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

September 11-13, 2001

Final Meeting 22 Highlights

U.S. Department of Transportation
DOT Headquarters/NASSIF Building, Rooms 8236-8240
400 7th Street, S.W., Washington, D.C.

INTRODUCTION

The first day of the NAC/AEGL-22 meeting was delayed until September 12 due to the terrorist attack. The meeting resumed on the second day and accomplished most of the items on the agenda.

George Rusch, NAC/AEGL Chair, opened the meeting on September 12, 2001, with welcoming remarks along with AEGL Program Director, Roger Garrett, who also welcomed the committee members and guests. Thanks were conveyed to George Cushmac for again making the arrangements for the meeting and to the Department of Transportation (DOT) for providing the facilities.

The highlights of the NAC/AEGL-21 meeting were reviewed, briefly discussed, and then a motion was proposed by John Hinz and seconded by Mark McClanahan to accept them with a few minor changes. The motion was passed unanimously. The revised highlights of NAC/AEGL-21 are attached (Appendix A).

The highlights of the NAC/AEGL-22 meeting are presented below along with the meeting agenda (Attachment 1) and the attendee list (Attachment 2). Ballots were taken during the meeting and are incorporated into the appropriate chemical specific section as Appendices.

GENERAL INTEREST ITEMS

Roger Garrett reported the highlights of the NAS/COT/AEGL Subcommittee (NAS/AEGL) meeting on August 29-31, 2001. A total of 11 chemicals were reviewed and nine were approved. He then focused on the white paper titled "*The relative susceptibility of childhood asthmatics and adult asthmatics to acute exposures of irritant chemicals*." The NAS/AEGL agreed that there were no data indicating a significant difference in the susceptibility of children and adult asthmatics to irritants. Therefore, there was no rationale to justify an additional safety factor for

asthmatic children vs. asthmatic adults. The safety factor of 3 or 10 to protect susceptible individuals would be addressed on a chemical by chemical basis: based on the data, an appropriate value would be determined.

Judy Strickland made a presentation on Categorical Regression (CR) using propylene oxide as an example to illustrate that CR can be considered as another approach for AEGL development. The NAS/AEGL Subcommittee would like to review additional examples (1-2 chemicals). They would also like to see CR applied to a chemical with limited data set. In addition, the utility of using PBPK modeling in AEGL development was discussed by the NAS/AEGL.

Representatives from the NAS/AEGL will be invited to attend the NAC/AEGL-23 meeting in December and to make a presentation to the NAC/AEGL as appropriate.

REVIEW OF PRIORITY CHEMICALS FOR AEGL VALUES

BORON TRIFLUORIDE
CAS Reg. No. 7637-07-2

BORON TRIFLUORIDE DIMETHYL ETHER
CAS Reg. No. 353-42-4

Chemical Manager: George Rusch, Chair NAC/AEGL, Honeywell
Staff Scientist: Claudia Troxel, ORNL

Boron trifluoride was reviewed a second time in order to address comments and suggestions which arose from the previous NAC/AEGL-21 meeting. It was noted that the older studies had reported only nominal concentrations while the newer studies used actual concentrations as presented by George Rusch (Attachment 3).

The AEGL-1 was based on exposure at 6 mg/m^3 for 6 hr/day, 5 days/week for 13 weeks resulting in lacrimation in the test rats at week 2 of the study (Rusch et al., 1986; Hoffman and Rusch, 1982). Because the AEGL-1 was based upon essentially a no-effect level for an acute exposure scenario, an interspecies uncertainty factor (UF) of 3 was applied, and an intraspecies UF of 3 was applied based on the evidence that boron trifluoride acts as an irritant. The value was set equal to all AEGL time-points because the endpoint is a no-effect level for an irritant. The AEGL-1, 0.6 mg/m^3, is supported by the human detection of odor at 1.5 ppm (4.1 mg/m^3).

The AEGL-2 derivation was based on the Rusch et al. (1986) study value of 180 mg/m^3 for 6 hr/day for 5 days. Although all rats died from renal toxicity at the end of 5 days of exposure, the only signs observed after one day of exposure were those of irritation. The 180 mg/m^3 value was divided by a modifying factor (MF) of 2 since no pathology was conducted after the first exposure; therefore, renal effects could not be characterized or quantified. The resulting 90 mg/m^3 value was then lowered to 9 mg/m^3 by using a total UF of 10 (3 for intraspecies and

3 for interspecies).

The AEGL-3 derivation was based on an estimated non-lethal exposure level of 737 mg/m^3 from the study which derived the 4-hr LC_{01} value of 1210 mg/m^3 as calculated from mortality data (Rusch et al., 1986; Hoffman, 1981), and was divided by a total UF of 30 (3 for interspecies and 10 for intraspecies). AEGL-2 and-3 values were scaled to AEGL time frames using a value of n=1 for extrapolation from shorter to longer exposures and a value of n=3 for extrapolation from longer to shorter periods. The 10-minute value was set equal to the 30-minute value for the AEGL-2 and AEGL-3 because it is not considered appropriate to extrapolate from a 6-hour or 4-hour exposure duration, respectively, to a 10-minute exposure duration. A motion to adopt the new values was made by Mark McClanahan and seconded by John Hinz. The motioned was approved unanimously [YES:15; NO: 0; Abstain:0] (Appendix B).

	10 min.	**30 min.**	**1 hr.**	**4 hr.**	**8 hr.**
AEGL-1	**0.6 mg/m^3**	**0.6 mg/m^3**	**0.6 mg/m^3**	**0.6 mg/m^3**	**0.6 mg/m^3**
AEGL-2	**21 mg/m^3**	**21 mg/m^3**	**16 mg/m^3**	**10 mg/m^3**	**6.8 mg/m^3**
AEGL-3	**49 mg/m^3**	**49 mg/m^3**	**39 mg/m^3**	**25 mg/m^3**	**12 mg/m^3**

HFE- 7100
METHYL NONAFLUOROBUTYL ETHER (40%)
CAS Reg. No. 163702-07-6

METHYL NONAFLUOROISOBUTYL ETHER (60%)
CAS Reg. No. 163702-08-7

Chemical Manager: George Rusch, NAC/AEGL, Chair; Honeywell
Staff Scientist: Sylvia Talmage, ORNL

The chemical review was presented by Sylvia Talmage and George Rusch (Attachment 4). HFE-7100 was developed as a replacement for chlorofluorocarbons in refrigeration. Except for a single monitoring study in which exposures were noted to be below 50 ppm, no studies with humans were located. Animal studies indicated that HFE-7100 is of low toxicity and non-anesthetic. The presence of the perfluoro group of HFE-7100 limits its solubility in biological fluids. Repeated exposures of rats at up to 30,000 ppm for 4 weeks did not result in neurotoxicity (Coombs et al., 1996a,b). In cardiac sensitization studies (with additional doses of adrenaline) using beagles, HFE-7100 was not a cardiac sensitizer at concentrations of 10,000 to 89,300 ppm for 10 minutes but signs of stress and reaction to the chemical (tremors, etc.) were apparent at ≥18,800 ppm. A concentration of 48,900 ppm was considered an adverse but reversible effect level.

The AEGL-1 value was based on the NOAEL of 15,159 ppm in the subchronic study with rats (Coombs et al. 1996b). In this study, reversible increased liver weights were attributed to the repeated nature of the study. Because the concentration was basically a NOAEL, the exposures were repeated, and initial uptake is greater in the rodent than in primates, an interspecies uncertainty factor of 1 was applied. Animal studies failed to identify significant toxicological endpoints relevant to humans. Furthermore, the compound is poorly soluble in biological fluids. Therefore, an intraspecies uncertainty factor of 3 was applied. An additional modifying factor of 2 was applied based on limited data on humans and low numbers of animals used in key studies. Based on the repeated nature of the study, the single value of 2500 ppm was applied across all time points. The value is supported by the cardiac sensitization study with dogs in which no clinical signs were observed at 10,000 ppm for 10 minutes.

The AEGL-2 value was based on the cardiac sensitization study with dogs exposed for 10 minutes to 49,800 ppm of HFE-7100 and during which exogenous adrenaline was administered. Signs of chemical exposure included restlessness, trembling, and limb rigidity without cardiac sensitization (Kenny et al., 1996). Because this is a conservative endpoint (the administered dose of adrenaline is up to 10 times the physiological level), an interspecies uncertainty factor of 1 was applied. Intraspecies and modifying factors of 3 and 2 were applied as for the AEGL-1 above. The value is further supported by the NOAEL of 30,000 ppm from a repeated exposure study with rats (Coombs et al. 1996a). The repeated nature of the support study allows the application of the same value of 8200 ppm across all time periods.

The AEGL-3 value was based on the same 10-minute cardiac sensitization study with beagle dogs (Kenny et al., 1996). A concentration of 89,300 ppm with 2 doses of adrenaline resulted in severe clinical signs followed by full recovery. Interspecies, intraspecies, and modifying factors of 1, 3, and 2, respectively were applied as for the AEGL-2 above. Supporting data for the AEGL-3 included a 3M Company (1995) memo that reported no deaths in four rats exposed to 100,000 ppm for 4 hours. A motion was made by Ernie Falke and seconded by Bob Snyder to adopt the values as presented in the following table. However, each AEGL level was voted on separately with the following results: AEGL-1: YES: 13; NO: 3; Abstain: l; AEGL-2: YES: 16; NO: 0; Abstain: 1; and, AEGL-3: YES: 16; NO: 0; Abstain: 1. All three AEGLs values were accepted (Appendix C).

SUMMARY OF AEGL VALUES FOR HFE-7100 [ppm (mg/m^3)]						
Classification	**10-minute**	**30-minute**	**1-hour**	**4-hour**	**8-hour**	**Endpoint**
AEGL–1	2500 (25,550)	2500 (25,550)	2500 (25,550)	2500 (25,550)	2500 (25,550)	Reversible organ weight changes, repeated exposures, rat
AEGL–2	8200 (84,000)	8200 (84,000)	8200 (84,000)	8200 (84,000)	8200 (84,000)	Clinical signs, cardiac sensitization test, dog
AEGL–3	15,000 (150,000)	15,000 (150,000)	15,000 (150,000)	15,000 (150,000)	15,000 (150,000)	Severe clinical signs, cardiac sensitization test, dog

REVIEW OF CHEMICALS WITH ISSUES FROM PREVIOUS MEETINGS

XYLENES: PBPK Modeling

This is a continuing effort to explore employing PBPK/ toxicokinetic approach to develop AEGL-2 and -3 values. Dr. Ursula Gundert-Remy described modeling data using a single compartment, mixed effect model (Attachment 5).

Derivation of AEGL-2 (10 minutes and 30 minutes):
The following assumptions were made: (1) the toxicological end point and the intensity of toxicological effect should be the same as observed after administration of 430/ppm for 4 hours; (2) it is the concentration and not the amount of the substance (AUC), which is responsible for the effect, qualitatively and quantitatively; (3) the data from kinetic studies in human volunteers (see table 11, page 52 in the NAC/Draft: 12/2000 attachment 2) are appropriate for further kinetic calculations; (4) the data of m-xylene were used to represent the mixture of all xylenes, and (5) the kinetics of m-xylene are linear in the concentration/dose range which is under consideration.

Calculations: The data of three studies were used. The external concentration in the air multiplied by inhalation volume and frequency was used as input rate. A one-compartment body model did describe the data appropriately. The calculations were done using NONMEM program. After the concentration at 4 hours was calculated the input rate to reach this concentration with 10 minutes and 30 minutes, respectively was estimated. As we assumed inhalation volume and frequency being constant, the external air concentration was obtained by eliminating the constant.

Outcome of the calculations: k which is the first order elimination constant was 2.74/ hr; the corresponding half life is 0.25 hrs. The concentration at 4 hours was 65 ± 10 μmol/L(mean ± 2

SD) for 430 ppm. The external air concentration to reach this concentration within 10 minutes is 1165 ±180 ppm (mean ± 2 SD) and within 30 minutes 570±87.5 (mean ± 2 SD).

Conc. (µmol/L)	65 (mean)	55(-2SD)	50(-3SD)
10 min	1165ppm	985 ppm	896 ppm
30 min	570 ppm	482.5 ppm	438 ppm

For visualization see figures (Attachment 5).

Derivation of AEGL-3 (10 minutes and 30 minutes):
At the NAC/AEGL-20 meeting the AEGL-3 values for xylene were discussed. As the key study was a study with 4-hours of exposure, extrapolation to shorter time periods was necessary. It has been considered to use a toxicokinetic approach to calculate AEGL-3 values for 10 minutes and 30 minutes.

The following assumptions were made: (1) the toxicological endpoint and the intensity of toxicological effect should be the same as observed after administration of 930 ppm for 4 hours; (2) it is the concentration and not the amount of the substance (AUC) which is responsible for the effect, qualitatively and quantitatively; (3) the data from kinetic studies in human volunteers (see table 11, page 52 in the NAC/Draft: 12/2000 Attachment 2) are appropriate for further kinetic calculations; (4) the data of m-xylene were used to represent the mixture of all xylenes; (5) the kinetics of m-xylene are linear in the concentration/dose range which is under consideration.

Calculations: The data of three studies were used. The external concentration in the air multiplied by inhalation volume and frequency was used as input rate. A one-compartment body model did describe the data appropriately. The calculations were done using NONMEM program. After the concentration at 4 hours was calculated the input rate to reach this concentration within 10 minutes and 30 minutes, respectively, was estimated. As we assumed inhalation volume and frequency being constant, the external air concentration was obtained by eliminating the constant.

Outcome of the calculations: k which is the first order elimination constant was 2.74/hr with a corresponding half life 0.25 hrs. The concentration at 4 hours was 141 ± 25 µmol/L (mean ± 2 SD) for 930 ppm. The external air concentrations to reach this concentration within 10 minutes is 2526 ± 455 ppm (mean ± 2SD) and within 30 min is 1237 ± 221 ppm (mean ± 2 SD).

conc µ/mol/L)	141 mean	116 (-2 SD)	103.5(-3 SD)
10 min	2526 ppm	2071 ppm	1790 ppm

30 min	1237 ppm	1016 ppm	963 ppm

For visualization see figures (Attachment 5).

At the end of presentation and discussion, NAC/AEGL would need a very strong rationale to support the inclusion of this method in TSD. Further discussion will be continued in December meeting.

CHLORINE DIOXIDE
CAS Reg. No. 10049-04-4

Chemical Manager: Bob Benson, US EPA
Staff Scientist: Cheryl Bast, ORNL

Bob Benson noted that a copy of the DuPont (1955) study in rats that was requested at the June meeting was received. He presented the study and considered it as a key study that could be used for the development of three levels of AEGL values (Attachment 6). The AEGL-1 was based on slight salivation, lacrimation, and chromodacryorrhea in rats exposed for 6 hours to 3 ppm of chlorine dioxide (DuPont 1955). Because of the highly reactive nature of the chemical and direct chemical effect to the tissues, interspecies and intraspecies uncertainty factors of 3 each were applied. A modifying factor 2 was also applied to account for the sparse database. Thus, the total uncertainty/modifying factor is 20. It was proposed by Steve Barbee and seconded by George Rodgers to adopt an AEGL-1 of 0.15 ppm for all time periods. The motion carried unanimously [YES:15; NO: 0; Abstain:0] (Appendix D).

The AEGL-2 was based on lacrimation, salvation, dyspnea, weakness, and pallor in rats exposed to 12 ppm chlorine dioxide for 6 hours (DuPont 1955). Because of the highly reactive nature of the chemical and direct chemical effect to the tissues, interspecies and intraspecies uncertainty factors of 3 each were applied. A modifying factor 2 was also applied to account for the sparse data base. The concentration-exposure time relationship was described by $C^n \times t = K$. In the absence of chemical specific, empirically-derived values for the exponent, *n*, a value of *n*=3 is used when extrapolating to shorter time points and *n*=1 when extrapolating to longer time points to provide conservative AEGL values. The 30-minute AEGL-2 values was also adopted as the 10-minute AEGL-2 values due to the added uncertainty of extrapolating from a 6-hour study. A motion was made by George Rodgers and seconded by Bill Bress to adopt AEGL-2 values as 1.4, 1.4, 1.1, 0.69, and 0.45 ppm for 10- and 30-minutes,1-, 4-, and 8- hours, respectively. The motion was approved unanimously. [YES: 14; NO: 0; Abstain: 0] (Appendix D).

The AEGL-3 was based the same study by DuPont 1955 showing no deaths in rats exposed to 26 ppm of chlorine dioxide for 6 hours. Because the highly reactive nature of the chemical and direct chemical effect to the tissues, interspecies and intraspecies uncertainty factors of 3 each were applied. A modifying factor 2 was also applied to account for the sparse data base. The

concentration-exposure time relationship was described by $C^n \times t = K$. In the absence of chemical specific, empirically-derived values for the exponent, *n*, a value of *n*=3 is used when extrapolating to shorter time points and *n*=1 when extrapolating to longer time points to provide conservative AEGL values. The 30-minute AEGL-3 value was also adopted as the 10-minute AEGL-3 value due to the added uncertainty of extrapolating from a 6-hours study. A motion was made by Bob Benson and seconded by Nancy Kim to accept the AEGL-3 values of 3.0, 3.0, 2.4, 1.5, and 0.98 ppm for 10 minutes, 30 minutes, and 1-, 4-, and 8- hours, respectively. The motion was also approved unanimously. [YES: 15; NO: 0; Abstain: 0] (Appendix D).

AEGL	10 minutes	30 minutes	1 hour	4 hours	8 hours
AEGL-1	0.15 ppm	0.15 ppm	0.15 ppm	0.15 ppm	0.15 ppm
AEGL-2	1.4 ppm	1.4 ppm	1.1 ppm	0.69 ppm	0.45 ppm
AEGL-3	3.0 ppm	3.0 ppm	2.4 ppm	1.5 ppm	0.98 ppm

HYDROGEN FLUORIDE
CAS Reg. No. 7664-39-3

Chemical Manager: Larry Gephart, Exxonmobil
Staff Scientist: Sylvia Talmage, ORNL

This discussion was in response to the NAS/COT/AEGL comments on HF from the August 2001 meeting. Sylvia Talmage made a brief overview of the issues raised by the NAS/AEGL on the relative toxicity issue between HF and HCl (Attachment 7). The NAS/COT/AEGL was concerned that the AEGL values for HF and HCl did not reflect their known relative toxicities. The NAC developed the AEGL values for HF and HCl independently, based on the empirical data for each chemical. It was noted that the relative toxicities of the AEGL-1 values of HF were appropriate, but that the same value for the HCl AEGL-1 (1.8 ppm) was used across all time periods, whereas two different values were used for the HF AEGL-1 (1.0 for the 10 minute, 30 minute, and 1 hour times and 0.5 ppm for the 4- and 8-hour times). Adapting 1.0 ppm for all time periods for the AEGL-1 values is consistent with other irritant chemicals and was deemed appropriate based on the repeated nature of some of the HF exposures. It was proposed by Mark McClanahan and seconded by Ernie Falke to raise the 4- and 8-hour AEGL-1 values to 1.0 ppm. The motion passed [YES: 13; NO: 0: Abstain: 1] (Appendix E).

Further discussion focused on the fact that for the AEGL-2 and -3, the relative toxicities of HF and HCl are not consistent at AEGL timepoints beyond 1 and 4 hours, respectively. The inconsistency is driven by the fact that an *n* value of 1 is used for time scaling for HCl whereas an *n* value of 2 is used for HF time-scaling. It was suggested that further discussion in defense of the values in both technical support documents should focus on the relative solubilities of these chemicals, supported by the efficient scrubbing of low concentrations of HF in the nasal passages

of test species (thus lowering the penetration to the lungs relative to HCl). AEGL-1values are summarized in the table below (new values are in bold type).

SUMMARY OF AEGL VALUES FOR HF AND HCl (ppm)					
Classification	**10-Minute**	**30-Minute**	**1-Hour**	**4-Hour**	**8-Hour**
AEGL-1					
HCl	1.8	1.8	1.8	1.8	1.8
HF	1.0	1.0	1.0	**1.0**	**1.0**

RESPONSES OF *FEDERAL REGISTER* COMMENTS TO THE PROPOSED AEGL VALUES

Comments from the *Federal Register Notice* of May 2, 2001, on the proposed AEGL values for phenol, methanol, and acrylic acid were received and discussed. The NAC/AEGL deliberation of these chemicals are briefly summarized as the following:

PHENOL
CAS Reg. No. 108-95-2

Chemical Manager: Bob Snyder, EOSHI/RU
Staff Scientist: Peter Griem, FoBiG

Comments were received from The Phenol Regulatory Panel, American Chemistry Council (ACC) and Department of Environmental Quality, State of Michigan (Michigan) regarding the proposed AEGL-1 and- 2 values, the selection of uncertainty factors, the selection of key studies, the time scaling and other minor issues. Dr. Ursula Gundert-Remy presented the *Federal Register* comments for the Phenol AEGL Development Team. Dr. Gundert-Remy also presented the AEGL Development Team's responses to these issues or concerns. The NAC/AEGL Committee discussed both the comments and the responses. The Committee found no compelling reasons or data to change the values or rationale for the AEGL in question at this time. The ACC and Michigan did not provide any new information, and the key information used to derive the AEGL values was not overlooked. Therefore, based on a motion made by Bob Benson and seconded by Mark McClanahan, the "Proposed" AEGL values were elevated to "Interim" status. The motion was approved unanimously [YES: 15; NO: 0; Abstain: 0] (Appendix F). Comments from the Phenol Regulatory Panel, ACC (Attachment 8) and the Department of Environmental Quality, Michigan (Attachment 9, Comment No.4) and the detailed responses from the Phenol TSD Development Team (Attachment 10) are attached.

METHANOL
CAS Reg. No. 67-56-1

Chemical Manager: Ernie Falke, U. S. EPA
Staff Scientist: Peter Griem, FoBiG

Comments were received from Dr. John S. Morawetz, International Chemical Workers Union (ICWU) regarding the proposed AEGL-1 and -2 values, the selection of key studies, the time scaling and other minor issues. Comments were also received from the Department of Environmental Quality, State of Michigan, expressing support for the proposed AEGL values. Dr. Ursula Gundert-Remy presented the *Federal Register* comments for the Methanol AEGL Development Team. Dr. Gundert-Remy also presented the AEGL Development Team's responses to these issues and concerns. The NAC/AEGL Committee postponed the discussion because the data from Burbacher et al. (1999) may lead to new AEGL-2 values. Comments from ICWU by John Morawetz (Attachment 11), The Methanol Institute and addendum (Attachment 12), the Department of Environmental Quality, Michigan (Attachment 9, Comment No. 5) and the detailed responses from the Methanol TSD Development Team (Attachment 13) are attached.

ACRYLIC ACID
CAS Reg. No. 79-10-7

Chemical Manager: Ernie Falke, U. S. EPA
Staff Scientist: Peter Griem, FoBiG

Comments were received from the Basic Acrylic Monomer Manufacturers, Inc. regarding the proposed AEGL-1, -2 and -3 values; the selection of uncertainty factors; the selection of key studies, and the time scaling and completeness of the considered data. Comments were also made by Rohm and Haas Company regarding the proposed AEGL-1 values, the selection of the key study and the time scaling. Comments were received from the Department of Environmental Quality, State of Michigan, regarding the proposed AEGL-1, -2 and -3 values, the selection of and given rationale for uncertainty factors and other minor issues. Dr. Ursula Gundert-Remy presented the Federal Register comments for the Acrylic Acid AEGL Development Team. She also presented the AEGL Development Team's responses to these issues and concerns. Clay Frederick, Rohm and Haas Company, made a brief presentation to express his concern on the process of deriving the proposed AEGL values including AEGL-1 definition, nasal irritation reversibility, olfactory ageing, and a recent publication (Attachment 14) and agreed to provide additional information to NAC/AEGL for the continuing discussion in the next meeting. The NAC/AEGL Committee then discussed both the comments and the responses and decided to postpone the discussion to the next meeting because more time is needed to complete the discussion. Public comments from the Basic Acrylic Monomer Manufacturers, Inc. (Attachment 15), and the Department of Environmental Quality (Attachment 9, Comment No.1) and the detailed responses from the Acrylic Acid TSD Development Team are attached (Attachment 16).

Review of 10-minutes AEGL Values

ETHYLENIMINE
CAS Reg. No. 151-56-4

Chemical Manager: Mark Mc Mclanahan, CDC
Staff Scientist: Kowetha Davidson, ORNL

In response to the comments made at the NAS/AEGL meeting in March 2001, efforts were made to revisit the issue of developing AEGL-1 values for ethyleneimine. A brief presentation was made by Mark McClanahan to derive AEGL-1 by dividing the AEGL-2 values by a factor of 2 because the average difference between AEGL-2 and 3 values is approximately 2 (Attachment 17). The AEGL-2 values were based on a no-effect-level for lethality in the guinea pig exposed at 10 ppm for four hours. However, it was pointed out by Marc Ruijten that he believed the ACGIH has reported odor values which range from 0.6 to 2.0 ppm. Marc offered to use the procedures described in the "*Guidance for the Application of Odor in the Derivation of AEGL-1*" to develop a "Level of Annoyance (LOA)" for ethyleneimine as well as propyleneimine. They will then be discussed at the December meeting.

CHLORINE
CAS Reg. No. 7782-50-5

Chemical Manager: Larry Gephart, Exxonmobil
Staff Scientist: Sylvia Talmage, ORNL

Sylvia Talmage made a brief presentation on chemical toxicity information pertinent to the development of 10-minute AEGLs (Attachment 18). The AEGL-1 for chlorine was based on an exercising atopic individual (supported by a study with asthmatics) which allowed application of an intraspecies uncertainty factor of 1. Based on the fact that asthmatic reaction to chemicals is more concentration related than time related, the NAC/AEGL proposed to adapt the same value of the 8-hour NOAEL for the exercising atopic individual of 0.5 ppm across the 10 minute to 8 Hours times for AEGL-1 values. The motion was proposed by Mark McClanahan and seconded by Ernie Falke. The motion carried [YES: 13; NO: 0; Abstain: 2] (Appendix G).

The AEGL-2 values were based on a 4-hour exposure of an exercising atopic individual (supported by a study with asthmatics) to 1 ppm which allowed application of an intraspecies uncertainty factor of 1. Values for the AEGL-2 were time scaled. In order to be protective of asthmatics and because the original data point was a 4-hour exposure, it was proposed that the 10-minute AEGL-2 be set equal to the 30-minute value of 2.8 ppm. Mark McClanahan moved to accept the value of 2.8 ppm for the 10-minute AEGL-2. There was a second of the motion by Ernie Falke. The motion carried [YES:12; NO: 2; Abstain:1] (Appendix G).

Time-scaling was considered appropriate for the 10-minute AEGL-3. The time-scaled AEGL-3 value was 50 ppm. It was also moved by McClanahan and seconded by Falke to accept the

proposed value of 50 ppm. The motion carried [YES: 12; NO: 2; Abstain: 1] (Appendix G).

SUMMARY OF AEGL VALUES FOR CHLORINE [ppm (mg/m^3)]						
Classification	**10-Minute**	**30-Minute**	**1-Hour**	**4-Hour**	**8-Hour**	**Endpoint**
AEGL-1	**0.5 (1.5)**	**0.5 (1.5)**	**0.5 (1.5)**	**0.5 (1.5)**	0.5 (1.5)	No clinical signs in atopic and asthmatic individuals
AEGL-2	**2.8 (8.1)**	2.8 (8.1)	2.0 (5.8)	1.0 (2.9)	0.7 (2.0)	Clinical signs in atopic and asthmatic individuals
AEGL-3	**50 (145)**	28 (81)	20 (58)	10 (29)	7.1 (21)	Lethality - rat

ANILINE
CAS Reg. No. 62-53-3

Chemical Manager: Bob Snyder, EOSHI/RU
Staff Scientist: Sylvia Talmage, ORNL

It was noted that there was only one well-conducted key study with aniline. The endpoint in rats as well as humans is formation of methemoglobin (Kim and Carlson, 1986) as commented by Sylvia Talmage (Attachment 19). Time-scaling with $n = 1$ had been considered appropriate for the earlier derivation of 30-minute to 8-hour values as there appeared to be linear relationships between aniline concentration and methemoglobin formation and the formation of methemoglobin over time at a constant concentration. In addition, the full effect of methemoglobin formation is not present until several hours into an exposure. Therefore, it was considered appropriate to derive the 10-minute values for all AEGL levels by time scaling from the earlier derived values. The proposed time-scaled AEGL-1, -2, and -3 values were 48, 72, and 120 ppm based on amounts (22%, 41%, greater than 70% in rats) of the methemoglobin formation, respectively. George Rogers moved to adopt the 10-minute values as presented; the motion was seconded by Bob Snyder. The motion unanimously approved [YES: 16; NO: 0; Abstain: 0] (Appendix H).

CARBON TETRACHLORIDE
CAS Reg. No. 56-23-5

Chemical Manager: Bill Bress, ASTHO
Staff Scientist: Bob Young, ORNL

Chemical toxicity information was described briefly by Bill Bress (Attachment 20). The data

used in deriving the values for AEGL-1 and AEGL-2 came from human studies by Davis (1934). AEGL-1 endpoint was the nervousness and slight nausea when exposed to 158 ppm of CCl4 for 30 minutes. The 10-minute AEGL-1 was extrapolated from C^n x t=K, where *n*=2.5 and UF=10 was applied for protection of sensitive populations. The proposed AEGL-1 value of 25 ppm was obtained. The AEGL-2 endpoint was the nausea, vomiting, and headache in subjects exposed to 1191 ppm for 15 minutes. The 10-minutes AEGL-2 was also derived with the same parameters and calculated as 140 ppm. AEGL-3 values were derived from studies conducted by Adams et al. (1952) and Dow Chemical Co. (1986) by estimating the LC_{01} at 1 hour in lethality of rats. The AEGL-3 had a total UF of 30 (10 for protection of sensitive individuals and 3 for interspecies variability). The AEGL-3 value was calculated as 350 ppm. A motion to accept these values as presented was made by Mark McClanahan and seconded by Dave Belluck. The motion was unanimously approved (YES:16, NO:0, Abstain: 0) (Appendix I).

The following note was submitted by John Morawetz during the process of highlights approval at NAC/AEGL-23 meeting. " John Morawetz was unable to attend the September meeting and the discussion of carbon tetrachloride. He strongly disagreed with the 10 minutes AEGL-3 level of 350 ppm based on the fatality described by Norwood (1950) and proposed that the 30 minutes value of 230 ppm be used for 10 minutes as well."

CHLOROFORM
CAS Reg. No. 67-66-3

Chemical Manager: Steve Barbee, Arch Chem. Inc.
Staff Scientist: Bob Young, ORNL

Chemical toxicity information of chloroform for deriving the 10-minute values was presented by Steve Barbee (Attachment 21). There was concern about using fetotoxicity data (Schwetz et al., 1974) to establish very short term exposure values. In addition, the AEGL-3 levels proposed were significantly lower than levels which had been safely used in humans for decades. Therefore, the data will be examined again at the next meeting.

ARSINE
CAS Reg. No. 7784-42-1

Chemical Manager: Richard Thomas, ICEH
Staff Scientist: Bob Young, ORNL

Chemical toxicity information for arsine was presented by George Rusch (Attachment 22). The 10-minutes AEGL-1 value was not recommended because the steep dose-response relationship, mechanism of toxicity, and toxicity occurs at or below the odor threshold. The AEGL-1 value could be greater than the AEGL-2 values for the corresponding time period.

AEGL-2 values were derived from the Peterson and Bhattacharyya (1985) study using a NOAEL

of 5 ppm from the absence of hematological changes in mice following a 1-hour exposure. According to the SOP, *n*=3 is applied for this case to extrapolate from 1 hour to 10-minutes. A total UF of 30 was applied (based on 10 for interspecies variability and 3 for intraspecies variability). The 10 minute AEGL-2 value was 0.30 ppm.

Again the data of Peterson and Bhattacharyya (1985) provided for an estimation of the lethality threshold (15 ppm) in mice. Using *n*=3 and the same total UF of 30, a 10 minute AEGL-3 value was derived as 0.91 ppm. A motion was made by George Rogers and seconded by Bob Benson to not recommend a 10-minute AEGL-1. In addition to accept 10-minute AEGL-2 of 0.3 ppm; and 10-minute AEGL-3 of 0.91 ppm. The motion was carried [YES: 15; NO: 0; Abstain: 0] (Appendix J).

Due to time constraint, three hydrazine analogs were considered needing a group comparison and evaluation and were subsequently passed over until the next meeting in December.

TOPICAL ITEMS FOR DISCUSSION

GUIDANCE FOR THE USE OF ODOR IN AEGL-1 DEVELOPMENT

Because circumstances curtailed the meeting on September 11 (Tuesday), Marc Ruijten presented a brief overview of "*Guidance for the Application of Odor in the Derivation of AEGL-1*" to the committee on Wednesday morning. A handout was distributed prior to the meeting by e-mail as well as made available at the meeting (Attachment 23). Marc briefly discussed the definition of "Level of Annoyance (LOA)" and criteria of the derivation for odor during accidental exposure. If LOA is lower than the concentration which causes other responses, such as irritation, it is considered as an estimate for an AEGL-1. More discussion with sample chemical illustrations will be delivered in the December meeting.

Administrative Matters

The next meeting, NAC/AEGL-23, has been set for December 3-5, 2001, in San Antonio, Texas. Lodging and conference facilities have been set up at the Holiday Inn Riverwalk by John Hinz (local host). More information about the upcoming meeting will be provided by John soon.

Consideration of the April 2002 meeting (NAC/AEGL-24) was taken up and though Nashville, TN was proposed in conjunction with the Society of Toxicology annual meeting after discussion regarding other meetings and dates, further consideration was given to Washington, D.C. again for April 9-11, 2002.

The meeting highlights were prepared by Hanks Spencer and Po-Yung Lu, Oak Ridge National Laboratory.

LIST OF ATTACHMENTS

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

Attachment 1. NAC/AEGL-22 meeting agenda
Attachment 2. NAC/AEGL-22 attendee list
Attachment 3. Data Analysis of Boron trifluoride
Attachment 4. Data Analysis of HFE-7100
Attachment 5. PBPK Data Analysis of Xylenes
Attachment 6. Data Analysis of Chlorine dioxide
Attachment 7. Data Analysis of Hydrogen fluoride
Attachment 8. Federal Register Comments from The Phenol Regulatory Panel, American Chemistry Council
Attachment 9. Federal Register Comments from The Department of Environmental Quality, Michigan
Attachment 10. Response of Federal Register Comments of Phenol AEGL Development Team
Attachment 11. Federal Register Comments from ICWU (John Morawetz)
Attachment 12. Federal Register Comments ans addendum from The Methanol Institute
Attachment 13 Response of Federal Register Comments of Methanol AEGL Development Team
Attachment 14. Federal Register Comments from The Rohm and Haas Company
Attachment 15. Federal Register Comments from The Basic Acrylic Monomer Manufacturers, Inc.
Attachment 16. Response of Federal Register Comments of Acrylic acid AEGL Development Team
Attachment 17. Data Analysis of Ethyleneimine
Attachment 18. Data Analysis of Chlorine
Attachment 19 Data Analysis of Aniline
Attachment 20. Data Analysis of Carbon tetrachloride
Attachment 21. Data Analysis of Chloroform
Attachment 22. Data Analysis of Arsine
Attachment 23. Guidance for the use of odor in AEGL-1 development

LIST OF APPENDICES

Appendix A. Revised meeting high lights of NAC/AEGL-21
Appendix B. Ballot for Boron trifluoride
Appendix C. Ballot for HFE-7100
Appendix D. Ballot for Chlorine dioxide
Appendix E. Ballot for Hydrogen fluoride
Appendix F. Ballot for Phenol
Appendix G. Ballot for Chlorine
Appendix H. Ballot for Aniline
Appendix I . Ballot for Carbon tetrachloride
Appendix J. Ballot for Arsine

National Advisory Committee for Acute Exposure Guideline Levels for Hazardous Substances

NAC/AEGL-22
September 11-13, 2001

U.S. Department of Transportation
DOT Headquarters/Nassif Building, Rooms 8236-8240
400 7th Street, S.W., Washington, D. C.

AGENDA

Tuesday, September 11, 2001

10:00 AM	Introductory remarks and approval of NAC/AEGL-21 Highlights (George Rusch, Roger Garrett, and Paul Tobin)
10:15	NAS/AEGL review status (Roger Garrett, Ernie Falke, George Rusch, and Jonathan Borak)
10:45	Consideration of odor in AEGL-1 development (Mac Ruijten)
12:00 PM	Lunch
1:00	Consideration of odor in AEGL-1 development (continued)
1:30	Review of Xylenes - PBPK modeling (Ursula Gundert-Remy)
2:15	Review of Boron Trifluoride (George Rusch/ClaudiaTroxel)
3:00	Break
3:15	Review of comments received from May 2, 2001, *Federal Register Notice*- Acrylic acid and Phenol (Ursula Gundert-Remy/Ernie Falke, Bob Snyder)
5:00	Adjourn for the day

Wednesday, September 12, 2001

8:30 AM	Review of comments received from May 2, 2001, *Federal Register Notice* - Methanol (Ursula Gundert-Remy/Ernie Falke)
9:30	Response to NAS/COT comments on Hydrogen Fluoride (including review of Hydrogen Chloride) [Larry Gephart/Sylvia Talmage (John Hinz, Ernie Falke)]
10:00	AEGL-1 values for Ethyleneimene and Propyleneimine (Mark McClanahan/Kowetha Davidson)
10:30	Break
10:45	AEGL-1 values for Ethyleneimene and Propyleneimine (continued)
11:15	AEGL 10-minute values for Aniline, Chlorine, and Fluorine (Bob Snyder, Larry Gephart, Ernie Falke/SylviaTalmage)
12:00 PM	Lunch
1:00	AEGL10-minutes values for Aniline, Chlorine, and Fluorine (continued)
1:30	Comment on Chlorine Dioxide - new study (Bob Benson/Cheryl Bast)
2:30	Review of Methyl Ethyl Ketone (Mark McClanahan/Sylvia Talmage)
3:30	Break
3:45	Review of Methyl Ethyl Ketone (Continued)
5:00	Administrative matters
5:15	Adjourn for the day

Thursday, September 13, 2001

8:00 AM	HFE-7100 (George Rusch/Sylvia Talmage)
10:15	Break
10:30	AEGL 10-minutes value for AEGL 10-minute values for Arsine, Hyrdrazine, Methyl Hydrazine, and Dimethyl Hydrazine (Richard Thomas/Bob Young); Carbon Tetrachloride (Bill Bress/Bob Young); Chloroform (Steve Barbee/Bob Young)
12:30 PM	Adjourn meeting

Attachment 2

NAC/AEGL-22
Sept 11-13, 2001

Name	Affiliation	Phone No.
Po-Tung Su	ORNL	(865) 574-7587
John P. Hinz	[illegible]	(215) 536-6126
MARK A. MCCLUSKEY	CDC	770 458 2258
JIM HOLLER	ATSDR	404-498-0701
Lynn Beasley	USEPA/Superfund	703-603-9086
BILL BRESS	ASTHO/Vermont	802-863-7598
STEVEN J BARBEE	Arch Chem/AIHA	203-229-2693
Bob Benson	EPA Region 8	303-312-7070
VALERI VARENIK	Ministry of Public Health of Russia	(095) 190-54-56.
Vladimir A. Tchernov	South Center for Chemical Emergencies	(011-7-8442) 716834 E-mail: tchernov@vlink.ru
Boris Filatov	SCCE Director Volgograd, Russia	(011-7-8442) 727876 E: filatov@vlink.ru
Robert Snyder	Rutgers Univ/EINST	732-445-0205
Paul Tobin	US EPA	202 260-1236
George Rusch	Honeywell	973-455-3672
Ernest V. Falke	US EPA	202 564-7646
Roger Garrett	US EPA	202-564-7662
Marc Ruijten	RIVM, Netherlands	+3130 274 4566
TOM HORNSHAW	ILL EPA	217-785-5735
Nancy Kim	NYS DOH	518-402-7511
SURENDER AHIR	OSHA	202-693-2280
DAVID Belluck	MNDOT	651-284-3756
George Rodgers	UMDNJ-Rowan Univ/IARPC	562-852-8626 or 3720
Betty Hakes	EPA/OPPT/RAD	202 564 9676
Sylvia Talmage	ORNL	865-576-7758

Name	Affiliation	Phone #
Henry Spencer	ORNL	540-832-2347
GEORGE CUSHMAC	DOT	202-366-4493
Clay B Frederick	Rohm + Haas	(215) 641-7496
Pat Phibbs	BNA	202 452 4105
Marinelle Payton	JSU	(601) 368-2052
URSULA GUNDERT-REMY	BgW	+49 30 691 42 30
Thomas J Schultz	FBI	301 827-8444
Steve Via	AWWA	202-628-8303

AEGL-1 Derivation

Key study: Torkelson et al., 1961

Effects:
Worker noted conc. of 1.5 ppm [4.1 mg/m^3] BF_3 to have "rather pleasant acidic odor," indicating odor threshold reached. Although worker noted smell of BF_3 to be pleasant, it is likely others would find odor unpleasant.

Uncertainty factors: 1
Interspecies UF: 1
Intraspecies UF: 1 odor not irritating at this level

Time scaling: Value set equal to all time periods

AEGL-1 Values for BF_3 (mg/m^3) [given in mg/m^3 because BF_3 gas becomes aerosol upon contact with moist air]				
10-min	**30-min**	**1-hr**	**4-hr**	**8-hr**
4 0.6	4 0.6	4 0.6	4 0.6	4 0.6

Level appears to approach threshold for irritant effects: minimal signs of irritation noted in rats exposed to 2 or 6 mg/m^3 for 6 h/d, 5 d/wk for 13 wk. (Rusch et al., 1986)

AEGL-2 Derivation

AEGL-3 levels) 3 to obtain an estimate of AEGL-2:

< Data meeting definition of AEGL-2 endpoint not available

< Dose-response curve for lethality was steep (Rusch et al, 1986)

AEGL-2 Values for BF_3 (mg/m^3) [given in mg/m^3 because BF_3 gas becomes aerosol upon contact with moist air]				
10-min	**30-min**	**1-hr**	**4-hr**	**8-hr**
27 21	27 21	24 16	18 10	6.7 6.8

AEGL-2 based on the Rusch et al. (1986) 2-week study:

< Apply same UF (30) and time extrapolation as for AEGL-3; set 10-min value equal to 30-min value

< One obtains the following values:
5.0, 5.0, 4.0, 2.5, and 1.7 mg/m^3, respectively.

< These values inconsistent with existing animal data: exposure of rats, rabbits, and guinea pigs to 4 mg/m^3 for 7 h/d, 5 d/wk for 127-128 exp. resulted in minimal effects (Torkelson et al., 1961).

AEGL-3 Derivation

Key study:
Rusch et al., 1986

Effects:
4-hour LC_{50} of 1200 mg/m^3

Uncertainty factors: 30
Interspecies UF: ~~10~~ 3 - species differences exist in sensitivity to BF_3, with the guinea pig being the most sensitive to lethality
Intraspecies UF: ~~3~~ 10 based on evidence that at acute exposures, BF_3 acts as an irritant

Time scaling: Default:
n = 1 for shorter to longer times
n = 3 for longer to shorter times
10-min value set equal to 30-min (4-h exposure)

AEGL-3 Values for BF_3 (mg/m^3) [given in mg/m^3 because BF_3 gas becomes aerosol upon contact with moist air]				
10-min	**30-min**	**1-hr**	**4-hr**	**8-hr**
~~80~~ 49	~~80~~ 49	~~63~~ 39	~~40~~ 25	~~20~~ 12

Summary of AEGL Values for BF_3 (mg/m^3)					
Level	**10-min**	**30-min**	**1-hr**	**4-hr**	**8-hr**
AEGL-1	4.1 0.6	4.1 0.6	4.1 0.6	4.1 0.6	4.1 0.6
AEGL-2	27 21	27 21	21 16	13 10	6.7 6.8
AEGL-3	80 49	80 49	63 39	40 25	20 12

ACUTE EXPOSURE GUIDELINE LEVELS FOR HFE-7100

National Advisory Committee for AEGLs Meeting
September 11-13, 2001

ORNL Staff Scientist:
Sylvia S. Talmage

Chemical Manager:
George Rusch

Attachment 4

HFE-7100

Acute Studies

Lethal

Rat: 214,000 ppm for >20 minutes, lethal to 3 of 4 (Eger et al. 1998)

Non-lethal

Rat: 100,000 ppm for 4 hours, no deaths (3M Company 1995)

Dog: 10,000 to 89,900 ppm for 5+ minutes

clinical signs at 48,900 and 89,900 ppm (Kenny et al. 1996)

Repeated Exposures (Coombs et al. 1996a, b)

Rat: 1489, 2935, 9283, and 28,881 ppm for 6 hours/day, 5 days/week for 4 weeks

Reversible liver weight increase, hepatocyte hypertrophy at 28,881 ppm

Slight affect at 9283 ppm

Effects attributable to repeated exposures

Effects considered a NOAEL (adaptive response to chemical treatment)

Rat: 1502, 4550, 7533, 15,159 ppm for 6 hours/day, 5 days/week for 13 weeks

Minimal organ weight increases in males at 15,159 ppm

Effects attributable to repeated exposures

Effects considered a NOAEL (adaptive response to chemical treatment)

HFE-7100

AEGL-1

Based on NOAEL in subchronic study with 20 rats/group (Coombs et al. 1996b)
15,159 ppm for 6 hours/day, 5 days/week for 13 weeks
Reversible increase in liver weight in 15,159 ppm group
Uncertainty factors
- Interspecies: 1, rats have higher uptake than humans
  - Conservative endpoint
- Intraspecies: 3, no significant toxicological endpoints identified relevant to human populations
- Modifying factor: 2, limited data on humans and limited number of animals used in some of the key studies

Time scaling
- Repeated nature of exposures allows use of single value across all timepoints

Support: no clinical signs in dogs exposed to 10,000 ppm for 10 minutes and dosed with adrenaline (Kenny et al. 1996)

HFE-7100

Studies of anesthetic properties - Rat (Eger et al. 1998)
- No anesthetic properties
- Limited solubility in biological fluids

Neurotoxicity Studies - Rat, repeated exposures (Coombs et al. 1996a, 1996b)
- No neurotoxicity up to 30,000 ppm

Developmental Studies - Rat (Huntingdon Life Sciences)
- 4629, 7538, 15,076, and 30,000 ppm 6 hours/day, GD 6-19
- Extra ribs, a common skeletal variant more common in exposed groups
  - Not dose-related, not statistically significant
  - Not considered an adverse fetal endpoint (slight maternal toxicity)

Cardiac Sensitization - Dog (Kenny et al. 1996)
- Exposures: 10,000, 18,800, 48,900, and 89,300 ppm for 10 minutes
- Not a cardiac sensitizer up to 89,300 ppm
- Signs of stress and reaction to chemical treatment increased with increasing concentrations $\geq$18,800 ppm

HFE-7100

AEGL-3

Based on 10-minute cardiac sensitization test with 6 beagles (Kenny et al. 1996)
89,300 ppm plus two doses of adrenaline (1-12 μg/kg)
Severe clinical signs (following 2 adrenaline injections), full recovery
No cardiac sensitization

Uncertainty factors
- Interspecies: 1, conservative endpoint
- Intraspecies: 3, no significant toxicological endpoints identified relevant to human populations
- Modifying factor: 2, limited data on humans and limited number of animals used in some of the key studies

Time scaling: low solubility of test compound, rapidly reaches equilibrium in blood; repeated nature of other support study allows use of same value for all AEGL-2 time points

Support: no deaths in 4 rats exposed to 100,000 ppm for 4 hours
(3M Company 1995)

HFE-7100

AEGL-2

Based on 10-minute cardiac sensitization test with 6 beagles (Kenny et al. 1996)
49,800 ppm plus two doses of adrenaline (1-12 μg/kg)
Some restlessness, trembling and limb rigidity
No cardiac sensitization

Uncertainty factors
- Interspecies: 1, conservative endpoint
- Intraspecies: 3, no significant toxicological endpoints identified relevant to human populations
- Modifying factor: 2, limited data on humans and limited number of animals used in some of the key studies

Time scaling: repeated nature of support study allows use of same value for all AEGL-2 time points

Support: NOAEL of 30,000 ppm in repeated exposure of rats for 4 weeks (Coombs et al. 1996a)

AEGL-2 VALUES				
10-minute	**30-minute**	**1-hour**	**4-hour**	**8-hour**
8200 ppm	**8200 ppm**	**8200 ppm**	**8200 ppm**	**8200 ppm**

Key Reference: Kenny, T.J., C.K. Shepherd, M. Bannerman, C.J. Hardy, and I.S. Gilkison. 1996. T-6334: Assessment of cardiac sensitization potential in dogs. MIN 182/953117, Huntingdon Life Sciences, Limited.

Test Species/Strain/Number: Dog/beagle/6

Exposure Route/Concentrations/Durations: Inhalation/10,000, 18,800, 48,900, and 89,300 ppm/10 minutes

Effects:

10,000 ppm: no effects
18,800 ppm: minimal effects
48,900 ppm: signs of stress and reaction to chemical (restlessness, trembling, limb rigidity)
89,300 ppm: severe signs of stress and reaction to chemical (salivation, tremors, limb rigidity)

All dogs recovered; not a cardiac sensitizer when injected with adrenaline

Endpoint/Concentration/Rationale: Signs of stress, discomfort/48,900 ppm/reversible signs

Uncertainty Factors/Rationale:

Total uncertainty factor: 3
Interspecies: 1, conservative endpoint; adrenaline dose is up to 10 times human physiological level
Intraspecies: 3, no significant toxicological endpoints identified

Modifying Factor: 2, limited data on humans; limited number of animals in several studies

Animal to Human Dosimetric Adjustment: Not applied

Time Scaling: Repeated nature of support study allows use of same value for all AEGL-2 timepoints

Data Adequacy: Limited human data; limited number of animals in some key studies. Supported by NOAEL of 30,000 ppm in a repeated exposure study (4 weeks) with rats.

AEGL-3 VALUES				
10-minute	**30-minute**	**1-hour**	**4-hour**	**8-hour**
280 ppm	**280 ppm**	**280 ppm**	**280 ppm**	**280 ppm**

Key Reference: Kenny, T.J., C.K. Shepherd, M. Bannerman, C.J. Hardy, and I.S. Gilkison. 1996. T-6334: Assessment of cardiac sensitization potential in dogs. MIN 182/953117, Huntingdon Life Sciences, Limited.

Test Species/Strain/Number: Dog/beagle/6

Exposure Route/Concentrations/Durations: Inhalation/10,000, 18,800, 48,900, and 89,300 ppm/10 minutes

Effects:
10,000 ppm: no effects
18,800 ppm: minimal effects
48,900 ppm: signs of stress and reaction to chemical (restlessness, trembling, limb rigidity)
89,300 ppm: severe signs of stress and reaction to chemical (salivation, tremors, limb rigidity)
All dogs recovered; not a cardiac sensitizer when injected with adrenaline

Endpoint/Concentration/Rationale: Severe clinical signs/89,300 ppm/no deaths

Uncertainty Factors/Rationale:
Total uncertainty factor: 3
Interspecies: 1, conservative endpoint; adrenaline dose is up to 10 times human physiological level
Intraspecies: 3, no significant toxicological endpoints identified

Modifying Factor: 2, limited data on humans; limited number of animals in several studies

Animal to Human Dosimetric Adjustment: Not applied

Time Scaling: Not applied, low solubility of test compound, rapidly reaches equilibrium in blood; repeated nature of other support studies

Data Adequacy: Limited human studies; limited number of animals in this and several support studies. The 89,300 ppm concentration may be a conservative estimate as no rats died after a 4-hour exposure to 100,000 ppm.

XYLENE

Derivation of AEGL-2 (10 minutes and 30 minutes)

At the NAC/AEGL-20 meeting the AEGL-2-values for xylene were discussed. As the key study was a study with 4-hours exposure extrapolation to shorter time periods was necessary. It has been unanimously decided to use a toxicokinetic approach to calculate AEGL-2 values for 10 min and for 30 min.

The following assumptions were made: (i) the toxicological endpoint and the intensity of toxicological effect should be the same as observed after administration of 430/ppm for 4 hours (ii) it is the concentration and not the amount of the substance (AUC), which is responsible for the effect, qualitatively and quantitatively (iii) the data from kinetic studies in human volunteers (see table 11, page 52 in the NAC/Draft: 12/2000 attachment 2) are appropriate for further kinetic calculations (iv) the data of m-xylene were used to represent the mixture of all xylenes (v) the kinetics of m-xylene are linear in the concentration/dose range which is under consideration.

Calculations: The data of three studies were used. The external concentration in the air multiplied by inhalation volume and frequency was used as input rate. An one-compartment body model did describe the data appropriately. The calculations were done using NONMEM program. After the concentration at 4 hours was calculated the input rate to reach this concentration with 10 min and 30 min respectively was estimated. As we assumed inhalation volume and frequency being constant, the external air concentration was obtained by eliminating the constant. Outcome of the calculations: k which is the first order elimination constant was 2.74/ hr the corresponding half life is 0,25 hrs. The concentration at 4 hours was 6,5 ± 10 µmol/L(mean ±2 SD) for 430ppm. The external air concentration to reach this concentration within 10 minutes is 1165 ±180ppm (mean ±2 SD) and within 30 min is 570±87,5 (mean±2 SD).

Calculating the lower boundary value for 2 SD results in

10 min: 985 ppm

30 min: 482,5ppm

Calculating the lower boundary value for 3 SD results in

10 min: 896ppm

30 min: 438,4ppm

Conc. (µmol/L)	65 (mean)	55 (-2SD)	50 (-3SD)
10 min	1165ppm	985ppm	896ppm
30 min	570ppm	482,5ppm	438,ppm

For visualization see figures.

XYLENE

Derivation of AEGL-3 (10 minutes and 30 minutes)

At the NAC/AEGL-20 meeting the AEGL-3 values for xylene were discussed. As the key study was a study with 4-hours exposure extrapolation to shorter time periods was necessary. It has been unanimously decided to use a toxicokinetic approach to calculate AEGL-3 values for 10 and for 30 min.

The following assumptions were made: (i) the toxicological endpoint and the intensity of toxicological effect should be the same as observed after administration of 930ppm for 4 hours (ii) it is the concentration and not the amount of the substance (Auc) which is responsible for the effect, qualitatively and quantitatively (iii) the data from kinetic studies in human volunteers (see table 11, page 52 in the NAC/Draft: 12/2000 attachment 2) are appropriate for further kinetic calculations (iv) the data of m-xylene

were used to represent the mixture of all xylenes (v) the kinetics of m-xylene are linear in the concentration/dose range which is under consideration.

Calculations: The data of three studies were used. The external concentration in the air multiplied by inhalation volume and frequency was used as input rate. A one-compartment body model did describe the data appropriately. The calculations were done using NONMEM program. After the concentration at 4 hours was calculated the input rate to reach this concentration within 10 min and 30 min respectively was estimated. As we assumed inhalation volume and frequency being constant, the external air concentration was obtained by eliminating the constant.

Outcome of the calculations: k which is the first order elimination constant was 2.74/hr corresponding half life is 0.25hrs. The concentration at 4 hrs. Was 141 ± 25μmol/L (mean ± 2 SD) for 930ppm. The external air concentrations to reach this concentration within 10 min is 2526 ± 455ppm (mean ± 2SD) and within 30 min is 1237 ± 221ppm (mean ± 2 SD).

Calculating the lower boundary value for 2 SD results in

10 min: 2071 ppm
30 min. 1016 ppm

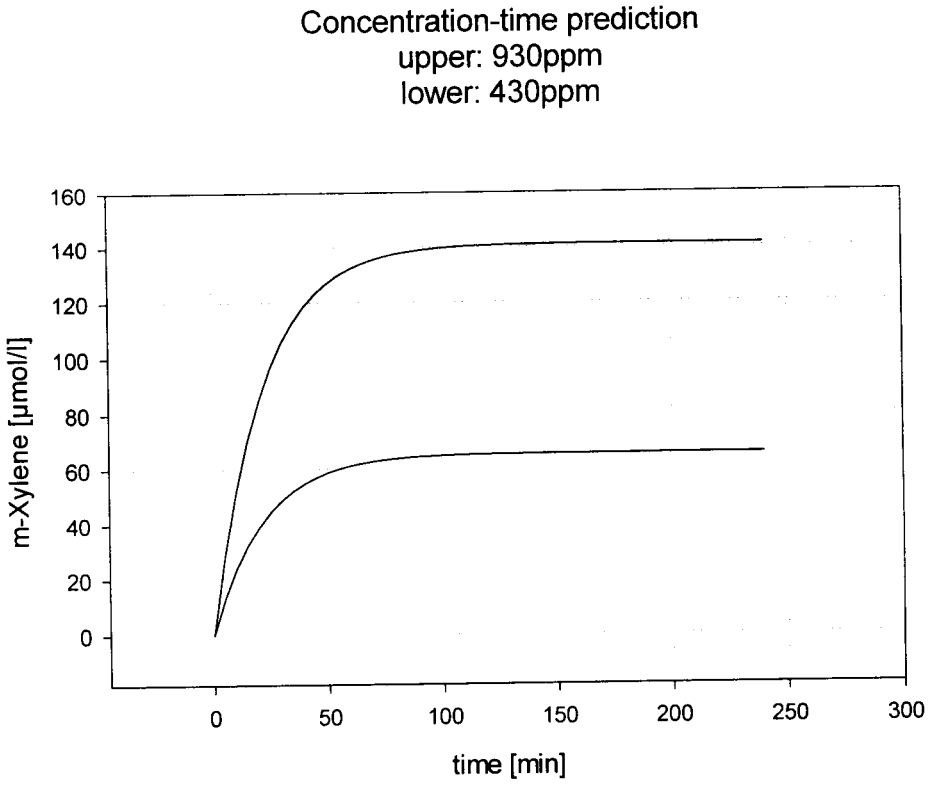
Calculating the lower boundary value for 3 SD results in

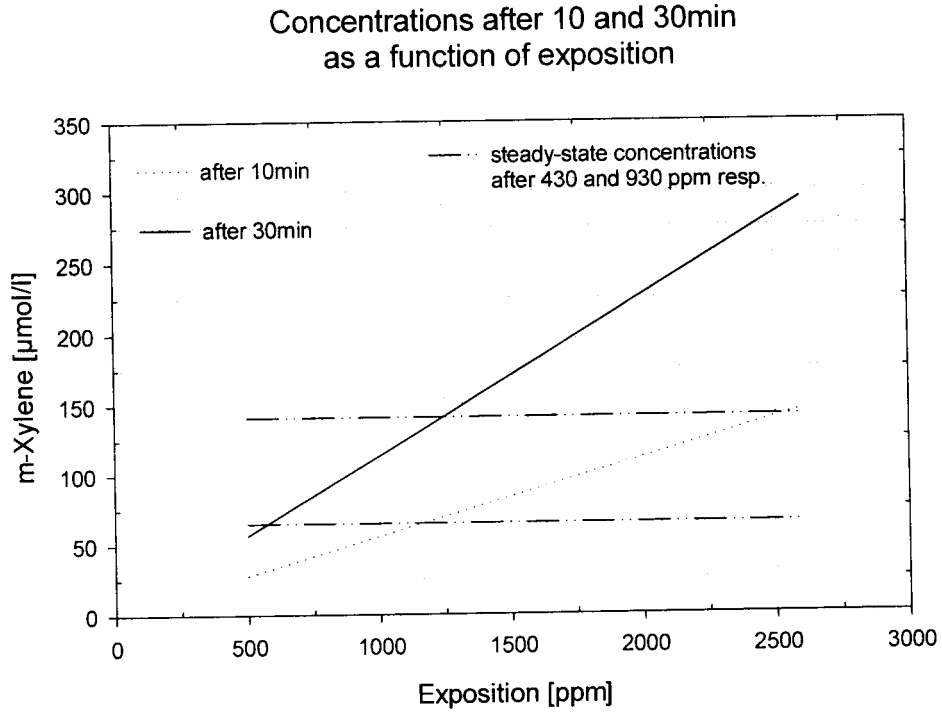
10 min: 1790 ppm
30 Min: 963 ppm

conc μmol/L)	141 mean	116 (-2 SD)	103.5 (-3 SD)
10 min	2526ppm	2071ppm	1790ppm
30 min	1237ppm	1016ppm	963ppm

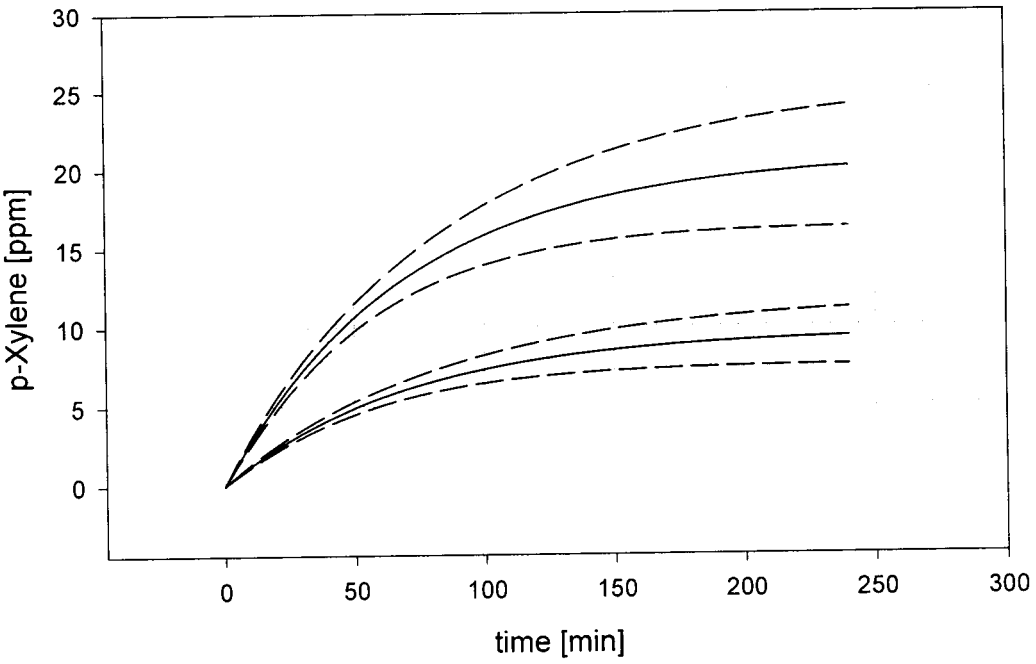
For visualization see figures.

Fig. 1: a)Concentration-time course prediction for an 4 hour exposure with 930 ppm and with 430 ppm based on experimental data in human volunteers exposed to m- xylene for 2 to 3 hours. b) Steady state concentration for 930 ppm and for 430 ppm were taken from calculations (see Fig. 1a) and the external exposure which has to be present to result in this concentrations were calculated assuming linear kinetics (resulting from the intersection).

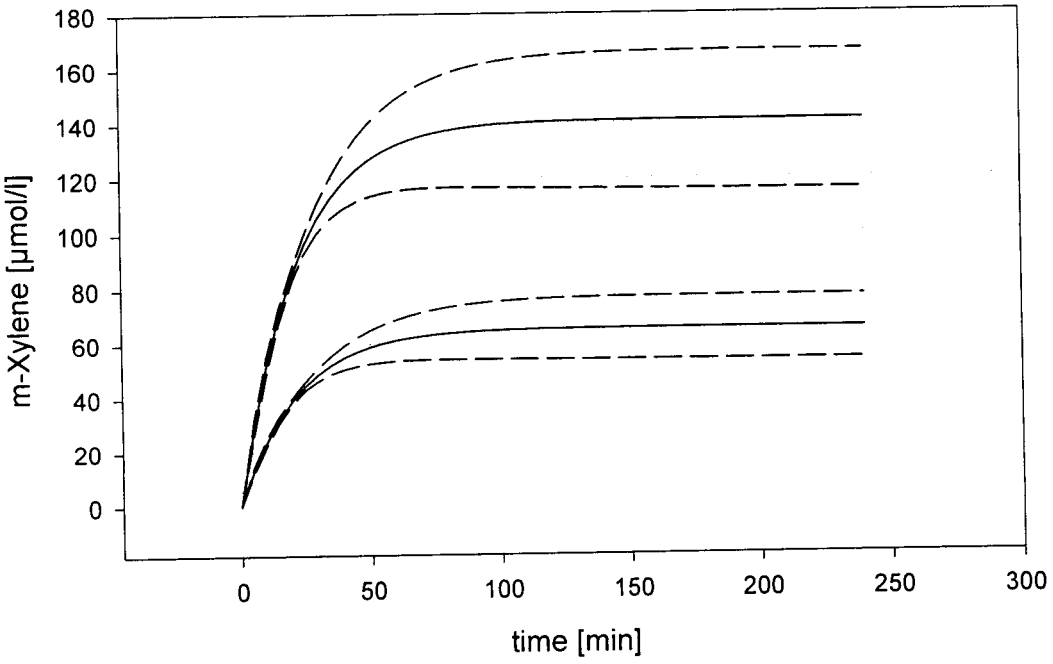




Concentration-time predictions ± 2SD
upper: 930ppm
lower: 430ppm



Concentration-time predictions ± 2SD
upper: 930ppm
lower: 430ppm



ACUTE EXPOSURE GUIDELINE LEVELS FOR

CHLORINE DIOXIDE

NAC/AEGL-22
September 11-13, 2001

Chemical Manager: Robert Benson
ORNL Staff Scientist: Cheryl Bast

AEGL-1 FOR CHLORINE DIOXIDE (ppm [mg/m^3])					
AEGL Level	**10-min**	**30-min**	**1-hr**	**4-hr**	**8-hr**
AEGL-1	**NR**	**NR**	**NR**	**NR**	**NR**

Data are insufficient for derivation of AEGL-1 values.

