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INTERIM ACUTE EXPOSURE GUIDELINE LEVELS (AEGLs)

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

For
NAS/COT Subcommittee for AEGLs

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PREFACE

Under the authority of the Federal Advisory Committee Act (FACA) P. L. 92-463 of 1972, the National Advisory Committee for Acute Exposure Guideline Levels for Hazardous Substances (NAC/AEGL Committee) has been established to identify, review and interpret relevant toxicologic and other scientific data and develop AEGLs for high priority, acutely toxic chemicals.

AEGLs represent threshold exposure limits for the general public and are applicable to emergency exposure periods ranging from 10 minutes to 8 hours. AEGL-2 and AEGL-3 levels, and AEGL-1 levels as appropriate, will be developed for each of five exposure periods (10 and 30 minutes, 1 hour, 4 hours, and 8 hours) and will be distinguished by varying degrees of severity of toxic effects. It is believed that the recommended exposure levels are applicable to the general population including infants and children, and other individuals who may be sensitive or susceptible. The three AEGLs have been defined as follows:

AEGL-1 is the airborne concentration (expressed as ppm or mg/m^3) of a substance above which it is predicted that the general population, including susceptible individuals, could experience notable discomfort, irritation, or certain asymptomatic, non-sensory effects. However, the effects are not disabling and are transient and reversible upon cessation of exposure.

AEGL-2 is the airborne concentration (expressed as ppm or mg/m^3) 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.

AEGL-3 is the airborne concentration (expressed as ppm or mg/m^3) of a substance above which it is predicted that the general population, including susceptible individuals, could experience life-threatening health effects or death.

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. With increasing airborne concentrations above each AEGL level, there is a progressive increase in the likelihood of occurrence and the severity of effects described for each corresponding AEGL level. Although the AEGL values represent threshold levels for the general public, including sensitive subpopulations, it is recognized that certain individuals, subject to unique or idiosyncratic responses, could experience the effects described at concentrations below the corresponding AEGL level.

40 **TABLE OF CONTENTS**

105 **LIST OF TABLES**

LIST OF FIGURES

EXECUTIVE SUMMARY

Acrylic acid is a clear, colorless, corrosive liquid with a pungent odor. The primary use of acrylic acid, accounting for about two thirds of its use, is in the production of acrylic esters and resins, which are used primarily in coatings, paint, plastics and adhesives. Acrylic acid is also used in oil treatment chemicals, detergent intermediates, and water treatment chemicals.

Except for reports on odor threshold (Hellman and Small, 1974) and a personal communication regarding irritative effects in occupationally exposed individuals (Renshaw, 1988), no studies reporting effects in humans are available. Irritative effects, affecting esp. the nasal mucosa and the eyes, have been described in rabbits, rats and mice following repeated 6-hour exposures to acrylic acid vapor. Consistently, histopathological alterations of the nasal mucosa (evaluated at the end of the exposure period) was a more sensitive toxicological endpoint than the appearance of clinical signs of irritation (observed during the first day or the first week of exposure): the lowest concentrations leading to clinical signs of irritation (concentrations without effect given in brackets) were 129 (77) ppm in rabbits (blepharospasm, perinasal and perioral wetness), 218 (114) ppm in rats (eyelid closure, discharge from eyes) and 223 (72) ppm in mice (scratching at the nose). Repeated exposure for 1 - 2 weeks led to histopathological changes of the nasal mucosa at the lowest concentrations tested, which were 34 ppm for rabbits, 74 ppm for rats and 25 ppm for mice. In mice, effects were found after exposure to 5 ppm for 22 hours/day, but not 6 hours/day, for 2 weeks. Similar histopathological changes of the nasal mucosa were seen in rats after single exposure for 3 and 6 hours at 75 ppm (Frederick et al., 1998) and in monkeys after single exposure for 3 and 6 hours to 75 ppm (Rohm and Haas Co., 1995; Harkema, 2001; Harkema et al., 1997). A number of studies described lethal effects in rats. In a study in which rats were exposed to acrylic acid aerosol (Hagan and Emmons, 1988), LC_{50} values of 1890 mg/m³ (equivalent to 5670 ppm), 1268 mg/m³ (equivalent to 3804 ppm) and 851 mg/m³ (equivalent to 2553 ppm) were reported for 30 minutes, 1 hour and 2 hours, respectively. Studies evaluating the acute toxicity of acrylic acid vapors used very small numbers of animals or were not reported in detail and gave somewhat varying results. In summary, the available studies do not indicate a large difference in the toxicity of acrylic acid vapor and aerosol. No developmental toxic effects of acrylic acid were found in several inhalation studies. Acrylic acid did not cause gene mutations in bacterial or mammalian cell systems. It caused clastogenic effects in vitro in the mouse lymphoma assay and in the chromosomal aberration assay in CHO cells. No mutagenic effects were observed in vivo using the mouse bone marrow micronucleus assay and the dominant lethal assay in mice. No carcinogenic effects were found after application of acrylic acid in the drinking water, while after subcutaneous and topical application tumors were found (probably attributable to repeated local irritation).

AEGL-1 values were based on irritation in humans. The data on irritative effects in humans by Renshaw (1988; personal communication) was used as key study because human data were considered most relevant for AEGL derivation. Renshaw (1988) reported that eye irritation was experienced after exposure to 4.5 - 23 ppm for 30 minutes. For AEGL-1 derivation, the lower bound of 4.5 ppm was used. Since the Renshaw (1988) study has obvious shortcomings, e.g. the limited number of subjects and lack of exact characterization of exposure time and exposure concentration, the study by Lomax et al. (1994) reporting exposure to 5 ppm for 6 hours as a NOEL for histopathological alterations in mice was used as supportive evidence. An uncertainty factor of 3 was applied for intraspecies variability. The intraspecies uncertainty factor is used to compensate for both, toxicokinetic and toxicodynamic differences between individuals. For local effects, the toxicokinetic differences between individuals are usually much smaller when compared to systemic

effects. Therefore, a reduced uncertainty factor of 3 was retained to account for toxicodynamic differences between individuals. Since very slight irritative effects depend primarily on the actual exposure concentration and not much on exposure time, it was considered adequate to use the same exposure concentration for all exposure durations between 10 minutes and 8 hours (i.e. a flat line was used for time scaling).

A level of distinct odor awareness (LOA) for acrylic acid of 0.20 ppm was derived on the basis of the odor detection threshold from the study of Hellman and Small (1974). The LOA represents the concentration above which it is predicted that more than half of the exposed population will experience at least a distinct odor intensity, about 10 % of the population will experience a strong odor intensity. The LOA should help chemical emergency responders in assessing the public awareness of the exposure due to odor perception.

In studies in monkeys, rabbits, rats and mice, histopathological alteration of the nasal mucosa consistently was a more sensitive toxicological endpoint than the appearance of clinical signs of irritation. It was therefore considered appropriate to use the single inhalation exposure studies in monkeys (Rohm and Haas Co., 1995; Harkema, 2001; Harkema et al., 1997) as key study for the derivation of AEGL-2 values. Exposure to 75 ppm acrylic acid for 6 hours resulted in severe histopathological changes of the nasal epithelium (olfactory epithelial cell degeneration, sustentacular cell necrosis), while exposure for 3 hours resulted in less severe changes and a lesser percentage of the olfactory epithelium was affected. No obvious clinical symptoms were reported. The NAC/AEGL committee evaluated the histological damage and considered the effects after the 6-hour exposure as severe and probably irreversible, while the changes after the 3-hour exposure were considered reversible. Therefore, AEGL-2 values were derived on the basis of a 3-hour exposure to 75 ppm. In supporting animal studies, this exposure level was found to be the NOEL for blepharospasm and involuntary eye lid closure. A total uncertainty factor of 3 was used. An uncertainty factor of 1 was applied for interspecies variability: for the toxicokinetic component a factor of 1 was used because a monkey inhalation study was used and because acrylic acid is a locally acting irritant not requiring metabolic activation. The toxicodynamic component of the uncertainty factor was reduced to 1 because single inhalation exposure of monkeys resulted in similar olfactory lesions than in rats (Rohm and Haas Co., 1995; Harkema, 2001; Harkema et al., 1997). An uncertainty factor of 3 was applied for intraspecies variability because tissue damage of the nasal mucosa by local cytotoxicity was considered not to vary considerably between individuals. The other exposure duration-specific values were derived by time scaling according to the dose-response regression equation $C^n * t = k$, using the default of n=3 for shorter exposure periods and n=1 for longer exposure periods, due to the lack of suitable experimental data for deriving the concentration exponent. The time extrapolation was continued to the 10-minute period because the resulting 10-minute AEGL-2 value was still below the threshold for blepharospasm in rabbits.

For the derivation of AEGL-3 values, the animal studies using vapor exposure were considered more relevant than the aerosol studies, because for emergency situations a vapor exposure was considered more likely than an aerosol exposure. The derivation was based on the study by BASF (1980) reporting no deaths of rats after exposure to 1705 ppm for 4 hours. This result is supported by the study of Hagan and Emmons (1988) which found no lethality in rats at 2142 ppm for 1 hour. While these studies did not report a LOEL for vapor lethality, the results of the study by Carpenter et al. (1974) indicated that a level of about 4000 ppm for 4 hours was clearly above the LOEL. A total uncertainty factor of 10 was used. An uncertainty factor of 3 for interspecies variability and another uncertainty factor of 3 for intraspecies variability were applied based on the following reasoning: acrylic acid causes lethal effects by local tissue destruction in the lung with limited

influence of systemic distribution, metabolism and elimination. Therefore, the toxicokinetic differences do not vary considerably within and between species. Also the toxicodynamic variability within and between species is considered to be limited because acrylic acid causes cell necrosis by reducing the pH and destroying mitochondria, which are unlikely to be influenced by species-specific differences. Overall these arguments support reduced interspecies and intraspecies uncertainty factors of 3 each. The other exposure duration-specific values were derived by time scaling according to the dose-response regression equation $C^n * t = k$, using the default of n=3 for shorter exposure periods and n=1 for longer exposure periods, due to the lack of suitable experimental data for deriving the concentration exponent. For the 10-minute AEGL-3 the 30-minute value was applied because the derivation of AEGL values was based on a long experimental exposure period and no supporting studies using short exposure periods were available for characterizing the concentration-time-response relationship.

The AEGL values are listed in the table below.

SUMMARY TABLE OF AEGL VALUES FOR ACRYLIC ACID

Classification	10-Minute	30-Minute	1-Hour	4-Hour	8-Hour	Endpoint (Reference)
AEGL-1 (Nondisabling)	1.5 ppm (4.5 mg/m³)	1.5 ppm (4.5 mg/m³)	1.5 ppm (4.5 mg/m³)	1.5 ppm (4.5 mg/m³)	1.5 ppm (4.5 mg/m³)	Eye irritation in humans (Renshaw, 1988) and histopathological effects on nasal mucosa in mice (Lomax et al., 1994)
AEGL-2 (Disabling)	66 ppm (200 mg/m³)	45 ppm (140 mg/m³)	36 ppm (110 mg/m³)	19 ppm (56 mg/m³)	9.4 ppm (28 mg/m³)	Histopathological alterations of the nasal mucosa in monkeys (Rohm and Haas Co., 1995; Harkema, 2001; Harkema et al., 1997)
AEGL-3 (Lethal)	340 ppm (1000 mg/m³)	340 ppm (1000 mg/m³)	270 ppm (810 mg/m³)	170 ppm (510 mg/m³)	85 ppm (260 mg/m³)	No lethality in rats (BASF, 1980)

References

BASF AG, 1980. Bestimmung der akuten Inhalationstoxizität LC_{50} von Acrylsäure rein als Dampf bei 4stündiger Exposition an Sprague-Dawley-Ratten. Unpublished report, BASF AG, Ludwigshafen, Germany, 1980.

