-3	27 ppm	18 ppm	9 ppm	6 ppm

Comments on the draft AEGL's for Hydrogen Cyanide

Presented by

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Outline

◆ The health effects database contains both human and animal studies

◆ An AEGL-1 is not appropriate

◆ There are sufficient data to set an AEGL-2

◆ The AEGL-3 should be re-evaluated in light of the available data

Toxicology Information

- ◆ The acute toxicity of HCN is based upon a mechanism of action which is the same across species - but there are important differences in the dose which produces the effects.

- ◆ Dogs are more sensitive than monkeys and humans and monkeys are more sensitive than humans.

- ◆ HCN is a fast acting toxin and the effects are readily apparent.

- ◆ These are data suggestive of chronic effects in humans.

Data Supporting an AEGL-2

- ◆ An Emergency Response Planning Guideline - Level 2 - for HCN has been set at 10 ppm (a maximum one hour exposure value which would not cause irreversible or serious health effects or impair escape).

- ◆ Based on human data - Wexler, et al. 1947 - Intravenous Injection of NaCN. Transient EKG effects at 0.11 to 0.2 mg NaCN/kg (equivalent to 0.06 - 0.11 mg/kg HCN) or about 10 ppm for one hour.

- ◆ A level of 10 ppm for 4 hours and 8 hours, and 20 ppm for 30 minutes should be considered.

Data Supporting an AEGL - 3

AEGL - 3 - A concentration in air which is not life-threatening or fatal

◆ For the 30 minute and one hour value, use of the probit calculation method by Ten Berge is acceptable. However, extending this beyond one hour is not appropriate.

  – it is beyond the data set

  – there appears to be a mixing of incapacitation data with lethal data

  – experience in the occupational setting is not sufficiently considered

  – HCN has the largest range of confidence limits of all compounds examined by Ten Berge

Recommendation for an AEGL-3, ppm

30 min.	1 hr.	4 hr.	8 hr.
30	25	20	10

Basis

◆ Lethal to humans above 100 ppm for 30 min. or longer - TLV documentation

◆ The ERPG for 1 hr. is 25 ppm

◆ Important symptoms not occuring at 18-36 ppm for 6 hr. exposure - Flury and Zernik

breathlessness, feeling "shaky," headache, and nausea. Three of the exposed men became unconscious but they recovered rapidly after being moved into fresh air. The symptoms reported are very similar to those described in earlier reports that have been summarized by various authors.[2,41] In cases of severe exposure, unconsciousness is rapidly followed by death.

For humans, concentration-related effects have been cited by Dudley et al.[8] and Flury and Zernik[42] (Table 2). From these data, it would appear that 10 ppm HCN provides a twofold margin of safety against mild, acute symptoms of HCN poisoning. Grabois[43] found that workers in plants processing apricot kernels reported no ill effects when exposed at HCN air concentrations on the order of 10 ppm; however, medical history questionnaires were not given.

The principal routes of occupational HCN exposure are inhalation and absorption through the skin.[2] In addition, sodium cyanide (NaCN), KCN, and $Ca(CN)_2$ will liberate HCN gas upon hydrolysis or in the presence of acids.[2] Elkins[44] reported that nasal irritation and ulceration of the septum were found in an electroplating room where the concentration of cyanide did not greatly exceed 5 ppm. HCN may be absorbed through the skin in lethal amounts.[2]

In a review of literature prior to 1959, Wolfsie and Shaffer[41] considered the question of sequelae and the question of chronic poisoning. Their analysis of data suggests that following acute exposure, if death does not occur, recovery is complete and usually prompt. Regarding the question of chronic poisoning, the authors[41] mentioned that while many investigators firmly deny the existence of chronic cyanide poisoning, there have been reports of occasional illness have appeared in cyanide-exposure-related occupations. Symptoms include asthenia, headache, vertigo, irritability, loss of weight, anorexia, and various gastrointestinal complaints. These illnesses were attributed to chronic cyanide exposure because they disappeared completely when working conditions improved or employment was terminated, only to recur when the individuals returned to their former exposures.

Although endemic goiter is widespread in tropical areas where cyanogenic glycosides are found in edible plants (e.g., cassava),[23] cumulative cyanide toxicity is thought to represent "persistent neuropsychiatric sequelae from one or more acute exposure episodes. The clinical syndrome of delayed neurological deterioration sometimes follows hypoxia irrespective of its cause."[6]

The National Institute for Occupational Safety and Health (NIOSH)[2] cited additional studies reporting chronic cyanide poisoning going back to 1899. However, in recommending a 4.7 ppm ceiling limit for HCN, NIOSH based the value largely on the report by El Ghawabi et al.[45] which describes workers exposed for periods on the order of 7 years to breathing zone concentrations in the

TABLE 2. Acute Concentration-Related Effects of Hydrogen Cyanide

Concentration (ppm)	Effect
270	Immediately fatal
181	Fatal after 10 minutes
135	Fatal after 30 minutes
110	Fatal after 1 hour
45–54	Tolerated for 0.5 to 1 hour without immediate or delayed effects
18–36	May result in some symptoms after an exposure of several hours

range of 4.2 to 12.4 ppm HCN. An increased incidence of several symptoms was seen in exposed individuals compared to the control subjects. The subjective symptoms experienced, in order of their frequency, were headache, weakness, changes in senses of taste and smell, irritation of the throat, vomiting, and effort dyspnea. Less common symptoms included lachrymation, abdominal colic, salivation, and nervous instability. Mild to moderate goiter, attributed to the competitive inhibition of iodine uptake by the thyroid due to elevated thiocyanate, the chief metabolite of cyanide, was reported in 56% of the workers in this study.[45]

TLV Recommendation

Since 1980, a TLV–Ceiling of 10 ppm has been recommended for HCN to prevent acute poisoning.[8,42] A skin notation is also recommended owing to skin absorption of HCN in aqueous solution[46,47] and lethal effects.[2]

The TLV Committee is reviewing the basis of the NIOSH recommendation[2] and the adequacy of the report by El Ghawabi et al.[45] for possible establishment of a TLV–TWA to prevent potential chronic effects of HCN exposure.

Other Recommendations

OSHA PEL: OSHA established a PEL of 4.7 ppm, as a 15-minute TWA–STEL, with a skin notation, for HCN. OSHA concluded that the PEL would protect workers from the significant risks of headache, fatigue, colic, and nervousness observed in individuals exposed at the 10-ppm level over a full working shift.[48]

NIOSH REL/IDLH: NIOSH [Ex 8-47, Table N1] established a REL of 4.7 ppm, as a 15-minute TWA–STEL, with a skin notation, by concurrence with the OSHA PEL for HCN.[48] NIOSH established an IDLH value of 50 ppm for this substance.

ACGIH Rationale for TLVs that Differ from the PEL or REL: The ACGIH TLV as a ceiling was established on the basis of preventing acute poisoning by HCN. There are no rigorous studies demonstrating objective signs of cyanide-induced adverse health effects from long-term

pooled. The red blood count, white blood count, and hemoglobin determinations remained within normal limits. The differential counts revealed an increase in eosinophiles in both the rats and rabbits, ranging from no eosinophiles at the end of the first week of exposure to a maximum of 35, 42, 36, and 25 per cent in the rabbits, and from 1 per cent at the end of the first week of exposure to a maximum of 21 per cent in the rats. The cause of this marked increase in eosinophiles is not known.

DISCUSSION

These experiments dealing with the repeated exposure of animals to various concentrations of acrylonitrile confirm the observations made in a previous paper (1), dealing with the acute toxicity of the material, namely that the action of acrylonitrile is that of a typical nitrile and that the susceptibility to the toxic action of acrylonitrile varies considerably with the different species. There is very little evidence of a cumulative action to repeated exposures.

Although kidney damage was most marked in both acute and chronic series of exposures in guinea pigs, which are the most resistant species to the effects of acrylonitrile, this does not disprove the tenant of species susceptibility. Rather it suggests either that the observed changes are brought about by greater elimination of acrylonitrile through the kidney, or it may indicate irritation from detoxication products of acrylonitrile produced in the body. This may mean that guinea pigs metabolize acrylonitrile differently than other species.