AEGL-2 FOR CHLORINE DIOXIDE (ppm [mg/m^3])					
AEGL Level	10-min	30-min	1-hr	4-hr	8-hr
AEGL-2	0.92 (2.5)	0.92 (2.5)	0.73 (2.0)	0.45 (1.2)	0.30 (0.83)

Species: Rat
Concentration: 12 ppm
Time: 6 hrs.
Endpoint: Lacrimation, salivation, dyspnea, weakness, and pallor
Reference: DuPont, 1955

Time Scaling: Default Values

n = 1 (8-hr.) Or n = 3 (30-min., 1-hr., &4-hr.)

The 30-min. AEGL-2 value was adopted as the 10-minute AEGL-2 value since the starting exposure duration was 6 hr.

Uncertainty Factor: 3 x 10 = 30 MF = 2

Interspecies = 10

(The most sensitive species was not used. Guinea pigs and rabbits were more sensitive to chlorine dioxide-induced effects than rats and mice (Hecht, 1950)).

Intraspecies = 3

(Irritation/direct chemical effect on tissue from highly reactive compound is unlikely to vary greatly among individuals)

AEGL-3 FOR CHLORINE DIOXIDE (ppm [mg/m^3])					
AEGL Level	10-min	30-min	1-hr	4-hr	8-hr
AEGL-3	2.0 (5.5)	2.0 (5.5)	1.6 (4.4)	0.97 (2.7)	0.63 (1.7)

Species: Rat
Concentration: 26 ppm
Time: 6 hr.
Endpoint: No Lethality Observed
References: DuPont, 1955

Time Scaling: Default Values

n = 1 (8-hr.) Or n = 3 (30-min., 1-hr., &4-hr.)

The 30-min. AEGL-3 value was adopted as the 10-minute AEGL-3 value since the starting exposure duration was 6 hr.

Uncertainty Factor: 3 x 10 = 30

Interspecies = 10

(The most sensitive species was not used. Guinea pigs and rabbits were more sensitive to chlorine dioxide-induced effects than rats and mice (Hecht, 1950)).

Intraspecies = 3

(Congestion and pulmonary edema/direct chemical effect on tissue from highly reactive compound is unlikely to vary greatly among individuals)

Summary Table of AEGL Values for Chlorine Dioxide [ppm (mg/m^3)]						
Classification	**10-Minute**	**30-Minute**	**1-Hour**	**4-Hour**	**8-Hour**	**Endpoint (Reference)**
AEGL-1 (Nondisabling)	NR	NR	NR	NR	NR	Insufficient data for AEGL-1 derivation. Not recommended
AEGL-2 (Disabling)	0.92 (2.5) 1.37	0.92 (2.5) 1.37	0.73 (2.0) ~1.1 ?	0.45 (1.2) 0.68	0.30 (0.83) 0.45	Lacrimation, salivation, dyspnea, weakness, and pallor in rats exposed to 12 ppm for 6 hours (DuPont, 1955)
AEGL-3 (Lethal)	2.0 (5.5) 3.0	2.0 (5.5) 3.0	1.6 (4.4) 2.4	0.97 (2.7) 1.5	0.63 (1.7) 0.98	No lethality in rats exposed to 26 ppm for 6 hr (DuPont, 1955)

ACGIH TLV-TWA:	**0.1 ppm**
ACGIH TLV-STEL:	**0.3 ppm**
NIOSH IDLH:	**5 ppm**
NIOSH REL:	**0.1 ppm**
NIOSH STEL:	**0.3 ppm**
OSHA PEL:	**0.1 ppm**
MAK (German):	**0.1 ppm**
MAC (Dutch):	**0.1 ppm**

AEGLs

Classification	Exposure Duration				
	10-Minute	30-Minute	1-Hour	4-Hour	8-Hour
AEGL-1 HCl	1.8	1.8	1.8	1.8	1.8
(Nondisabling) HF	1.0	1.0	1.0	~~0.5~~ 1.0	~~0.5~~ 1.0
AEGL-2 HCl	130	43	22	5.4	2.7
(Disabling) HF	95	34	24	12	8.6
AEGL-3 HCl	620	210	100	26	13
(Lethal) HF	170	62	44	22	15

HCl: n=1 Based on 1-100 minutes

HF: n=2 Based on 5-60 minutes

Attachment 7

12pp

MR 48401

00312

C-002

American Chemistry Council

Attachment 8

June 1, 2001

Via Hand Delivery

OPPT Document Control Office
United States Environmental Protection Agency
East Tower
Room G-099
Waterside Mall
401 M Street, S.W.
Washington, D.C. 20460

Re: Notice Concerning the National Advisory Committee for Acute Exposure Guideline Levels for Hazardous Substances Proposed AEGL Values for Phenol, 66 Fed. Reg. 21940 (May 2, 2001); OPPTS-00312

Dear OPPT Document Control Office:

The Phenol Regulatory Panel (Panel) of the American Chemistry Council submits the appended comments on the United States Environmental Protection Agency's proposed acute exposure guideline levels for phenol. The Panel is comprised of domestic manufacturers of phenol that represent approximately 95 percent of United States production of the chemical.

Please direct any questions concerning these comments to Mr. Jonathon T. Busch, Manager of the Phenol Regulatory Panel, at (703) 741-5633.

Sincerely yours,

Jon Busch

Attachment

RECEIVED
OPPT/NCIC
2001 JUN -5 AM 10:37

Responsible Care®

1300 Wilson Boulevard, Arlington, VA 22209 • Tel 703-741-5000 • Fax 703-741-6000 • http://www.americanchemistry.com

BEFORE THE
UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

COMMENTS OF THE AMERICAN CHEMISTRY COUNCIL'S PHENOL REGULATORY PANEL ON THE NATIONAL ADVISORY COMMITTEE FOR ACUTE EXPOSURE GUIDELINE LEVELS (AEGLs) FOR HAZARDOUS SUBSTANCES PROPOSED AEGL VALUES FOR PHENOL

Notice Concerning the National Advisory Committee for Acute Exposure Guideline Levels for Hazardous Substances Proposed AEGL Values for Phenol, 66 Fed. Reg. 21940 (May 2, 2001).	OPPTS – 00312 FRL – 6776-3

Courtney M. Price
Vice President, CHEMSTAR

Mr. Jonathon T. Busch
Manager
Phenol Regulatory Panel

David F. Zoll, Esquire
Vice President and
General Counsel

Theodore R. Waugh, Esquire
CHEMSTAR Counsel

Of Counsel:

Lynn L. Bergeson, Esquire
Lisa M. Campbell, Esquire
Richard P. Bozof, Esquire
Bergeson & Campbell, P.C.
1300 Eye Street, N.W.
Suite 1000 West
Washington, D.C. 20005

June 1, 2001

AMERICAN CHEMISTRY COUNCIL
1300 Wilson Boulevard
Arlington, VA 22209
(703) 741-5000

- Application of an *intraspecies* variability uncertainty factor of 3 to the Flickinger study, rather than the 10-fold *intraspecies* uncertainty factor used in the Support Document, and therefore application of a 9- to 10-fold *overall* uncertainty factor, rather than the 30-fold uncertainty factor assumed in the Support Document, are justified on several grounds. These include, among other considerations, the fact that in the well-conducted multiple dose, multiple exposure study by CMA (1998), no adverse effects were observed in rats administered 25 ppm phenol 6 hours/day, 5 days/week for 2 weeks (the highest dose administered).

- While the CMA study is a superior study, with multiple doses, because it has a free-standing no observed adverse effect level for adverse effects, use of the Flickinger study after applying an *overall* 9- to 10-fold uncertainty factor is warranted.

- The 10-minute AEGL-2 value should have been derived by applying the time-scaling equation in the same manner the equation was used to derive values for other time periods.

INTRODUCTION

The American Chemistry Council's Phenol Regulatory Panel (Panel) submits these comments on the U.S. Environmental Protection Agency's (EPA) proposed acute exposure guideline levels (AEGLs) for phenol, published in the *Federal Register* on May 2, 2001. 66 Fed. Reg. 21940, 21952-4. The Panel is comprised of domestic manufacturers of phenol that represent approximately 95 percent of United States production of the chemical.[1]

I. THE PROPOSED AEGL-3 VALUES FOR PHENOL ARE BASED ON UNREASONABLE ASSUMPTIONS AND METHODOLOGY AND ACCORDINGLY ARE SUBSTANTIALLY TOO LOW

The Panel urges the NAC/AEGL Committee to revise the proposed AEGL-3 values for phenol and adopt values that are no lower than the 1-hour level Emergency Response Planning Guideline, Level 3 (ERPG-3) of 200 ppm, established by the American Industrial Hygiene Association (AIHA) with appropriate time scaling for different exposure periods. The ERPG-3 is intended to be based on essentially the same criteria that are used to establish the AEGL-3.[2] Alternatively, the Panel suggests the NAC/AEGL Committee consider concluding that the database is insufficient to derive AEGL-3 values and therefore decline to do so.

---

[1] Panel members include: Aristech Chemical Corporation; Dakota Gasification Company; The Dow Chemical Company; Fenoquimia, S.A. de C.V.; General Electric Corporation; Georgia Gulf Corporation; JLM Industries, Inc.; Merisol Company (Merichem-Sasol USA LLC); Phenolchemie Inc.; Shell Chemical Company; and Sunoco Inc. Associate members are: BF Goodrich; Borden Inc.; and The Procter & Gamble Company.

[2] The AEGL-3 is defined as the "airborne concentration. . . . of a substance above which it is predicted that the general population, including susceptible individuals, could experience life-threatening health effects or death." 66 Fed. Reg. at 21941. The ERPG-3

A number of other considerations indicate that the proposed AEGL-3 values are substantially too low:

- It is scientifically unsound to establish an AEGL-3 value, which is intended to indicate the strong potential for lethality after up to 8 hours of exposure in a single day, at a level similar to a level that induced no adverse effects in laboratory animals after multiple days of exposure. For example, the proposed AEGL-3 value of 23 ppm for 8 hours of exposure is on its face inappropriate given that in the CMA (1998) study, rats exposed to 25 ppm for 6 hours/day for 10 days exhibited no adverse effects.

- The Support Document inappropriately utilizes case studies reporting lethal effects in humans after ingestion of phenol in justifying application of a 10-fold uncertainty factor, rather than a smaller uncertainty factor, to the exposure level in the Flickinger study. The Support Document indicates that the calculated AEGL-3 values for the various time periods, from 30 minutes to 8 hours, were 8-fold to 48-fold lower than the lower boundary of the estimated dose range of the reported lethal cases after oral and dermal exposure.[7] The lower boundary estimates for the human lethality cases, however, are based on the lower end of tissue concentration measurements, which showed a wide range in each subject where exposure levels were estimated in that manner.

  This is a highly unreliable method of estimating exposure levels as the variation in these data are likely derived from differences in the analytical techniques used to measure phenol in human tissue, as well as the variability in reporting of the dose or exposure of phenol which occurred in these human poisonings, rather than intraspecies variation in metabolism or pharmacokinetics. Indeed, pharmacokinetic studies conducted on phenol have shown very good animal-to-animal reproducibility in the data (Hiser *et al.*, 1994; Piotrowski, 1971, *Br. J. Ind. Med.* 28: 172-178). The few case reports where the intake appeared to be known with more certainty indicated intakes two and a half to six-fold higher than the lower boundary assumed in the report, and these levels were all above the exposure level in the Flickinger study. In addition, the manner in which the human reports are used does not take into account that the ingestions occurred as a single incident, resulting in absorption of the phenol into the body over a short period of time. Therefore, the peak blood concentrations or estimated delivered doses in effect were somewhat higher than if the exposures occurred over several hours as

---

7 *See* Support Document at 33-34.

adverse effect level (NOAEL) of 25 ppm. The Support Document further indicates that the proposed AEGL-2 values were corroborated by deriving similar, but slightly higher, AEGL-2 values from the Flickinger study.[10] The Panel recommends that the AEGL-2 values be based on the Flickinger study, but only after application of a total uncertainty factor of 9 or 10, rather than the 30-fold uncertainty factor applied by the NAC/AEGL Committee to that study. Because the CMA (1998) study indicates no adverse effects, that study should be used to corroborate application of a much smaller uncertainty factor to the Flickinger study. This recommendation is based on several considerations.

First, the endpoints observed in the Flickinger study do not clearly meet the AEGL-2 criteria. Those criteria define AEGL-2 as the airborne concentration of a substance "above which it is predicted that the general population, including susceptible individuals, could experience irreversible or other serious, long-lasting adverse health effects, or an impaired ability to escape."[11] As discussed above, the test animals were all normal the day after the exposure. Accordingly, the study does not indicate irreversible or other serious, long-lasting adverse health effects. Moreover, the muscle spasms and slight loss of coordination that were reported are not sufficiently severe to result in an impaired ability to escape. Further, the fact that tremors and prostration were observed in only one of six mice, makes questionable the inference that such effects were induced by the test substance.

---

9 *See* Support Document at 29.

10 Support Document at 30-31.

11 66 Fed. Reg. at 21941.

document for using the time-scaling equation in deriving the 10-minute AEGL-1 value also applies to the derivation of the 10-minute AEGL-2 value.[13]

Alternatively, the Panel suggests that the NAC/AEGL Committee consider concluding that the database is insufficient to derive AEGL-2 values and therefore decline to do so.

CONCLUSION

The Panel appreciates the opportunity to comment on the proposed AEGL values for phenol. The Panel urges the NAC/AEGL Committee to revise the AEGL values and the Support Document consistent with these comments.

---

[13] *See* Support Document at 29.

.00312

C-01

Attachment 9

Dawn Baeske <BAESKEDA@state.mi.us> on 06/01/2001 10:27:44 AM

To: NCIC OPPT/DC/USEPA/US@EPA
cc: Mary Lee Hultin <HULTINM@state.mi.us>

Subject: Comments to Docket Control Numbers OPPTS-00312

Attached are our comments for the subject Docket number - in ASCI II format.

If you have any questions, please feel free to contact:

Mary Lee Hultin
Michigan Department of Environmental Quality
Air Quality Division
517-373-9845
hultinm@state.mi.us

Thank you,
Dawn Baeske
Department of Environmental Quality
Air Quality Division
517-373-7063
baeskeda@state.mi.us

ProposedAEGLCommentsMay2001.txt

STATE OF MICHIGAN

JOHN ENGLER, Governor

DEPARTMENT OF ENVIRONMENTAL QUALITY

"Better Service for a Better Environment"

HOLLISTER BUILDING, PO BOX 30473, LANSING MI 48909-7973

INTERNET: www.deq.state.mi.us

RUSSELL J. HARDING, Director

REPLY TO:

AIR QUALITY DIVISION
PO BOX 30260
LANSING MI 48909-7760

May 31, 2001

Document Control Office (7407)
Office of Pollution Prevention and Toxics
Environmental Protection Agency
1200 Pennsylvania Avenue, NW
Washington, DC 20460

Dear Document Control Office:

SUBJECT: OPPTS-00312

The following comments are being offered pursuant to the Federal Register Notice issued May 2, 2001, regarding Proposed Acute Exposure Guidance Levels (AEGL).

1. Comments on the derivation of AEGLs for acrylic acid:

The derivations of the AEGL-1 values appear to be supported with the background literature. The presumption that an interspecies uncertainty factor of 1 is warranted due to the "higher acrylic acid concentration deposited on the olfactory epitehelium of rodents compared to humans" does not seem sufficiently supported. The theories summarized from the Frederick, et al, 1998 paper, and used as support for the lowered uncertainty factor, are interesting. However, their suitability for use in risk assessment is questionable. Has the model they developed been tested and/or validated by any other researchers?

In addition, the justification for using an intraspecies uncertainty factor of 3 due to the presumption of "limited interindividual variability for local effects on the respiratory tract" does not contain a supportive reference. In fact, the data cited from Renshaw, 1988, includes reports for eye irritation ranging from 0.3-23 ppm, a range spanning approximately an order of magnitude. This report (to AIHA) is presumed to include occupationally exposed individuals, a group with considerably less heterogeneity than the general population. Since the Preface to the report (p. iii) states, "recommended exposure levels are applicable to the general population including infants and children," this degree of reduction in the intraspecies uncertainty factor does not seem appropriate.

Derivations of the AEGL-2 values: Use of the data from the Miller, 1981, subchronic study seems to be a good choice as this was also the key study used by U.S.

Environmental Protection Agency (EPA) in the derivation of the RfC for this compound. As in the development of the AEGL-1 values, reduction of the interspecies uncertainty factor based on the Frederick study is questioned. For both the AEGL-2 and AEGL-3 values, reduction of the interspecies UF's based on the rationale of, "limited interindividual variability for local effects," does not seem appropriate for the reasons given above under the discussion of AEGL-1 uncertainty factors.

More detail in Appendix B on the derivation of the time-scaling factor and how ten Berge, et al., used the data in their model would provide a better template for providing comments.

One editorial note: the symbols in the key on page 20, depicting Figure 1, do not match the symbols in the graph. Therefore, it is not possible to determine precisely what the graph is intended to represent.

2. Comments on the derivation of AEGLs for tetrachloroethylene:

Obviously, use of human studies in the development of AEGL values is preferred. However, the descriptions of the exposure estimates in the Rowe and Carpenter studies (used in derivation of the AEGL-1, and given as support for the other values) raise a question as to the accuracy/precision of the measured values. Perhaps an uncertainty factor for adequacy of database should be applied due to this fact? In the derivation of the AEGL-2 values, a reduction in the interspecies uncertainty factor is performed, reportedly due to the fact that rodents and humans experience similar effects when exposed to CNS depressants. Although this may seem to be a reasonable argument for the pharmacodynamics, the pharmacokinetics may be different between species. The interspecies and intraspecies uncertainty factors generally take both aspects into account (Renwick, A.G. 1999. Subdivision of uncertainty factors to allow for toxicokinetics and toxicodynamics. HERA, v. 5(5):1035-1050). Without supportive data, the reduction given may not be appropriate. The rationale provided for reducing the interspecies uncertainty factor in the AEGL-3 derivations relates to similar lethal values in rodents. Unless data indicates that the difference pertains to non-rodent species as well, this reduction is not appropriate.

The summary states that no developmental anomalies were found in the studies reviewed. However, the Tepe (1980) and Nelson (1980) studies describe some adverse effects in the offspring.

The positive carcinogenicity data is not noted in the descriptions of AEGL derivations. Is the increased cancer risk not considered in derivations of AEGLs?

3. Comments on the derivation of AEGLs for Allyl Alcohol (107-18-6):

The overall approach taken by the NAC/AEGL Committee in deriving the AEGLs for allyl alcohol was based on the AEGL-1's odor threshold of 1.8 ppm for all time values. This action limited the use of uncertainty factors for the AEGL-2 and -3 values. According to the Committee, use of traditional uncertainty factors, i.e., 3 to 10-fold interspecies and intraspecies, would result in inconsistent values compared with the AEGL-1 value. However, the use of uncertainty factors for an AEGL should not be dependent on constraints from other AEGL values, but should independently reflect the health and safety concerns of a particular AEGL. It appears that a combined uncertainty factor of 30 would have been used (which is the traditional method) had it not interfered with the preceding AEGL.

Another discussion point is the NAC/AEGL Committee's proposed AEGL-1 value of 1.8 ppm for all time frames. It is hoped that the committee reviewed all current relevant documentation when establishing these values. During the course of this review, it was found that The American Council of Governmental Industrial Hygienists (ACGIH) has a threshold limit value (TLV) of **0.5 ppm** for allyl alcohol. This value was originally 2 ppm, but in 1998 the new value of 0.5 ppm was published under *Notice of Intended Changes* in their Threshold Limit Values guidebook. According to their by-laws, "if, after one year, no evidence comes to light that questions the appropriateness of the values herein, the values will be reconsidered for the "adopted" list." In 1999, the ACGIH adopted this value. A request was sent to the ACGIH for supporting documentation of this value, but this information has not yet been received to send along with this review. We urge the NAC/AEGL Committee to investigate this issue, since there is no mention of it in the proposed AEGL document for allyl alcohol.

4. Comments on the derivation of AEGLs for Phenol (108-95-2):

The NAC/AEGL Committee selected key studies that seem to appropriately support the derivation for each of the AEGL values. But, the actual derivations didn't follow the conventional use of uncertainty factors. Typically, when using conventional uncertainty factor methodology [*U.S. EPA's Method for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry guidance document (EPA/600/8-90/066F; October 1994; Table 4-8.)]* there can be a three-fold uncertainty factor for inter-specie extrapolation from valid results of long-term studies on experimental animals. This is in stark contrast to the rationale used for the AEGL-2, that an inter-specie uncertainty factor of one is acceptable from a two-week inhalation study (CMA). Although the other key study for the AEGL-2 produced similar results using more conventional uncertainty factors, it seems inappropriate to extrapolate results from a two-week study, and use an uncertainty factor that is less than what would be used for a long-term study. Another troublesome point is the use of 3 for an intra-specie uncertainty factor. This factor is used to account for the variation in sensitivity among members of the human population and should not be weakened, according to conventional use (Table 4-8, see above). For as the preface to the AEGL document states, "...the recommended exposure levels are applicable to the general

population including infants and children, and other individuals who may be sensitive or susceptible". Unless the data is bioassay material, the uncertainty factor should not be less than ten.

5. Comments on the derivation of the proposed AEGL values for methanol (CAS # 67-56-1):

The AEGL support documents explain in sufficient detail the methods used to obtain the AEGL values for methanol. The proposed AEGL values and methodology used seem appropriate.

6. Comments on the derivation of the proposed AEGL values for tetranitromethane (CAS # 509-14-8):

The AEGL support documents explain in sufficient detail the methods used to obtain the AEGL values for tetranitromethane. The proposed AEGL values and methodology used seem appropriate. One comment on the tetranitromethane support document involves Appendix B, which evaluates the calculation of cancer risk to acute exposure. Our office has found that a higher cancer potency value can be obtained using the male mice lung adenoma and carcinoma incidence rather than the female mice values as was used in the support document. Use of this higher potency factor would result in a slightly lower exposure to a very potent carcinogen. There is some question, however, regarding the appropriateness of trying to evaluate the lifetime cancer risk from an acute exposure.

7. Comments on the derivation of the AEGL values for Toluene (108-88-3):

Overall, the derivation of the AEGLs for Toluene seemed well reasoned. However, the 10-minute AEGL-1 of 260 ppm and the 30-minute AEGL-2 of 270 may be disproportionately close, but this could simply be reflective of a high threshold for irritation.

8. Comments on the derivation of the AEGL values for Furan (110-00-9):

A NOAEL was not identified in the only quantitative toxicology study by Terrill et al., (1989). This uncertainty was not specifically accounted for in the AEGL-2. A three-fold increase in the uncertainty factor for AEGL-2 is suggested based on LOAEL to NOAEL conversion. Concerning AEGL-3, metabolism to reactive metabolite cis-2-butene-1,4-dial may be altered at higher exposure levels, shorter time intervals, and severity of effect (i.e. lethality). A three-fold increase in the total uncertainty factor for AEGL-3 is suggested based on incomplete acute pharmacokinetic information for this endpoint. This could be tacked on to the modifying factor of three for a total modifying factor of 10. For AEGL-2 and -3 the total UF would be 300. Alternatively, an increase in the intraspecies UF from 3 to 10 could be justified based on uncertainty of metabolism. The good use of the concentration-time equation exponent n for shorter time intervals may have been part of the reasoning to keep total UF at 100, but this was not stated. It is understood that the suggested total UF of 300 for furan is larger than the other

substances reviewed by the NAC/AEGL Committee, however, the poor toxicological database on furan justifies a higher UF determination.

If you have any questions on the aforementioned comments, please do not hesitate to contact me. Thank you for the opportunity to provide comment on these important values.

Sincerely,

Mary Lee Hultin
Air Quality Division
517-373-9845

MLH:DB
cc: Ms. Catherine Simon, DEQ
Mr. Marco Bianchi, DEQ
Mr. Gary Butterfield, DEQ
Mr. Michael Depa, DEQ

AEGLs for Phenol

The Proposed AEGL values for phenol were published for public comment in the Federal Register, May 2, 2001 (Volume 66, Number 85, Page 21940-21964).

Until the end of the comment period, June 1, 2001, EPA received comments from:

- Phenol Regulatory Panel, American Chemistry Council
- Department of Environmental Quality, State of Michigan

Reply to Comments from the Phenol Regulatory Panel, American Chemistry Council

- ***AEGL-3 values should be no lower than the 1-hour ERPG-3 of 200 ppm or the AEGL Committee should conclude that the database is insufficient to derive AEGL-3 values.***

- ***The lethal or life-threatening endpoints in rats occur at a substantially higher dose than the 8-hour exposure to 234 ppm used in the study by Flickinger (1976), because the occurrence of tremors and prostration, observed in one of six animals, are not life-threatening, and the animals appeared normal the following day and exhibited no lesions at gross autopsy.***

Reply

- Tremors and prostration were observed shortly before death in rabbits and rats after oral dosing in the study of Deichmann and Witherup (1944).

- The estimated body dose in the Flickinger (1976) study of 321 mg/kg is not far below the oral LD_{50} of about 500 mg/kg in rats and within the estimated dose range for lethal oral and dermal intoxications of humans.

- Due to the very small number of animals used in the Flickinger (1976) study, an effect in one of the animals can neither be ascribed with certainty to the exposure nor excluded as not exposure-related.

- In summary, use of the exposure level of 234 ppm for 8 hours as a NOEL for lethality in deriving AEGL-3 values is considered adequate.

- ***An AEGL-3 value at 23 ppm for 8 hours is scientifically unsound because multiple exposure of rats to 25 ppm for 6 hours/day was a NOAEL.***

Reply

- It is inappropriate to directly compare an exposure concentration for humans derived by the application of uncertainty factors with an exposure level in an animal study.

- ***The total uncertainty factor should be smaller than 10 because the calculated doses for AEGL-3 values for various time periods, from 30 min to 8 hours, were 8-fold to 48-fold lower than the lower boundary of the estimated dose range of reported lethal cases after oral and dermal exposure.***

Reply

- The available data on interspecies and intraspecies variability are not considered a sufficient basis in itself to reduce the total uncertainty factor of 100.

- The case reports were considered adequate to reduce the total uncertainty factor from 100 to 10.

- Given the variability and uncertainty in the doses, which was also emphasized by the Phenol Regulatory Panel, the case reports were not considered a sound scientific basis for a further reduction of the uncertainty factor.

- Using the lower boundary of reported human lethal doses of 106 mg/kg and applying a factor of 3 to extrapolate to a nonlethal dose and a factor of 10 for intraspecies variability, a dose of about 3 mg/kg is derived, which is equal to the estimated body dose at the 1-hour AEGL-3 concentration of 47 ppm.

- Based on this comparison and in view of the lack of more definitive data, the use of a total uncertainty factor of 10 is considered adequate.

- ***Time extrapolation should be continued to 10 minutes because the TSD does not provide adequate justification for using the same AEGL-3 value for both 30 and 10 minutes.***

Reply

- The 30-minute exposure concentration is applied to the 10-minute period because of a lack of data that would support extention of the time scaling over more than about one order of magnitude.

- ***The time scaling exponent of 3 may be inappropriate as the 8-hour AEGL-3 value is inconsistent with the repeated inhalation exposure study in rats (CMA, 1998).***

Reply

- The fact that a derived AEGL-3 value for 8 hours is at the NOAEL in a repeated inhalation study in rats does not constitute an appropriate argument for choosing a time extrapolation exponent different from the default value of 3.

- ***The AEGL-2 values should be higher than the currently proposed values.***

- ***The Flickinger (1976) study does not indicate irreversible or other serious, long-lasting adverse health effects and thus does not meet the AEGL-2 criteria because all test animals were normal the day after the exposure, the musle spasms and slight loss of coordination were not sufficiently severe to result in an impaired ability to escape, and the fact that tremors and prostration were observed in only one of six animals makes it questionable that these effects were induced by the test substance.***

Reply

- Tremors and prostration in one animal are attributed to the phenol:

- because these effects constitute a higher degree of severity of similar effects (muscle tremors and incoordination) seen in all other animals,

- because these effects can be explained with what is known about the mechanism of the toxic effects of phenol (interference with acetylcholine release at the motor nerve endings and stimulatory effects on the central nervous system followed by central nervous system depression,

- because similar symptoms were observed before death oral studies in rats and rabbits.

- ***The intraspecies factor of of 10 should be reduced to 3 because no adverse effects were observed in rats repeatedly exposed to 25 ppm for 6 hours/day (CMA, 1998) and the TSD states that available human data do not point at a large intraspecies variability.***

Reply

- The fact that no effects, even with repeated exposure, were seen in the CMA (1998) study at about one tenth the concentration used in the Flickinger (1976) study might reveal something about the dose-response relationship, but is inappropriate for drawing a conclusion with regard to intraspecies variability.

- The TSD made this statement about the variability in humans in context with AEGL-1 and not in the derivation of AEGL-2 values.

- ***While the CMA (1998) study is the superior study, use of the Flickinger (1976) study with a total uncertainty factor of 9 to 10 is warranted.***

Reply

- This point is a mere repetition of the Panels request concerning AEGL-2, but does not include any

further reasoning.

- ***The time extrapolation should be continiued to 10 minutes because 1) there is no adequate justification for using the same concentration for both the 30 and 10 minute values and 2) the 8-hour AEGL-2 value is inconsistent with the repeated inhalation exposure study in rats (CMA, 1998).***

Reply

- The 30-minute exposure concentration is applied to the 10-minute period because because of a lack of data that would support extention of the time scaling over more than about one order of magnitude.

- The AEGL Committee extensively discussed time scaling and the relevance of the RD_{50} for the 10-minute AEGL-2 on its deliberations on January 8, 2001. The RD_{50} would be a valid argument for continuation of time scaling if the effects were caused by irritation, while a flat line should be used if the effects were caused by neurotoxicity. Since neurotoxicity could not be excluded as the relevant mechanism, the 30-minute value was also used for 10 minutes.

Conclusion

Since the Phenol Regulatory Panel, American Chemistry Council has not provided any new data and has not shown that relevant data were not available to the AEGL Committee, it is unnecessary to revisit the proposed AEGL values for phenol at this time.

Reply to Comments from the Department of Environmental Quality, State of Michigan

- ***Extrapolation from a two-week inhalation study using an interspecies uncertainty factor of 1 in the derivation of AEGL-2 is inappropriate.***

- ***According to EPA's conventional uncertainty factor methodology used in the derivation of Inhalation Reference Concentrations (EPA/600/9-90/066F) it seems inappropriate to extrapolate results from a two-week study and to use a reduced uncertainty factor.***

Reply

- AEGLs are derived for an acute, once-in-a-lifetime exposure situation. In contrast, EPA's Reference Concentration Methodology is designed to derive concentrations for lifetime 24-hours-per-day exposures. Consequently, AEGL values are derived on a different methodology laid down in the AEGLs Standing Operating Procedures.

- For the selection of an AEGL key study, an acute, single-exposure inhalation study is normally the best choice. When a repeated exposure study, such as a two-week repeated inhalation study, is used and effects are evaluated for the whole duration of the study, additional safety is gained when extrapolating to a single exposure event. In the overall evaluation of the study this may justify a reduction of the default interspecies uncertainty factor.

- In the case of the two-week inhalation study with phenol (CMA, 1998) an interspecies uncertainty factor was justified because a repeated exposure study was used for the derivation and, in addition, the effect level observed at the highest exposure concentration was below that of an AEGL-2.

Conclusion

Since the Department of Environmental Quality, Michigan has not provided a convincing reasoning that the selection of uncertainty factors was inappropriate within the AEGL methodology, it is unnecessary to revisit the proposed AEGL values for phenol at this time.

Document Control Office (7407)
Office of Pollution Prevention and Toxics (OPPTS)
EPA
1200 Pennsylvania Avenue
Washington, DC 20460

June 1, 2001

Docket control # OPPTS-00312: Methanol AEGL 1 and 2 values

I would like to raise two concerns regarding the AEGL values recommended by the AEGL Committee for methanol. The committee should be aware that this chemical is released in significant amount to the environment (192 million pounds in 1998 as air releases: TRI data).

For the AEGL-1 level, the committee has recommended that an uncertainty factor of 3 be applied when extrapolating from a finding of no adverse outcome (Batterman study) to arrive at the recommended 8 hour value. The basis of this is an email communication by an investigator of their memory of what study subjects said to him in a casual conversation 4 years earlier. It should be noted that demographics are presented on only 4 of 27 participants in the study. These four were age 41-63 while all subjects were nonsmokers. Although of interest and worth noting in the TSD it's quality should be taken into account when relying on it to extrapolate back to other values. The committee relied on this value to extrapolate back to a 30 minute value of 670 ppm. If the uncertainty factor of 3 is protective, there should be no evidence of effects below a value three times the 30 minute value. This would mean that an exposure of 2,010 ppm for 30 minutes should be a threshold of AEGL-1 effects. A NIOSH HHE report (1981-177, 178-988), however, reports that "the operator experienced eye irritation during the sampling period" which was at a measured level of 1,025 ppm methanol for 25 minutes.

This is also supported by the Kawai 1991 study. The high exposed group reported 50% dimmed vision when compared to a low exposed group (0%); 11 of the 22 workers in the high group. Their mean exposure was 459 ppm (upper range around 5,500 ppm). Even if this symptom is attributed to those workers with the highest exposure, the lowest level that all 11 would have to be exposed to is approximately 1,200 ppm for 8 hours (Figure 3 includes the exposure level for 33 high and low exposed workers). It is more likely that at least one of these workers experienced the symptom at a lower level, which would further lower the threshold for this symptom. In either case, this is supportive evidence that levels around 1,200 ppm can produce AEGL-1 health effects (dimmed vision). This is consistent with the AEGL SOP - Elements for the Evaluation of Data and Studies which states "identifying the lowest does at which it (the effects) is seen for each AEGL severity level strengthens the confidence in the study" (point 18, page 38).

Therefore the Committee's recommended 30 minute AEGL-1 value does not afford the protection of an uncertainty factor of 3. In addition there have been substantial revisions of the draft document since the committee's deliberations. With the new TSD and more accurate descriptions of some studies, I would hope the committee would reconsider the AEGL-1 value. Alternatives are setting the AEGL-1 value at: 1)

270 ppm for all time ds or 2) starting from the 1,025 ppm value for 25 minutes found by NIOSH (supported by Kawa nmed vision at 1,200 ppm), dividing by 3 for human variability and extrapolating to lon ne periods.

A recent report by PA of May 2, 2001 contains comments that are relevant to the Committee's AEGL-2 value, spec y related to adverse reproductive outcomes from the (Federal Register: May 2, 2001; pages 21929 0). This describes the "Reproductive and Offspring Developmental Effects Following Inhalatic posure to Methanol in Nonhuman Primates"; Burbacher et al, 1999; Health Research Report N er 89 and concludes:

"Taken together, tudies of Rodgers et al and Burbacher et al provide a pattern of evidence indicative of reproductive a velopmental toxicity associated with exposure of mice and monkeys to methanol vapor during ges . In our judgment, this evidence is relevant for evaluating potential risks of methanol to hum ealth."

I request that th mmittee examine this report and determine if their findings lower the current recommended A -2 levels.

John S. Morawe

c: Fra D. Martino
Secretary Treasurer's Office
Eric Bray
Micnael Sprinker
Bill Kojola, AFL-CIO
George Rusch, AEGL Chairman
Rodger Garrett, EPA

00312 48007

C-001a

Methanol Institute

Phone: 202 467-5050
Fax: 202 331-9055

1P

May 25, 2001

Attachment 12

2001 JUN -5 AM 10:38 RECEIVED OPPT NCIC

Ms. Barbara Cunningham, Acting Director
Environmental Assistance Division (7401)
Office of Pollution Prevention and Toxics
Environmental Protection Agency (EPA)
1200 Pennsylvania Avenue, N.W.
Washington, D.C. 20460

Re: Docket Control No. OPPTS-00312 – Acute Exposure Guideline Levels (AEGL) for Methanol (CAS No. 67-56-1)

Dear Ms. Cunningham:

This letter responds to the May 2, 2001, announcement in the Federal Register (Vol. 66, No. 85) concerning the efforts by the National Advisory Committee for Acute Exposure Guideline Levels for Hazardous Substances (NAC/AEGL Committee) to develop Acute Exposure Guideline Levels (AEGLs) for Methanol (CAS No. 67-56-1). We understand that AEGLs are developed to provide federal, state and local agencies with information on short-term exposure to potentially hazardous chemicals and welcome the opportunity by the U.S. Environmental Protection Agency (EPA) to review and comment on the established AEGL values.

The Methanol Institute (MI) and its member companies have reviewed extant data and compared the proposed AEGL values to methanol exposure standards established by various governmental agencies in several countries including the United States, Canada, Germany and the Netherlands.

It is our opinion that the AEGL levels proposed by the NAC/AEGL Committee are consistent with similar standards found in other countries. Therefore, the Methanol Institute wishes to express its categorical support of the AEGL values proposed by the national Advisory Committee for Acute Exposure Guideline Levels for Hazardous Substances Committee. If the proposed AEGL for methanol should change as the proposal works it way through the process, the Methanol Institute will re-evaluate its support.

It is extremely important for our industry to be engaged and supportive with the EPA throughout its evaluation process on methanol, as already evidenced by our participation in the EPA HPV process and the Integrated Risk Information System (IRIS) evaluation process. We will continue to assist all agencies and provide whatever data and information is needed to carry out initiatives and produce the most thorough assessments possible on our product.

Please do not hesitate to contact me or Bailey Condrey, Methanol Institute Communications Director, if you have any questions or would like further information. The main number of the Methanol Institute is (202) 467-5050.

We look forward to working with you and other staff members throughout the methanol evaluation process.

Sincerely,

John Lynn
President & CEO

Contain NO CBI

800 Connecticut Avenue, NW, Suite 620• Washington, DC 20006• E-mail: MI@methanol.org• Internet: www.methanol.org

Methanol Institute

Phone: 202 / 467-5050
Fax: 202 / 331-9055

Methanol Institute Addendum, September 21, 2001:

After further review the Methanol Institute would like to submit additional comments to [illegible] submission of May 25, 2001. Although MI remains supportive, we believe the mouse study of Rogers et al 1993 [illegible] as the basis for AEGL 2 for methanol. In the Rogers et al. (1993) study, mice were exposed to methanol by inhalation. The blood methanol data in this experiment supports the saturation of the catalase enzyme [illegible] 2,000 ppm in this mouse study. The developmental effects are noted only after the catalase pathway is saturated. The results of this dose study show a LOAEL for fetal effects at 2,000 ppm with a NOAEL of 1000 ppm. The ultimate toxin appears to be related to high blood methanol levels, not the blood formate, which is the ultimate toxin in humans.

Because of species difference in minute ventilation, and body weight, a comparison of [illegible] appears to be the best way to compare the mouse data to humans. The levels tested are much higher [illegible] could be seen in a human exposure situation based on the total daily delivered mg/kg bw dose.

Daily Delivered dose = mg/m3 x minute ventilation x length of daily exposure [illegible]

See Table1 for comparison of total delivered daily dose to airborne concentrations, blood [illegible] and lethal dose in humans (see Table 1).

Table 1
RESPONSE IN MICE COMPARING TOTAL DAILY DELIVERED DOSE AND BLOOD METHANOL TO LETHAL DOSE IN HUMANS (ROGERS ET AL.)

Total dose (mg/kg)	Exposure conditions	Blood methanol (mg/l)	Effect	Ratio of total dose in mice to lethal dose in humans (300-1000 mg/kg)
819	1000 ppm (1300 mg/m3) for 7 hours	97	NOAEL	~1
1638	2000 ppm (2600 mg/m3) for 7 hours	537	LOAEL Develop- ribs	~3 – 5.5
4095	5000 ppm (6500 mg/m3) for 7 hours	1650		~7 – 14
6142	75000 ppm (9750 mg/m3) for 7 hours	3178		~10 – 20
8190	10000 ppm (13000 mg/m3) for 7 hours	4204		~14 – 27
12285	15000 ppm (19500 mg/m3) for 7 hours	7330		~20 – 41

The total daily delivered dose in mg/kg bw at all levels tested in this rodent study would be potentially lethal to humans.

It is our opinion that differences in metabolism, saturation of the enzyme system, a difference in the ultimate toxic agent and the high doses tested (lethal to humans) make this study not relevant for humans and a poor choice for the AEGL 2.

REFERENCES

Perkins RA, Ward KW, Pollack GM. A pharmacokinetic model of inhaled methanol in humans and comparison to methanol disposition in mice and rats. Environ Health Perspect 103:72633(1995).

Rogers JM, Mole ML, Chernoff N, Barbee BD, Turner CI, Logsdon TR, Kavlock RJ. The developmental toxicity of inhaled methanol in the CD-1 mouse, with quantitative dose-response modeling for estimation of benchmark doses. Teratology 47:175-88(1993).

AEGLs for Methanol

The Proposed AEGL values for methanol were published for public comment in the Federal Register, May 2, 2001 (Volume 66, Number 85, Page 21940-21964).

Until the end of the comment period, June 1, 2001, EPA received comments from:

- John S. Morawetz,
- The Methanol Institute,
- Department of Environmental Quality, State of Michigan.

Reply to Comments from John S. Morawetz, representing the International Chemical Workers Union at the NAC/AEGL Committee

General
The comments were submitted as a letter, dated June 1, 2001 and comprise 2 pages.

Request 1
Dr. Morawetz proposes that the NAC/AEGL Committee adopts lower AEGL-1 values, either 270 ppm for all time periods or by deriving values based on an exposure to 1025 ppm for 25 minutes and applying an intraspecies uncertainty factor of 3. From his letter three reasons were identified for this request.

Reason 1
Dr. Morawetz questions that the Proposed AEGL-1 value for the 30-minute period of 670 ppm, which was derived by time extrapolation using an exponent of 3 starting from an exposure without effects of 800 ppm for 8 hours and application of an intraspecies uncertainty factor of 3, is protective. If the uncertainty factor of 3 were protective, there should be no evidence of effects below a value three times the 30-minute value, i.e., 2010 ppm. However, a NIOSH HHE report reported that exposure to 1025 ppm for 25 minutes caused eye irritation in one operator.

Reply to Reason 1
The NAC/AEGL Committee during its deliberations on methanol discussed the NIOSH HHE report. While the report was not correctly presented in the Draft TSD, it was correctly presented in the presentation preceding the deliberations because Dr. Morawetz provided a copy of the report to the AEGL development team the day before the deliberations. The report does not answer several questions relevant to the evaluation of the report, such as whether the irritation severity was below or above the AEGL-1 severity level. Therefore, the evaluation of this case report remains inconclusive. Moreover, since the study involved only one subject the report is considered inadequate as AEGL key study.

Reason 2
Dr. Morawetz suggests that data in the Kawai et al. (1991) study also supports his Request because he concluded from Figure 3 of the article that the lowest exposure level that led to dimmed vision in exposed workers was approximately 1200 ppm for 8 hours at the highest, but more likely below this level.

Reply to Reason 2
In the study by Kawai et al. (1991) the only subjective complaints that were reported significantly more often in the high-exposure group compared to the low-exposure group were dimmed vision during work and nasal irritation during work. The symptom of "dimmed vision" has been questioned by the authors of the study and may have been a result of fumes in the workroom. The fact that headaches did not occur more frequently supports the author's interpretation that the ‚dimmed vision' was a physical rather than a health-related problem because in other occupational studies, headaches occurred at lower concentrations than effects on vision (Kingsley and Hirsch, 1955) or, at higher exposure concentrations, as a more frequent symptom than blurred vision (NIOSH, 1980; Frederick et al., 1984). In conclusion, the reported "dimmed vision" in the study by Kawai et al. (1991) is most likely not a methanol-caused health effect. Therefore, the observations in this study do not contrast with the Proposed AEGL-1 values. In fact, the study reports even for exposures as high as 5500 ppm for 8 hours no health effects exceeding the AEGL-1 level.

Reason 3
Dr. Morawetz suggested that a reconsideration of the AEGL-1 values by the NAC/AEGL Committee might be required because "there had been substantial revisions of the draft document since the Committee's deliberations".

Reply to Reason 3
This comment by Dr. Morawetz probably alludes to the NIOSH HHE report, which was incorrrectly presented in the Draft TSD. As already explained above, the NAC/AEGL Committee was fully informed of the report before it started its discussion on the methanol AEGL values. The other changes to the TSD were the result of the Committee's deliberations, especially the change of the basis for the AEGL-2 derivation, resulting in very similar values compared to the Draft TSD and the clarifications in the descriptions of the studies of Kawai et al. (1991) and Batterman et al. (1998). No substantial new or other data were additionally incorporated into the TSD after the Committee's deliberations. Thus, a reconsideration of the TSD by the NAC/AEGL Committee is not considered justified by Dr. Morawetz' argument.

Request 2
Dr. Morawetz proposes that the NAC/AEGL Committee revisits the AEGL-2 values for methanol because of a recent US-EPA evaluation of developmental toxic effects published in a Federal Register Notice. From his letter the following reason was identified for this request.

Reason 1
The US-EPA, in a ‚Notice of denial of a petition to delist methanol from the list of hazardous air pollutants' (Federal Register, Vol. 66, May 2, 2001, pages 21929-21940), has evaluated the study by Burbacher et al. (1999) as well as other studies EPA concluded that "... the studies of Rodgers et al and Burbacher et al provide a pattern of evidence indicative of reproductive and

developmental toxicity associated with exposure of mice and monkeys to methanol vapor during gestation. In our judgement, this evidence is relevant for evaluating potential risks of methanol to human health."

Reply to Reason 1
The NAC/AEGL Committee has identified the developmental toxicity of methanol as the relevant endpoint for the derivation of AEGL-2 values. It discussed the available data in rats, mice and monkeys. The study by Burbacher et al. (1999) was included in the Draft TSD and discussed during the Committee's deliberations. The Proposed TSD reads that "in the study by Burbacher et al. (1999a; 1999b), hints, but no clear-cut effects were found for neurobehavioral effects (delayed development of visually directed reaching and absence of novelty preference) in monkeys after prenatal exposure to 200, 600 and 1800 ppm for 2 hours/day, 7 days/week throughout pregnancy. It is difficult to decide whether these slight effects would also be seen after reducing the number of exposure days to a single day. It seems reasonable, however, to assume that a single exposure during pregnancy would have a much lesser effect than a daily exposure during the whole intrauterine development and that, therefore, the results of Burbacher et al. (1999a; 1999b) are not incompatible with the derived AEGL-2 values." This evaluation of the Burbacher et al. (1999) study is fully in line with the evaluation by EPA: "Although the findings from Burbacher et al. provide reasonable qualitative evidence of reproductive and developmental toxicity associated with methanol exposure during pregnancy, characterizing the dose-reponse relationship in these data is more problematic." Therefore, the evaluation of the Burbacher et al. (1999) study by EPA in the Federal Register Notice does not warrant a rediscussion of the AEGL-2 values for methanol.

Conclusion

Since the comments of Dr. Morawetz did not provide any new data or convincingly demonstrated that available data were used incorrectly, it is considered unnecessary to revisit the Proposed AEGL values for methanol at this time.

Reply to Comments from The Methanol Institute

General
The comments were submitted as a letter, dated May 25, 2001 and comprise 1 page.

Comment
The Methanol Institute commented that "... the AEGL levels propsed by the NAC/AEGL Committee are consistent with similar standards found in other contries. Therefore, the Methanol Institute wishes to express its categorical support of the AEGL values proposed...".

Comments from The Methanol Institute , Addendum

- ***The developmental toxic effects in mice, described in the Rogers et al. (1993) study are inappropriate as the basis for AEGL-2.***

- ***The developmental toxic effects, which are caused by methanol, are noted only after saturation of the catalase pathway at a concentration of about 1000 ppm.***

- ***A comparison of daily delivered dose appears to be the best way to compare the mouse data to humans: the LOEL for teratogenic effects corresponds to a total body dose 1.6-5.5 times higher than the lethal dose in humans.***

- ***Differences in metabolism, saturation of the enzyme system, a difference in the ultimate toxic agent and the high doses tested (lethal to humans) make this study not relevant for humans.***

Reply

- The authors do not provide any reason why the total daily delivered dose and not the blood methanol concentration, which is closer to a target organ concentration, should be used for species comparison.

- For comparison of total body doses it is inappropriate to compare a body dose from a 7-hour inhalation exposure (mouse study by Rogers et al., 1993) with an oral bolus dose for humans, because the time during which the dose is delivered is critical. For example, in the Kawai et al. (1991) study, workers were exposed virtually without effects to up to 5500 ppm for 8 hours , which corresponds to a total body dose of about 1020 mg/kg. This dose would be lethal if taken up (orally) in a shorter time.

- The Burbacher et al. (1999a; b) study indicated that effects on neurobehavioral development in primates might occur at sustantially lower exposure concentrations and blood methanol levels compared to rodents.

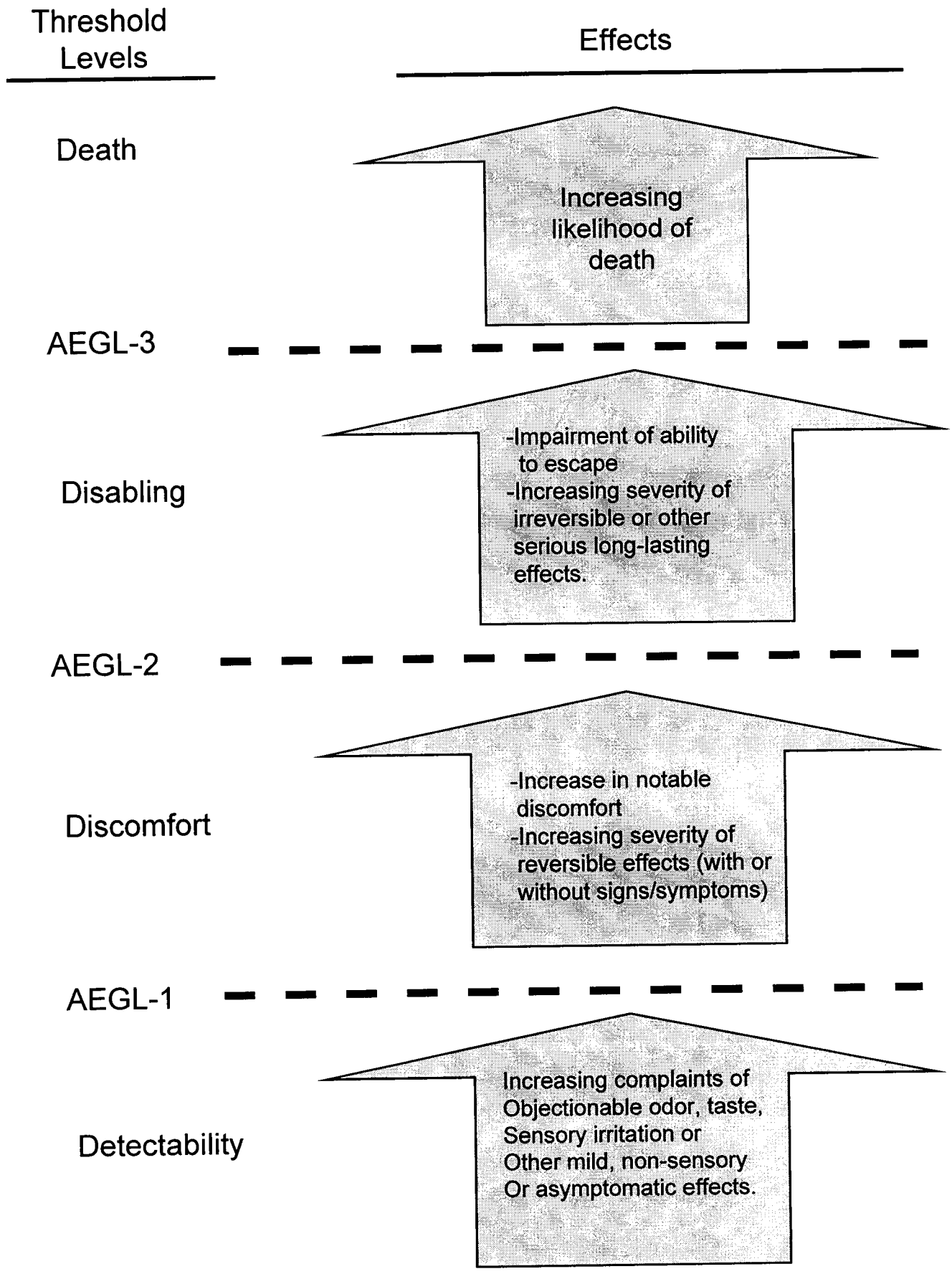
- In summary, developmental toxicity is a relevant endpoint for human exposure and, because primate data adequate for AEGL-2 derivation are not available, the mouse studies are used.

- An alternative derivation of AEGL-2 as a fraction (1/3) of AEGL-3 would have resulted in very similar AEGL-2 values (5000, 2600, 830 and 530 ppm for 30 min, 1 h, 4 h and 8 h, respectively) compared to the proposed values (4000, 2100, 720 and 510 ppm, respectively).

Reply to Comments from the Department of Environmental Quality (DEQ), State of Michigan

General
The comments (on Acrylic Acid and Methanol) were submitted as a letter, dated May 31, 2001 and comprise 2 pages.

Comment
DEQ commented that the TSD explains in sufficient detail the methods used to obtain the AEGL values for methanol and that the Proposed AEGL values and methodology used seem appropriate to DEQ.


Threshold Levels
Effects
Death
Increasing likelihood of death
AEGL-3
Disabling
-Impairment of ability to escape
-Increasing severity of irreversible or other serious long-lasting effects.
AEGL-2
Discomfort
-Increase in notable discomfort
-Increasing severity of reversible effects (with or without signs/symptoms)
AEGL-1
Detectability
Increasing complaints of Objectionable odor, taste, Sensory irritation or Other mild, non-sensory Or asymptomatic effects.

SUMMARY TABLE OF PROPOSED AEGL VALUES FOR ACRYLIC ACID						
Classification	10-Minute	30-Minute	1-Hour	4-Hour	8-Hour	Endpoint (Reference)
AEGL-1 (Nondisabling)	1.0 ppm (3.0 mg/m^3)	1.0 ppm (3.0 mg/m^3)	1.0 ppm (3.0 mg/m^3)	1.0 ppm (3.0 mg/m^3)	1.0 ppm (3.0 mg/m^3)	**Odor recognition threshold and slight irritation in humans (Hellman and Small, 1974; Renshaw, 1988)**
AEGL-2 (Disabling)	30 ppm (90 mg/m^3)	30 ppm (90 mg/m^3)	20 ppm (60 mg/m^3)	9.4 ppm (28 mg/m^3)	6.4 ppm (19 mg/m^3)	**Histopathological alterations of the nasal mucosa in rats (Frederick et al., 1998)**
AEGL-3 (Lethal)	480 ppm (1400 mg/m^3)	260 ppm (780 mg/m^3)	180 ppm (540 mg/m^3)	85 ppm (260 mg/m^3)	58 ppm (170 mg/m^3)	**LC_{01} for lethality in rats (Hagan and Emmons, 1988)**

TOXICOLOGY AND APPLIED PHARMACOLOGY 152, 211–231 (1998)
ARTICLE NO. TO988492

Application of a Hybrid Computational Fluid Dynamics and Physiologically Based Inhalation Model for Interspecies Dosimetry Extrapolation of Acidic Vapors in the Upper Airways

Clay B. Frederick,*[,1] Michele L. Bush,† Larry G. Lomax,* Kurt A. Black,* Lavorgie Finch,* Julia S. Kimbell,‡ Kevin T. Morgan,‡ Ravi P. Subramaniam,‡ John B. Morris,§ and James S. Ultman†

*Toxicology Department, Rohm and Haas Company, Spring House, Pennsylvania 19477; †Physiological Transport Studies Laboratory, Department of Chemical Engineering, The Pennsylvania State University, University Park, Pennsylvania 16802-4400; ‡Chemical Industry Institute of Toxicology, Research Triangle Park, North Carolina 27709; and §Toxicology Program, School of Pharmacy, University of Connecticut, Storrs, Connecticut 06269-2092

Received February 11, 1998; accepted May 26, 1998

Application of a Hybrid Computational Fluid Dynamics and Physiologically Based Inhalation Model for Interspecies Dosimetry Extrapolation of Acidic Vapors in the Upper Airways. Frederick, C. B., Bush, M. L., Lomax, L. G., Black, K. A., Finch, L., Kimbell, J. S., Morgan, K. T., Subramaniam, R. P., Morris, J. B., and Ultman, J. S. (1998). *Toxicol. Appl. Pharmacol.* 152, 211–231.

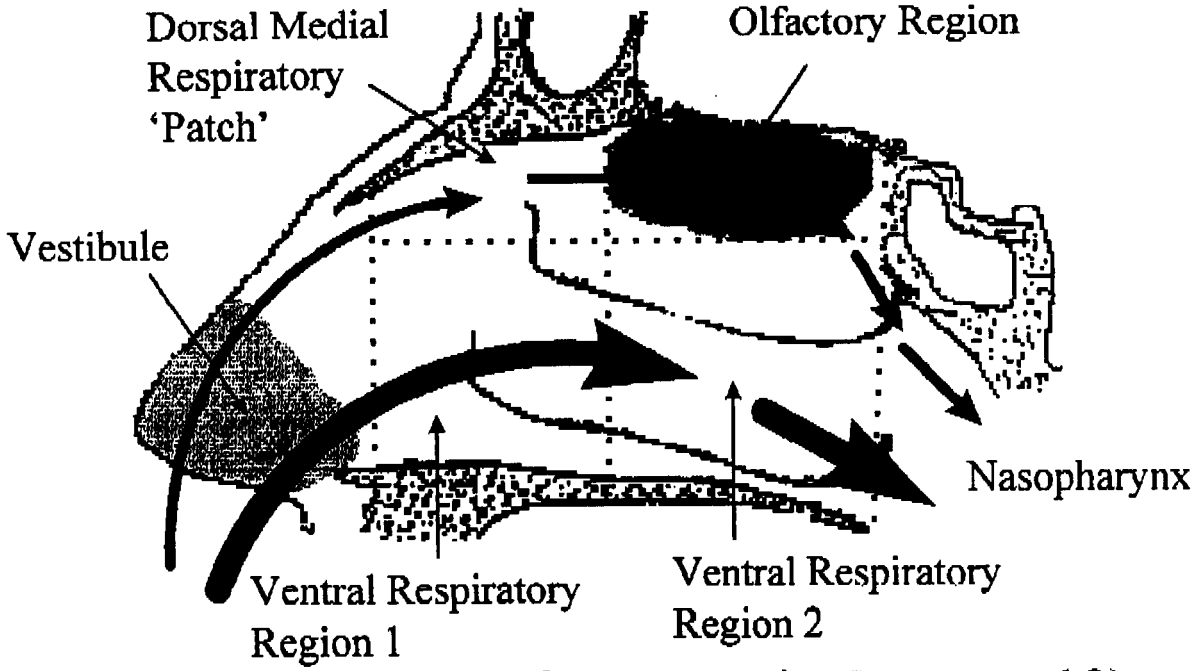
This study provides a scientific basis for interspecies extrapolation of nasal olfactory irritants from rodents to humans. By using a series of short-term *in vivo* studies, *in vitro* studies with nasal explants, and computer modeling, regional nasal tissue dose estimates were made and comparisons of tissue doses between species were conducted. To make these comparisons, this study assumes that human and rodent olfactory epithelium have similar susceptibility to the cytotoxic effects of organic acids based on similar histological structure and common mode of action considerations. Interspecies differences in susceptibility to the toxic effects of acidic vapors are therefore assumed to be driven primarily by differences in nasal tissue concentrations that result from regional differences in nasal air flow patterns relative to the species-specific distribution of olfactory epithelium in the nasal cavity. The acute, subchronic, and *in vitro* studies have demonstrated that the nasal olfactory epithelium is the most sensitive tissue to the effects of inhalation exposure to organic acids and that the sustentacular cells are the most sensitive cell type of this epithelium. A hybrid computational fluid dynamics (CFD) and physiologically based pharmacokinetic (PBPK) dosimetry model was constructed to estimate the regional tissue dose of organic acids in the rodent and human nasal cavity. The CFD–PBPK model simulations indicate that the olfactory epithelium of the human nasal cavity is exposed to two- to threefold lower tissue concentrations of a representative inhaled organic acid vapor, acrylic acid, than the olfactory epithelium of the rodent nasal cavity when the exposure conditions are the same. The magnitude of this difference varies somewhat with the specific exposure scenario that is simulated. The increased olfactory tissue dose in rats relative to humans may be attributed to the large rodent olfactory surface area (greater than 50% of the nasal cavity) and its highly susceptible location (particularly, a projection of olfactory epithelium extending anteriorly in the dorsal meatus region). In contrast, human olfactory epithelium occupies a much smaller surface area (less than 5% of the nasal cavity), and it is in a much less accessible dorsal posterior location. In addition, CFD simulations indicate that human olfactory epithelium is poorly ventilated relative to rodent olfactory epithelium. These studies suggest that the human olfactory epithelium is protected from irritating acidic vapors significantly better than rat olfactory epithelium due to substantive differences in nasal anatomy and nasal air flow. Furthermore, the general structure of the hybrid CFD–PBPK model used for this study appears to be useful for target tissue dosimetry and interspecies dose comparisons for a wide range of inhaled vapors. © 1998 Academic Press

A variety of volatile compounds induce toxic effects in the rodent nasal cavity following inhalation exposure. Interestingly, the distribution of histopathological lesions is often localized in specific regions or is limited to one epithelial type (reviewed in Morgan and Monticello, 1990; Mery *et al.*, 1994). The regional distribution of toxic effects from inhaled vapors has been correlated with the nasal air flow patterns, i.e., regions of high air flow tend to exhibit a higher incidence and greater severity of toxic effects than regions of low air flow (Morgan and Monticello, 1990; Kimbell *et al.*, 1993, 1997; Mery *et al.*, 1994). This pattern of localized toxicity emphasizes the importance of local tissue dose for interspecies extrapolation and risk assessment. Furthermore, observation of toxic effects localized in specific epithelial types (variable depending on the inhaled vapor) emphasizes the importance of chemical-specific differences in mode of action and tissue susceptibility.

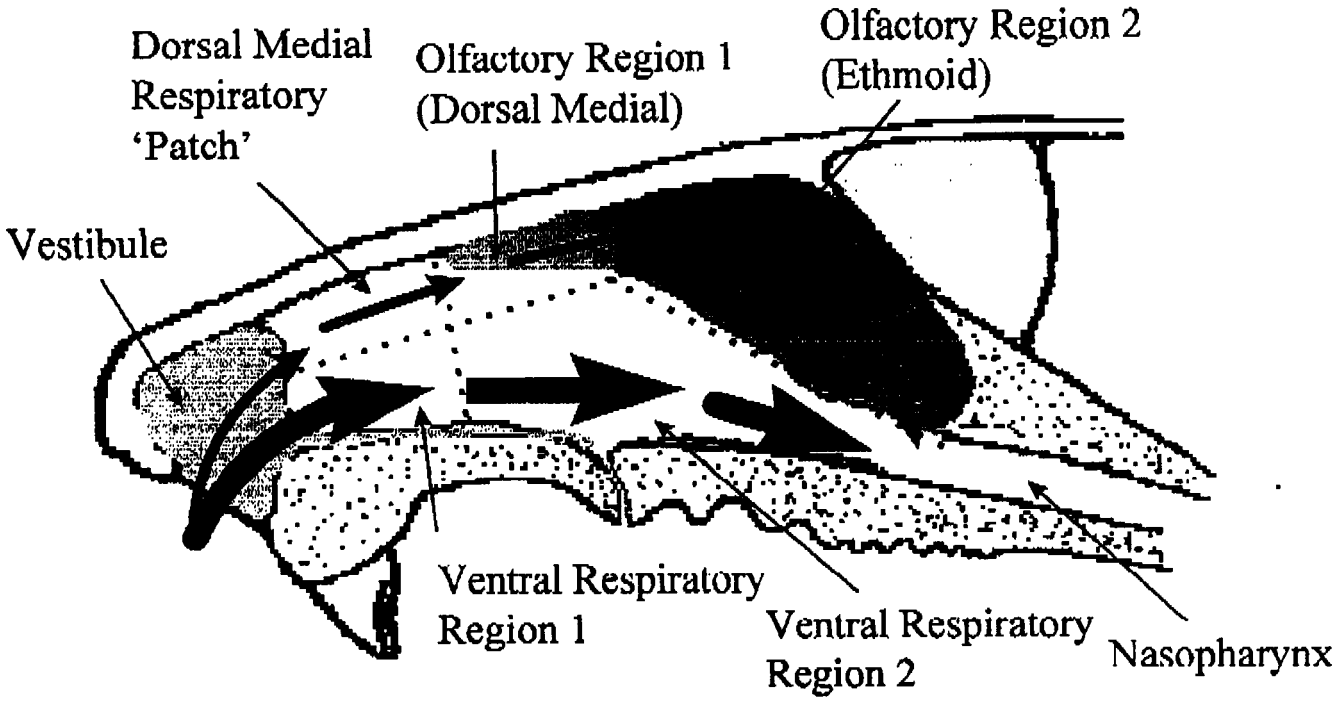
Typically, high vapor concentrations of irritating organic acids and esters preferentially induce cytotoxicity of the olfactory epithelium in the nasal cavity (e.g. Keenan *et al.*, 1990;

[1] To whom correspondence should be addressed. Fax: (215) 619-1621. E-mail: cfrederick@rohmhaas.com.