Carpenter C.P., C.S. Weil and H.F. Smyth, 1974. Range-finding toxicity data: List VIII. *Toxicology and Applied Pharmacology* 28, 313-319.

Frederick C.B., M.L. Bush, L.G. Lomax, K.A. Black, L. Finch, J.S. Kimbell, K.T. Morgan, R.P. Subramaniam, J.B. Morris and J.S. Ultman, 1998. Application of a hybrid computational fluid dynamics and physiologically based inhalation model for interspecies dosimetry extrapolation of acidic vapors in the upper airways. *Toxicology and Applied Pharmacology* 152, 211-231.

Hellman, T.M. and F.H. Small, 1974. Characterization of the odor properties of 101 petrochemicals using sensory methods. *Journal of the Air Pollution Control Association* 24, 979-982.

Hagan, J.V. and H.F. Emmons, 1988. Acrylic acid - acute inhalation toxicity study in rats. Unpublished report No. 87R-106, Rohm and Haas Company, Spring House, PA, USA, 1988.

Harkema, 2001. Single Dose Inhalation Toxicity Study of Ethyl Acrylate And Acrylic Acid in Nonhuman Primates: Histopathology Report. Letter of Dr. Jack R. Harkema, Michigan State University, East Lansing to BAMM, dated November 26, 2001.

Harkema, J.R., J.K. Lee, K.T. Morgan and C.B. Frederick, 1997. Olfactory Epithelial Injury in Monkeys After Acute Inhalation Exposure to Acrylic Monomers, *The Toxicologist*, 36, No. 1, Part 2, abstract No. 576.

Lomax, L.G., D.W. Brown and C.B. Frederick, 1994. Regional histopathology of the mouse nasal cavity following two weeks of exposure to acrylic acid for either 6 or 22 h per day. Abstract presented at a Meeting on Nasal Toxicity and dosimetry of Inhaled Xenobiotics: Implications for human health, Durham, North Carolina, 20-22 September 1993, *Inhalation Toxicology*, 6 (Suppl.), 445-449.

Renshaw, F.M., 1988. F.M. Renshaw, Rohm & Haas Company, *personal communication* cited in *Emergency Response Planning Guidelines*, Acrylic acid. AIHA, American Industrial Hygiene Association, Akron, OH, USA, 1991 and provided by fax by Dr. J.E. McLaughlin, Rohm & Haas Co. on 18 July 2000.

Rohm and Haas Co., 1995. Single Dose Inhalation Toxicity Study of Ethyl Acrylate (EA) And Acrylic Acid (AA). Unpublished study report, dated September 12, 1995.

1. INTRODUCTION

Acrylic acid is a clear, colorless, corrosive liquid with a pungent odor. The primary use of acrylic acid, accounting for about two thirds of its use, is in the production of acrylic esters and resins, which are used primarily in coatings, paint, plastics and adhesives. The fastest growing use of acrylic acid is in the production of superabsorbent polyacrylic acid polymers. Acrylic acid is also used in oil treatment chemicals, detergent intermediates, and water treatment chemicals (Cascieri and Clary, 1993). About 2 million metric tons of acrylic acid were produced worldwide in 1994, principally by vapor oxidation of propylene to acrolein, and further oxidation of acrolein to acrylic acid (WHO, 1997). Production in the US was about 589,000 metric tons in 1993 (HSDB, 2004). The TRI database (DHHS, 2004) lists 143 sites in the US where production and/or use of acrylic acid causes emissions to the air. Acrylic acid is pumped in liquid form through pipes on industrial sites and is also transported in molten form in tank trucks and rail tank cars between industrial sites (ECB, 2002). Therefore, an inhalation exposure during accidental releases cannot be ruled out.

Chemical and physical properties of acrylic acid are listed in Table 1.

In order to prevent dimerization and polymerization of acrylic acid, commercial batches of acrylic acid contain polymerization inhibitors, e.g. benzoquinone or 4-methoxyphenol, in concentrations of approximately 0.01-0.2 %. Heat or contact with acids, iron salts or oxidizing chemicals can cause acrylic acid to undergo auto-accelerating polymerization which can cause explosion of (closed) containers and auto-ignition (HSDB, 2004).

TABLE 1: CHEMICAL AND PHYSICAL DATA

Parameter	Value	Reference
Molecular formula	$C_3H_4O_2$; $CH_2CHCOOH$	Cascieri and Clary, 1993
Molecular weight	72.06	HSDB, 2004
CAS Registry Number	79-10-7	HSDB, 2004
Physical state	liquid	Cascieri and Clary, 1993
Color	colorless	Cascieri and Clary, 1993
Synonyms	glacial acrylic acid; 2-propenoic acid; propene acid; vinylformic acid; acroleic acid; Acrylsäure	HSDB, 2004
Vapor pressure	4 mm Hg at 20 ˚C (corresponding to 5300 ppm) 3.8 hPa at 20 ˚C (corresponding to 3800 ppm) 10 mm Hg at 39 ˚C (corresponding to 13000 ppm) 13.5 hPa at 40 ˚C (corresponding to 13300 ppm) 39.9 hPa at 60 ˚C (corresponding to 39000 ppm) 60 mm Hg at 75 ˚C (corresponding to 79000 ppm)	Cascieri and Clary, 1993 IUCLID, 1996 WHO ,1997 IUCLID, 1996 IUCLID, 1996 WHO, 1997
Density	1.051 g/cm^3 at 20 ˚C	Lide, 1995
Melting point	12.3 ˚C	Lide, 1995

Parameter	Value	Reference
Boiling point	141 ˚C at 760 mm Hg	HSDB, 2004
Solubility	miscible with water, ethanol and several ethers	Cascieri and Clary, 1993
Odor	acrid rancid, sweet, unpleasant	Cascieri and Clary, 1993 Hellman and Small, 1974
Explosive limits in air	2 % (lower), 8 % (upper)	Cascieri and Clary, 1993
Conversion factors	1 ppm = 3.0 mg/m³ 1 mg/m³ = 0.33 ppm	WHO, 1997

2. HUMAN TOXICITY DATA

2.1. Acute Lethality

No studies documenting lethal effects in humans after inhalation, oral or dermal exposure to acrylic acid were identified (WHO, 1997).

2.2. Nonlethal Toxicity

While some studies describe effects of acrylic acid in humans after repeated exposure at the workplace, no experimental studies using single exposures with defined exposure conditions were located in the available literature.

2.2.1. Experimental Studies

Hellman and Small (1974) reported the absolute (detection) and recognition thresholds of 101 petrochemicals, determined using a trained odor panel in the Union Carbide Technical Center, South Charleston, WV. Details of the procedure used are not reported. The absolute odor threshold (detection limit) for acrylic acid was 0.094 ppm. At this concentration "50 % of the odor panel observed an odor in the working fountain". The odor recognition threshold was the concentration at which 50 % "of the odor panel defined the odor as being representative of the odorant being studied". The odor recognition threshold was 1.04 ppm (at this concentration all subjects recognized the odor, the 50 % recognition level was not established). The American Industrial Hygiene Association also reported these detection and recognition thresholds (AIHA,1989).

Grudzinskii (1988) exposed 21 subjects (age between 22 and 30 years) to acrylic acid concentrations of 0.1, 0.2, 0.3, 0.5, 1.0 or 1.5 mg/m³ (0.033, 0.066, 0.099, 0.165, 0.33 or 0.495 ppm). The exposure duration was not explicitly stated. Exposure concentrations were measured by gas chromatography. No irritative effects on eyes or the upper respiratory tract were observed. Odor detection was reported with increasing incidence for concentrations between 0.066 and 0.495 ppm.

Based on evaluation of the industrial hygiene literature, Ruth (1986) reported an odor detection threshold of 0.28 mg/m³ (0.09 ppm) and an upper (recognition) threshold of 3.12 mg/m³ (1.04 ppm); no threshold for irritation was reported. The study on which this value is based was not explicitly indicated by

the authors.

Izmerov et al. (1982) reported the lowest effect concentration of irritation in humans after a 1-minute exposure as 40 mg/m³ (13.3 ppm).

2.2.2. Occupational Exposure

Renshaw (1988; personal communication) reported on irritative effects in occupationally exposed humans. Individual exposure concentrations and effects reported are given in Table 2. Eye irritation was noted at exposure for 16 - 30 minutes to 4.5 - 23 ppm, measured by personal breathing zone sampling. Slight eye irritation was experienced during exposures for 30 minutes to 2.5 hours at measured area concentrations of 0.3 - 1.6 ppm. Exposure to 63 ppm for 10 minutes resulted in slight throat irritation in one individual.

TABLE 2: REPORTED INDUSTRIAL EXPERIENCE FROM OCCUPATIONAL EXPOSURE TO ACRYLIC ACID, adopted from Renshaw, 1988

Exposure time (min)	Exposure concentration (ppm)	Sampling type	Number of samples / individuals [a]	Effects / operation
10	63	personal	1 / 1	slight throat irritation / pumping from drums to mix tank
16 - 20	5.0 - 17.2	personal, area	3 / ≥3	eye irritation, sharp but intermittent / cleaning basket stainer
30	4.5 - 23.0	personal	2 / 2	eye irritation / loading tank truck
36 - 152	0.3 - 1.6	area	3 / ≥3	odor very noticeable, slight eye irritation / drums in hot room
78 - 93	5.8 - 11.6	personal	2 / 2	no sign of symptom among veteran chemical workers / filling drums

[a] Dr. Frank Renshaw "suggested to assume each sample represents feedback from a single individual, as in "personal" sampling. While it is likely that more than one employee was monitored in "area" sampling, the historical records do not support exactly how many were monitored. Thus, it is reasonable and conservative to conclude that this table represents at least 11 exposed individuals".

2.3. Developmental/Reproductive Toxicity

No studies evaluating developmental or reproductive toxic effects of acrylic acid in humans were identified.

2.4. Genotoxicity

No studies evaluating genotoxic effects of acrylic acid in humans were identified.

2.5. Carcinogenicity

No studies evaluating carcinogenic effects of acrylic acid in humans were identified.

2.6. Summary

In the available literature, only data concerning irritation and olfactory recognition, but no other toxicological effects were located. Exposure to acrylic acid concentrations of 0.3 - 1.6 ppm for 30 minutes to 2.5 hours caused a slight eye irritation and exposure to 4.5 - 23 ppm for 15 - 30 minutes caused eye irritation (Renshaw, 1988). The odor detection threshold has been reported at 0.09 ppm (Hellman and Small, 1974) or 0.066 ppm (Grudzinskii, 1988) and the recognition threshold at 1.04 ppm (Hellman and Small, 1974).

3. ANIMAL TOXICITY DATA

3.1. Acute Lethality

The lethality data are available mainly for the rat and are summarized in Table 4.