ADDENDUM BY SURGEON PAUL A. NEAL AND
PRINCIPAL INDUSTRIAL TOXICOLOGIST W.
F. VON OETTINGEN

It has been pointed out previously and is borne out in the present paper that the toxicological picture of acrylonitrile poisoning closely resembles that of hydrocyanic acid poisoning. This is in accordance with the present conception of the toxic action of nitriles in general. There is no information in the available literature on the toxicity of acrylonitrile for man. Comparison of the toxic concentrations of acrylonitrile and hydrocyanic acid in animals as given in Table 1, and as reported in the literature, shows that they are of a very similar order of toxicity when compared on the basis of cyanide content. This allows the utilization of data on the toxicity of hydrocyanic acid, as reported for man, in the appraisal of the toxicity of acrylonitrile for humans. Data on the

TABLE 2

TOXICITY OF HCN FOR HUMANS (FLURY AND ZERNIK, 1931)

CONCENTRATION		SYMPTOMS
mg./liter	p.p.m.	
0.3	270	Immediately fatal
0.12–0.15	110–135	Fatal after ½–1 hour or later or dangerous to life
0.05–0.06	45–54	Tolerated for ½–1 hour without immediate or late effects
0.02–0.04	18–36	Some effects after exposure for several hours

acute toxicity of hydrocyanic acid as published by Lehmann and Hess and quoted from Flury and Zernik are summarized in Table 2.

At present, the maximal permissible concentrations of hydrocyanic acid for eight hours exposure is tentatively accepted as 20 p.p.m. by several States and, on the basis of the above consideration, a maximal concentration of acrylonitrile for eight hours exposure of 0.43 mg./l. (20 p.p.m.) is proposed until further information has been gathered. It may be pointed out that this figure represents approximately one-half that concentration which has produced toxic effects in dogs, which are the most susceptible species yet studied.

REFERENCES

(1) DUDLEY, H. C., AND NEAL, PAUL A.: Toxicology of acrylonitrile (vinyl cyanide) I. A study of the acute toxicity. THIS J. 24: 27–36, 1942.

(2) LILLIE, R. D.: Romanowsky staining with buffered solutions. III. Extension of the method to Romanowsky stains in general. Stain Technology 16: 1–6, 1941.

2. Beim Menschen: Die akute Vergiftung bei langsamer Einatmung von Blau-
säure verläuft beim Menschen gewöhnlich in vier Stadien:

a) Initialstadium: Zunehmender örtlicher Reiz an den Schleimhäuten von
Auge, Rachen und oberen Atemwegen, Brennen auf der Zunge, eigenartig metal-
lisch-kratzender Geschmack in Mund und Rachen. Die ausgeatmete Luft riecht
nach Blausäure, Druckgefühl in der Stirngegend, Beklemmung, Schwindel,
Schwanken, reißender Kopfschmerz; Übelkeit, Erbrechen, Stuhldrang; Atmung
erst beschleunigt, dann vertieft, Blutandrang nach dem Kopf, Herzklopfen.

b) Asthmatisches Stadium: Unter allmählich zunehmender Schwäche oft plötz-
lich Verlangsamung der Atmung bei verhältnismäßig gut erhaltener Herztätig-
keit, stärkere Atemnot, aber noch keine Krämpfe und keine Bewußtseinsstörungen.

c) Konvulsivisches Stadium: Angstgefühl und Atemnot nehmen zu; das Be-
wußtsein schwindet, es treten tonisch-klonische und tetanische Krämpfe auf.

d) Asphyktisches Stadium: Die Pupillen sind erweitert; die Atmung wird
immer flacher und steht schließlich still. Der Tod erfolgt rasch.

Einfluß der Konzentration: Die Stärke der Blausäurewirkung ist, wie bereits
oben erwähnt, vor allem abhängig von der eingeatmeten Konzentration.

Geringe Konzentrationen (etwa 0,05 mg/l entspr. 45 T. : 1 Million erzeugen
nur Kopfschmerz, Übelkeit, Erbrechen, Herzklopfen; diese Symptome schwinden
nach einiger Zeit wieder. Höhere Konzentrationen, etwa von 0,1 mg/l entspr.
90 T. : 1 Million an, sind schon lebensgefährlich bezw. rasch tödlich. Bei mittel-
hohen Konzentrationen erscheinen die ersten Symptome erst nach einigen Mi-
nuten. Der Tod erfolgt meist binnen einer Stunde. Ist nach dieser Zeit die Atmung
noch erhalten, so ist Rettung noch möglich. Bisweilen aber tritt Spättod noch
nach 24 Stunden ein. Hohe Dosen — etwa um 0,3 mg/l entspr. etwa 270 T. : 1 Mil-
lion führen schnell zum Tode: unter heftigem Beengungsgefühl, oft mit Auf-
schreien, sog. „hydrocephalischem Schrei" (LEWIN), verbunden, erfolgt plötz-
liches Zusammenbrechen; es schließen sich Krämpfe an, nach wenigen Minuten
setzt die Atmung aus und nach 6—8 Minuten tritt der Tod ein.

Bei der *Sektion* nach akuter Blausäurevergiftung durch Einatmung zeigen
sich die üblichen Erstickungserscheinungen: flüssiges Blut, Hyperämie der Hirn-
häute, Blutaustritte. Im Gehirn soll der Geruch nach Blausäure deutlich wahr-
nehmbar sein, ebenso in der Lunge; bei Druck auf den Leib kann dieser Geruch
auch am Munde der Leiche auftreten. Das Blut der Leichen ist in der Regel
auffällig rot gefärbt. Wegen der Farbe der Totenflecke s. ebenfalls oben. Die
Leichen zeigen oft nur geringe Fäulniserscheinungen.

Der Grad der Giftigkeit von eingeatmeter Blausäure für den Menschen ist
wohl der gleiche wie für den Affen, den Hund oder die Katze.

Giftigkeit von eingeatmeter Blausäure nach LEHMANN-HESS.

	mg l	Teile Dampf in 1 Million (cm³ m³) etwa
Sofort tödlich	0.3	270
In ¹/₂—1 Std. sofort oder später tödlich	0.12—0.15	110—135
In ¹/₂—1 Std. lebensgefährlich (HESS)	0.12—0.15	110—135
¹/₂—1 Std. ohne sofortige oder spätere Folgen ertragen . .	0.05—0.06	45—54
Bei mehrstündiger Einwirkung bereits wirksam (HESS) . .	0.02—0.04	18—36
6 Std. ohne wesentliche Symptome ertragen	0.02 (—0,04)	18 (—36)

1 mg/kg eingeatmete Blausäure ist nach LEHMANN absolut tödlich für den
Menschen.

AEGL VALUES FOR 1,2-DICHLOROETHYLENE

- ENDPOINTS OF CONCERN

- SELECTION OF THE KEY STUDY

- SCALING BETWEEN ANIMAL EXPOSURE LEVELS AND HUMAN EXPOSURE LEVELS FOR AN EFFECT

- UNCERTAINTY FACTOR TO ACCOUNT FOR EXTRAPOLATION FROM ANIMAL TO HUMAN EXPOSURE VALUES

- UNCERTAINTY FACTOR TO ACCOUNT FOR SENSITIVE HUMAN POPULATIONS

- SCALING BETWEEN TIME VALUES FOR AN EFFECT

- STEEPNESS OF THE DOSE RESPONSE CURVE

- DEVELOPMENT OF AEGL VALUES

- LAUGH TEST

PROPOSED AEGL VALUES FOR 1,2-DICHLOROETHENE					
Classification	30-min	1-hour	4-hour	8-hour	Endpoint (Reference)
AEGL-1 (Nondisabling)	19 ppm (75 mg/m^3)	13 ppm (53 mg/m^3)	7 ppm (26 mg/m^3)	5 ppm (19 mg/m^3)	no effect in humans (Lehmann and Schmidt-Kehl, 1936)
AEGL-2 (Disabling)	56 ppm (224 mg/m^3)	40 ppm (160 mg/m^3)	20 ppm (80 mg/m^3)	14 ppm (56 mg/m^3)	slight dizziness in humans (Lehmann and Schmidt-Kehl, 1936)
AEGL-3 (Lethality)	200 ppm (800 mg/m^3)	141 ppm (564 mg/m^3)	71 ppm (284 mg/m^3)	50 ppm (200 mg/m^3)	fibrous swelling and hyperemia of cardiac muscle with poorly maintained striation in rats (Freundt et al., 1977)

Inhalation Exposure of trans-1,2-Dichloroethene to two Human Subjects[a]

Concentration (ppm)	Time (minutes)	Effect
275	5	no effect
825	10	slight dizziness after 5 min.
950	5	slight burning of eyes
1000	30	dizziness after 10 min.; slight burning of eyes
1200	10	dizziness after 5 min.; drowsiness; initially, slight burning of eyes
1700	5	dizziness after 3 min.; slight burning of eyes; intracranial pressure; nausea (symptoms persist for ½ hour after exposure)
2200	5	severe dizziness after 5 min; intracranial pressure; nausea (symptoms persist for ½ hour after exposure)

[a]Lehmann and Schmidt-Kehl, 1936

AEGL-1 FOR 1,2-DICHLOROETHENE (ppm [mg/m^3])				
AEGL Level	30-min	1-hr	4-hr	8-hr
AEGL-1	19 [75]	13 [53]	7 [26]	5 [19]