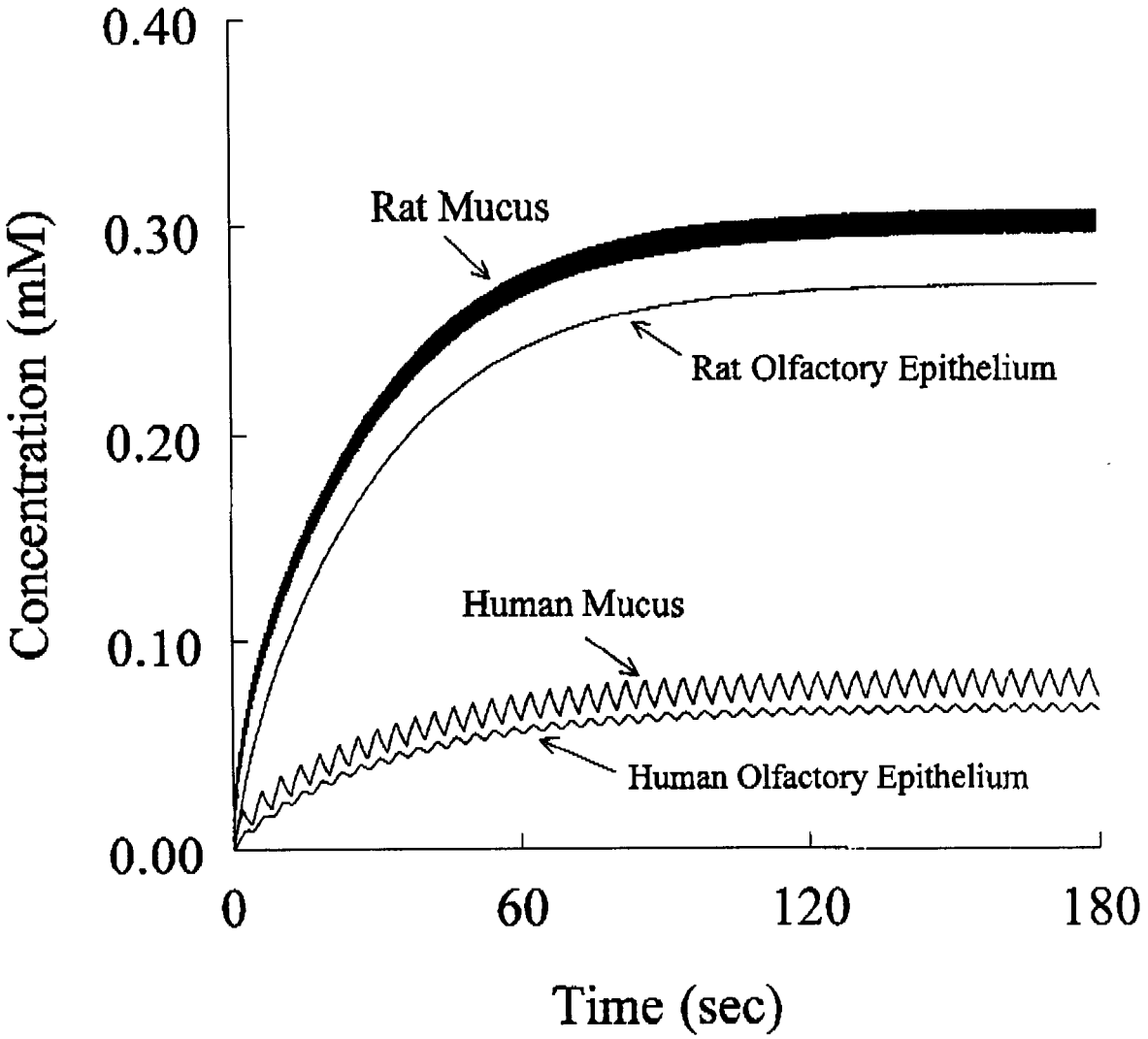
0041-008X/98 $25.00



Human (nasal surface area/volume = 10)



Rat (nasal surface area/volume = 26)


0.40
0.30
0.20
0.10
0.00
Concentration (mM)
Rat Mucus
Rat Olfactory Epithelium
Human Mucus
Human Olfactory Epithelium
0
60
120
180
Time (sec)

20 Years of Industrial Hygiene Monitoring

The 8 hr TWA monitoring results have ranged from 0.003 ppm (or a nondetect at the limit of detection of the analytical method at the timc) to 4.27 ppm with a single outlier at 26 ppm. The median TWA measurement was 0.15 ppm. Of the total of 259 samples, 8% of the samples were equal to or greater than 1 ppm (includes measurements with a limit of detection above 1 ppm). The short term exposure limit (typically 15 min STEL) monitoring results ranged from <0.001 ppm to 63 ppm (or a nondetect at the limit of detection of the analytical method at the time). The median STEL measurement was 0.5 ppm. Of the total of 631 samples, 34% of the samples were equal to or greater than 1 ppm (includes measurements with a limit of detection equal to or greater than 1 ppm). In addition, the companies monitor the health of their workers and keep a record of adverse medical reports associated with chemical exposure. As described in the attached reports from Corporate Medical Departments, employee exposures to acrylic acid within the 2-5 ppm 8 hr TLV exposure limits (including both current and historical TLV limits) have not resulted in employee complaints of nose or eye irritation.

The few reports of eye or nose irritation that were recorded have related to spills or accidents that produced unusual exposure scenarios (described in an attached letter). These accidents undoubtably involved inhalation exposures significantly in excess of the TLV, although the transient nature of the incidents prevented exposure monitoring. In all cases, rapid and complete recovery was noted from the signs of irritation that were reported. Given these data from the longterm use of acrylic acid in industry, it may bc concluded that the chronic exposure of workers to acrylic acid under the current ACGIH TWA exposure limit of 2 ppm has not produced an adverse effect on health.

Classification	10-Minute	30-Minute	1-Hour	4-Hour	8-Hour
AEGL-1 (Nondisabling)	6.0 ppm (18.0 mg/m^3)	5.0 ppm (15.0 mg/m^3)	4.0 ppm (12.0 mg/m^3)	3.0 ppm (9.0 mg/m^3)	2.0 ppm (6.0 mg/m^3)
AEGL-2 (Disabling)	75.0 ppm (225 mg/m^3)	75.0 ppm (225 mg/m^3)	75.0 ppm (225 mg/m^3)	75.0 ppm (225 mg/m^3)	75.0 ppm (225 mg/m^3)
AEGL-3 (Lethal)	1500 ppm (4500 mg/m^3)	1200 ppm (3600 mg/m^3)	750 ppm (2250 mg/m^3)	625 ppm (1875 mg/m^3)	500 ppm (1500 mg/m^3)

AEGL-1 (Nondisabling)--- This recommendation is based upon nasal irritation (minimal olfactory toxicity) that might be observed in either animals or humans following inhalation exposure to acrylic acid in the 5-25 ppm concentration range. No other clinical signs or indications of pathology have been observed with mice, rats, or rabbits in this dose range.

AEGL-2 (Disabling) --- We propose an AEGL-2 value of 75 ppm for all time periods based on the following considerations: [1] the lack of eye blinking or squinting in rabbits at inhalation exposures of 77 and 61 ppm (Neeper-Bradley et al., 1997), [2] the lack of eye blinking or other clinical signs of toxicity in monkeys during an inhalation exposure of 75 ppm, [3] the cytotoxicity and nasal irritation observed in the 75 ppm acute inhalation exposure studies is reversible, not disabling, and it does not impair the ability to escape, and [4] eye irritation (blinking and tearing) at inhalation concentrations above 100 ppm might impede sight and escape.

AEGL-3 (Lethal) --- There are no credible reports of acute lethality in any species at inhalation exposure concentrations less than 1000 ppm. In addition, repeat-dose inhalation studies with acrylic acid have repeatedly been conducted with various animal species at concentrations up to approximately 250 ppm without lethality.We note that in the best designed study for providing AEGL-3 data that is available (Hagan and Emmons, 1988), no lethality was observed at the highest vapor concentration that could be generated (2142 ppm). Therefore, we suggest an intraspecies conversion factor of 3, a species to species conversion factor of 1, and an AEGL-3 (lethal) value consistent with the AIHA ERPG-3 value of 750 ppm for 1 hr exposures. This AEGL-3 value would decrease to approximately 500 ppm for an 8 hr exposure and increase to approximately 1500 ppm for a 10 minute exposure.

BASIC ACRYLIC MONOMER MANUFACTURERS, INC.
1250 Connecticut Ave., N.W., Suite 700, Washington, DC 20036
Office: (202) 637-9040 Facsimile (202) 637-9178 Attachment 15

May 31, 2001

JUN 12 2001

Mr. Paul S. Tobin
Designated Federal Officer
Office of Prevention, Pesticides, and Toxic Substances (7406)
1200 Pennsylvania Ave., NW
Washington, DC 20460

Subject: Comments on the proposed AEGL values for acrylic acid published in the Federal Register on May 2, 2001 (Docket Control Number OPPTS-00312)

Dear Mr. Tobin:

General Comments

We would like to commend the National Advisory Committee for Acute Exposure Guideline Levels for Hazardous Substances (NAC/AEGL Committee) for its thorough evaluation of the relevant scientific information for the establishment of AEGL values for a wide variety of substances exhibiting very different toxicological profiles. The Standard Operating Procedures developed by the NAC/AEGL committee are obviously a valuable resource for data evaluation for establishing AEGLs. However, we would like to encourage the committee to "step back and see if the numbers make sense" in the context of the relevant substance-specific datasets at the end of the standard setting process.

We would also like to encourage the committee to consult the information that is being collected for the European Union (EU) Risk Assessments for industrial chemicals when they are available. The EU risk assessments are valuable resources for human exposure information that has not been readily available. In addition, the EU risk assessments list exposure limits that have been established by other authoritative bodies, and these may provide useful perspectives relative to the proposed AEGL values.

General Comments on the Dose Response for Effects Associated with Inhalation Exposure to Acrylic Acid

The specific issue that we would like to address is the nasal and eye irritant, acrylic acid. As noted in the NAC draft Technical Support Document for acrylic acid (Public Draft; February, 2001), the only non-lethal adverse effects observed in any animal species following inhalation exposure to acrylic acid in acute and subchronic exposures at concentrations up to 100 ppm were cytotoxicity in the nasal olfactory epithelium (observed in all species evaluated). At vapor concentrations of 100-400 ppm, nasal toxicity was accompanied by watery discharges from the eyes and nose indicative of irritation, restlessness, and eye blinking or eyelid closure in some studies. Credible mortality studies have only produced lethal effects at inhalation exposure concentrations

in excess of 1000 ppm. NOAELs typically observed in a wide range of acrylic acid inhalation studies have ranged from 5-25 ppm with no toxic effects observed in any species at exposure concentrations less than 5 ppm. As noted in the Technical Support Document, aside from the nasal and eye irritation at lower inhalation exposure concentrations (useful for setting an AEGL-1 value) and mortality observed at very high concentrations (useful for setting an AEGL-3 value), there is no reported systemic toxicity and very little else to use as a basis for setting an AEGL-2 value.

Comments on an Additional Acute Inhalation Study with Primates

In addition to the studies cited in the Technical Support Document for acrylic acid, we are submitting an additional inhalation study. The attached report is for the in-life portion of an inhalation study with Cynomolgus monkeys. The study design is basically the same as that reported for rats in Frederick et al. (1998) as cited in the Technical Support Document (either 3 or 6 hr exposure at 75 ppm acrylic acid vapor relative to a control group; 3 animals/group; exposure to ethyl acrylate vapor was also evaluated in the study). The animals were exposed using an exposure helmet that allowed uniform exposure of the entire head. The study report is incomplete only in that the histopathology report has not been completed by the academic group collaborating on the study (although a Society of Toxicology abstract reporting his preliminary findings is attached). We have encouraged the pathologist to complete his report, and we anticipate that he will publish his findings upon completion.

The study was designed to evaluate the susceptibility of primate olfactory epithelium to cytotoxicity induced by acrylic acid exposure relative to rodent olfactory epithelium. Mapping of the histopathology induced in the primate nasal cavity was an important part of the experimental design. Note that Cynomolgus monkeys have an elongated nasal cavity with a very large olfactory region covering the posterior region of the nasal cavity in a very similar manner to rodents (although the turbinate structure is quite different). Clinical observations were recorded before and after exposure. Upon necropsy after exposure, the major organs were evaluated for abnormal findings. **The in-life report indicates that inhalation exposure of Cynomolgus monkeys to 75 ppm acrylic acid vapor for either 3 or 6 hr resulted in no clinical signs of toxicity and no treatment related findings on gross pathology evaluation of the major organs. An animal exposed to ethyl acrylate vapor in the same experiment was reported to demonstrate an increased rate of eye blinking, but the animals exposed to acrylic acid did not exhibit this response.** The SOT abstract indicates that olfactory cytotoxicity was observed that was comparable to that observed in the rat nasal cavity under the same exposure protocol. This suggests that the tissue dosimetry and susceptibility is comparable between these two species.

Comments Regarding Acute Inhalation Exposures and Olfactory Toxicity

We would like to address a comment that we believe to be in error in the technical support document. Unique among neuronal tissues, nasal olfactory epithelium is characterized by a normal rate of cellular turnover and can regenerate following damage. Loss of olfactory epithelium that is accompanied by replacement with respiratory

epithelium is a well-documented component of human aging (e.g. Loo et al., 1996, Paik et al., 1992, Talamo et al., 1994 and references cited therein). These references note that olfactory sensitivity declines with age in humans. In addition, olfaction is compromised by allergies, rhinitis, and a variety of other common disease states. Although lack of normal olfaction is an important 'quality of life' issue, it is not generally associated with an 'impaired ability to escape.'

An extensive set of studies by Youngentob and Schwob and others (some representative papers are listed below) have demonstrated that the olfactory epithelium can recover following an acute inhalation exposure that causes extensive olfactory cytotoxicity (e.g., with >90-95% of the olfactory epithelium destroyed with methyl bromide vapor). In addition, these authors have demonstrated that the olfactory epithelium can exhibit a considerable amount of cytotoxicity and yet still retain sufficient functional capacity to adequately perform a series of olfaction tests. Therefore, although damage to the olfactory epithelium is not desirable and should be avoided, a single acute exposure would not be predicted to result in a permanent functional deficit. The Technical Support Document correctly reports that recovery of damaged olfactory epithelium has been demonstrated following inhalation exposure to acrylic acid vapors in an toxicology study (Lomax et al., 1994).

Human Occupational Exposure Monitoring Data

Concerning ongoing human inhalation exposure to acrylic acid, the current EU risk assessment provides additional valuable information. The document lists occupational exposures for a wide range of tasks that range from 0.01 to 5 ppm with a 90th percentile at 1 ppm. Short term exposure values ranged from 0.01 to 62.4 ppm. The EU risk assessment reports occupational exposure limits for 9 countries (United Kingdom, Switzerland, Sweden, United States, Belgium, Austria, Netherlands, Denmark, and France) as ranging from 2 to 10 ppm with short term exposure limits in 3 countries (United Kingdom, Sweden, and France) ranging from 10 to 20 ppm. The widespread adoption of these occupational exposure limits without reports of adverse effects suggests that humans can be exposed to acrylic acid vapors in this concentration range for long periods of time without harm. Notably, there is an absence of reports linking human exposure to acrylic acid vapors with mortality.

In addition to the EU documentation of human exposures, the member companies of the Basic Acrylic Monomer Manufacturers (BAMM) and the European Basic Acrylate Manufacturers (EBAM) have conducted air monitoring studies of acrylic acid in the workplace. A summary of these data from for the last 20 years is attached. The 8 hr TWA monitoring results have ranged from 0.003 ppm (or a nondetect at the limit of detection of the analytical method at the time) to 4.27 ppm with a single outlier at 26 ppm. The median TWA measurement was 0.15 ppm. Of the total of 259 samples, 8% of the samples were equal to or greater than 1 ppm (includes measurements with a limit of detection above 1 ppm). The short term exposure limit (typically 15 min STEL) monitoring results ranged from <0.001 ppm to 63 ppm (or a nondetect at the limit of detection of the analytical method at the time). The median STEL measurement was 0.5

ppm. Of the total of 631 samples, 34% of the samples were equal to or greater than 1 ppm (includes measurements with a limit of detection equal to or greater than 1 ppm). In addition, the companies monitor the health of their workers and keep a record of adverse medical reports associated with chemical exposure. As described in the attached reports from Corporate Medical Departments, employee exposures to acrylic acid within the 2-5 ppm 8 hr TLV exposure limits (including both current and historical TLV limits) have not resulted in employee complaints of nose or eye irritation. Note that workers are encouraged to report safety problems in the workplace including chemical exposures that result in adverse health effects. The few reports of eye or nose irritation that were recorded have related to spills or accidents that produced unusual exposure scenarios (described in an attached letter). These accidents undoubtably involved inhalation exposures significantly in excess of the TLV, although the transient nature of the incidents prevented exposure monitoring. In all cases, rapid and complete recovery was noted from the signs of irritation that were reported. Given these data from the longterm use of acrylic acid in industry, it may be concluded that the chronic exposure of workers to acrylic acid under the current ACGIH TWA exposure limit of 2 ppm has not produced an adverse effect on health.

AEGL-1

Acrylic acid is a "contact site irritant" that exerts its effects based upon the concentration of the vapor that is absorbed into the contact site tissue. The initial clinical signs of irritation typically occur relatively quickly, and would not be expected to dramatically increase during the course of a single exposure of 8 hr or less. Given the widespread adoption of 2 ppm as an occupational exposure limit, we suggest that a value no lower than 2 ppm be adopted as an AEGL-1 value (nondisabling) for an 8 hr exposure. The short term exposure limit (15 minute STEL) that is commonly used in industry is 6 ppm, and we propose this value as the exposure limit for 10 min exposure. Exposure limits for other times would be interpolated between these values. This recommendation is based upon nasal irritation (minimal olfactory toxicity) that might be observed in either animals or humans following inhalation exposure to acrylic acid in the 5-25 ppm concentration range. No other clinical signs or indications of pathology have been observed with mice, rats, or rabbits in this dose range. Given the consistency in effect across species (including rats relative to monkeys at 75 ppm) and lack of toxicity reported with the current occupational exposure limits (ranging from 2 to 10 ppm), we propose a species to species conversion factor of 1. Given the inherent variability in individual response, we propose an intraspecies extrapolation factor of 3. The Preface to the Technical Support Document provides a definition of AEGL-1 that is consistent with this proposed value. In addition, the Preface notes that "Airborne concentrations below the AEGL-1 represent exposure levels that could produce mild and progressively increasing odor, taste, and sensory irritation, or certain asymptomatic, non-sensory effects." The odor detection threshold of acrylic acid clearly falls within this provision.

Classification	10-Minute	30-Minute	1-Hour	4-Hour	8-Hour
AEGL-1 (Nondisabling)	6.0 ppm (18.0 mg/m^3)	5.0 ppm (15.0 mg/m^3)	4.0 ppm (12.0 mg/m^3)	3.0 ppm (9.0 mg/m^3)	2.0 ppm (6.0 mg/m^3)

AEGL-3

Regarding AEGL-3 values (lethal) for acrylic acid, we note that there are no credible reports of acute lethality in any species at inhalation exposure concentrations less than 1000 ppm. In addition, repeat-dose inhalation studies with acrylic acid have repeatedly been conducted with various animal species at concentrations up to approximately 250 ppm without lethality. Addressing the issue of interspecies extrapolation between rodents and primates, the attached monkey study was conducted at inhalation exposures of 75 ppm without any clinical signs of toxicity. No reports link human inhalation exposure to acrylic acid with lethality despite its widespread and long term use in industry. Under these circumstances, we do not believe that a large species to species conversion factor is justifiable --- particularly, since definition of the AEGL values based upon vapor concentration automatically introduces an allometric scaling factor due to the inherent differences in respiratory physiology between species. AEGL-3 values below 250 ppm lack scientific credibility in the context of this extensive database. We note that in the best designed study for providing AEGL-3 data that is available (Hagan and Emmons, 1988), no lethality was observed at the highest vapor concentration that could be generated (2142 ppm). Therefore, we suggest an intraspecies conversion factor of 3, a species to species conversion factor of 1, and an AEGL-3 (lethal) value consistent with the AIHA ERPG-3 value of 750 ppm for 1 hr exposures. This AEGL-3 value would decrease to approximately 500 ppm for an 8 hr exposure and increase to approximately 1500 ppm for a 10 minute exposure.

Classification	10-Minute	30-Minute	1-Hour	4-Hour	8-Hour
AEGL-3 (Lethal)	1500 ppm ($4500\ mg/m^3$)	1200 ppm ($3600\ mg/m^3$)	750 ppm ($2250\ mg/m^3$)	625 ppm ($1875\ mg/m^3$)	500 ppm ($1500\ mg/m^3$)

AEGL-2

The establishment of an AEGL-2 value (disabling) is problematic, since the available data on the toxic effects associated with acrylic acid exposure do not provide endpoints that are very appropriate. The blinking reported in rabbits in the Neeper-Bradley et al. (1997) study is hardly sufficient (study used as a basis for the AEGL-2 proposal at the July, 2000 NAC/AEGL meeting), since it could be argued that eye blinking or squinting (blepharospasm) of a sendentary animal in a toxicology study does not necessarily represent a disabling effect. A functional evaluation to determine whether the animals eyesight was impaired would have been much more convincing. The slides presented at the NAC/AEGL meeting on July 26-28, 2000, appeared to draw comparisons to the increased rate of blinking or squinting observed in the Neeper-Bradley et al. (1997) study with the dramatic effects of the very potent lacrimators used in tear gas. This comparison is inappropriate due to the very high potency of the agents used in tear gas relative to the much weaker effects exhibited by acrylic acid vapors; i.e., clinical signs of the range and magnitude induced by tear gas have not been reported in either animal studies or human occupational exposures with acrylic acid.

The Technical Support Document for this AEGL/NAC meeting refers to a single dose acute inhalation study with rats exposed to acrylic acid at 75 ppm for either 3 or 6 hr

(Frederick et al., 1998). This study was conducted as part of the validation process for a nasal dosimetry model for acrylic acid. An inhalation study with the same basic experimental design using Cynomolgous monkeys is attached to these comments. In these studies, the cytotoxicity that was observed in the olfactory epithelium of the exposed animals was relatively comparable across species. Although clinical signs were not recorded in the acute rat study, prior repeat-dose studies with rats at 75 ppm have documented no discernable changes in posture or appearance at this vapor concentration (Miller et al., 1981). The monkey study also did not report clinical signs of irritation or distress at the 75 ppm exposure concentration. The Technical Support Document invokes the use of time scaling in a $C^n \times t = k$ with $n = 1.8$ based upon the dose response curve for lethality from the Hagan and Emmons (1988) study and a total uncertainty factor of 10 (3 for interspecies and 3 for intraspecies). The resulting proposed AEGL-2 values for acrylic acid range from 6.4 ppm (8 hr) to 30 ppm (10 min). These proposed AEGL-2 values are in the range of effects that range from NOAELs to mild and reversible nasal irritation in every species that has been evaluated. The effects that have been observed in this dose range clearly do not fall into the range of "irreversible or other serious, long-lasting adverse health effects, or an impaired ability to escape" which form the basis of the definition of an AEGL-2.

We propose an AEGL-2 value of 75 ppm for all time periods based on the following considerations: [1] the lack of eye blinking or squinting in rabbits at inhalation exposures of 77 and 61 ppm (Neeper-Bradley et al., 1997), [2] the lack of eye blinking or other clinical signs of toxicity in monkeys during an inhalation exposure of 75 ppm (attached study), [3] the cytotoxicity and nasal irritation observed in the 75 ppm acute inhalation exposure studies is reversible, not disabling, and it does not impair the ability to escape (see references on olfactory toxicity cited above), and [4] eye irritation (blinking and tearing) at inhalation concentrations above 100 ppm which might impede sight and escape. This would be accompanied by a species to species conversion factor of 1, since there does not seem to be much difference in response across several species tested. We propose an intraspecies variability factor of 1 based on the lack of severity of the response and the wide range of functional deficit that can be accomodated for this endpoint. In particular, this intraspecies variability factor is based upon the fact that 75 ppm is a NOAEL for blinking and tearing in multiple species, humans would be expected to exhibit either no effects or only mild effects for these symptoms in this dose range, and it takes a lot of tearing and blinking to incapacitate an individual to the extent that the ability to escape is impaired.

Classification	10-Minute	30-Minute	1-Hour	4-Hour	8-Hour
AEGL-2 (Disabling)	75.0 ppm (225 mg/m^3)	75.0 ppm (225 mg/m^3)	75.0 ppm (225 mg/m^3)	75.0 ppm (225 mg/m^3)	75.0 ppm (225 mg/m^3)

Summary

In summary, our proposed AEGL values based upon the above considerations are the following:

Classification	10-Minute	30-Minute	1-Hour	4-Hour	8-Hour
AEGL-1 (Nondisabling)	6.0 ppm (18.0 mg/m^3)	5.0 ppm (15.0 mg/m^3)	4.0 ppm (12.0 mg/m^3)	3.0 ppm (9.0 mg/m^3)	2.0 ppm (6.0 mg/m^3)
AEGL-2 (Disabling)	75.0 ppm (225 mg/m^3)	75.0 ppm (225 mg/m^3)	75.0 ppm (225 mg/m^3)	75.0 ppm (225 mg/m^3)	75.0 ppm (225 mg/m^3)
AEGL-3 (Lethal)	1500 ppm (4500 mg/m^3)	1200 ppm (3600 mg/m^3)	750 ppm (2250 mg/m^3)	625 ppm (1875 mg/m^3)	500 ppm (1500 mg/m^3)

In closing, we note the recent publication of a mechanistic study that supplements the Custodio et al. (1998) study on acrylic acid that is cited in the Technical Support Document. The recent publication (Palmeira et al., 2000) is from the same research group and it further explores the proposed mechanism of cytotoxicity invoked by acrylic acid (induction of the mitochondrial permeability transition). The study demonstrates that this response is common for a wide range of short-chain carboxylic acids. We hope that you find the additional data that we are submitting useful in your deliberations, and we encourage your evaluation of the proposed AEGL values for acrylic acid in the context of its safe use in industry for many years.

With our regards,

Clay B. Frederick, Ph.D., DABT
Representing the Technical Committee
of the Basic Acrylic Monomer Manufacturers, Inc.
and the
European Basic Acrylate Manufacturers

The Basic Acrylic Monomer Manufacturers Inc. (BAMM) is an industry trade association, promoting the safe manufacture, handling and use of the basic acrylic monomers by addressing product aspects related to human health, environmental safety and associated regulatory issues.

Members of the Basic Acrylic Monomer Manufacturers, Inc.:

ATOFINA Chemicals, Inc.
BASF Corporation
Celanese Ltd.
The Dow Chemical Co.
Rohm and Haas Co.

Members of the CEFIC European Basic Acrylate Manufacturers (EBAM):

ATOFINA
BASF AG
Celanese GmbH
Rohm and Haas Co.
Chemicke Zavody Sokolov
Stockhausen GmbH

Some representative references on the structure and normal turnover of human olfactory epithelium including observations on the loss of olfactory epithelium on aging:

Loo AT, Youngentob SL, Kent PF, Schwob JE (1996). The aging olfactory epithelium: Neurogenesis, response to damage, and odorant-induced activity, INTERNATIONAL JOURNAL OF DEVELOPMENTAL NEUROSCIENCE, 14:881-900.

Paik SI, Lehman MN, Seiden AM, Duncan HJ, Smith DV (1992). Human olfactory biopsy - the influence of age and receptor distribution, ARCHIVES OF OTOLARYNGOLOGY-HEAD & NECK SURGERY, 118: 731-738.

Talamo BR, Feng WH, Stockmayer M (1994). Human olfactory epithelium - normal patterns and types of lesions found in the genrall-population, INHALATION TOXICOLOGY, 6 (Suppl.): 249-275.

Some representative references on chemically-induced olfactory damage, functional evaluation of olfaction in animals with olfactory damage, and recovery of olfactory epithelium:

Schwob JE, Youngentob SL, Ring G, Iwema CL, Mezza RC (1999). Reinnervation of the rat olfactory bulb after methyl bromide-induced lesion: Timing and extent of reinnervation, JOURNAL OF COMPARATIVE NEUROLOGY, 412:439-457.

Huard JMT, Youngentob SL, Goldstein BJ, Luskin MB, Schwob JE (1998). Adult olfactory epithelium contains multipotent progenitors that give rise to neurons and non-neural cells, JOURNAL OF COMPARATIVE NEUROLOGY, 400:469-486.

Youngentob SL, Schwob JE, Sheehe PR, Youngentob LM (1997). Odorant threshold following methyl bromide-induced lesions of the olfactory epithelium, PHYSIOLOGY & BEHAVIOR, 62:1241-1252.

The current version of the EU risk assessment for acrylic acid, "Comprehensive Risk Assessment Report 2-Propenoic Acid," may be obtained from:
Bundesanstalt fur Arbeitsschutz und Arbeitsmedizin
Anmeldestelle Chemikaliengesetz
Friedrich-Henkel-Weg 1-25
44149 Dortmund
email: amst@baua.do.shuttle.de

The in-life report from an acute monkey inhalation study and an accompanying Society of Toxicology abstract are attached:
Michael J. Brooker and Michael E. Placke (1995). Final Report on Single Dose Inhalation Toxicity Study of Ethyl Acrylate (EA) and Acrylic Acid (AA). Battelle/Columbus Study Number SC940138.

J. R. Harkema, J. K. Lee, K. T. Morgan, and C. B. Frederick (1997). Olfactory epithelial injury in monkeys after acute inhalation exposure to acrylic monomers. Abstract #576. The Toxicologist, 36, p. 113.

A recent mechanistic study exploring the mechanism of cytotoxicity of short-chain carboxylic acids (including acrylic acid):
C. M. Palmeira, M. I. Rana, C. B. Frederick, and K. B. Wallace (2000). Induction of the mitochondrial permeability transition in vitro by short-chain carboxylic acids, BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, 272: 431-435.

100 INDEPENDENCE MALL WEST PHILADELPHIA PA 19106-2399 U.S.A.
TELEPHONE (215) 592-3000 CABLE ADDRESS ROHMHAAS CENTRAL FAX (215) 592-3377

REPLY TO:
SAFETY, HEALTH & ENVIRONMENT
BOX 584
BRISTOL, PA 19007
(215) 785-7000 FAX (215) 785-7227

ROHM AND HAAS COMPANY

May 30, 2001

Mr. Paul S. Tobin
Designated Federal Officer
Office of Prevention, Pesticides, and Toxic Substances (7406)
1200 Pennsylvania Ave., NW
Washington, DC 20460

Subject: Comments on the proposed AEGL values for acrylic acid published in the Federal Register on May 2, 2001

Dear Mr. Tobin:

After reviewing the proposed AEGL values for acrylic acid published in the Federal Register, we request that the National Advisory Committee for Acute Exposure Guideline Levels for Hazardous Substances reassess the values chosen, using research data from inhalation studies (a number of studies exist using a number of species), and human data where available. We believe the proposed AEGL-1 value of 1ppm for acrylic acid is not consistent with toxicology information from animal studies and human observations that indicate that 8hr TWA concentration of 2 - 5 ppm does not cause respiratory or eye irritation as defined for AEGL-1, even with chronic exposure. Indeed, the 2 - 10 ppm permissible exposure limit used by most countries is believed to protect workers who are chronically exposed throughout a 40-year working career from all deleterious health effects. We respectfully request that the committee re-evaluate the scientific information before establishing an AEGL-1 value for acrylic acid that is half of the U.S. permissible exposure limit used for chronic exposure in the workplace.

We wish to report on our company's experience with acrylic acid in an effort to contribute human data to the scientific information the committee uses to establish AEGL values. We believe this data demonstrates that the proposed AEGL-1 value of 1ppm is too low.

Rohm and Haas Company is a global specialty chemical company based in Philadelphia; we have approximately 20,000 employees. Acrylic acid is used at 30 of our plants worldwide as either a raw material or finished product. Our workplace exposure limit is 2ppm 8 hr TWA, with a STEL of 6ppm. We reviewed our U.S. workplace injury and illness reports from 1990, and our worldwide workplace injury and illness reports from 1994 (total of 12,774 records) and found four reports of respiratory or eye irritation involving monomer. In 1994, three employees complained of respiratory irritation after cleaning up a spill of glacial acrylic acid at a railcar loading station. Two employees required first aid, and the third required no treatment. These employees did not require

time off work or medical treatment after the initial first aid. These employees were not wearing personal protective equipment. Air monitoring was not conducted at the time of the spill, but it is reasonable to assume the exposures were substantially higher than our workplace exposure limit. A fourth report involves a release of an inhibitor during tank car loading; the inhibitor was 88% acrylic acid by weight. An employee involved in the release complained of burning eyes. No treatment was required. Again, there was no air monitoring done. However, we believe the small number of cases of respiratory or eye irritation we have experienced despite the large number of employees regularly using acrylic acid around the world are indicative of the safety afforded by the current workplace exposure limit of 2ppm. Additionally, we have no reports of chronic illness due to acrylic acid.

Lastly, we reviewed the health effect allegations reports we maintain for Toxic Substances Control Act reporting purposes. These reports are generated from customer and neighbor calls to the company within the U.S., as well as employee allegations from any plant worldwide. Reviewing these records back to 1983 reveals one incident involving an employee of our customer who was handling acrylic acid and experienced chest pain, leg tingling, and respiratory irritation. Symptoms resolved overnight without treatment. There are no other reports involving acrylic acid.

Sincerely,

Eileen M. Bonner, M.D., M.P.H.
Corporate Medical Director
Rohm and Haas Company

EMB/tt

BASF Corporation

BASF

May 30, 2001

Clay Frederick, Ph.D.
Rohm and Haas Co.
Toxicology Department
727 Norristown Rd.
Spring House, PA 19477

Dear Dr. Frederick,

As per your request, here is a summary of BASF Freeport acrylic acid employee medical surveillance information and workplace air monitoring data for acrylic acid, for use in the BAMM written submission regarding the proposed AEGL values.

Health surveillance and workplace air monitoring data for one producer's acrylic acid plant employees from 1998 to present were reviewed. For the symptoms of concern, odor perception and nasal irritation, limited data were available.

The producer's medical surveillance program does inquire about ear, nose and throat symptoms, but not about odor perception. The producer's medical surveillance program includes a question, "do you have ear, nose or throat trouble?" Nine of 104 employees of the acrylic acid plants evaluated during this period responded affirmatively to this question. Their responses were reviewed, and did not include any specific symptoms of nasal irritation. The reasons for affirmative answer were hayfever, allergies, throat infection, ear infection and sinus infection. All of the employees worked in jobs where they were exposed to acrylic acid below the ACGIH 8 – hour TWA of 2 ppm, as per the producer's industrial hygiene data.

A review of incident reports, injury and illness reports, and first aid reports from 1998 to present demonstrated that there were no employee reports of adverse effects or odor complaints from exposure to acrylic acid vapor. There was one first aid report of redness and irritation from direct contact with acrylic acid liquid mist when a pump seal ruptured and sprayed acrylic acid on employee's face. There were no TSCA 8c reports for acrylic acid.

The BASF Corporate Medical Department would be interested in any additional information from other acrylic acid producers, similar to that we have provided above.

Sincerely,

Julia E. Klees, M.D., M.P.H.
Associate Corporate Medical Director

3000 Continental Drive - North, Mount Olive, New Jersey 07828-1234 Telephone (973) 426-2600

Acrylic Acid Data Summary (1980 to Present)

Units of "Value Found" and "WEL" are in "PPM"

	A	B	C	D	E	F	G	H	I
1	CODE 1	CODE 2	PERSONAL (P) OR AREA (A) MONITORING	<	VALUE FOUND	WEL	% OF WEL	WEL TYPE	STANDARD DATE FOR WEL AT THE TIME
2	HTGA	5	A		26	1.0	2600.00%	TWA	19920901
3	008D	831	A		4.27	2.0	213.50%	TWA	19800630
4	801D	3	P		3.7	2.0	185.00%	TWA	19800630
5	DRFA	5	P	<	3.25	1.0	325.00%	TWA	19920901
6	HTMA	5	P		2.6	1.0	260.00%	TWA	19920901
7	HT2A	5	P		2.6	1.0	260.00%	TWA	19920901
8	801D	3	P		2.4	2.0	120.00%	TWA	19800630
9	804D	3	P	<	2.3	2.0	115.00%	TWA	19800630
10	804D	3	P	<	2	2.0	100.00%	TWA	19800630
11	HTMA	5	P	>	1.7	1.0	170.00%	TWA	19920901
12	801B	3	P	<	1.5	2.0	75.00%	TWA	19800630
13	804D	3	P	<	1.5	2.0	75.00%	TWA	19800630
14	HTMA	5	P	>	1.5	1.0	150.00%	TWA	19920901
15	HTEA	5	P		1.4	2.0	70.00%	TWA	19981015
16	017K	632	P		1.2	2.0	60.00%	TWA	19800630
17	028A	3	P	<	1.1	2.0	55.00%	TWA	19800630
18	HT2A	5	P		1.1	1.0	110.00%	TWA	19920901
19	HT2A	5	A		1.1	1.0	110.00%	TWA	19920901
20	010A	632	P		1.06	2.0	53.00%	TWA	19800630
21	017H	632	P		1.01	2.0	50.50%	TWA	19800630
22	HTSA	5	P		1	2.0	50.00%	TWA	19981015
23	HTSA	5	P		1	2.0	50.00%	TWA	19981015
24	HT2A	5	P		0.93	1.0	93.00%	TWA	19920901
25	HT2A	5	P		0.91	1.0	91.00%	TWA	19920901
26	HT2A	5	P		0.91	1.0	91.00%	TWA	19920901
27	801D	3	P	<	0.9	2.0	45.00%	TWA	19800630
28	804D	3	P	<	0.9	2.0	45.00%	TWA	19800630
29	804D	3	P	<	0.9	2.0	45.00%	TWA	19800630
30	HT2M	5	P		0.9	1.0	90.00%	TWA	19920901
31	017H	632	P		0.87	2.0	43.50%	TWA	19800630
32	017B	632	P		0.87	2.0	43.50%	TWA	19800630
33	8WH2	3	P	<	0.8	2.0	40.00%	TWA	19800630
34	801B	3	P	<	0.8	2.0	40.00%	TWA	19800630
35	804D	3	P	<	0.8	2.0	40.00%	TWA	19800630
36	HTGA	5	P		0.79	1.0	79.00%	TWA	19920901
37	017K	632	P		0.74	2.0	37.00%	TWA	19800630
38	804D	3	P	<	0.7	2.0	35.00%	TWA	19800630
39	804D	3	P	<	0.7	2.0	35.00%	TWA	19800630
40	RHTA	5	P		0.7	2.0	35.00%	TWA	19800630
41	HT2A	5	P		0.7	1.0	70.00%	TWA	19920901
42	801D	3	P	<	0.6	2.0	30.00%	TWA	19800630
43	804D	3	P	<	0.6	2.0	30.00%	TWA	19800630
44	804D	3	P	<	0.6	2.0	30.00%	TWA	19800630
45	804D	3	P	<	0.6	2.0	30.00%	TWA	19800630
46	017H	632	P		0.6	2.0	30.00%	TWA	19800630
47	008D	831	A	<	0.6	2.0	30.00%	TWA	19800630
48	005A	5	P		0.59	2.0	29.50%	TWA	19981015

"<" symbol signifies "Not Detected". "Value Found" represents "Limit of Detection".
"Standard Date" is when the Workplace Exposure Limit was established by Rohm and Haas.

Acrylic Acid Data Summary (1980 to Present)

Units of "Value Found" and "WEL" are in "PPM"

	A	B	C	D	E	F	G	H	I
49	HTEA	5	P		0.59	1.0	59.00%	TWA	19920901
50	HTSA	5	P		0.58	1.0	58.00%	TWA	19920901
51	HT2A	5	P		0.58	1.0	58.00%	TWA	19920901
52	PH1A	5	P		0.55	2.0	27.50%	TWA	19981015
53	HTGA	5	P		0.55	2.0	27.50%	TWA	19981015
54	HT2A	5	P		0.53	1.0	53.00%	TWA	19920901
55	PH1A	5	P		0.52	2.0	26.00%	TWA	19981015
56	HT2A	5	P		0.52	1.0	52.00%	TWA	19920901
57	HT2A	5	P		0.52	1.0	52.00%	TWA	19920901
58	DRFA	5	P		0.5	1.0	50.00%	TWA	19920901
59	RB3A	5	P		0.46	1.0	46.00%	TWA	19920901
60	HT2M	5	P		0.45	1.0	45.00%	TWA	19920901
61	HTMA	5	P		0.44	2.0	22.00%	TWA	19981015
62	DRFA	5	P		0.43	1.0	43.00%	TWA	19920901
63	DRFA	5	P		0.43	1.0	43.00%	TWA	19920901
64	HT2A	5	P		0.43	1.0	43.00%	TWA	19920901
65	HT2M	5	P		0.42	2.0	21.00%	TWA	19981015
66	801D	3	P	<	0.4	2.0	20.00%	TWA	19800630
67	801D	3	P	<	0.4	2.0	20.00%	TWA	19800630
68	801D	3	P	<	0.4	2.0	20.00%	TWA	19800630
69	801D	3	P	<	0.4	2.0	20.00%	TWA	19800630
70	801D	3	P	<	0.4	2.0	20.00%	TWA	19800630
71	801D	3	P	<	0.4	2.0	20.00%	TWA	19800630
72	801D	3	P	<	0.4	2.0	20.00%	TWA	19800630
73	801D	3	P	<	0.4	2.0	20.00%	TWA	19800630
74	HT2A	5	P		0.4	1.0	40.00%	TWA	19920901
75	HT2A	5	P	<	0.39	1.0	39.00%	TWA	19920901
76	HTXA	5	P		0.38	1.0	38.00%	TWA	19920901
77	HT2A	5	P		0.37	2.0	18.50%	TWA	19800630
78	HTXA	5	P		0.33	1.0	33.00%	TWA	19920901
79	HTXA	5	P		0.33	1.0	33.00%	TWA	19920901
80	005A	5	P		0.31	2.0	15.50%	TWA	19981015
81	017H	632	P		0.31	2.0	15.50%	TWA	19800630
82	HTEA	5	P		0.3	2.0	15.00%	TWA	19800630
83	HTSA	5	P		0.3	2.0	15.00%	TWA	19981015
84	008D	831	A	<	0.3	2.0	15.00%	TWA	19800630
85	DRFA	5	P		0.29	1.0	29.00%	TWA	19920901
86	HTSA	5	P		0.29	1.0	29.00%	TWA	19920901
87	DRFA	5	P		0.28	2.0	14.00%	TWA	19981015
88	DRFA	5	P		0.28	2.0	14.00%	TWA	19981015
89	RB3A	5	P		0.27	2.0	13.50%	TWA	19981015
90	HTSA	5	P		0.26	2.0	13.00%	TWA	19981015
91	HT2A	5	P		0.26	1.0	26.00%	TWA	19920901
92	HTSA	5	P	<	0.25	1.0	25.00%	TWA	19920901
93	PH1A	5	P		0.24	2.0	12.00%	TWA	19981015
94	HTGA	5	P		0.24	2.0	12.00%	TWA	19981015
95	HTSA	5	P	<	0.24	1.0	24.00%	TWA	19920901
96	017K	632	P		0.24	2.0	12.00%	TWA	19800630
97	PH1A	5	P		0.23	2.0	11.50%	TWA	19981015
98	HTMA	5	P	<	0.23	1.0	23.00%	TWA	19920901
99	HTEA	5	P		0.23	1.0	23.00%	TWA	19920901

"<" symbol signifies "Not Detected". "Value Found" represents "Limit of Detection".
"Standard Date" is when the Workplace Exposure Limit was established by Rohm and Haas.

Acrylic Acid Data Summary (1980 to Present)

Units of "Value Found" and "WEL" are in "PPM"

	A	B	C	D	E	F	G	H	I
100	HT2M	5	P		0.23	1.0	23.00%	TWA	19920901
101	HTXA	5	P	<	0.23	1.0	23.00%	TWA	19920901
102	HTEA	5	P	<	0.23	1.0	23.00%	TWA	19920901
103	HTMA	5	P		0.23	1.0	23.00%	TWA	19920901
104	HTGA	5	P	<	0.22	1.0	22.00%	TWA	19920901
105	HTEA	5	P		0.21	2.0	10.50%	TWA	19981015
106	RHTA	5	P		0.21	1.0	21.00%	TWA	19920901
107	HTEA	5	P	<	0.21	1.0	21.00%	TWA	19920901
108	028A	3	A		0.2	2.0	10.00%	TWA	19800630
109	RHTA	5	P		0.2	2.0	10.00%	TWA	19800630
110	HTEA	5	P		0.2	2.0	10.00%	TWA	19800630
111	PH1A	5	P		0.2	2.0	10.00%	TWA	19981015
112	PH1A	5	P		0.2	2.0	10.00%	TWA	19981015
113	HT2M	5	P		0.2	1.0	20.00%	TWA	19920901
114	HTGA	5	P		0.2	1.0	20.00%	TWA	19920901
115	010A	632	P		0.2	2.0	10.00%	TWA	19800630
116	017K	632	P	<	0.2	1.0	20.00%	TWA	19920901
117	HTEA	5	P	<	0.19	1.0	19.00%	TWA	19920901
118	HTXA	5	P	<	0.19	1.0	19.00%	TWA	19920901
119	HTXA	5	P	<	0.19	1.0	19.00%	TWA	19920901
120	HTSA	5	P		0.18	1.0	18.00%	TWA	19920901
121	HTSA	5	P		0.18	1.0	18.00%	TWA	19920901
122	HTEA	5	P		0.18	1.0	18.00%	TWA	19920901
123	007E	751	P		0.18	2.0	9.00%	TWA	19800630
124	HTMA	5	P		0.17	1.0	17.00%	TWA	19920901
125	HT2M	5	P		0.17	1.0	17.00%	TWA	19920901
126	HTEA	5	P		0.17	1.0	17.00%	TWA	19920901
127	PH1A	5	P		0.16	2.0	8.00%	TWA	19981015
128	HTSA	5	P		0.16	1.0	16.00%	TWA	19920901
129	005A	5	P		0.15	2.0	7.50%	TWA	19981015
130	HTGA	5	P		0.15	1.0	15.00%	TWA	19920901
131	HTSA	5	P		0.15	1.0	15.00%	TWA	19920901
132	TRAK	5	P		0.14	2.0	7.00%	TWA	19981015
133	HTEA	5	P		0.14	1.0	14.00%	TWA	19920901
134	HT2A	5	P		0.14	1.0	14.00%	TWA	19920901
135	HTSA	5	P		0.14	1.0	14.00%	TWA	19920901
136	RHTA	5	P		0.13	1.0	13.00%	TWA	19920901
137	HT2A	5	P		0.12	1.0	12.00%	TWA	19920901
138	HTEA	5	P		0.11	1.0	11.00%	TWA	19920901
139	HTEA	5	P		0.11	1.0	11.00%	TWA	19920901
140	HTXA	5	P	<	0.11	1.0	11.00%	TWA	19920901
141	HTGA	5	P	<	0.11	1.0	11.00%	TWA	19920901
142	017K	632	P		0.11	2.0	5.50%	TWA	19800630
143	028A	3	P	<	0.1	2.0	5.00%	TWA	19800630
144	HTEA	5	P		0.1	2.0	5.00%	TWA	19800630
145	HTGA	5	P		0.1	2.0	5.00%	TWA	19981015
146	RHTA	5	P		0.1	1.0	10.00%	TWA	19920901
147	HT2A	5	P		0.1	1.0	10.00%	TWA	19920901
148	HTEA	5	P		0.1	1.0	10.00%	TWA	19920901
149	HT2A	5	P		0.1	1.0	10.00%	TWA	19920901
150	HT2A	5	P		0.1	1.0	10.00%	TWA	19920901

"<" symbol signifies "Not Detected". "Value Found" represents "Limit of Detection".
"Standard Date" is when the Workplace Exposure Limit was established by Rohm and Haas.

Acrylic Acid Data Summary (1980 to Present)

Units of "Value Found" and "WEL" are in "PPM"

	A	B	C	D	E	F	G	H	I
151	600B	611	A	<	0.1	5.0	2.00%	TWA	19780926
152	017K	632	P	<	0.1	2.0	5.00%	TWA	19800630
153	002F	632	P	<	0.1	2.0	5.00%	TWA	19800630
154	017B	632	P	<	0.1	1.0	10.00%	TWA	19920901
155	PH1A	5	P		0.098	2.0	4.90%	TWA	19981015
156	HTSA	5	P		0.096	1.0	9.60%	TWA	19920901
157	DRFA	5	P		0.094	1.0	9.40%	TWA	19920901
158	HTMA	5	P		0.091	2.0	4.60%	TWA	19981015
159	PDLA	5	P		0.09	2.0	4.50%	TWA	19800630
160	HT2A	5	P		0.09	2.0	4.50%	TWA	19981015
161	017B	632	P		0.09	1.0	9.00%	TWA	19920901
162	008D	831	A		0.09	2.0	4.50%	TWA	19800630
163	017D	632	P		0.086	2.0	4.30%	TWA	19981015
164	HT2A	5	P		0.085	1.0	8.50%	TWA	19920901
165	002B	396	A	<	0.081	1.0	8.10%	TWA	19920901
166	008D	831	A		0.0752	2.0	3.80%	TWA	19800630
167	RHTA	5	P		0.073	1.0	7.30%	TWA	19920901
168	HTEA	5	P		0.072	1.0	7.20%	TWA	19920901
169	HT2M	5	P		0.068	1.0	6.80%	TWA	19920901
170	DRFA	5	P		0.067	1.0	6.70%	TWA	19920901
171	005A	5	P		0.063	2.0	3.20%	TWA	19981015
172	HTEA	5	P		0.062	2.0	3.10%	TWA	19981015
173	HT2A	5	P		0.062	1.0	6.20%	TWA	19920901
174	HT2M	5	A		0.06	1.0	6.00%	TWA	19920901
175	005A	808	A		0.06	2.0	3.00%	TWA	19981015
176	HTSA	5	P		0.058	1.0	5.80%	TWA	19920901
177	HTEA	5	P	<	0.058	1.0	5.80%	TWA	19920901
178	HT2A	5	P	<	0.057	1.0	5.70%	TWA	19920901
179	HT2A	5	P	<	0.057	1.0	5.70%	TWA	19920901
180	HT2A	5	A		0.057	1.0	5.70%	TWA	19920901
181	HTSA	5	P		0.056	2.0	2.80%	TWA	19981015
182	HT2A	5	P		0.056	1.0	5.60%	TWA	19920901
183	HTEA	5	P		0.055	2.0	2.80%	TWA	19981015
184	HTMA	5	P		0.054	2.0	2.70%	TWA	19981015
185	HTXA	5	P		0.052	1.0	5.20%	TWA	19920901
186	HTEA	5	P		0.05	2.0	2.50%	TWA	19800630
187	HT2A	5	P		0.05	1.0	5.00%	TWA	19920901
188	HTEA	5	P	<	0.049	1.0	4.90%	TWA	19920901
189	HTXA	5	P		0.048	1.0	4.80%	TWA	19920901
190	HTEA	5	P	<	0.047	1.0	4.70%	TWA	19920901
191	HTXA	5	P		0.047	1.0	4.70%	TWA	19920901
192	HT2A	5	P		0.047	1.0	4.70%	TWA	19920901
193	HTXA	5	P	<	0.046	1.0	4.60%	TWA	19920901
194	HTXA	5	P	<	0.046	1.0	4.60%	TWA	19920901
195	HTXA	5	P		0.046	1.0	4.60%	TWA	19920901
196	HTEA	5	A	<	0.046	1.0	4.60%	TWA	19920901
197	HTXA	5	A	<	0.046	1.0	4.60%	TWA	19920901
198	HTEA	5	P	<	0.045	1.0	4.50%	TWA	19920901
199	HTXA	5	P	<	0.045	1.0	4.50%	TWA	19920901
200	HTXA	5	P	<	0.045	1.0	4.50%	TWA	19920901
201	HTSA	5	A	<	0.045	1.0	4.50%	TWA	19920901

"<" symbol signifies "Not Detected". "Value Found" represents "Limit of Detection".
"Standard Date" is when the Workplace Exposure Limit was established by Rohm and Haas.

Acrylic Acid Data Summary (1980 to Present)

Units of "Value Found" and "WEL" are in "PPM"

	A	B	C	D	E	F	G	H	I
202	HTEA	5	P		0.044	2.0	2.20%	TWA	19981015
203	HTEA	5	P	<	0.044	1.0	4.40%	TWA	19920901
204	HTEA	5	P		0.044	1.0	4.40%	TWA	19920901
205	HTXA	5	P		0.042	2.0	2.10%	TWA	19981015
206	HTXA	5	A	<	0.042	1.0	4.20%	TWA	19920901
207	03AC	9	A	<	0.04	2.0	2.00%	TWA	19981015
208	RHTA	5	P		0.039	1.0	3.90%	TWA	19920901
209	HT2A	5	P		0.038	2.0	1.90%	TWA	19981015
210	HTEA	5	P	<	0.038	1.0	3.80%	TWA	19920901
211	HT2A	5	P		0.037	2.0	1.90%	TWA	19981015
212	HT2A	5	P		0.037	2.0	1.90%	TWA	19981015
213	HTEA	5	A	<	0.037	1.0	3.70%	TWA	19920901
214	HTSA	5	P		0.035	1.0	3.50%	TWA	19920901
215	HT2A	5	P		0.033	2.0	1.70%	TWA	19981015
216	03AC	9	A	<	0.033	2.0	1.70%	TWA	19981015
217	03AC	9	A	<	0.033	2.0	1.70%	TWA	19981015
218	HTGA	5	P	<	0.031	2.0	1.60%	TWA	19981015
219	HTGA	5	P	<	0.031	2.0	1.60%	TWA	19981015
220	DPAA	5	P	<	0.031	2.0	1.60%	TWA	19981015
221	64BD	3	P	<	0.03	2.0	1.50%	TWA	19800630
222	017K	632	A		0.03	2.0	1.50%	TWA	19800630
223	081A	751	P	<	0.03	1.0	3.00%	TWA	19920901
224	081A	751	P	<	0.03	1.0	3.00%	TWA	19920901
225	PH1A	5	P	<	0.029	2.0	1.50%	TWA	19981015
226	HTSA	5	P		0.029	2.0	1.50%	TWA	19981015
227	HT2A	5	P	<	0.029	2.0	1.50%	TWA	19981015
228	HT2A	5	P	<	0.028	2.0	1.40%	TWA	19981015
229	005A	5	P	<	0.025	2.0	1.30%	TWA	19981015
230	HT2A	5	P	<	0.025	2.0	1.30%	TWA	19981015
231	HT2A	5	P	<	0.022	2.0	1.10%	TWA	19981015
232	HTXA	5	P	<	0.021	2.0	1.10%	TWA	19981015
233	HTXA	5	P	<	0.021	1.0	2.10%	TWA	19920901
234	HTEA	5	P	<	0.021	1.0	2.10%	TWA	19920901
235	HTXA	5	P	<	0.02	2.0	1.00%	TWA	19981015
236	HTXA	5	P	<	0.02	2.0	1.00%	TWA	19981015
237	HT2A	5	P	<	0.02	2.0	1.00%	TWA	19981015
238	002B	396	A		0.02	1.0	2.00%	TWA	19920901
239	017K	632	P	<	0.02	2.0	1.00%	TWA	19800630
240	017B	632	P	<	0.02	2.0	1.00%	TWA	19800630
241	002C	632	P		0.02	2.0	1.00%	TWA	19800630
242	017K	632	A	<	0.02	2.0	1.00%	TWA	19800630
243	HT2A	5	P		0.018	1.0	1.80%	TWA	19920901
244	005A	808	A		0.018	2.0	0.90%	TWA	19981015
245	03AC	9	A		0.017	2.0	0.90%	TWA	19981015
246	001E	319	A	<	0.016	2.0	0.80%	TWA	19800630
247	HTXA	5	P		0.014	1.0	1.40%	TWA	19920901
248	002C	396	A	<	0.014	1.0	1.40%	TWA	19920901
249	017B	632	P		0.012	1.0	1.20%	TWA	19920901
250	HT2A	5	P	<	0.01	2.0	0.50%	TWA	19981015
251	HT2A	5	P		0.01	1.0	1.00%	TWA	19920901
252	017B	632	P	<	0.01	2.0	0.50%	TWA	19800630

"<" symbol signifies "Not Detected". "Value Found" represents "Limit of Detection".
"Standard Date" is when the Workplace Exposure Limit was established by Rohm and Haas.

Acrylic Acid Data Summary (1980 to Present)

Units of "Value Found" and "WEL" are in "PPM"

	A	B	C	D	E	F	G	H	I
253	017K	632	P	<	0.01	2.0	0.50%	TWA	19800630
254	017K	632	P	<	0.01	2.0	0.50%	TWA	19800630
255	002C	632	P	<	0.01	2.0	0.50%	TWA	19800630
256	HT2M	5	P	<	0.0066	2.0	0.30%	TWA	19981015
257	HT2M	5	P		0.0065	2.0	0.30%	TWA	19981015
258	HT2A	5	P		0.0063	2.0	0.30%	TWA	19981015
259	017K	632	P		0.003	1.0	0.30%	TWA	19920901
260	HT2A	5	P		0.0028	1.0	0.30%	TWA	19920901
261			Average =		0.3513	(Does not include 26 ppm value as outlier)			
262			Geometric Mean =		0.1375	(Does not include 26 ppm value as outlier)			
263			Median =		0.15				
264	22 values of 1 ppm or over for 8% of total					(Includes limit of detection samples)			
265	9 values of 2 ppm or over for 3% of total					(Includes limit of detection samples)			
266	Range = 0.003 (or nondetect at the limit of detection of the analytical method								
267	used at the time) to 4.3 ppm excluding the single 26 ppm outlier								

"<" symbol signifies "Not Detected". "Value Found" represents "Limit of Detection".
"Standard Date" is when the Workplace Exposure Limit was established by Rohm and Haas.

Acrylic Acid Data Summary (1980 to Present)

Units of "Value Found" and "WEL" are in "PPM"

	A	B	C	D	E	F	G	H	I
1	CODE 1	CODE 2	PERSONAL (P) OR AREA (A) MONITORING	<	VALUE FOUND	WEL	% OF WEL	WEL TYPE	STANDARD DATE FOR WEL AT THE TIME
2	003C	16	P		63	5.0	1260.00%	STEL	19800630
3	009C	15	P		62.4	3.0	2080.00%	STEL	19920901
4	ELYA	4	A		57	5.0	1140.00%	STEL	19800630
5	WTFA	4	A		48	3.0	1600.00%	STEL	19920901
6	WTFA	4	P		32	3.0	1066.70%	STEL	19920901
7	002A	912	P	<	30	5.0	600.00%	STEL	19800630
8	RHTA	5	P		24	5.0	480.00%	STEL	19800630
9	ETFA	4	P		23	5.0	460.00%	STEL	19800630
10	HTSA	5	P		23	15.0	153.30%	STEL	19780417
11	HTEA	5	P		18	3.0	600.00%	STEL	19920901
12	008D	831	A	<	15	5.0	300.00%	STEL	19800630
13	046D	751	P		14.8	5.0	296.00%	STEL	19800630
14	001E	319	P		13.8	5.0	276.00%	STEL	19800630
15	028A	3	P		11.6	5.0	232.00%	STEL	19800630
16	046D	751	P		11.4	5.0	228.00%	STEL	19800630
17	030B	3	A		10.8	5.0	216.00%	STEL	19800630
18	015A	735	P		10.1	5.0	202.00%	STEL	19800630
19	RHTA	5	P		9.8	5.0	196.00%	STEL	19800630
20	HTEA	5	P		9.8	3.0	326.70%	STEL	19920901
21	HTMA	5	P		9.4	15.0	62.70%	STEL	19780417
22	ETFA	4	A		9	5.0	180.00%	STEL	19800630
23	HTSA	5	P		8.9	5.0	178.00%	STEL	19800630
24	ETFA	4	P		8.4	5.0	168.00%	STEL	19800630
25	ETFA	4	P		8.3	5.0	166.00%	STEL	19800630
26	028A	3	P	<	7.9	5.0	158.00%	STEL	19800630
27	039D	3	P		7.8	5.0	156.00%	STEL	19800630
28	031C	2	P		7	15.0	46.70%	STEL	19780417
29	046D	751	P		7	5.0	140.00%	STEL	19800630
30	015A	735	P		6.9	5.0	138.00%	STEL	19800630
31	001E	735	P		6.8	5.0	136.00%	STEL	19800630
32	046D	751	P		6.6	5.0	132.00%	STEL	19800630
33	ETFA	4	P		6.5	5.0	130.00%	STEL	19800630
34	008D	831	A		6.4	5.0	128.00%	STEL	19800630
35	028A	3	P		6.2	5.0	124.00%	STEL	19800630
36	004A	912	P	<	6	5.0	120.00%	STEL	19800630
37	001C	4	P		5.9	5.0	118.00%	STEL	19800630
38	HTMA	5	A		5.9	3.0	196.70%	STEL	19920901
39	028A	3	P		5.77	5.0	115.40%	STEL	19800630
40	WTFA	4	A		5.7	5.0	114.00%	STEL	19800630
41	046B	751	A		5.5	3.0	183.30%	STEL	19920901
42	030B	3	A		5.4	5.0	108.00%	STEL	19800630
43	HTSA	5	P		5.2	15.0	34.70%	STEL	19780417
44	HT2M	5	P		5.2	3.0	173.30%	STEL	19920901
45	801D	3	P		5	5.0	100.00%	STEL	19800630
46	003C	16	P	<	5	5.0	100.00%	STEL	19800630
47	001D	16	P	<	5	3.0	166.70%	STEL	19920901
48	ETFA	4	P		4.9	3.0	163.30%	STEL	19920901

"<" symbol signifies "Not Detected". "Value Found" represents "Limit of Detection".
"Standard Date" is when the Workplace Exposure Limit was established by Rohm and Haas.

Acrylic Acid Data Summary (1980 to Present)

Units of "Value Found" and "WEL" are in "PPM"

	A	B	C	D	E	F	G	H	I
49	008D	831	A		4.9	5.0	98.00%	STEL	19800630
50	HT2M	5	A		4.8	3.0	160.00%	STEL	19920901
51	ETFA	4	P		4.76	5.0	95.20%	STEL	19800630
52	ETFA	4	P		4.6	5.0	92.00%	STEL	19800630
53	HTMA	5	A		4.6	3.0	153.30%	STEL	19920901
54	ETFA	4	P		4.5	5.0	90.00%	STEL	19800630
55	ELYA	4	A		4.5	5.0	90.00%	STEL	19800630
56	HTMA	5	P		4.5	5.0	90.00%	STEL	19800630
57	006A	319	A		4.48	5.0	89.60%	STEL	19800630
58	BDSA	3	P	<	4.3	5.0	86.00%	STEL	19800630
59	BDSA	3	P	<	4.2	5.0	84.00%	STEL	19800630
60	WTFA	4	P	<	4	5.0	80.00%	STEL	19800630
61	HTMA	5	P		4	3.0	133.30%	STEL	19920901
62	003C	16	P	<	4	5.0	80.00%	STEL	19800630
63	001B	735	P	<	4	5.0	80.00%	STEL	19800630
64	015A	735	P		4	5.0	80.00%	STEL	19800630
65	HT2M	5	A		3.95	3.0	131.70%	STEL	19920901
66	030C	3	P		3.9	5.0	78.00%	STEL	19800630
67	01AA	4	P	<	3.81	5.0	76.20%	STEL	19800630
68	001E	319	P		3.78	5.0	75.60%	STEL	19800630
69	001B	319	P		3.78	5.0	75.60%	STEL	19800630
70	HT2A	5	P	<	3.7	5.0	74.00%	STEL	19800630
71	ETFA	4	P		3.6	6.0	60.00%	STEL	19981015
72	009C	15	P		3.6	3.0	120.00%	STEL	19920901
73	028A	3	P	<	3.5	5.0	70.00%	STEL	19800630
74	030F	3	P		3.5	5.0	70.00%	STEL	19800630
75	014G	7	P	<	3.5	6.0	58.30%	STEL	19981015
76	007E	751	P		3.5	5.0	70.00%	STEL	19800630
77	ETFA	4	P		3.41	5.0	68.20%	STEL	19800630
78	030F	3	P		3.4	5.0	68.00%	STEL	19800630
79	030B	3	P		3.4	5.0	68.00%	STEL	19800630
80	01AA	4	P	<	3.4	5.0	68.00%	STEL	19800630
81	DPAA	5	A		3.2	5.0	64.00%	STEL	19800630
82	134B	3	A		3.1	5.0	62.00%	STEL	19800630
83	HTMA	5	A		3.1	3.0	103.30%	STEL	19920901
84	001B	735	P		3.1	5.0	62.00%	STEL	19800630
85	ETFA	4	P		3	5.0	60.00%	STEL	19800630
86	001G	735	P	<	3	5.0	60.00%	STEL	19800630
87	015A	735	P		3	5.0	60.00%	STEL	19800630
88	046B	751	A		3	5.0	60.00%	STEL	19800630
89	R12E	2	P		2.9	5.0	58.00%	STEL	19800630
90	RHTA	5	P		2.9	5.0	58.00%	STEL	19800630
91	100E	641	P		2.9	3.0	96.70%	STEL	19920901
92	134B	3	A	<	2.8	5.0	56.00%	STEL	19800630
93	028A	3	P	<	2.7	5.0	54.00%	STEL	19800630
94	B3AA	5	P	<	2.7	3.0	90.00%	STEL	19920901
95	046B	751	A		2.7	5.0	54.00%	STEL	19800630
96	030F	3	P		2.6	5.0	52.00%	STEL	19800630
97	046B	751	P		2.6	5.0	52.00%	STEL	19800630
98	ETFA	4	P		2.5	6.0	41.70%	STEL	19981015
99	ETFA	4	P	<	2.5	5.0	50.00%	STEL	19800630

"<" symbol signifies "Not Detected". "Value Found" represents "Limit of Detection".
"Standard Date" is when the Workplace Exposure Limit was established by Rohm and Haas.