3.1.1. Rats

BASF AG (1980) exposed groups of 10 male and 10 female Sprague-Dawley rats to vapor concentrations of 5120 or 4250 mg/m³ (1705 or 1415 ppm, analytical concentrations) for 4 hours in a 200-liter stainless steal/glass exposure chamber. Acrylic acid purity was >99 %. A constant air flow of 3000 liters/hour was used. Analytical concentrations were determined by gas chromatography and were 67.5 and 69.7 % or the nominal concentrations for the low and high dose, respectively. No deaths occurred during the 14-day observation period. During and up to 4 days after the exposure, the following symptoms were observed: clear to slightly reddish discharge from eyes and nose, salivation, eye lid closure, dyspnea and rough/clotted hair. No symptoms were observed after 5 days or later.

Hagan and Emmons (1988) determined the time-mortality response relationship by exposing CrL:CDBR rats by 1) nose-only exposure to aerosol, 2) whole-body exposure to aerosol and 3) whole-body exposure to acrylic acid vapor. The chamber atmosphere was measured 3 - 4 times during the exposure period by drawing air though a sorbent tube at a rate of 0.1 l/min for a defined time (depending on exposure concentrations) and subsequent high-pressure liquid chromatography. The relative standard deviation was 5 - 10 %. The aerosol particle size distribution was determined using an 8-stage Andersen cascade impactor. A mean mass median diameter of 2.4±0.5 µm, a mean geometric standard deviation of 2.3±0.6 and a mean respirable fraction of 65±10 % were determined.

Initially, the study was designed to use nose-only exposure to aerosol. Accordingly, nose-only exposure to different acrylic acid aerosol concentrations was performed with a total of 30 male and 30 female rats in 8 groups for 30 minutes, a total of 17 male and 17 female rats in 6 groups for 60 minutes and a total 13 male and 13 female rats in 5 groups for 120 minutes. In addition, groups of 5 male and 5 female rats were

whole-body exposed for 120 minutes against different aerosol concentrations. When the study authors observed lethality after whole-body, but not after nose-only exposure, additional whole-body experiments were performed, exposing a total of 50 male and 50 female rats in 10 groups for 30 minutes, a total of 36 male and 36 female rats in 7 groups for 60 minutes and a total of 35 male and 35 female rats for 120 minutes against different aerosol concentrations (see Appendix B). In addition to these aerosol experiments, a total of 35 male and 35 female rats were exposed for 60 minutes against different concentrations of acrylic acid vapor.

The post-observation period was 14 days and parameters examined included morbidity, mortality, clinical signs, body weights, body weight changes and gross pathology. Taking together all data, equal number of deaths occurred on the exposure day and the following two days and a smaller number on post-exposure day 3. Exposure to acrylic acid produced treatment-related signs of nasal mucosa, upper airway and lower airway irritation, ocular irritation, corneal opacities and dermal toxicity (sloughing of distal part of the tail) in all experimental groups. Gross necropsy revealed red foci in the lungs. The incidence and number of foci/animal increased with higher exposure concentrations and exposure time. All other necropsy observations not pertaining to the lungs, skin or eyes occurred at incidences consistent with those seen in the historical controls.

No deaths resulted from exposure to vapor concentrations up to 2142 ppm for 60 minutes. The authors reported that it was impossible to achieve vapor concentrations much higher than 2000 ppm and suggested the adsorption of acrylic acid to the walls of the exposure chamber (made of plexiglass) as a possible cause. Throughout the study, the authors consistently expressed the aerosol concentration in ppm (and not in mg/m³ as it is usually done for aerosols) without commenting on this.

TABLE 3: RESULTS OF PROBIT ANALYSIS OF LETHALITY DATA FOR SINGLE EXPOSURE TO ACRYLIC ACID AEROSOLS OF RATS; Hagan and Emmons (1988) (see Appendix B)

Effect level	Calculated exposure concentration (mg/m³) (equivalent in ppm)		
	30 Minutes	60 Minutes	120 Minutes
LC_{50}	1884 (5652)	1283 (3850)	879 (2636)
LC_{01}	879 (2638)	602 (1806)	412 (1236)

Union Carbide Co. (1977) exposed 6 rats to an acrylic acid vapor concentration of 12000 mg/m³ (3996 ppm; it was not stated if this concentration was measured or if this was the assumed saturated vapor concentration) for 4 hours. No deaths occurred during the 14-day observation period.

Gage (1970) exposed 2 male and 2 female Alderley-Park rats to a saturated acrylic acid vapor for 5 hours. During exposure nose and eye irritation and respiratory difficulty were noted. One animal died. Autopsy revealed lung hemorrhage and degenerative changes of liver and kidney tubules. The validity of these findings is limited because no analytical determinations of exposure concentrations were reported. Since Hagan and Emmons (1988) reported difficulties in generating exposure concentrations close to the theoretical value for a saturated vapor, it seems unclear what vapor concentration of acrylic acid was really achieved in this experiment.

Carpenter et al. (1974) reported that following inhalation exposure to vapor concentrations of 2000 ppm for 4 hours, none of 6 rats died, whereas 6/6 rats died following exposure to 4000 ppm for 4 hours. The data are only presented in a table and no details on analytical methods and signs and symptoms during or after exposure were reported.

Majka et al. (1974) reported an acute inhalation toxicity data in male rats. The animals were exposed to acrylic acid (purity 99 %) in an inhalation chamber of 0.045 m³ volume (dynamic system with air flow of 100-120 liter/hour; no more data on methodology). A 4-hour LC_{50} of 3600 mg/m³ (1200 ppm) was reported with mortalities occurring within 48 hours after exposure. Histopathology in rats killed 48 hours after exposure revealed in the 2970 mg/m³ (non-lethal concentration) and 3600 mg/m³ groups hyperemia of inner organs. In the respiratory system severe irritation of the bronchial mucosa, exsudate into the bronchial lumen, macrophages in the vesicle and focal intraparenchymal irritation in the lungs was observed. Necropsy at the end of the 14-day observation period demonstrated signs of respiratory irritation.

3.1.2. Mice

Izmerov et al. (1982) reported a 2-hour LC_{50} of 5300±500 mg/m³ (1765±167 ppm) in the mouse.

TABLE 4: SUMMARY OF ACUTE LETHAL INHALATION DATA IN LABORATORY ANIMALS

Species	Exposure Time (h)	Concentration (physical state)	Total number of animals used	Effect	Reference
rat	0.5	1884 mg/m³ (aerosol) (5652 ppm)	100 (different concentrations)	LC_{50} for aerosol	Hagan and Emmons, 1988
rat	1	1283 mg/m³ (aerosol) (3850 ppm)	72 (different concentrations)	LC_{50} for aerosol	Hagan and Emmons, 1988
rat	2	879 mg/m³ (aerosol) (2636 ppm)	70 (different concentrations)	LC_{50} for aerosol	Hagan and Emmons, 1988
rat	1	2142 (vapor)	10	no deaths	Hagan and Emmons, 1988
rat	4	1200 (vapor)	not stated	LC_{50}	Majka et al. (1974)
rat	4	1705 (vapor)	20	0/20 animals died	BASF, 1980
rat	4	1415 (vapor)	20	0/20 animals died	BASF, 1980
rat	4	4000 (vapor)	6	6/6 animals died	Carpenter et al. (1974)
rat	4	3996 (vapor)	6	no deaths	Union Carbide Co., 1977
rat	4	2000 (vapor)	6	0/6 animals died	Carpenter et al. (1974)

Species	Exposure Time (h)	Concentration (physical state)	Total number of animals used	Effect	Reference
rat	5	saturated vapor	4	1/4 animals died	Gage (1970)
mouse	2	1765 (not stated)	not stated	LC_{50}	Izmerov et al. (1982)

3.2. Nonlethal Toxicity

The nonlethal effects of acrylic acid reported for rabbits, rats and mice comprise exclusively irritation and pathological changes of the nasal mucosa. These data are summarized in Tables 8 and 9.

3.2.1 Monkeys

Rohm and Haas Co. (1995) exposed five groups of three cynomolgus monkeys each 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 75 ppm ethyl acrylate for 3 and 6 hours. The mean analytical exposure concentrations of acrylic acid 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 anesthetized 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.

Harkema (2001; also published as abstract by Harkema et al., 1997) reported the histopathology of the study described above. The nasal cavities were transversely sectioned into serial 5-10 mm-thick blocks from the nares to the posterior aspect of the soft palate. The blocks were decalcified using EDTA, embedded in paraffin and sectioned at a thickness of 4-6 microns. Sections were stained with hematoxylin and eosin. Nasal lesions were restricted to the olfactory epithelium lining the dorsal medial meatus at the level of the maxillary sinus in the proximal aspect of both nasal passages. The morphologic alterations (see Figure 1) consistently found in all acrylic acid-exposed monkeys were focal degeneration and necrosis of the olfactory epithelium with mild inflammation (influx of neutrophils and lymphocytes). No exposure-related lesions were present in the nasal respiratory, transitional or squamous epithelium in any of the monkeys examined. The Bowman's glands and olfactory nerves in the lamina propria underlying the degenerating olfactory epithelium were also histologically normal. The extent and severity of the lesions were greater in monkeys exposed for 6 hours compared to those exposed for 3 hours. The severity of epithelial injury ranged from mild apical blebbing and cytoplasmic vacuolation of the olfactory sustentacular cells to marked necrosis, exfoliation and attenuation of the olfactory epithelium with only a few remaining basal or sensory cells attached to the basement membrane. Approximately 20 % and 40-60 % of the olfactory epithelium in the examined sections had ethyl acrylate or acrylic acid induced damage after 3 or 6 hours, respectively. The character, severity and distribution of the morphologic alterations induced by acrylic acid and ethyl acrylate were similar. The author concluded that monkeys exposed to acrylic acid or ethyl acrylate had focal, olfactory epithelial lesions that

resembled in both nature and severity those reported in rodents.

FIGURE 1: HISTOPATHOLOGIC EFFECTS ON THE OLFACTORY EPITHELIUM IN MONKEYS

Figures are taken from Harkema (2001) and show section from air exposed monkeys (A) and monkeys exposed to 75 ppm acrylic acid for 3 hours (C) and 6 hours (D).

3.2.2 Rabbits

Studies with repeated inhalation exposure

Neeper-Bradley et al. (1997) assessed the developmental toxicity of acrylic acid in New Zealand White rabbits. In a range finding study, groups of 8 pregnant rabbits were exposed to nominal concentrations of 0, 30, 60, 125 and 250 ppm acrylic acid vapor for 6 hours/day on gestational days 10 - 22. After the exposure period, 3 animals/group were killed on day 23 and the rest on day 29. Vapor concentrations in the exposure chambers were measured three times during each 6-hour exposure by sampling with XAD-8 sorbent tubes and subsequent HPLC analysis. The nominal concentration was calculated by dividing the total quantity of acrylic acid delivered to the chamber by the chamber air-flow rate. Mean chamber analytical concentrations were 34±3.1, 61±5.4, 129±10 and 245±41 ppm. Throughout exposures, perinasal and perioral wetness were observed in 8/8 animals at 250 ppm. At 125 ppm, perinasal wetness in 2/7 and perioral wetness in 4/7 animals were observed only on the first day of exposure. Blepharospasm was observed throughout exposures at 250 ppm and also at 125 ppm. A single animal from the 60-ppm group exhibited perinasal wetness on the morning following the last day of exposure. No signs of sensory irritation were found at 30 ppm. Decreases in food consumption were noted in all acrylic acid-exposed groups during the first 4 - 5 days of the exposure period and thereafter for the 60-, 120- and 250-ppm groups. Significantly reduced body weights were found on day 29 in the 30-, 125- and 250-ppm, but not the 60-ppm, group. Interpretation of this finding was confounded, however, by the lack of a consistent concentration-related pattern, the reduced animal number and large standard deviations. A consistent effect on body weight was found in the 250-ppm group; no effects on weight gain and uterine weight were observed. Microscopic evaluation of the nasal turbinates is summarized in Table 5.