Species: Human
Concentration: 275 ppm *trans*-1,2-dichloroethene
Time: 5 Minutes
Endpoint: No effect, odor present

n = 2

Uncertainty Factor = 6

    2: probable difference in isomer toxicity

    3: sentivive human subpopulations

n =   3.869099

k =   1.1E+19

Minutes	Conc.	Hours	Conc.
30	34326.05	0.5	98901.18
60	28695.93	1	82679.5
240	20054.55	4	57781.73
480	16765.22	8	48304.43

Best Fit Concentration x Time Curve

$R^2 = 0.971$

$n = 3.9$
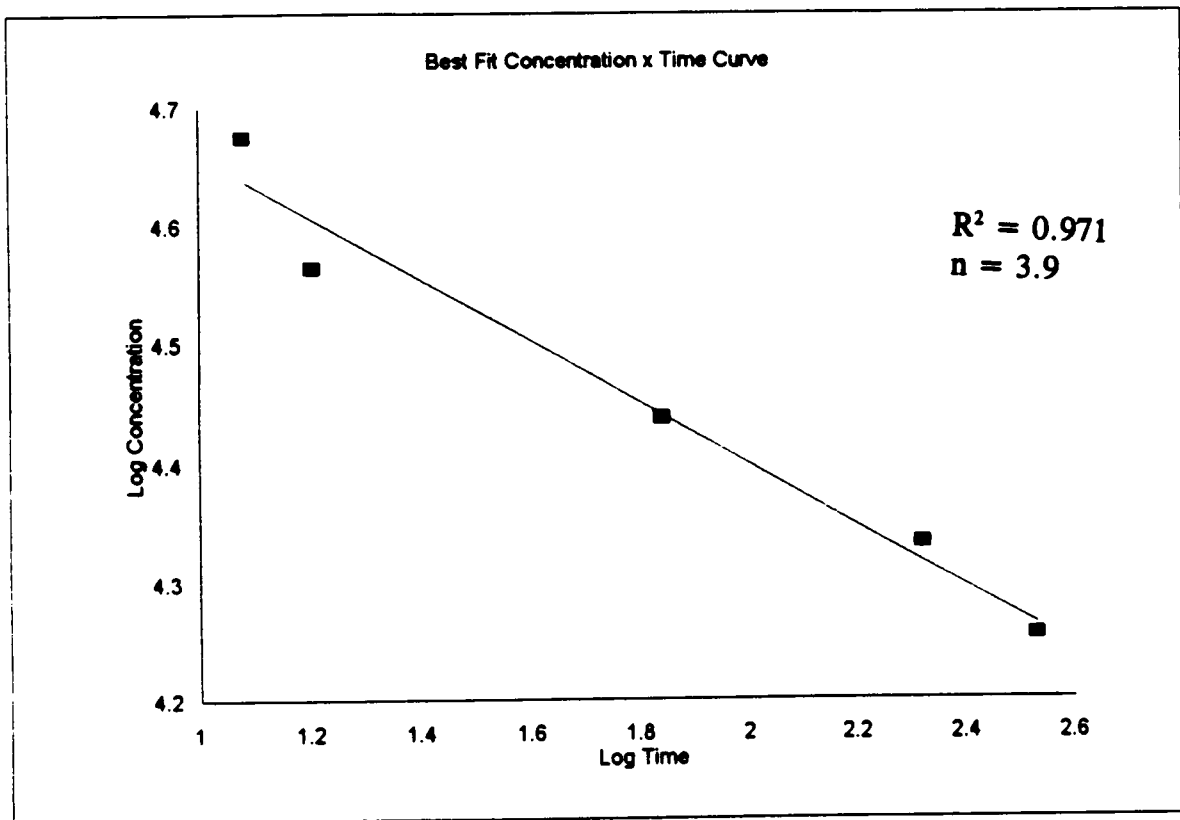
AEGL-2 FOR 1,2-DICHLOROETHENE (ppm [mg/m^3])				
AEGL Level	30-min	1-hr	4-hr	8-hr
AEGL-2	56 [224]	40 [160]	20 [80]	14 [56]

Species: Human
Concentration: 825 ppm *trans*-1,2-dichloroethene
Time: 5 Minutes
Endpoint: Slight dizziness

n = 2

Uncertainty Factor = 6

    2: probable difference in isomer toxicity

    3: sentivive human subpopulations

Inhalation Exposure of Rats to trans-1,2-Dichloroethene for 8 hours[a]	
Concentration (ppm)	Effect
0	no effect
200	Fatty degeneration of hepatic lobules and Kupffer cells, Pulmonary capillary hyperemia and alveolar septum distention, Decreased leukocyte count
1000	Fatty degeneration of hepatic lobules and Kupffer cells, Pulmonary capillary hyperemia and alveolar septum distention, Decreased erythrocyte count
3000	Fatty degeneration of hepatic lobules and Kupffer cells, Pulmonary capillary hyperemia and alveolar septum distention, Pnuemonic infiltration, **Fibrous swelling and hyperemia of cardiac muscle with poorly maintained striation**

[a]Freundt et al., 1977

AEGL-3 FOR 1,2-DICHLOROETHENE (ppm [mg/m^3])				
AEGL Level	30-min	1-hr	4-hr	8-hr
AEGL-3	200 [800]	141 [564]	71 [284]	50 [200]

Species: Rat
Concentration: 3000 ppm *trans*-1,2-dichloroethene
Time: 8 Hours
Endpoint: Fibrous swelling and hyperemia of cardiac
                  muscle with poorly maintained striation

n = 2

Uncertainty Factor = 60

    10: rat to human

    2: probable difference in isomer toxicity

    3: sentivive human subpopulations

Methyl Mercaptan

	0.5 Hr	1 Hr	4 Hr	8 Hr	Exp. Conc. (Effect) [species]	UF (inter x intra)
AEGL 1						
AEGL 2	3 ppm	2 ppm	1 ppm	1 ppm	112 ppm (Shallow breathing) [mouse]	10 x 10
AEGL 3	31 ppm	23 ppm	13 ppm	10 ppm	400 ppm (Highest nonlethal concentration) [rat]	10 x 3

Methyl Mercaptan

	0.5 Hr	1 Hr	4 Hr	8 Hr	Exp. Conc. (Effect) [species]	UF (inter x intra)
AEGL 1	3 ppm	2 ppm	1 ppm	1 ppm	112 ppm (Shallow breathing) [mouse]	10 x 10
AEGL 2	10 ppm *7*	7 ppm *5*	4 ppm *3*	3 ppm *2*	374 ppm *Range* (Shallow breathing & hypoactivity) *278* [mouse] *Definitive*	10 x 10
AEGL 3	31 ppm	23 ppm	13 ppm	.10 ppm	400 ppm (Highest nonlethal concentration) [rat]	10 x 3

ATTACHMENT 18

Hansen 9/18/96

Methyl Mercaptan

Seluzhitsky (1972)   MPC ~ 0.000025 ppm
                                       (based on odor)

Katz & Talbert (1930)	"Intensity"	mg/l	ppm
"no odor"	0	0.0059	
"threshold"	1	0.081	0.041
"faint"	2	1.1	
"median-easily noticeable"	3	16	
"strong"	4	220	~110
"most intense"	5	3000	~1,500

		mg/m^3	ppm
Wilby (1969)	(r)	0.002	0.0010
Williams (1977)	(d)	0.0000003	0.0000002
Nishida (1979)	(d)	0.038	0.019

Kangas (1984)   0-15 ppm peaks, headaches & decreased
                                       concentration ($p<0.25$)

TLV-TWA   0.5 ppm (based on odor)

NIOSH REL   0.5 ppm, ceiling

Elf-Atochem (1996)   0.5 ppm AEGL-1 (all time periods)

Phillips Petroleum (1996)   0.5 ppm (or less) AEGL-1 (all time periods)

Arsine AEGL

Arsine (AsH_3) is a gas extensively used in the semiconductor industry as gallium arsenide and as a dopant in silicon-based electronic devices. Also extensively used in production of pesticides and other products.

Arsine produces hemolysis and ultimately renal failure.

Mechanism of toxicity is not known. Arsine probably reacts directly with HbO_2 at the heme-ligand binding site, causing destabilization of the protein, degradation of hemoglobin, and release of hemin and Heinz bodies.

Renal damage involves either an arsine oxidized species or another active oxygen species such as a superoxide anion.

Biologic marker for human exposure is urinary porphyrins.

Issues for development of AEGL's:

1. Arsine is highly toxic with very little marg between exposures that cause reversible hemolysis and lethality.

2. It is a colorless gas with a slight garlic-like odor. The odor may be undetectable. Many occupational arsine-exposure victims have reported detecting no odor. An AEGL-1 level may not be appropriate.