Acrylic Acid Data Summary (1980 to Present)

Units of "Value Found" and "WEL" are in "PPM"

	A	B	C	D	E	F	G	H	I
100	011F	9	P		2.5	3.0	83.30%	STEL	19920901
101	003C	16	A		2.5	5.0	50.00%	STEL	19800630
102	046B	751	P		2.5	5.0	50.00%	STEL	19800630
103	028A	3	P	<	2.4	15.0	16.00%	STEL	19780417
104	028A	3	P		2.4	5.0	48.00%	STEL	19800630
105	ETFA	4	P		2.4	5.0	48.00%	STEL	19800630
106	007E	751	P	<	2.4	5.0	48.00%	STEL	19800630
107	008D	831	A		2.38	5.0	47.60%	STEL	19800630
108	014G	7	P	<	2.3	6.0	38.30%	STEL	19981015
109	978A	840	P		2.3	3.0	76.70%	STEL	19920901
110	ETFA	4	P	<	2.26	5.0	45.20%	STEL	19800630
111	028A	3	P	<	2.2	15.0	14.70%	STEL	19780417
112	007E	751	P		2.18	5.0	43.60%	STEL	19800630
113	030B	3	A		2.1	5.0	42.00%	STEL	19800630
114	002C	318	P		2.1	3.0	70.00%	STEL	19920901
115	ETFA	4	P		2	5.0	40.00%	STEL	19800630
116	001C	4	P		2	5.0	40.00%	STEL	19800630
117	003C	16	P	<	2	5.0	40.00%	STEL	19800630
118	003C	16	P	<	2	3.0	66.70%	STEL	19920901
119	003C	16	P	<	2	3.0	66.70%	STEL	19920901
120	003C	16	P	<	2	3.0	66.70%	STEL	19920901
121	009A	396	P		2	3.0	66.70%	STEL	19920901
122	009A	396	A	<	2	3.0	66.70%	STEL	19920901
123	009A	396	A	<	2	3.0	66.70%	STEL	19920901
124	005C	399	P	<	2	3.0	66.70%	STEL	19920901
125	002C	681	P	<	2	5.0	40.00%	STEL	19800630
126	001E	735	P	<	2	5.0	40.00%	STEL	19800630
127	YARD	831	P		2	3.0	66.70%	STEL	19920901
128	HTEA	5	P		1.9	3.0	63.30%	STEL	19920901
129	HT2M	5	A		1.9	3.0	63.30%	STEL	19920901
130	001B	319	A		1.84	5.0	36.80%	STEL	19800630
131	ETFA	4	P		1.8	3.0	60.00%	STEL	19920901
132	HTEA	5	P		1.8	15.0	12.00%	STEL	19780417
133	B3AA	5	P	<	1.8	3.0	60.00%	STEL	19920901
134	HT2M	5	P		1.8	3.0	60.00%	STEL	19920901
135	HT2M	5	A		1.8	3.0	60.00%	STEL	19920901
136	WTFA	4	P	<	1.77	5.0	35.40%	STEL	19800630
137	WTFA	4	P	<	1.76	5.0	35.20%	STEL	19800630
138	028A	3	A	<	1.7	5.0	34.00%	STEL	19800630
139	030F	3	A		1.7	5.0	34.00%	STEL	19800630
140	030F	3	A		1.7	5.0	34.00%	STEL	19800630
141	028A	3	A		1.7	3.0	56.70%	STEL	19920901
142	001C	4	P		1.7	5.0	34.00%	STEL	19800630
143	009A	4	A		1.7	3.0	56.70%	STEL	19920901
144	011F	9	P		1.7	3.0	56.70%	STEL	19920901
145	100E	641	P		1.7	5.0	34.00%	STEL	19800630
146	046B	751	P		1.7	3.0	56.70%	STEL	19920901
147	005A	808	P		1.7	3.0	56.70%	STEL	19920901
148	008D	831	A		1.7	5.0	34.00%	STEL	19800630
149	028A	3	P		1.6	5.0	32.00%	STEL	19800630
150	030D	3	P	<	1.6	5.0	32.00%	STEL	19800630

"<" symbol signifies "Not Detected". "Value Found" represents "Limit of Detection".

"Standard Date" is when the Workplace Exposure Limit was established by Rohm and Haas.

Acrylic Acid Data Summary (1980 to Present)

Units of "Value Found" and "WEL" are in "PPM"

	A	B	C	D	E	F	G	H	I
151	001C	4	P		1.6	5.0	32.00%	STEL	19800630
152	HTEA	5	P		1.6	15.0	10.70%	STEL	19780417
153	002C	318	P	<	1.6	3.0	53.30%	STEL	19920901
154	002A	852	P		1.6	3.0	53.30%	STEL	19920901
155	ETFA	4	P		1.54	5.0	30.80%	STEL	19800630
156	WTFA	4	P		1.5	6.0	25.00%	STEL	19981015
157	RHTA	5	P		1.5	5.0	30.00%	STEL	19800630
158	014G	7	P	<	1.5	6.0	25.00%	STEL	19981015
159	009C	15	P		1.5	3.0	50.00%	STEL	19920901
160	ETFA	4	P		1.4	5.0	28.00%	STEL	19800630
161	01AA	4	P	<	1.4	5.0	28.00%	STEL	19800630
162	ETFA	4	A		1.4	6.0	23.30%	STEL	19981015
163	HT2M	5	P		1.4	3.0	46.70%	STEL	19920901
164	060F	711	P	<	1.4	5.0	28.00%	STEL	19800630
165	002A	852	P		1.4	6.0	23.30%	STEL	19981015
166	WTFA	4	P	<	1.3	5.0	26.00%	STEL	19800630
167	003C	16	P		1.3	3.0	43.30%	STEL	19920901
168	003C	16	P		1.3	3.0	43.30%	STEL	19920901
169	046B	751	P	<	1.3	3.0	43.30%	STEL	19920901
170	010L	821	P		1.3	5.0	26.00%	STEL	19800630
171	ETFA	4	P	<	1.26	5.0	25.20%	STEL	19800630
172	501B	222	P		1.25	3.0	41.70%	STEL	19920901
173	64BD	3	P	<	1.23	5.0	24.60%	STEL	19800630
174	01AA	4	P	<	1.21	5.0	24.20%	STEL	19800630
175	028A	3	A	<	1.2	5.0	24.00%	STEL	19800630
176	030F	3	A	<	1.2	5.0	24.00%	STEL	19800630
177	ETFA	4	P		1.2	5.0	24.00%	STEL	19800630
178	01AA	4	P		1.2	3.0	40.00%	STEL	19920901
179	001B	4	A		1.2	3.0	40.00%	STEL	19920901
180	HTEA	5	P		1.2	15.0	8.00%	STEL	19780417
181	HT2M	5	A		1.2	3.0	40.00%	STEL	19920901
182	003C	7	P	<	1.2	6.0	20.00%	STEL	19981015
183	03AC	9	P	<	1.2	6.0	20.00%	STEL	19981015
184	002C	808	P	<	1.2	3.0	40.00%	STEL	19920901
185	RHTA	5	P		1.17	5.0	23.40%	STEL	19800630
186	007E	751	P		1.15	5.0	23.00%	STEL	19800630
187	002C	808	P	<	1.1	3.0	36.70%	STEL	19920901
188	010S	821	P		1.1	3.0	36.70%	STEL	19920901
189	007E	751	P		1.03	5.0	20.60%	STEL	19800630
190	028A	3	P	<	1	5.0	20.00%	STEL	19800630
191	028A	3	P		1	5.0	20.00%	STEL	19800630
192	028A	3	P	<	1	5.0	20.00%	STEL	19800630
193	028A	3	P	<	1	5.0	20.00%	STEL	19800630
194	028A	3	A		1	5.0	20.00%	STEL	19800630
195	016C	4	A	<	1	5.0	20.00%	STEL	19800630
196	001B	4	A	<	1	5.0	20.00%	STEL	19800630
197	RHTA	5	P	<	1	5.0	20.00%	STEL	19800630
198	DRFA	5	P		1	3.0	33.30%	STEL	19920901
199	B3MA	5	P	<	1	3.0	33.30%	STEL	19920901
200	03AC	9	P	<	1	5.0	20.00%	STEL	19800630
201	006D	15	P	<	1	5.0	20.00%	STEL	19800630

"<" symbol signifies "Not Detected". "Value Found" represents "Limit of Detection".
"Standard Date" is when the Workplace Exposure Limit was established by Rohm and Haas.

Acrylic Acid Data Summary (1980 to Present)

Units of "Value Found" and "WEL" are in "PPM"

	A	B	C	D	E	F	G	H	I
202	009A	396	P		1	3.0	33.30%	STEL	19920901
203	002C	396	P	<	1	3.0	33.30%	STEL	19920901
204	001H	399	P	<	1	5.0	20.00%	STEL	19800630
205	005A	681	P	<	1	5.0	20.00%	STEL	19800630
206	002C	681	A	<	1	5.0	20.00%	STEL	19800630
207	002C	681	A	<	1	5.0	20.00%	STEL	19800630
208	005A	808	P		1	3.0	33.30%	STEL	19920901
209	010L	821	P	<	1	5.0	20.00%	STEL	19800630
210	070A	821	A	<	1	5.0	20.00%	STEL	19800630
211	010L	821	A	<	1	5.0	20.00%	STEL	19800630
212	010L	821	A	<	1	5.0	20.00%	STEL	19800630
213	010L	821	A	<	1	5.0	20.00%	STEL	19800630
214	010L	821	A	<	1	5.0	20.00%	STEL	19800630
215	008D	831	A	<	1	5.0	20.00%	STEL	19800630
216	014L	7	P		0.99	6.0	16.50%	STEL	19981015
217	057E	7	P		0.98	3.0	32.70%	STEL	19920901
218	002A	912	P		0.98	3.0	32.70%	STEL	19920901
219	003C	16	P		0.97	3.0	32.30%	STEL	19920901
220	001F	396	P		0.96	3.0	32.00%	STEL	19920901
221	010A	632	P		0.96	5.0	19.20%	STEL	19800630
222	B3AA	5	P	<	0.95	3.0	31.70%	STEL	19920901
223	072C	711	P	<	0.95	5.0	19.00%	STEL	19800630
224	022I	622	A		0.94	5.0	18.80%	STEL	19800630
225	022F	622	A		0.94	5.0	18.80%	STEL	19800630
226	B3AA	5	P	<	0.93	3.0	31.00%	STEL	19920901
227	053A	2	P		0.9	5.0	18.00%	STEL	19800630
228	089B	3	P		0.9	5.0	18.00%	STEL	19800630
229	030F	3	A	<	0.9	5.0	18.00%	STEL	19800630
230	ETFA	4	P	<	0.9	5.0	18.00%	STEL	19800630
231	HTSA	5	P		0.9	15.0	6.00%	STEL	19780417
232	005C	399	P	<	0.9	3.0	30.00%	STEL	19920901
233	001H	399	A		0.9	5.0	18.00%	STEL	19800630
234	057E	7	P		0.89	3.0	29.70%	STEL	19920901
235	022I	622	A		0.89	5.0	17.80%	STEL	19800630
236	022F	622	A		0.88	5.0	17.60%	STEL	19800630
237	022F	622	A		0.88	5.0	17.60%	STEL	19800630
238	072C	711	P	<	0.87	5.0	17.40%	STEL	19800630
239	022F	622	A		0.86	5.0	17.20%	STEL	19800630
240	010A	821	P		0.86	6.0	14.30%	STEL	19981015
241	801D	3	P		0.85	5.0	17.00%	STEL	19800630
242	022I	622	A		0.85	5.0	17.00%	STEL	19800630
243	022I	622	A		0.85	5.0	17.00%	STEL	19800630
244	002C	808	P	<	0.85	3.0	28.30%	STEL	19920901
245	022I	622	A		0.84	5.0	16.80%	STEL	19800630
246	022I	622	A		0.83	5.0	16.60%	STEL	19800630
247	001D	16	P		0.82	6.0	13.70%	STEL	19981015
248	022I	622	A		0.82	5.0	16.40%	STEL	19800630
249	017L	651	P		0.82	6.0	13.70%	STEL	19981015
250	WTFA	4	P		0.8	3.0	26.70%	STEL	19920901
251	WTFA	4	A	<	0.8	5.0	16.00%	STEL	19800630
252	006A	319	P		0.8	5.0	16.00%	STEL	19800630

"<" symbol signifies "Not Detected". "Value Found" represents "Limit of Detection".
"Standard Date" is when the Workplace Exposure Limit was established by Rohm and Haas.

Acrylic Acid Data Summary (1980 to Present)

Units of "Value Found" and "WEL" are in "PPM"

	A	B	C	D	E	F	G	H	I
253	005C	399	P	<	0.8	3.0	26.70%	STEL	19920901
254	017K	632	A		0.79	5.0	15.80%	STEL	19800630
255	978D	840	A		0.79	6.0	13.20%	STEL	19981015
256	009A	4	P		0.78	6.0	13.00%	STEL	19981015
257	048A	632	P		0.78	5.0	15.60%	STEL	19800630
258	046B	751	P		0.78	3.0	26.00%	STEL	19920901
259	001B	4	A	<	0.77	3.0	25.70%	STEL	19920901
260	008D	831	P		0.77	6.0	12.80%	STEL	19981015
261	022I	622	A		0.76	5.0	15.20%	STEL	19800630
262	ETFA	4	P	<	0.75	5.0	15.00%	STEL	19800630
263	001C	4	P		0.75	3.0	25.00%	STEL	19920901
264	014L	7	P		0.74	6.0	12.30%	STEL	19981015
265	072C	711	P	<	0.74	5.0	14.80%	STEL	19800630
266	003C	16	P		0.73	6.0	12.20%	STEL	19981015
267	003C	16	P		0.73	3.0	24.30%	STEL	19920901
268	028A	3	P		0.71	5.0	14.20%	STEL	19800630
269	01AA	4	P	<	0.7	5.0	14.00%	STEL	19800630
270	01AA	4	P		0.7	3.0	23.30%	STEL	19920901
271	HTEA	5	P		0.7	15.0	4.70%	STEL	19780417
272	RHTA	5	P		0.7	5.0	14.00%	STEL	19800630
273	001H	399	A	<	0.7	5.0	14.00%	STEL	19800630
274	017K	632	A		0.69	5.0	13.80%	STEL	19800630
275	028A	3	P		0.66	5.0	13.20%	STEL	19800630
276	014L	7	P	<	0.65	6.0	10.80%	STEL	19981015
277	004A	912	P	<	0.65	5.0	13.00%	STEL	19800630
278	003C	16	P		0.64	3.0	21.30%	STEL	19920901
279	B3AA	5	A	<	0.63	3.0	21.00%	STEL	19920901
280	057E	7	A		0.63	3.0	21.00%	STEL	19920901
281	010F	735	P	<	0.63	3.0	21.00%	STEL	19920901
282	005A	808	P		0.63	3.0	21.00%	STEL	19920901
283	ETFA	4	P		0.62	5.0	12.40%	STEL	19800630
284	WTFA	4	P		0.62	5.0	12.40%	STEL	19800630
285	004A	8	P		0.62	6.0	10.30%	STEL	19981015
286	003C	16	P		0.62	6.0	10.30%	STEL	19981015
287	003C	16	P		0.61	3.0	20.30%	STEL	19920901
288	ETFA	4	P	<	0.6	5.0	12.00%	STEL	19800630
289	ETFA	4	P	<	0.6	5.0	12.00%	STEL	19800630
290	ETFA	4	P		0.6	3.0	20.00%	STEL	19920901
291	ETFA	4	P	<	0.6	3.0	20.00%	STEL	19920901
292	WTFA	4	P	<	0.6	3.0	20.00%	STEL	19920901
293	HTSA	5	P		0.6	15.0	4.00%	STEL	19780417
294	PDLA	5	P		0.6	5.0	12.00%	STEL	19800630
295	HTEA	5	P	<	0.6	3.0	20.00%	STEL	19920901
296	03AB	9	P	<	0.6	3.0	20.00%	STEL	19920901
297	006D	15	P		0.6	5.0	12.00%	STEL	19800630
298	003C	16	P		0.6	3.0	20.00%	STEL	19920901
299	048A	632	P		0.6	5.0	12.00%	STEL	19800630
300	017L	651	P		0.59	6.0	9.80%	STEL	19981015
301	028A	3	A		0.58	5.0	11.60%	STEL	19800630
302	057A	7	P		0.58	3.0	19.30%	STEL	19920901
303	001B	319	A		0.58	5.0	11.60%	STEL	19800630

"<" symbol signifies "Not Detected". "Value Found" represents "Limit of Detection".
"Standard Date" is when the Workplace Exposure Limit was established by Rohm and Haas.

Acrylic Acid Data Summary (1980 to Present)

Units of "Value Found" and "WEL" are in "PPM"

	A	B	C	D	E	F	G	H	I
304	010S	821	P		0.58	3.0	19.30%	STEL	19920901
305	009C	15	P		0.57	3.0	19.00%	STEL	19920901
306	072C	711	P		0.57	6.0	9.50%	STEL	19981015
307	010S	821	P		0.56	5.0	11.20%	STEL	19800630
308	978D	840	A	<	0.55	6.0	9.20%	STEL	19981015
309	01AA	4	P	<	0.54	5.0	10.80%	STEL	19800630
310	001D	16	P	<	0.54	3.0	18.00%	STEL	19920901
311	978D	840	A	<	0.54	6.0	9.00%	STEL	19981015
312	004C	889	P	<	0.54	3.0	18.00%	STEL	19920901
313	HTSA	5	P		0.52	6.0	8.70%	STEL	19981015
314	003C	16	P		0.52	6.0	8.70%	STEL	19981015
315	003C	16	P		0.52	3.0	17.30%	STEL	19920901
316	028A	3	A		0.51	5.0	10.20%	STEL	19800630
317	134B	3	A	<	0.5	5.0	10.00%	STEL	19800630
318	01AA	4	P	<	0.5	5.0	10.00%	STEL	19800630
319	01AA	4	P	<	0.5	5.0	10.00%	STEL	19800630
320	ETFA	4	P	<	0.5	3.0	16.70%	STEL	19920901
321	009A	4	P		0.5	3.0	16.70%	STEL	19920901
322	01AA	4	P	<	0.5	3.0	16.70%	STEL	19920901
323	01AA	4	P	<	0.5	3.0	16.70%	STEL	19920901
324	072C	711	P	<	0.5	5.0	10.00%	STEL	19800630
325	010F	735	P	<	0.5	5.0	10.00%	STEL	19800630
326	008D	831	A	<	0.5	5.0	10.00%	STEL	19800630
327	008D	831	A		0.5	5.0	10.00%	STEL	19800630
328	ETFA	4	P		0.49	6.0	8.20%	STEL	19981015
329	WTFA	4	P		0.49	5.0	9.80%	STEL	19800630
330	001C	4	P		0.49	3.0	16.30%	STEL	19920901
331	017H	632	A		0.49	5.0	9.80%	STEL	19800630
332	072A	711	P		0.48	5.0	9.60%	STEL	19800630
333	072C	711	P		0.47	6.0	7.80%	STEL	19981015
334	WTFA	4	P		0.44	5.0	8.80%	STEL	19800630
335	ETFA	4	P		0.44	3.0	14.70%	STEL	19920901
336	003C	16	P		0.44	3.0	14.70%	STEL	19920901
337	014G	7	P	<	0.43	6.0	7.20%	STEL	19981015
338	001D	16	P	<	0.43	3.0	14.30%	STEL	19920901
339	501B	222	P	<	0.43	3.0	14.30%	STEL	19920901
340	072C	711	A		0.43	6.0	7.20%	STEL	19981015
341	005A	808	P		0.43	3.0	14.30%	STEL	19920901
342	001D	16	P		0.42	3.0	14.00%	STEL	19920901
343	001D	16	P		0.42	3.0	14.00%	STEL	19920901
344	031A	2	P		0.41	15.0	2.70%	STEL	19780417
345	HT2M	5	P		0.405	3.0	13.50%	STEL	19920901
346	137A	3	P	<	0.4	6.0	6.70%	STEL	19981015
347	007A	3	P	<	0.4	5.0	8.00%	STEL	19800630
348	028A	3	P	<	0.4	5.0	8.00%	STEL	19800630
349	028A	3	A	<	0.4	5.0	8.00%	STEL	19800630
350	ETFA	4	P		0.4	3.0	13.30%	STEL	19920901
351	01AA	4	P	<	0.4	3.0	13.30%	STEL	19920901
352	01AA	4	P	<	0.4	3.0	13.30%	STEL	19920901
353	005A	681	P	<	0.4	5.0	8.00%	STEL	19800630
354	005A	681	P	<	0.4	5.0	8.00%	STEL	19800630

"<" symbol signifies "Not Detected". "Value Found" represents "Limit of Detection".
"Standard Date" is when the Workplace Exposure Limit was established by Rohm and Haas.

Acrylic Acid Data Summary (1980 to Present)

Units of "Value Found" and "WEL" are in "PPM"

	A	B	C	D	E	F	G	H	I
355	046B	751	P	<	0.4	5.0	8.00%	STEL	19800630
356	008D	831	A		0.4	5.0	8.00%	STEL	19800630
357	002A	852	P		0.4	3.0	13.30%	STEL	19920901
358	030D	3	P		0.39	3.0	13.00%	STEL	19920901
359	ETFA	4	P		0.39	5.0	7.80%	STEL	19800630
360	001B	735	P		0.39	5.0	7.80%	STEL	19800630
361	ETFA	4	A	<	0.38	5.0	7.60%	STEL	19800630
362	057A	7	P	<	0.37	3.0	12.30%	STEL	19920901
363	501B	222	P	<	0.37	3.0	12.30%	STEL	19920901
364	ETFA	4	P	<	0.36	5.0	7.20%	STEL	19800630
365	WTFA	4	P		0.35	3.0	11.70%	STEL	19920901
366	008A	15	P		0.35	5.0	7.00%	STEL	19800630
367	017K	651	P		0.35	6.0	5.80%	STEL	19981015
368	009A	735	P		0.35	3.0	11.70%	STEL	19920901
369	ETFA	4	P		0.32	6.0	5.30%	STEL	19981015
370	003C	16	P		0.31	3.0	10.30%	STEL	19920901
371	007C	394	P		0.31	6.0	5.20%	STEL	19981015
372	028A	3	A		0.3	3.0	10.00%	STEL	19920901
373	ETFA	4	P	<	0.3	5.0	6.00%	STEL	19800630
374	ETFA	4	P		0.3	5.0	6.00%	STEL	19800630
375	ETFA	4	P	<	0.3	3.0	10.00%	STEL	19920901
376	WTFA	4	P		0.3	3.0	10.00%	STEL	19920901
377	01AA	4	P	<	0.3	3.0	10.00%	STEL	19920901
378	RHTA	5	P	<	0.3	5.0	6.00%	STEL	19800630
379	B3MA	5	P	<	0.3	3.0	10.00%	STEL	19920901
380	DPAA	5	A	<	0.3	5.0	6.00%	STEL	19800630
381	DPAA	5	A	<	0.3	5.0	6.00%	STEL	19800630
382	DPAA	5	A	<	0.3	5.0	6.00%	STEL	19800630
383	03AB	9	P	<	0.3	5.0	6.00%	STEL	19800630
384	006D	15	P	<	0.3	5.0	6.00%	STEL	19800630
385	501B	222	P	<	0.3	3.0	10.00%	STEL	19920901
386	072B	711	P		0.3	5.0	6.00%	STEL	19800630
387	010A	821	P		0.3	6.0	5.00%	STEL	19981015
388	007B	394	P	<	0.29	6.0	4.80%	STEL	19981015
389	007B	394	P	<	0.29	6.0	4.80%	STEL	19981015
390	007B	394	P	<	0.29	6.0	4.80%	STEL	19981015
391	010T	821	P		0.29	3.0	9.70%	STEL	19920901
392	008D	831	P		0.29	6.0	4.80%	STEL	19981015
393	WTFA	4	P	<	0.28	3.0	9.30%	STEL	19920901
394	B3AA	5	P	<	0.28	3.0	9.30%	STEL	19920901
395	501B	222	P	<	0.28	3.0	9.30%	STEL	19920901
396	501B	222	P	<	0.28	3.0	9.30%	STEL	19920901
397	501B	222	P	<	0.28	3.0	9.30%	STEL	19920901
398	048A	632	P		0.28	3.0	9.30%	STEL	19920901
399	ETFA	4	P		0.27	5.0	5.40%	STEL	19800630
400	03AB	9	P	<	0.27	6.0	4.50%	STEL	19981015
401	03AB	9	P	<	0.27	6.0	4.50%	STEL	19981015
402	009C	15	P	<	0.27	3.0	9.00%	STEL	19920901
403	003C	16	P	<	0.27	6.0	4.50%	STEL	19981015
404	001D	16	P		0.27	3.0	9.00%	STEL	19920901
405	007C	394	P		0.27	6.0	4.50%	STEL	19981015

"<" symbol signifies "Not Detected". "Value Found" represents "Limit of Detection".
"Standard Date" is when the Workplace Exposure Limit was established by Rohm and Haas.

Acrylic Acid Data Summary (1980 to Present)

Units of "Value Found" and "WEL" are in "PPM"

	A	B	C	D	E	F	G	H	I
406	ETFA	4	P	<	0.26	5.0	5.20%	STEL	19800630
407	01AA	4	P	<	0.26	3.0	8.70%	STEL	19920901
408	DRFA	5	P		0.26	3.0	8.70%	STEL	19920901
409	057E	7	P	<	0.26	3.0	8.70%	STEL	19920901
410	005A	681	P		0.26	6.0	4.30%	STEL	19981015
411	001C	4	P		0.25	3.0	8.30%	STEL	19920901
412	001B	4	A		0.25	3.0	8.30%	STEL	19920901
413	B3AA	5	P	<	0.25	3.0	8.30%	STEL	19920901
414	HT2A	5	P		0.25	3.0	8.30%	STEL	19920901
415	014G	7	P	<	0.25	6.0	4.20%	STEL	19981015
416	007C	394	P	<	0.25	3.0	8.30%	STEL	19920901
417	007C	394	P	<	0.25	3.0	8.30%	STEL	19920901
418	072C	711	P	<	0.25	6.0	4.20%	STEL	19981015
419	072C	711	P	<	0.25	6.0	4.20%	STEL	19981015
420	072C	711	A	<	0.25	6.0	4.20%	STEL	19981015
421	005A	808	P		0.25	3.0	8.30%	STEL	19920901
422	01AA	4	P	<	0.24	3.0	8.00%	STEL	19920901
423	HTSA	5	P		0.24	6.0	4.00%	STEL	19981015
424	TRAK	5	P		0.24	6.0	4.00%	STEL	19981015
425	009C	15	P	<	0.24	3.0	8.00%	STEL	19920901
426	003C	16	P		0.24	3.0	8.00%	STEL	19920901
427	001D	16	P	<	0.24	3.0	8.00%	STEL	19920901
428	048A	632	P		0.24	3.0	8.00%	STEL	19920901
429	001E	735	P		0.24	5.0	4.80%	STEL	19800630
430	009A	735	A		0.24	6.0	4.00%	STEL	19981015
431	010A	821	P		0.24	6.0	4.00%	STEL	19981015
432	010A	821	P	<	0.24	6.0	4.00%	STEL	19981015
433	008D	831	A	<	0.24	3.0	8.00%	STEL	19920901
434	ETFA	4	P		0.23	5.0	4.60%	STEL	19800630
435	DPAA	5	A	<	0.23	5.0	4.60%	STEL	19800630
436	010S	821	P		0.23	3.0	7.70%	STEL	19920901
437	137A	3	P		0.22	3.0	7.30%	STEL	19920901
438	005B	398	A		0.22	3.0	7.30%	STEL	19920901
439	072C	711	A	<	0.22	6.0	3.70%	STEL	19981015
440	ETFA	4	P	<	0.21	3.0	7.00%	STEL	19920901
441	001C	681	P	<	0.21	3.0	7.00%	STEL	19920901
442	010T	821	P		0.21	5.0	4.20%	STEL	19800630
443	028A	3	P		0.2	5.0	4.00%	STEL	19800630
444	ETFA	4	P	<	0.2	5.0	4.00%	STEL	19800630
445	01AA	4	P	<	0.2	5.0	4.00%	STEL	19800630
446	WTFA	4	P		0.2	3.0	6.70%	STEL	19920901
447	WTFA	4	P	<	0.2	3.0	6.70%	STEL	19920901
448	WTFA	4	P	<	0.2	3.0	6.70%	STEL	19920901
449	001A	4	P	<	0.2	3.0	6.70%	STEL	19920901
450	01AA	4	P	<	0.2	3.0	6.70%	STEL	19920901
451	ETFA	4	A	<	0.2	3.0	6.70%	STEL	19920901
452	WTFA	4	A	<	0.2	3.0	6.70%	STEL	19920901
453	B3AA	5	P	<	0.2	3.0	6.70%	STEL	19920901
454	DPAA	5	A	<	0.2	5.0	4.00%	STEL	19800630
455	009C	15	P	<	0.2	3.0	6.70%	STEL	19920901
456	003D	395	P	<	0.2	5.0	4.00%	STEL	19800630

"<" symbol signifies "Not Detected". "Value Found" represents "Limit of Detection".
"Standard Date" is when the Workplace Exposure Limit was established by Rohm and Haas.

Acrylic Acid Data Summary (1980 to Present)

Units of "Value Found" and "WEL" are in "PPM"

	A	B	C	D	E	F	G	H	I
457	017K	632	P		0.2	3.0	6.70%	STEL	19920901
458	004A	912	P		0.2	5.0	4.00%	STEL	19800630
459	HTGA	5	P	<	0.19	6.0	3.20%	STEL	19981015
460	HTSA	5	P	<	0.19	3.0	6.30%	STEL	19920901
461	010S	821	P	<	0.19	3.0	6.30%	STEL	19920901
462	01AA	4	P		0.18	5.0	3.60%	STEL	19800630
463	014N	7	P	<	0.18	6.0	3.00%	STEL	19981015
464	010A	821	P		0.18	6.0	3.00%	STEL	19981015
465	008D	831	P	<	0.18	6.0	3.00%	STEL	19981015
466	01AA	4	P	<	0.17	6.0	2.80%	STEL	19981015
467	01AA	4	P	<	0.17	6.0	2.80%	STEL	19981015
468	009A	4	P		0.17	3.0	5.70%	STEL	19920901
469	009C	15	P	<	0.17	3.0	5.70%	STEL	19920901
470	001D	16	P		0.17	3.0	5.70%	STEL	19920901
471	017K	632	A		0.17	5.0	3.40%	STEL	19800630
472	B3AA	5	P	<	0.16	3.0	5.30%	STEL	19920901
473	048A	632	P		0.16	3.0	5.30%	STEL	19920901
474	031A	2	P	<	0.15	15.0	1.00%	STEL	19780417
475	028A	3	A	<	0.15	5.0	3.00%	STEL	19800630
476	009A	4	P	<	0.15	6.0	2.50%	STEL	19981015
477	059B	7	A	<	0.15	5.0	3.00%	STEL	19800630
478	059B	7	A	<	0.15	5.0	3.00%	STEL	19800630
479	048A	632	P		0.15	5.0	3.00%	STEL	19800630
480	002C	632	P		0.15	5.0	3.00%	STEL	19800630
481	CRYA	3	A		0.14	5.0	2.80%	STEL	19800630
482	ETFA	4	P	<	0.14	3.0	4.70%	STEL	19920901
483	WTFA	4	P	<	0.14	3.0	4.70%	STEL	19920901
484	004F	397	P	<	0.14	3.0	4.70%	STEL	19920901
485	010A	821	P		0.14	6.0	2.30%	STEL	19981015
486	002A	852	P	<	0.14	6.0	2.30%	STEL	19981015
487	048A	632	P		0.138	5.0	2.80%	STEL	19800630
488	002C	632	P		0.138	5.0	2.80%	STEL	19800630
489	WTFA	4	P	<	0.13	3.0	4.30%	STEL	19920901
490	01AA	4	P	<	0.13	3.0	4.30%	STEL	19920901
491	008D	831	P		0.13	3.0	4.30%	STEL	19920901
492	008D	831	A	<	0.13	3.0	4.30%	STEL	19920901
493	01AA	4	P	<	0.12	6.0	2.00%	STEL	19981015
494	HTGA	5	P	<	0.12	3.0	4.00%	STEL	19920901
495	HTGA	5	P	<	0.12	3.0	4.00%	STEL	19920901
496	022A	622	P	<	0.12	3.0	4.00%	STEL	19920901
497	048A	632	P		0.12	3.0	4.00%	STEL	19920901
498	010A	821	P		0.12	6.0	2.00%	STEL	19981015
499	01AA	4	P	<	0.11	6.0	1.80%	STEL	19981015
500	ETFA	4	P	<	0.11	5.0	2.20%	STEL	19800630
501	HTGA	5	P	<	0.11	3.0	3.70%	STEL	19920901
502	HTXA	5	P		0.11	3.0	3.70%	STEL	19920901
503	08AF	9	P		0.11	3.0	3.70%	STEL	19920901
504	009C	15	P	<	0.11	3.0	3.70%	STEL	19920901
505	B3AR	5	P	<	0.101	3.0	3.40%	STEL	19920901
506	031A	2	P	<	0.1	5.0	2.00%	STEL	19800630
507	01AA	4	P	<	0.1	5.0	2.00%	STEL	19800630

"<" symbol signifies "Not Detected". "Value Found" represents "Limit of Detection".
"Standard Date" is when the Workplace Exposure Limit was established by Rohm and Haas.

Acrylic Acid Data Summary (1980 to Present)

Units of "Value Found" and "WEL" are in "PPM"

	A	B	C	D	E	F	G	H	I
508	01AA	4	P	<	0.1	5.0	2.00%	STEL	19800630
509	WTFA	4	P	<	0.1	3.0	3.30%	STEL	19920901
510	ETFA	4	A	<	0.1	6.0	1.70%	STEL	19981015
511	HTEA	5	P		0.1	3.0	3.30%	STEL	19920901
512	HT2C	5	A	<	0.1	3.0	3.30%	STEL	19920901
513	005B	398	P		0.1	3.0	3.30%	STEL	19920901
514	005B	398	P	<	0.1	3.0	3.30%	STEL	19920901
515	017B	632	P	<	0.1	5.0	2.00%	STEL	19800630
516	017B	632	P	<	0.1	3.0	3.30%	STEL	19920901
517	017K	632	P	<	0.1	3.0	3.30%	STEL	19920901
518	072B	711	P	<	0.1	5.0	2.00%	STEL	19800630
519	001C	753	P	<	0.1	3.0	3.30%	STEL	19920901
520	010A	821	P	<	0.1	6.0	1.70%	STEL	19981015
521	008D	831	P	<	0.1	6.0	1.70%	STEL	19981015
522	008D	831	P	<	0.1	3.0	3.30%	STEL	19920901
523	008D	831	P	<	0.1	3.0	3.30%	STEL	19920901
524	008D	831	A	<	0.1	3.0	3.30%	STEL	19920901
525	072C	711	P	<	0.099	3.0	3.30%	STEL	19920901
526	WTFA	4	P	<	0.098	3.0	3.30%	STEL	19920901
527	WTFA	4	A	<	0.098	6.0	1.60%	STEL	19981015
528	01AA	4	P	<	0.092	6.0	1.50%	STEL	19981015
529	031A	2	P	<	0.09	15.0	0.60%	STEL	19780417
530	ETFA	4	P	<	0.09	3.0	3.00%	STEL	19920901
531	HT2A	5	P	<	0.09	3.0	3.00%	STEL	19920901
532	022A	622	P	<	0.09	3.0	3.00%	STEL	19920901
533	022A	622	P	<	0.09	3.0	3.00%	STEL	19920901
534	022A	622	P	<	0.09	3.0	3.00%	STEL	19920901
535	01AA	4	P	<	0.086	6.0	1.40%	STEL	19981015
536	001A	4	P	<	0.085	3.0	2.80%	STEL	19920901
537	005A	808	P	<	0.085	3.0	2.80%	STEL	19920901
538	005A	808	P	<	0.085	3.0	2.80%	STEL	19920901
539	OFFS	9	A	<	0.083	6.0	1.40%	STEL	19981015
540	01AA	4	P	<	0.082	3.0	2.70%	STEL	19920901
541	OFFS	9	A	<	0.081	6.0	1.40%	STEL	19981015
542	HR2A	5	P	<	0.08	3.0	2.70%	STEL	19920901
543	HR2A	5	P	<	0.08	3.0	2.70%	STEL	19920901
544	022A	622	P	<	0.08	3.0	2.70%	STEL	19920901
545	022E	622	P	<	0.08	3.0	2.70%	STEL	19920901
546	022A	622	P	<	0.08	3.0	2.70%	STEL	19920901
547	002C	632	P		0.08	3.0	2.70%	STEL	19920901
548	WTFA	4	P		0.079	5.0	1.60%	STEL	19800630
549	ETFA	4	P	<	0.078	3.0	2.60%	STEL	19920901
550	ETFA	4	P	<	0.077	3.0	2.60%	STEL	19920901
551	08AF	9	P		0.077	3.0	2.60%	STEL	19920901
552	100G	641	P		0.073	3.0	2.40%	STEL	19920901
553	01AA	4	P	<	0.072	3.0	2.40%	STEL	19920901
554	OFFS	9	A	<	0.072	6.0	1.20%	STEL	19981015
555	ETFA	4	P	<	0.071	3.0	2.40%	STEL	19920901
556	002B	808	A	<	0.071	3.0	2.40%	STEL	19920901
557	022A	622	P	<	0.07	3.0	2.30%	STEL	19920901
558	WTFA	4	A	<	0.068	3.0	2.30%	STEL	19920901

"<" symbol signifies "Not Detected". "Value Found" represents "Limit of Detection".
"Standard Date" is when the Workplace Exposure Limit was established by Rohm and Haas.

Acrylic Acid Data Summary (1980 to Present)

Units of "Value Found" and "WEL" are in "PPM"

	A	B	C	D	E	F	G	H	I
559	HT2A	5	P	<	0.068	3.0	2.30%	STEL	19920901
560	ETFA	4	P	<	0.067	3.0	2.20%	STEL	19920901
561	01AA	4	P	<	0.065	3.0	2.20%	STEL	19920901
562	01AA	4	P	<	0.065	3.0	2.20%	STEL	19920901
563	ETFA	4	A	<	0.065	3.0	2.20%	STEL	19920901
564	WTFA	4	P	<	0.064	3.0	2.10%	STEL	19920901
565	01AA	4	P	<	0.064	3.0	2.10%	STEL	19920901
566	ETFA	4	A	<	0.063	3.0	2.10%	STEL	19920901
567	WTFA	4	P	<	0.062	3.0	2.10%	STEL	19920901
568	01AA	4	P	<	0.062	3.0	2.10%	STEL	19920901
569	01AA	4	P	<	0.062	3.0	2.10%	STEL	19920901
570	HT2M	5	P	<	0.061	3.0	2.00%	STEL	19920901
571	005B	398	P	<	0.061	3.0	2.00%	STEL	19920901
572	008D	831	A	<	0.061	3.0	2.00%	STEL	19920901
573	01AA	4	P	<	0.06	5.0	1.20%	STEL	19800630
574	022A	622	P	<	0.06	3.0	2.00%	STEL	19920901
575	017K	632	P		0.06	3.0	2.00%	STEL	19920901
576	009C	681	P	<	0.058	6.0	1.00%	STEL	19981015
577	978A	840	A		0.058	3.0	1.90%	STEL	19920901
578	WTFA	4	A	<	0.056	3.0	1.90%	STEL	19920901
579	08AF	9	A	<	0.055	3.0	1.80%	STEL	19920901
580	WTFA	4	A	<	0.054	3.0	1.80%	STEL	19920901
581	03BC	9	P	<	0.051	3.0	1.70%	STEL	19920901
582	072D	711	P		0.051	3.0	1.70%	STEL	19920901
583	HTEA	5	P	<	0.05	3.0	1.70%	STEL	19920901
584	002C	632	P	<	0.05	3.0	1.70%	STEL	19920901
585	040D	821	P	<	0.05	3.0	1.70%	STEL	19920901
586	040D	821	P	<	0.05	3.0	1.70%	STEL	19920901
587	ETFA	4	A	<	0.048	3.0	1.60%	STEL	19920901
588	005A	681	A		0.048	3.0	1.60%	STEL	19920901
589	005A	681	P		0.045	3.0	1.50%	STEL	19920901
590	ETFA	4	P	<	0.044	3.0	1.50%	STEL	19920901
591	005A	681	P	<	0.044	6.0	0.70%	STEL	19981015
592	01AA	4	P	<	0.043	3.0	1.40%	STEL	19920901
593	002A	808	A	<	0.043	6.0	0.70%	STEL	19981015
594	735A	735	A	<	0.041	6.0	0.70%	STEL	19981015
595	005A	681	P	<	0.039	3.0	1.30%	STEL	19920901
596	735A	735	A	<	0.039	6.0	0.70%	STEL	19981015
597	735A	735	A	<	0.037	6.0	0.60%	STEL	19981015
598	735A	735	A	<	0.036	6.0	0.60%	STEL	19981015
599	009A	735	A	<	0.032	6.0	0.50%	STEL	19981015
600	DPAA	5	P	<	0.03	5.0	0.60%	STEL	19800630
601	002C	396	A	<	0.03	3.0	1.00%	STEL	19920901
602	DPAA	5	P	<	0.029	5.0	0.60%	STEL	19800630
603	008A	831	A	<	0.029	6.0	0.50%	STEL	19981015
604	DPAA	5	P	<	0.028	5.0	0.60%	STEL	19800630
605	DPAA	5	P	<	0.026	5.0	0.50%	STEL	19800630
606	03AB	9	P	<	0.024	3.0	0.80%	STEL	19920901
607	08AF	9	P	<	0.022	3.0	0.70%	STEL	19920901
608	WHSE	16	A	<	0.022	3.0	0.70%	STEL	19920901
609	TRAK	5	P	<	0.02	6.0	0.30%	STEL	19981015

"<" symbol signifies "Not Detected". "Value Found" represents "Limit of Detection".
"Standard Date" is when the Workplace Exposure Limit was established by Rohm and Haas.

Acrylic Acid Data Summary (1980 to Present)

Units of "Value Found" and "WEL" are in "PPM"

	A	B	C	D	E	F	G	H	I
610	B3AA	5	P	<	0.02	3.0	0.70%	STEL	19920901
611	008D	831	P	<	0.02	3.0	0.70%	STEL	19920901
612	978A	840	A	<	0.02	3.0	0.70%	STEL	19920901
613	DPAA	5	A	<	0.016	5.0	0.30%	STEL	19800630
614	013A	831	A	<	0.016	3.0	0.50%	STEL	19920901
615	03BC	9	P		0.015	3.0	0.50%	STEL	19920901
616	801D	3	A		0.013	5.0	0.30%	STEL	19800630
617	801D	3	A		0.013	5.0	0.30%	STEL	19800630
618	SPHB	9	A	<	0.013	6.0	0.20%	STEL	19981015
619	03AC	9	A	<	0.012	6.0	0.20%	STEL	19981015
620	072B	711	P	<	0.011	5.0	0.20%	STEL	19800630
621	ETFA	4	P	<	0.01	5.0	0.20%	STEL	19800630
622	RHTA	5	P	<	0.01	5.0	0.20%	STEL	19800630
623	08AF	9	A	<	0.0092	3.0	0.30%	STEL	19920901
624	001D	16	P	<	0.009	5.0	0.20%	STEL	19800630
625	003C	16	A		0.007	5.0	0.10%	STEL	19800630
626	017E	632	P		0.007	5.0	0.10%	STEL	19800630
627	RHTA	5	P	<	0.006	5.0	0.10%	STEL	19800630
628	501B	222	P	<	0.006	3.0	0.20%	STEL	19920901
629	501B	222	P	<	0.006	3.0	0.20%	STEL	19920901
630	001C	753	P		0.005	5.0	0.10%	STEL	19800630
631	DPAA	5	A	<	0.004	5.0	0.10%	STEL	19800630
632	017K	632	P	<	0.001	3.0	0.03%	STEL	19920901
633			Average =		1.8464				
634			Geometric Mean =		0.4759				
635			Median =		0.5				
636	214 values of 1 ppm or over for 34% of total						(Includes limit of detection samples)		
637	126 values of 2 ppm or over for 20% of total						(Includes limit of detection samples)		
638	46 values of 5 ppm or over for 7% of total						(Includes limit of detection samples)		
639	17 values of 10 ppm or over for 3% of total						(Includes limit of detection samples)		
640	Range = < 0.001 (or nondetect at the limit of detection of the analytical method								
641	used at the time) to 63 ppm								

"<" symbol signifies "Not Detected". "Value Found" represents "Limit of Detection".
"Standard Date" is when the Workplace Exposure Limit was established by Rohm and Haas.

FINAL REPORT

on

SINGLE DOSE INHALATION TOXICITY STUDY OF ETHYL ACRYLATE (EA) AND ACRYLIC ACID (AA)

to

Rohm and Haas Co.
727 Norristown Rd.
Springhouse, PA 19477

September, 1995

by

Michael J. Brooker and Michael E. Placke

BATTELLE
505 King Avenue
Columbus, Ohio 43201-2693

GOOD LABORATORY PRACTICES COMPLIANCE STATEMENT

Study Title: Single Dose Inhalation Toxicity Study of Ethyl Acrylate (EA) and Acrylic Acid (AA)

Battelle Study Number: SC940138

This study was conducted in compliance with EPA GLP Regulations 40 CFR Part 792. This study was conducted according to the study protocol and Battelle's Standard Operating Procedures and to the best of my knowledge the data presented accurately reflect the results of this study.

Michael J. Brooker 9/12/95

Michael J. Brooker, B.S.
Study Director

FINAL REPORT

on

SINGLE DOSE INHALATION TOXICITY STUDY OF ETHYL ACRYLATE (EA) AND ACRYLIC ACID (AA)

September, 1995

Michael J. Brooker, B.S.
Study Director

September 12, 1995
Date

Michael E. Placke, Ph.D., DABT
Program Manager

9/12/95
Date

QUALITY ASSURANCE STATEMENT

This study was inspected by the Quality Assurance Unit and reports were submitted to the study director and management as follows:

Phase Inspected	Date Inspected	Date Reported to Study Director	Date of Report to Management
Randomization	12//08/94	1/04/95	1/04/95
Acclimation	12/16/94	1/04/95	1/04/95
Body weights	12/16/94	1/04/95	1/04/95
Euthanasia	12/16/94	1/04/95	1/04/95
Infrared spectroscopy analysis	12/16/94	1/04/95	1/04/95
Necropsy/tissue collection	12/16/94	1/04/95	1/04/95
Respiratory parameters collection	12/16/94	1/04/95	1/04/95
Test substance administration - inhalation	12/16/94	1/04/95	1/04/95
Audit: Study File	2/06/95	2/06/95	3/27/95
Audit: Draft Final Report	2/06/95	2/06/95	9/12/95
Audit: Final Report	9/12/95	9/12/95	9/12/95

Kathleen C. Reed 9-12-95

Quality Assurance Unit Date

CONTENTS

	Page
GOOD LABORATORY PRACTICES COMPLIANCE STATEMENT	ii
SIGNATURE PAGE	iii
QUALITY ASSURANCE PAGE	iv
SUMMARY	viii
1.0 INTRODUCTION	1
2.0 MATERIALS AND METHODS	2
2.1 Experimental Design	2
2.2 Test Substances	2
2.3 Test Substance Identity, Purity and Stability	2
2.4 Inhalation Methods	3
2.4.1 Test Substance Generation and Delivery	3
2.4.2 Exposure System	3
2.4.3 Pulmonary Function Measurements	3
2.4.4 Test Substance Atmosphere Concentration Analysis	4
2.4.5 Instrument Calibration	4
2.4.6 Pre-Exposure System Validation	5
2.5 Experimental Animals	5
2.5.1 Animal Housing and Environmental Conditions	5
2.6 Animal Randomization and Identification	6
2.7 Clinical Pathology and Health Evaluations	6
2.8 Body Weights	7
2.9 Clinical Observations	7
2.10 Necropsy	7
2.11 Statistical Evaluation of the Data	8
3.0 RESULTS	9
3.1 Pre-Exposure Health Evaluation Results	9
3.2 Body Weight Determinations	9
3.3 Clinical Observations	9
3.4 Necropsy Results	10
3.5 Pre-Exposure System Validation	10
3.5.1 Infrared Analyzer Calibration Results	10
3.5.2 System Uniformity and Trial Run Results	11
3.5.3 Test Substance Concentrations	11
3.5.4 Pulmonary Function Measurements	12
3.5.5 Inhaled Dose Estimates	12

CONTENTS

Page

4.0 DISCUSSION 13
5.0 SPECIMEN STORAGE AND RECORD ARCHIVES 14
6.0 ACKNOWLEDGMENTS 15

TABLES

Table 1. Pre-Exposure Individual Animal Cell Count Data for the Single Dose Inhalation Toxicity Study of Ethyl Acrylate and Acrylic Acid 16

Table 2. Pre-Exposure Individual Animal WBC Differential Data for the Single Dose Inhalation Toxicity Study of Ethyl Acrylate and Acrylic Acid 17

Table 3. Pre-Exposure Individual Animal Serum Chemistry Data for the Single Dose Inhalation Toxicity Study of Ethyl Acrylate and Acrylic Acid 18

Table 4. Pre-Exposure Individual Animal Body Weight Data for the Single Dose Inhalation Toxicity Study of Ethyl Acrylate and Acrylic Acid 19

Table 5. Ethyl Acrylate Calibration Data for the Single Dose Inhalation Toxicity Study of Ethyl Acrylate and Acrylic Acid 20

Table 6. Acrylic Acid Calibration Data for the Single Dose Inhalation Toxicity Study of Ethyl Acrylate and Acrylic Acid 21

Table 7. Ethyl Acrylate Concentration Uniformity Data for the Single Dose Inhalation Toxicity Study of Ethyl Acrylate and Acrylic Acid 22

Table 8. Acrylic Acid Concentration Uniformity Data for the Single Dose Inhalation Toxicity Study of Ethyl Acrylate and Acrylic Acid 23

Table 9. Ethyl Acrylate Pretest Trial Run Data for the Single Dose Inhalation Toxicity Study of Ethyl Acrylate and Acrylic Acid 24

Table 10. Acrylic Acid Pretest Trial Run Data for the Single Dose Inhalation Toxicity Study of Ethyl Acrylate and Acrylic Acid 25

Table 11. Mean Test Substance Concentration Data for the Single Dose Inhalation Toxicity Study of Ethyl Acrylate and Acrylic Acid 26

Table 12. Test Substance Concentration Data (Individual Analyses) for the Single Dose Inhalation Toxicity Study of Ethyl Acrylate and Acrylic Acid 27

CONTENTS

Page

Table 13. Individual Animal Pulmonary Function Data for the Single Dose Inhalation Toxicity Study of Ethyl Acrylate and Acrylic Acid 28

Table 14. Group Mean Inhaled Dose Estimates for the Single Dose Inhalation Toxicity Study of Ethyl Acrylate and Acrylic Acid 29

Table 15. Individual Animal Estimated Inhaled Dose Data for the Single Dose Inhalation Toxicity Study of Ethyl Acrylate and Acrylic Acid 30

FIGURES

Figure 1. Schematic Diagram of Exposure System 31

APPENDICES

APPENDIX A. STUDY PROTOCOL, AMENDMENTS, AND DEVIATIONS A-1

APPENDIX B. MIRAN 980 CALIBRATION DATA B-1

1.0 INTRODUCTION

The objective of this study was to evaluate the acute toxicity of Ethyl Acrylate (EA) and Acrylic Acid (AA) in monkeys after a single inhalation exposure. Rohm and Haas Inc. was the Project Sponsor. Dr. Clay Frederick was the designated Sponsor Project Monitor and approved the study protocol. The study was conducted in compliance with the EPA guidelines (40 CFR Part 792) and was listed on Battelle's list of regulated studies. The study protocol, amendments to the protocol, and any deviations from the protocol are contained in Appendix A. The study was conducted at Battelle Columbus Operations under the direction of Mr. Michael J. Brooker. The study was initiated on November 22, 1994 with the signing of the protocol and completed on September 12, 1995 with the signing of the final report.

2.0 MATERIALS AND METHODS

2.1 Experimental Design

Five groups of primates, three animals per group, were exposed via head-only inhalation exposure to one target concentration (75 ppm) of one of vapors of the two test compounds or filtered air (controls). Each animal received a single exposure for either three or six hour duration. The following table details the treatment groups:

Group Number	Test Substance	No. of Animals	Vapor Concentration (ppm)	Exposure Duration (hours)
1	Air Control	3	0	6
2	Ethyl Acrylate	3	75	3
3	Ethyl Acrylate	3	75	6
4	Acrylic Acid	3	75	3
5	Acrylic Acid	3	75	6

A sixteenth animal (non-exposed) was anesthetized, euthanized and necropsied for magnetic resonance image analysis by Dr. Kevin Morgan at the Chemical Institute of Industrial Toxicology (CIIT).

2.2 Test Substances

Two different test substances, Ethyl Acrylate and Acrylic Acid, were received from Rohm and Haas. Approximately 250 mL of each compound was received on November 22, 1994. The lot number for the Ethyl Acrylate was TD93-047. The lot number for the Acrylic Acid was TD94-095. The test substances were stored at room temperature. No expiration dates were listed for either of the test substances.

2.3 Test Substance Identity, Purity and Stability

The test substance identity, purity and stability were the responsibility of the Project Sponsor.

2.4 Inhalation Methods

2.4.1 Test Substance Generation and Delivery

Both of the test substances were generated in a similar manner. A small amount of the liquid test substance was placed in a 25 mL midget impinger and a measured flow of nitrogen was bubbled through the test substance in the impinger, vaporizing the test substance. The resultant vapors were ducted directly to the exposure plenum.

2.4.2 Exposure System

The output of the vapor generator (impinger) was delivered directly into a stainless steel vessel used as a dilution plenum. Within the plenum, Hepa filtered compressed air was added as dilution and carrier air to achieve a total flow through the system of 40 Liters per minute. The test atmosphere was transported through stainless steel tubing to each of the exposure helmets. Stainless steel venturi's (0.169 inch throat) were placed into the delivery line just prior to the exposure helmets.

The exposure helmets were constructed of 8-inch diameter acrylic cylinder approximately 6 inches tall. An air inlet was placed tangential to the radius near the top of the helmet. This produced a swirling effect within the helmet as air was drawn from smaller ports near the bottom of the helmet. The bias flow through each of the helmets was regulated at 10 L/min. An additional 10 liters per minute was supplied to the monitoring system.

2.4.3 Pulmonary Function Measurements

The volume of test atmosphere inhaled during exposure was determined for each animal by measuring the flow changes into the helmet through the venturi. Pressure drop at the throat of the venturi was monitored with a Validyne pressure transducer. Signals from the transducer were amplified by PO-NE-MAH preamplifiers for variable reluctance transducers.

A flow versus voltage relationship was documented for each venturi/amp/transducer set-up using a calibrated mass flow meter. Based upon the fluctuations in airflow through the venturi, the

respiration rate, and tidal volume were measured for each animal. Additionally, the total inhaled volume was calculated for each animal during the exposure period.

2.4.4 Test Substance Atmosphere Concentration Analysis

An infrared spectrophotometer system was used to monitor the concentration of the test substances in the exposure atmospheres. The Miran-980 infrared spectrometer (IR) Wilks (Foxboro Company, South Norfolk, CT) is a single-beam spectrometer, equipped with an adjustable cell pathlength (0.75 to 20.25 meters), and can be operated over a wavelength range from 2.5 to 14.5 micrometers (μm). Prior to initiating exposures a thorough calibration of the MIRAN-980 was completed. The wavelengths were selected based on absorbance versus wavelength scans of test substance standards. A reference wavelength was used to correct for instrument drift.

After selecting the sample location and waiting the required flushing time (approximately 5 minutes was needed at 10 L/minute air flow), the operator closed the outlet valve from the IR instrument, recorded the time and cell pressure, and initiated the recording of absorbance readings. Three successive absorbance readings were taken for the analytical wavelength of interest. The average of the three successive readings was used as a single analysis in subsequent calculations, substantially reducing analytical variability.

Samples were collected from the exposure plenum and the primate helmets during the pretest validation phase to determine the test substance concentration uniformity. After determining the concentration in the helmets was equal to the concentration in the exposure plenum, only the plenum was sampled during the animal exposures. Samples were collected at least twice per hour during the animal exposures.

2.4.5 Instrument Calibration

Calibration of the infrared spectrophotometer was based upon the injection of measured amounts of the respective test substances into the calibration loop of the IR cell. For the ethyl acrylate calibration, liquid ethyl acrylate was injected into the cell to give nominal concentrations of 19.5, 39, 78, and 117 ppm (0.5, 1, 2, and 3 μL injected, respectively). For the acrylic acid

calibration, liquid acrylic acid was injected into the cell to give nominal concentrations of 15.8, 31.6, 63.2, and 126.4 ppm (0.25, 0.5, 1, and 2 μL injected, respectively).

For each calibration, a control chart was developed with control limits determined from the multipoint calibration for a single point on the curve. The limit of acceptability was defined by the Study Director as 10 percent of the mean value of all injections for that point. During the study, the IR was challenged daily with a zero and a single calibration concentration. The results of the daily calibration check were compared immediately with the control chart limits before proceeding with the animal exposures.

2.4.6 Pre-Exposure System Validation

Prior to the start of exposures the system concentration uniformity was evaluated for each test compound. Additionally, a trial run was completed for each test compound to verify the readiness of the generation and exposure system.

2.5 Experimental Animals

A total of 15 Cynomolgus monkeys were required for the study. These animals were originally obtained from Charles River Primates, Inc. The animals were wild captured, young mature males and females that were previously quarantined and used in nonlethal experimentation at Battelle. During the original quarantine period, the animals tested negative to three sequential intradermal tuberculin tests at approximately two week intervals. At least one clinical pathology screen and fecal examination for internal parasites was made during the original quarantine period.

Cynomolgus monkeys were chosen as the test system since an extensive biochemical and physiological data base for the Cynomolgus monkey is available. In addition, there have been numerous studies concerned with the inhalation of agents by non-human primates.

2.5.1 Animal Housing and Environmental Conditions

All animals were individually housed in stainless steel, wire bottom cages. All housing and care practices conformed to the requirements stated in the NIH "Guide for Care and Use of

Laboratory Animals" (National Institute of Health Publication No. 86-23). All environmental conditions conformed to the Standard Operating Procedures of the Battelle Animal Facility.

All animals were fed Purina Certified Monkey chow twice daily during the pretest period and the study. Monkey diets were supplemented with fresh fruit and/or other supplements. Animals were not fed prior to exposure on the day of treatment. Water was provided *ad libitum* to all animals at all times other than restraint and exposure. There were no known contaminants in the food or water supplied to the animals which would adversely effect the results of this study.

2.6 Animal Randomization and Identification

Animals used on study were obtained from the pool of animals maintained in the Battelle Animal Facility. All animals were allocated to treatment groups prior to the start of any exposures. Animals were assigned randomly to treatment groups and identified by animal tattoo as well as cage cards with individual study numbers. A cross reference list of tattoo numbers and study numbers was maintained in the study file.

2.7 Clinical Pathology and Health Evaluations

A clinical pathology screening was completed prior to the allocation of animals into treatment groups along with a general health evaluation by the veterinary staff and study director. The following clinical pathology evaluations were conducted on each of the samples collected:

Hematology
Erythrocyte count (RBC)
Hematocrit (HCT)
Hemoglobin (HGB)
Leukocyte cell count (WBC)
Mean corpuscular hemoglobin (MCH)
Mean corpuscular hemoglobin concentration (MCHC)
Mean corpuscular volume (MCV)
Platelet count (PLT)
WBC differential

Serum Chemistry
Alanine aminotransferase (SGPT) (ALT)
Albumin (ALB)
Alkaline phosphatase (ALP)
Aspartate aminotransferase (SGOT) (AST)
Blood urea nitrogen (BUN)
Chloride (Cl)
Creatinine (CRE)
Glucose (GLU)
Potassium (K)
Sodium (Na)
Total protein (TP)

2.8 Body Weights

Body weights were determined during the pretest period for all animals and again on the day of treatment prior to the exposure.

2.9 Clinical Observations

Clinical observations were recorded twice (once prior and once post-exposure) for each animal on the day of treatment.

2.10 Necropsy

After the end of the exposure, each monkey was anesthetized with Ketamine and Sodium Pentobarbital and then euthanized by exsanguination. Immediately after death the head was removed from the carcass and both nasal passages were flushed via the nasopharyngeal orifice with 100-200 mL of 10 percent neutral buffered formalin. The eyes, skin, brain, lower jaw and musculature were then removed and discarded. The remainder of the head was preserved in fixative.

In addition, the lungs were removed and fixed by trachea cannulation with 10 percent neutral buffered formalin at 30 cm fixative pressure for at least two hours. The trachea and lungs were then stored in fixative as well. No other tissues were saved.

All tissues were shipped to Dr. Jack Harkema at Michigan State University for sectioning and histopathologic evaluation.

2.11 Statistical Evaluation of the Data

Group means and standard deviations will be reported for data sets. No group to group comparisons or statistical analyses will be completed.

3.0 RESULTS

3.1 Pre-Exposure Health Evaluation Results

The results of the pre-exposure health evaluations revealed that all the animals were healthy and acceptable for study. The results of the pre-exposure clinical pathology screenings are detailed in Tables 1 through 3. Table 1 contains the individual animal cell count data. Table 2 contains the individual animal WBC differential count data, and Table 3 contains the individual animal serum chemistry values. These data were reviewed in addition to a general physical evaluation of the animals and all were determined to be acceptable for study.

3.2 Body Weight Determinations

Body weight data was collected on each animal once pretest and again prior to exposure. These data are detailed in Table 4. Two animals ((#103 and #503) were slightly heavier than the protocol listed range of 2 to 5 kilograms. All other animals were within the protocol specified range.

3.3 Clinical Observations

All animals in group one (six hour air control) were normal before and after exposure. In group two (three hour Ethyl Acrylate) all animals were normal at the start of exposure however one animal, #201, developed a mild nasal discharge shortly after the start of exposure and was observed with labored breathing. The exposure was halted while the neck dam on this animal was adjusted and the exposure was restarted. At the end of exposure, the animal still had a nasal discharge however all other clinical signs were normal. The remaining two animals in group two were normal; however, animal #202 was noted as having an increased rate of eye blinking. There were no abnormal clinical observations recorded for any of the animals in groups three through five before or after exposure.

3.4 Necropsy Results

Three of the fifteen animals observed at necropsy were noted with abnormal findings. Animal #301 was noted with some pleural adhesions to diaphragm near the right lung. Animal #303 was noted with multiple adhesions between the lung lobes and the visceral and parietal pleura. The lesions in both animals were thought to be parasitic in origin and not treatment related. Animal #501 was noted to have multiple yellow nodules with black specks, possibly mites. This finding was also not thought to be treatment related.

3.5 Pre-Exposure System Validation

3.5.1 Infrared Analyzer Calibration Results

The infrared analyzer was calibrated for each test compound during the pre-exposure validation phase. The results of the calibration using Ethyl Acrylate are listed in Table 5. The calibration curve ranged from 19.5 ppm to 117 ppm. The percent relative standard deviations of the data from the repeat injections at each calibration point were less than two percent at all levels indicating good reproducibility in the amount of material provided as the standard and the response of the instrument to the injection.

The data in Table 6 are the results of the instrument calibration with Acrylic Acid. The calibration curve for Acrylic Acid ranged from 15.8 to 126.4 ppm. The percent relative standard deviations of the data from the repeat injections were less than 5 percent again showing good reproducibility and instrument response.

A nonlinear relationship was observed with each test substance over the range covered by the calibration. This nonlinear relationship would have introduced a significant bias in estimating concentration from absorbance values using a linear calibration curve. In order to compensate for this non-linearity, the calibration data was fit to a quadratic function. The regression procedure PROC REG in the Statistical Analysis System (SAS®) software package was used to calculate the regression parameters.

3.5.2 System Uniformity and Trial Run Results

The exposure system was evaluated for the uniformity of the test atmosphere in the plenum and the three exposure helmets with each compound. Table 7 (EA) and Table 8 (AA) contain the data from these analyses. Each compound showed a uniform distribution throughout the exposure system. A comparison of the mean value from the samples collected in the plenum and the mean value for the samples collected within the different exposure helmets revealed that the different locations were within 10 percent of each other for both test compounds.

The pretest trial run data are contained in Table 9 (EA) and Table 10 (AA). The results indicated the generation system was operating at the target concentration and was stable over time. The mean test substance concentration value was 76.13 ppm (101.5 percent of target) for the Ethyl Acrylate and 80.98 ppm (108 percent of target) for the Acrylic Acid.

3.5.3 Test Substance Concentrations

The mean test substance concentration data for each of the exposure groups are listed in Table 11. Table 12 contains the individual concentration analyses by exposure group. The mean test substance concentration values were all within eight percent of the target concentration and the percent relative standard deviations were all less than 10 percent. The mean concentration values were also calculated in a mass to volume measurement (mg/L), as well. These values were calculated using the following formula:

$$C_{ppm} = C_{mg/L} * 22.414 \text{ X } 10^3/mw * T/273 * 760/P$$

where

C is the concentration
mw is the molecular weight of the compound
T is the temperature in degrees Kelvin (298)
P is standard pressure (760 mmHg)

3.5.4 Pulmonary Function Measurements

The individual animal mean respiration rate (b/min), tidal volume, and total inhaled volume are listed in Table 13. The mean respiration rates ranged from 33.2 (animal #202) to 61.0 (animal #103) breathes per minute. The mean tidal volume measurements ranged from 0.019 L (animal #301) to 0.049 L (animal #503). The total inhaled volumes for the three hour exposures ranged from 147.24 liters (animal #202) to 314.39 liters (animal #403). The total inhaled volumes for the six hour exposures ranged from 294.55 liters (animal #301) to 776.14 liters (animal #503).

3.5.5 Inhaled Dose Estimates

The inhaled dose was calculated for each animal based on it's body weight, mean test substance concentration value and total inhaled volume. The group mean inhaled dose values are listed in Table 14. The individual animal values are listed in Table 15. The individual animal inhaled doses for Ethyl Acrylate ranged from 13.9 mg/kg (animal #202) to 36.9 mg/kg (animal #302). The inhaled doses for Acrylic Acid ranged from 12.7 mg/kg (animal #401) to 35.2 mg/kg (animal #503).