In the definitive study, 16 rabbits/group were exposed to nominal concentrations of 0, 25, 75 or 225 ppm for 6 hours/day on gestational days 6 - 18. Mean analytical concentrations were 25±2.2 (SD), 77±3.5 and 227±9 ppm. During actual exposures, perinasal/perioral wetness and blepharospasm were observed throughout the exposure period at 225 ppm. Perioral wetness was observed only on the fourth day in the 75-ppm group. No irritative effects were observed at 25 ppm. Decreases in food consumption were found during the first 5 days in the 225- and 75-ppm groups and during the remainder of the exposure period only in the 225-ppm group. There were not statistically significant losses in body weight gain. Reduced values in the 75- and 225-ppm groups for days 6 - 12 were considered to be an exposure-related effect since the reductions were coincident with consistent reductions in food consumption for the first 5 days of exposure. The initial reduced body weight development was compensated later by increased body weight gains in the 75- and 225-ppm groups for days 18 - 29, which were associated with increases in food consumption. For evaluation of developmental toxicity see Section 3.3.1.

TABLE 5: SUMMARY OF MICROSCOPIC EVALUATION OF NASAL TURBINATES OF RABBITS AFTER REPEATED EXPOSURE TO ACRYLIC ACID VAPOR; adopted from (Neeper-Bradley et al., 1997)

Effect	Nominal (analytical) exposure concentrations (ppm)				
	0	30 (34)	60 (61)	125 (129)	250 (245)
	No. of affected/total female pregnant rabbits on day 23 and 29				
	day 23 / 29	day 23 / 29	day 23 / 29	day 23 / 29	day 23 / 29
Squamous metaplasia					
mild	0/3 / 0/4	2/3 / 0/5	1/2 / 3/4	0/2 / 3/5	0/3 / 2/5
moderate	0/3 / -*	0/3 / -	0/2 / -	2/2 / -	1/3 / -
marked	0/3 / -	0/3 / -	0/2 / -	0/2 / -	2/3 / -
Erosion of epithelium					
mild	0/3 / 0/4	1/3 / 0/5	1/2 / 0/4	0/2 / 2/5	0/3 / 1/5
marked	0/3 / 0/4	0/3 / 0/5	0/2 / 1/4	1/2 / 0/5	0/3 / 1/5
Ulceration of epithelium	0/3 / 0/4	0/3 / 0/5	0/2 / 0/4	0/2 / 0/5	3/3 / 1/5

* category not used in analysis on day 29

3.2.3. Rats

Frederick et al. (1998) exposed groups of 5 female Fisher 344/N rats to 0 or 75 ppm acrylic acid for 3 or 6 hours. The exposure atmosphere was monitored by an infrared gas analyzer calibrated using gas chromatography. Immediately after the exposure, animals were killed. The nasal cavity was fixed with 10 % neutral-buffered formalin, the head was then immersed and fixed in formalin, decalcified and sectioned transversely at levels I through IV according to Young (1981). Microtome sections of 4 - 6 µm were stained with hematoxylin and eosin and evaluated histopathologically. Control animals exhibited no detectable lesions in the nasal cavity. Lesions were small and confined to the dorsal aspects of the nasal cavity, in particular the dorsal meatus, the dorsomedial aspects of the nasal turbinate, and ethmoturbinate. The extent of the lesions increased with exposure time. Olfactory epithelial cell degeneration, accompanied by sustentacular cell necrosis, was found in all four sections of the nasal cavity at both 3 and 6 hours. Limited regions of respiratory epithelial degeneration and desquamation were present in the dorsal meatus after exposure to acrylic acid for 6 hours, but not after 3 hours.

Nachreiner and Dodd (1988) exposed groups of 5 Sprague-Dawley rats by inhalation for 1 hour to static (no air flow through chamber) concentrations of 1394 ppm and 1442 ppm acrylic acid, or to a dynamic (continuous air flow through chamber) concentration of 2352 ppm. Signs of ocular and respiratory irritation, but no mortality in any group were observed. No gross lesions were found at the end of the observation period of 14 days.

Buckley et al. (1984) reported concentrations resulting in a 50% decrease in respiratory rate (RD_{50}) of 513 ppm in Fischer 344 rats. No study details were reported.

Studies with repeated inhalation exposure

Miller et al. (1981) exposed groups of 5 male and 5 female Fischer 344 rats to acrylic acid concentrations of 0, 25, 75 or 225 ppm for 6 hours/day, 5 days/week for 2 weeks. The actual mean exposure concentrations measured 2 - 3 times per hour by infrared spectrophotometry using a Miran I® infrared analyzer were 25±1 (SD), 74±1 and 223±2 ppm and were identical to the nominal concentrations calculated from the total amount of evaporated acrylic acid and the total chamber air flow. Rats in the 225-ppm group exhibited signs of nasal irritation characterized by scratching at the nose (time point of onset of signs was not reported). At 75 and 25 ppm, no discernible changes in appearance or posture were observed. Body weight gains of male and female rats were significantly lower than controls after 4, 7 and 10 days of exposure at 225 ppm. No effects on body weight gain were observed in the lower two exposure groups. No treatment-related effects on organ weights or organ-to-body ratios of brain, heart, liver, kidney or testes were found in any exposure group. Histopathologic examinations revealed inflammatory and degenerative lesions of the nasal mucosa in 5/5 males and 3/5 females in the control group, which were considered to have occurred spontaneously. Similar, but more severe lesions, including focal squamous metaplasia were observed in the 225-ppm group. Nasal lesions in the 25 and 75-ppm group were not different from that in control animals (the authors stated that the "lesions in control animals were apparently spontaneous in nature", but did not report if these were typical for historical controls).

In the same study by Miller et al. (1981) groups of 15 male and 15 female Fischer 344 rats were exposed to acrylic acid concentrations of 0, 5, 25 or 75 ppm for 6 hours/day, 5 days/week for 13 weeks. Measured exposure concentrations were 5±0.33 (SD), 25±1 and 75±1 ppm. Mean body weight gains in the exposure groups were comparable to controls at all times, except for higher body weight gains of female rats during the first two weeks of exposure to 5 or 25 ppm. Hematologic and clinical chemistry analyses revealed no treatment related effects of acrylic acid. Mean hemoglobin concentrations after exposure to 25 or 75 ppm were significantly lower than those of the control group, but were still in the range of unexposed historical controls. Lesions of the nasal mucosa were found in 10/10 females and 7/10 males in the 75-ppm group, but not animals of the 25- or 5-ppm groups (see Table 6). Lesions consisted of slight focal degeneration of the olfactory epithelium on the dorsomedial aspect of nasal passage and were detected mainly in the most rostral of four cross sections. Slight inflammatory lesions were found in 1/10 female rats in the control group (the authors did not comment on the absence of lesions for this segment of the study, which contrasts with the effects found in the range-finding segment).

TABLE 6: SUMMARY OF HISTOPATHOLOGIC OBSERVATIONS IN THE NASAL MUCOSA OF RATS AFTER REPEATED INHALATION OF ACRYLIC ACID FOR 13 WEEKS; adopted from Miller et al., 1981

	Male rats				Female rats			
nominal (analytical) exposure concentration (ppm)	**0**	**5 (5)**	**25 (25)**	**75 (75)**	**0**	**5 (5)**	**25 (25)**	**75 (75)**
slight focal degeneration of olfactory epithelium	0/10	0/10	0/10	7/10	0/10	0/10	0/10	10/10
slight inflammation characterized by infiltration of mononuclear cells in the mucosa and submucosa	0/10	0/10	0/10	0/10	1/10	0/10	0/10	0/10

Klimisch and Hellwig (1991) exposed groups of 30 pregnant Sprague-Dawley rats to nominal acrylic acid concentrations of 0, 40, 120 or 360 ppm for 6 hours/day during gestational days 6 - 15. The acrylic acid concentration in the exposure chambers was sampled continuously at the animals breathing zones and monitored using a total hydrocarbon analyzer. Calibration of the total hydrocarbon analzyer was made using an infrared gas analyzer. A calibration curve for the infrared analyzer was prepared by injecting known volumes of acrylic acid into the calibration loop. The infrared analyzer was then used to calibrate the total hydrocarbon analyzer run in parallel. Mean analytical concentrations were 39.4±1.3 (SD), 114.0±3.9 and 356±12 ppm. From the first exposure, animals exposed to 360 ppm, but not those exposed to 120 or 40 ppm, showed a pronounced watery discharge from the eyes and nose, with accompanying restless behavior, which persisted for 1 - 2 hours after each exposure. A dose-related decrease in body weight and body-weight gain relative to the control group was found. Both effects were statistically significant for the 360-ppm group. Body-weight gain was significantly reduced during the first few days of exposure also in the 120-ppm group. Corresponding to the effects on body weights, a dose-related decrease in food consumption relative to controls was found. This was significant in the 120-ppm group at the beginning of the exposure period and in the 360-ppm group throughout the exposure period. No evidence for exposure-related developmental toxic effects was found after exposure to acrylic acid (cf. Section 3.3.2). In a pretest, exposure concentrations of 225 and 450 ppm were used (measured concentrations were 218±3 and 439±9 ppm). At 225 ppm, all animals showed signs of sensory irritation during the first and subsequent exposures, consisting of eyelid closure, discharge from the eyes and slightly reddened noses. These signs subsided rapidly after each exposure. At 450 ppm, the signs of irritation during exposure were more marked, with eyelid closure and considerable discharge from eyes and nose. Animals were particularly restless and wiped their snouts often.

Barrow et al. (1986) exposed male F-344 rats (between 7 and 10 animals) to 75 ppm acrylic acid for 6 hours/day for 4 days. On the fifth day, respiratory rates and tidal volumes were measured before and during exposure by a body plethysmograph technique. Exposure resulted in a 17 % decrease in respiratory rate within the first 10 minutes of exposure. This decrease remained constant for the 6-hour exposure, ranging between 16 % and 23 %. Very little effect was found on tidal volume (93 - 103 % of controls) and thus the decrease in minute volume was about 23 %.

Silver et al. (1981) exposed male Holtzman rats to acrylic acid for 1 hour and reported a decrease in respiration rates of about 10 % for acrylic acid concentrations of 100 and 300 ppm and of about 30 % for 500 ppm. The tidal volume varied between 90 and 110 %.

Gage (1970) exposed groups of 4 female and 4 male Alderley Park-rats for 6 hours/day to acrylic acid concentrations of 1500 ppm for a total of 4 days or 300 or 80 ppm for a total of 20 days. During the exposure period, nasal discharge, lethargy and weight loss was observed in the 1500-ppm group, some nose irritation, lethargy and retarded weight gain was observed in the 300-ppm group and no signs of toxicity in the 80-ppm group. Autopsy revealed lung hemorrhage and degenerative changes in liver and kidney tubules in the 1500-ppm group, congested kidneys in the 300-ppm group and no pathological findings in the 80-ppm group. The study was not reported in detail.