3. To what extent should dosimetric adjustments be used?

4. Because there is little difference between exposures causing non lethal effect and lethality, should there be different values for AEGL-2 and AEGL-3?

5. Because of high and delayed toxicity low values for Arsine are probably appropriate.

SUMMARY OF PROPOSED AEGL VALUES FOR ARSINE (ppm)*					
Classification	0.5 hr	1-hr	4-hr	8-hr	Endpoint(Reference)
AEGL-1 (Nondisabling)	0.3 [0.06]	0.2 [0.04]	0.1 [0.02]	0.1 [0.01]	No-effect level for hematological changes in mice (Blair et al. ,1990)
AEGL-2 (Disabling)	2 [0.4]	1 [0.3]	0.7 [0.2]	0.5 [0.1]	Significant hematological alterations in mice consistent with the known continuum of arsine toxicity (Peterson and Bhattacharyya, 1985)
AEGL-3 (Lethality)	2 [0.4]	1 [0.3]	0.7 [0.1]	0.5 [0.1]	Lethality in mice (Peterson and Bhattacharyya, 1985)

* Values in brackets [ ] represent AEGLs (in ppm) derived without HEC adjustment.

AEGL-1   NO HEC ADJUSTMENT

AEGL-1 FOR ARSINE (ppm)				
	30-min	1-hr	4-hr	8-hr
AEGL-1	0.06	0.04	0.02	0.01

KEY STUDY: NOAEL for spleen weight, hematological changes, and overt signs of toxicity in male and female mice exposed to 0.5 ppm for 6 hrs (Blair et al., 1990).

SCALING: $C^2 \times t = k$

(0.5 ppm)^2 x 6 hr = 1.7 ppm·hr

UF: 10 for interspecies extrapolation
3 for intraspecies variability

AEGL-2   NO HEC ADJUSTMENT

AEGL-2 FOR ARSINE (ppm)				
	30-min	**1-hr**	**4-hr**	**8-hr**
AEGL-2	0.4	0.3	0.2	0.1

KEY STUDY: LOAEL of 9 ppm based upon minor, reversible hematological changes in mice following 1-hour exposure.   At 15 ppm, hematological changes were significant and at 26 ppm there was 100% mortality. (Peterson and Bhattacharyya, 1985).

SCALING: $C^2 \times t = k$

$(9 \text{ ppm})^2 \times 1 \text{ hr} = 81 \text{ ppm·hr}$

UF: 10 for interspecies extrapolatio
3 for intraspecies variability

AEGL-3 NO HEC ADJUSTMENT

AEGL-3 FOR ARSINE (ppm)				
AEGL Level	30-min	1-hr	4-hr	8-hr
AEGL-3	0.4	0.3	0.1	0.1

KEY STUDY: Lethality in mice exposed to 26 ppm for 1 hr. (Peterson and Bhattacharyya, 1985)

SCALING: $C^2 \times t = k$

$(26 \text{ ppm})^2 \times 1 \text{ hr} = 676 \text{ ppm·hr}$

UF: 10 for interspecies extrapolation
3 for intraspecies variability
3 for estimation of lethality

DERIVATION OF AEGL-2 VALUES FROM DIFFERENT DATA SETS				
Time Point	Peterson and Bhattacharyya (1985); rats, UF = 30[a]; hematological alterations at 9 ppm, 1 hr	Peterson and Bhattacharyya (1985); rats, UF = 30[a]; hematological alterations at 11 ppm, 1 hr	Blair et al. (1990) rats; UF = 30[a]; hematological alterations at 5 ppm, 6 hrs	Flury and Zernik (1931), humans UF = 3[a]; no toxic effect at 3.1 ppm, 6 hrs
0.5 hr	0.4 ppm	0.5 ppm	0.6 ppm	4 ppm
1 hr	0.3 ppm	0.4 ppm	0.4 ppm	3 ppm
4 hr	0.2 ppm	0.1 ppm	0.2 ppm	1 ppm
8 hr	0.1 ppm	0.1 ppm	0.1 ppm	1 ppm

[a]   UF of 30 includes 10 for interspecies variability and 3 for intraspecies variability; UF of 3 includes 3 for interspecies variability

No HEC Adjustment

Time Point	Kensler et al. (1946); monkeys, UF = 30[a]; 50% mortality at 35 ppm, 15 min.[b]	Peterson and Bhattacharyya (1985); mice, UF = 90[c], 60% mortality at 26 ppm, 1 hr	Henderson and Haggard (1943); human 30-min LC_{lo}: 250 ppm, UF = 30[d]	Flury and Zernik (1931): potentially lethal to humans, 6.25 ppm for 1 hr, UF = 3[e]
0.5 hr	1 ppm	0.4 ppm	8 ppm	3 ppm
1 hr	0.6 ppm	0.3 ppm	6 ppm	2 ppm
4 hr	0.3 ppm	0.1 ppm	3 ppm	1 ppm
8 hr	0.2 ppm	0.1 ppm	2 ppm	1 ppm

[a]   UF of 30 includes 10 for interspecies variability and 3 for intraspecies variability.

[b]   One of two animals tested died shortly after exposure.

[c]   Within 4 days postexposure, mortality was 100%; UF of 90 includes 10 for interspecies variability, 3 for intraspecies variability, and 3 for estimating a lethality threshold.

[d]   UF of 30 includes 3 for intraspecies variability and 10 to adjust LC_{lo} endpoint to threshold for lethality.

[e]   UF of 3 for protection of sensitive individuals; 6.25 ppm considered a threshold based upon "dangerous to life" comment by Flury and Zernik (1931).

No HEC Adjustment

AEGL VALUES FOR DIMETHYLDICHLOROSILANE

- ◆ ENDPOINTS OF CONCERN

- ◆ SELECTION OF THE KEY STUDY

- ◆ SCALING BETWEEN ANIMAL EXPOSURE LEVELS AND HUMAN EXPOSURE LEVELS FOR AN EFFECT

- ◆ UNCERTAINTY FACTOR TO ACCOUNT FOR EXTRAPOLATION FROM ANIMAL TO HUMAN EXPOSURE VALUES

- ◆ UNCERTAINTY FACTOR TO ACCOUNT FOR SENSITIVE HUMAN POPULATIONS

- ◆ SCALING BETWEEN TIME VALUES FOR AN EFFECT

- ◆ STEEPNESS OF THE DOSE RESPONSE CURVE

- ◆ DEVELOPMENT OF AEGL VALUES

  ▸ SHOULD WE DEVELOP AEGL-1 AND AEGL-2 VALUES FROM RD50 VALUES AND SAFETY FACTORS?

- ◆ LAUGH TEST

DIMETHYLDICHLOROSILANE REACTS AND COMPOSES IN THE PRESENCE OF WATER AS FOLLOWS:

1 MOLE DIMETHYLDICHLOROSILANE YIELDS 2 MOLES OF HYDROGEN CHLORIDE

DIMETHYLDICHLOROSILANE ITSELF IS OFTEN NOT DETECTED IN EXPERIMENTAL EXPOSURE CHAMBERS

CO, CO_2, AND SiO MAY ALSO BE PRODUCED FROM COMBUSTION

Classification	30-min	1-hour	4-hour	8-hour	Endpoint (Reference)
	PROPOSED AEGL VALUES FOR DIMETHYLDICHLOROSILANE				
AEGL-1 (Nondisabling)	·1.03 ppm (5.5 mg/m^3)	0.73 ppm (3.87 mg/m^3)	0.36 ppm (1.91 mg/m^3)	0.26 ppm (1.38 mg/m^3)	RD$_{50}$ for HCl in mice modified by 0.01 to estimate a no irritation level in humans (Alarie, 1981)
AEGL-2 (Disabling)	10.3 ppm (54.6 mg/m^3)	7.3 ppm (38.7 mg/m^3)	3.6 ppm (19.1 mg/m^3)	2.6 ppm (13.8 mg/m^3)	RD$_{50}$ for HCl in mice modified by 0.1 to estimate an irritation level in humans (Alarie, 1981)
AEGL-3 (Lethality)	36.8 ppm (195 mg/m^3)	26 ppm (138 mg/m^3)	13 ppm (68.9 mg/m^3)	9.2 ppm (48.8 mg/m^3)	10% of 1-hour rat LC$_{50}$ for dimethhyldichlorosilane (Kolesar et al., 1987)

1-HOUR LC$_{50}$ VALUES OF HCL AND CHLOROSILANES IN SPRAGUE-DAWLEY RATS*		
Compound	Actual LC$_{50}$ (ppm)	Predicted LC$_{50}$ (ppm) Based on HCl Equivalents
HCl	8800	8800
Trimethylchlorosilane	2928	2928
Dimethyldichlorosilane	2341	4682
Methyltrichlorosilane	1547	4641
Trichlorosilane	2767	8301

*Kolesar et al, 1987

Table 3. Predictions of level and type of responses in humans at various multiples of RD$_{50}$ value found in mice.