4.0 DISCUSSION

The objective of this study was to evaluate the acute toxicity of Ethyl Acrylate (EA) and Acrylic Acid (AA) in monkeys after a single inhalation exposure. Five groups of three animals each were exposed via head-only inhalation exposure to one target concentration (75 ppm) of one of the two test compounds or filtered air (controls). Each animal received a single exposure of either three or six hour duration. Animals used on study were obtained from the pool of animals maintained in the Battelle Animal Facility and were found to be in good health prior to treatment.

The mean test substance concentration values were all within eight percent of the target concentration and the percent relative standard deviations were all less than 10 percent. The individual animal inhaled doses for Ethyl Acrylate ranged from 13.9 mg/kg (animal #202) to 36.9 mg/kg (animal #302). The inhaled doses for Acrylic Acid ranged from 12.7 mg/kg (animal #401) to 35.2 mg/kg (animal #503). All animals survived the exposures in good condition. No clinical signs of toxicity were noted and no treatment related findings were recorded during the gross pathological examination. All protocol required tissues were shipped to Dr. Jack Harkema for further evaluation.

The histopathologic data and evaluation will be added to the report at a later date by the Sponsor.

5.0 SPECIMEN STORAGE AND RECORD ARCHIVES

All remaining test substances will be returned to the Sponsor after acceptance of the final report. All original records required to reconstruct the conduct of the study will be shipped to the Sponsor after acceptance of the final report. A copy of the entire study file and final report will be archived at Battelle. Battelle will not retain any specimens or tissues.

6.0 ACKNOWLEDGMENTS

Members of the Battelle General Toxicology, Animal Resources, and Pathology Departments whose signatures appear in the report or in the study records are acknowledged for their participation in the conduct of the study. The names of the principal contributors in this study are listed below:

Principal Contributors

Name	Study Role	Department
Michael J. Brooker, B.S.	Study Director	General Toxicology
Russ Antel, A.S., VT, L.A.T.G.	Primary Technician	Animal Resources
Allen Singer, D.V.M., D.A.C.V.P., D.A.B.T	Study Pathologist	Pathology
Michael J. Ryan, D.V.M., Ph.D., D.A.B.T., D.A.C.V.P.	Clinical Pathologist	Pathology
Michael E. Placke, Ph.D., D.A.B.T.	Senior Program Manager	Preclinical Drug Development

Table 1. Pre-Exposure Individual Animal Cell Count Data for the Single Dose Inhalation Toxicity Study of Ethyl Acrylate and Acrylic Acid

Animal ID	WBC (10^3/mm^3)	HGB (g/dL)	HCT (%)	MCV (fL)	MCH (pg)	MCHC (g/dL)	Platelet (10^3/mm^3)	RBC (10^6/mm^3)
122-55M	5.6	11.6	36.8	61.3	19.3	31.5	350	6.01
53-283M	7.1	12.3	40.7	58.6	17.7	30.2	445	6.95
73-2M	15.7	10.7	34.3	63.8	19.9	31.2	298	5.38
73-32M	5.8	11.8	40.6	59.3	17.3	29.1	413	6.84
73-6M	6.3	12.0	38.4	57.7	18.0	31.3	569	6.65
73-410M	10.2	12.4	42.0	63.7	18.8	29.5	315	6.59
73-461M	2.3	12.7	41.0	60.7	18.8	31.0	296	6.75
30-537F	17.3	8.8	27.4	56.4	18.1	32.1	323	4.85
30-544F	9.1	10.7	34.1	59.8	18.7	31.4	268	5.71
53-198F	5.2	9.5	31.6	52.4	15.7	30.1	254	6.04
53-203F	9.6	11.0	36.4	57.2	17.3	30.2	623	6.36
53-295F	3.4	10.0	33.8	56.9	16.8	29.6	357	5.94
63-290F	3.8	9.5	30.5	65.4	20.4	31.1	356	4.66
63-362F	3.4	10.6	35.0	57.6	17.4	30.3	253	6.08
63-372F	8.6	11.5	36.4	60.3	19.1	31.6	431	6.03

Table 2. Pre-Exposure Individual Animal WBC Differential Data for the Single Dose Inhalation Toxicity Study of Ethyl Acrylate and Acrylic Acid

Animal ID	Segmented Neutrophils (%)	Band Neutrophils (%)	Lymphocytes (%)	Monocytes (%)	Eosinophils (%)	Basophils (%)	Nucleated RBC's (nRBC/100WBC)	Reticulocytes (%)
122-55M	51	0	30	15	4	0	0	0.4
53-283M	25	0	66	7	2	0	0	0.1
73-2M	80	0	8	12	0	0	0	0.1
73-32M	30	0	62	5	2	1	0	0.1
73-6M	37	0	51	6	5	0	0	0.1
73-410M	53	0	38	9	0	0	0	0.3
73-461M	38	0	47	4	10	1	0	0.2
30-537F	57	0	38	5	0	0	0	1.3
30-544F	28	0	65	3	4	0	0	0.5
53-198F	22	0	71	4	3	0	0	0.2
53-203F	65	0	22	8	5	0	0	0.3
53-295F	15	0	68	14	2	0	0	0.2
63-290F	36	0	51	4	6	0	0	0.6
63-362F	58	0	36	1	3	2	0	0.1
63-372F	52	0	45	1	2	0	0	0.3

Table 3. Pre-Exposure Individual Animal Serum Chemistry Data for the Single Dose Inhalation Toxicity Study of Ethyl Acrylate and Acrylic Acid

Animal ID	ALP (IU/L)	AST (IU/L)	ALT (IU/L)	Total Protein (g/dL)	Albumin (g/dL)	Glucose (mg/dL)	BUN (mg/dL)	Creatine (mg/dL)	Na (mEq/L)	K (mEq/L)	Chloride (mEq/L)
122-55M	603	33	29	6.6	3.9	61	19	1.1	148	3.8	107
53-283M	1250	22	45	7.5	4.8	62	17	0.8	148	3.5	111
73-2M	759	23	41	7.1	4.0	80	15	1.2	144	3.5	101
73-32M	1420	34	22	7.3	4.5	47	20	0.9	150	4.0	107
73-6M	1126	21	27	6.9	4.5	57	21	0.8	149	3.5	109
73-410M	2025	30	52	7.1	4.1	55	22	0.8	152	3.3	114
73-461M	1425	22	44	7.1	4.2	56	20	1.0	146	3.4	108
30-537F	1531	17	40	6.6	2.7	53	10	0.8	147	3.2	108
30-544F	317	24	43	7.7	4.1	72	17	0.8	147	2.9	109
53-198F	1093	18	15	6.5	4.0	68	16	0.7	148	3.6	111
53-203F	1120	22	25	6.3	4.1	58	20	0.8	148	3.9	110
53-295F	571	26	19	6.6	3.9	56	20	0.8	147	3.4	114
63-290F	705	32	65	7.2	4.2	54	19	0.7	148	3.5	109
63-362F	919	38	50	7.6	4.3	58	15	0.8	147	3.7	112
63-372F	630	22	31	7.4	4.6	62	20	0.9	148	3.6	109

Table 4. Individual Animal Body Weight Data for the Single Dose Inhalation Toxicity Study of Ethyl Acrylate and Acrylic Acid

Animal ID	Animal Study Number	Exposure Date	Body Weight (kg)
73-461M	101	12/14/94	4.06
73-32M	102	12/14/94	3.97
122-55M	103	12/14/94	5.26
53-203F	201	12/16/94	2.87
63-362F	202	12/16/94	3.17
53-295F	203	12/16/94	3.13
63-372F	301	12/19/94	2.94
63-290F	302	12/19/94	2.75
30-537F	303	12/19/94	2.58
53-283M	401	12/20/94	4.04
53-198F	402	12/20/94	2.73
73-6M	403	12/20/94	4.81
30-544F	501	12/21/94	2.65
73-410M	502	12/21/94	3.98
73-2M	503	12/21/94	5.07

Table 5. Ethyl Acrylate Calibration Data for the Single Dose Inhalation Toxicity Study of Ethyl Acrylate and Acrylic Acid

Amount Injected (μL)	Calculated Concentration (ppm)	Absorb. 1	Absorb. 2	Absorb. 3	Mean Absorb.	Grand Mean	Standard Deviation	Percent Rel. Std. Deviation
0.5	19.5	0.3202	0.3204	0.3206	0.3204			
0.5	19.5	0.3189	0.3203	0.3201	0.3198	0.3176	0.0044	1.38
0.5	19.5	0.3122	0.3127	0.3125	0.3125			
1	39	0.5028	0.5036	0.5024	0.5029			
1	39	0.5079	0.5076	0.5085	0.5080	0.5056	0.0026	0.51
1	39	0.5054	0.5062	0.5063	0.5060			
2	78	0.6808	0.6805	0.6815	0.6809			
2	78	0.6835	0.6852	0.6853	0.6847	0.6827	0.0019	0.28
2	78	0.6817	0.6833	0.6825	0.6825			
3	117	0.7979	0.7984	0.8002	0.7988			
3	117	0.7953	0.7955	0.7960	0.7956	0.7999	0.0035	0.43
3	117	0.8031	0.8012	0.8007	0.8017			
3	117	0.8053	0.8021	0.8031	0.8035			

Table 6. Acrylic Acid Calibration Data for the Single Dose Inhalation Toxicity Study of Ethyl Acrylate and Acrylic Acid

Amount Injected (μL)	Calculated Concentration (ppm)	Reference Absorb.	Absorb. 1	Absorb. 2	Absorb. 3	Mean Absorb.	Grand Mean	Standard Deviation	Percent Rel. Std. Deviation
0.25	15.8	0.0008	0.0979	0.0977	0.0974	0.0977			
0.25	15.8	0.0012	0.1050	0.1049	0.1046	0.1048	0.0994	0.0047	4.77
0.25	15.8	0.0028	0.0956	0.0961	0.0956	0.0958			
0.5	31.6	0.0051	0.1984	0.1978	0.1969	0.1977			
0.5	31.6	0.0055	0.2102	0.2091	0.2094	0.2096	0.2038	0.0060	2.92
0.5	31.6	0.0053	0.2041	0.2039	0.2040	0.2040			
1	63.2	0.0120	0.3517	0.3511	0.3506	0.3511			
1	63.2	0.0124	0.3511	0.3515	0.3513	0.3513	0.3530	0.0031	0.88
1	63.2	0.0124	0.3574	0.3567	0.3556	0.3566			
2	126.4	0.0408	0.5740	0.5750	0.5737	0.5742			
2	126.4	0.0401	0.5740	0.5728	0.5739	0.5736	0.5724	0.0026	0.45
2	126.4	0.0389	0.5702	0.5685	0.5699	0.5695			

Table 7. Ethyl Acrylate Concentration Uniformity Data for the Single Dose Inhalation Toxicity Study of Ethyl Acrylate and Acrylic Acid

Sample ID Number (12/9/94)	Sample Location	Concentration (ppm)
14	Plenum	77.76
15	Helmet - 1	72.60
16	Plenum	78.17
17	Helmet - 2	76.59
18	Plenum	78.52
19	Helmet - 3	77.84
20	Plenum	75.83
	Plenum Mean (Std. Dev.)	77.57 (1.2)
	Helmet Mean (Std. Dev.)	75.68 (2.7)

Table 8. Acrylic Acid Concentration Uniformity Data for the Single Dose Inhalation Toxicity Study of Ethyl Acrylate and Acrylic Acid

Sample ID Number (12/12/94)	Sample Location	Concentration (ppm)
14	Plenum	81.21
15	Helmet - 1	71.03
16	Plenum	80.34
17	Helmet - 2	75.35
18	Plenum	80.15
19	Helmet - 3	79.80
20	Plenum	81.98
	Plenum Mean (Std. Dev.)	80.92 (0.8)
	Helmet Mean (Std. Dev.)	75.39 (4.4)

Table 9. Ethyl Acrylate Pretest Trial Run Data for the Single Dose Inhalation Toxicity Study of Ethyl Acrylate and Acrylic Acid

Sample ID Number (12/9/94)	Sample Location	Concentration (ppm)
14	Plenum	77.76
16	Plenum	78.17
18	Plenum	78.52
20	Plenum	75.83
21	Plenum	75.51
22	Plenum	74.64
23	Plenum	74.38
24	Plenum	74.23
	Mean (% Rel. Std. Dev.)	76.13 (2.3)
	Percent of Target	101.5

Table 10. Acrylic Acid Pretest Trial Run Data for the Single Dose Inhalation Toxicity Study of Ethyl Acrylate and Acrylic Acid

Sample ID Number (12/12/94)	Sample Location	Concentration (ppm)
14	Plenum	81.21
16	Plenum	80.34
18	Plenum	80.15
20	Plenum	81.98
21	Plenum	81.89
22	Plenum	79.93
23	Plenum	81.35
	Mean (% Rel. Std. Dev.)	80.98 (1.0)
	Percent of Target	108.0

Table 11. Mean Test Substance Concentration Data for the Single Dose Inhalation Toxicity Study of Ethyl Acrylate and Acrylic Acid

Group Number	Compound	Duration (hrs)	Mean Concentration (ppm)	Standard Deviation	% Relative Standard Deviation	Percent of Target	Calculated Concentration (mg/L)
1	Air Control	6	--	--	--	--	0
2	EA	3	73.37	6.56	8.94	97.8	0.30
3	EA	6	76.28	1.85	2.42	101.7	0.31
4	AA	3	80.51	3.61	4.48	107.3	0.24
5	AA	6	78.06	3.12	4.00	104.1	0.23

Table 12. Test Substance Concentration Data (Individual Analyses) for the Single Dose Inhalation Toxicity Study of Ethyl Acrylate and Acrylic Acid

Sample Collected	Ethyl Acrylate Three Hour Exposure Concentration (ppm)	Ethyl Acrylate Six Hour Exposure Concentration (ppm)	Acrylic Acid Three Hour Exposure Concentration (ppm)	Acrylic Acid Six Hour Exposure Concentration (ppm)
1	76.88	79.49	74.90	73.93
2	76.51	79.88	81.68	76.64
3	75.95	77.23	83.40	78.48
4	75.23	76.32	84.93	77.67
5	75.60	75.64	78.84	78.71
6	60.03	74.60	79.28	83.02
7		76.15		80.81
8		76.62		82.72
9		75.30		78.51
10		75.11		78.03
11		75.30		75.04
12		73.70		73.19
Mean	73.37	76.278	80.51	78.06

Table 12. Test Substance Concentration Data (Individual Analyses) for the Single Dose Inhalation Toxicity Study of Ethyl Acrylate and Acrylic Acid

Sample Collected	Ethyl Acrylate Three Hour Exposure Concentration (ppm)	Ethyl Acrylate Six Hour Exposure Concentration (ppm)	Acrylic Acid Three Hour Exposure Concentration (ppm)	Acrylic Acid Six Hour Exposure Concentration (ppm)
1	76.88	79.49	74.90	73.93
2	76.51	79.88	81.68	76.64
3	75.95	77.23	83.40	78.48
4	75.23	76.32	84.93	77.67
5	75.60	75.64	78.84	78.71
6	60.03	74.60	79.28	83.02
7		76.15		80.81
8		76.62		82.72
9		75.30		78.51
10		75.11		78.03
11		75.30		75.04
12		73.70		73.19
Mean	73.37	76.278	80.51	78.06

Table 13. Individual Animal Pulmonary Function Data for the Single Dose Inhalation Toxicity Study of Ethyl Acrylate and Acrylic Acid

Animal Number	Mean Respiration Rate (b/min)	Mean Tidal Volume (L)	Total Inhaled Volume (L)
101	55.4	.032	623.18
102	38.0	.028	387.58
103	61.0	.038	770.92
201	42.4	.021	154.13
202	33.2	.024	147.24
203	53.0	.026	251.72
301	44.2	.019	294.55
302	40.1	.023	327.14
303	34.5	.025	295.68
401	44.4	.028	214.23
402	55.6	.023	214.37
403	43.4	.042	314.39
501	33.6	.029	309.83
502	39.4	.028	371.87
503	45.9	.049	776.14

Table 14. Group Mean Inhaled Dose Estimates for the Single Dose Inhalation Toxicity Study of Ethyl Acrylate and Acrylic Acid

Group Number	Compound	Duration (hrs)	Mean Inhaled Dose (mg/kg)	Standard Deviation	% Relative Standard Deviation
1	Air Control	6	--	--	--
2	EA	3	18.0	5.37	29.8
3	EA	6	34.5	3.03	8.77
4	AA	3	15.7	3.05	19.4
5	AA	6	27.9	6.90	24.7

Table 15. Individual Animal Estimated Inhaled Dose Data for the Single Dose Inhalation Toxicity Study of Ethyl Acrylate and Acrylic Acid

Animal ID	Body Weight (kg)	Test Compound	Concentration (mg/L)	Total Inhaled Volume (L)	Total Inhaled Dose (mg/kg)
101	4.06	Air	0.00	623.18	0.0
102	3.97	Air	0.00	387.58	0.0
103	5.26	Air	0.00	770.92	0.0
201	2.87	EA	0.30	154.13	16.1
202	3.17	EA	0.30	147.24	13.9
203	3.13	EA	0.30	251.72	24.1
301	2.94	EA	0.31	294.55	31.1
302	2.75	EA	0.31	327.14	36.9
303	2.58	EA	0.31	295.68	35.5
401	4.04	AA	0.24	214.23	12.7
402	2.73	AA	0.24	214.37	18.8
403	4.81	AA	0.24	314.39	15.7
501	2.65	AA	0.23	309.83	26.9
502	3.98	AA	0.23	371.87	21.5
503	5.07	AA	0.23	776.14	35.2

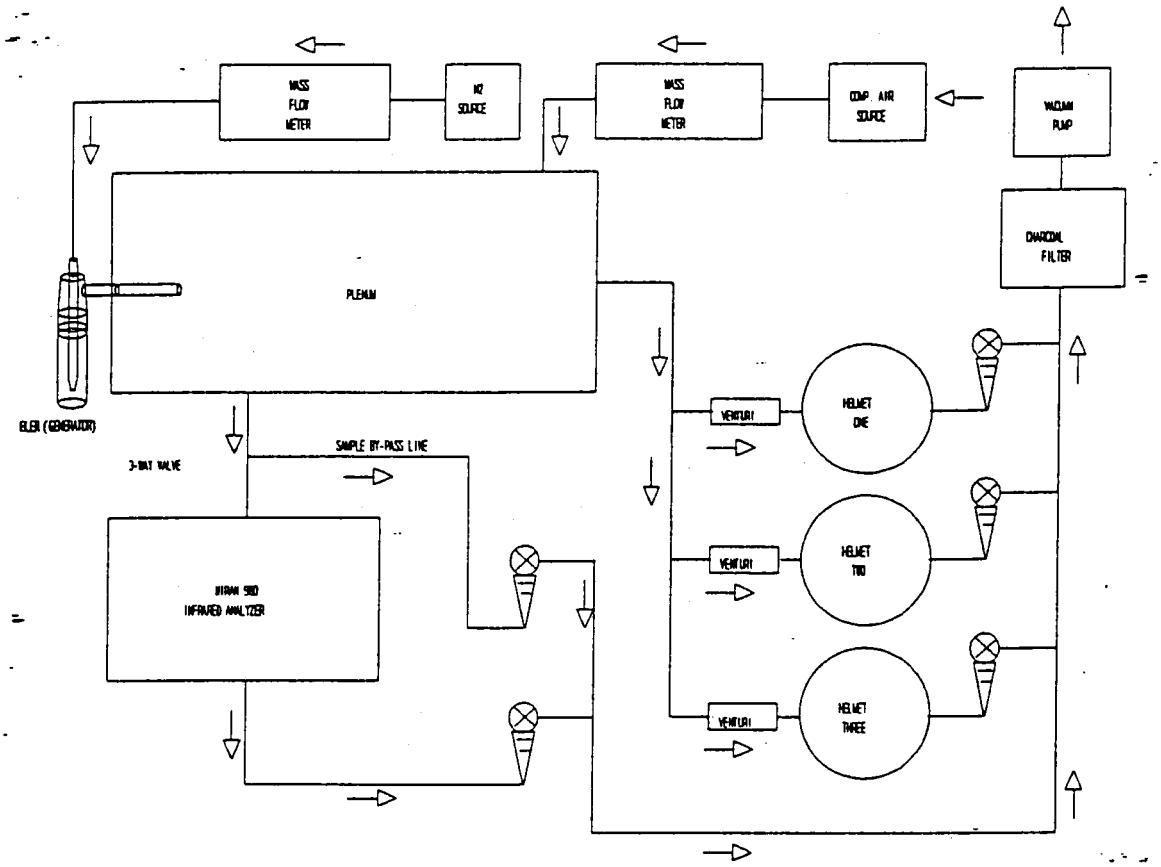


Figure 1. Schematic Diagram of Exposure System

APPENDIX A

STUDY PROTOCOL, AMENDMENTS, AND DEVIATIONS

Sponsor Study No.: 94P-227
Battelle Study No.: SC940138
November 22, 1994

STUDY PROTOCOL

SINGLE DOSE INHALATION TOXICITY STUDY OF ETHYL ACRYLATE (EA) AND ACRYLIC ACID (AA)

Sponsor's Test Article: Ethyl Acrylate (EA) and Acrylic Acid (AA)

Prepared For: Rohm and Haas Co.

Battelle

. . . Putting Technology To Work

SINGLE DOSE INHALATION TOXICITY STUDY OF ETHYL ACRYLATE (EA) AND ACRYLIC ACID (AA)

Sponsor's Test Article: Ethyl Acrylate (EA) and Acrylic Acid (AA)

APPROVED, BATTELLE:

Michael J. Brooker — 11/22/94

Michael Brooker, B.S.
Battelle Study Director — Date

Kathleen C. Reed — 11-22-94

Quality Assurance — Date

APPROVED, SPONSOR:

Clay B. Frederick — 11/28/94

Clay B. Frederick, Ph.D.
Project Monitor — Date

(Signature indicates that the activities in this protocol do not unnecessarily duplicate experiments on animal subjects.)

SINGLE DOSE INHALATION TOXICITY STUDY OF ETHYL ACRYLATE (EA) AND ACRYLIC ACID (AA)

1.0 TITLE

Single Dose Inhalation Toxicity Study of Ethyl Acrylate (EA) and Acrylic Acid (AA)

2.0 OBJECTIVE

The objective of this study is to evaluate the acute toxicity of AA and EA in monkeys after a single inhalation exposure.

3.0 ROUTE AND DURATION OF ADMINISTRATION

A single (either 3-hour or 6-hour) head-only inhalation exposure to one target vapor concentration of each compound; plus an air control.

4.0 SPONSOR

Rohm & Haas
727 Norristown Rd.
Spring House, PA 19477

5.0 TESTING LABORATORY

A. Facility

Battelle Columbus Division (BCD)
505 King Avenue
Columbus, Ohio 43201-2693

B. Study Team

Study Director: Mr. Michael Brooker
Study Pathologist: To be determined (TBD)
Study Clinical Pathologist: Dr. Michael Ryan
Laboratory Animal Veterinarian: Dr. Tracy Peace

6.0 TENTATIVE SCHEDULE

- Experimental Start Date: Week of 11/21/94
- Termination Date: To be determined

7.0 TEST SYSTEM

A. Species: Monkey

B. Strain: *Macaca fascicularis* (Cynomolgus)

C. Supplier: Charles River Primates, Inc.

D. Age and Sex: Young mature males and females; wild captured, exact age unknown; serologically negative for Herpes Simian B Virus

E. Weight of animals at initiation of treatment: 2-5 kg.

F. Number of animals in study: 15

G. Test System Justification: Considerable scientific documentation of the Cynomolgus monkey as a predictive animal model for humans exists. An extensive biochemical and physiological data base for the Cynomolgus monkey is available. In addition there have been numerous studies concerned with the inhalation of agents by non-human primates.

8.0 ANIMAL CARE, HOUSING, AND ENVIRONMENTAL CONDITIONS

A. Quarantine and Acceptance

1. a. The Cynomolgus monkeys (2-5 kg) have been supplied by Charles River Primates and serologically screened for a negative titer against Herpes Simian B virus prior to shipment.

   b. Within 1 week after arrival all animals were examined by a veterinarian. This included a complete physical examination, in conjunction with the first TB test and the recording of body weight.

   c. All animals received and tested negative to three sequential intradermal tuberculin tests at approximately two week intervals.

   d. At least one clinical pathology screen and fecal examination for intestinal parasites was made during quarantine. Clinical pathology screen will be repeated prior to exposure and include the following parameters.

Hematology
Erythrocyte count (RBC)
Hematocrit (HCT)
Hemoglobin (HGB)
Leukocyte cell count (WBC)
Mean corpuscular hemoglobin (MCH)
Mean corpuscular hemoglobin concentration (MCHC)
Mean corpuscular volume (MCV)
Platelet count (PLT)
WBC differential

Serum Chemistry
Alanine aminotransferase (SGPT) (ALT)
Albumin (ALB)
Alkaline phosphatase (ALP)
Aspartate aminotransferase (SGOT) (AST)
Blood urea nitrogen (BUN)
Chloride (Cl)
Creatinine (CRE)
Glucose (GLU)
Potassium (K)
Sodium (Na)
Total protein (TP)

2. The animals will be individually housed, in stainless steel, wire-bottom cages. The cage space will meet the requirements stated in the NIH "Guide for the Care and Use of Laboratory Animals" (National Institutes of Health Publication No. 86-23), as specified by the facility standard operating procedure. All environmental conditions will conform to facility standard operating procedures (light/dark cycle, temperature, humidity, and fresh air exchanges).

3. Acceptability for Study--Animals suitable for study will be selected by the Study Director and Study Veterinarian. They will be in good physical condition based on appearance, and demonstration of normal hematology and serum chemistry values.

4. Animal Identification--Animals will be uniquely identified by tattoos in addition to cage card.

5. Animals will be accustomed to restraint and exposure procedure prior to the initiation of treatment.

B. Feed

Monkeys will be fed Purina Certified monkey Chow 5048® (approximately six-eight biscuits) twice daily during the pretest period and the study. Monkey diets will be supplemented with fresh fruit and/or other supplements. Animals will not be fed biscuits or supplements prior to dosing. No contaminants are known to be present in the feed or supplements which would interfere with or affect the results of the study. Certified analyses of the Purina Monkey Chow 5048® will be retained in the Battelle Animal Resources Facility and be available for inspection upon request.

C. Water

Water will be provided *ad libitum* except during restraint. The City of Columbus municipal water supply will be used. The quality of the water will meet the standards set by the Columbus Water Department and Ohio Environmental Protection Agency. Periodic chemical analysis and microbial analysis of the water will be performed at Lancaster Laboratories (Lancaster, PA). Results of these analyses are kept on file at Battelle. There are no suspected containments in the water which could adversely affect the results of this study.

D. Animal Randomization

Animals will be allocated to treatment groups prior to exposure. Animals will be assigned randomly to treatment groups.

9.0 TEST ARTICLE

A log of receipt and use of the Sponsor's test article will be maintained.

A. Test Article

1. Ethyl Acrylate (EA) and Acrylic Acid (AA)

2. Supplier: Sponsor or specified by the Sponsor.

3. Storage Conditions: To be specified by the Sponsor.

4. Identity, Purity and Stability of the test article will be the responsibility of the Sponsor.

10.0 AEROSOL GENERATION AND EXPOSURE SYSTEMS

A. Test Article Generation

The test articles will be generated from a liquid state. Initially an inert gas (N_2) will be entrained into the liquid phase of the test article in a closed container. The head space vapor will be drawn off and allowed to equilibrate in a central plenum before dilution and transport to the exposure units.

Test article concentrations will be monitored using an Infrared Spectrophotometer such as a Miran 980 or similar device. A multipoint calibration curve will be developed during the pretest period to monitor concentrations for each test compound.

B. Exposure System

Each animal will be placed in a head-only exposure unit designed to provide a fresh supply of the test atmosphere at an adequate flow rate to provide minimum oxygen requirements of the animal. The actual exposure system and primary containment system will be a whole-head hood with an air dam encompassing the neck of the primate. The hood will be clear allowing the animal complete visualization of his environment. The animal exposure hood will have a continuous bias flow of approximately 7 to 10 L/min. Test atmosphere will be drawn from the generator to test subjects, and the Miran Infrared Analyzer. Test atmosphere will enter near the top and be exhausted near the bottom of the helmet.

11.0 PHYSICAL AND CHEMICAL CHARACTERIZATIONS OF THE TEST ATMOSPHERE

Before the animal exposures begin, satisfactory achievement of vapor concentrations encompassing the anticipated range will be documented for the test article.

A. Pre-Study Characterization of Test Atmospheres

1. Generation and analysis of the vapor concentration will be performed to characterize the exposure systems.

2. Uniformity of dose between helmet units will be determined prestudy using the Infrared Analyzer. A single reference location will be established and all helmet locations will be compared to the reference location during pretest validation.

B. Monitoring During Animal Exposures

Concentration of test vapors will be monitored using the Infrared Analyzer at least twice per hour from the reference location as established in the pretest validation, for the duration of exposure.

C. Target Vapor Concentrations

The inhalation exposure will be designed to expose animals to a vapor of the test article. The following table lists the target vapor concentrations.

Group Number	Test Article	No. of Animals	Vapor Conc. (ppm)	Exposure Duration (Hour)
1	Air Control	3	0	6
2	EA	3	75	3
3	EA	3	75	6
4	AA	3	75	3
5	AA	3	75	6

D. Dosimetry Measurements

Venturi's will be installed in the delivery line to each exposure helmet. The measurement of the airflow through the venturi during exposure will be used to determine the total inhaled volume of air for each animal during the exposure.

12.0 EXPERIMENTAL DESIGN

Five groups of three animals each will be exposed via head-only inhalation exposure to one target concentration level of each test compound or an air control.

A. Inhalation Exposures

Each animal will receive either a single three-hour or six-hour exposure at the target dose concentration described in Section 11.0 C.

B. Clinical Observation

Clinical observations will be recorded twice (once prior and once post-exposure) on Study Day 1.

C. Body Weight

Body weight will be determined for all animals once pretest and prior to exposure on Study Day 1.

D. Necropsy and Tissue Processing

After the end of the exposures, each monkey will be anesthetized with ketamine and sodium pentobarbital and then euthanatized by exsanguination via the femoral arteries.

Immediately after death, the head will be removed from the carcass and both nasal passages will be flushed via the nasopharyngeal orifice with 100-200 mL of 10% neutral buffered formalin. After this intranasal flush, the eyes, skin, brain, lower jaw and musculature will be removed from the head and discarded. The head will be immersed in a large volume of the same fixative for at least 24 hours until further processing.

In addition, the lungs will be removed, the trachea will be cannulated and the lungs will be suspended and fixed by tracheal infusion of 10% neutral buffered formalin at 30 cm fixative pressure for at least 2 hours. After intratracheal infusion the cannula will be removed and the proximal aspect of the trachea will be tied off by string or clamped and the trachea and lungs will be stored in a large volume of the same fixative until further tissue processing. No other tissues will be saved.

All tissues will be shipped to Dr. Jack R. Harkema for sectioning and histopathological evaluation:

Michigan State University
Dept. of Pathology
A54 Veterinary Medical Center
East Lansing, MI 48824-1314
Phone: (517) 353-8627
Fax: (517) 355-2152

13.0 REPORTING

A draft report of this study will be submitted within 60 days after completion of the in-life phase. The report will include, but not be limited to the following:

- Objectives and procedures as stated in the approved protocol.
- Description of the test article generation and exposure system and the operating conditions.
- Performance of the exposure system (i.e., chemical and physical data).
- Statistical methods employed and results obtained.

- Discussion of the results.
- Deviations from the laboratory's SOPs or the approved protocol, if any.
- No data or interpretation from the histopathological evaluation will be included in the final report.

Final Report

Final report will be submitted to Sponsor within 30 days of receipt of the Sponsor's comments on the draft report.

14.0 STUDY CONDUCT, STORAGE OF STUDY MATERIALS, AND RECORDS RETENTION

This protocol will be the controlling document in case of discrepancies between the Protocol and SOPs. All remaining test articles will be returned to the Sponsor or their designated archive facility upon completion of the final report. All original records required to reconstruct the conduct of the study will be shipped to the Sponsor for archival in the Rohm & Haas archives. A copy of all data and the final report will be retained in the Battelle archives. Battelle will not retain any specimens or tissues.

15.0 STUDY CHANGES

If after the study is underway, it becomes necessary to change the approved protocol, verbal agreement to make this change will be made between the study director and the Sponsor's representative. As soon as practical, the change and reasons for it will be formally approved by the Study Director and Sponsor's representative in writing and amended to the study protocol. This document will be added to the study file.

16.0 STATISTICAL ANALYSIS

Only means and standard deviations will be reported for animal group data. No statistical comparisons will be conducted between expsoure groups.

17.0 GOOD LABORATORY PRACTICES COMPLIANCE

This study will be conducted in accordance with the U.S. Environmental Protection Agency Good Laboratory Practice (GLP) Standards (40 CFR Part 792). The study will be conducted in compliance with Battelle Standard Operating Procedures (SOPs). Maintenance and use of animals will be in accordance with the guideline contained in NIH publication 86-23 (Guide for the Care and Use of Laboratory Animals).

Study No.: SC940138

PROTOCOL AMENDMENT NUMBER 1

Effective Date: December 14, 1994

To: The Single Dose Inhalation Toxicity Study of Ethyl Acrylate and Acrylic Acid

1. Part to be Ammended: Section 5.0 B, Study Team, Page 3.

   Add the following statement to the section:

   Study Pathologist: Dr. Allen Singer

   Reason for the Ammendment:

   At the time the protocol was signed, the study pathologist had not been assigned to the study team.

APPROVED BY:

Michael J. Brooker
Study Director

2/14/95
Date

Clay B. Frederick, Ph.D., D.A.B.T.
Project Monitor

2/15/95
Date

Study No.: SC940138

PROTOCOL AMENDMENT NUMBER 2

Effective Date: March 20, 1995

To: The Single Dose Inhalation Toxicity Study of Ethyl Acrylate and Acrylic Acid

1. Part to be Amended: Section 7.0 F, Page 4.

   Change the section to read:

   Number of animals on study: 16

2. Part to be Amended: Section 12.0 Experimental Design, Page 8.

   Add Section 12.0 E. Image Analysis Animal, to the protocol:

A single animal will be used to collect image analysis data and define the parameters for tissue sectioning. This animal will not be exposed via the head-only inhalation system. The animal will be anesthetized, euthanized and the head processed as described in section 12.0 D, then wrapped in formalin soaked cotton, placed in a plastic bag and shipped. This animal will be shipped to:

Dr. Kevin Morgan
CIIT
6 Davis Drive
Research Triangle Park, NC, 27709
Phone 919-558-1297

No other tissues will be saved for this single animal. Relevant animal history data (as defined by this protocol) for this animal will be maintained in the study file.

Reason For Changes: Sponsor requested the changes be made to the protocol.

APPROVED BY:

Michael J. Brooker
Study Director

3/25/95
Date

Clay B. Frederick, Ph.D., D.A.B.T.
Project Monitor

3/29/95
Date

PROTOCOL DEVIATION REPORT

for

The Single Dose Inhalation Toxicity Study of Ethyl Acrylate and Acrylic Acid
(Study #: SC940138)

Date of deviation: November 22, 1994

Nature of deviation:

Two animals did not conform to the standards described in the protocol in Section 8.0 A. Quarantine and Acceptance.

Cause of deviation:

Animals #30-544 and #30-537 received a physical examination 10 days after arrival which was not in the first week after arrival as stated in the protocol.

Impact on the Study:

None.

Corrective action:

Protocol Deviation added to study file.

Approved by: Michael J. Brooker Date: 3/24/95
Study Director

Distribution: Study file (original)

PROTOCOL DEVIATION REPORT

for

Single Dose Inhalation Toxicity
Study of Ethyl Acrylate and Acrylic Acid

(Study #: SC940138)

Date of deviation: 12/14/94, 12/21/94

Nature of deviation:

Two animals were outside of the protocol specified weight range on their respective exposure day.

Cause of deviation:

Animals were slightly larger than anticipated when the weight range was defined.

Impact on the study:

None. Animals were weighed as required by the protocol and the total inhaled dosages were calculated based on the current animal body weight.

Corrective action:

None.

Approved by: Michael J. Brooker Date: 2/1/95
Study Director

Distribution: Study file (original)

PROTOCOL DEVIATION REPORT

for

The Single Dose Inhalation Toxicity Study of Ethyl Acrylate and Acrylic Acid
(Study #: SC940138)

Date of deviation: December 13 and 16, 1995

Nature of deviation:

Three animals did not conform to the standards described in the protocol in Section 7.0 D, Age and Sex.

Cause of deviation:

Animals 30-537, 30-544, and 122-55 tested positive for Herpes B virus.

Impact on the Study:

None.

Corrective action:

Protocol Deviation added to study file along with documentation of test results.

Approved by: Michael J. Brooks Date: 2/15/95
Study Director

Distribution: Study file (original)

APPENDIX B

MIRAN 980 CALIBRATION DATA

Table B-1. Individual Data Points for the Miran 980 Calibration with Ethyl Acrylate for the Single Dose Inhalation Toxicity Study of Ethyl Acrylate and Acrylic Acid

Injection Amount (μL)	Calculated Conc. (ppm)	Reference Absorb.	Absorb. 1	Absorb. 2	Absorb. 3	Mean Absorb.
0	0	0.0013	-0.0002	0.0007	0.0007	0.0004
0	0	0.0011	0.0018	0.0015	0.0020	0.0018
0	0	0.0014	0.0019	0.0023	0.0019	0.0020
0.5	19.5	0.0020	0.3202	0.3204	0.3206	0.3204
0	0	0.0009	0.0014	0.0021	0.0016	0.0017
0.5	19.5	0.0020	0.3189	0.3203	0.3201	0.3198
0	0	0.0010	0.0007	0.0010	0.0009	0.0009
0.5	19.5	0.0020	0.3122	0.3127	0.3125	0.3125
0	0	-0.0001	-0.0057	-0.0056	-0.0056	-0.0056
1	39	0.0013	0.5028	0.5036	0.5024	0.5029
0	0	0.0002	-0.0055	-0.0052	-0.0052	-0.0053
1	39	0.0024	0.5079	0.5076	0.5085	0.5080
0	0	0.0007	-0.0054	-0.0047	-0.0051	-0.0051
1	39	0.0029	0.5054	0.5062	0.5063	0.5060
0	0	0.0010	0.0037	0.0041	0.0038	0.0039
2	78	0.0051	0.6808	0.6805	0.6815	0.6809
0	0	0.0012	-0.0006	0.0004	-0.0001	-0.0001
0	0	0.0014	-0.0021	-0.0013	-0.0017	-0.0017
2	78	0.0050	0.6835	0.6852	0.6853	0.6847
0	0	0.0012	-0.0008	-0.0007	-0.0010	-0.0008
2	78	0.0058	0.6817	0.6833	0.6825	0.6825
0	0	0.0016	-0.0037	-0.0034	-0.0035	-0.0035
3	117	0.0075	0.7979	0.7984	0.8002	0.7988
0	0	0.0012	0.0014	0.0023	0.0017	0.0018
3	117	0.0076	0.7953	0.7955	0.7960	0.7956
0	0	0.0020	-0.0032	-0.0023	-0.0030	-0.0028
3	117	0.0076	0.8031	0.8012	0.8007	0.8017
0	0	0.0024	-0.0047	-0.0044	-0.0047	-0.0046
3	117	0.0083	0.8053	0.8021	0.8031	0.8035
0	0	0.0021	-0.0052	-0.0048	-0.0047	-0.0049

Table B-2. Individual data points for the Miran 980 calibration with Acrylic Acid for the Single Dose Inhalation Toxicity Study of Ethyl Acrylate and Acrylic Acid

Injected Amount (μL)	Calculated Conc. (ppm)	Reference Absorb.	Absorb. 1	Absorb. 2	Absorb. 3	Mean Absorb.
0	0	-0.0001	0.0004	0.0009	0.0000	0.0004
0	0	0.0002	0.0009	0.0012	0.0006	0.0009
0	0	0.0001	0.0009	0.0007	0.0009	0.0008
0	0	-0.0001	0.0011	0.0012	0.0013	0.0012
0.25	15.8	0.0008	0.0979	0.0977	0.0974	0.0977
0	0	0.0002	0.0034	0.0038	0.0037	0.0036
0.25	15.8	0.0012	0.1050	0.1049	0.1046	0.1048
0	0	0.0009	-0.0002	-0.0001	0.0000	-0.0001
0.25	15.8	0.0028	0.0956	0.0961	0.0956	0.0958
0	0	0.0006	0.0005	0.0006	0.0005	0.0005
0.5	31.6	0.0051	0.1984	0.1978	0.1969	0.1977
0	0	0.0012	0.0037	0.0040	0.0039	0.0039
0.5	31.6	0.0055	0.2102	0.2091	0.2094	0.2096
0	0	0.0015	0.0010	0.0010	0.0011	0.0010
0.5	31.6	0.0053	0.2041	0.2039	0.2040	0.2040
0	0	0.0006	0.0001	-0.0005	-0.0004	-0.0003
1	63.2	0.0120	0.3517	0.3511	0.3506	0.3511
0	0	0.0012	-0.0045	-0.0041	-0.0046	-0.0044
1	63.2	0.0124	0.3511	0.3515	0.3513	0.3513
0	0	0.0012	-0.0039	-0.0035	-0.0042	-0.0039
1	63.2	0.0124	0.3574	0.3567	0.3556	0.3566
0	0	0.0012	-0.0045	-0.0044	-0.0045	-0.0045
2	126.4	0.0408	0.5740	0.5750	0.5737	0.5742
0	0	0.0012	-0.0017	-0.0010	-0.0014	-0.0014
2	126.4	0.0401	0.5740	0.5728	0.5739	0.5736
0	0	0.0009	-0.0051	-0.0051	-0.0055	-0.0052
2	126.4	0.0389	0.5702	0.5685	0.5699	0.5695

576 OLFACTORY EPITHELIAL INJURY IN MONKEYS AFTER ACUTE INHALATION EXPOSURE TO ACRYLIC MONOMERS.

J R Harkema[1], J K Lee[1], K T Morgan[2], and C B Frederick[3]. [1]*Department of Pathology, Michigan State University, East Lansing, MI;* [2]*Chemical Industry Institute of Toxicology, Research Triangle Park, NC; and* [3]*Rohm and Haas Co., Spring House, PA.*

Inhalation exposures of acrylic monomers induce toxic responses in the nasal olfactory epithelium of rodents, but such effects have not been investigated in other species. The purpose of the present study was to determine the effects of inhaled ethyl acrylate (EA) and acrylic acid vapors (AA) on the nasal epithelium of monkeys. Cynomolgus monkeys were exposed to 0 (filtered air) or 75 ppm EA or AA for 3 or 6 h (3 animals/exposure group). The nasal cavity from each monkey was processed for light microscopic analysis. The nose was cut in a series of transverse sections extending from the nares to the nasopharynx. Diagrams of the transverse airway profiles were used to map the distribution of exposure-related lesions. The severity of lesions was estimated using standard morphometric techniques. EA- and AA-induced lesions were restricted to the olfactory epithelium lining the dorsal medial meatus. Both EA and AA caused focal degeneration, necrosis, and exfoliation of the olfactory epithelium with mild inflammation. Lesion distribution and severity were greater in animals exposed for 6 h compared with those in monkeys exposed for 3 h. Approximately 15% and 50% of the olfactory epithelium had EA- or AA-induced damage after 3 and 6 h, respectively. The results of this study indicate that monkeys exposed to EA or AA have focal, olfactory epithelial lesions that resemble, in both nature and severity, those previously reported in rodents. (Research was supported by the Basic Acrylic Monomer Manufacturers.)

The Toxicologist

An Official Publication of the Society of Toxicology

and

Abstract Issues of

Fundamental and Applied Toxicology

An Official Journal of the Society of Toxicology

Published by Academic Press, Inc.

Abstracts of the
36th Annual Meeting
Volume 36, No. 1, Part 2,
March 97

AEGLs for Acrylic Acid

The Proposed AEGL values for acrylic acid were published for public comment in the Federal Register, May 2, 2001 (Volume 66, Number 85, Page 21940-21964).

Until the end of the comment period, June 1, 2001, EPA received comments from:

- Basic Acrylic Monomer Manufacturers, Inc.,
- Rohm and Haas Company,
- Department of Environmental Quality, State of Michigan.

Reply to Comments from the Basic Acrylic Monomer Manufacturers, Inc. (BAMM)

General
The comments were submitted as a letter, dated May 31, 2001 and comprise 10 pages. The attachment to the letter comprises a one-page letter plus a 13-page summary of workplace air monitoring data from BASF Corporation, the final report of a study titled ‚Single Dose Inhalation Toxicity Study of Ethyl Acrylate (EA) And Acrylic Acid (AA)', sponsored by Rohm and Haas Co., dates September 12, 1995 as well as a one-page abstract titled ‚Olfactory Epithelial Injury in Monkeys After Acute Inhalation Exposure to Acrylic Monomers' by J.R. Harkema, J.K. Lee, K.T. Morgan and C.B. Frederick, published in The Toxicologist, Vol. 36, No. 1, Part 2, abstract No.576.

The Rohm and Haas (1995) toxicity study reports on an acute inhalation study in Cynomolgus monkeys. Five groups of three animals each, were exposed via head-only inhalation exposure to 75 ppm acrylic acid for 3 hours, 75 ppm acrylic acid for 6 hours or air for 6 hours (control group); two additional groups were exposed to ethyl acrylate. The mean analytical exposure concentrations were 80.51 and 78.06 ppm, respectively. Based upon the fluctuations in airflow through the exposure helmet, the respiration rate and tidal volume were measured for each animal. There were no abnormal clinical observations recorded for any of the animals exposed to acrylic acid or control air. From the respiration rate, tidal volume and body weights, the individual animal inhaled doses were calculated. The doses for the monkeys exposed for 3 hours were 12.7, 18.8 and 15.7 mg/kg, while doses for the 6-hour exposed animals were 26.9, 21.5 and 35.2 mg/kg. After the end of the exposure, each monkey was anesthetizsed and killed by exsanguination. At necropsy, no gross pathological treatment-related effects were observed. The nasopharyneal orifice and trachea and lungs were fixed by formalin treatment and shipped for sectioning and histopathologic evaluation. The final report on the histological examination has not been published; however the preliminary results were published as an abstract (Harkema et al., 1997). According to this abstract, the acrylic acid-induced lesions were restricted to the olfactory epithelium lining the dorsal medial meatus. Focal degeneration, necrosis and exfoliation of the olfactory epithelium with mild inflammation were found. Lesion distribution and severity were greater in animals exposed for 6 hours compared to those in monkeys exposed for 3 hours. Approximately 15 % and 50 % of the olfactory epithelium had acrylic acid-induced damage after 3 and 6 hours, respectively. The authors concluded that monkeys exposed to acrylic acid exposed focal, olfactory epithelial lesions that resemble, in both nature and severity, those reported in rodents.

Request 1
BAMM suggests to adopt AEGL-1 values of 6.0, 5.0, 4.0, 3.0 and 2.0 ppm for 10 minutes, 30 minutes, 1 hours, 4 hours and 8 hours, respectively.

Reason for Request 1
BAMM argues that, given the widespread adoption of 2 ppm as an occupational exposure limit, a value not lower than 2 ppm should be adopted as the 8-hour AEGL-1. In addition, the short term exposure limit (15 minute STEL) of 6 ppm, which is commonly used in industry, should be adopted as the 10-minute AEGL-1 and values for other times should be interpolated between these values. In support of the 2 ppm and the 6 ppm level, BAMM presents the workplace air monitoring data from BASF Corporation from the last 20 years. The 8-hour TWA monitoring results have ranged from 0.003 ppm (or a nondetect at the limit of detection of the analytical method at the time) to 4.27 ppm with a single outlier at 26 ppm. The median TWA measurement was 0.15 ppm. Of the 259 samples, 8 % were equal to or greater than 1 ppm (includes measurements with a limit of detection above 1 ppm). The short term exposure monitoring (typically 15 min STEL) results ranged from <0.001 to 63 ppm (or a nondetect at the limit of detection of the analytical method at the time). The median STEL measurement was 0.5 ppm. The routine medical surveillance did not record cases of nose or eye irritation. The health monitoring did not inquire about odor perception, but includes a question "do you have ear, nose or throat trouble?".

Reply to Request 1
AEGL values are derived on the basis of one (or a few) ***experimental*** studies, selected for the quality of study design and data presentation, relevance of investigated toxicity endpoints, exposure time and species employed as well as ability to characterize the dose-response relationship. AEGL values cannot be derived directly from existing workplace exposure limits or other limit or guideline values, because these values are derived for other purposes, subpopulations, exposure times and exposure frequencies and are derived using methodologies different from the AEGLs Standing Operating Procedures. Workplace monitoring and health surveillance data may, in principle, be used in the AEGL derivation. However, the problem with this kind of data is that medical examination generally is not performed in correlation with one defined and measured exposure, but is performed independently as periodically repeated medical examinations. This is also the case for the BASF Corporation monitoring data submitted by BAMM. In this instances, it is always debateble whether, for example, single episodes of higher than usual exposure resulting in irritative effects that disappear quickly after cessation of exposure, a adequately recorded when the worker is asked weeks or month later whether he ***has*** ear, nose or throat ***trouble***. In addition, the workplace air monitoring data are inadequate to support the 2 ppm and the 6 ppm limits because the show that the actual exposure concentrations were about one order of magnitude below these values. The median values reported by BASF and BAMM were 0.15 ppm (TWA) and 0.5 ppm (STEL), respectively. Evaluation of the individual values reveals that in the case of the 8-hour TWA only 6 of the 259 samples were 2 ppm or higher and only 4 of these 6 samples were obtained using personal sampling equipment and that in the case of the STEL values only 31 of 632 samples were 6 ppm or higher. Finally, it should be noted that the NAC/AEGL Committee decided to base the AEGL-1 values on the odor threshold and to use the irritation data (workplace monitoring data, Renshaw, 1988) as supportive evidence. BAMM obviously did not question the odor recognition threshold of 1 ppm.

Request 2
BAMM suggests to adopt an AEGL-2 value of 75 ppm for all time periods (10 minutes, 30 minutes, 1 hours, 4 hours and 8 hours).

Reason for Request 2
BAMM argues that a value of 75 ppm is adequate for all time periods as the AEGL-2 because 1) no eye blinking or squinting occurred in rabbits at 77 and 61 ppm (Neeper-Bradley et al., 1997) and in monkeys at 75 ppm (Rohm and Haas, 1995), 2) the cytotoxicity and nasal irritation observed in 75 ppm in acute inhalation studies is reversible and does not impair the ability to escape and 3) eye irritation (blinking and tearing) which might impede sight and escape is observed at concentrations above 100 ppm. BAMM suggests use of an interspecies factor of 1 because there dose not seem to be much difference in response across several species tested and use of an intraspecies factor of 1 based on the lack of severity of the response and the wide range of functional deficit that can be accomodated for this endpoint.

Reply to Request 2
BAMM obviously does not question the level of 75 ppm as a starting point for the AEGL-2 derivation. The TSD states that exposure to 75 ppm for 6 hours did not resulted in clinical signs of irritation in rats, but in histopathological changes of the nasal epithelium (olfactory epithelial cell degeneration, sustentacular cell necrosis and limited respiratory epithelial cell degeneration), while higher exposure concentrations caused more severe symptoms that can be interpreted as signs of impaired ability to escape. Whether the olfactory lesions are reversible, as suggested by BAMM, must be questioned. A capacity for regeneration of the olfactory epithelium has been found after methyl bromide-induced lesion (Yougentob et al., Physiol. Behavior 62 (1997) 1241-1252; Schwob et al., J. Comp. Neurol. 412 (1999) 439-457). However, the regeneration seems to be dependent on the survival of pluripotent stem cells in the musocal area. Since these cannot effectively migrate laterally to reconstitute sensory epithelium, complete stem cell destruction in one area will likely lead to permanent replacement with nonfunctional epithelium (Talamo et al., Inhal. Toxicol. 6 suppl. (1994) 249-275). This mechanism might explain why respiratory epithelial patches in the olfactory mucosa seem to increase as a function of age in humans (Paik et al., Arch. Otolaryngol. Head Neck Surg. 118 (1992) 731-738).
The inhalation exposure study in monkeys (Rohm and Haas, 1995; Harkema et al., 1997) contributes new experimental information which is not presented in the Proposed TSD. Unfortunately, the histopathological analysis has not been presented in a final report or a full publication up until now. Therefore, it is not possible to adequately evaluate the findings claimed and the study is not considered useful evidence for a further reduction of the interspecies factor. BAMM does not provide any new evidence that would justify a further reduction of the intraspecies factor. Alteration of the currently used intraspecies factor is therefore considered unnecessary. The level of 75 ppm is considered an adequate threshold for an AEGL-2 effect because at higher concentrations (staring at about 100 ppm), clinical effects occurred in animals (tearing and blepharospasm) that could impair the ability to escape, as also recognized by BAMM, and because olfactory tissue destruction which is increasing with the exposure concentration is increasingly likely to result in permanent damage of the olfactory epithelium. Thus, a reduction of the uncertainty factor cannot be supported with the argument that the effect level at 75 pppm is well below the AEGL-2 threshold.

With regard to time extrapolation, the available animal data in rats (e.g. Lomax et al., 1994) clearly demonstrate that the degree of olfactory epithelium damage increases with increasing exposure time and, thus, argue against using the same exposure concentration as AEGL-2 value for all relevant periods of time. Therefore, the time scaling as used in the Proposed TSD is considered adequate.

Request 3
BAMM suggests to adopt AEGL-3 values of 1500, 1200, 750, 625 and 500 ppm for 10 minutes, 30 minutes, 1 hours, 4 hours and 8 hours, respectively.

Reason for Request 3
BAMM argues that for the derivation of AEGL-3 values, the highest achievable vapor concentration of 2142 ppm in the study of Hagan and Emmons (1988), which did not cause lethal effects in rats upon exposure of 1 hour, should be used as a basis. It argues that an interspecies factor of 1 should be used because 1) there are no credible reports of acute lethality in any species at concentrations less than 1000 ppm, 2) repeated inhalation studies have been conducted in various animal species at concentrations up to 250 ppm without lethality, 3) no reports link human inhalation exposure to acrylic acid with lethality and 4) the cited study by Rohm and Haas (1995) indicated very similar effects on the olfactory mucosa in monkeys compared to rats.

Reply to Request 3
The use of the aerosol data from the study of Hagan and Emmons (1988) is considered a better basis for the derivation of AEGL-3 values because these experiments, in contrast to the vapor exposure part of the study, were performed for three different exposure times and thus provided information on the dose-response relationship and used a considerable higher number of rats. The evaluation in the TSD found no reason for not using the aerosol data and showed that the aerosol data are compatible with the available vapor studies. Also the comments by BAMM did not provide any argument for not using the aerosol data. For the 1-hour period, the LC_{01}, which was used as the starting point, of 1806 ppm for the aerosol is close to the highest vapor concentration of 2142 ppm. It is therefore considered adequate to use the aerosol data from the Hagan and Emmons (1988) study for derivation of AEGL-3 values.
In the Proposed TSD, an uncertainty factor of 3 was applied for interspecies variability because "the mechanism of action of lethal effects, which involves local tissue destruction in the lung by a direct-acting toxicant with limited influences of metabolism, detoxification and elimination, is unlikely to differ between species". The inhalation exposure study in monkeys (Rohm and Haas, 1995; Harkema et al., 1997) contributes new experimental information which is not presented in the Proposed TSD. Unfortunately, the histopathological analysis has not been presented in a final report or a full publication up until now. Therefore, it is not possible to adequately evaluate the findings claimed and the study is not considered useful evidence for a further reduction of the interspecies factor. It is not considered necessary to change the time extrapolation exponent of 1.8 derived from the experimental aerosol data. It is unclear how BAMM used time extrapolation to derive its proposed values. Therefore, the time scaling as used in the Proposed TSD is considered adequate.

Conclusion
With presentation of the inhalation exposure study in monkeys (Rohm and Haas, 1995; Harkema et al., 1997) BAMM presented data that is not included in the Propsed TSD. It is suggested that this study is

incorporated into the TSD. Since the histopathological findings have only been described in an abstract, these findings are not considered adequate for a further reduction of the interspecies uncertainty factor. It is thus considered unnecessary to revisit the Proposed AEGL values for acrylic acid at this time.

Reply to Comments from Rohm and Haas Company

General
The comments were submitted as a letter, dated May 30, 2001 and comprise 2 pages.

Request 1
Rohm and Haas requests that the NAC/AEGL Committee reassesses the AEGL-1 values.

> ***Reason for Request 1***
> ***Rohm and Haas argues that the Proposed AEGL-1 value of 1 ppm is not consistent with toxicology information from animal studies and human observations that indicate that a 8-hour TWA concentration of 2 - 5 ppm does not cause respiratory or eye irritation as defined for AEGL-1. It believes that the 2 - 10 ppm permissible exposure limit used in most countries protects workers who are chronically exposed throughout a 40-year working career from all deleterious health effects. Rohm and Haas further sustantiates its request by stating that reviewing their workplace injury and illness reports for their 30 plants worldwide from 1990 for U.S. based plants and from 1994 for plants outside the U.S. found only four reports (from a total of 12774 records) of respiratory or eye irritation. In three cases employees were involved in the clean-up of a spill of glacial acrylic acid and the fourth case involved release of 88% acrylic acid during tank car loading. No air monitoring was conducted in theses cases, however, Rohm and Haas assumes that exposures were substantially higher than the company's workplace exposure limit, which is a 2 ppm 8-hour TWA and a 6 ppm STEL. Rohm and Haas also reviewed the health effect allegation reports maintained by the company for Toxic Substances Control Act reporting purposes back to 1983 and found only one incident in which an employee of a company's customer experienced chest pain, leg tingling and respiratory irritation after handling acrylic acid.***

Reply to Request 1
Rohm and Haas provides no argument for its claim that animal toxicity data would be inconsistent with the Proposed AEGL-1 value. As presented in the Proposed TSD as an alternative derivation of AEGL-1, the use of local effects on the olfactory epithelium of mice as endpoint instead of the odor recognition threshold in humans and the use of time scaling in the former, but not in the latter derivation would lead to very similar values. Thus, no incompatibility of animal data with the derived AEGL-1 values can be found, but, to the contrary, the available animal data support the derived AEGL-1 values. It has already been discussed in the Reply to Request 1 of BAMM that the occupational limit values per se are not useful for a direct derivation of AEGL values. The workplace air monitoring data from BASF Corporation cited above indicate that for most of the time actual workplace concentrations are far below the limit values. Rohm and Haas fail to prove that exposures to their workplace exposure limit concentrations really take place and at the same time do not cause any health effects. The scarcity of acrylic acid-related health effects in the records

of Rohm and Haas speak in favor of the high occupational hygiene standards of the company, but is inadequate as an argument when setting AEGL values. Generally, reports of accidental exposure to high concentrations are useful for AEGL derivation, however, the cases mentioned by Rohm and Haas are not useful due to the lack of exposure measurements.

Conclusion

Since the comments of Rohm and Haas did not provide any new data or convincingly demonstrated that available data were used incorrectly, it is considered unnecessary to revisit the Proposed AEGL values for acrylic acid.

Reply to Comments from the Department of Environmental Quality (DEQ), State of Michigan

General

The comments (on Acrylic Acid and Methanol) were submitted as a letter, dated May 31, 2001 and comprise 2 pages.

Request 1

DEQ requested clarification of the following points regarding the AEGL-1 values.

Comment 1

DEQ questions that the use of an interspecies factor of 1 is sufficiently supported by the computational fluid dynamics model (Frederick et al., 1998) which predicts that a higher acrylic acid concentration is deposited on the olfactory epithelium or rodents compared to humans. DEQ asks whether the model has been validated by other researchers.

Reply to Comment 1

It should be noted that the derivation of the AEGL-1 values was based on the odor recognition threshold in humans, supported by a personal communication that reported on irritative effects from occupational exposure. Therefore, no interspecies uncertainty factor had to be used in the AEGL-1 derivation. As another supportive argument, an alternative derivation, based on animal studies is presented subsequently in the Proposed TSD. In this alternative AEGL-1 derivation, an interspecies uncertainty factor of 1 was used because, in addition to the argument of the deposited dose, which was used to reduce the interspecies factor to 3 in the AEGL-2 and -3 derivations (for discussion of this factor see Reply to Request 2, Comment 1), the alternative derivation was based on a NOAEL, which was considered somewhat below an AEGL-1 threshold level. It is proposed to explicitly state this additional argument in the alternative derivation of AEGL-1.

Comment 2

DEQ considers the used intraspecies factor of 3 as too small for the general population because 1) the argument for this factor, which reads "limited interindividual variability for local effects on the respiratory trace", does not contain a supportive evidence, 2) the data cited from Renshaw (1988) includes reports for eye irritation ranging from 0.3 - 23 ppm and 3) the Renshaw (1988)

report included occupationally exposed individuals, a group with considerably less heterogeneity than the general population.

Reply to Comment 2
Again, it should be noted that the intraspecies factor of 3 was not used in the principal derivation of AEGL-1, but in the presented alternative derivation, based on animals studies. In the principal derivation, which was based on the odor threshold in humans, the NAC/AEGL Committee considered it unnecessary to apply an intraspecies factor. Its intention was that the AEGL-1should have warning properties since most people should perceive the odor of acrylic acid at this concentration. This goal would not have been achieved if the concentration was reduced below the odor threshold level by application of an uncertainty factor. In the alternative derivation, an intraspecies uncertainty factor of 3 was used as in the derivation of AEGL-2 values (for discussion of this factor see Reply to Request 2, Comment 2). With regard to the Renshaw data, it should be noted that the reported concentrations were no experimentally determined threshold concentrations for eye irritation, but mean exposure concentrations measured by personal sampling or area sampling. Thus, exposures are unlikely to have been constant during sampling time and short exposures to higher concentrations are likely to have occurred. Also, the range of reported concentrations of 0.3 to 23 ppm corresponds to a range in exposure time, ranging from 10 to 153 minutes. The shorter exposure times tended to be associated with the higher exposure concentrations and vice versa. In summary, the report by Renshaw (1988) is not considered adequate for the assessment of the human variability of irritative effects from exposure to acrylic acid.

Request 2
DEQ requested clarification of the following points regarding the AEGL-2 values.

Comment 1
DEQ welcomes the use of the Miller et al. (1981) study as key study because this study was also used by US-EPA for derivation of the Reference Concentration. As in the derivation of AEGL-1, DEQ considers the reduction of the default interspecies uncertainty factor on basis of the Frederick et al. (1998) study as insufficiently supported.

Reply to Comment 1
It is recognized that the toxicokinetic model by Frederick et al. (1998) has neither been validated nor falsified by other investigations. However, with the experiments described, the study by Frederick et al. (1998) is considered adequate evidence for the reduction of the interspecies factor from 10 to 3.

Comment 2
DEQ also considers the rationale of "limited interindividual variability for local effects" not as appropriate for reduction of the default intraspecies factor.

Reply to Comment 2
The intraspecies uncertainty factor is used to compensate for both, toxicokinetic and toxicodynamic differences between species. For local effects occuring at the air-tissue interphase, toxicokinetic differences between species are much smaller when compared to systemic effects after inhalation

exposure, where interindividual differences might exist with regard to absorption, entering of circulation, distribution through circulation and tissue distribution etc. For this reason, it is considered adequate that to use a reduced intraspecies factor of 3 in cases of locally acting, reactive chemicals not requiring metabolic activation. It is suggested to incorporate this reasoning into the argumentation for reduction of the intraspecies factor in the Proposed TSD.

Request 3
DEQ requested clarification of the following points regarding the AEGL-3 values.

Comment 1
As in the derivation of AEGL-2 values, DEQ considers the rationale of "limited interindividual variability for local effects" not as appropriate for reduction of the default intraspecies factor.

Reply to Comment 1
Same as Reply to Request 2, Comment 2

Request 4
DEQ requested more detail in Appendix B on the derivation of the time-scaling factor and how Ten Berge et al. used the data in their model.

Reply to Request 4
For more information on using Probit analysis for the derivation of the exponent for time scaling, the corresponding section of the AEGL Standing Operating Procedures (SOP) and the literature article of Ten Berge et al., (1986) should be consulted. The "conventional" way of determining the exponent is by calculating the slope of the linear regression line as presented in Figure 3 in Appendix B (see also SOP). Linear regression leads to a very similar value for the exponent (1.7) compared to Probit analysis (1.8).

Request 5
DEQ criticized that the symbols in the key on page 20, depicting Figure 1, do not match the symbols in the graph, which impedes precise determination what the graph is intended to represent.

Reply to Request 5
While it is admitted that the symbols in the graph seem somewhat elongated or streched, the symbols, nevertheless, should be readily identifiable. It is proposed to correct the symbols in the Proposed TSD so that symbols in the graph and in the legend match exactly.

Conclusion

Since the comments of DEQ did not provide any new data for the setting of uncertainty factors or convincingly demonstrated that available data were used incorrectly in the setting of uncertainty factors, it is considered unnecessary to revisit the Proposed AEGL values for acrylic acid.

In response to the DEQ request for a better argumentation for reduction of the intraspecies uncertainty factor in the derivation of AEGL-2 and AEGL-3 factors, it is suggested to improve the reasoning by stating more clearly that the intraspecies uncertainty factor is used to compensate for both, toxicokinetic and toxicodynamic differences between species and that for local effects toxicokinetic differences between species are much smaller when compared to systemic effects. Likewise, the argumentation of the reduction in interspecies uncertainty factor in the alterantive AEGL-1 derivation should be improved as indicated above. The depiction of symbols in the graph and legend of Figure 1 should be improved.