Vodicka et al. (1986) exposed groups of 6 Wistar rats for 6 hours to 0, 250, 500 or 1000 mg/m³ (83.3, 167 or 333 ppm). A slight hypoglycemia was observed after exposure to 500 mg/m³ (3.72±0.05 mmol/l vs. 4.37±0.11 mmol/l in controls), but not after 250 or 1000 mg/m³.

640 **3.2.4. Mice**

641 Buckley et al. (1984) reported concentrations resulting in a 50% decrease in respiratory rate (RD_{50})
642 of 685 ppm in B6C3F1 mice. No study details were reported.

643 ***Studies with repeated inhalation exposure***
644 Lomax et al. (1994) exposed groups of 10 female $B6C3F_1$ mice by whole-body inhalation exposure
645 to 0, 5 or 25 ppm for 6 or 22 hours/day or to 25 ppm for 4.4 hours/day for 2 weeks. Histopathologic analysis
646 was performed either immediately after termination of exposure or after a 6-week recovery period. The
647 olfactory epithelium in the dorsal meatus region was the only target tissue in the nasal cavity of mice after
648 exposure to 5 ppm for 22 hours/day or 25 ppm for 4.4, 6 or 22 hours/day. The histopathologic lesions
649 observed were disorganization and atrophy of the olfactory epithelium, basal-cell hypertrophy, necrosis and
650 desquamation of olfactory epithelium, and Bowman‘s gland degeneration. No histologic lesions were
651 observed in control mice or mice exposed to 5 ppm for 6 hours/day. After the 6-week recovery period, the
652 olfactory epithelium was normal in all groups except those exposed to 25 ppm for 22 hours/day. These
653 animals exhibited regions of respiratory metaplasia (replacement of sensitive olfactory epithelium with
654 resistant respiratory-like epithelium). The three treatment groups with similar concentration-time products (5
655 ppm x 22 hours/day, 25 ppm x 4.4 hours/day and 25 ppm x 6 hours/day) had a very similar incidence and
656 severity of lesions.

657 Miller et al. (1981) exposed groups of 5 male and 5 female $B6C3F_1$ mice to acrylic acid
658 concentrations of 0, 25, 75 or 225 ppm (see Section 3.2.4 for measured concentrations) for 6 hours/day, 5
659 days/week for 2 weeks. Mice in the 225-ppm group exhibited signs of nasal irritation characterized by
660 scratching at the nose (time point of onset of signs was not reported). At 75 and 25 ppm, no discernible
661 changes in appearance or demeanor were observed. During exposure to 225 ppm, body weight gains of male
662 and female mice were significantly lower than controls after 4, 7 and 10 days of exposure, with the exception
663 of female mice after 4 days. At day 4, body weight changes of male, but not female, mice were also
664 significantly lower after exposure to 25 and 75 ppm. No treatment-related effects on organ weights or organ-
665 to-body ratios of brain, heart, liver, kidney or testes were found in any exposure group. Histopathologic
666 examinations revealed lesions of the nasal mucosa in all mice exposed to 225 or 75 ppm and in 2/5 males and
667 4/5 females in the 25-ppm group. A similar lesion, consisting of a focal degeneration of the olfactory
668 epithelium occurred spontaneously in 1/5 male mice of the control group. Grading the lesions on a scale from
669 very slight to moderate revealed a definitive dose-response relationship and suggested that the lesions in the
670 25-ppm group were also attributable to the acrylic acid treatment.

671 In the same study by Miller et al. (1981), groups of 15 male and 15 female $B6C3F_1$ mice were
672 exposed to acrylic acid concentrations of 0, 5, 25 or 75 ppm for 6 hours/day, 5 days/week for 13 weeks. No
673 signs of irritation were observed during the exposure period. Two female mice of the 75-ppm group and one
674 male mouse of the 25-ppm group died or had to be killed due to trauma caused by handling. A significantly
675 reduced body weight gain was found only in female mice after 12 weeks exposure to 25 or 75 ppm.
676 Histopathological examination was performed for 10 male and 10 female mice of each group. Lesions of the
677 olfactory epithelium were detected in all male and female mice in the 75-ppm group, as well as in 9/10
678 females and 10/11 males of the 25-ppm group and in 4/10 females and 1/10 males of the 5-ppm group.
679 Lesions were confined to the olfactory portion of the nasal mucosa and showed a clear dose-response
680 relationship, based upon size of affected area, severity of effects and percentage of affected animals/group.

Similar lesions were not found in the control animals. Lesions in the 75-ppm group consisted of focal degeneration, mononuclear cell infiltration and slight hyperplasia of the submucosal glands. Lesions in the 25-ppm group were limited to slight focal degeneration without inflammation and in the 5-ppm group only very slight degeneration was observed. The results are summarized in Table 7.

TABLE 7: SUMMARY OF HISTOPATHOLOGIC OBSERVATIONS IN THE NASAL MUCOSA OF MICE AFTER REPEATED INHALATION OF ACRYLIC ACID; adopted from Miller et al., 1981

	Male mice				Female mice			
2-week study								
nominal (analytical) exposure concentration (ppm)	**0**	**25 (25)**	**75 (74)**	**225 (223)**	**0**	**25 (25)**	**75 (74)**	**225 (223)**
focal degeneration of olfactory epithelium with slight accumulation of mucopurulent exudate in the lumen of the nasal passages [a]	1/5	2/5	5/5	5/5	0/5	4/5	5/5	5/5
13-week study								
nominal (analytical) exposure concentration (ppm)	**0**	**5 (5)**	**25 (25)**	**75 (75)**	**0**	**5 (5)**	**25 (25)**	**75 (75)**
focal degeneration of olfactory epithelium with partial replacement by epithelium resembling respiratory epithelium - slight to moderate	1/10	1/10	0/11	10/10	0/10	0/10	0/10	10/12
focal degeneration of olfactory epithelium - slight	0/10	0/10	10/11	0/10	0/10	0/10	9/10	1/12
- very slight	0/10	1/10	1/11	0/10	0/10	4/10	0/10	0/12
- ungraded due to autolysis	0/10	0/10	0/11	0/10	0/10	0/10	0/10	1/12
focal infiltration of inflammatory cells in the degenerative areas of mucosa and submucosa - slight	0/10	0/10	0/11	0/10	0/10	0/10	2/10	0/12
- very slight	0/10	0/10	1/11	10/10	0/10	0/10	0/10	10/12
focal hyperplasia of submucosal glands in the degenerative areas of mucosa - very slight	0/10	0/10	0/11	10/10	0/10	0/10	0/10	10/12

[a] according to the authors, grading of the lesions on a scale from very slight to moderate revealed a definitive dose-response relationship (number of affected animals in each category was not stated)

Barrow et al. (1986) exposed male B6C3F$_1$ mice (between 7 and 10 animals) to 75 ppm acrylic acid for 6 hours/day for 4 days. On the fifth day, respiratory rates and tidal volumes were measured before and during exposure by a body plethysmograph technique. Exposure resulted in a 32 - 37 % decrease in respiratory rate and was constant during the 6-hour exposure. Very little effect was found on tidal volume and thus the decrease in minute volume was between 27 and 34 % with an average of 31 %.

719

TABLE 8: SUMMARY OF OBSERVABLE IRRITATIVE EFFECTS IN LABORATORY ANIMALS

720

Species	Analytical concentration (ppm)	Exposure duration	Effect	Reference
721 rabbit	245	6 h/d; gd10-22	pregnant animals; perinasal and perioral wetness, blepharospasm in 8/8 animals; after first and subsequent exposures	Neeper-Bradley et al., 1997
722 rabbit	227	6 h/d; gd 6-18	pregnant animals; perinasal and perioral wetness, blepharospasm in 14/15 animals; after first and subsequent exposures	Neeper-Bradley et al., 1997
723 rabbit	129	6 h/d; gd10-22	pregnant animals; perinasal wetness in 2/7, perioral wetness in 4/7 animals, blepharospasm; after first and subsequent exposures	Neeper-Bradley et al., 1997
724 rabbit	77	6 h/d; gd 6-18	pregnant animals; perioral wetness only on forth day of exposure; no blepharospasm reported	Neeper-Bradley et al., 1997
725 rabbit	61	6 h/d; gd10-22	pregnant animals; perinasal wetness in 1/6 animals after the last exposure, no perioral wetness or blepharospasm	Neeper-Bradley et al., 1997
726 rabbit	34	6 h/d; gd10-22	pregnant animals; no signs of irritation (perinasal/perioral wetness or blepharospasm)	Neeper-Bradley et al., 1997
727 rat	1500	6 h/d; 4 d	nasal discharge, lethargy	Gage, 1970
728 rat	439	6 h/d; gd 6-15	pregnant animals; considerable discharge from eyes and nose, eyelid closure, restless behavior with snout wiping; after first and subsequent exposures	Klimisch and Hellwig, 1991
729 rat	356	6 h/d; gd 6-15	pregnant animals; pronounced watery discharge from eyes and nose, restless behavior; after first and subsequent exposures	Klimisch and Hellwig, 1991
730 rat	300	6 h/d; 4 d	some nose irritation, lethargy	Gage, 1970
731 rat	223	6 h/d; 5 d/w, 2 w	scratching at the nose as sign of irritation	Miller et al., 1981
732 rat	218	6 h/d; gd 6-15	pregnant animals; discharge from eyes, slightly reddened nose, eyelid closure; after first and subsequent exposures	Klimisch and Hellwig, 1991