Multiples of RD$_{50}$	Response
10	Severe injury, possibly lethal
1	Intolerable to humans
0.1	Some sensory irritation
0.01	No sensory irritation
0.001	No effect of any kind on respiratory system

AEGL-1 FOR DIMETHYLDICHLOROSILANE (ppm [mg/m^3])				
AEGL Level	30-min	1-hr	4-hr	8-hr
AEGL-1	1.03 [5.5]	0.73 [3.87]	0.36 [1.91]	0.26 [1.38]

Species: Mouse
Concentration: 309 ppm hydrogen chloride
Time: 10 minutes
Endpoint: RD_{50}

RD_{50} x 0.01 = 8-hour human exposure level corresponding to no sensory irritation

n = 2

Adjustment Factors:

    2: HCl molar equivalents

    2: Relative toxicity of dimethyldichlorosilane vs. HCl

Uncertainty Factor:

    3: Sensitive human subpopulations

(No factor is used for mouse to human extrapolation. The multiplicative factor yields a human response level)

Total adjustment/uncertainty factor: 12

AEGL-2 FOR DIMETHYLDICHLOROSILANE (ppm [mg/m^3])				
AEGL Level	30-min	1-hr	4-hr	8-hr
AEGL-2	10.3 [54.6]	7.3 [38.7]	3.6 [19.1]	2.6 [13.8]

Species: Mouse
Concentration: 309 ppm hydrogen chloride
Time: 10 minutes
Endpoint: RD$_{50}$

RD$_{50}$ x 0.1 = 8-hour human exposure level corresponding to some
                    sensory irritation

n = 2

Adjustment Factors:

    2: HCl molar equivalents

    2: Relative toxicity of dimethyldichlorosilane vs. HCl

Uncertainty Factor:

    3: Sensitive human subpopulations

(No factor is used for mouse to human extrapolation. The multiplicative facto
yields a human response level)

Total adjustment/uncertainty factor: 12

AEGL-3 FOR DIMETHYLDICHLOROSILANE (ppm [mg/m^3])				
AEGL Level	30-min	1-hr	4-hr	8-hr
AEGL-3	36.8 [195]	26 [138]	13 [68.9]	9.2 [48.8]

Species: Rat
Concentration: 2341 ppm dimethyldichlorosilane
Time: 1 hour
Endpoint: LC_{50}

LC_{50} x 0.1 = "conservative toxicity value"

n = 2

Uncertainty Factors:

    3: Sensitive human subpopulations

    3: Rat to human

(Factors of 3 rather than 10 are justified since using 10% of the LC_{50} is inherently conservative)

Total uncertainty factor: 9

PROPOSED AEGL VALUES FOR DIMETHYLDICHLOROSILANE

Classification	30-min	1-hour	4-hour	8-hour	Endpoint (Reference)
AEGL-1 (Nondisabling)	1.03 ppm (5.5 mg/m^3)	0.73 ppm (3.87 mg/m^3)	0.36 ppm (1.91 mg/m^3)	0.26 ppm (1.38 mg/m^3)	RD$_{50}$ for HCl in mice modified by 0.01 to estimate a no irritation level in humans (Alarie, 1981)
AEGL-2 (Disabling)	10.3 ppm (54.6 mg/m^3)	7.3 ppm (38.7 mg/m^3)	3.6 ppm (19.1 mg/m^3)	2.6 ppm (13.8 mg/m^3)	RD$_{50}$ for HCl in mice modified by 0.1 to estimate an irritation level in humans (Alarie, 1981)
AEGL-3 (Lethality)	36.8 ppm (195 mg/m^3)	26 ppm (138 mg/m^3)	13 ppm (68.9 mg/m^3)	9.2 ppm (48.8 mg/m^3)	10% of 1-hour rat LC$_{50}$ for dimethhyldichlorosilane (Kolesar et al., 1987)

ERPG values for dimethyldichlorosilane (AIHA, 1996):

ERPG-1: 0.8 ppm

ERPG-2: 5 ppm

ERPG-3: 25 ppm

Belluck, David [ASEPRO]

From:	Belluck, David [ASEPRO]
To:	Goldsmith, Leslie [HWPDS]; Lu, Po-Yung; Norris, James
Cc:	Belluck, David [ASEPRO]
Subject:	Discussion Points for AEGL Support Document Format
Date:	Wednesday, August 28, 1996 9:26AM

Hi guys. Here are a few ideas that I thought we could kick around. Most involve a summary section that would uniformly pull all important data into a single tabular form. They are in no specific order at this time and are for discussion purposes only. I spoke with several committee members, including the Chairman, at the last meeting and they thought these might be useful and simple additions to text or appendices.

The checklist format provides a concise summary of all data and evaluation elements you normally use in your documents and addresses many of the repetitive questions asked by the committee. It allows for data summation with minimal prose.

Please get back to me at your earliest opportunity.
DAB

FIRST DRAFT: IDEAS FOR FORMAT CHANGES IN AEGL SUPPORT DOCUMENTS

AEGL DATA AGGREGATION, CALCULATION AND SELECTION

AEGL Using Standard Calculation

Critical Study:
Source of Data Peer Reviewed?:
Route of Exposure:
Critical Toxic Lesion:
Reversible Effect?:
Secondary Lesions:
Reversible Effect?:
Concentration Selection:
Reason for Selection:
Confidence in Study (High, Medium, Low):
Study Strengths for AEGL Purposes:
Study Deficiencies for AEGL Purposes:
Interspecies UF (Directly Related to Study Confidence):
Intraspecies UF (Directly Related to Study Confidence):
Complete AEGL Calculations: −
Proposed AEGL and Reasons for its Selection:
Proposed AEGL and Reasons for Its Rejection:

AEGL Using Alternate Calculations

Critical Study:
Source of Data Peer Reviewed?:
Route of Exposure:
Critical Toxic Lesion:
Reversible Effect?:
Secondary Lesions:
Reversible Effect?:
Concentration Selection:
Reason for Selection:
Confidence in Study (High, Medium, Low):
Study Strengths for AEGL Purposes:
Study Deficiencies for AEGL Purposes:
Interspecies UF (Directly Related to Study Confidence):
Intraspecies UF (Directly Related to Study Confidence):
Complete AEGL Calculations:

Proposed AEGL and Reasons for its Selection:
Proposed AEGL and Reasons for Its Rejection:

Benchmark Value

Critical Study:
Source of Data Peer Reviewed?:
Route of Exposure:
Critical Toxic Lesion:
Reversible Effect?:
Secondary Lesions:
Reversible Effect?:
Concentration Selection:
Reason for Selection:
Confidence in Study (High, Medium, Low):
Study Strengths for AEGL Purposes:
Study Deficiencies for AEGL Purposes:
Interspecies UF (Directly Related to Study Confidence):
Intraspecies UF (Directly Related to Study Confidence):
Complete AEGL Calculations:
Proposed AEGL and Reasons for its Selection:
Proposed AEGL and Reasons for Its Rejection:
Slope of Benchmark Value (High, Medium, Low):

QSAR Based AEGL

Critical Study:
Source of Data Peer Reviewed?:
Route of Exposure:
Critical Toxic Lesion:
Reversible Effect?:
Secondary Lesions:
Reversible Effect?:
Concentration Selection:
Reason for Selection:
Confidence in Study (High, Medium, Low):
Study Strengths for AEGL Purposes:
Study Deficiencies for AEGL Purposes:
Interspecies UF (Directly Related to Study Confidence):
Intraspecies UF (Directly Related to Study Confidence):
Complete AEGL Calculations:
Proposed AEGL and Reasons for its Selection:
Proposed AEGL and Reasons for Its Rejection:

Taste Threshold of Chemical

Taste Threshold Concentration:
Does AEGL exceed taste threshold?:
Relationship of threshold to AEGL concentrations:

Odor Threshold of Chemical

Odor Threshold Concentration:
Does AEGL exceed odor threshold?:
Relationship of threshold to AEGL concentrations:

AEGLs Vs. Existing Regulatory Concentrations.

Comparison of Calculated AEGLs to Existing Regulatory Concentrations:

Proposed AEGL and Reason for its Selection

SUMMARY OF ORNL PREFERRED AEGL METHOD AND CONCENTRATION

Proposed future chemicals for AEGLs NAC meetings

December 16-18, 1996*: Ariel Rios Building, Washington, D.C.