ACUTE EXPOSURE GUIDELINE LEVELS FOR

ETHYLENIMINE

(AEGL-1 VALUES)

PRESENTED BY
MARK McCLANAHAN, CHEMICAL MANAGER

NAC/AEGL MEETING, WASHINGTON, DC
September 11-13, 2001

Attachment 17

Summary of Proposed AEGL Values for Ethylenimine[a,b] [ppm (mg/m^3)]						
Classification	**10 min.**	**30min.**	**1 hour**	**4 hours**	**8 hours**	**Endpoint (Reference)**
AEGL-1	17 (30)	4.9 (8.8)	2.3 (4.1)	No values derived[c]		AEGL-2 values scaled by a factor of 2
AEGL-2 (Approved by COT)	33 (59)	9.8 (18)	4.6 (8.2)	1.0 (1.8)	0.47 (0.84)	NOEL for extreme respiratory difficulty (Carpenter et al., 1948)
AEGL-3 (Approved by COT)	51 (91)	19 (34)	9.9 (18)	2.8 (5.0)	1.5 (2.7)	Threshold for lethality Carpenter et al., 1948

[a]AEGL-2 and -3 values do not take into consideration the potential cancer risk due to exposure to ethylenimine.

[b]Effects at these concentrations may be delayed following exposure; toxic levels may be absorbed through the skin.

[c]Values would be below the odor threshold for ethylenimine.

AEGL -1 VALUES				
10 minutes	**30 minute**	**1 hour**	**4 hour**	**8 hour**
17 ppm	**4.9 ppm**	**2.3 ppm**	**No values derived**	

Key Reference: Carpenter, C.P.; Smyth, H.F., Jr.; Shaffer, C.B. 1948. The acute toxicity of ethylene imine to small animals. J. Ind. Hyg. Toxicol. 30:2-6.

Test Species/Strain/Number: Details presented in the Derivation Summary of AEGL-2 Values

Exposure Route/Concentration/Durations: See the Derivation Summary of AEGL-2 Values

Effects: See Effects for the Derivation Summary of AEGL-2 Values

Endpoint/Concentration/Rationale: AEGL-1 values were based on dividing the AEGL-2 values by a factor of 2, because the average difference between AEGL-2 and AEGL-3 values is approximately 2. The AEGL-2 values were based on a no-effect-level for lethality in the guinea pig, 10 ppm exposure for 4 hours; effects at 25 ppm and higher were more severe than those defined for AEGL 2.

Uncertainty Factors/Rationale:
Total uncertainty factor: The total uncertainty factor for AEGL-2 was equal to 10
Interspecies: same as described for the Derivation Summary of AEGL-2 Values
Intraspecies: same as described for the Derivation Summary of AEGL-2 Values

Modifying Factor: not applicable

Animal to Human Dosimetric Adjustment: not applicable

Time Scaling: See the rationale for AEGL-2

Data Adequacy: No specific data were not available for deriving AEGL-1 values; therefore, AEGL-2 values were scaled by a factor of 2 to derive AEGL-1 values for exposure duration of 10, 30, and 60 minutes. No values were derived for the 4- and 8-hour durations, because they would be below the published odor detection level of 2 ppm for ethylenimine.

AEGL -2 VALUES				
10 minute	**30 minute**	**1 hour**	**4 hour**	**8 hour**
33 ppm	**9.8 ppm**	**4.6 ppm**	**1.0 ppm**	**0.47 ppm**

Key Reference: Carpenter, C.P.; Smyth, H.F., Jr.; Shaffer, C.B. 1948. The acute toxicity of ethylene imine to small animals. J. Ind. Hyg. Toxicol. 30:2-6.

Test Species/Strain/Number: male guinea pigs, 6 per group

Exposure Route/Concentration/Durations: Inhalation; 10, 25, 50, 100, or 250 ppm for 240 minutes

Effects: Guinea pigs were exposed for 240 minutes.

Clinical signs: eye and respiratory irritation, and extreme respiratory difficulty at 25-250 ppm; prostration at 250 ppm; no effects at 10 ppm

Gross pathologic effects: congestion and hemorrhage in the lungs, congestion in all internal organs at 25-250 ppm; no effects at 10 ppm

Microscopic effects: lung congestion leakage of fluid and red blood cells into bronchioles, tubular necrosis and cloudy swelling in the kidneys at 25-250 ppm; no effects at 10 ppm

Mortality: 10 ppm, (0/6), 25 ppm (2/6), 50 ppm (2/6), 100 ppm (6/6), and 250 ppm (6/6)

Endpoint/Concentration/Rationale: No-effect-level for lethality in the guinea pig, 10 ppm exposure for 4 hours; effects at 25 ppm and higher were more severe than those defined for AEGL 2.

AEGL-2 FOR ETHYLENIMINE (CONTINUED)

Uncertainty Factors/Rationale:

Total uncertainty factor: 10

Interspecies: 3 - Ethylenimine is a very reactive direct-acting alkylating agent, the alkylating activity is not expected to vary across species (pharmacokinetics may differ but pharmacodynamics are expected to be similar); humans appear to be less sensitive than rats and guinea pigs; the AEGL-2 value for 10 minutes is below the reported threshold for irritation in humans.

Intraspecies: 3 - Ethylenimine is a very reactive direct-acting alkylating agent, and the alkylating activity is not expected to vary among individuals in the population; the delayed onset of overt signs and symptoms suggests that effects may involve an accumulation of damage in target tissues, and there is no evidence that ethylenimine is a sensory irritant; five humans accidentally exposed to the same concentration of ethylenimine responded at similar times after exposure and experienced similar effects, the onset of which occurred at similar times after exposure.

Modifying Factor: 1

Animal to Human Dosimetric Adjustment: 1

Time Scaling: $C^n \times k = t$, where $n = 0.91$ derived empirically from guinea pig LC50 data with exposure times ranging from 5 minutes to 480 minutes.

Data Adequacy: The only studies available for deriving AEGL-2 values were the acute lethality studies in rats and guinea pigs. The AEGL-2 values were, therefore, derived from a no-effect-level for extreme respiratory difficulty determined from the guinea pig study. Ethylenimine has carcinogenic activity; but these values do not take into consideration the potential excess lifetime cancer risk due to a single exposure.

CHLORINE AEGLs

Classification	Exposure Duration				
	10-Minute	**30-Minute**	**1-Hour**	**4-Hour**	**8-Hour**
AEGL-1 (Nondisabling)	2.5 ppm	1.4 ppm	1.0 ppm	0.5 ppm	0.5 ppm
AEGL-2 (Disabling)	4.9 ppm	2.8 ppm	2.0 ppm	1.0 ppm	0.7 ppm
AEGL-3 (Lethal)	50 ppm	28 ppm	20 ppm	10 ppm	7.1 ppm

Attachment 18

ANILINE AEGLs

Classification	Exposure Duration				
	10-Minute	30-Minute	1-Hour	4-Hour	8-Hour
AEGL-1 (Nondisabling)	48 ppm	16 ppm	8 ppm	2 ppm	1 ppm
AEGL-2 (Disabling)	72 ppm	24 ppm	12 ppm	3 ppm	1.5 ppm
AEGL-3 (Lethal)	120 ppm	40 ppm	20 ppm	5 ppm	2.5 ppm

All values based on methemoglobin formation in rat (Kim and Carlson 1986)
Interspecies and intraspecies uncertainty factors of 10 each (to protect infants)

AEGL-1: 100 ppm for 8 hours resulted in 22% methemoglobin
Clinical cyanosis but no hypoxic symptoms
AEGL-2: 150 ppm for 8 hours resulted in 41% methemoglobin
Symptoms of fatigue, lethargy, exertional dyspnea
AEGL-3: 250 ppm for 8 hours (data extrapolation)
Predicted threshold for lethality
Time-scaling: n = 1

Attachment 19

DRAFT PROPOSED AEGL VALUES FOR CARBON TETRACHLORIDE (ppm [mg/m^3])						
Classification	***10-min***	**30-min**	**1-hour**	**4-hour**	**8-hour**	**Endpoint (Reference)**
AEGL-1	*25* *157*	16 101	12 75	6.9 43	5.2 33	**Nervousness and slight nausea in human subjects exposed for 30 minutes to 158 ppm (Davis, 1934)**
AEGL-2	*140* *881*	90 566	68 428	39 245	30 189	**Nausea, vomiting, headache in human subjects exposed to 1191 ppm for 15 minutes (Davis, 1934)**
AEGL-3	*350* *2,202*	230 1447	170 1069	99 623	75 472	**Lethality in rats; estimated LC_{01} (Adams et al., 1952; Dow Chemical, 1986)**

Attachment 20

Justification/Rationale for 10-Minute AEGLs for Carbon Tetrachloride:

- **The 10-minute AEGL-1 value (25 ppm) is based upon a human exposure resulting in AEGL-1 effects (nervousness, slight nausea) and is consistent with the available data. For example, human subjects exposed to 317 ppm for 30 minutes experienced headache, nausea, vomiting. This exposure concentration is over 12-fold greater than the proposed 10-min AEGL-1 (and is ~30% greater even with a UF of 10 applied) and was for a 30-minute duration.**

- **The 10-minute AEGL-2 is consistent with the available data and only minimal time extrapolation was required as the reference point was a 15-minute exposure.**

- **The 10-minute AEGL-3 is also consistent with available data. Nausea, vomiting, and narcosis onset were reported for human subjects exposed to 12,800 ppm for 7-10 minutes. Even with a UF of 10 applied to protect sensitive individuals (12,800 ppm/10 = 1,280 ppm), the 10-min AEGL-3 is >3-fold less.**

DERIVATION OF AEGL-1 VALUES

Key study: Davis, 1934

Toxicity endpoint: humans; feeling of nervousness and slight nausea following 30-minute exposure to 158 ppm

Scaling: $C^{2.5} \times t = k$

Uncertainty factors: 10 for protection of sensitive individuals

Calculations:

158 ppm/10 = 15.8 ppm

$C^{2.5} \times t = k$

$(15.8 \text{ ppm})^{2.5} \times 30 \text{ min} = 29{,}768.98 \text{ ppm} \cdot \text{min}$

<u>10-min AEGL-1</u>

$C^{2.5} \times 10 \text{ min} = 29{,}768.98 \text{ ppm}^{2.5} \cdot \text{min}$

$C = 24.5 \text{ ppm}$

AEGL-2

Key study: Davis et al., 1934

Toxicity endpoint: humans; nausea, vomiting, headache, intolerance in one subject following 15-minute exposure to 1,191 ppm

Scaling: $C^{2.5} \times t = k$ (ten Berge, 1986)

Uncertainty factors: 10 for protection of sensitive individuals (e.g., p-450 induction from ethanol consumption)

Calculations:

1,191 ppm/10 = 119 ppm

$C^{2.5} \times t = k$

$(119 \text{ ppm})^{2.5} \times 15 \text{ min} = 2{,}317{,}174.1 \text{ ppm·min}$

<u>10-min AEGL-2</u>

$C^{2.5} \times 10 \text{ min} = 2{,}317{,}174.1 \text{ ppm·min}$

$C = 140 \text{ ppm}$

AEGL-3

Key study: Union Carbide 1946; Adams et al., 1952; Dow Chemical 1986

Toxicity endpoint: Rats; lethality; estimate of LC_{01} (5,153.5 ppm) based upon 1-hr exposure (see Appendix C)

Scaling: $C^{2.5} \times t = k$ (ten Berge, 1986)·hr

Uncertainty factors: 10 for protection of sensitive individuals (e.g.,ethanol-induced P-450)
3 for interspecies variability; data suggest that species variability in lethal response does not vary 10-fold; long-term animal studies show that exposures greater than the AEGL values do not results in lethal responses

Calculations:
5,153.5 ppm/30 = 171.8 ppm
$C^{2.5} \times t = k$
$(515.4 \text{ ppm})^{2.5} \times 60 \text{ min} = 23{,}211{,}817.6 \text{ ppm·min}$

10-min AEGL-3

$C^{2.5} \times 10 \text{ min} = 23{,}211{,}817.6 \text{ ppm·min}$
C = 352 ppm (rounded to 350 ppm)

PROPOSED AEGL VALUES FOR CHLOROFORM (ppm [mg/m^3])						
Classification	10-min	30-min	1-hour	4-hour	8-hour	Endpoint (Reference)
AEGL-1	NR	NR	NR	NR	NR	Not recommended due to properties of the chemical; AEGL-1 effects unlikely to occur in the absence of notable toxicity.
AEGL-2	116 [565]	80 [390]	64 [312]	40 [195]	29 ppm 141 mg/m^3	Fetotoxicity in rats exposed for 7 hrs/day on gestation days 6-15 (Schwetz et al., 1974)
AEGL-3	940 [4,578]	652 [3,175]	518 [2,523]	326 [1,588]	163 [794]	Estimated lethality threshold for rats; 3-fold reduction in 4-hr LC_{50} of 9780 ppm to 3260 ppm (Lundberg et al., 1986)

Attachment 21

Justification/Rationale for 10-Minute AEGLs for Chloroform

- There are no available data in animals or humans that invalidate the 10 minute AEGL values.

- All AEGL values are at or below the narcosis threshold for humans.

DERIVATION OF AEGL-1 VALUES

AEGL-1 values were not recommended by the NAC/AEGL due to properties of the chemical. Based upon the available data, it was not possible to identify a definitive effect consistent with the AEGL-1 definition. Exposures to concentrations approaching those inducing narcosis or hepatic and renal effects are not necessarily accompanied by overt signs or symptoms. Furthermore, the odor of chloroform is not unpleasant or irritating.

DERIVATION OF AEGL-2

Key study:	**Schwetz et al., 1974**
Toxicity endpoint:	**Fetotoxicity in rats exposed to 100 ppm for 7 hrs/day on gestation days 6-15. The assumption was made that effects could result from a single 7-hour exposure if the exposure occurred during a critical window in the development process.**
Scaling:	**$C^2 \times t = k$;The concentration-exposure time relationship for many irritant and systemically acting vapors and gases may be described by $C^n \times t = k$, where the exponent n ranges from 0.8 to 3.5 (ten Berge et al., 1986) Data were unavailable to empirically derive a scaling factor (n) for chloroform. In the absence of an empirically derived exponent (n), and to obtain conservative and protective AEGL values, temporal scaling was performed using $n = 3$ when extrapolating to shorter time points and $n = 1$ when extrapolating to longer time points using the $C^n \times t = k$ equation.**
Uncertainty factors:	**No interspecies uncertainty factor was applied because the available metabolism/kinetics data and PB-PK models (Corley et al., 1990) indicate that humans may be less sensitive to the toxic effects of chloroform. Additional adjustments were also considered excessive because a single 7-hour exposure was utilized for AEGL-2 development rather than the full exposure period specified in the study protocol (7 hrs/day on gestation days 6-15). An intraspecies uncertainty factor of 3 was applied to account for individual variability in metabolism and disposition of chloroform. Additional adjustment was not made because the fetus was considered a sensitive subgroup. Total uncertainty factor application = 3.**

Calculations:

100 ppm/3 = 33.3 ppm
$C^1 \times t = k$
$(33.3 \text{ ppm})^1 \times 420 \text{ min} = 13{,}999.99 \text{ ppm·min}$

100 ppm/10 = 33.3 ppm
$C^3 \times t = k$
$(33.3 \text{ ppm})^3 \times 420 \text{ min} = 15{,}508{,}935.5 \text{ ppm·min}$

<u>10-min AEGL-2</u>

$C^3 \times 10 \text{ min} = 15{,}508{,}935.5 \text{ ppm}^3\text{·min}$
$C = 116 \text{ ppm}$

DERIVATION OF AEGL-3

Key study: Based upon a 3-fold reduction in a 4-hour LC_{50} (9,780 ppm) for rats (Lundberg et al., 1986); 9,780 ppm/3 = 3,260 ppm.

Toxicity endpoint: Estimated lethality threshold.

Scaling: $C^2 \times t = k$; The concentration-exposure time relationship for many irritant and systemically acting vapors and gases may be described by $C^n \times t = k$, where the exponent n ranges from 0.8 to 3.5 (ten Berge et al., 1986). Data were unavailable to empirically derive a scaling factor (n) for chloroform. In the absence of an empirically derived exponent (n), and to obtain conservative and protective AEGL values, temporal scaling was performed using $n = 3$ when extrapolating to shorter time points and $n = 1$ when extrapolating to longer time points using the $C^n \times t = k$ equation.

Uncertainty factors: An uncertainty factor of 3 was applied to account for possible interspecies variability in the lethal response to chloroform. Metabolism/kinetics data and PB-PK models (Corley et al., 1990) indicate that humans may be less sensitive to the toxic effects of chloroform and, therefore, the uncertainty factor of 3 was considered adequate. An intraspecies uncertainty factor of 3 was applied to account for individual variability in metabolism and disposition of chloroform (e.g., induction of P-450 enzymes and subsequent enhancement of toxicity) and because there were no definitive lethality data for humans. Total uncertainty factor application = 10 (each uncertainty factor of 3 is actually the geometric mean of 10 which is 3.16, hence 3.16 x 3.16 = 10.

Calculations:

3,260 ppm/10 = 326 ppm

$C^1 \times t = k$

$(326 \text{ ppm})^1 \times 240 \text{ min} = 78{,}240 \text{ ppm·min}$

3,260 ppm/10 = 326 ppm

$C^3 \times t = k$

$(326 \text{ ppm})^3 \times 240 \text{ min} = 8{,}315{,}034{,}240 \text{ ppm·min}$

<u>10-min AEGL-3</u>

$C^3 \times 10 \text{ min} = 8{,}315{,}034{,}240 \text{ ppm}^3\text{·min}$

$C = 940 \text{ ppm}$

SUMMARY OF AEGL VALUES FOR ARSINE (ppm [mg/m^3])						
Classification	**10-min**	**30-min**	**1-hour**	**4-hour**	**8-hour**	**Endpoint**
AEGL-1	***NR***	**NR**	**NR**	**NR**	**NR**	**Not recommended due to steep dose-response relationship, mechanism of toxicity, and because toxicity occurs at or below the odor threshold**
AEGL-2	***0.30 [0.9]***	**0.21 [0.7]**	**0.17 [0.5]**	**0.04 [0.1]**	**0.02 [0.06]**	**Absence of significant hematological alterations in mice consistent with the known continuum of arsine toxicity (Peterson and Bhattacharyya, 1985)**
AEGL-3	***0.91 [2.9]***	**0.63 [2.0]**	**0.50 [1.6]**	**0.13 [0.4]**	**0.06 [0.2]**	**Estimated threshold for lethality in mice (Peterson and Bhattacharyya, 1985)**

NR: Not recommended. Numeric values for AEGL-1 are not recommended because (1) the lack of available data, (2) an inadequate margin of safety exists between the derived AEGL-1 and the AEGL-2, or (3) the derived AEGL-1 is greater than the AEGL-2. Absence of an AEGL-1 does not imply that exposure below the AEGL-2 is without adverse effects.

Justification/Rationale for 10-Minute AEGLs for Arsine:

- AEGL-1 values were not recommended.

- The 10-minute AEGL-2 is sufficiently below any exposures that would induce signs or symptoms of toxicity. This contention is based upon comparison with available human and animal data, and the fact that the endpoint used to develop the AEGL-2 is actually based upon an absence of even subclinical effects consistent with arsine poisoning.

- The 10-minute AEGL-3 is sufficiently below any exposures that would cause lethality. This contention is based upon comparison with available human and animal data, and the fact that the endpoint used to develop the AEGL-2 is actually based upon an absence of even subclinical effects consistent with arsine poisoning.

- Due the absence of an empirically-derived n value, time scaling for development of the 10-minute AEGL-2 and AEGL-3 values for arsine used $n = 3$. These AEGL values were both based upon a reference exposure duration of 1 hour from the Peterson and Bhattacharya (1985) study and, therefore, the 10-minute AEGL values are not an extreme departure from the reference exposure.

AEGL-1

- **Not recommended**

AEGL-2

Key study: Peterson and Bhattacharyya, 1985. NOAEL of 5 ppm based upon absence of hematological changes in mice following 1-hour exposure. At 15 ppm hematological changes were significant and at 26 ppm there was 100% mortality.

Scaling: $(5\ ppm)^1 \times 1\ hr = 5\ ppm \cdot hr$

$(5\ ppm)^3 \times 1\ hr = 125\ ppm^3 \cdot hr$

Uncertainty factors: An uncertainty factor of 10 was retained for interspecies variability to account for possible variability in arsine-induced hemolysis and progression to renal effects. Uncertainty regarding intraspecies variability was limited to 3 because the hemolytic response is likely to occur to a similar extent and with similar susceptibility in most individuals. This was based on the assumption that physiologic parameters (e.g., absorption, distribution, metabolism, structure of the erythrocyte and its response to arsine, renal responses) would not vary among individuals of the same species to such an extent that the response severity to arsine would be altered by an order of magnitude. I individual variability (i.e., variability in erythrocyte structure/function or response of the kidney to hemolysis) would not likely have a significant impact on any of the proposed subcellular mechanisms of arsine toxicity. The steep exposure-response curves from animal data also affirm the limited variability in response. Further more, the AEGL-2 values were developed using a conservative estimate of a toxic response (no significant indication of hemolysis in mice exposed for 1 hour to 5 ppm arsine) and additional reduction of the values would seem unwarranted.

<u>10-min AEGL-2</u>

$(5\ ppm)^3 \times 1\ hr = 125\ ppm^3 \cdot hr$

$C^3 \times 0.1667\ hr = 125\ ppm^3 \cdot hr$

$C = 9.09\ ppm$

30-min AEGL-2 $= 9.09\ ppm/30 = 0.30\ ppm$

AEGL-3

Key study: Peterson and Bhattacharyya, 1985. Based upon a conservative estimate of a lethality threshold (15 ppm) in mice exposed for 1 hour. Hematological changes were significant at 15 ppm and at 26 ppm there was 100% mortality.

Scaling: $(15\ ppm)^1 \times 1\ hr = 15\ ppm \cdot hr$

$(15\ ppm)^3 \times 1\ hr = 3{,}375\ ppm^3 \cdot hr$

Uncertainty factors: An uncertainty factor of 10 was retained for interspecies variability to account for possible variability in arsine-induced hemolysis and progression to renal effects. Uncertainty regarding intraspecies variability was limited to 3 because the hemolytic response is likely to occur to a similar extent and with similar susceptibility in most individuals. This was based on the assumption that physiologic parameters (e.g., absorption, distribution, metabolism, structure of the erythrocyte and its response to arsine, renal responses) would not vary among individuals of the same species to such an extent that the response severity to arsine would be altered by an order of magnitude. Individual variability (i.e., variability in erythrocyte structure/function or response of the kidney to hemolysis) would not likely have a significant impact on any of the proposed subcellular mechanisms of arsine toxicity. The steep exposure-response curves from animal data also affirm the limited variability in response. Further more, the AEGL-3 values were developed using a conservative estimate of a toxic response (hemolysis in the absence of lethality) and additional reduction of the values would seem unwarranted.

<u>10-min AEGL-3</u>

$$(15\ ppm)^3 \times 1\ hr = 3{,}375\ ppm^3 \cdot hr$$

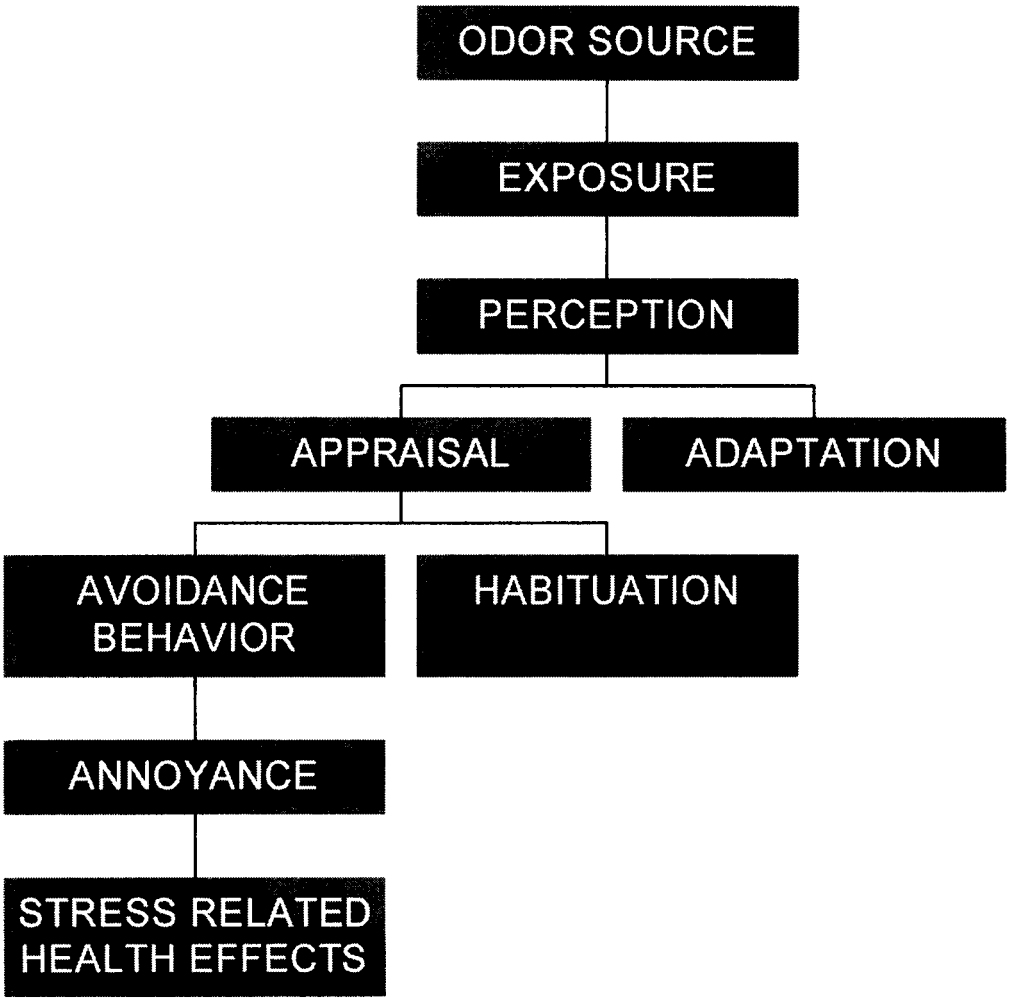
$$C^3 \times 0.5\ hr = 3{,}375\ ppm^3 \cdot hr$$

$$C = 27.26 ppm$$

$$30\text{-min AEGL-3} = 27.26\ ppm/30 = 0.91\ ppm$$

Guidance for the Application of Odor in the Derivation of AEGL-1

Reind van Doorn[1], Marc Ruijten[2] and Ton van Harreveld[3]



1 Environmental Health Department (MMK), Municipal Health Service Rotterdam, the Netherlands

2 Medical Emergency Preparedness and Planning Office (GHOR Rotterdam-Rijnmond), the Netherlands

3 Odournet, Project Research Amsterdam BV (PRA), the Netherlands

Contents

1. Executive Summary 4
1.1. Dimensions of odor 4
1.2. Annoyance caused by odorants 5
1.3. Derivation of a level of annoyance 5
1.3.1. Step one: determine the odor threshold 5
1.3.2. Step two: determine the Weber-Fechner coefficient 6
1.3.3. Step three: calculate concentration that is distinctly detectable 7
1.3.4. Step four: determine the peak-to-mean ratio 7
1.3.5. Step five: calculate a level of annoyance 8
1.4. Evaluation 8
2. Introduction 10
2.1. Scope of this paper 10
2.2. The relevance of odor perception in chemical emergency response 10
3. The olfactory system 12
3.1. Anatomy and physiology 12
3.2. Olfactory Receptors 13
3.3. The odor code 14
3.4. Olfaction and sensory irritation 14
4. Psychophysical dimensions of odor perception 16
4.1. Detectability 16
4.2. Intensity 16
4.3. Odor quality 19
4.4. Hedonic tone 20
5. The determination of odor thresholds 23
5.1. Methodology 23
5.2. The unit of measurement 23
5.3. Quality criteria 24
5.4. Consequences of quality criteria for odor measurements 25
6. Field considerations 27
6.1. Variation of sensitivity to odorants within the population 27
6.2. Adaptation 29

6.3. Perception of mixtures 29
6.4. Sensory irritation and odor perception 29
6.5. Somatic symptoms 30
7. Annoyance and nuisance caused by environmental odors 32
7.1. Definition of annoyance and nuisance 32
7.2. Odor nuisance caused by intermittent long-term exposure 33
7.3. Annoyance caused by short term, acute exposure to odors 35
7.4. Uncertainty in odor annoyance potential of accidental exposures 35
8. A conceptual model for a Level of Annoyance 39
8.1. The odor threshold of the compound 39
8.2. Weber-Fechner coefficient k_w, for the compound 40
8.3. Odor concentration that is distinctly detectable 40
8.4. Peak to mean ratio to account for peaks within hourly exposure 41
8.5. Calculate a level of annoyance 43
9. Discussion 44
10. References 46
11. annex 1 49

1. Executive Summary

Any individual can perceive unusual odor as a threat, especially in the context of chemical incidents. Awareness of exposure might cause anxiety and manifest itself by somatic symptoms of arousal, such as dyspnea, sweating and hyperventilation. Although these symptoms are normal physiologic responses to frightening occurrences, they could lead to avoidance behavior (e.g. closing windows, seeking contact with environmental agencies and/or health authorities). Therefore, environmental health professionals must have and user information about the odor annoyance potential of compounds as well as they need information about irritative and toxic properties of these compounds.

Notification (i.e., informing the public about properties of the unusual odor) can modulate appraisal of odor and the resulting behavior. This guidance provides criteria for the derivation of a 'Level of Annoyance' (LOA) for odor during accidental exposure. If this LOA is lower than the concentration which causes other responses, such as irritation, it is considered the best estimate for an AEGL-1

1.1. Dimensions of odor

The sensory perception of odorants can be characterized by four major attributes or dimensions:

- Detectability (or odor threshold) refers to the minimum concentration of the chemical in air necessary for detection in 50% of the test population. Threshold values are not fixed physiological facts or physical constants, but are a statistically derived best estimate value from a group of individual responses (much like an LC50). The range for this parameter is from less than 10 ppt to the ppm range (roughly five orders of magnitude). At the detection threshold the odor concentration is 1 odor unit per meter cubed (1 ou/m3).
- Intensity is a supra-threshold phenomenon, and refers to the perceived strength or magnitude of the odor sensation. Intensity increases as a function of concentration. The relation between perceived intensity (I) and the odor concentration is log-linear. Odor intensity is often described as a logarithmic function according to Fechner:

  $I = k_w . \log (C/C_0) + 0.5$ [Eq. 1]

  where

  k_w= Weber-Fechner coefficient,

  C= odor concentration (in mg/m^3 or ppm or ou/m^3),

  C_0 = odor threshold concentration (in mg/m^3 or ppm or ou/m^3; use same unit as in C).

  The Weber-Fechner coefficient equals the perceived increase in intensity from a ten-fold increase in the supra-threshold chemical concentration. Intensity is measured on an ordinal 7-point scale, ranging from 0 (= no odor) to 6 (= overwhelming). For example, given k_w= 2.0, C= 56 mg/m^3 and C_0 = 1 mg/m^3, then Intensity (I) would be 4 (= strong) At the odor threshold ($C = C_0$), the perceived intensity is defined to be 0.5.

- Odor quality is expressed in descriptors, i.e. words that expresses what the substance smells like. This is a qualitative attribute, expressed in words, such as fruity, fishy, hay, nutty etc. The quality of an odor may change with concentration level.
- Hedonic tone is a category judgement of the relative pleasantness or unpleasantness of the odor. Hedonic tone is often expressed as a value on a nine-point scale, ranging from +4 (very pleasant) to -4 (offensive).

1.2. Annoyance caused by odorants

Human perception and response is influenced by psychological factors. The prevalence of somatic symptoms, like throat irritation, headache, and nausea, decreased about twofold if subjects received positively biased information about the chemical they were about to be exposed to. Neutral or negatively biased subjects responded similarly. It is probable that during the first phase of an accidental chemical release, when no information is available to the public, subjects will usually respond to odorants as if they are exposed to a threat

The likelihood of experiencing odor as an annoyance, depends on perception, attention and appraisal. If the odorant is not appraised as harmful, it is considered benign and habituation is expected.

On the other hand, if the odor is appraised as harmful, with possible health effects, annoyance may result. Annoyance involves coping behavior. Coping efforts fall into two major categories:

1. Problem-oriented: attacking the problem caused by the stressor, e.g. closing windows;
2. Emotion-oriented: regulating emotions caused by the stressor, e.g. comforting cognition about health effects.

Annoyance potential is the attribute of a specific chemical (or mixture of chemicals) to cause a negative appraisal in humans that may initiate coping behavior when the odor is perceived.

When odor annoyance is likely to occur, the coping behavior and potential anxiety as a result of the odor exposure can be modulated by providing information on the health risk, expected duration, remediation actions etc. to those exposed.

1.3. Derivation of a level of annoyance

This chapter provides a step-by-step method to derive a level of annoyance for odor. Development of an AEGL-1 requires the calculation of thresholds for all possible effects compatible with an AEGL-1; odor annoyance is just one of the possible eligible effects. The lowest of such thresholds would typically be used as a proposed AEGL-1 value.

1.3.1. Step one: determine the odor threshold

The preferred method for the determination of odor thresholds(C_0) is the European CEN standard EN 13725. Similar methods are more and more used in Australia, in Singapore, and by American university institutes. The odor detection threshold is pegged to a reference value, which functions as an internal standard: the stimulus provided by 40 ppb of n-butanol in air. This threshold is called European Reference Odor Mass, EROM.

Published values of odor thresholds generally report measurements where the results were not related to a reference odorant. That implies that the measurements were determined, to a large degree, by the luck of the draw of a handful of panel members out of a population with significant variability in their ability to detect odors.

An additional bias was introduced by presenting diluted odor flows to panel members well below the inhalation rate. This causes additional dilution during the 'sniff' of the panel member. This latter factor caused an important bias in data collected in the USA, where flow rates of less than 1 liter per minute were typically used, while inhalation flow rates are between 15 and 20 liters per minute. A threshold determined as 1ou/m^3 using the less sensitive earlier methodology could be 3 -20 ou/m^3 when repeated using modern methodology.

The number of chemicals with an odor threshold established according to EN 13725 or an equivalent method is limited. The following quality levels for odor thresholds determined by methods other than EN 13725 have been defined to avoid limitation of the proposed methodology for the development of an LOA to these few chemicals:

- Level 1: the threshold of a compound determined according to EN 13725 or an equivalent method.
- Level 2: thresholds from a source which includes a reported value for n-butanol. The butanol value is used to correct the threshold to EROM. The standardized odor threshold ($C_{0,stand}$) is the odor detection threshold determined according to or compatible with CEN13725. The ratio of the C_0 for n-butanol determined in a test panel and the EROM reference value of 40 ppb can be used to calculate a standardized odor threshold. For example: The C_0 for styrene in a test panel was 0.030 ppm. In that same panel the C_0 for n-butanol was assessed as 50 ppb. In this case the estimated standardized odor threshold $C_{0,stand}$ for styrene would be 30 x 40/50 = 0.024 ppm.
- Level 3: thresholds without an internal reference to an n-butanol odor threshold. Such thresholds are often found in compilations such as by AIHA or US EPA. These compilations critique thresholds reported in literature. The best choice would be the lowest reported value from all acceptable sources and not the geometric mean, because the bias introduced by older testing methodology is always towards higher odor thresholds.

1.3.2. Step two: determine the Weber-Fechner coefficient

The second step in the development of an LOC for odor annoyance accounts for odor intensity. The relationship between odorant concentration and the perceived odor intensity is usually described by the Fechner equation (cf. chapter 2). This guidance applies the Fechner equation and the Weber-Fechner coefficient as a parameter for odor intensity calculations.

The Weber-Fechner coefficient can be calculated from the intensity curve, giving the relationship between concentration and perceived intensity of the odor. The value can be determined according to the standard method as described in VDI3882 part 1.

Perceived intensity can be derived using different units on the concentration (horizontal) axis: odor units (ou/m^3) or mass concentration units (mg/m^3 or ppb). The value of k_w can be derived from any of these curves, the slope is independent of the concentration unit used.

An added advantage of the k_w coefficient is that it is expected to be relatively independent of the sample of the population used. The way in which each individual perceives weaker or stronger odors seems to be much less variable than the actual sensitivity of individuals at or near the selection threshold. Solid data on the distribution of kw values for individuals in the general population is not available. Reported values of kw for specific compounds determined according to VDI 3882 varied between 1.65 and 3.5, with 2.33 as a median value.

There are other sources for kw coefficients, f.i. sources without description of methodology and k_w calculated from the so-called Stevens exponent. These kw are not sufficiently reliable. When no kw determined according to VDI 3882 is available, a default of 2.33 can be used.

1.3.3. Step three: calculate concentration that is distinctly detectable

Any unusual odor not common to the normal 'odor landscape' will have the potential to cause annoyance in individuals at perceived intensities that can be described by 'distinctly detectable'. This intensity equals I =3 and the corresponding concentration $C_{distinct}$ can be calculated from the odor threshold and the Weber-Fechner coefficient:

$$C_{distinct} = C_0 \times 10^{2.5/kw} \qquad \textit{[Eq. 2]}$$

Outside of the laboratory, factors such as sex, age, sleep, smoking, head cold and nasal allergy influence the perception of odors. Distraction (i.e. the fact that in a laboratory the individual's attention is purposely focused on detecting odors, whereas this in not the case in ordinary life situations) increases the odor detection threshold by a factor of 4 ($= 10^{0.6}$).

In practice this means that under field conditions a distinct odor is probably distinctly detectable at intensities in the range of I=3 (distinct odor in the laboratory) to I=4 (strongly odor in the laboratory). An intermediate value of I=3.5 is proposed as a value that leads to a distinctly detectable odor under field conditions

$$C_{distinct,\ field\ conditions} = C_0 \times 10^{3/kw} \qquad \textit{[Eq. 3]}$$

1.3.4. Step four: determine the peak-to-mean ratio

The perception of odors is very quick. One breath inhalation takes approx. 3 seconds. One inhalation can lead to odor detection, perception and appraisal. For such rapid effects, we clearly need to account for peaks in the exposure pattern.

A practical value for the smallest period of interest to assessing the effects of odors is approx. 5 seconds. Therefore, time periods of 5 seconds are considered to be a relevant timeframe for peak exposures in this context. In predicting exposure for emergency planning, we typically use dispersion models. These models have been designed and found effective in predicting

annual, monthly and daily averages of predicted concentrations. The smallest time-'byte' of calculation is 10 min to one hour, as this is the common smallest timeframe over which meteorological data are recorded. Models have been found reasonably reliable in predicting the frequency of occurrence of concentrations over a long period of time, even at high percentile values, e.g. the 98-percentile. The capability of a model to predict concentration fluctuations during one particular hour is less favorable, mainly because it is very difficult to obtain a good estimate of the turbulence of the mixing layer within that timeframe.

Definitive data (both meteorological and downwind concentrations), to assess the variability at the 5-second interval level (the minimum relevant interval for odor perception) are not available. However, it is known that the peaks, the height of peaks and the frequency of occurrence of peaks determine the perception of the odor. To account for the peaks, various 'peak-to-mean' ratios have been proposed and applied for odor control policy.

Generally such 'peak-to-mean' values are proposed as a generally applicable value, not differentiated for different states of mixing layer turbulence. For point surface sources peak to mean ratios for long averaging times (typically 1 hour) and far field conditions (more than 200-1000 meters) have values between 3 and 7 at a probability of 10^{-3} for various Pasquill-Gifford stability classes. Every hour contains 720 5-second time periods. So, in practical terms, this observation translates to about one peak per hour that would rise to a level of 3-7 times the TWA. Data on peak-to-mean ratios for higher probabilities are lacking, but would result in lower peak-to-mean ration values.

For practical purposes, a default value of 3 ($=10^{0.48}$) is proposed for transforming one-hourly TWA values to 5 second averaged concentrations of the peak exposure concentrations.

1.3.5. Step five: calculate a level of annoyance

A Level of Annoyance is reached when exposure to odor occurs in a sufficient concentration and duration to cause frequent perception of a distinct odor:

$$\text{LOA} = C_{0,stand} \times 10^{(3/kw)} / \text{peak-to-mean ratio}$$
$$= C_{0,stand} \times 10^{(3/kw)} / 10^{0.48}$$
$$= C_{0,stand} \times 10^{(2.52/kw)}$$

If no k_w, determined according to VDI 3882 is available, a default of 2.33 is recommended and the LOA defaults to $C_{0,stand} \times 10^{(2.52/2.33)} = 12$ standardized odor units.

In the absence of data that allow time scaling for periods shorter or longer than one hour, the use of a constant value is recommended

1.4. Evaluation

The determination of a correct odor threshold value of a compound is by far the greatest contribution to improving the assessment of the short term impact of an odorant on an exposed population and the prediction of a 'level of annoyance'. The Weber-Fechner coefficient however has a substantial influence as well, modifying a Level of Annoyance by a

factor of 500 between the lowest and the highest reported value. The table below presents some selected compounds with a listing of standardized odor detection thresholds, Weber Fechner coefficients, Levels of Annoyance calculated according to this guideline and the current AEGL-1. In most cases a k_w value of 2.33 is used. This value is the median of eleven values reported for eight compounds, using VDI 3882 methodology as well as the median of three values reported for hydrogen sulfide.

Compound	Odor threshold (ppb)	K_w	LOA (ppb)	AEGL-1 (ppb)
Styrene	34.5	-	400	50,000
Benzene	1,700	-	20,000	50,000
n-Butylacetate	76	-	900	-
n-Butanol	39	1.9	450	-
Toluene	1,270	-	15,200	50,000
Dimethyldisulfide	0.35	-	4.2	10
Methyl mercaptan	0.12	-	1.4	5
Dimethylsulfide	0.12	-	1.4	500
Trimethylamine	0.14	-	1.7	100
Hydrogen sulfide	0.6	2.33	7	30

For various compounds which are relevant in emergency response, no standardized odor thresholds and Weber Fechner coefficients are available. For these compounds we suggest to use the lowest reported acceptable odor detection treshold. This concentration is then multiplied by twelve to calculate the expected Level of Annoyance. For example, AIHA (AIH89) reported 5 odor thresholds for ethyl acrylate. Two sources were rejected. The other sources were critiqued and two were found acceptable with a lowest reported value of 0.24 ppb. The resulting LOA for ethyl acrylate is 3 ppb. Using the same procedure would result in a LOA of 1 ppm for chlorine (equal to the current AEGL-1).

2. Introduction

2.1. Scope of this paper

This paper investigates the possibility of using odor perception in emergency response planning and is written on request of BOT-mi (the Dutch Governmental Policy Support Team for Environmental Incidents). The authors have explored the scientific basis for making use of odor characteristics in determining the response to chemical incidents.

The paper aims to provide scientific underpinning of a 'Level of Annoyance' for odor perception during accidental exposure. This Level of Annoyance can be used to estimate the area where members of the public become sufficiently anxious to call the emergency services or environmental complaints lines in significant numbers ('telephone zone').

The interest of the authors in odor as an endpoint for emergency response planning arose from their experience as regional environmental health officials in the Rotterdam-Rijnmond region. Odor nuisance is common phenomenon in this industrialized area.

Episodes where more than 20 persons call the regional environmental protection agency (DCMR) agency within a short time span trigger involvement of environmental health professionals. Examples of compounds that caused such episodes in recent years are methylmercaptan, styrene, and ethylacrylate. In many instances communication is necessary regarding properties of the substances involved, including odor characteristic and health effects. In this process, it is important to be aware of the relationship between odor detection, perception, and appraisal.

In this paper, we first address the relevance of odor perception in chemical emergency response. In section 3, structure and function of the olfactory system are described in short, followed by essential information on the psychophysical dimensions of odor perception in section 4. Methodological aspects of odor threshold determination (section 5) and field considerations (section 6) are subsequently presented. In section 7, annoyance caused by odorants is the key issue. The information presented in the preceding sections, brings us to a conceptual model for a level of annoyance (section 8).

2.2. The relevance of odor perception in chemical emergency response

Humans, like most creatures, need information on their environment continuously, to survive. They rely on their senses to obtain this information and to assess their environment. All sensory perception is provided to the brain for appraisal and is then used to determine and adapt our behavior is such a way as to optimize survival.

In simple terms of behavior, perception of odors can lead to two basic behavioral responses: *avoidance* or *approach* (CAR98). These responses can occur for example in judging food or water or air, but also in a social or sexual context. Humans can distinguish thousands of odors and can detect odors of some chemicals at concentrations as low as a few parts per trillion. For example, our nose is very sensitive to certain repulsive-smelling compounds, produced in trace amounts by some bacteria and molds in rotting processes, such as methyl mercaptan and

trimethylamine. The evolution of heightened odor sensitivity may have developed from the protection offered against dangerous infection or food poisoning (AMO83). In general, however, there is no correlation between odorous and toxic properties of chemicals. Some compounds cannot be detected by smell, even when they are present in toxic concentrations. A prominent representative of such compounds is carbon monoxide. Other compounds, like hydrogen sulfide, trigger a response as a result of their odorous properties, although they are present in concentrations well below toxic levels. In the case of hydrogen sulfide, the perception of the odor even changes to more pleasant and diminishes at higher, toxic concentrations.

The molecular and physiological processes that enable humans to detect and identify thousands of odors, are being clarified only in recent research. A detailed introduction of smell physiology is provided in section 2. In the end, the function of our smell sensor is similar to that of all senses: to translate environmental information into electrical pulses, transmitted by neurons firing in our brain. This information is then evaluated in the brain. This process is broadly termed appraisal.

Appraisal is a complex process, involving various parts of the brain. Smell is different form other senses, because the olfactory information goes straight to the limbic system – a fast route to the brain's emotional center. Unlike all other senses the nerves do not cross over from sensor to the opposite half of the brain. The *hippocampus* and the attached *amygdala* initially process the information and also reflect the information to a part of the cortex directly below the frontal lobes. Whether we find a smell nice or nasty depends crucially on what memories are associated with it. The same smell may have positive connotations for one individual and negative connotations for another. Scanning studies suggest that pleasant odors activate the frontal lobes' smell area, particularly on the right hand side. Unpleasant odors activate the *amygdala* and the cortex in the temporal lobe (*insula*). The direct connection to the limbic system, the brain's emotional and memory organization center, gives smell its power to elicit strong emotional memories (CAR98).

We use our sense of smell to appraise the chemical nature of our direct environment, using our memory as a reference. This function makes the sense of smell immediately relevant to emergency response planning. Exposed humans will be guided by their own sensory information, combined with their reference of previous experiences in their individual memory, and relevant cognitive information. Emergency response actions can add to the cognitive information and hence modulate appraisal and the resulting behavior.

During chemical incidents any unusual odor can be perceived as a threat. Awareness of exposure might cause anxiety and manifest itself by somatic symptoms of arousal, such as *dyspnea* and sweating. Hyperventilation may be a response to anxiety and may also lead to chest pain, dizziness, and fainting. Although these symptoms are normal physiologic responses to life-threatening situations and frightening occurrences, they might lead to avoidance behavior (e.g., closing windows, seeking contact with environmental agencies and/or health authorities). This behavior triggers involvement of local authorities. Modulation of appraisal through communication may be required to avoid anxiety related effects on wellbeing, and to reduce the level of public anxiety.

3. The olfactory system

In olfactory sensory systems, peripheral neurons receive information from the environment and transmit this information to the brain, where it is processed. The olfactory system is intimately involved with limbic system function, and odors have a powerful ability to elicit stirring emotions and memories of past events. Olfactory neurons actually physically link our brain to the environment, and thus represent the most direct interface between the brain and the external world. When a chemical excites a neuron, the signal is transferred to the olfactory bulb. This structure, located in the very front of the brain, is the clearinghouse for the sense of smell. From the olfactory bulb, odor signals are relayed to both the brain's higher cortex, which handles conscious thought processes, and to the limbic system, which generates emotional feelings. In the brain, nervous signals coming from olfactory cells are linked to signals from other sensory input information.

3.1. Anatomy and physiology

Odor as perceived in the brain may be a response based on a range of different olfactory receptor stimuli experienced as sensations in the individual's olfactory system. The olfactory region of the nasal *mucosa* is located in the cribiform plate of the ethmoidal bone and comprises an area of about 5 cm^2, containing in total approximately 50 million primary sensor receptor cells (LEF2000).

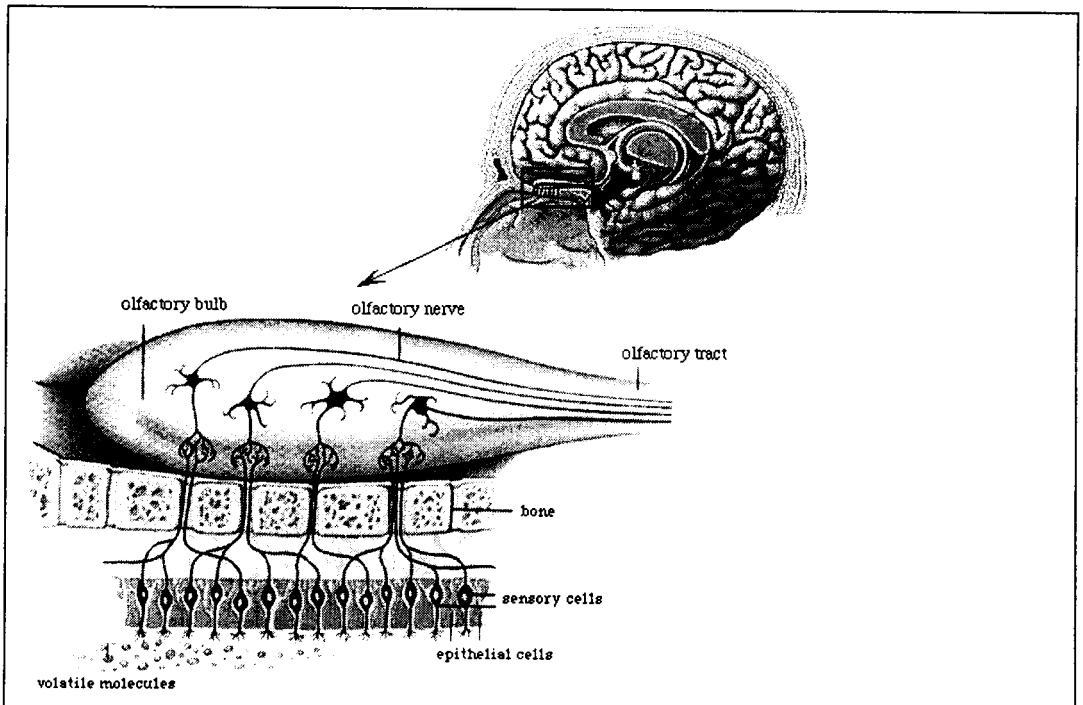


Figure 1. *The physiology of odor perception.*
Source: http://www.sciencenet.org.uk/database/Social/Senses/s00122b.html

The olfactory region consists of cilia projecting from the olfactory epithelium into a layer of mucous (Figure 1). This mucous layer is a lipid-rich secretion that bathes the surface of the receptors at the epithelium surface. The mucous lipids assist in transporting the odorant molecules because only materials that are soluble in the mucous can interact with the olfactory receptors to produce the signals that our brains interpret as odor. Each olfactory receptor neuron has 8-20 cilia that are whip-like extensions 30-200 micrometers in length. The olfactory cilia are the sites where molecular binding of the odorant occurs and sensory transduction starts. Above the mucous layer is the base olfactory epithelium which consists partially of basal cells which are capable of mitotic cell division to form olfactory receptor neurons when functionally mature. The olfactory receptor neurons turnover approximately every 40 days.

Sensory neurons extend a single unbranched axon to the olfactory bulb in the brain such that the projections from neurons expressing a specific receptor converge upon discrete loci called *glomeruli*, which then converge onto mitral cells. The olfactory bulb provides a spatial map that identifies which of the numerous receptors have been activated within the sensory epithelium.

3.2. Olfactory Receptors

The olfactory receptor sites are on the ciliary surface membrane. Odorant stimuli bind to a protein receptor site in the membrane. The stimulus activates G-proteins which evoke an enzyme cascade. At the end channel proteins are phosphorylated that may affect gating of ion channels (Figure 2).

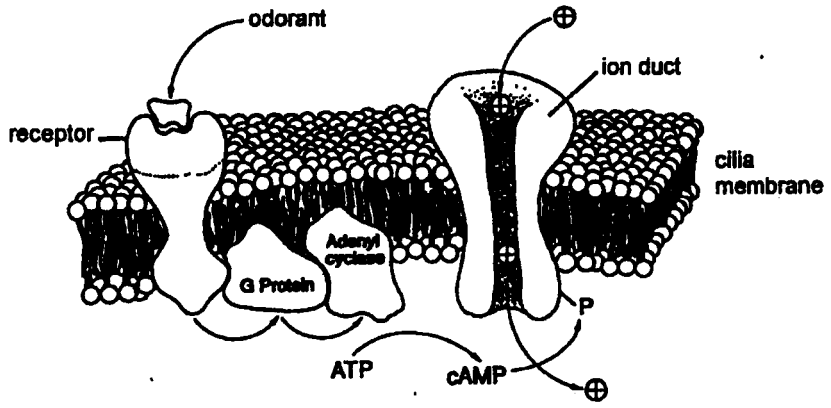


Figure A2 Model of olfactory membrane and transmission of signals. Modified from Plattig, H.H. Spürnasen und Feinschmecker. Die Chemische Sinne des Menschen., Berlin, Heidelberg, New York, Springer Verlag,1995.

Figure 2. *Model of olfactory membrane and transmission of signals. Source: Plattig H.H., Spürnasen und Feinschmecker. Die Chemische Sinne des Menschen, Berlin, Heidelberg, New York, Springer Verlag, 1995*

In 1991, Linda Buck and Richard Axel discovered both the family of transmembrane proteins that are believed to be the odor receptors and some of the genes that encode them (BUC91). They cloned and characterized different members of an extremely large multigene family that encodes the seven transmembrane proteins whose expression is restricted to the olfactory epithelium. This was a breakthrough in our understanding of the olfactory system. It is now estimated that there are between 500-1000 odorant receptor genes in humans. This number of genes, specific to the olfactory system, comprises 2.5% of the approximately 30,000 genes thought to make up the human genome. This number is second only to the receptors of the immune system. The enormous amount of genetic information devoted to smell perhaps reflects the evolutionary significance of this sensory system for the survival of most mammalian species (AXE95).

3.3. The odor code

Using a technique called calcium imaging, researchers detected which nerve cells were stimulated by a particular odor (MAL99). It was shown that

(1) single receptors can recognize multiple odorants,

(2) a single odorant is typically recognized by multiple receptors, and

(3) different odorants are recognized by different combinations of receptors.

It appears that the sense of smell in mammals is based on a combined approach to recognizing and processing odors.

Instead of dedicating an individual odor receptor to a specific odor, the olfactory system uses an "alphabet" of receptors to create a specific smell response within the neurons of the brain. As in language, the olfactory system appears to use combinations of receptors to reduce the number of receptor types required to convey a broad range of odors. Thus, 1,000 or so receptors can detect many thousands of distinct chemicals.

Slight changes in chemical structure activate different combinations of receptors. For example octanol smells like oranges, but the structurally similar compound octanoic acid smells like sweat, based on the receptors activated. It was found that large amounts of a chemical bind to a wider variety of receptors than do small amounts of the same chemical. This may explain why a large whiff of the chemical indole smells putrid, while a trace of the same chemical smells flowery.

3.4. Olfaction and sensory irritation

Some chemicals, besides having a true odor, also cause immediate irritation of the eyes, throat and nose. The sensation of stinging, prickling, or burning, mediated by the trigeminal or 5th cranial nerve, is quite distinct from the smell sensation carried out by the olfactory or 1st cranial nerve (Figure 3). The free nerve endings of the trigeminal nerve are located over the nasal, oral, and ocular mucosae. Stimulation of the trigeminal nerve in the nose produces chemical irritation (CAI80).

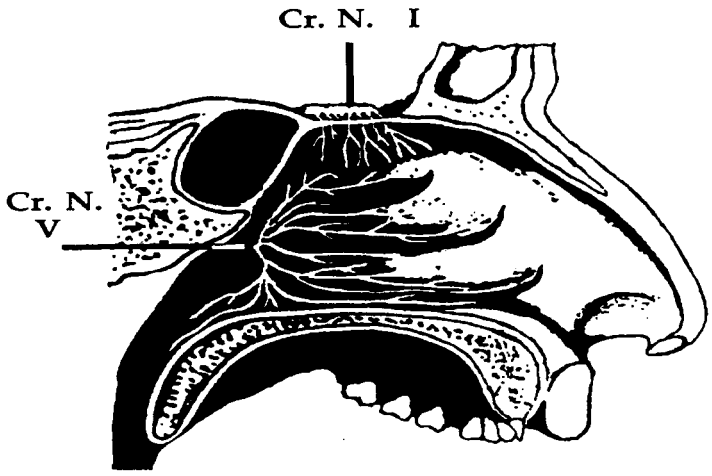


Figure 3. *Simplified anatomy and innervation of the lateral wall of the nasal cavity: Cr.N. I = first cranial (olfactory) nerve; Cr.N.V. = fifth cranial (trigeminal) nerve. Source: SHU92*

435
436
437
438
439 Sensory irritation combines with olfaction to form an overall perception. For example, at low
440 concentrations ammonia has a distinct odor; at a high concentration however, ammonia is also
441 pungent, which is the chemesthetic component of the overall perception. The lowest observed
442 level at which a chemical exposure produces sensory irritation has been the putative basis for
443 establishing exposure limits for a substantial number of compounds.
444
445

4. Psychophysical dimensions of odor perception

Sensory testing has been developed into a precise, formal, and structured methodology that is continually being updated to include refinements in the existing techniques. Measurement of the stimulus-response characteristics of odorants constitutes a branch of science known as 'psychophysics' (SHU92). The sensory perception of odorants can be characterized by four major attributes or dimensions:

- detectability;
- intensity;
- odor quality;
- hedonic tone.

These attributes and the methods to characterize them through measurement are described in more detail in the sections below.

4.1. Detectability

Odor concentration is the most common attribute used to characterize odors. It provides the most common measure to characterize the magnitude of stimulus for determining the other attributes of an odor.

Detectability (or odor threshold) refers to the minimum concentration of odorant stimulus necessary for detection in some specified percentage of the test population. The odor threshold is determined by diluting the odor to the point where 50% of the test population cannot detect the odor any more. At the detection threshold the odor concentration is 1 odor unit per meter cubed.

Threshold values are not fixed physiological facts or physical constants but a statistically best estimate value from a group of individual responses (sections 4 and 5 describe more details). In the European draft CEN standard (CEN99) the threshold value is pegged to an agreed reference value: the stimulus provided by 40 ppb/v n-butanol in air.

In this paper the term $C_{0,\,stand}$ refers to the standardized odor detection threshold.

4.2. Intensity

Intensity (I) is the second dimension of the sensory perception of odorants, which refers to the perceived strength or magnitude of the odor sensation. Intensity increases as a function of concentration. The relation between perceived intensity and the *logarithm* of odor concentration is linear.

The relationship between perceived intensity I and the stimulus concentration may be described as a theoretically derived logarithmic function according to Fechner:

$$I = k_w \cdot \log(c / c_o) + 0.5$$

where

	I	perceived intensity of sensation (theoretically determined)
	c	odor concentration
	c_o	threshold concentration
	k_w	Weber-Fechner coefficient

or as a power function according to Stevens:

$$I = k_s \cdot (c - c_0)^n$$

where

	I	perceived intensity of sensation (empirically determined)
	c	odor concentration
	c_0	threshold concentration
	n	Stevens' exponent
	k_s	a constant

The preferred method for measuring intensity is derived from a German standard (VDI97). The principle of measurement is the presentation of odor to human assessors in an odor panel, at varying degrees of dilution, hence varying perceived intensity. The members of the panel are asked to indicate perceived intensity at each presentation as a value I on an ordinal seven point intensity scale:

0	no odor
1	very faint odor
2	faint odor
3	distinct odor
4	strong odor
5	very strong odor
6	overwhelming odor

The values for I are then plotted against the logarithm of the odor concentration or the dilution factor. The regression line characterizes the relation between perceived intensity and odor concentration. The point where the regression line intersects with the horizontal axis is approximately equivalent to the detection threshold.

For example, the regression equation for menthone was:

$$I = 2.35 \log C - 2{,}24 \quad (r^2 = 0.98)$$

From this it may be calculated that a strong menthone odor (I=4) was perceived at a concentration level of approximately 50 odor units and that the odor threshold concentration (I=0.5) is approximately 15 ppb/v.

For a selection of investigated odorants a 10-fold increase in suprathreshold odorant concentration leads to a 1.9 - 3.5 scale point increase in intensity. Odors with high slope values, such as ammonia dissipate quickly with dilution. Odors with lower slope values, such as hydrogen sulfide are more difficult to control.

Patte et al (PAT75) reported values for the standardized intensity slopes of 110 odorant compounds. In fact these were the linear growth slopes of perceived intensity as a function of the stimulus concentration on log-log coordinates (the exponent n in Stevens power function). Slopes varied from 0.12 (1-decanol) to 0.87 (allyl isothiocyanate). The median value was 0.35. A value of 0.35 means that a 10 fold increase in the suprathreshold odorant concentration compounds leads to $10^{0.35}$ (= 2.2 scale units) increase in perceived intensity. Values were reported for eight compounds with ERPG's. For the majority of compounds presented in PAT75 a strong odor perception is expected at a concentration of 10-100 odor units. Table 1 lists Fechner ratios, some estimated from Stevens coefficients (presented in *italics*) and the odor concentration in ou/m^3 associated with intensity 'distinct odor' from that relationship. The odor threshold concentrations were derived from the Fechner intensity curves where possible, and presented with results from actual threshold measurements from the same report, where possible. These values are not necessarily compatible with European odor units ($ou_E \cdot m^{-3}$).

Table 1 Intensity data based on Fechner coefficient's and Stevens power

Compound	Threshold	Threshold estimate from intensity	Odor concentration at I =3 (distinct)		Fechner coefficient	
	Stevens	Fechner	Fechner	Stevens		
	ppm	ppm	Ou/m^3	Ou/m^3	k_w	
Styrene		0.033199	25.6		1.42	ONSL0135 Japan
Styrene	*0.093000*			*10.9*	*2.26*	*Patte 1975*
Butyric acid		0.000069	35.5		1.29	ONSL0135 Japan
Methylisobutylketone		0.169943	16.3		1.65	ONSL0135 Japan
Toluene		0.921055	26.8		1.4	ONSL0135 Japan
Toluene	*0.980000*			*8.9*	*2.55*	*Patte 1975*
Valeric acid		0.000111	18.1		1.59	ONSL0135 Japan
Valericaldehyde		0.000713	29.6		1.36	ONSL0135 Japan
Propion aldehyde		0.001473	95.5		1.01	ONSL0135 Japan

Butyraldehyde		0.000313	87.4		1.03	ONSL0135 Japan
Xylene		0.114505	20.3		1.53	ONSL0135 Japan
Ethylacetate		0.249493	29.6		1.36	ONSL0135 Japan
Isovaleric acid		0.000054	68.4		1.09	ONSL0135 Japan
Isovalericaldehyde		0.000194	30.3		1.35	ONSL0135 Japan
Dimethyl disulphide		0.000285	104.8		0.99	ONSL0135 Japan
Aceton	20.85825		12.2		2.3	VDI3882blatt1
Benzene	1.400000			6.4	3.37	Patte 1975
n-butanol		0.045773	32.7		1.65	VDI3882blatt1
n-butanol	0.116951		15.5		2.1	VDI3882blatt1
Methyl mercaptan		0.000102	39.8		1.25	ONSL0135 Japan
Methyl mercaptan	0.021000			26.3	1.59	Patte 1975
Acetaldehyde		0.001507	95.5		1.01	ONSL0135 Japan
Acetaldehyde	0.430000			69.4	1.28	Patte 1975
Dimethyl sulfide		0.000119	366.5		0.78	ONSL0135 Japan
Trimethylamine		0.000111	166.8		0.9	ONSL0135 Japan
Ammonia		0.149160	15.8		1.67	ONSL0135 Japan
Ammonia	2.828235		5.2		3.5	VDI3882blatt1
Hydrogen sulfide		0.000495	127.4		0.95	ONSL0135 Japan
Hydrogen sulfide	0.001300			9.6		Patte 1975
Hydrogen sulfide			11.8		2.33	VDI3882blatt1
Hydrogen sulfide	0.003818		20.7		1.9	VDI3882blatt1
Hydrogen sulfide		0.000765	10.9		2.41	VDI3882blatt1
Isobutyl alcohol		0.011569	340.1		0.79	ONSL0135 Japan
Isobutyraldehyde		0.000897	77.1		1.06	ONSL0135 Japan
Proprionic acid		0.002462	28.1		1.38	ONSL0135 Japan
Acrylicacidmethylester	0.005870		8.4		2.7	VDI3882blatt1
Furfural				14.7	1.95	Patte 1975
Carbon tetrachloride	11.20000			7.4	2.94	Patte 1975
Menthon		0.014654	11.6		2.35	VDI3882blatt1
Guajacol		0.007386	8.7		2.66	VDI3882blatt1
Isoamylalcohol			13.7		2.2	VDI3882blatt1

4.3. Odor quality

In contrast to the odor threshold, which on its own fails to permit any evaluation of possible annoyance, the intensity variation provides indications of the annoyance potential. In addition however, other factors have to be taken into consideration, for example odor quality and hedonic tone.

Odor quality is the third dimension of odor. It is expressed in descriptors, i.e. words that describe what the substance smells like. This is a qualitative attribute, expressed in words,

such as *fruity, fishy, hay, nutty* etc. The American Society for Testing and Materials (ASTM) developed a list of 146 descriptors and used it to characterize 160 compounds and mixtures in a standardized manner, with a large panel of 120-140 individuals. The results are published in an 'Atlas of Odor profiles' (AST68).

The character of an odor may change with concentration level. For example, hydrogen sulfide at levels of 20 ppm or above ceases to be perceived as a "rotten egg" smell. At higher concentrations it is perceived as 'sweet' and at even higher concentrations, which are acutely toxic, hydrogen sulfide becomes odorless.

A special area in odor quality is *masking*. When an odor is unpleasant, strong odors are usually considered "pungent", not just strong. Deodorants may affect the quality (pleasantness) of the overall just because they mix with the malodors. The mixtures of the smells may be less intense and thus less unpleasant than the malodor.