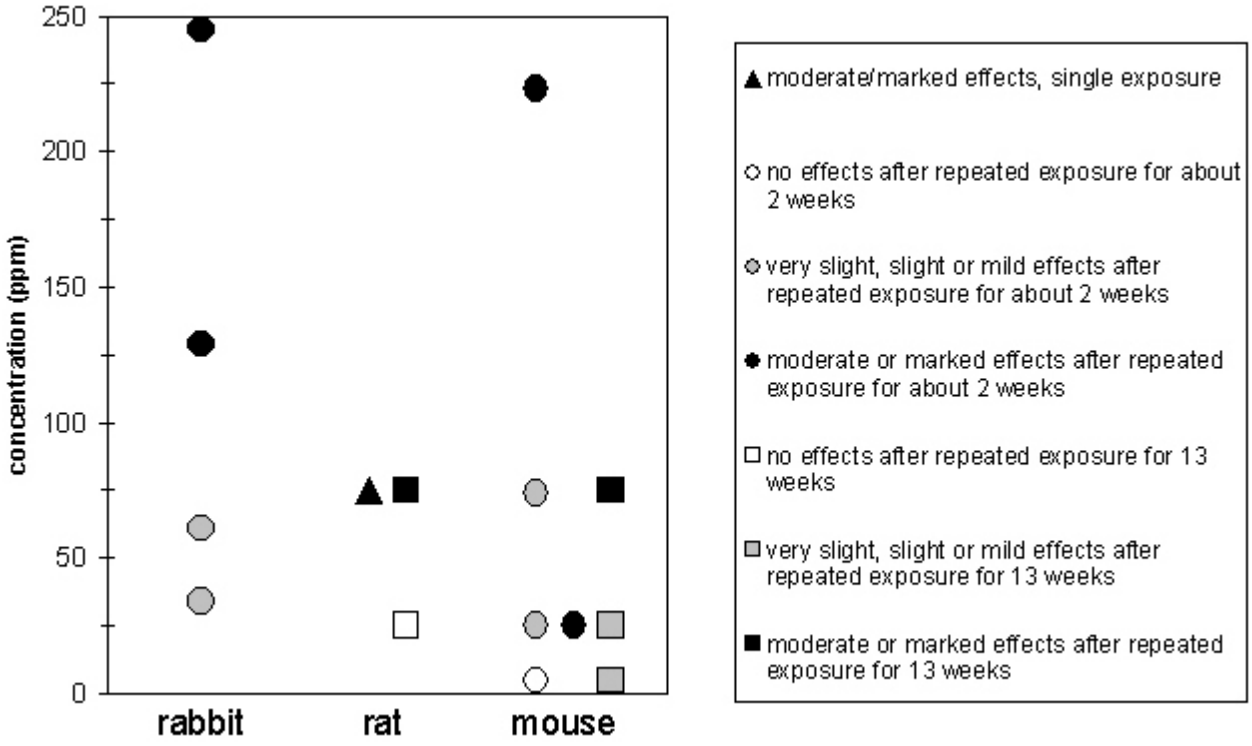
Species	Analytical concentration (ppm)	Exposure duration	Effect	Reference
rat	114	6 h/d; gd 6-15	pregnant animals; no signs of irritation	Klimisch and Hellwig, 1991
rat	80	6 h/d; 4 d	no signs of irritation	Gage, 1970
rat	74	6 h/d; 5 d/w, 2 w	no signs of irritation	Miller et al., 1981
rat	39	6 h/d; gd 6-15	pregnant animals; no signs of irritation	Klimisch and Hellwig, 1991
rat	25	6 h/d; 5 d/w, 2 w	no signs of irritation	Miller et al., 1981
mouse	223	6 h/d; 5 d/w, 2 w	scratching at the nose as sign of irritation	Miller et al., 1981
mouse	75	6 h/d; 5 d/w, 13 w	no signs of irritation	Miller et al., 1981
mouse	74	6 h/d; 5 d/w, 2 w	no signs of irritation	Miller et al., 1981
mouse	25	6 h/d; 5 d/w, 13 w	no signs of irritation	Miller et al., 1981
mouse	25	6 h/d; 5 d/w, 2 w	no signs of irritation	Miller et al., 1981

TABLE 9: SUMMARY OF HISTOPATHOLOGIC EFFECTS IN LABORATORY ANIMALS

Species	Analytical concentration (ppm)	Exposure duration	Effect	Reference
monkey	78	6 h	mild apical blebbing and cytoplasmic vacuolation of olfactory sustentacular cells to marked necrosis, exfoliation and attenuation of the olfactory epithelium	Rohm and Haas Co., 1995; Harkema, 2001; Harkema et al., 1997
monkey	81	3 h	same as above, but less severe olfactory lesions and affecting a smaller area of the olfactory epithelium	Rohm and Haas Co., 1995; Harkema, 2001; Harkema et al., 1997
rabbit	245	6 h/d; gd10-22	pregnant animals; on day 23 marked squamous metaplasia and ulceration of the olfactory epithelium	Neeper-Bradley et al., 1997

Species	Analytical concentration (ppm)	Exposure duration	Effect	Reference
rabbit	129	6 h/d; gd10-22	pregnant animals; on day 23 squamous metaplasia and marked erosion of the olfactory epithelium	Neeper-Bradley et al., 1997
rabbit	61	6 h/d; gd10-22	pregnant animals; on day 23 mild squamous metaplasia and mild to marked erosion of the olfactory epithelium	Neeper-Bradley et al., 1997
rabbit	34	6 h/d; gd10-22	pregnant animals; on day 23 mild squamous metaplasia and mild erosion of the olfactory epithelium	Neeper-Bradley et al., 1997
rat	223	6 h/d; 5 d/w, 2 w	focal squamous metaplasia of nasal mucosa more severe than in control group	Miller et al., 1981
rat	75	6	olfactory epithelial cell degeneration, sustentacular cell necrosis, limited respiratory epithelial cell degeneration	Frederick et al., 1998
rat	75	3	olfactory epithelial cell degeneration, sustentacular cell necrosis	Frederick et al., 1998
rat	75	6 h/d; 5 d/w, 13 w	focal degeneration of olfactory epithelium in 10/10 females and 7/10 males	Miller et al., 1981
rat	74	6 h/d; 5 d/w, 2 w	focal squamous metaplasia of nasal mucosa not more severe than in control group	Miller et al., 1981
rat	25	6 h/d; 5 d/w, 13 w	no lesions of olfactory epithelium	Miller et al., 1981
rat	5	6 h/d; 5 d/w, 13 w	no lesions of olfactory epithelium	Miller et al., 1981
mouse	223	6 h/d; 5 d/w, 2 w	moderate lesions of the olfactory epithelium	Miller et al., 1981
mouse	75	6 h/d; 5 d/w, 13 w	focal degeneration of the olfactory epithelium with inflammation	Miller et al., 1981
mouse	74	6 h/d; 5 d/w, 2 w	slight lesions of the olfactory epithelium	Miller et al., 1981
mouse	25	22 h/d; 2 w	olfactory atrophy, Bowman‘s gland degeneration, basal cell hyperplasia with squamous differentiation (permanent replacement of olfactory with respiratory epithelium after 6 week recovery period)	Lomax et al., 1994
mouse	25	6 h/d; 5 d/w, 2 w	very slight lesions of the olfactory epithelium	Miller et al., 1981
mouse	25	6 h/d; 5 d/w, 13 w	slight focal degeneration of the olfactory epithelium without inflammation	Miller et al., 1981

Species	Analytical concentration (ppm)	Exposure duration	Effect	Reference
mouse	25	4.4 h/d; 2 w	atrophy, necrosis and desquamation of olfactory epithelium (reversible after 6 week recovery period)	Lomax et al., 1994
mouse	5	22 h/d; 2 w	atrophy, necrosis and desquamation of olfactory epithelium (reversible after 6 week recovery period)	Lomax et al., 1994
mouse	5	6 h/d; 5 d/w, 13 w	very slight focal degeneration of the olfactory epithelium	Miller et al., 1981
mouse	5	6 h/d; 2 w	no histopathological alterations	Lomax et al., 1994



768 **FIGURE 2: HISTOPATHOLOGIC EFFECTS ON THE OLFACTORY EPITHELIUM IN ANIMALS**
769 **AFTER REPEATED 6-HOURS EXPOSURES TO ACRYLIC ACID**
770 Data are taken from Table 9.

771 **3.3. Developmental/Reproductive Toxicity**
772 **3.3.1 Rabbits**

773 ***Studies with repeated inhalation exposure***
774 Neeper-Bradley et al. (1997) assessed the developmental toxicity of acrylic acid in New Zealand
775 White rabbits. Non-developmental toxic effects of the pretest and definitive studies are described in Section
776 3.2.2. In the definitive study, rabbits were exposed to 0, 25, 77 or 227 ppm (measured concentrations) for 6
777 hours/day on gestational days 10 - 23. At the two highest concentrations, reduced body weight gains were
778 observed during the second week of exposure. No effects of exposure were found on the total number of
779 ovarian corpora lutea and the number of total, viable or non-viable implantations/litter. Fetal body weights
780 were unaffected by acrylic acid exposure. There were no exposure-related increases in the incidents of
781 external, visceral or skeletal malformations or variations.

782 **3.3.2 Rats**

783 ***Studies with repeated inhalation exposure***
784 Saillenfait et al. (1999) exposed groups of 17 - 25 pregnant Sprague-Dawley rats to 0, 50, 100, 200
785 or 300 ppm acrylic acid for 6 hours/day during gestational days 6 - 20. The concentration in the exposure
786 chamber was analyzed by gas chromatography and was found to be 48.0±5.1, 98.0±9.7, 203.1±19.2 and
787 313.1±34.4 ppm. Maternal body weight gain was significantly reduced during the first half of gestation at 200
788 ppm and throughout the whole exposure period at 300 ppm. Absolute weight gain was significantly reduced
789 in groups exposed to 200 ppm or higher. A decrease in maternal food intake was observed during the first half
790 of gestation at 50 and 100 ppm and throughout gestation at higher exposure concentrations. A dose-dependent
791 decrease of fetal body weights was observed, but was significant only in the 300-ppm group. Only sporadic
792 visceral and skeletal malformations were observed. Significant increases of visceral variations occurred in the
793 50-ppm group, but not in groups exposed to higher acrylic acid concentrations. According to the authors these
794 findings were not related to acrylic acid exposure. The authors did not evaluate possible irritative effects
795 during exposures.

796 Klimisch and Hellwig (1991) exposed groups of 30 pregnant Sprague-Dawley rats to acrylic acid
797 concentrations of 0, 40, 120 or 360 ppm for 6 hours/day during gestational days 6 - 15 (see Section 3.2.3 for
798 experimental details). A dose-related decrease in body weight and body-weight gain relative to the control
799 group was found at 360 ppm. For the 120-ppm group, a decrease body weight gain was observed during the
800 first week of exposure. At the highest exposure concentration, rats showed a pronounced discharge from eyes
801 and nose during exposure. A trend for slightly higher fetal body weights with increasing exposure
802 concentrations was found for both sexes and this effect was statistically significant at 120 and 360 ppm;
803 however, the body weights in the control group were atypically low and the mean fetal body weight from
804 historical control data was, in fact, a little higher than that in the exposure groups. There were no effects on
805 preimplantation loss, the number of live fetuses and resorption, fetal size or on the appearance of the soft
806 tissues and skeleton of the fetuses.

807 ***Studies with repeated non-inhalation exposure***
808 Hellwig et al. (1997) performed a two-generation reproduction toxicity study in Wistar rats. Groups
809 of 25 male and 25 female rats received acrylic acid in the drinking water at concentrations of 0, 500, 2500 or
810 5000 ppm (corresponding to about 52, 240 and 450 mg/kg/day for adult male and female rats and 85, 380

and 750 mg/kg/day for females during lactation) for at least 70 days prior to mating, though mating, gestation, lactation and weaning. The study continued through weaning of the F_2 offspring at 21 days of age. Exposure to acrylic acid had no adverse effects on fertility and reproductive performance of the parent rats. Reduced food and water consumption was apparent in F_0 parents of 5000 ppm and in F_1 parents at 5000 and 2500 ppm. Reduced body weights were found in F_0 and F_1 parents of the 5000-ppm group. Dose-related signs of developmental toxicity were detected in F_1 and F_2 pups at 2500 and 5000 ppm consisting of retarded growth (normal weight at birth, but reduced weight at weaning) and some delay in the eye/auditory canal opening in F_2 pups (no results reported for F_1 pups). No changes in pup morphology were observed.