CAS no.	Chemical name	Chemical manager	Chemical reviewer	ORNL author	Doc. release date	Notes
57-14-7	Dimethyl hydrazine	Thomas	Blackman/Rogers	Young	11/15/96	
60-34-4	Methyl hydrazine	Thomas	Blackman/??	Young	11/15/96	
75-21-8	Ethylene oxide	Borak	Alexeeff/Blackman	Davidson	11/15/96 (?)	
75-44-5	Phosgene	Bress	Belluck/Gephart	Norris	11/7/96	
7782-50-5	Chlorine	Gephart	Alexeeff/Blackman	Talmage	10/31/96	
7803-51-2	Phosphine	Alexeeff	Falke/Post	Bast	10/31/96	

* *Ammonia*: Final review
  Cyanogen chloride: Final status review
  Nitric acid: Any new relevant studies of NO_2

March 1997

CAS no.	Chemical name	Chemical manager	Chemical reviewer	ORNL author	Doc. release date	Notes
56-23-5	Carbon terachloride	Bress	Hansen/Thomas	Young		
62-53-3	Aniline	Colonna	??/??	Talmage		
91-08-7 & 584-84-9	Toluene 2,6-diisocyanate & 2,4-isomer	Barbee	Borak/Hansen	Forsyth		
108-23-6	Isopropyl chloroformate	Hansen	??/??	Bast		
151-56-4	Ethyleneimine	McClanahan	Niemeier/??	Davidson		
624-83-9	Methyl isocyanate	Koller	Post/??	Norris		
7647-01-0	Hydrogen chloride	Hinz	??/??	Bast		

National Advisory Committee (NAC)
for Acute Exposure Guideline Levels (AEGL) for Hazardous Substances
Final Meeting 2 Highlights
Green Room, 3rd Floor, Ariel Rios Building
1200 Pennsylvania Avenue, NW
Washington, D.C.
August 5-7, 1996

INTRODUCTION

The highlights of the meeting are outlined below, and the meeting agenda (Attachment 1) and attendee lists (Attachment 2) are attached.

The highlights for the initial meeting (June 19-21, 1996) were distributed and were approved with minor changes. The final version of NAC Meeting 1 Highlight is attached as Appendix A.

Dr. Roger Garrett welcomed the committee members. Dr. Garrett indicated that in FY 1997 only four committee meetings would be scheduled, thereby allowing adequate time for preparation of the draft AEGL documents and for members to review the draft documents. He emphasized that sound science was the objective and that it would not be compromised for the sake of the schedule. Also he hoped that committee members would not have to be the chemical manager for more than two chemicals. He was pleased that the committee had reached consensus on the proposed fluorine AEGL values from last meeting and considered this a good start.

Following Dr. Garrett's remarks, Dr. Richard Thomas led a discussion on the wording of the AEGL definitions, and some changes were made (see Attachment 3 for revised definitions).

The next order of business was three topical presentations on the use of intraspecies (Mr. Robert Ross, Drs. Jonathan Borak and George Alexeeff, Attachments 4,5,6) and interspecies (Dr. Robert Young, Attachment 7) uncertainty factors (UF). The purpose of these short presentations was to emphasize that the choice of a numerical value for each UF was a chemical-specific decision and that defaults of 10 were not always necessary.

Dr. Borak presented information on sulfur dioxide that suggests that the sensitivity among humans may vary only by a factor of 3 or 4.

Following these presentations, chemical-specific discussions began. The highlights of each discussion are presented below followed by a section on comments and suggestions for improving the AEGL process.

Ammonia, CAS No. 7664-41-7

Chemical manager: Mr. Larry Gephart, Exxon Biomedical Sciences
Author: Dr. Kowetha A. Davidson, ORNL

At NAC Meeting 1, AEGL-1 values were approved but the AEGL-2 &3 values were deferred to meeting 2. Mr. Larry Gephart led the discussion(Attachment 8) and later was expanded by Dr. George Alexeeff (Attachment 9).   Two individuals representing industry groups, Dr. Robert Michaels and Mr. Ken Anderson, and Mr. Fred Millar, representing Friends of the Earth, gave presentations/statements. Dr. Michaels (Attachment 10) and Mr. Anderson were concerned that the AEGL values were too low and indicated that additional information was available that would assist the committee. Mr. Millar stated that he thought that a number of industry reports regarding ammonia exposures in the workplace were available. The committee agreed to defer Ammonia to the next meeting to consider additional information that was to be provided by Mr. Ken Anderson by August 26, l996.

Cyanogen Chloride, CAS No. 506-77-4

Chemical manager: Dr. Mark McClanahan, CDC
Author: Dr. Carol Forsyth, ORNL

As summarized by Dr. Forsyth's presentation (Attachment 11), there was a paucity of data on this compound. The information available for analysis was quite out-dated and had been cited from secondary sources. An effort will be made to determine if primary literature does exist, but from the citation trail available, it is doubtful that much will be found. The compound was deferred to the next meeting. The possibility of laboratory tests to fill data gaps was mentioned, but no decision was made.

Methyl Mercaptan, CAS No. 74-93-1

Chemical manager: Dr. Doan Hansen, BNL
Author: Dr. James C. Norris, ORNL

This chemical was introduced by Dr. Doan Hansen (Attachment 12) and revisited because the availability of industrial data that had not been acquired prior to Meeting 1. This information contained data potentially useful for AEGL 1 and 2. The author of the study sent Dr. Norris what he considered relevant portions of the methyl mercaptan toxicology report. After presentation by Dr. Norris (Attachment 13) and some discussion by committee members it was decided that indeed the information looked promising regarding establishing AEGL-1 and AEGL-2 values, but the entire report would be needed to thoroughly consider the situation. Thus, a decision on these values was deferred until the next meeting. Regarding the AEGL-3 values the committee reached a consensus 31, 23, 13, and 10 ppm as the proposed values for 30 min., 1 h, 4 h, and 8 h, respectively (Ballot attached: Appendix B). These values were based on the Tansy et al. (1981) study, which identified a highest nonlethal value of 400 ppm to which an uncertainty factor of 30 (10 for intraspecies and

3 for interspecies) was applied. A factor of 3 instead of 10 was used for interspecies extrapolation because of the steep dose-response curve. For scaling using the ten Berge equation, *n* was equal to 2.5, which was the value assigned to the structurally related hydrogen sulfide.

Hydrogen Fluoride, CAS No. 7664-39-3

Chemical manager: Mr. Larry Gephart, Exxon Biomedical Sciences
Author: Dr. Sylvia Talmage, ORNL

Mr. Larry Gephart presented a summary of the draft technical support document as shown in Attachment 14. Additional unpublished animal data from studies conducted by the Petroleum Environmental Research Forum (PERF) were presented by Dr. Walden Dalbey of the Mobil Business Resources Corporation (Attachment 15). The PERF studies were conducted with mouth-breathing rats (a potentially more realistic model for the human breathing pattern during exposure to irritant chemicals than nose-breathing rats).

The AEGL-1 values presented in the technical support document were discussed and accepted by the AEGL NAC on August 6, 1996, with the following revisions: the numbers should be rounded to the nearest whole integer and the curve should be flattened. The NAC noted that these are approximate values that reflect the imprecision of the data.

In addition to the AEGL-2 values proposed in the technical support document, additional values from the rat data of the PERF report as they pertain to the AEGL-2 definition were discussed. These values for 10-min. exposures were: 1764 ppm, serious effects; 950 ppm, no serious effects; and 271 ppm, slight local irritation. The 30-min. and 1-h AEGL-2 values were derived from the 10-min. 950 ppm value for no serious effects. This value was divided by an uncertainty factor of 30 (for interspecies and intraspecies differences) and scaled to the different time periods using $C^2 \times t = k$. The 4- and 8-h AEGL-2 values were based on the human exposure study as discussed in the original draft technical support document.

The proposed AEGL-3 values as derived in the technical support document were accepted by NAC (Ballot attached: Appendix C). The following is a summary of proposed values.

Additional discussion focused on the merit of a single 10-min. AEGL value since a 10-min. exposure is characteristic of actual accident emergency situations.

SUMMARY TABLE OF PROPOSED AEGL VALUES FOR HYDROGEN FLUORIDE					
Classification	30-min.	1-h	4-h	8-h	Endpoint (Reference)
AEGL-1	2 ppm, 1.6 mg/m^3	2 ppm, 1.6 mg/m^3	1 ppm, 0.8 mg/m^3	1 ppm, 0.8 mg/m^3	Slight eye and nose irritation in humans (Largent 1960, 1961)
AEGL-2	18 ppm, 15 mg/m^3	13 ppm, 11 mg/m^3	10 ppm, 8 mg/m^3	7 ppm, 6 mg/m^3	NOAEL for serious lung effects in rats (PERF 1996)[a]; highest concentration for slight eye and nose irritation and red dening of facial skin in humans (Largent 1960, 1961)[b]
AEGL-3	62 ppm, 51 mg/m^3	44 ppm, 36 mg/m^3	22 ppm, 18 mg/m^3	15 ppm, 13 mg/m^3	Threshold for lethality in mice (Wohlslagel et al. 1976)

[a]30-min. and 1-h AEGL-2 values.
[b]4-h and 8-h AEGL-2 values.