4.4. Hedonic tone

Hedonic Tone ***(H)*** is the fourth dimension of odor. This is a category judgement of the relative like (pleasantness) or dislike (unpleasantness) of the odor. The method for measuring intensity is derived from a German standard method VDI 3882 (VDI97).

The principle of measurement is presentation of the odor to human assessors in an odor panel, at varying degrees of dilution, hence varying perceived intensity and hedonic tone. The members of a panel of assessors are requested to indicate the perceived hedonic tone at each presentation as a value from the nine-point hedonic tone scale:

+4	very pleasant
+3	pleasant
+2	moderately pleasant
+1	mildly pleasant
0	neutral odor / no odor
-1	mildly unpleasant
-2	moderately unpleasant
-3	unpleasant
-4	offensive

For each concentration level, the mean of the values for H of all panel members is calculated, and plotted against the odor concentration in odor units. A fictitious example of the plotted result is presented in figure 4. Using a suitable curve fitting procedure a line can be fitted through the points obtained in the experiment. Using this interpolation, characteristic values can be derived from the plot, such as the odor concentration at $H = -2$.

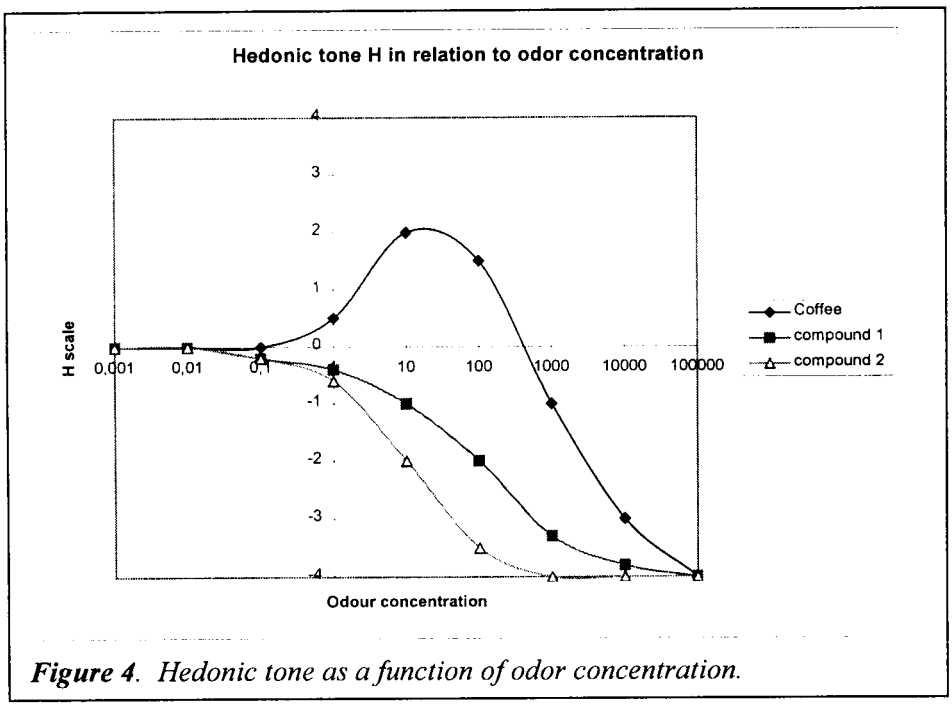


***Figure 4**. Hedonic tone as a function of odor concentration.*

There is no simple general relationship between intensity and hedonic tone. For example, a number of odorants (pure substances as well as mixtures) were diluted to reach strong odor detection ($I = 4$) in an odor panel (WIN95). Members of the panel were subsequently asked to estimate the hedonic tone. The results are shown in table 3.

***Table 3.** Hedonic perception of odorant concentrations at strong intensity level. Source: Win95*

Hedonic value	Hedonic description	Odor quality
$H = > 0$	Neutral or pleasant	Pine, menthone, perfume, bakery
$H = < 0$ and > -1	Neutral to mildly unpleasant	Amylacetate, thinner, butanol
$H = < -1$ and > -2	Mildly to moderately unpleasant	Chlorine, perchloroethylene, biofilter
$H = < -2$ and > -3	Moderately to clearly unpleasant	Pig house, sulfur disulfide, teflon melting

Hangartner performed laboratory investigations to ascertain the concentration of various odors that resulted in equal hedonic appraisal (HAN95). Some results for hedonic tone 'moderately unpleasant' (H= -2) are presented in figure 5.

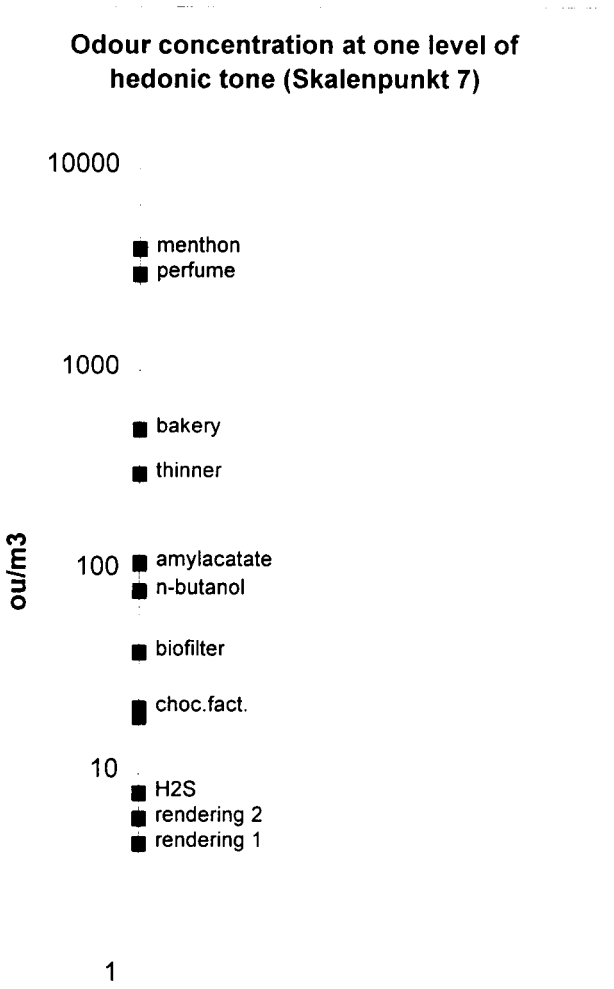


***Figure 5**. Odor concentration at H=-2 (from HAN95)*

In contrast to the small interindividual variation in the perceived intensity of a certain odorant at suprathreshold concentrations, the interindividual variation in hedonic perception is substantial, among other factors dependant on odor experience, education and cultural setting (PAD95).

In summary: research on odor thresholds, intensity and hedonic tone give weight to the conclusion that *for most compounds* a concentration between 5-50 odor units results in clear odor detection, which is perceived as neutral to clearly unpleasant.

5. The determination of odor thresholds

5.1. Methodology

Because no methods exist at present that simulate and predict the responses of our sense of smell to a satisfactory degree, the human nose is the most suitable 'sensor'. Olfactometry employs a panel of human noses as sensors. The *detection threshold* can be measured with better repeatability (within a laboratory) and better reproducibility (between laboratories) than the *recognition threshold* and so is preferable for environmental assessment purposes.

In one of the modern olfactometry testing procedures (CEN99), a diluted odorous mixture and an odor-free gas (as a reference) are presented separately from two sniffing ports at 20 ℓ/min to a group of eight panelists in succession. In comparing the gases emitted from each port, the panelists are asked to report the presence of odor together with a confidence level such as guessing, inkling, or certainty. The gas diluting ratio is then decreased by a factor of two (i.e., chemical concentration is increased by a factor of two). The panelists are asked to repeat their judgment. This continues for five - six different dilution levels, resulting in a total of almost hundred judgments (sniffings) from eight panelists.

Figure 6: Dynamic olfactometry with human assessors, to measure odor concentration according to EN13725, photo courtesy of Odornet UK Ltd.

Using panelist responses over a range of dilution settings, the odor threshold concentration can be calculated from individual threshold estimates. At the *odor threshold*, 50% of panelists in olfactometry analysis respond to the odor during olfactometry testing and 50% do not. At the odor threshold, the *odor concentration* of an odor sample (single compound or mixture) is defined as 1 *odor unit* per cubic meter.

5.2. The unit of measurement

The way in which the response of our sense of smell is reduced to a single value of a parameter amounts to a gross simplification of the rich spectrum of sensory information that is actually perceived by the brain. Such a simplification may be useful, however, in describing potential effects. The reduction of a very complex physiological process to a simple parameter is methodologically very similar to expressing the effects of toxic substances on an organism as the LC_{50}, which indicates the concentration causing lethality in 50% of a well-defined test population. The complex physiological response is regarded as the unifying reaction that can be caused by a wide range of substances, at an equally wide range of concentrations.

In general terms, this approach can be used to describe the potential of a certain amount of a substance to cause a physiological effect, by expressing the dose as a multiple of the dose that would cause an effect in 50% of a population. The definition and use of the unit are highly

analogous to that of the odor unit. In odor research, the D_{50} could be described as the concentration at which 50% of a population that can detect a sensory stimulus. Odor detection thresholds were reported for a large number of compounds. There are a few compilations available (cf. annex 1). Unfortunately most reported odor thresholds were measured without reference to a standard odorant and reported values can therefore be far apart.

In the past odor researchers have not used populations of standard test subjects, and have only related the physiological response to the number of dilutions of the dose of a sample to be measured. That practice implies a fundamental inability to compare the dosage of the samples through other means than the population itself.

This can only be justified if the researcher is convinced that the samples of the population are sufficiently large to compensate for biological variability within this population. This assumption, however, cannot be fulfilled in the practice of odor measurement. The small sample from the population (typically 4-8 subjects, more or less randomly chosen) is far too limited a sample to be representative, knowing the variability of sensitivity within the population. This practice does not comply with statistical requirements as used in toxicological experimental design, as the sample size from the population required to be representative (hundreds) is far greater than the regular number of panel members used in olfactometry for environmental applications.

The solution is to standardize the test subjects used to assess the sensory response without introducing a bias. Reproducible results can be obtained by selecting panel members with a known sensitivity to an accepted reference material (currently n-butanol CAS-nr [71-36-3]). The assumption is that the sensitivity for the reference odorant will predict the sensitivity to other substances. The dose of other substances and mixtures is then expressed in multiples of the dose that would elicit a physiological reaction equivalent to that of the reference.

5.3. Quality criteria

Since the early 1990s, the introduction of improved instrument calibration, improved panel screening procedures and the adoption of n-butanol as a reference material, have enabled more objective odor concentration measurement (HAR99).

Olfactometry requires a very high standard of testing conditions. These include an odor-free testing environment, a highly accurate and repeatable olfactometer and effective panelist management. A dynamic olfactometer is a gas diluting apparatus and also an interface between a panel of human observers and an odorous gas sample diluted at various concentrations.

The performance of an odor laboratory can now be assessed in terms of measurement accuracy in relation to an agreed reference material such as *n*-butanol. The 'trueness' of a measurement method is described by two terms, 'accuracy' and 'precision'. *Accuracy* (absence of bias) is defined as the closeness of agreement between the average test result of a method and an accepted reference value and may be investigated by comparing an accepted reference value with the level of the results given by the measurement method. *Precision* (repeatability and reproducibility) involves the random errors inherent in every measurement procedure. Precision describes how close repeated measurements are to each other. While the

term *'repeatability'* is used to describe precision in the same laboratory, the term *'reproducibility'* is used to describe precision of a method as attained between laboratories. Currently, the preferred and internationally standardized methods of measuring odor are the Dutch NVN2820 and the more recent CEN standard (CEN99).The performance of odor concentration measurements has been defined in the performance criteria of the standard. At standard conditions for olfactometry, the reference value corresponds to an *n*-butanol concentration of 40 ppb. The overall sensory quality criteria for accuracy and precision are:

- bias equal to or less than 0.217
- repeatability not greater than 0.477

This means that only results of laboratories are accepted that are able to reproduce the odor threshold of *n*-butanol within a factor $10^{0.477}$ in 95% of cases, corresponding to 13-120 ppb. Each separate determination of an *n*-butanol odor threshold should fall within a factor of $10^{0.217}$, corresponding to 24-66 ppb.

Eighteen European countries have been able to agree on an olfactometry standard in a relatively short time. An inter-laboratory comparison study of olfactometry in Europe was undertaken in 1996. The study demonstrated that individual laboratories following the methods specified in the draft CEN standard for odor concentration measurement can achieve quality requirements in terms of bias and repeatability as specified in the standard (SCH96). The value of the European odor unit, at 0.123 mg/m^3 n-butanol reference (or 40 ppb/v), is a consensus value. The laboratories that use this criterion in practice find that they discard candidates for their panels at either end of the 20 - 40 ppb/v acceptable range, with perhaps a larger fraction too sensitive rather than not sensitive enough.

5.4. Consequences of quality criteria for odor measurements

None of the odor thresholds of n-butanol reported by AIHA in 1989 would be accepted according to the bias criterion (range of reported detection thresholds 120-11.000 ppb). Modern performance based forced choice dynamic olfactometry has greatly improved the sensitivity, repeatability and reproducibility of odor measurement. For instance, the butanol threshold measured using a three port IITRI olfactometer ranged from 80 - 200 ppb, while modern dynamic olfactometry is capable of measuring butanol threshold levels in the range of 20 to 80 ppb. Correspondingly, a threshold determined as 1 odor unit per m^3 using the less sensitive earlier methodology could be rated at 3 - 20 odor units per m^3 using modern equipment. So, the use of advanced olfactometry based methods could result in much stricter odor concentration limits being specified in odor impact criteria.

It is useful to specify some definitions:

Odor detection threshold

The odor detection threshold (C_0) is the odorant concentration which has a probability of 50% of being detected under the conditions of a test.

Odor unit

An odor unit (C/C_0; ou) is the amount of odorant present in one cubic meter of odorous gas at the panel threshold

Standardized odor unit

The European odor unit [ou_E] is that amount of odorant that, when evaporated into 1 cubic meter of neutral gas at standard conditions, elicits a physiological response from a panel (detection threshold) equivalent to that elicited by one 123 µg n-butanol. One European Reference Odor Mass (EROM), evaporated in one cubic meter of neutral gas at standard conditions, is equivalent to the D50 physiological response (detection threshold), assessed by an odor panel in conformity with CEN13725 and has, by definition, a concentration of 1 $ou_E \cdot m^{-3}$

Standardized odor threshold

The standardized odor threshold ($C_{0,\,stand}$) is the odor detection threshold determined according to or compatible with CEN13725. The ratio of the C_0 for n-butanol determined in a test panel and the EROM reference value of 40 ppb can be used to calculate a standardized odor threshold. For example:

The C_0 for styrene in a test panel was 0.040 ppm. In that same panel the C_0 for n-butanol turned out to be 50 ppb. In this example the standardized odor threshold $C_{0,\,stand}$ for styrene is 30 x 40/50 = 0.024 ppm

6. Field considerations

6.1. Variation of sensitivity to odorants within the population

Subjects in good health can normally reproduce their individual odor thresholds for a certain compound within a factor 2 (AMO70). So, intra-individual variation is relatively small as compared to inter-individual variation .

Olfactory responses of individuals vary with age. Increasing age is correlated with decreasing sensitivity. Furthermore, female panelists usually have a lower odor threshold than male panelists from the same age group. Factors such as health status (e.g., cold, nasal allergy), smoking behavior, personality, educational background and training may contribute in some degree to the ability to assess an odor. The magnitude of the influence is shown in Table 4 as the ratio of the threshold in a subgroup as compared to an average healthy forty-year-old male (from AMO83).

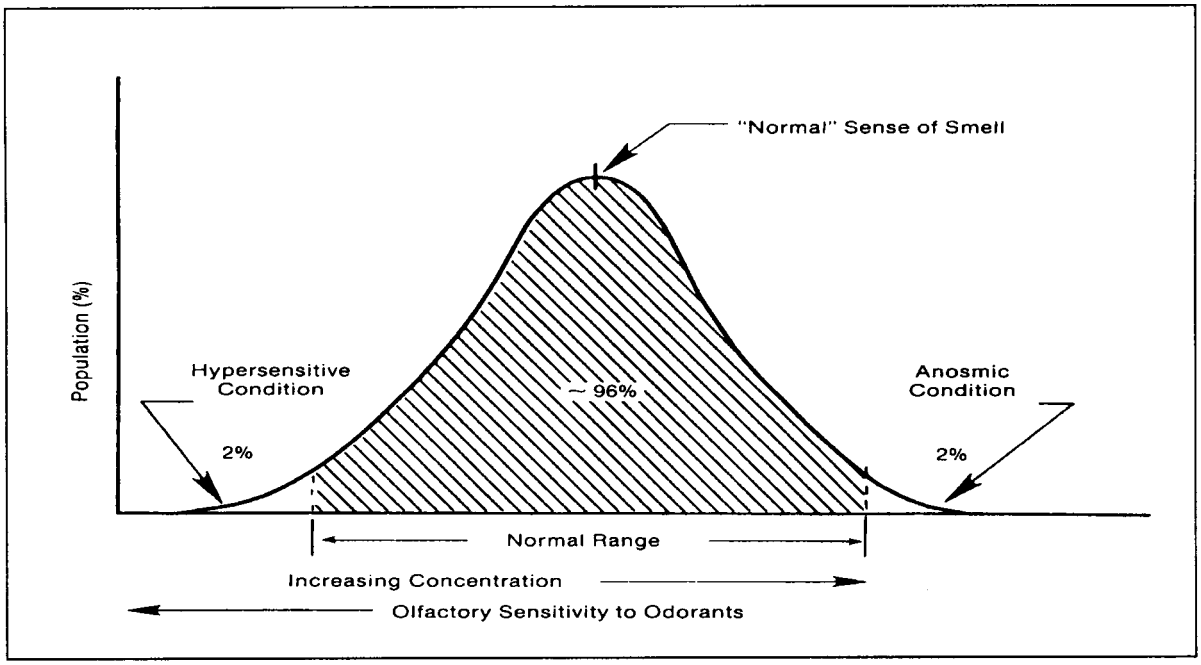
Table 4. Factors influencing the odor detection threshold (from AMO83).

Factor	Odor perception threshold versus average healthy forty year old male
Average woman	0.8
18 yr. male	0.5
62 yr. male	2
Smoking during test	4
Chewing during test	4
Head cold	4
Nasal allergy	4
Undirected test	4

The sensitivity in sense of smell within the population follows a log normal distribution (AIH89). Two percent of the population are predictably hypersensitive, and two percent are insensitive. The insensitive range includes people who are anosmic (unable to smell) and hyposmic (partially unable to smell). A person may be hyposmic to one odorant and hyperosmic (hypersensitive) to another.

The standard deviation in the distribution of individual odor thresholds is approximately the same for all odorants so far tested, averaging very close to a factor of 4 (AMO85). Accordingly, for a certain odorant, 68% of persons tested are expected to have individual thresholds within a sixteen-fold range of one-quarter of the median, and four times the median. Data on the actual distribution of detection thresholds in the general population as a

773 whole (including infants and the aged) are unavailable, as far as the authors are aware. Partial
774 information is currently being compiled by PRA Odournet, Amsterdam, using intake selection
775 data for its panel members. Data are available for over 1000 individuals, but the sample
776 consists of those who answered to panel recruitment which may not make this group quite a
777 proper random sample of the population. The indications are that the variation in odor
778 thresholds in this group is large, with difference of approximately a factor 30 between the top
779 and bottom 5% of the distribution.



780

781 ***Figure** 7. The sensitivity in the sense of smell within the population. From AIH89.*

782

783 There is a substantial difference between the level of odorant that *can* be detected, and the
784 level that *will* be detected (WHI77). In a study on the influence of various degrees of
785 **distraction** on the responsiveness of people to well-known warning odors, substantial
786 differences where found between directed and undirected tests. In a *directed test*, the attention
787 of the subject is purposely focused on the sole objective of detecting odor. In the *undirected*
788 *test*, the subjects were given no indication of the object of the exercise. Recalculation of the
789 data on log/probit coordinates resulted in a four-fold increased detection threshold for the
790 undirected test as compared to the directed test (AMO85).
791 Three compounds (ethyl mercaptan, phenyl ether, and isoamyl acetate) were tested for their
792 capability to **wake a sleeping person** (FIE31). These odorants can be regarded as more or
793 less purely olfactory stimulants, i.e., they cause little or no irritation through stimulation of the
794 trigeminal nerve. An odorant concentration of about 20,000 times the detection threshold was
795 required to awaken 50% of soundly sleeping persons.

6.2. Adaptation

With continuing exposure to a certain odor concentration, the sensation gradually decreases, and may even disappear. Fatigue from continued exposure to an odor may affect a person's sense of smell. This phenomenon is called adaptation. Adaptation begins to reduce perceived odor intensity and quality during the first inhalation. Adaptation may reduce both perceived odor intensity and perceived odor quality. The degree of adaptation resulting from exposure to an odorous air will depend on the odor concentration experienced. The weaker the odor concentration of an air sample, the more does adaptation affect perceived strength. This is because at a lower concentration it may be necessary to sniff harder and to take more than one sniff in order for the odor to be detected. Although adaptation takes some time to develop, recovery takes place more quickly. Recovery periods may range from seconds to minutes depending upon type of odor, odor concentration, and duration of exposure. It has been pointed out that while sensitivity to an odor may decrease after sniffing a sample, 80 to 90% recovery generally occurs within a minute with complete recovery in several minutes.

During exposure to hydrogen sulfide, most subjects experienced an exponential decrease of intensity, that dropped to a steady level within 2-5 minutes, and did not change appreciably up to 15 minutes later (EKM67). One of eight subjects indicated virtually complete loss of odor sensation and another a substantial loss. The other six showed an approximately 50% decrease of perceived intensity, which - based on a slope value of 0.51 - corresponds to an apparent four-fold reduction in the hydrogen sulfide concentration. After breathing pure air, the sensitivity recovered almost completely in about four minutes.

6.3. Perception of mixtures

In most situations, not just a single compound but a mixture of odorants is responsible for odor detection. Studies have been undertaken on the perceived intensity of odor mixtures by mixing two odorants, both above the detection threshold. The typical finding was that the perceived intensity of a mixture is less than the arithmetic sum of the individual intensities (hypo-addition). For example, the perceived odor strength of a mixture of five odorants, each of equal perceived odor intensity, does not exceed that of the single component odorant by more than 10% (BER73).

6.4. Sensory irritation and odor perception

When a volatile compound is inhaled into one nostril and air into the other, the stimulated side can be determined (lateralized) only after the concentration reaches a level that stimulates the trigeminal nerve; compounds (at concentrations) stimulating olfaction alone cannot be lateralized. The distinction between olfaction and chemesthesis allows to establish both olfactory and intranasal irritation thresholds.

Individuals who lack a sense of smell (anosmics) cannot detect some odorants, indicating that these odorants do not stimulate the trigeminal nerve. For anosmics the average *n*-butanol lateralization threshold was equivalent to the average *n*-butanol detection threshold. These thresholds for anosmics were equal to the average butanol lateralization threshold from normosmics, whose detection thresholds for *n*-butanol were substantially lower. This suggests

836 that the detection of *n*-butanol in normosmics is driven by olfaction rather than by irritation.
837 However, several studies have suggested that anosmics may have lowered sensitivity to
838 irritants, thus raising concern about the use of anosmic data to predict irritation thresholds for
839 individuals with intact olfactory and trigeminal systems (KEN96;HUM96).
840 Wysocki assessed the sensitivity of olfaction and chemesthesis for acetone and *n*-butanol in
841 acetone-exposed workers during a workday and in unexposed (naive) subjects (WYS97). The
842 naive subjects experienced a different perception of irritation at concentrations of acetone that
843 were below the intranasal irritation threshold. In general, the workers treated the stimuli
844 simply as nonirritating odors, whereas the unexposed subjects ascribed irritating qualities to
845 the stimuli. The authors speculated about the possibility that concentrations of acetone and
846 *n*-butanol that were well above the olfactory detection threshold but below the lateralization
847 threshold could be annoying to some subjects, simply because they do not recognize the odor
848 and attribute liabilities, e.g. toxicity, to the compound.
849 Odor and irritation sensitivity for methyl isobutyl ketone (MIBK) were evaluated by obtaining
850 olfactory detection and irritation (lateralization) thresholds, as well as perceived odor intensity
851 and irritation ratings (DAL00). The best predictors of perceived irritation to high
852 concentrations of MIBK were those measures related to its odor, not to the threshold for
853 sensory irritation. This suggests that negative responses to MIBK involve reactions to
854 olfactory properties.

855 ### *6.5. Somatic symptoms*

856 The human perception and response to supra threshold odor stimuli and irritants may be more
857 driven by psychology than by the concentration of the odorants. For example, in one
858 experiment 90 adults were divided into three groups, each of which was given different
859 information about chemicals to which they would be exposed (DAL97). Researchers told the
860 neutral group that the chemical they were to be exposed to, is approved for, and commonly
861 used in olfactory research. The positive bias group was told that the odor was from natural
862 extracts that are used in aroma therapy and that it is reported to have beneficial effects on
863 mood and health. The negative bias group was told that the chemical was an industrial
864 solvents that is reported to cause adverse health effects and cognitive problems following
865 long-term exposure.
866 Following the exposure the subjects completed questionnaires to collect information on health
867 symptoms. The positively biased group reported far fewer symptoms than the other two
868 groups. Neutrally biased subjects responded similar to the negatively biased group. One
869 interpretation for this finding may be that a normative response exists to many odors which is
870 negative.
871

Table 5. *Selected Reported Health Symptoms in Subjects (n=30 for each group) after 20 min Exposure to 800 ppm Acetone compared.. Adapted from DAL99.*

Symptom	Subjects exposed to odorant		
	Positive bias	Negative bias	Neutral
Throat irritation	4.36	8.69	8.59
Eye irritation	2.42	4.70	4.63
Nasal irritation	6.05	12.95	14.43
Lightheadedness	5.35	8.53	12.57
Headache	2.37	4.87	5.09
Nausea	1.9	2.60	5.17
Drowsiness	3.04	6.98	5.64

872

873 The overall pattern of results of this and other studies suggests that many of the health-related
874 effects of exposure to odorants are mediated by cognitive variables, such as mental models of
875 the relationship between environmental odors and health (DAL99).

876

7. Annoyance and nuisance caused by environmental odors

Investigations on the effects of odor exposure on health and well-being in the population have typically assessed annoyance as the main target (STE99).

Whether or not one experiences odor as annoyance, depends on perception and *attention.* When attention is drawn, a process of *appraisal* is started. If the odorant is not appraised as harmful, it is considered benign and *habituation* is expected. On the other hand, when the odor is appraised as harmful with possible health effects, *annoyance* will result. Annoyance initiates *coping* efforts. These coping efforts fall into two major categories:

1. Problem-oriented: attacking the problem caused by the stressor, e.g., closing windows to avoid malodorous air.
2. Emotion-oriented: regulating emotions caused by the stressor, e.g., comforting cognition about health effects.

Annoyance has been described in terms of three components (CLA84):

- An emotional component (e.g., a feeling of anger).
- An interference component (e.g., disturbance of desired activities).
- A somatic component (e.g., headache, nausea).

Since these three dimensions have been found to correlate rather well, simple one-dimensional annoyance scales have been used in field studies (CAV91, STE99).

Most work on managing odor nuisance has been directed towards long-term intermittent exposure to odors caused by stationary sources. This is a different perspective from the main objective of this paper, which is aimed at acute, short term effects and their management. In the following section the model for long term odor exposure is described first. From that starting point, a model for acute odor annoyance is developed.

7.1. Definition of annoyance and nuisance

Annoyance

Annoyance is the complex of human reactions that occurs as a result of an immediate exposure to an ambient stressor (odor) that, once perceived, causes negative cognitive appraisal that requires a degree of coping.

Annoyance potential

Annoyance potential is the attribute of a specific *chemical* (or mixture of chemicals) to cause a negative appraisal in humans that requires coping behavior when perceived as an ambient odor in the living environment. It is an attribute of a chemical that can cause annoyance or nuisance. Annoyance potential indicates the magnitude of the ability of a specific chemical (mixture), relative, to other chemicals (mixtures), to cause annoyance in humans when repeatedly exposed to weak to moderate perceived intensity in the living environment.

914
915 *Nuisance*
916 Nuisance is the cumulative effect on man, caused by repeated events of annoyance over an
917 extended period of time, that leads to modified or altered behavior. This behavior can be
918 active (e.g., registering complaints, closing windows, keeping 'odor diaries', avoiding use of
919 the garden) or passive (only made visible by different behavior in test situations, e.g.
920 responding to questionnaires or different responses in interviews). Odor nuisance can lead to
921 infringement of our sense of well-being, and hence a negative health effect. Nuisance occurs
922 when people are affected by an odor they can perceive in their living environment (home,
923 work environment, recreation environment) and:
924 - the appraisal of the odor is negative,
925 - the perception occurs repeatedly,
926 - it is difficult to avoid perception of the odor ,
927 - the odor is considered a negative effect on their well-being.
928
929 *Nuisance potential*
930 Nuisance potential is the characteristic of an *exposure situation*, which describes the
931 magnitude of the nuisance that can be expected in a human population when exposed to an
932 odor intermittently, but over an extended period of time, in their living environment.
933 Nuisance potential is a function of many factors, such as the attributes of the chemical
934 (mixture) in question, the frequency and dynamics of variation of the exposure (caused both
935 at source and as a result of atmospheric dispersion) and attributes of the specific population
936 that is exposed.
937
938 *Nuisance sensitivity*
939 Nuisance sensitivity is an attribute of a *specific population* (or an individual) that indicates the
940 propensity, relative to that of other individuals or populations, to experience nuisance when
941 exposed to an odor intermittently, but over an extended period of time, in their living
942 environment.

943 ### *7.2. Odor nuisance caused by intermittent long-term exposure*

944 Odor nuisance can develop after long-term intermittent exposure to odors that causes a
945 negative appraisal in the individual concerned. It directly reflects with the way we value our
946 environment, and the development of nuisance is not a straightforward process. Our attitudes
947 towards the source, the inevitability of the exposure, and the aesthetic expectations regarding
948 our residential environment are some of the less tangible factors that are relevant to the
949 probability of experiencing nuisance. Once the balance tips, and an environmental stressor,
950 such as a chemical or livestock odor, becomes a nuisance to an individual, it is very difficult
951 to reverse the process.

What used to be a faint odor has now become a stimulus associated with annoyance. Once the first complaint has been made, the problem is much more serious for all those affected than before. The mechanism that leads from an emission of odorants into the atmosphere to actual odor nuisance is quite complex.

Odor nuisance involves the following main factors:

- The characteristics of the odor that is released (detectability, intensity, hedonic tone, annoyance potential);
- Variable dilution in the atmosphere through turbulent dispersion (turbulence or stability of boundary layer, wind direction and speed, etc.);
- Exposure of the receptors in the population (location of residence, movement of people, time spent outdoors, etc.);
- Context of perception (i.e. exposure to additional odors, background of odors, activity, and state of mind within the perception context);
- Receptor characteristics (exposure history, association with risks, activity during exposure episodes, psychological factors such as coping behavior, perceived health, and perceived threats to health).

This process can be summarized as:

formation of odorants → atmospheric dispersion → exposure → perception → appraisal → annoyance → nuisance→ complaints

When we look at the underlying mechanisms, the factors that play a role are more diverse and often mutually interactive. For practical purposes, such as regulatory use, the complex relation between nuisance (effect) and exposure to odors (dose) can be described in a simplified model that does not take all these different factors into account.

The exposure-effect model linking 'exposure to odors' to 'nuisance' is typically described as the relation between modeled exposure and annoyance as assessed by a standardized telephone questionnaire or, alternatively, complaint records. Epidemiological methods are used to describe this relationship.

The exposure is typically quantified in terms of a frequency of occurrence of hourly average concentrations above a certain limit odor concentration; e.g. 5 odor units per meter cubed ($ou_E \cdot m^{-3}$) as a 98-percentile of hourly averages of odor concentration for a year with average meteorology. In short notation: $C_{98} = 5\ ou_E \cdot m^{-3}$. This measure of exposure is calculated from an estimated or measured odor emission from the source, using an atmospheric dispersion model.

Air quality criteria for odor can be set on the basis combining calculated exposure with knowledge of the dose response relationship to quantify and assess odor impact. However, this relationship will not be the same for every community. It is determined by factors such as crowding, expectations of environmental quality, economic priorities, etc. Although odor can

have direct effects on well-being, and hence on health, it is to some degree an aesthetic factor in environmental quality.

To set environmental exposure criteria with a view to avoiding odor nuisance is therefore not only a scientific, but also a political process. The range of political discretion is limited, however. Unlike other air pollutants, every citizen with a functioning nose can assess odor real-time. The appraisal is immediate and the outcome is readily communicated to the relevant authority in the form of complaints.

7.3. Annoyance caused by short term, acute exposure to odors

The conceptual model for annoyance and anxiety arising as a result of short term exposure in emergency situations caused by chemical incidents is, in a way, more straightforward than the mechanism leading to long-term exposure effects. The following statements are the starting point of the development of a short term odor exposure model:

- The odor concentration will need to intermittently peak well above the detection threshold as established under laboratory test conditions to be distinctly detectable and sufficiently present to cause cognitive appraisal.
- Exposure to odors after dispersion in the atmosphere is inherently variable. The peak to mean ratio is dependent on the turbulence characteristics of the atmosphere and the distance from the source.
- The peaks in the variable concentration are determining the probability of detection and perception. The peaks need to be of sufficient duration (at least one inhalation, or approx. 5 seconds) and frequency to lead to cognitive appraisal. For practical reasons a frequency of at least 10 % of time is proposed, approximately equivalent to one or more 'occurrences of odor perception' per minute, on average.
- If a chemical incident occurs, any unusual odor not common to the normal 'odor landscape' will have the potential to cause annoyance in individuals at perceived intensities that can be described by 'distinctly detectable' (intensity $I = 3$).
- A 'Level of Annoyance' is reached when exposure to odors occurs at sufficient concentrations, in excess of a perceived intensity equal to or greater than 'distinct odor'.
- When annoyance is likely to occur, the coping behavior and the potential anxiety as a result of the odor exposure can be modulated by providing information on the health risk, expected duration, remediation actions etc. to those exposed in an emergency response planning framework.

7.4. Uncertainty in odor annoyance potential of accidental exposures

In order to assess the feasibility of making useful estimates of trigger levels for interventions in emergency planning and response, it is useful to assess:

- which parameters contribute to uncertainty in the determination of such a trigger level,
- their range of variation in terms of their descriptive parameter,
- the uncertainty of the estimated value.

Although a detailed analysis of uncertainty at this stage goes beyond the scope of this paper, indicative estimates can be provided (cf. Figure 8). In this figure a number of variables are reviewed, that could each contribute to predicting a level of annoyance in a population. For each variable, the magnitude of the range over which the parameter can vary, as well as the uncertainty in the assessment (measurement) of the variable, are estimated. If the uncertainty is large relative compared to the range, the variable will be less useful as a predictor. If the range of variation of a variable is large compared to that of another variable, the first variable will potentially contribute more to the prediction of annoyance. The estimates in the figure can be used to decide where effort can be applied most efficiently, when the aim is to arrive at a best prediction of annoyance with minimum investment of effort.

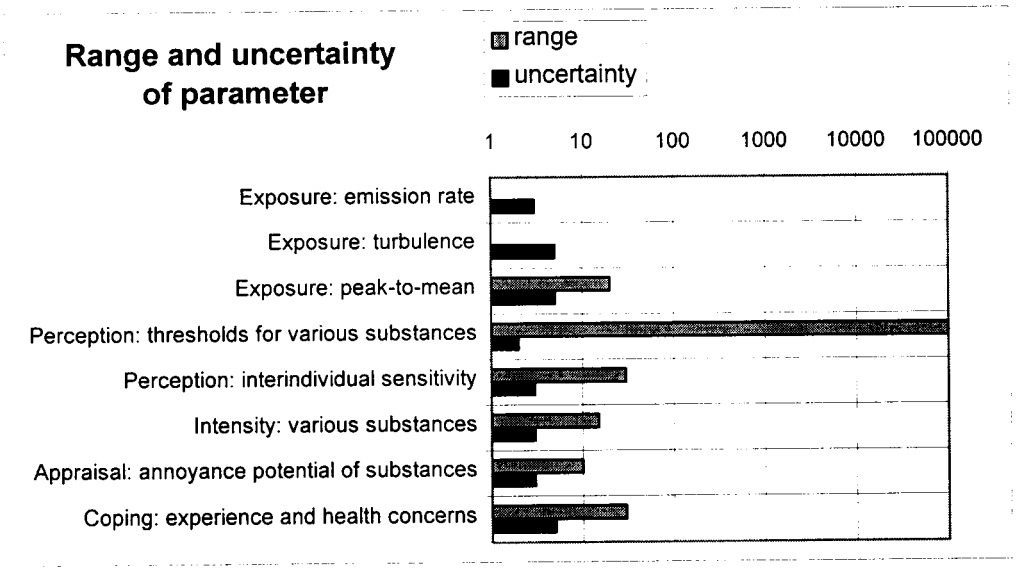


Figure 8. *Range and expected uncertainty for variables relevant to estimating acute odor annoyance*

These estimates are discussed in the list below:

- Exposure: emission rate
  The uncertainty of the emission rate from a chemical incident is likely to be estimated within a factor three.
- Exposure: turbulence
  An error in determining the turbulence of the atmosphere will cause uncertainties / variability in the order of a factor five.
- Exposure: peak-to mean
  The information on actual fluctuations in the order of 5 seconds duration relative to a one hour mean calculated concentration is sketchy, as far as experimental data are concerned. The estimated range of the parameter, between the most and least turbulence class, is approx. a factor 20. The uncertainty is estimated to be approx. a factor five.

- Perception: odor detection threshold for substance
  The range for this parameter is from less than 10 ppt to the ppm range: roughly five orders of magnitude. Using modern, standardized olfactometry, the uncertainty can be reduced to less than a factor two.
- Perception: inter individual variation in sensitivity
  The difference between the top and bottom of the 90% confidence interval for n-butanol is approx. a factor 30. The uncertainty of assessing an individual sensitivity is approx. a factor three.
- Intensity: various substances
  The differences in odor concentration to cause a perceived intensity of 'distinctly perceptible' varies according to the slope of the intensity curve for the compound in question. The range of variation is estimated to be a factor 10, while the uncertainty of assessment is estimated to be a factor three.
- Appraisal: annoyance potential
  The differences in response to an odor, at the same perceived intensity of 'distinctly perceptible' are not known, but can be estimated on the basis of measurements of hedonic tone. The variation in odor concentration at the hedonic tone scale value H = -2 is estimated to be at most a factor 10, with an assessment uncertainty of a factor three.
- Coping: experience and health concerns
  This is a difficult factor to estimate, as little information is available. However, the maximum sensitivity will be reached when annoyance is triggered at the odor threshold. The difference between odor threshold and 'distinctly perceptible' intensity or 'annoyance threshold' is unlikely to be greater than a factor 30, with an uncertainty in assessment estimated at a factor five.

In addition to the sensitivity analysis provided above, the relevance of parameters can be influenced by correlation between predictive parameters. Based on an initial analysis of data for samples of environmental odors, for which odor concentration, odor intensity curve and hedonic tone curve were analyzed, it appears that there is a correlation between the odor concentrations at which hedonic tone reaches H=-2 and intensity is distinct (I=3), both measured according to VDI 3882. The results are plotted in figure 9.

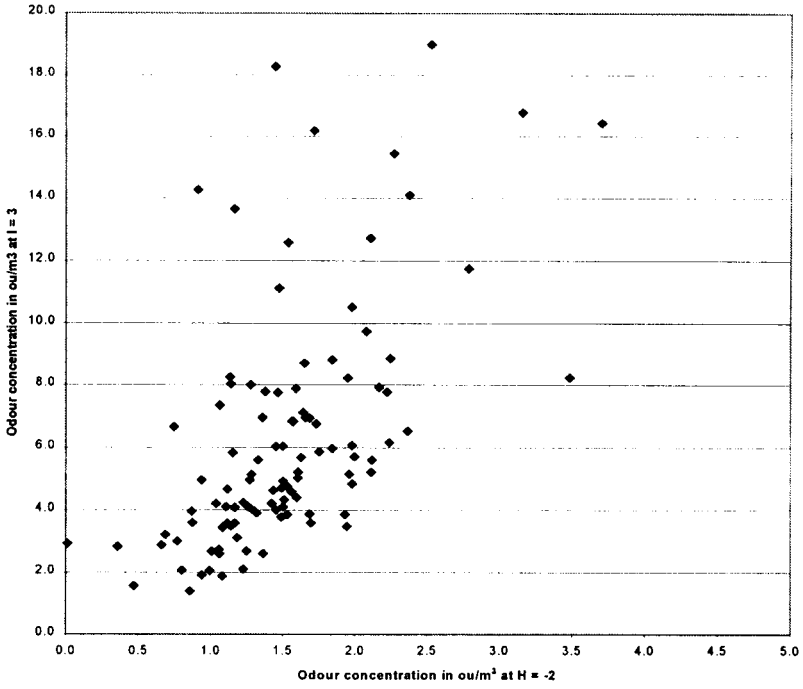
Because of this correlation, the effect of hedonic tone on the impact of the odor can be at least partially predicted from the concentration at a certain intensity level. From this assessment it can be concluded that:

- The concentration associated with a perceived intensity of 'distinct odor' is a good overall starting point for defining a 'Level of Annoyance' concentration.
- The differences in 'annoyance potential' of different odorants because of differences in hedonic tone characteristic will be a relatively minor factor in arriving at an estimate of the 'Level of Concern'.
- A correct value of the odor threshold of the compound in question will be by far the greatest contribution to improving the assessment its short term impact on an exposed population and the prediction of a 'level of concern' concentration.

1098 ***Figure 9.*** *The relation between the odor concentration in ou/m3 at which hedonic tone reaches the*
1099 *value H = -2 and the perceived intensity reaches I = 3 (distinct odor), for a variety of environmental*
1100 *odors (Data: PRA OdourNet BV, Amsterdam)*

1101

1102



8. A conceptual model for a Level of Annoyance

The conceptual model to derive of a 'Level of Annoyance' (LOA) for a short term exposure to a compound, to support decisions on the necessity and urgency of emergency response actions, to modulate public appraisal and to avoid excessive anxiety based on odor, is illustrated in figure 10. In this model, a number of inputs are required. These inputs will be discussed in the following sections.

1. Determine or select the odor detection threshold
2. Determine or select the Weber-Fechner coefficient
3. Estimate the concentration that leads to a distinctly detectable odor under field conditions
4. Estimate a peak-to-mean ratio
5. Calculate a LOA from estimates above

Figure 10. *Tentative model identifying a level of concern in emergency response planning, based on odor threshold and curve of perceived odor intensity for a specific compound*

8.1. The odor threshold of the compound

The odor detection threshold of compound value is by far the most significant for determining a Level of Concern. A list of values of the odor threshold is included in the table of Annex 1. It should be noted that published values of odor thresholds generally report measurements where the results were not related to a reference odorant. That implies that the measurements were determined, to a large degree, by the luck of the draw of a handful of panel members out of a population with significant variability in their ability to detect odors. An additional bias was introduced by presenting diluted odor flows to panel members well inferior to the inhalation rate. Non-standardized odor detection thresholds will be refered to as C_0, whereas a standardized odor detection threshold will be referred to as $C_{0,\,stand}$.

Several procedures can be defined in the selection of an $C_{0,\,stand}$ for the derivation of a LOC:

- Level 1: the threshold of a compound determined according to EN 13725 or an equivalent method.
- Level 2: thresholds from a source which includes a reported value for n-butanol. The butanol value is needed for correcting the threshold to EROM.
- Level 3: thresholds from compilations by AIHA or US EPA. These compilations critique thresholds reported in literature. The best choice would be the lowest reported value from all acceptable sources (and not the geometric mean, because bias nearly always results in higher odor thresholds).

8.2. Weber-Fechner coefficient k_w, for the compound

The Weber-Fechner coefficient can be calculated from the intensity curve, giving the relationship between concentration and perceived intensity of the odor. The value can be determined according to the standard method as described in VDI3882 part 1.

Perceived intensity can be derived using different units on the concentration (horizontal) axis: odor units (ou/m^3 or $ou_E \cdot m^{-3}$) or mass concentration units (mg/m^3 or ppb). The value of k_w can be derived from any of these curves, the slope is independent of the concentration unit used.

An added advantage of the k_w coefficient is that it is expected to be relatively independent of the sample of the population used. The way in which each individual perceives weaker or stronger odors seems to be much less variable than the actual sensitivity of individuals at or near the selection threshold. Solid data on the distribution of k_w values for individuals in the general population are, however, not available, as far as the authors are aware.

The Stevens exponent can be used to estimate Fechner coefficients. The models are fundamentally different (linear and curved) but provide comparable results for intensity at an odor concentration of 8 ou_E/m^3. This practical relationship was established on the basis of data presented in standard VDI3882 part 1. To convert the Stevens coefficient n into the Fechner coefficient k_w the following equation will provide a pragmatic estimate:

$$k_w = k_s \times 1.10731 \times 7^n - 0.55365$$

When stimulus is in odor units the constant k_s defaults to 1.

The value of k_w for specific compounds varies between 0.78 and 3.5, approximately (cf. Table 1). The median value of coefficient determined according to VDI 3882 is estimated to be 2.33, which is proposed as a default value to apply when no actual data for the compound at hand are available. Given this value a distinct odor (I=3) under field conditions is expected to be associated with approximately 12 ou_E/m^3.

8.3. Odor concentration that is distinctly detectable

Any unusual odor not common to the normal 'odor landscape' will have the potential to cause annoyance in individuals at perceived intensities that can be described by 'distinctly detectable'. This intensity equals I =3 and the corresponding concentration $C_{distinct}$ can be calculated from the standardized odor threshold and the Weber-Fechner coefficient:

$$C_{distinct} = C_{0,\,stand} \times 10^{2.5/kw}$$

Outside of the laboratory, factors such as sex, age, sleep, smoking, head cold and nasal allergy influence the perception of odors. Distraction (i.e. the fact that in a laboratory the individual's attention is purposely focused on detecting odors, whereas this in not the case in ordinary life situations) increases the odor detection threshold by a factor of 4 (= $10^{0.6}$).

In practice this means that under field conditions an odor is probably distinctly detectable at intensities in the range of I=3 (distinct odor in the laboratory panel) to I=4 (strongly odor in

the laboratory panel). An intermediate value of I=3.5 is proposed as a best estimate for distinctly detectable odor under field conditions

$$C_{\text{distinct. field conditions}} = C_{0.\text{ stand}} \times 10^{3/kw}$$

8.4. Peak to mean ratio to account for peaks within hourly exposure

The perception of odors is very quick. One breath inhalation takes approximately 3 seconds. One inhalation can lead to odor detection, perception, and appraisal. As we spend approximately half of our time exhaling, a practical value for the smallest period of interest to assessing the effects of odors is therefore approx. 5 seconds.

In predicting exposure, we typically use dispersion models. These models have been designed and found effective in predicting annual, monthly and daily averages of predicted concentrations. The smallest time-'byte' of calculation is typically one hour, as this is the common smallest timeframe over which meteorological data are recorded. Models have been found reasonably reliable in predicting the frequency of occurrence of concentrations over a long period of time, even at high percentile values, e.g., the 98-percentile. What happens within one hour is a matter that has prompted a range of opinions in odor assessment discussions. However, the simple fact is that we lack data, both meteorological data and downwind concentration data, for an assessment at the 5-second interval level, that is the minimum relevant interval for odor perception.

However, it is known that the peaks, the height of peaks and the frequency of occurrence of peaks are integrated in determining the perception of the odor.

To account for the peaks, various 'peak-to-mean' ratios have been proposed and applied.

Generally such values are proposed as a generally applicable value, not differentiated for different states of mixing layer turbulence.

From simulation data we can see that the issue is not so simple.

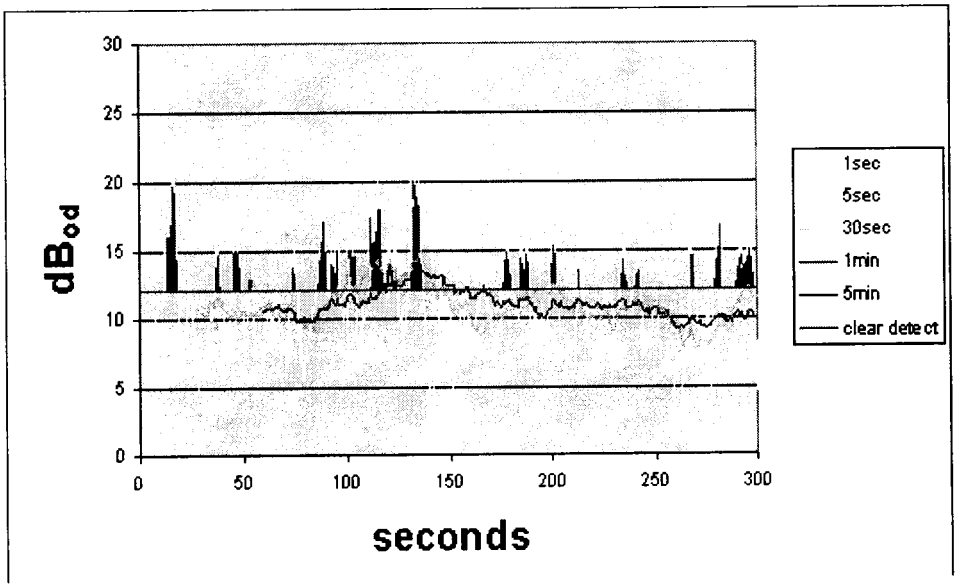


Figure 11. *Simulation*

From the simulation in the figure, it can be observed that the peak to mean ratio increases sharply with reduction of the interval. The peaks of the 5 sec line that are above a clearly detectable perceived intensity have been filled in with red. Although this is a simulation, the figure provides a good insight in the issues at hand.

The application of peak-to-mean factors is an issue still very much under discussion. In a recent proposed odor guideline for New South Wales, Australia, a detailed table was produced (NSW01). Table 2 shows recommended factors for estimating peak concentrations for different source types, stability's and distances, for use in screening procedures for flat terrain situations.

Table 2

Source type	Pasquill-Gifford stability class	Near field i_{max}	Near field x_{max}	Near field P/M60	Far field I	Far field P/M60
Area	D	0.5	500 to 1000	2.5	0.4	2.3
	E,F	0.5	300 to 800	2.3	0.3	1.9
	A,B,C	0.5	500 to 1000	2.5	0.4	2.3
Line	D	1	350	6	0.75	6
	E,F	1	250	6	0.65	6
	A,B,C	1	350	6	0.75	6
Point, surface	D	2.5	200	25	1.2	5 to 7
	E,F	2.5	200	25	1.2	5 to 7
	A,B,C	2	1000	12	0.6	3 to 4
Point, tall, wake-free	D	4.5	5 x height	35	1	6
	E,F	4.5	5 x height	35	1	6
	A,B,C	2.3	2.5 x height	17	0.5	3
Point, wake affected	A to F	0.4		2.3	0.4	2.3
Volume	A to F	0.4		2.3	0.4	2.3

i_{max} maximum centreline intensity of concentration.

x_{max} approximate location of imax in metres.

P/M60 Peak to mean ratio for long averaging times (typically 1 hour), at a probability of 10^{-3}

h stack height in meters.

The capability of a model to predict concentrations during one particular hour is less favorable, mainly because it is very difficult to obtain a good estimate of the turbulence of the mixing layer within that timeframe. However, it is known that the peaks, the height of peaks and the frequency of occurrence of peaks are determining the perception of the odor.

To account for peaks, various 'peak-to-mean' ratios have been proposed and applied.

Ratios were estimated at distances of more than 200-1000 meters from a point surface source. There was a 10^{-3} probability that various Pasquill-Gifford stability classes lead to values

between 3 and 7. A value of 3 ($=10^{0.48}$) is proposed for transforming one-hourly values to 5 second averaged concentrations.

8.5. Calculate a level of annoyance

A level of annoyance is reached when exposure to odor occurs in a sufficient concentration and duration to cause frequent perception of distinct odor within a timeframe of an hour:

$$LOA = C_{0,\,stand} \times 10^{(3/kw)} / \text{peak-to-mean ratio} = C_{0,stand} \times 10^{(2.52/kw)}$$

If no acceptable k_w value is available a default LOC of $C_{0,stand} \times 10^{2.52/2.33}$ = approximately 12 ou_E/m^3 can be used.

9. Discussion

ERPG's and AEGL's are intended as levels of concern during chemical incidents. The Emergency Response Planning Guideline ERPG-1 identifies a level which may be noticeable due to slight odor or mild irritation. In the event of a release at which exposure would reach this defined level, the community could be notified that they might perceive an odor or slight irritation. Their anxiety levels could be modulated by providing the information that the concentrations that they can perceive have been assessed, have a known cause and are occurring at concentrations lower than those that could cause other, more serious, health effects.

The definition of the Acute Exposure Guideline Limit AEGL-1 is somewhat different and may imply higher levels of exposure. AEGL-1 is the concentration at or above which it is predicted that the general population, including 'susceptible' individuals, could experience notable discomfort, irritation, or certain subclinical non-sensory effects. However the effects are not disabling and are reversible upon cessation of exposure. The AEGL-1 value, by definition, is an attempt to define the concentration that distinguishes discomfort from detection.

The determination of an accurate odor threshold value of a compound is by far the greatest contribution to improving the assessment of the short term impact of an odorant on an exposed population and the prediction of a 'level of annoyance'. The table below presents some selected compounds with a listing of odor detection thresholds in EROM, Weber-Fechner coefficients, Levels of Annoyance calculated according to this guideline and the current AEGL-1.

Compound	Odor threshold (ppb)	K_w	LOA (ppb)	AEGL-1 (ppb)
Styrene	34.5	-	400	50,000
Benzene	1,700	-	20,000	50,000
n-Butylacetate	76	-	900	-
n-Butanol	39	1.9	450	-
Toluene	1,270	-	15,200	50,000
Dimethyldisulfide	0.35	-	4.2	10
Methyl mercaptan	0.12	-	1.4	5
Dimethylsulfide	0.12	-	1.4	500
Trimethylamine	0.14	-	1.7	100
Hydrogen sulfide	0.6	2.33	7	30

For various compounds which are relevant in emergency planning and response, no standardized odor thresholds and Weber Fechner coefficients are available. For these compounds we suggest to use the lowest reported acceptable odor detection treshold. This concentration is then multiplied by twelve to calculate the expected Level of Annoyance. For example, AIHA (AIH89) reported 5 odor thresholds for ethyl acrylate. Two sources were rejected. The other sources were critiqued and two were found acceptable with a lowest reported value of 0.24 ppb. The resulting LOA for ethyl acrylate is 3 ppb. Using the same procedure would result in a LOA of 1 ppm for chlorine (equal to the current AEGL-1). Acceptance of odor annoyance as an adequate endpoint may result in a downward correction of AEGL-1 levels for a number of odorants.

10. References

American Industrial Hygiene Association: Odor Thresholds for Chemicals with Established Occupational Health Standards. Akron, OH (1989).

Amoore, J.E: Molecular Basis of Odor. Charles C Thomas, Springfield, Illinois (1970).

Amoore, J.E., and E. Hautala: Odor as an Aid to Chemical Safety: Odor Thresholds Compared with Threshold Limit Values and Volatilities for 214 Industrial Chemicals in Air and Water Dilution. J. *Appl. Toxicol. 3:* 272-290 (1983).

Amoore, J.E: The Perception of Hydrogen Sulfide Odor in Relation to Setting an Ambient Standard. Prepared for California Air Resources Board. ARB Contract A4-046-33 (1985)

Amerine, M.A., R.M. Pangborn, and E.B. Roessler: Principals of Sensory Evaluation of Food. New York Academic Press (1965).

ASTM: Manual on Sensory Testing Methods, no. 434. American Society for Testing and Materials, Philadelphia, Pa. (1968).

Axel, R.: The Molecular Logic of Smell. *Scientific American 273:* 130-137 (1995).

Beek, B., C.J. Valk, and M. Pereboom: (in Dutch) De herhaalhaarheid van hedonische geurhindermetingen. *Lucht 3:* 82-87 (1999).

Berglund, B., U. Berglund, and T. Lindvall: A quantitative principle of perceived intensity summation in odor mixtures. *J. Exp. Psychol. 100:* 29-38 (1973)

Buck, L., and Axel, R.: A novel multigen family may encode odorant receptors: A molecular basis for odor reception. *Cell 65*: 175-187 (1991).

Cain, W.S., and C.L. Murphy: Interaction between chemoreceptive modalities of odor and irritation. *Nature 284:* 255-257 (1980).

Carter, R. : Mapping the mind, ISBN 0 297 62330 2, Weidenfeld & Nicholson, London, (1998)

Cavalini, P.M., Koeter-Kemmerling, L.G., and Pulles, M.P.J.: Coping with odor annoyance and odor concentrations: three field studies *J. Environ. Psychol. 11:* 123-142 (1991).

CEN (European Committe for Standardization): Air quality - Determination of odour concentration by dynamic olfactometry. CEN 13725. Brussels, Belgium 1999.

Clanton, C Panel and Olfactometer http://www.bae.umn.edu/annrpt/1998/research

Clark, C.R.: The effects of noise on health. In: Jones, D.M. and A.J. Chapman, editors. *Noise and Society.* Chichester: John Wiley 111-124 (1984).

Dalton, P., C.J. Wysocki, M.J. Brody, and H.J. Lawley: The influence of cognitive bias on the perceived odor, irritation and health symptoms from chemical exposure. *Int. Arch. Occup. Environ. Health 69:* 407-417 (1997).

Dalton, P: Cognitive influences on health symptoms from acute chemical exposure. *Health Psychol .18:* 579-90 (1999).

Dalton, P.H., D.D. Dilks, and M.I. Banton: Evaluation of Odor and Sensory Irritation Thresholds for Methyl Isobutyl Ketone in Humans. *AIHAJ 61:* 340-350 (2000).

Dravnieks, A., and F. Jarke: Odor threshold measurements by dynamic olfactometry: significant operational variables. *Journal Air. Poll. Contr. Ass. 30:* 1284-1289 (1980).

Dupraz

Ekman, G., B. Berglund, and U. Berglund: Perceived intensity of odor as a function of time adaptation. *Scand. J. Psychol. 8:* 177-186 (1967).

Fieldner, A.C., R.R. Sayers, W.P. Yant, S.H. Katz, J.B. Shohan, and R.D. Leitch: Warning agents for fuel gases. U.S. Department of Commerce, Bureau of Mines, Monograph 4 (1931).

Gemert, L.J. van, and A.H. Nettenbreijer: Compilation of Odor Threshold Values in Air and Water. Central Institute for Nutrition and Food Research TNO (CIVO-TNO) Zeist, the Netherlands (1977).

Gemert, L.J. van: Compilation of Odor Threshold Values in Air. Supplement IV. Central Institute for Nutrition and Food Research TNO (CIVO-TNO) Zeist, the Netherlands (1982).

Hangartner, M., R. Both, F.-B. Frechen, W. Medrow, M.Paduch, K.-H. Plattig, P.H. Punter, and G. Winneke: Charakterisierung von Geruchbelaestigungen. Teil 3: Nationale Regelungfen: Loesungsansaetze und vorhandene Wissensluecken (Characterization of odour annoyance. Part 3: National regulations: Approaches to solve the Problem and Lack of Knowledge) *Staub-Reinhaltung der Luft 55:* 155-157 (1995)

Harreveld, A.Ph. van, A. Schakel, C.J. Valk, and S. Vreeburg: Feasibility study for the development of a standardized method for assessment of odor annoyance and odor annoyance potential., Project PD 207 Action programme Standardisation and Validation of Environmental Assessment Methods. (English Summary, Project Research Amsterdam BV, Amsterdam, 1999. ISBN90-805641-1-7 (available at www.odornet.com) (1999)

Harreveld, A.Ph. van , Heeres, P., Harssema, H., A review of 20 years of standardization of odor concentration measurement by dynamic olfactometry in Europe, Journal of the Air ans Waste Management Association, 1999 (6), Pittsburgh, June (1999)

Harreveld, A.Ph. van: From odorant formation to nuisance: new definitions for discussing a complex process, in press, IWA conference on odors, Sudney, March 25-29, 2000.

Hummel, T., S. Barz, J. Loetsch, S. Roscher, B. Kettenmann, and G. Kobal: Loss of olfactory function leads to a decrease of trigeminal sensitivity. *Chem. Senses 21:* 75-80 (1996).

Kendal-Reed, M., and J.C. Walker: Human normosmics and anosmic sensory responses to propionic acid. *Chem. Senses 21:* 622 (1996)

Kuijk, A., and T. Boom: Verschillen tussen geurlaboratoria in de praktijk (Differences between odor laboratories in practise). *Lucht 17:* 114-118 (2000).

Leffingwell, R.C.: Olfaction: a review in progress. http://www.leffingwell.com/olfaction.htm

Malnic B, Hirono J, Sato T, Buck LB: Combinatorial receptor codes for odors. *Cell 96:* 713-23 (1999).

NSW EPA Technical Notes - Draft Policy: Assessment and Management of Odour from Stationary Sources In NSW, Environment Protection Authority, NSW, Sydney, Australia (2001)

Oberthür, R., Ein logarithmischer Maßstab mit dB-Einheiten zur Darstellung des Geruchsstoffpegels (translation: a logarithmic measure opf odor intensity, using decibel units), Staub - Reinhalt. luft 50, pp. 175--183 (1990)

ONSL0135 Anon. Control measures against offensive odour, translated from Japanese, Nagoya International Training Center, Japan International Coorperation Agency and the International Center for Environmental Technology Transfer, Tokyo, Japan.

Patte, F., M. Etcheto, and P. Laffort: Selected and standardized values of suprathreshold odor intensities for 110 substances. *Chemical Senses and Flavor 1:* 283-305 (1975)

Paduch, M. R, R. Both, F.-B. Frechen, M. Hangartner, W. Medrow, K.-H. Plattig, P.H. Punter, and G. Winneke: Charakterisierung von Geruchbelaestigung. Teil 1: Beschreibung der Geruchsparameter (Characterization of odour annoyance. Part 1: Description of underlying odour parameters) *Staub-Reinhaltung der Luft 55:* 41-44 (1995)

Rosenstock, L., and M.R. Cullen: Clinical Occupational Medicine. p.142. W. B. Saunders Company Philadelphia, 1986.

Ruth, J.H.: Odor thresholds and irritation levels of several chemical substances: a review. *Am. Ind. Hyg. Assoc. J. 47(A)*: 142-151 (1986).

Shusterman, D: Critical Review: The Health Significance of Environmental Odor Pollution. *Arch. Environ. Hlth 47:* 76-88 (1992).

Steinheider, B: Environmental Odours and Somatic Complaints. *Zbl. Hyg. Umweltmed. 202:* 101-119 (1998/1999).

U.S. EPA Air Risk Information Support Center, Reference Guide to Odor Thresholds for Hazardous Air Pollutants Listed in the Clean Air Act Amendments of 1990 (EPA600/R-92/047) March 1992.

VDI 3882:1997, part 1, *Determination of Odor Intensity,* Düsseldorf, Germany.

VDI 3882:1997, part 2; *Determination of Hedonic Tone,* Düsseldorf, Germany

Whisman, M.L., J.W. Goetzinger, F.O. Cotton, D.W. Brinkman, and C.J. Thompson: A new Look at Odorization Levels for Propane Gas. Bartlesville Energy Research Center, Bartlesville, Oklahoma (1977)

Winneke, G, R. Both, F.-B. Frechen, M. Hangartner, W. Medrow, M. Paduch, K.-H. Plattig, and P.H. Punter: Charakterisierung von Geruchbelaestigung. Teil 2: Verknuepfung von ausgesuchten Geruchsparametern in Hinblick asuf Belaestigungsrelevanz (Characterization of odour annoyance. Part 2: Interdependance of specific odour parameters affecting the annoyance level). *Staub-Reinhaltung der Luft 55:* 113-118 (1995)

Wysocki, C.J., P. Dalton, M.J. Brody and H.J. Lawley: Acetone Odor and Irritation Thresholds Obtained From Acetone-Exposed Factory Workers and From Control (Occupationally Unexposed) Subjects. *Am. Ind. Hyg. Assoc. J. 58:* 704-712 (1997).

Zhao, H., L.Ivic, J.M. Otaki, M. Hashimoto, K. Mikoshiba, and S. Firestein: Functional expression of a mammalian odorant receptor. *Science 279:* 237-242 (1998).

11. annex 1

There are a number of odor threshold compilations available (AMO83; RUT86, USE92). A major source is a Dutch publication, which lists 913 chemicals with odor thresholds (GEM77; GEM82). Odor thresholds reported more than 50 years ago probably were not obtained under the same conditions of methodological precision that are taken for granted today. Additionally some values are reported from many interdisciplinary sources in which the intent is not threshold measurement per se. The lack of standardization of methods for odor threshold determination, taken in conjunction with inconsistent purity of chemical samples and the variability of human sensitivity, is responsible for the wide range of threshold concentrations usually found in the literature for a given compound. For example, 26 values were reported for hydrogen sulfide, ranging from 0.072 - 1400 ppb, i.e. a factor 10.000 (AMO85).

An AIHA Review Subcommittee presented a critique of the experimental odor thresholds reported in the literature (AIH89). They considered this a necessary refinement for obtaining best estimates of odor thresholds. A two-phase review was conducted of 366 references from two odor threshold compilations. The review was limited to chemicals with published occupational threshold limit values. Ninety percent of the references were rejected, based on review (e.g. secondary source, incidental reference) or criteria for acceptability (sufficient panel size, actual analytical measurement of odorants, calibration procedure). A similar approach was followed in the more recent compilation by the U.S. EPA (USE92).