3.4. Genotoxicity

Acrylic acid was found to be without mutagenic activity in several Salmonella assay, both in the presence and absence of liver S9 mix (ECB, 2002). In mammalian gene mutation assays, no increase in mutation frequency in the CHO/HPRT gene mutation assay was seen (McCarthy et al., 1992). An increased frequency of mutations were found in two studies with mouse lymphoma L5148Y TK+/- cells in the presence and absence of metabolic activation. Since the majority of mutants gave small colonies, a clastogenic effect of acrylic acid seems likely to have occurred in these experiments (ECB, 2002). An increased frequency of chromosomal aberrations was observed in the presence and the absence of rat liver S9 mix in CHO cells at concentrations not resulting in drastic cytotoxic effects (ECB, 2002). The in vitro clastogenicity was not reproduced in in vivo experiments: two in vivo bone marrow chromosomal aberration assays with rats gave negative results. Chromosome aberrations were analyzed (5 animals per sex, 50 metaphases per animal) at 6, 12 and 24 hours after oral doses of 100, 333 or 1,000 mg/kg or after exposure to 2,000 or 5,000 ppm acrylic acid in drinking water for 5 days (McCarthy et al., 1992). A dominant lethal assay in which male mice received single oral doses (gavage) of up to 324 mg/kg or five daily oral doses up to 162 mg/kg did not reveal any mutagenic effects (McCarthy et al., 1992). No in vivo studies with inhalation exposure were performed.

3.5. Carcinogenicity

In a carcinogenicity study (Hellwig et al., 1993), Wistar rats (50/group/sex) were given acrylic acid in the drinking water at concentrations of 0, 120, 400 or 1200 mg/l (corresponding to 0, 8, 27 or 78 mg/kg/day over 26 (males) or 28 (females) months. The highest concentration was selected because of evidence of palatability problems at 2000 and 5000 mg/l in a 3-month study. The extensive histopathological examination revealed no treatment-related non-neoplastic tissue changes. The incidence and organ distribution of the tumors found in the groups treated with acrylic acid did not differ from those of the controls.

After repeated subcutaneous injection of 20 µmol acrylic acid once a week for 52 weeks, sarcomas at the injection site were observed in 2/30 mice. This effect was attributed to the irritative effect of acrylic acid. After topical application of 0.25 ml of a 1 % acrylic acid (corresponding to 0.25 mg) solution in acetone three times a week over lifetime, no malignancies were observed at the site of application in C3H mice. A positive finding in ICR/HA mice after topical application of 1 mg acrylic acid in acetone three times a week for 1.5 years, has not been published fully and the validity of the findings have been questioned (WHO, 1997). A more recent study (McLaughlin et al., 1995) in three different mouse strains identified repeated topical application of a 1 % solution in acrylic acid as the maximum tolerated dose, while a 4 % concentration clearly exceeded maximum-tolerated-dose definitions based on microscopic histopathological findings.

3.6. Summary

A number of studies described lethal effects in rats. BASF (1980) reported that exposure of 20 rats at 1705 ppm acrylic acid vapor for 4 hours did not result in deaths. No deaths occurred in rats after 1-hour exposure to 2142 ppm vapor (Hagan and Emmons, 1988). From the data of the aerosol study of Hagan and Emmons (1988), LC_{50} values of 1884, 1283 and 879 mg/m³ and LC_{01} values of 879, 602 and 412 mg/m³ were calculated for 30 minutes, 1 hour and 2 hours, respectively.

Irritative effects of acrylic acid have been described in studies using repeated 6-hour exposures in rabbits, rats and mice. Consistently, histopathological alterations of the nasal mucosa was a more sensitive toxicological endpoint than the appearance of clinical signs of irritation: the lowest concentrations leading to clinical signs of irritation (concentrations without effect given in brackets) were 129 (77) ppm in rabbits (Neeper-Bradley et al., 1997), 218 (114) ppm in rats (Klimisch and Hellwig, 1991) and 223 (72) ppm in mice (Miller et al., 1981). Repeated exposure for 1 - 2 weeks led to histopathological changes of the nasal mucosa at the lowest concentrations tested, which were 34 ppm for rabbits (Neeper-Bradley et al., 1997), 74 ppm for rats and 25 ppm for mice (Miller et al., 1981). In mice, effects were found after exposure to 5 ppm for 22 hours/day, but not 6 hours/day, for 2 weeks (Lomax et al., 1994). In a single exposure study, olfactory epithelial cell degeneration and sustentacular cell necrosis was observed in rats after exposure to 75 ppm acrylic acid vapor for 3 or 6 hours; additionally, limited respiratory epithelial cell degeneration was observed after the 6-hour exposure (Frederick et al., 1998). A single exposure of cynomolgous monkeys at 75 ppm for 6 hours resulted in severe histopathological changes of the nasal epithelium (olfactory epithelial cell degeneration, sustentacular cell necrosis), while exposure for 3 hours resulted in less severe changes and a lesser area of the olfactory epithelium was affected (Rohm and Haas Co., 1995; Harkema, 2001; Harkema et al., 1997).

No developmental toxic effects of acrylic acid were found in several inhalation studies. Acrylic acid may have a weak clastogenic effect. No carcinogenic effects were found after application of acrylic acid in the drinking water, while after subcutaneous and topical application tumors were found (probably attributable to local irritative effects).

4. SPECIAL CONSIDERATIONS

4.1. Metabolism and Disposition

Regardless of the route of exposure, acrylic acid is rapidly absorbed. It is quickly metabolized, mainly to 3-hydroxy propionic acid (a physiologic metabolite), carbon dioxide and mercapturic acid, which are eliminated in the expired air and urine. The half-life of acrylic acid is short.

Sixty-five minutes after a one-minute nose-only exposure of rats to 1-^{14}C-labeled acrylic acid, 60 % of the radiolabel was expired as carbon dioxide, 25 % was retained and about 15 % was eliminated in the urine and feces. Ninety seconds after exposure, 18.3 % of the delivered dose remained in the rats. Only 1.5 % of the radiolabel was retained in the lungs. About 28 % of the radioactivity was associated with the snout and an additional 42.9 % was found in the head. This was considered to be solubilized in the mucous of the nasal turbinates and nasopharynx, suggesting the gastrointestinal tract might be a site of absorption after inhalation exposure (Kutzman et al., 1982).

After cutaneous administration of single doses of 10 or 40 mg/kg 1-^{14}C-labeled acrylic acid (as a 1 % solution in acetone) to C3H mice or Fischer 344 rats (Black et al., 1995), acrylic acid absorption and elimination were rapid and nearly complete within 8 hours. After administration of 10 mg/kg, 12.4 and 19.4 % of the dose was absorbed in mice and rats, respectively, and after administration of 40 mg/kg absorption was 11.4 and 25.6 %, respectively. Evaporation from the dosing site accounted for the largest fraction of the applied dose.

In vitro studies of dermal penetration of 1-^{14}C labeled acrylic acid have shown mouse skin to be an order of magnitude more permeable than human skin to radioactivity from the test material. The absorption rate was proportional to acrylic acid concentration in a concentration range of 0.01 - 4 %. For this concentration range and using acetone, water and phosphate buffer as solvents, the absorption rates through human skin were 0.2 - 99.8, 0.037 - 28.9 and 0.0007 - 7.23 $\mu g/cm^2$ h, respectively (Cascieri and Clary, 1993; WHO, 1997).

Results of metabolic studies are consistent with the following pathway of acrylic acid metabolism: acrylic acid is activated to acrylyl-CoA and then hydroxylated to 3-hydroxypropionyl-CoA after which the coenzyme A is regenerated by hydrolytic cleavage. The 3-hydroxypropionic acid formed is oxidized to malonic semialdehyde. A dehydrogenase oxidizes the aldehyde group and after decarboxylation transfers the acetyl group to CoA yielding acetyl-CoA (Black et al., 1993; DeBethizy et al., 1987; Custodio et al., 1998).

Using 2,3-^{14}C-labeled (DeBethizy et al., 1987) or 1-^{14}C-labeled (Black et al., 1995) acrylic acid, 24 hours after oral application of doses between 4 and 400 mg/kg to rats 50 - 65 % and 80 - 90 %, respectively, of the administered radioactivity had been eliminated as carbon dioxide.

4.2. Mechanism of Toxicity

Acrylic acid is highly water soluble and thus is solubilized in the mucus covering the epithelia of the upper respiratory airways, e.g. in rats it is completely absorbed in the mucus of the nasal turbinates. Irritation is caused most likely by acrylic acid itself and there is no evidence in the literature that the effects observed after exposure to acrylic acid are caused by a metabolite.

In in vitro experiments, Custodio et al. (1998) found acrylic acid to be an inducer of the mitochondrial permeability transition. This transition is manifest by the transformation of a complex of membrane-spanning proteins into a nonspecific pore allowing free diffusion of solutes of $\leq$1500 dalton. This results in rapid loss of calcium and glutathione and in dissipation of the electrochemical gradient and uncoupling of ATP biosynthesis, which has been suggested to account for both the necrotic and apoptotic cell death observed with acrylic acid and other inducers of the mitochondrial permeability transition.

Experiments in monkeys (Rohm and Haas Co., 1995; Harkema, 2001; Harkema et al., 1997), rabbits (Neeper-Bradley et al., 1997) rats (Frederick et al., 1998) and mice (Lomax et al., 1994) showed that the olfactory epithelium is the tissue most susceptible to damage upon inhalation exposure. Short-term organ culture of rat nasal explants with media containing acrylic acid resulted in histopathological lesions very similar to those observed in vivo (Frederick et al., 1998). The sustentacular cells were the most susceptible cells of the olfactory epithelium. Since neutralized acrylic acid was used in vitro, it seems likely that the histological changes are caused by the toxic effect on the mitochondria rather than by lowering of the pH

value.

Miller et al. (1981) found that the spontaneous reaction of acrylic acid with glutathione and other low molecular weight thiols was slow compared to ethyl acrylate.

The olfactory epithelium seems to be the primary target for acrylic acid, because 1) the sustentacular cells are more sensitive than other cell types and 2) the olfactory epithelium in the dorsal meatus region is highly exposed because of the characteristics of the air flow in the nasal turbinates, due to which the dorsal meatus region of the rat nose receives 12 to 21 % of the inhaled air (Frederick et al., 1998).

Necropsy of animals that had died after a single inhalation exposure of acrylic acid aerosol revealed no toxic effects of inner organs other than the lungs (Hagan and Emmons, 1988). Also, Gage (1970) reported lung hemorrhage in rats that had died from a single 5-hour exposure to acrylic acid vapor. It can thus be concluded that death had resulted from local damage of lung tissue ultimately resulting in cardiopulmonary collapse.

For comparison with oral lethality data, the equivalent dose for an inhalation exposure of rats to the 1-hour LC_{50} of 1283 mg/m³ (Hagan and Emmons, 1988) can be calculated:
dose (for 8-h exposure) = 1283 mg/m³ x 0.222 m³/day x 1 h x 1/24 hours/day x 1/0.21 kg = 56.5 mg/kg
using a body weight of 0.21 kg for rats (Hagan and Emmons, 1988), a resorption rate of 100 % and calculating the respiration rate according to the allometric relationship for the ventilation rate (m³/day) of rats given by EPA (EPA, 1988):
ventilation rate (m³/day) = 0.80 x body weight (kg) $^{0.8206}$ (EPA, 1988)
ventilation rate = 0.80 x 0.21 $^{0.8206}$ = 0.222 m³/day

The estimated lethal dose after inhalation is low compared with the oral LD_{50} reported for rats, which are mostly between 1350 and 2600 mg/kg (ECB, 2002; IUCLID, 1996) and thus support the interpretation that local effects in the lung lead to lethality upon inhalation.