Hydrazine, CAS No. 302-01-2
Chemical manager: Dr. Richard Thomas, I.C.E.H.
Author: Dr. Robert A. Young, ORNL

At Meeting 1, Dr. Thomas indicated that some epidemiological studies needed to be evaluated, and this was done with the result that no additional useful information was found (Attachment 16). Also, a cancer assessment was conducted since the last meeting and showed that the cancer risk would be inconsequential relative to noncancer effects of hydrazine acute exposure. The proposed AEGL values in the following table were presented by Dr. Robert Young, ORNL (Attachment 17) and were accepted by the committee. There were two "no" votes for AEGL-1, one " no"ote for AEGL-2, and none for AEGL-3 (Ballot attached: Appendix D). The AEGL-1 values for the four time periods are the same because the effect of concern was irritancy that is time independent.

SUMMARY TABLE OF PROPOSED AEGL VALUES FOR HYDRAZINE					
Classification	30 - Min.	1-h	4-h	8-h	Endpoint/Reference
AEGL-1	0.1 ppm, 0.13mg/m^3	0.1 ppm, 0.13mg/m^3	0.1 ppm, 0.13mg/m^3	0.1 ppm, 0.13mg/m^3	Eye and facial irritation in monkeys (House, 1964)
AEGL-2	8 ppm, 10mg/m^3	6 ppm, 8mg/m^3	3 ppm, 4mg/m^3	2 ppm, 3mg/m^3	Nasal lesions in rats (Latendresse et al., 1995)
AEGL-3	47 ppm, 61mg/m^3	33 ppm, 43mg/m^3	17 ppm, 22mg/m^3	12 ppm, 16mg/m^3	Lethality in rats (HRC, 1993)

Comments and Suggestions for Improvements to AEGL Process

The following are comments from the committee members regarding the AEGL process. The order of presentation does not imply a ranking of importance.

1. Preparation of IRIS-like summaries of key studies in table format that contains values, uncertainty factors, and confidence assessment would be helpful.

2. A list of what signs and symptoms constitute the respective AEGL values is needed.

3. In addition to the chemical manager, two committee members should be assigned to each chemical.

4. The rationale for chemical selection needs to be provided.

5. Odor threshold should be considered for establishing AEGL-1 values.

6. Material requiring evaluation should be sent to committee members prior to the meeting and not be distributed at meetings.

7. Each AEGL document should provide the calculations, perhaps in an appendix.

8. Participation by the Office of Research and Development of EPA is needed to ensure overall EPA concurrence.

9. Standardization of decision criteria is needed.

10. Guidelines are needed to determine when and when not to use the Benchmark Dose approach.

11. Committee members' comments to the chemical manager are needed at least two weeks prior to each meeting.

12. Validation of analytical methods is needed.

13. The reason for a "no" vote on a chemical needs to be recorded.

14. Upcoming chemicals should be "advertised" in the *Federal Register* to ensure that all data are obtained and appropriate interest groups are notified.

15. Biology should be more important than models.

This meeting highlight was prepared by Mr. Robert Young and Dr. Po-Yung Lu, ORNL.

LIST of ATTACHMENTS

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

Attachment 1. NAC/AEGL meeting No. 2 agenda
Attachment 2. Attendee list
Attachment 3. Revised definitions of AEGLs
Attachment 4. Interspecies uncertainty
Attachment 5. An update on sulfur dioxide
Attachment 6. Use of uncertainty and modifying factors for developing threshold-based AEGLs
Attachment 7. Adjustment of interspecies uncertainty factor
Attachment 8. Data analysis of Ammonia
Attachment 9. Benchmark dose level for Ammonia
Attachment 10. Public comment from RAM TRAC Corporation on ammonia
Attachment 11. Data analysis of Cyanogen chloride
Attachment 12. Summary of changes in draft AEGL TSD of Methylmercaptan
Attachment 13. Data analysis of Methylmercaptan
Attachment 14. Data analysis of Hydrogen fluoride
Attachment 15. Summary of PERF project 92-09
Attachment 16. Discussion of issues identified at first NAC./AEGL meeting
Attachment 17. Data analysis of Hydrazine

LIST OF APPENDICES

Appendix A. Revised meeting highlights of NAC/AEGL-1

Appendix B

PREFACE

Under the authority of the Federal Advisory Committee Act (FACA) P.L. 92-463 of 1972, which authorizes development of Acute Exposure Guidelines Levels (AEGLs), the National Advisory Committee has been established to identify, review, and interpret relevant toxicological and other scientific data and to develop AEGLs for high-priority, acutely toxic chemicals.

AEGLs represent ceiling exposure values for the general public and are applicable to emergency exposure periods ranging from less than 1 hour to 8 hours. Three AEGLs will be developed for each of four exposure periods (30 minutes, 1 hour, 4 hours, and 8 hours) and will be distinguished by varying degrees of severity of toxic effects. The three AEGLs have been defined as follows:

AEGL-3 is the airborne concentration (expressed as ppm and mg/m^3) of a substance at or above which it is predicted that the general population, including "susceptible" but excluding "hypersusceptible" individuals, could experience life-threatening effects or death. Airborne concentrations below AEGL-3 but at or above AEGL-2 represent exposure levels that may cause irreversible or other serious, long-lasting effects or impaired ability to escape.

AEGL-2 is the airborne concentration (expressed as ppm and mg/m^3) of a substance at or above which it is predicted that the general population, including "susceptible" but excluding "hypersusceptible" individuals, could experience irreversible or other serious, long-lasting effects or impaired ability to escape. Airborne concentrations below AEGL-2 but at or above AEGL-1 represent exposure levels that may cause notable discomfort.

AEGL-1 is the airborne concentration (expressed as ppm and mg/m^3) of a substance at or above which it is predicted that the general population, including "susceptible" but excluding "hypersusceptible" individuals, could experience notable discomfort. Airborne concentrations below AEGL-1 represent exposure levels that could produce mild odor, taste, or other sensory irritations.

APPENDIX C

Date of AEGL NAC meeting: **Chemical :** CYANOGEN CHLORIDE

NAC member	AEGL 1	AEGL 2	AEGL 3
George Alexeeff	Y	Y	Y
Steven Barbee	Y	Y	Y
Lynn Beasley			
David Belluck	Y	Y	Y
Kyle Blackman	Y	Y	Y
Jonathan Borak	Y	Y	Y
William Bress	Y	Y	Y
Guy Colonna			
George Cushmac	Y	Y	Y
Ernest Falke	Y	Y	Y
Larry Gephart	Y	Y	Y
Dan Guth			
Jim Holler	150	150	150
Loren Koller	N	N	Y
Mark A. McClanahan	Y	Y	Y
Zarena Post			
George Rodgers			
George Rusch			
Bob Snyder			
Thomas J. Sobotka			
Richard Thomas	Y	Y	Y
Thomas Tuccinardi			
Tally	11/12	11/12	12/12

PPM, (mg/m³)	30 Min	60 Min	4 Hr	8 Hr
AEGL 1	, (NA)	, (NA)	, (NA)	, (NA)
AEGL 2	, (NA)	, (NA)	, (NA)	, (NA)
AEGL 3 INSUFFICIANT DATA	NA , (N/A)	NA , (NA)	NA , (NA)	NA , (NA)

Approved by Chair: _____   **Date:** 9/17/96

DFO: Paul S. Tobin _____   **Date:** 9/17/96

Date of AEGL NAC meeting: **Chemical :** NITRIC ACID

NAC member	AEGL 1	AEGL 2	AEGL 3
George Alexeeff	Y	Y	Y
Steven Barbee	Y	Y	Y
Lynn Beasley	Y	Y	Y
David Belluck	Y	Y	Y
Kyle Blackman	Y	Y	Y
Jonathan Borak	Y	Y	Y
William Bress	Y	Y	Y
Guy Colonna			
George Cushmac	Y	Y	Y
Ernest Falke	Y	Y	Y
Larry Gephart	Y	Y	Y
Dan Guth			
Jim Holler	Y	Y	Y
Loren Koller	Y	Y	Y
Mark A. McClanahan	Y	Y	Y
Zarena Post			
George Rodgers	Y	Y	Y
George Rusch			
~~Bob Snyder~~ JOHN HINZ			
Thomas J. Sobotka RICHARD NIEMEIER	Y	Y	Y
Richard Thomas	Y	Y	Y
Thomas Tuccinardi -			
Tally	16/16	16/16	16/16

PPM, (mg/m³)	30 Min	60 Min	4 Hr	8 Hr
AEGL 1	0.5 , ( )	0.5 , ( )	0.5 , ( )	0.5 , ( )
AEGL 2	5 , ( )	4 , ( )	3 , ( )	2 , ( )
AEGL 3	27 , ( )	22 , ( )	15 , ( )	12 , ( )