Table A		**Odor detection thresholds in ppm**						**Differences**	
Compound	Odor quality	Reported thresholds AIHA	Geometric mean in ppm	Geometric standard deviation	NL	Japan	EROM	Factor Japan/NL	factor US/EROM
Acetone	Sweet/fruity	4	62	11	28.0		28.0		2.2
Benzene	Aromatic/sweet	3	61	1.9	1.7		1.7		35.9
n-Butylacetate	Sweet/banana	3	0.31	36	0.076		0.076		4.1
n-Butanol	Sweet/alcohol	6	1.2	4.3	0.040	0.038	0.039	0.95	30.8
2-Butanol	Sweet/alcohol	3	3.2	17					
Carbon tetrachloride	Sweet/dry cleaner	3	252	2.1					
Dioxane	Sweet/alcohol	3	12	18					
Ethyl Alcohol	Sweet/alcohol	3	180	3.8	0.370		0.370		486.5
Hydrogen Sulfide	Rotten eggs	8	0.0094	5	0.0005	0.000495	0.000497	0.99	18.9
Isoamyl Acetate	Banana	3	0.22	398					
Isobutyl Alcohol	Sweet/musty	3	3.6	8.3		0.012	0.012		310.3
Isopropyl Alcohol	Sharp/ rubbing alcohol	4	43	8.6					
Methyl Ethyl Ketone	Sweet/sharp	3	16	6.9	3.1		3.1		5.1
Methyl Mercaptan	Rotten cabbage	3	0.000540	1110		0.000102	0.000102		5.3
1-Propanol	Sweet/alcohol	5	5.3	23					
Styrene	Sharp/sweet	3	0.140	11	0.025	0.033	0.029	1.32	4.9
Toluene	Sour/burnt	6	1.6	11	1.6	0.9	1.2	0.58	1.3

The AIHA review resulted in 110 compounds, from 36 reference sources, that had odor threshold values that met evaluation criteria. In Table A all compounds are shown which had three or more acceptable values. For each compound the odor quality, the mean odor detection threshold and the geometric standard deviation are presented.

The geometric median standard deviation ranged from 1.9-1110. Based on the AIHA approach one might conclude that approximately 95% of all acceptable odor threshold values are within a range of one-thirtieth and thirty times the mean, a nearly thousand-fold range.

However, when the results of measurements in Japan (Triangle Method) (ONSL0135) and the Netherlands are compared, the results agree much better. These data are quite different and independent, but share a common reference and selection of panel members. The Dutch data are from 1988, using a precursor of the EN13725 standard, the NVN2820. The Dutch original results were corrected for a difference in n-butanol reference. The original data showed an n-butanol threshold of 25 ppb/v n-butanol, where the agreed European reference value is 40 ppb/v. A simple correction of 40/25 = 1.6 was applied to make the data compatible to the European Odour Mass (EROM). The Japanese Triangle Method has a mean value for n-butanol of 38 ppb/v, very close to the EROM. The data for the Japanese and Dutch methods agree very well for the four compounds where data can be compared, with difference factors between 0.58 and 1.32. The differences between the EROM estimates, based on a geometric mean of the Japanese and Dutch data, and the threshold values from the AIHA compilation show very large differences indeed, with factors between 1.3 and 486.

This demonstrates the need for threshold values for relevant compounds that are measured using standardized methodology, traceable to reference materials.

Table B	Odor threshold, mean of ABC	NVN2820 compatible (A)	TNO 1988 (B)	Japan, C	Factor of difference		
					B/A	C/A	C/B
Styrene (vinylbenzeen)	0.0345	0.049	0.025	0.033	0.51	0.67	1.32
Butyric acid	0.000086	0.00011		0.00007		0.64	
4-methylpentanon-2	0.144	0.123		0.170		1.39	
m-xylene (1,3, dimethylbenzene)	0.19	0.18	0.20		1.09		
Toluene (methylbenzene)	1.27	1.39	1.59	0.92	1.14	0.66	0.58
Phenol	0.017	0.018	0.016		0.89		
Pentanal (valeraldehyde)	0.0007	0.0008		0.0007		0.93	
Propanal (propionaldehyde)	0.0016	0.0017		0.0015		0.88	
butanal (butyraldehyde)	0.00031	0.00031		0.00031		0.99	
Tetrachlooretheen	2.28	2.67	1.95		0.73		
Ethyl acetate	0.26	0.27		0.25		0.91	
Isovaleric acid	0.00005	0.00006		0.00005		0.97	
Dimethyldisulphide	0.00035	0.00043		0.00028		0.67	
n-butanol	0.039		0.040	0.038			0.95

Methanethiol (methylmercaptan)	0.00012	0.00014		0.00010		0.74	
Dimethylsulphide	0.00012	0.00013		0.00012		0.92	
Trimethylamine	0.00014	0.00017		0.00011		0.66	
Ammonia		1.59	1.07	0.15	0.676	0.094	0.139
Hydrogen sulphide	0.0006	0.00075	0.00049	0.00050	0.65	0.66	1.02
Isobutanol	0.012	0.013		0.012		0.90	
Propionic acid	0.0021	0.0019		0.0025		1.31	

Table B shows a collection of data, comparing results of odor thresholds for compounds in ppm. Again, the following methods are compared:

- A. Methods of olfactometry considered compatible with a precursor of the NVN2820 and EN 13725 methods
- B. Measured by TNO in the Netherlands, 1988, using a precursor of the NVN2820 and EN 13725 methods, with a mean n-butanol threshold of 25 ppb. Results of A and B have been converted to the EROM reference value agreed in EN13725 of 40 ppb/v n-butanol by applying a correction factor of 40/25 = 1.6
- The Japanese triangle olfactometer method. The method uses panel selection based on screening of assessors using reference odors and produces an an-butanol threshold of 38 ppb/v, which is compatible with the EROM of EN13725

The results are very clearly supportive of the benefit that can be obtained by standardization and use of reference odors for quality assurance. The differences between the methods are quite small compared to those commonly reported for olfactometry. Only for ammonia the differences are two orders of magnitude. Ammonia is mainly an irritant and therefore not all that relevant for comparisons of odor thresholds. It is suggested to use the geometric mean values presented in the table as a basis for determining the Level of Concern.

Appendix A

National Advisory Committee (NAC)
for Acute Exposure Guideline Levels (AEGLs) for Hazardous Substances
Final Meeting 21 Highlights
June 11-13, 2001
U.S. Department of Transportation
DOT Headquarter/Nassif Building, Rooms 8236-8240
400 7th Street, S. W., Washington, D. C.

INTRODUCTION

George Rusch, NAC/AEGL Chair, opened the meeting with welcoming remarks along with AEGL Program Director, Roger Garrett, who also welcomed the committee members and guests. Thanks were conveyed to George Cushmac for making the necessary arrangements for the meeting and to the Department of Transporation (DOT) for providing the facilities.

The approval of the meeting highlights for NAC/AEGL-20 were postponed until John Morawetz's arrival in the afternoon since he had provided input for the revision of the hydrogen cyanide section as well as other sections. After a brief period of review and discussion, a motion was made by Mark McClanahan and seconded by Doan Hansen to approve the meeting highlights with minor editorial changes. The revised highlights of NAC/AEGL-20 are attached (Appendix A). The motion was unanimously approved (Appendix B)

The highlights of the NAC/AEGL-21 meeting are presented below along with the meeting agenda (Attachment 1) and the attendee list (Attachment 2). Ballots were taken during the meeting and are incorporated into the appropriate chemical-specific section.

GENERAL INTEREST ITEMS

Roger Garrett expressed the importance of the AEGL development process and the valuable contributions of the NAC/AEGL Committee. The AEGL values developed by the committee are extremely useful for many domestic and international groups. More input from these groups on the overall development of the AEGL values is expected in the future.

The next meeting was set for September 11-13, 2001, at this same DOT facility. At the suggestion of John Hinz, the last meeting of the year will be held (tentatively) from December 3-7, 2001, in San Antonio, Texas. After local lodging arrangements are finalized, John Hinz will notify the NAC/AEGL members and guests.

REVIEW OF PRIORITY CHEMICAL FOR AEGL VALUES

BORON TRIFLUORIDE, CAS Reg. No. 763-07-2

Boron Trifluoride: Dimethyl ether, CAS Reg. No. 353-42-4

Chemical Manager: George Rusch, Honeywell, NAC/AEGL Chair
Staff Scientist: Claudia Troxel, ORNL Staff Scientist

The review was presented by Claudia Troxel (Attachment 3). Quantitative toxicity data were not available for the boron trifluoride:dimethyl ether complex. Because the complex breaks down into dimethyl ether and boron trifluoride, the AEGL derivations were based upon boron trifluoride toxicity data alone. The following summary is what was proposed, but no vote was taken. These values are to be reconsidered at the next AEGL meeting.

The proposed AEGL-1 derivation is based upon the statement that a concentration of 1.5 ppm (4.1 mg/m^3) boron trifluoride has a "rather pleasant acidic odor," indicating that the odor threshold had been reached. Although the worker noted the smell of boron trifluoride to be pleasant, it is likely that others would find the odor unpleasant. This level does appear to be near the threshold for irritant effects: the subchronic study by Rusch et al. (1986) reports that minimal signs of irritation were noted in rats exposed to 2 or 6 mg/m^3 for 6 hours/day, 5 days/week for 13 weeks. An interspecies uncertainty factor was not needed, and an intraspecies uncertainty was not applied to account for inter-individual differences because the odor was not irritating. The value was set equal for all AEGL time-points because the endpoint is based on odor.

Data were not available for derivation of an AEGL-2. Because data meeting the definition of an AEGL-2 defined endpoint were not available and the dose-response curve for lethality was steep (Rusch et al, 1986), it was proposed that the AEGL-3 levels be divided by 3 to obtain an estimate of the AEGL-2.

The proposed AEGL-3 derivation is based upon the 4-hour LC_{50} value of 1200 mg/m^3 determined by Rusch et al. (1986). An interspecies uncertainty factor of 10 was applied because there appeared to be some species differences in sensitivity to boron trifluoride, with the guinea pig being the most sensitive to lethality. An intraspecies uncertainty factor of 3 was applied based on the evidence that boron trifluoride acts as an irritant.

Experimentally derived exposure values are scaled to AEGL time frames using the default value of $n = 1$ for extrapolating from shorter to longer exposure periods and a value of $n = 3$ to extrapolate from longer to shorter exposure periods. The 10-minute value was set equal to the 30-minute value because it is not considered appropriate to extrapolate from a 4-hour to a 10-minute time point.

The proposed values are listed in the tables below. AEGL values are given in terms of mg/m^3 because boron trifluoride gas becomes an aerosol upon contact with moisture in the air.

Summary of AEGL Values					
Classification	**Exposure Duration**				
	10-minute	**30-minute**	**1-hour**	**4-hour**	**8-hour**
AEGL-1	4.1 mg/m^3	4.1 mg/m^3	4.1 mg/m^3	4.1 mg/m^3	4.1 mg/m^3
AEGL-2	27 mg/m^3	27 mg/m^3	21 mg/m^3	13 mg/m^3	6.7 mg/m^3
AEGL-3	80 mg/m^3	80 mg/m^3	63 mg/m^3	40 mg/m^3	20 mg/m^3

Several NAC/AEGL members thought that the guinea pig appeared to be more sensitive. A question arose as to whether there was a sex differential in the studies. It was reported that it was minimal. Further questions concerned the time at which the signs of toxicity appeared in the study and the possibility of using a BMD approach with the data. It was also mentioned that obtaining the individual animal data from the Rusch et al. study might prove useful. Final conclusion was that these comments and suggestions will be addressed in a revised TSD for final review in the next meeting.

CHLORINE DIOXIDE, CAS Reg. No. 10049-04-4

Chemical Manager: Robert Benson, US EPA
Staff Scientist: Cheryl Bast, ORNL Staff Scientist

Cheryl Bast presented a review of the Chlorine Dioxide TSD (Attachment 4) and described a summary of an unpublished industrial study from the 1950s (DuPont) that had not yet been obtained by the committee. After extensive discussion it was decided that data were insufficient for development of AEGL-1 values. Ernie Falke made a motion, seconded by Robert Benson, not to develop AEGL-1 values for chlorine dioxide. The motion carried for AEGL-1 [YES: 24, NO: 0, Abstain:2] (Appendix C).

AEGL-3 values were based on a study showing no lethality in rats exposed to 26 ppm for 6 hours (Dupont, 195x). As rats appear not to be the most sensitive species, an interspecies uncertainty factor of 10 was applied. Chlorine dioxide is highly reactive and causes a variety of serious adverse effects in the lung that are likely a direct chemical effect on the tissue in the lung. As this effect is not likely to vary greatly among individuals, an intraspecies uncertainty factor of 3 was used. Thus, a total uncertainty factor of 30 was applied. The default values of the exponent 'n' (n =1 for 8-hours, and n=3 for 10-min, 30-min, 1-hr and 4-hr) were applied for scaling across time. The motion was made by Bob Snyder and seconded by John Hinz to adopt the AEGL-3 values presented in the table below. The motion was approved [Yes: 24; No:2; Abstain: 0] (Appendix C).

AEGL-2 values were obtained by dividing the AEGL-3 values by 3 as there is no appropriate study using a single exposure showing effects consistent with the definition of AEGL-2. This

approach is supported by several repeat-exposure studies in rats. A motion was made by Mark McClanahan and seconded by Larry Gephart to accept the AEGL-2 values presented in the table below. The motion was approved [YES: 17; No: 6 Abstain: 3] (Appendix D).

The values for chlorine dioxide are contingent on obtaining the DuPont study and verifying that the summary used accurately reflects the study design and results. If this is the case, then the revised TSD will be provided to the NAC/AEGL for approval. Otherwise, the NAC/AEGL will discuss this chemical at a future meeting.

Proposed AEGL Values for Chlorine Dioxide

	10-min	30-min	1-hr	4-hr	8-hr
AEGL-1	NR	NR	NR	NR	NR
AEGL-2	0.97 ppm	0.67 ppm	0.53 ppm	0.32 ppm	0.21 ppm
AEGL-3	2.9 ppm	2.0 ppm	1.6 ppm	0.97 ppm	0.63 ppm

NR=Not Recommended

N, N-DIMETHYL FORMAMIDE, CAS Reg. No.68-12-2

Chemical Manager: Loren Koller, OSU
Staff Scientist: Claudia Troxel, ORNL Staff Scientist

Claudia Troxel presented an overview of available data/information on production, physical aspects and exposure effects of N, N-dimethyl formamide (DMF) (Attachment 5).

The AEGL-3 was based on a study by MacDonald (1982) in which groups of 3 male and 3 female rats were exposed to 3700 ppm DMF for 1 or 3 hours with no mortality, while exposure for 7 hours resulted in 83% mortality. Clinical signs were limited to excess grooming in all exposure groups, with lethargy additionally noted in rats exposed for 7 hours. A no-effect level for lethality at 3700 ppm for 3 hours was chosen for the derivation. A total uncertainty factor of 30 was applied to the data. An interspecies uncertainty factor of 3 was applied based upon the fact that the mechanism of toxicity is believed to be related to the metabolism of DMF, and evidence indicates that the primary enzyme responsible for metabolism of DMF (P450 2E1) is similar in both rats and humans. Additionally, occupational exposures in humans demonstrate similar hepatic effects as those seen in animals (cats, mice, rats) following repeated exposure to DMF. Although the mechanism of action has not yet been clearly defined, limited species differences have been identified in the manifestation of toxicity. An intraspecies uncertainty factor of 10 was applied to account for inter-individual differences in levels of P450 2E1 (which can be induced by alcohol consumption). Additionally, based upon the proposed mechanism of action, detoxification of the reactive intermediate is dependent upon conjugation with glutathione. If glutathione levels are depleted due to other reasons, the potential exists for greater exposure to the reactive intermediate. AEGL-3 values were scaled across time using an

n=3 for extrapolation to 10 and 30 minutes and 1 hour, and an n=2 for extrapolation to 4 or 8 hours. A default value of n of 2 was chosen instead of a default value of n of 1 based on available human data in which individuals were exposed up to 87 ppm DMF for 4 hours with no reported effects. A default value of n of 1 would result in AEGL values that are inconsistent with these data. A motion to adopt the values of AEGL-3 (in table below) was made by Loren Koller and seconded by Richard Thomas. The motion was approved [YES:15; NO: 6; Abstain: 5] (Appendix D).

AEGL-2: Data meeting the definition of an AEGL-2 defined endpoint were not available. Therefore, a motion to use the AEGL-3 value and divide by 2 was proposed by Jonathan Borak and seconded by Loren Koller. The motion was approved [YES:14; NO: 7; Abstain: 5] (appendix D).

AEGL-1: Ernie Falke immediately proposed a motion that the Committee not recommend a value for AEGL-1; it was seconded by George Rogers. The motion was approved [YES:20, NO: 5; Abstain: 0] (Appendix D).

Later, it was suggested that the Committee request data from major producers to improved the quality of TSD, if new data become available. After the vote, there was a considerable discussion on AEGL-1 , the Committee again decided there were insufficient data to set an appropriate value though some thought that enzyme changes fall under the AEGL-1 definition. It was noted that the IARC suggestions should be addressed before we leave the chemical.

Summary of AEGL Values					
Classification	**Exposure Duration**				
	10-minute	**30-minute**	**1-hour**	**4-hour**	**8-hour**
AEGL-1	NR	NR	NR	NR	NR
AEGL-2	160 ppm	110 ppm	90 ppm	55 ppm	38 ppm
AEGL-3	320 ppm	220 ppm	180 ppm	110 ppm	76 ppm

REVIEW OF CHEMICALS WITH ISSUES FROM PREVIOUS MEETINGS

HYDROGEN CYANIDE : revisit of AEGL-1

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

The discussion focused on the supporting scientific evidence of AEGL-1 values as pointed out by John Morawetz. George Rodgers and Sylvia Talmage proposed three options to handle the matter (Attachment 6). The committee agreed that option 3 be used with the added statement, "The committee agreed the Leeser study generally supported the approved NAC/AEGL values. It is used as supporting evidence for AEGL-1 values derived from El Ghawabi et al., (1975)." The AEGL-1 values are 2.5 , 2.5, 2.0, 1.3, and 1.0 ppm for the 10-min, 30 min, 1 hr, 4 hr, and 8 hr time periods, respectively as approved at the NAC/AEGL-19. Following this change, the committee approved the Meeting-20 Highlights (Appendix B, Refer to the INTRODUCTION Section).

PHOSGENE:

Chemical Manager: Bill Bress, ASTHO
Staff Scientist: Cheryl Bast, ORNL Staff Scientist

Cheryl Bast presented Comments received from the *Federal Register Notice* of January, 2001 (Attachment 7) There were questions on why the NAC/AEGL adopted the 30-minute AEGL-2 as the 10-minute AEGL-2 rather then extrapolating. This approach was used since extrapolating would yield a value similar to concentrations causing alveolar pulmonary edema in rats. A motion to retain the current values (10-minute AEGL-2 of 0.60 ppm and 30-minute AEGL-2 of 0.60 ppm) was made by George Rogers and seconded by Ernie Falke. The motion carried unanimously (Appendix E). Another motion was then made by John Hinz and seconded by Mark McClanahan to elevate AEGL values from proposed to interim status. The vote was unanimous by a show of hands (Appendix E).

XYLENES:

Chemical Manager: Loren Koller, OSU
Staff Scientist: Claudia Troxel, ORNL Staff Scientist

The reevaluation of the AEGLs using the additional information provided by PBK modeling was presented by Claudia Troxel (Attachment H). Additionally, Ursula Gundert-Remy provided the modeling information (Attachment I). At the January 2000 NAC/AEGL meeting, AEGL-2 and -3 values were set equal across time based on the endpoint of central nervous system effects. It was felt by some of the committee that the 10- and 30-minute AEGL-2 and -3 values were too

low. Therefore, PBK modeling was performed to determine 10- and 30-minute AEGL-2 and -3 values. Ursula Gundert-Remy performed the modeling for — and p-xylene assuming a 1-compartment model. Kinetics for — and p-xylene were calculated from data on pp 52 of the draft 12/2000 TSD

m-xylene	10 min	30 min
AEGL-2	1200 ppm	570 ppm
AEGL-3	2500 ppm	1200 ppm

p-xylene	10 min	30 min
AEGL-2	3100 ppm	1200 ppm
AEGL-3	6700 ppm	2600 ppm

By show of a straw ballot (hands) the votes were essentially split over 1) Entirely using the modeling numbers derived for m-xylene, 2) Using modeling numbers for both time intervals (1 to 8 hr model data), or 3) Using the older straight line numbers. No final votes were balloted, but the NAC/AEGL would like to look at the 95% C.L. for the next meeting and see if it could be incorporated into the TSD document. Ursula Gundert-Remy will be prepared to lead the discussion.

HYDROGEN SULFIDE:

Chemical Manager: Steve Barbee, Arch Chemicals, Inc.
Staff Scientist: Cheryl Bast, ORNL Staff Scientist

Steve Barbee led the discussion and explained that members of the NAC/AEGL had provided questions on potential studies for AEGL-1 development. Zarena Post presented the Texas Natural Resource Conservation Commission's (TNRCC's) response to questions posed by the NAC/AEGL committee members on the report by the Laboratory and Mobile Monitoring Section of the TNRCC, "Corpus Christi Mobile Laboratory Trip, January 31-February 6, 1998; Real-Time Gas Chromatography and Composite Sampling, Sulfur dioxide, Hydrogen sulfide, and Impinger Sampling" and answered questions from the floor. Figures were presented on overheads that showed the concentrations of H_2S measured by 2 separate sampling vans over the course of the sampling trip and the times that staff reported symptoms (Attachment 10). Questions concerned whether health effects could be attributed to hydrogen sulfide exposure, the accuracy of the analytical measurement techniques, possible concurrent exposures, and comparisons results from the two monitoring vans.

Cheryl Bast then presented answers to questions on the Jappinen et al., 1990, and Bhambhani et al., 1994 & 1996, studies (Attachment 11). These questions revolved around comparing the actual concentrations of hydrogen sulfide inhaled in the TNRCC vs. Bhambhani and Jappinen studies, concentration-response relationships, and differences in health effects between oral and nasal exposures. Steve Barbee then compared the Jappinen, Bhambhani and Texas studies with regard to methodology and observed effects/applicability to AEGL-1 development. A motion was made by John Hinz and seconded by George Rogers that the committee adopt an AEGL-1

based on headaches in asthmatic humans exposed to 2 ppm for 30 minutes (based on the Jappinen et al 1990 report). An uncertainty factor of 3 was applied since asthmatics may not be more sensitive than healthy individuals to headache induction. A modifying factor of 3 was also applied to account for the fact that headache may be more severe than endpoints defined by AEGL-1 and because of the shallow concentration-response curve for hydrogen sulfide. Values were scaled across time using the chemical-specific exponent of n = 4.36. The motion carried. (YES: 20; NO: 4; Abstain: 3) (Appendix F).

Proposed AEGL-1 Values for Hydrogen Sulfide

	10-min	30-min	1-hr	4-hr	8-hr
AEGL-1	0.25 ppm	0.20 ppm	0.17 ppm	0.12 ppm	0.11 ppm

TOPICAL ITEMS FOR DISCUSSION

USE OF ODOR IN AEGL-1 DEVELOPMENT:

The consideration of odor in AEGL-1 development to be presented by Marc van Raaij was deferred to the September meeting.

USE OF RD_{50} DATA FOR DEVELOPMENT OF AEGLs

Larry Gephart presented an outline (Attachment 12) showing the location of irritation sites in the respiratory tree. Sensory irritation stimulates the trigeminal nerve and nerves in the respiratory mucosa, while olfaction is sensed by Cranial Nerve 1 and specialized areas in the nasal area. The Yves Alarie method of determining sensory irritation was examined in the presentation. Both immediate and delayed responses were noted in the data. Mechanistic considerations were deemed important. Comments from other Committee members included: Whether hypoxia stimulated respiration and the difference in feed-back mechanisms between the two sites of stimulation. Other areas of consideration concerned differences in species response due to postural changes to avoid irritant exposure and individual and anatomical differences. The effects of time vs. breathing rates for 30-minute exposures to primary irritants and other chemicals were shown on the handouts. A question of recovery and possible adaption was noted with the information that some researchers have produced a conditioned response to exposure. It was suggested that RD_{50} values should not be based on chemicals that produce a mixed irritation response (sensory + pulmonary). It was suggested that the NAC look at available human data and compare the level of response to animal data. Committee members noted that there are several literature reviews that address irritancy data. At the close of the discussion, Larry Gephart requested that any data or literature citations that might be helpful in addressing the subject be sent to him.

John Hinz outlined the use and application of the American Society for Testing and Materials (ASTM) Standard Method E981-84 (re-approved 1996)(Attachment 13). E981-84 is based on Dr.

Yves Alarie's research published between 1966-82 and serves as the experimental design for the studies now under contract at ExxonMobil Biomedical Sciences, Inc., in New Jersey. These studies will attempt to quantitatively and comparatively characterize the potential of various jet fuels to cause respiratory tract sensory irritation.

The need for these studies was triggered a) by the United States Air Force (USAF) and the Department of Defense program to replace JP-4 with a heavier, less volatile fuel, JP-8; and, b) by the NAC/AEGL) targeting JP-8 for review. The NAC/AEGL specifically recommended that the USAF include irritancy studies – specifically Alarie's upper respiratory tract sensory irritation assay – in its study plans for JP-8. The NAC/AEGL expects to incorporate such data into its risk assessment for JP-8. To address this request, the USAF in concert with Army and Navy colleagues designed a comparative study using JP-4, JP-8 and JP-8+100 using a protocol predicated on "E 981-84" to characterize and compare the relative potency of three jet fuels to cause respiratory tract sensory irritation.

Per protocol, these fuels are being administered for 30 minute periods by means of a head-only exposure system to groups of four male Swiss-Webster mice. Test atmospheres laden with these fuels are presented as vapor-only (JP-4) or as a vapor/aerosol mixtures (JP-8, JP-8+100), depending on the physicochemical properties of the fuels. Analytical sampling data should reveal differences in the distribution and relative proportions of the hydrocarbon species contained in the vapor and aerosol phases, and permit construction of each fuel's dose/response curve. Each fuel's RD50 will be derived from these curves and their propensity for respiratory tract sensory irritation compared. John Hinz expects to report his findings to the NAC/AEGL at its December'01 meeting in San Antonio.

SENSITIVITY OF CHILD ASTHMATICS VS ADULT ASTHMATICS IN ACUTE EXPOSURES

An issue of the sensitivity of child asthmatics vs adult asthmatics with regard to acute exposures was addressed by Ernie Falke. Ernie presented the review of asthmatics and their relative susceptibility to acute exposure in a lengthy attachment (Attachment 14). The issues as set forth in his review were: 1) Are normal children more susceptible than normal adults to irritant gases, and 2) Are asthmatic children or adolescents more susceptible than adult asthmatics to exposure to irritant gases? His report indicated a definitive answer to these questions requires specific data sets to allow appropriate comparisons: nonasthmatic children and healthy adults and asthmatic children and asthmatic adults. In both cases, exposures would be to a range of concentrations of irritants sufficient to determine a threshold for a specific type and level of physiologically significant response. Relative susceptibilities of healthy and asthmatic individuals were considered and presented by AEGL levels. There are no data to support the concern that child asthmatics are more sensitive to exposure to irritant gases than adult asthmatics.

PRESENTATION OF KAIF: A COMPUTER-BASED SYSTEM TO EVALUATE POISONINGS

Boris Filatov, Director, and Vladimir Tchernov, Assistant Director, of the South Center for

Chemical Emergencies of Volgograd, Russia, presented an overview of a computer-based system designed to recognize poisoning based on symptomatology following exposure to a toxic chemical. Boris and Vladimir noted that the South Center for Chemical Emergencies, Institute of Hygiene, Toxicology and Occupational Pathology in Volgograd, Russia, was founded in 1971 as a direct result of the Cold War and chemical weapons production. Several thousand clinical histories with symptomatologies were compiled in the files. The Poisoning Differential Diagnostics Computer Software System (KAIF) (Attachment 15) is designed to both help in consultations with medical doctors and also train medical students. It contains two different inter-related software programs: DEFIT which is designed to recognize a chemical substance causing an acute neurotoxic action, and NEUROTOPIC which determines the most afflicted area in the nervous system. The committee thanked Boris and Vladimir for their interesting and informative presentation.

COMMENTS AND RESPONSE ON *FEDERAL REGISTER* CHEMICALS: 66 FR21940, May 2, 2000

DIBORANE

No comments were received from the *Federal Register Notices* of May 2, 2001. A motion to move the chemical from proposed to interim status was made by Jim Holler and seconded by Doan Hansen. The motion was approved unanimously by the NAC/AEGL (Appendix G).

BORON TRICHLORIDE

No comments were received from the *Federal Register Notices* of May 2, 2001. A motion to move the chemical from proposed to interim status was made by Mark McClanahan and seconded by John Hinz. The motion was approved unanimously by the NAC/AEGL (Appendix H).

CARBON MONOXIDE

No comments were received from the *Federal Register Notices* of May 2, 2001. A motion to move the chemical from proposed to interim status was made by John Hinz and seconded by Mark McClanahan. The motion was approved unanimously by the NAC/AEGL (Appendix I).

CHLOROMETHYL METHYL ETHER

No comments were received from the *Federal Register Notices* of May 2, 2001. A motion was made by John Hinz and seconded by Mark McClanahan to move the chemical from proposed to interim status. The motion was approved unanimously by the NAC/AEGL (Appendix J).

PERCHLOROMETHYL MERCAPTAN

One *Federal Register Notice* response was received from Tomen Agro (Attachment 16). The comments were: the subchronic studies were not appropriate for short term exposure, an UF of 3

x UF of 3 was only 9, the proposed 8-hour AEGLs for PMM are overly conservative when compared to 8-hour acceptable exposure levels set by other organizations, the need to establish an AEGL for PMM is not clear, and that Section B of the Notice is misleading as to the ability of certain individuals to detect chemicals relative to the AEGLS.

Reply: Chemical Manager, Zarena Post, addressed the comments. Zarena noted that we could reassess the studies. Zarena also noted that the UF is really the square root of 10, or 3.2. The NAC/AEGL noted that comparing AEGL values with the OSHA values is like comparing apples and oranges. The OSHA values are for chronic exposure of workers and limits, while the AEGL values are for the general public and acute single exposures. Chairman George Rusch suggested that Zarena send a letter of response within 60 days, and request that if there is additional data to consider, it be made available for consideration in a revision of the TSD and be discussed at the September meeting. A motion to elevate the chemical to interim status was made by John Hinz and seconded by Mark McClanahan. The motion was approved unanimously by the NAC/AEGL (Appendix K).

TETRANITROMETHANE

One *Federal Register Notice* response was received from the Michigan Department of Environmental Quality (MDEQ) with regard to this chemical (Attachment 17, Comment No. 6). The state agreed with the derived AEGL values for tetranitromethane. However, MDEQ questioned that the cancer assessment in the TSD would have yielded a higher potency value (and lower allowed exposures) if the incidence for adenoma/adenocarcinomas in the lung of the male mouse instead of the female mouse had used for the calculation.

Reply: Chemical Manager, Bill Bress addressed the concern. The NAC/AEGL replied that a review of the Global 86 runs conducted showed that the slope factor was ~5 % higher by using the female than the male data. The reason for the discrepancy between the MDEQ and the NAC/AEGL results is unclear. The MDEQ did not describe their method of calculating the slope factor using the males. MDEQ's questioning of the appropriateness of estimating lifetime cancer risk from acute exposure is perhaps the most important point here and the NAC/AEGL concluded that the 5 % difference in potency factors is of no practical significance. NAC/AEGL will adopt the AEGL values as published in the *Federal Register Notices* of May 2, 2001. A motion to elevate the chemical from proposed to interim status was made by Mark McClanahan and seconded by Bill Bress. The motion was approved unanimously by the NAC/AEGL) (Appendix L).

TOLUENE

One *Federal Register Notice* response was received from the Michigan Department of Environmental Quality (MDEQ) with regard to this chemical (Attachment 17, Comment No. 7). The MDEQ commented that overall the AEGLs for Toluene seemed to be well reasoned. However, the 10-min. AEGL-1 of 260 ppm and the 30-min. AEGL-2 of 270 ppm may be disproportionately close, but this could simply be reflective of a high threshold for irritation.

Reply: The comment was addressed by Chemical Manager Larry Gephart. The NAC/AEGL agreed that toluene concentrations of 260 ppm and 270 ppm are virtually identical. However, given the 3-fold difference in duration, the potential uptake of toluene could be 3-fold higher at 270 ppm for 30 minutes than 260 ppm for 10 minutes. Also, the concentration of toluene producing AEGL-1 effects (headache, eye irritation) are relatively close to those producing AEGL-2 effects (uncoordination, mental confusion). Hence, the "overlapping" noted occurs throughout the proposed scheme (e.g. , the 30 min. AEGL-1 value of 120 ppm is relatively close to the 1 hour. AEGL-2 value of 190 ppm). All AEGL-1 and -2 values were derived using n=2. So, the NAC/AEGL concluded that the proposed scheme is scientifically valid and should be maintained. A motion was made by Larry Gephart and seconded by Richard Thomas to elevate toluene from proposed to interim status. The motion was approved unanimously by the NAC/AEGL (Appendix M).

FURAN

One *Federal Register Notice* response was received from the Michigan Department of Environmental Quality (MDEQ) with regard to this chemical (Attachment 17, Comment No. 8). MDEQ expressed concerns in the following areas: l) A NOAEL was not identified in the only quantitative toxicology study by Terrill et al. (1989), and 2) applying uncertainty factors in the development of AEGL-2 and -3, especially the LOAEL to NOAEL conversion for the AEGL-2.

Reply: Chemical manager George Rogers responded to the comments. Both AEGL-2 and -3 values are based on a single rat study by Terrill et al. (1989). The AEGL-2 values were based on the threshold value for respiratory symptoms with an interspecies UF of 10, and intraspecies UF of 3, and a modifying factor of 3 because of the limited data. The AEGL-3 was based on the NOEL for mortality with the same UFs. The NAC/AEGL committee discussed the suggestions proposed by the Michigan DEQ, but felt that the present total UFs of 100 for each AEGL value were adequate and that AEGL-2 values are not usually set on the basis of a NOEL. A motion was made by Mark McClanahan to elevate the chemical from proposed to interim status. It was seconded by Steve Barbee. The motion was approved unanimously by the NAC/AEGL (Appendix N).

TETRACHLOROETHYLENE:

Two *Federal Register Notice* responses were received. They are from the Michigan Department of Environmental Quality (MDEQ) (Attachment 17, Comment No. 2), and John Morawetz (Attachment 19).

MDEQ noted that human data are preferred in the development of AEGLs. They question the accuracy /precision of the measured values when taking into account the descriptions of the exposure estimates in the Rowe and Carpenter studies. It was suggested that an UF be added for the adequacy of the data. MDEQ also questioned the reduction in the interspecies UF to 3 based on rodents and humans experiencing similar effects when exposed to CNS depressants. MDEQ thought this reasonable for the pharmacodynamics, but that the pharmacokinetic portion of the

uncertainty factor was not adequately addressed. Statements were also made that the summary noted no developmental anomalies, while the text describes some adverse effects in offspring. Lastly, they also questioned whether positive carcinogenicity data is considered in the derivation of AEGLs.

John Morawetz raised a concern regarding the AEGL-2 values recommended by the AEGL committee for tetrachloroethylene. He felt that the Rowe study supported by the Stewart (1961) study had indications that deserve greater weight in setting the AEGL-2 values. He also requested that the Committee reconsider and lower the current recommended AEGL-2 levels. An alternative proposal would be to start with the 600 ppm for 10 minutes and use an uncertainty factor of 3 for human variability.

Reply: Chemical manager, Bill Bress, responded to the comments. First, the NAC/AEGL addressed the comments from John Morawetz. The NAC/AEGL noted that the Rowe study has indications that should be considered in setting the AEGL-2. It was decided to set the 10- and 30-minute AEGL-2 values equal to the 1-hour AEGL-2 value of 230 ppm because the Rowe et al. (1952) study demonstrated an exposure to 600 ppm for 10 minutes caused significant effects (eye and nose irritation, dizziness, tightness and numbing about the mouth, some loss of inhibitions, and motor coordination required great effort). After applying an uncertainty factor of 3 for intraspecies variation, the AEGL values based upon this study are consistent with the 1-hour AEGL-2 value of 230 ppm.

With regard to the state of Michigan, it was felt by the NAC/AEGL that the UFs applied were adequate. With regard to reproductive effects, the NAC/AEGL considered the lack of an increase in litter effects as a lack of reproductive effects. With regard to positive cancer data, Robert Benson will provide a slope factor for tetrachloroethylene, and an appendix with numbers based on cancer as the endpoint of concern will be added to the TSD.

A motion was made by Robert Benson and seconded by John Morawetz to elevate the chemical from proposed to interim status. The motion was approved unanimously by the NAC/AEGL (Appendix O).

ALLYL ALCOHOL

One *Federal Register Notice* response was received from the Michigan Department of Environmental Quality (MDEQ) with regard to this chemical (Attachment 17, Comment No. 3). MDEQ made two comments. The first comment was that the values set for AEGL-1 were constraining to the setting of the AEGL-2 and -3. The second comment was that the TLV was 0.5 ppm while the AEGL-1 value was 1.8 ppm.

Reply: AEGL values are set independently of other guidelines depending on the values and effects found in the data. The second comment was replied to by noting that the NAC/AEGL did have a rational discussion on this topic. It was noted that the TLV of 0.5 ppm is an 8 hr per day exposure for the lifetime of the working individual while the 1.8 ppm AEGL value is for a single,

acute exposure. The AEGL value is different than the TLV based on the length of time of the exposure as well as who the value is intended to protect.

A motioned was made by John Morawetz and seconded by Mark McClanahan to uphold the current AEGL values. The motion was approved by the NAC/AEGL (YES: 22; NO:1; Abstain: 0) (Appendix P).

Additional comment was made during the NAC/AEGL meeting by Will Bell from Lyondale manufacturing who noted that the committee did a very good job in preparing the document.

AGENTS GA, GB, GD, GF, VX

A total of four sets of comments from the FR notice (66FR21940; May 2, 2001) of proposed AEGL values for the nerve agents GA, GB, GD, GF and VX were received. They are:

1. Monty Herr of the Lawrence Livermore National Laboratory (LLNL; Attachment 19)
2. Christopher Bittner of the Utah Dept. of Environmental Quality, Division of Solid and Hazardous Waste (UT DEQ; Attachment 20)
3. Paul Joe of the Centers for Disease Control and Prevention, Chemical Demilitarization Branch (DHHS/CDC; Attachment 21)
4. LTC Paula Lantzer, Product Manager of the U.S. Army Soldier and Biological Chemical Command, Chemical Stockpile Emergency Preparedness Program (USA SBCCOM/CSEPP; Attachment 22).

An overall summary of the FR comment responses was presented by Annetta Watson (Attachment 23) during the NAC/AEGL meeting. For brevity in the meeting highlights, a summary of the principal remarks made by each commentor and the corresponding NAC/AEGL replies are provided below. Each original FR comment on nerve agents is presented in Attachments 19-22, and is accompanied by detailed NAC/AEGL replies in **bold face** font.

Summary of Commentor No.1 Remarks: Monty Herr suggested a number of alternative values for UFs, including inclusion of an additional MF for an incomplete agent-specific database for nerve agents GA, GD and GF in comparison to the database for agent GB as well as noting that selection of SFEMG changes as a protective definition of AEGL-2 effects suggests that an Intraspecies UF < 10 is warranted. In addition, Dr. Herr provided additional source citations of technical and memo reports from Defense Research Establishment Suffield (Canada) and TNO Prins Maurits Laboratory, The Netherlands; and made a number of editorial suggestions regarding word selections, expanded treatment of certain source material, and alternate explanations of experimental observations.

Reply to Commentor No.1 by NAC/AEGL (Attachment 19): The database for G-agents as a group is considered complete in that

- experimental data are available for multiple species, including human (non-lethal)
- documented non-lethal and lethal endpoints exhibiting exposure-response data

- known mechanism of toxicity; all endpoints represent response continuum to anticholinesterase exposure
- there are no uncertainties regarding reproductive/developmental effects, or carcinogenicity

Since the mechanism of action is the same (cholinesterase inhibition), data uncertainty is reduced, and target organ effects are similar but differ in magnitude. The database for agent VX is considered much less complete than the composite database for G-series agents; thus, application of MF = 3 for agent VX is warranted and consistency in logic is maintained.

The NAC/AEGL had considered an intraspecies UF<10 for determination of the AEGL-2 for agent GB, but this option was previously rejected by a NAC/AEGL majority in favor of a UF = 10.

The additional citations are accepted with thanks and will be incorporated into the next edition of the TSD as summarized in a new report currently in press by DRES in Alberta, Canada. If analyses of these new experimental data indicate any need for a change in values of any nerve agent AEGL estimate, the document developer will return to the NAC/AEGL for further consideration.

It is further noted that the primary VX concern of the Office of the Army Surgeon General is focused on VX vapor rather than VX aerosol; a footnote will be added to each VX AEGL table pointing out that the AEGL estimates for agent VX are for vapor exposure only. All necessary editorial corrections will be made, and new reference material identified by Dr. Herr will be incorporated in an appropriate manner.

Summary of Commentor No. 2 Remarks: Christopher Bittner communicated an overall concern that a single relative potency factor ("of 10") comparing agent VX to agent GB was, in his opinion, not supported by information presented in Tables of the VX TSD and that the "relative potency should be derived based on the experimental data that match...exposure regime and toxicological endpoint." The Commentor further remarked that, in his opinion, the estimate of n=2 is not based on VX-specific data, and that the MF should be equal to10 and not 3.

Reply to Commentor No. 2 by NAC/AEGL (Attachment 20): For Agent VX, there are insufficient valid experimental data that match the needed "...exposure regime and toxicological endpoint." The TSD makes this finding very clear.

The NAC/AEGL and commentor are in agreement on the need for more and better data characterizing VX vapor toxicity. As a consequence, the

- NAC/AEGL identified research studies specifically designed to reduce uncertainties in estimates
- NAC/AEGL declared VX AEGL estimates "temporary" and subject to re-evaluation in 3 years
- NAC/AEGL acknowledged existing data gaps and made practical suggestions for collection of specific new data to elucidate dose-response curves and determination of "n"

Until additional data from well-conducted experimental studies are available, current assumptions and value of "n" (=2) are reasonable, are supported by existing experimental data, and meet requirements of the SOPs. The fact that these AEGL estimates for Agent VX are considered **Temporary** by the NAC/AEGL will be more highly emphasized in the next edition of the TSD for presentation to the COT.

Further, the Commentor is considering the range of relative potency ratios cited in Tables of Agent VX TSD without making any distinction between primary (text boldface) and secondary sources. NAC/AEGL SOPs require use of primary source data for AEGL derivations; verifiable EXPERIMENTAL data for humans, rats and rabbits provide a less variable range of ratios (range = 4.2 to 33). The NAC/AEGL determined that the Commentor's remarks were made without complete knowledge of the content of the NAC/AEGL SOPs, which were published in May, 2001. Until additional data from well-conducted experimental studies are available, the current relative potency approach (RP = 12) is reasonable, is supported by existing experimental data, and meets requirements of the SOPs.

Use of the full default value of 10 for the MF is reserved for cases where there are truly no data; that is the purpose of a default. In the case of agent VX, despite the acknowledged database limitations, much is known about the agent mechanism of action, and comparative experimental data exist for humans as well as the rat and rabbit. In the presence of limited data, the NAC/AEGL considers use of a MF of 3 to be appropriate at this time.

All necessary editorial corrections pointed out by the Commentor will be made.

Summary of Commentor No. 3 Remarks: There is no issue of disagreement. The CDC Chemical Demilitarization Branch is supportive of the NAC/AEGL effort, and wished to inform the NAC/AEGL that the Branch is presently involved in a related area–that of developing long-term occupational and general public exposure guidelines for airborne chemical warfare agents. Further, the Branch wished to state that they could benefit from being made aware of any additional research or insight identified in the FR comment process and requested communication of same from the NAC/AEGL.

Reply to Commentor No. 3 by NAC/AEGL (Attachment 21): The NAC/AEGL welcomes dialogue with the Chemical Demilitarization Branch of the National Center for Environmental Health, CDC, and will be pleased to share information and analyses with the Branch on a continuing basis.

Further, Dr. Mark McClanahan, NAC/AEGL member and staff scientist at the National Center for Environmental Health, CDC, made personal contact with Dr. Joe prior to NAC/AEGL-21 and communicated the NAC/AEGL's wish to continue dialogue.

Summary of Commentor No.4 Remarks: The complete statement of this Commentor's remark is presented below:

"As the Army proponent for emergency planning criteria for the U.S. stockpiled chemical warfare agents, I have coordinated an Army review of the specified AEGLs for G-series and VX nerve agents, and concur with the stated values."

Reply to Commentor No. 4 by NAC/AEGL: The comment provided by LTC Paula Lantzer represents official concurrence by the proponent US Department of the Army agency that originally commissioned development of AEGL estimates for the nerve agents. The NAC/AEGL welcomes this statement of official concurrence and its incorporation into the FR comment process.

Following summarization of the FR comments and replies, the NAC/AEGL Chair George Rusch invited comment by the NAC/AEGL guests, Boris Filatov and Vladimir Tchernov, Director and Assistant Director, respectively, of the South Center for Chemical Emergencies (Volgograd Research Institute of Hygiene, Toxicology and Occupational Pathology, Volgograd, Russia). Dr. Filatov counseled that it was important to develop planning estimates for use in potential emergencies given that the chemical munitions in storage in both the USA and Russia were aging and deteriorating. Boris Filatov encouraged the NAC/AEGL process and members in their efforts to develop appropriate estimates, and welcomed the opportunity to review the draft nerve agent TSDs as a means of collaboration in the NAC/AEGL process for these compounds of mutual international importance.

At the close of discussion, Bill Bress moved that the status of the AEGL estimates for nerve agents GA, GB, GD, GF and VX be elevated from "proposed" to "interim." Bill amended this motion to include the proviso that the document developer return to the NAC/AEGL if evaluation of any new information indicated any need for change in the AEGL estimates. The amended motion was seconded by Glenn Leach. The motion was carried (YES: 19; NO: 2; ABSTAIN; 0) (see Attachment Q).

ACRYLIC ACID

Two responses from the *Federal Register Notice* were received. They were submitted by MEDQ (Attachment 17, Comment No. 1) and The Acrylic Monomer Manufacturers, Inc. (Attachment 24). Due to the international collaboration procedures, these comments will be evaluated by the German Expert Group prior to the next NAC/AEGL discussion. The comments will be discussed by NAC/AEGL at the next meeting.

PHENOL

Two responses from the *Federal Register Notice* were received. They were submitted by MEDQ (Attachment 17, Comment No. 4) and The American Chemistry Council's Phenol Regulatory Panel (Attachment 25). Due to the international collaboration procedures, these comments will be evaluated by the German Expert Group prior to the next NAC/AEGL discussion. The comments will be discussed by NAC/AEGL at the next meeting.

METHANOL

Three responses from the *Federal Register Notice* were received. They were submitted by MEDQ (Attachment 17, Comment No. 5), the Methanol Institute (Attachment 26) and John Morawetz (Attachment 27). Due to the international collaboration procedures, these comments will be evaluated by the German Expert Group prior to the next NAC/AEGL discussion. The comments will be discussed by NAC/AEGL at the next meeting.

The meeting highlights were prepared by Hanks Spencer and Po-Yung Lu , Oak Ridge National Laboratory.

LIST OF ATTACHMENTS

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

Attachment 1. Meeting Agenda
Attachment 2. List of Attendees
Attachment 3. Data Analysis of Boron Trifluoride
Attachment 4. Data Analysis of Chlorine Dioxide
Attachment 5. Data Analysis of N,N-Dimethyl Formamide
Attachment 6. Clarification of AEGL-1 values of Hydrogen Cyanide
Attachment 7. Federal Register Notice Comments and Data Analysis of Phosgene
Attachment 8. Re-evaluation of Xylenes
Attachment 9. PBPK Modeling Extrapolation for Xylenes
Attachment 10. Monitoring Charts on H_2S from Texas
Attachment 11. Q&A Posed by NAC/AEGL Committee Members
Attachment 12. Use of RD50 data for Development of AEGLs by Larry Gephart
Attachment 13. Application of ASTM Standard Method E981-84 to "The Comparative and Qualitative Characterization of JP-8's Potential for Respiratory Irritation" by John Hinz
Attachment 14. The Relative Susceptibility of Childhood Asthmatics and Adult Asthmatics to Acute Exposures of Irritant Chemicals
Attachment 15. Handout on KAIF System
Attachment 16. *Federal Register* Comments of Perchloromethyl Mercaptan from Tomen Agro, Inc. by Scott A. Mobley
Attachment 17. *Federal Register* Comments of Acrylic acid, Tetrachloroethylene, Ally Alcohol, Phenol, Methanol, Tetranitromethane, Toluene, and Furan from Mary Lee Hultin, Michigan Department of Environmental Quality.
Attachment 18. *Federal Register* Comments of Tetrachloroethylene by John Morawetz
Attachment 19. *Federal Register* Comments on G-agents and Agent-VX from LLNL by Monty L Herr
Attachment 20. *Federal Register* Comments on Nerve agent VX from Utah Division of Solid and Hazardous Waste by Christopher Bittner
Attachment 21. *Federal Register* Comments on Nerve agents from Chemical Demilitarization Branch of CDC by Paul Joe
Attachment 22. *Federal Register* Comments on TSDs of Nerve agents from US Army, LTC Paula Lantzer
Attachment 23. Summary of overall *Federal Register* Comments on proposed nerve agent AEGL estimates by Annetta Watson
Attachment 24. *Federal Register* Comments of Acrylic acid from The Acrylic Monomer Manufacturers, Inc.
Attachment 25. *Federal Register* Comments of Phenol from American Chemistry Council
Attachment 26. *Federal Register* Comments of Methanol from Methanol Institute
Attachment 27. *Federal Register* Comments of Methanol from John Morawetz

LIST OF APPENDICES

A. Revised NAC/AEGL-20 Meeting 20 Highlights
B. Ballot for Approval of NAC/AEGL-20 Meeting 20 Highlights
C. Ballot for Chlorine dioxide
D. Ballot for N-Dimethyl Formamide
E. Ballot for Phosgene
F. Ballot for Hydrogen sulfide
G. Ballot for Diborane
H. Ballot for Boron trichloride
I. Ballot for Carbon monoxide
J. Ballot for Chloromethyl methyl ether
K. Ballot for Perchloromethyl mercaptan
L. Ballot for Tetranitromethane
M. Ballot for Toluene
N. Ballot for Furan
O. Ballot for Tetrachloroethylene
P. Ballot for Allyl alcohol
Q. Ballot for GA, GB, GD, GF, and VX

NAC/AEGL Meeting 22: September 11-13, 2001

Chemical: BORON TRIFLUORIDE **CAS Reg. No.:** 353-42-4

NAC Member	AEGL 1	AEGL 2	AEGL 3	NAC Member	AEGL 1	AEGL 2	AEGL 3
George Alexeeff	A	A	A	Nancy Kim	Y	Y	Y
Steven Barbee	Y	Y	Y	Loren Koller	Absent	Absent	Absent
Lynn Beasley	Y	Y	Y	Glenn Leach	A	A	A
David Belluck	Y	Y	Y	Mark McClanahan	Y	Y	Y
Robert Benson	Y	Y	Y	John Morawetz	Absent	A	A
Jonathan Borak	A	A	A	Richard Niemeier	A	A	A
William Bress	Y	Y	Y	Marinelle Payton	Y	Y	Y
George Cushmac	Y	Y	Y	Zarena Post	A	A	A
Ernest Falke	Y	Y	Y	George Rodgers	Y	Y	Y
Larry Gephart	A	A	A	George Rusch, Chair	P	P	P
Doan Hansen	A	A	A	Robert Snyder	Y	Y	Y
John Hinz	Y	Y	Y	Thomas Sobotka	A	A	A
Jim Holler	Y	Y	Y	Kenneth Still	A	A	A
Thomas Hornshaw	Y	Y	Y	Richard Thomas	A	A	A
				TALLY	15/15	15/15	15/15

mg/m^3

PPM, (mg/m^3)	10 Min	30 Min	1 Hr	4 Hr	8 Hr
AEGL 1	,(0.6)	,(0.6)	,(0.6)	,(0.6)	,(0.6)
AEGL 2	,(21)	,(21)	,(16)	,(10)	,(6.8)
AEGL 3	,(49)	,(49)	,(39)	,(25)	,(12)

AEGL 1 Motion: Mark McClanahan **Second:** John Hinz

AEGL 2 Motion: ↓ **Second:** ↓

AEGL 3 Motion: ↓ **Second:** ↓

Approved by Chair: [signature] **DFO:** [signature] **Date:** 9/12/01

NAC/AEGL Meeting 22: September 11-13, 2001

Chemical: HFE-7100 **CAS Reg. No.:**

NAC Member	AEGL 1	AEGL 2	AEGL 3	NAC Member	AEGL 1	AEGL 2	AEGL 3
George Alexeeff	A	A	A	Nancy Kim	N	Y	Y
Steven Barbee	Y			Loren Koller	Absent	Absent	Absent
Lynn Beasley	Y			Glenn Leach	A		
David Belluck	Y			Mark McClanahan	Y		
Robert Benson	P			John Morawetz	Absent		
Jonathan Borak	A			Richard Niemeier	A		
William Bress	Y			Marinelle Payton	Y		
George Cushmac	Y			Zarena Post	A		
Ernest Falke	N	Y	Y	George Rodgers	Y		
Larry Gephart	A			George Rusch, Chair	Y		
Doan Hansen	A			Robert Snyder	Y		
John Hinz	Y			Thomas Sobotka	N	Y	Y
Jim Holler	Y			Kenneth Still			
Thomas Hornshaw	Y			Richard Thomas			
				TALLY			

PPM, (mg/m^3)	10 Min	30 Min	1 Hr	4 Hr	8 Hr
AEGL 1	2500	,( )	,( )	,( )	,( )
AEGL 2	8200	,( )	,( )	,( )	,( )
AEGL 3	15,000	,( )	,( )	,( )	,( )

AEGL 1 Motion: E. FALKE **Second:** B. SNYDER

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

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

Approved by Chair: _____ **DFO:** Pamela Tobin **Date:** 9/13/01

AEGL-2+3

NAC/AEGL Meeting 22: September 11-13, 2001

Chemical: CHLORINE DIOXIDE **CAS Reg. No.:** 10049-04-4

NAC Member	AEGL 1	AEGL 2	AEGL 3	NAC Member	AEGL 1	AEGL 2	AEGL 3
George Alexeeff	A	A	A	Nancy Kim	Y	Y	Y
Steven Barbee	Y	Y	Y	Loren Koller	Absent	Absent	Absent
Lynn Beasley	Y	Y	Y	Glenn Leach	A	A	A
David Belluck	Y	Y	Y	Mark McClanahan	Y	Y	Y
Robert Benson	P	P	Y	John Morawetz	Absent	A	A
Jonathan Borak	A	A	A	Richard Niemeier	A	A	A
William Bress	Y	Y	Y	Marinelle Payton	A	A	A
George Cushmac	Y	Y	Y	Zarena Post	A	A	A
Ernest Falke	Y	Y	Y	George Rodgers	Y	Y	Y
Larry Gephart	A	A	A	George Rusch, Chair	Y	Y	Y
Doan Hansen	A	A	A	Robert Snyder	Y	Y	Y
John Hinz	Y	Y	Y	Thomas Sobotka	Y	P	A
Jim Holler	Y	Y	Y	Kenneth Still	A	A	A
Thomas Hornshaw	Y	Y	Y	Richard Thomas	A	A	A
				TALLY	15/15	14/14	15/15

PPM, (mg/m³)	10 Min	30 Min	1 Hr	4 Hr	8 Hr
AEGL 1	0.15 ( )	0.15 ( )	0.15 ( )	0.15 ( )	0.15 , ( )
AEGL 2	1.5 , ( )	1.5 , ( )	1.1 , ( )	0.68 ( )	0.45 , ( )
AEGL 3	~~2.0~~ , ( )	~~2.0~~ , ( )	~~2.0~~ , ( )	~~2.0~~ , ( )	~~2.0~~ , ( )
	3.0	3.0	2.4	1.5	1.0

VERIFY (CHEMTAX)

AEGL 1 **Motion:** ~~B. Benson~~ Belluck **Second:** ~~N. Kim~~ G. Rodgers

AEGL 2 **Motion:** G. Rodgers * **Second:** B. Bress

AEGL 3 **Motion:** B. Benson **Second:** N. Kim

* REVISE AEGL-2 + -3

Approved by Chair: [signature] **DFO:** Paul Tobin **Date:** 9/13/01

NAC/AEGL Meeting 22: September 11-13, 2001

Chemical: HF **CAS Reg. No.:** 7664-39-3

NAC Member	AEGL 1	AEGL 2	AEGL 3	NAC Member	AEGL 1	AEGL 2	AEGL 3
George Alexeeff	A			Nancy Kim	Y		
Steven Barbee	Y			Loren Koller	Absent	Absent	Absent
Lynn Beasley	Y			Glenn Leach	A		
David Belluck	*A Y			Mark McClanahan	Y		
Robert Benson	Y			John Morawetz	Absent		
Jonathan Borak	A			Richard Niemeier	A		
William Bress	Y			Marinelle Payton	Y		
George Cushmac	A			Zarena Post	A		
Ernest Falke	Y			George Rodgers	Y		
Larry Gephart	A			George Rusch, Chair	Y		
Doan Hansen	A			Robert Snyder	Y		
John Hinz	P			Thomas Sobotka	A		
Jim Holler	Y			Kenneth Still	A		
Thomas Hornshaw	Y			Richard Thomas	A		
				TALLY	~~13/13~~ 13/14		

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

* CONTACTED WHEN RETURNED TO ROOM (FOR VOTE) - JSD

AEGL 1 Motion: M. McClanahan **Second:** E. Falke

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

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

Approved by Chair: _____ **DFO:** _____ **Date:** 9/12/01

NAC/AEGL Meeting 22: September 11-13, 2001

Chemical: PHENOL → Interim **CAS Reg. No.:** 108-95-2

NAC Member	AEGL 1	AEGL 2	AEGL 3	NAC Member	AEGL 1	AEGL 2	AEGL 3
George Alexeeff	A	→	→	Nancy Kim	Y	→	→
Steven Barbee	Y	→	→	Loren Koller	Absent	Absent	Absent
Lynn Beasley	Y	→	→	Glenn Leach	A	→	→
David Belluck	P	→	→	Mark McClanahan	Y	→	→
Robert Benson	Y	→	→	John Morawetz	Absent	→	→
Jonathan Borak	A	→	→	Richard Niemeier	A	→	→
William Bress	Y	→	→	Marinelle Payton	Y	→	→
George Cushmac	Y	→	→	Zarena Post	A	→	→
Ernest Falke	Y	→	→	George Rodgers	Y	→	→
Larry Gephart	A	→	→	George Rusch, Chair	Y	→	→
Doan Hansen	A	→	→	Robert Snyder	Y	→	→
John Hinz	Y	→	→	Thomas Sobotka	A	→	→
Jim Holler	Y	→	→	Kenneth Still	A	→	→
Thomas Hornshaw	Y	→	→	Richard Thomas	A	→	→
				TALLY	15/15		

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

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

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

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

Approved by Chair: George Rusch **DFO:** Paul S. Tobin **Date:** 9/12/01

NAC/AEGL Meeting 22: September 11-13, 2001

Chemical: CHLORINE **CAS Reg. No.:** 7782-50-5

NAC Member	AEGL 1	AEGL 2	AEGL 3	NAC Member	AEGL 1	AEGL 2	AEGL 3
George Alexeeff	A	A		Nancy Kim	Y	Y	
Steven Barbee	Y	Y		Loren Koller	Absent	Absent	Absent
Lynn Beasley	Y	Y		Glenn Leach	A	A	
David Belluck	Y	Y		Mark McClanahan	Y	Y	
Robert Benson	Y	Y		John Morawetz	Absent	A	
Jonathan Borak	A	A		Richard Niemeier	A	A	
William Bress	Y	N		Marinelle Payton	P	Y	
George Cushmac	Y	Y	→	Zarena Post	A	A	→
Ernest Falke	Y	Y		George Rodgers	Y	N	
Larry Gephart	A	A		George Rusch, Chair	Y	P	
Doan Hansen	A	A		Robert Snyder	Y	N	
John Hinz	P	Y		Thomas Sobotka	A	A	
Jim Holler	Y	Y		Kenneth Still	A	A	
Thomas Hornshaw	Y	Y		Richard Thomas	A	A	
				TALLY	13/15	12/15	

PPM, (mg/m³)	10 Min	30 Min	1 Hr	4 Hr	8 Hr
AEGL 1	0.5 ,( )	0.5 ,( )	0.5 ,( )	0.5 ,( )	0.5 ,( )
AEGL 2	2.8 ,( )	,( )	,( )	,( )	,( )
AEGL 3	50 ,( )	,( )	,( )	,( )	,( )

AEGL 1 Motion: M. McClanahan **Second:** E. Falke

AEGL 2 Motion: M. McClanahan **Second:** E. Falke

AEGL 3 Motion: Mark McClanahan **Second:** E. Falke

Approved by Chair: [signature] **DFO:** Paul S. Tobin **Date:** 9/12/01

NAC/AEGL Meeting 22: September 11-13, 2001

Chemical: ANILINE (10 MIN) **CAS Reg. No.:** 62-53-3

NAC Member	AEGL 1	AEGL 2	AEGL 3
George Alexeeff	A		
Steven Barbee	Y		
Lynn Beasley	Y		
David Belluck	Y		
Robert Benson	Y		
Jonathan Borak	A		
William Bress	Y		
George Cushmac	[illegible]		
Ernest Falke	Y		
Larry Gephart	A		
Doan Hansen	A		
John Hinz	Y		
Jim Holler	Y		
Thomas Hornshaw	Y		

NAC Member	AEGL 1	AEGL 2	AEGL 3
Nancy Kim	Y		
Loren Koller	Absent	Absent	Absent
Glenn Leach	A		
Mark McClanahan	Y		
John Morawetz	Absent		
Richard Niemeier	A		
Marinelle Payton	Y		
Zarena Post	A		
George Rodgers	Y		
George Rusch, Chair	Y		
Robert Snyder	Y		
Thomas Sobotka	A		
Kenneth Still	A		
Richard Thomas	A		
TALLY			

PPM, (mg/m³)	10 Min	30 Min	1 Hr	4 Hr	8 Hr
AEGL 1	48 ,( )	,( )	,( )	,( )	,( )
AEGL 2	72 ,( )	,( )	,( )	,( )	,( )
AEGL 3	120 ,( )	,( )	,( )	,( )	,( )

AEGL 1 Motion: G. Rodgers **Second:** B. Snyder

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

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

Approved by Chair: [signature] **DFO:** Paul S. Tobin **Date:** 9/12/01

NAC/AEGL Meeting 22: September 11-13, 2001

10 MIN

Chemical: CARBON TETRACHLORIDE **CAS Reg. No.:** 67-66-3

NAC Member	AEGL 1	AEGL 2	AEGL 3	NAC Member	AEGL 1	AEGL 2	AEGL 3
George Alexeeff	A			Nancy Kim	Y		
Steven Barbee	Y			Loren Koller	Absent	Absent	Absent
Lynn Beasley	Y			Glenn Leach	A		
David Belluck	Y			Mark McClanahan	Y		
Robert Benson	Y			John Morawetz	Absent	→	
Jonathan Borak	A			Richard Niemeier	A		
William Bress	Y	→		Marinelle Payton	Y		
George Cushmac	Y			Zarena Post	A		
Ernest Falke	A			George Rodgers	Y		
Larry Gephart	A			George Rusch, Chair	Y		
Doan Hansen	A			Robert Snyder	Y		
John Hinz	Y			Thomas Sobotka	Y		
Jim Holler	Y			Kenneth Still	A		
Thomas Hornshaw	Y			Richard Thomas	A		
				TALLY	16/16		

PPM, (mg/m³)	10 Min	30 Min	1 Hr	4 Hr	8 Hr
AEGL 1	25 ,( )	,( )	,( )	,( )	,( )
AEGL 2	140 ,( )	,( )	,( )	,( )	,( )
AEGL 3	350 ,( )	,( )	,( )	,( )	,( )

AEGL 1 Motion: M. McClanahan **Second:** D. Belluck

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

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

Approved by Chair: [signature] **DFO:** Paul S. Tobin **Date:** 9/13/01

NAC/AEGL Meeting 22: September 11-13, 2001

Chemical: ARSINE 10 MIN **CAS Reg. No.:** 7784-42-1

NAC Member	AEGL 1	AEGL 2	AEGL 3
George Alexeeff	A		
Steven Barbee	Y		
Lynn Beasley	Y		
David Belluck	Y		
Robert Benson	Y		
Jonathan Borak	A		
William Bress	Y		
George Cushmac	Y		
Ernest Falke	A		
Larry Gephart	A		
Doan Hansen	A		
John Hinz	A		
Jim Holler	Y		
Thomas Hornshaw	Y		

NAC Member	AEGL 1	AEGL 2	AEGL 3
Nancy Kim	Y		
Loren Koller	Absent	Absent	Absent
Glenn Leach	A		
Mark McClanahan	Y		
John Morawetz	Absent		
Richard Niemeier	A		
Marinelle Payton	Y		
Zarena Post	A		
George Rodgers	Y		
George Rusch, Chair	Y		
Robert Snyder	Y		
Thomas Sobotka	Y		
Kenneth Still	A		
Richard Thomas	A		
TALLY	15/15		

PPM, (mg/m^3)	10 Min	30 Min	1 Hr	4 Hr	8 Hr
AEGL 1	NR , ( )	, ( )	, ( )	, ( )	, ( )
AEGL 2	0.30 , ( )	, ( )	, ( )	, ( )	, ( )
AEGL 3	[redacted] , ( )	, ( )	, ( )	, ( )	, ( )

0.91

AEGL 1 Motion: G. Rodgers **Second:** B. Benson

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

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

Approved by Chair: _____ **DFO:** _____ **Date:** 9/13/01