Approved by Chair: _____   **Date:** 9/18/96

DFO: Paul S. Tobin   **Date:** 9/18/96

Date of AEGL NAC meeting: **Chemical :** HYDROGEN CYANIDE

NAC member	AEGL 1	AEGL 2		AEGL 3
George Alexeeff	Y	Y	Y	Y
Steven Barbee	Y	N	Y	Y
Lynn Beasley	Y	N	Y	Y
David Belluck	Y	N	Y	Y
Kyle Blackman	Y	N	Y	Y
Jonathan Borak	Y	N	Y	Y
William Bress	Y	Y	Y	Y
Guy Colonna				
George Cushmac	Y	N	Y	Y
Ernest Falke	Y	Y	Y	Y
Larry Gephart	Y	N	Y	N
Dan Guth				
Jim Holler ✱	(Y)	(N)	(Y)	(Y)
Loren Koller	Y	N	Y	Y
Mark A. McClanahan	Y	N	Y	N
Zarena Post				
George Rodgers	Y	Y	Y	N
George Rusch				
Bob Snyder				
~~Thomas J. Sobotka~~ RICHARD NIEMEIER ✱	(Y)	(N)	(Y)	(N)
Richard Thomas	Y	N	Y	Y
Thomas Tuccinardi				
✚ = NOT OFFICIALLY A MEMBER AT THE TIME Tally	14/14	4/14	14/14	11/14

PPM, (mg/m³)	30 Min	60 Min	4 Hr	8 Hr
AEGL 1	NA , ( )	NA , ( )	NA , ( )	NA , ( )
AEGL 2	10 , ( )	7 , ( )	4 , ( )	3 , ( )
AEGL 3	20 , ( )	14 , ( )	7 , ( )	5 , ( )

AEGL 2'   7   5   3   2

Approved by Chair: _____   **Date:** 9/19/96

DFO: _____   **Date:** 9/18/96

Date of AEGL NAC meeting: **Chemical :** 1,2-DICHLOROETHENE

NAC member	AEGL 1	AEGL 2	AEGL 3
George Alexeeff	N	N	N
Steven Barbee	Y	Y	Y
Lynn Beasley	Y	Y	Y
David Belluck	Y	Y	Y
Kyle Blackman	Y	Y	Y
Jonathan Borak	Y	Y	Y
William Bress	Y	Y	Y
Guy Colonna			
George Cushmac	Y	Y	Y
Ernest Falke	Y	Y	Y
Larry Gephart	N	N	N
Dan Guth			
Jim Holler ✸	(Y)	(Y)	(Y)
Loren Koller			
Mark A. McClanahan	Y	Y	Y
Zarena Post			
George Rodgers	Y	Y	Y
George Rusch			
Bob Snyder			
~~Thomas J. Sobotka~~ ✸ RICHARD NIEMEIER	(Y)	(Y)	(Y)
Richard Thomas	Y	Y	Y
Thomas Tuccinardi			
✸ NOT OFFICIALLY A MEMBER AT THIS TIME Tally =	¹¹/₁₃	¹¹/₁₃	¹¹/₁₃

PPM, (mg/m³)	30 Min	60 Min	4 Hr	8 Hr
AEGL 1	19 , ( )	13 , ( )	7 , ( )	5 , ( )
AEGL 2	56 , ( )	40 , ( )	20 , ( )	14 , ( )
AEGL 3	200 , ( )	141 , ( )	71 , ( )	50 , ( )

Approved by Chair: _____   **Date:** 9/18/96

DFO: _____   **Date:** 9/18/96

Date of AEGL NAC meeting: **Chemical :** METHI MERCAPTAN

NAC member	AEGL 1	AEGL 2	AEGL 3
George Alexeeff	ABSTAIN	Y	
Steven Barbee	Y	Y	
Lynn Beasley	Y	Y	
David Belluck	Y	Y	
Kyle Blackman	Y	Y	
Jonathan Borak	ABSENT		
William Bress	Y	Y	
Guy Colonna	ABSENT		
George Cushmac	Y	Y	
Ernest Falke	Y	Y	
Larry Gephart	Y	Y	
Dan Guth	ABSENT		
Jim Holler ✱	(Y)	(Y)	
Loren Koller	ABSENT		
Mark A. McClanahan	ABSENT		
Zarena Post	ABSENT		
George Rodgers	Y	Y	
George Rusch	NOT VOTING		
Bob Snyder	ABSENT		
Thomas J. Sobotka (NIEMEIER)✱	(Y)	(Y)	
Richard Thomas	Y	Y	
Thomas Tuccinardi = (DOAN HANSEN)✱✱	Y	Y	
Tally =	10/10	10/10	

✱ - NOT CURRENTLY A MEMBER
✱✱ - NOT A MEMBER

PPM, (mg/m³)	30 Min	60 Min	4 Hr	8 Hr
AEGL 1	0.5 , ( )	0.5 , ( )	0.5 , ( )	0.5 , ( )
AEGL 2	7 , ( )	5 , ( )	3 , ( )	2 , ( )
AEGL 3	, ( )	, ( )	, ( )	, ( )

Approved by Chair: _____ **Date:** 8/19/97

DFO: _____ **Date:** 9/19/96

Date of AEGL NAC meeting: **Chemical :** ARSINE

NAC member	AEGL 1	AEGL 2	AEGL 3
George Alexeeff	Y	Y	Y
Steven Barbee	Y	Y	Y
Lynn Beasley	Y	Y	Y
David Belluck	Y	Y	Y
Kyle Blackman	Y	Y	Y
Jonathan Borak			
William Bress	Y	Y	Y
Guy Colonna			
George Cushmac	Y	Y	Y
Ernest Falke	Y	Y	Y
Larry Gephart	Y	Y	Y
Dan Guth			
Jim Holler ✶	(Y)	(Y)	(Y) ✶
Loren Koller			
Mark A. McClanahan			
Zarena Post			
George Rodgers	Y	Y	Y
George Rusch			
Bob Snyder			
Thomas J. Sobotka (R. NIEMEIER)✶	(Y)	(Y)	(Y)✶
Richard Thomas	Y	Y	Y
~~Thomas Tuccinardi~~ (NOAH HANSEN)✶✶	Y	Y	(Y)✶✶
Tally	- ¹¹/₁₁	¹¹/₁₁	¹¹/₁₁

PPM, (mg/m³)	30 Min	60 Min	4 Hr	8 Hr
AEGL 1	✶✶✶ , ( )	✶✶✶ , ( )	✶✶✶ , ( )	✶✶✶ , ( )
AEGL 2	0.24 , ( )	0.17 , ( )	0.08 , ( )	0.06 , ( )
AEGL 3	0.7 , ( )	0.5 , ( )	0.25 , ( )	0.18 , ( )

✶✶✶ - NOT RECOMMENDED DUE TO DANGER AT ODOR LEVELS

Approved by Chair: _[signature]_   **Date:** 9/19/96

DFO: _[signature]_   **Date:** 9/19/96

APPENDIX I

Date of AEGL NAC meeting: **Chemical :** DIMETHYL DICHLOROSILANE

NAC member	AEGL 1	AEGL 2	AEGL 3
George Alexeeff			
Steven Barbee	Y	Y	Y
Lynn Beasley	Y	Y	Y
David Belluck	Y	Y	Y
Kyle Blackman	Y	Y	Y
Jonathan Borak			
William Bress	Y	Y	Y
Guy Colonna			
George Cushmac	Y	Y	Y
Ernest Falke	Y	Y	Y
Larry Gephart	Y	Y	Y
Dan Guth			
~~━━━━━~~ PASS			
Jim Holler ✱	(Y)	(Y)	(Y)
Loren Koller			
Mark A. McClanahan			
Zarena Post			
George Rodgers			
George Rusch			
Bob Snyder			
~~Thomas J. Sobotka~~ NIEMEIER ✱	(Y)	(Y)	(Y)
Richard Thomas	Y	Y	Y
Thomas Tuccinardi DOAN HANSEN ✱✱	(Y)	(Y)	(Y)
✱ NOT OFFICIALLY A MEMBER AT THIS TIME. ✱✱ NOT A MEMBER **Tally**	9/9	9/9	9/9

PPM, (mg/m³)	30 Min	60 Min	4 Hr	8 Hr
AEGL 1	1 , ( )	0.75, ( )	0.4, ( )	0.3 , ( )
AEGL 2	10 , ( )	7 , ( )	4 , ( )	3 , ( )
AEGL 3	37, ( )	26 , ( )	13, ( )	9 , ( )

Approved by Chair: _George M. Rusch_   **Date:** 9/19/96

DFO: _Paul S. Tobin_   **Date:** 9/19/96