4.3. Structure-Activity Relationships

The irritative effects of acrylic acid and the esters of acrylic acid cannot be directly compared because 1) the deposition in the upper respiratory tract is much higher for acrylic acid than for its esters and 2) the exertion of irritative effects by acrylic acid ester requires their enzymatic cleavage (Morris and Frederick, 1995).

4.5. Other Relevant Information

4.5.1. Interspecies Variability

Acrylic acid is a contact-site, direct-acting toxicant and no metabolic component determines acrylic acid-induced effects. Thus, there is likely little difference between species or among individuals in the response of biological tissues to acrylic acid.

Frederick et al. (1998) stated that the histological structure of olfactory epithelium varies little between

mammalian species. Furthermore, they assumed the mode of action for cytotoxicity of inhaled short chain organic acid vapors, mitochondrial toxicity, is fundamentally the same across species. They suggested the susceptibility of the tissues to inhaled irritants also varies relatively little between mammalian species and, therefore, the dominant factor influencing interspecies differences in susceptibility to inhaled irritants would be the olfactory dose. As a tool for determining the dose distribution, a mathematical model based on a combination of computational fluid dynamics and physiologically-based pharmacokinetic modeling was constructed to estimate the regional tissue dose of acrylic acid in the rodent and human nasal cavity (Frederick et al., 1998; Bush et al., 1998). The simulations indicated that the olfactory epithelium in the dorsal meatus region of the rat nasal cavity is exposed to two- to threefold greater concentrations of acrylic acid in the mucus than the human olfactory epithelium. Accordingly, when rats were exposed to 0 and 75 ppm acrylic acid for 3 or 6 hours the pH of the mucus covering the rat olfactory epithelium fell to slightly lower values than the predicted human mucus pH. The drop in mucus pH could be a factor contributing to the cytotoxicity observed in the apical sustentacular cells, which lie immediately under the mucus layer and which have been reported to be the cells most sensitive to acidic vapors (Miller et al., 1981).

Barrow et al. (1986) quantified the "nasal dose" after whole-body inhalation exposure of rats and mice to 75 ppm acrylic acid (see Sections 3.2.1 and 3.2.2). The calculated dose delivered to the nasal epithelium was about 2 times higher in mice compared to rats (3.5 - 3.8 µg/min cm² vs. 1.8 - 2.1 µg/min cm²). Both species showed severe lesions that were confined to the nasal passages and particularly the olfactory epithelium of the dorsal meatus. Mice had more severe lesions, as seen by the presence of more cellular exudate in the lumen and a much greater loss of sensory cells.

From a single inhalation exposure of cynomolgus monkeys to 75 ppm acrylic acid for 3 and 6 hours (Rohm and Haas Co., 1995; Harkema, 2001; Harkema et al., 1997), the authors concluded that the character, severity and distribution of the morphologic alterations of the olfactory epithelium induced by acrylic acid and ethyl acrylate were similar. The author concluded that monkeys exposed to acrylic acid or ethyl acrylate had focal, olfactory epithelial lesions that resembled in both nature and severity those reported in rodents after identical exposure.

4.5.2. Intraspecies Variability

Acrylic acid is a contact-site, direct-acting toxicant and no metabolic component determines acrylic acid-induced effects. Thus, there is likely little difference between individuals in the response of biological tissues to acrylic acid.

4.5.3. Skin Irritation and Sensitization

Solutions containing acrylic acid concentrations of 10 % or higher are corrosive to the skin and the eyes of rabbits and concentrations of 1 % or higher cause irritation to the skin of rabbits and mice and to the eyes of rabbits (WHO, 1997; BG Chemie, 1991). Sensitization test in guinea pigs yielded both negative and positive results. In one study, the positive response was attributed to an impurity, diacryloxypropionic acid, found in acrylic acid of one of three suppliers. It is unknown, if the low concentrations of polymerization inhibitors in technical acrylic acid, such as hydroquinone, 4-methoxyphenol, diphenyl-p-phenylenediamine and phenothiazine, which all are known sensitizers, contributed to the positive sensitization results (WHO, 1997; BG Chemie, 1991). Two case reports of hypersensitivity reactions to acrylic acid have been reported

in the literature (Fowler, 1990; Daecke et al., 1993). In summary, the sensitizing capacity of acrylic acid if at all is uncertain.

5. DATA ANALYSIS FOR AEGL-1

5.1. Human Data Relevant to AEGL-1

Irritation has been observed after occupational exposure to acrylic acid: Renshaw (1988; personal communication) reported that eye irritation was noted at exposure for 16 - 30 minutes to 4.5 - 23 ppm, measured by personal breathing zone sampling and that slight eye irritation was experienced during exposures for 30 minutes to 2.5 hours at measured area concentrations of 0.3 - 1.6 ppm. Grudzinskii (1988) observed no irritation in test subjects exposed to concentrations up to 1.5 mg/m³ (0.495 ppm).

The odor threshold for acrylic acid was reported to be in the range of 0.066 - 1.04 ppm (Hellman and Small, 1974; Ruth, 1986; Grudzinskii, 1988). The study by Hellman and Small (1974) reported a detection limit of 0.094 ppm and a recognition threshold of 1.04 ppm (at the latter level, 100 % of the test subjects recognized the acrylic acid odor).

5.2. Animal Data Relevant to AEGL-1

Reports on irritative effects of acrylic acid are available for rabbits (Neeper-Bradley et al., 1997), rats (Miller et al., 1981; Frederick et al., 1998; Klimisch and Hellwig, 1991; Gage, 1970) and mice (Miller et al., 1981; Lomax et al., 1994). Consistently, histopathological alteration of the nasal mucosa was a more sensitive toxicological endpoint than the appearance of clinical signs of irritation (see Tables 8 and 9): the lowest concentrations leading to clinical signs of irritation after the first 6-hour exposure in rabbit, rat and mouse were 129, 218 and 223 ppm, respectively, while no signs of irritation after the first exposure were found for 77, 114 and 75 ppm, respectively (see Table 8). Histological examinations of the nasal mucosa after repeated exposure (considering only exposure periods of 2 weeks) revealed damage to the olfactory epithelium after exposure to 34 ppm for 6 hours/day in rabbits (Neeper-Bradley et al., 1997) and 25 ppm for 4.4 hours/day or 5 ppm for 22 hours/day in mice (Lomax et al., 1994). No histologic lesions were observed in control mice or mice exposed to 5 ppm for 6 hours/day (Lomax et al., 1994). In a single exposure study, olfactory epithelial cell degeneration and sustentacular cell necrosis was observed in rats after exposure to 75 ppm acrylic acid vapor for 3 or 6 hours; additionally, limited respiratory epithelial cell degeneration was observed after the 6-hour exposure (Frederick et al., 1998).

5.3. Derivation of AEGL-1

Irritation is the most relevant endpoint for deriving of AEGL-1 values. The data on irritative effects in humans by Renshaw (1988; personal communication) was used as key study because human data were considered most relevant for AEGL derivation. Renshaw (1988) reported that slight eye irritation was experienced at 0.3 - 1.6 ppm for 30 minutes to 2.5 hours. However, the exposure concentrations were measured by area sampling, which is unlikely to accurately reflect the breathing zone concentrations to which the workers were exposed. Therefore, the concentration of 4.5 ppm, which was the lowest personal sampling measurement at which eye irritation was observed, was used as a point of departure for AEGL-1 derivation.

Since the Renshaw (1988) study has obvious shortcomings, e.g. the limited number of and information on subjects and lack of exact characterization of exposure time-exposure concentration combinations, the study by Lomax et al. (1994) investigating histopathological alterations in mice was used as supportive evidence: exposure at 5 ppm for 6 hours per day for 2 weeks caused no histopathological alterations of the nasal mucosa in mice, while atrophy, necrosis and desquamation of olfactory epithelium were observed after repeated exposure at 25 ppm for 4.4 hours/day for 2 weeks (Lomax et al., 1994). Thus, the NOEL in mice for histopathological changes of the nasal olfactory mucosa supports the chosen AEGL-1 derivation starting point.

Since very slight irritative effects depend primarily on the actual exposure concentration and not much on exposure time, the same exposure concentration was used for all exposure durations between 10 minutes and 8 hours (i.e. a flat line was used for time scaling). This approach is in accordance with the Standing Operating Procedures for slight irritation effects.

A total uncertainty factor of 3 was used. An uncertainty factor of 3 was applied for intraspecies variability because tissue damage of the nasal mucosa by local cytotoxicity was considered not to vary considerably between individuals. The calculations of exposure concentrations for AEGL-1 time points are shown in Appendix A.

The derived AEGL-1 value of 1.5 ppm for all time points is supported by the RD_{50} values of 513 ppm for rats and 685 ppm in mice (Buckley et al., 1984) because it is about two orders of magnitude below the reported RD_{50} values.

The values are listed in Table 10 below.

TABLE 10: AEGL-1 VALUES FOR ACRYLIC ACID

AEGL Level	10 minutes	30 minutes	1 hour	4 hours	8 hours
AEGL-1	1.5 ppm (4.5 mg/m³)	1.5 ppm (4.5 mg/m³)	1.5 ppm (4.5 mg/m³)	1.5 ppm (4.5 mg/m³)	1.5 ppm (4.5 mg/m³)

A level of distinct odor awareness (LOA) for acrylic acid of 0.20 ppm was derived on the basis of the odor detection threshold from the study of Hellman and Small (1974) (see Appendix C for LOA derivation). The LOA represents the concentration above which it is predicted that more than half of the exposed population will experience at least a distinct odor intensity, about 10 % of the population will experience a strong odor intensity. The LOA should help chemical emergency responders in assessing the public awareness of the exposure due to odor perception.

6. DATA ANALYSIS FOR AEGL-2

6.1. Human Data Relevant to AEGL-2

Relevant human data for the derivation of AEGL-2 values are lacking.

6.2. Animal Data Relevant to AEGL-2

Reports on irritative effects of acrylic acid are available for rabbits (Neeper-Bradley et al., 1997), rats (Miller et al., 1981; Frederick et al., 1998; Klimisch and Hellwig, 1991; Gage, 1970) and mice (Miller et al., 1981; Lomax et al., 1994). Consistently, histopathological alteration of the nasal mucosa was a more sensitive toxicological endpoint than the appearance of clinical signs of irritation (see Tables 8 and 9): the lowest concentrations leading to clinical signs of irritation after the first 6-hour exposure in rabbit, rat and mouse were 129, 218 and 223 ppm, respectively, while no signs of irritation after the first exposure were found for 77, 114 and 75 ppm, respectively (see Table 8). Histological examinations of the nasal mucosa after repeated exposure (considering only exposure periods of 2 weeks) revealed damage to the olfactory epithelium after exposure to 34 ppm for 6 hours/day in rabbits (Neeper-Bradley et al., 1997) and 25 ppm for 4.4 hours/day or 5 ppm for 22 hours/day in mice (Lomax et al., 1994). The two-week prestudy of Miller (1981) was considered to be of limited validity due to the high incidence of histopathologic lesions in the control group.

In a single exposure study, cynomolgus monkeys were exposed to 75 ppm acrylic acid vapor for 3 or 6 hours. No abnormal clinical observations were recorded. Histopathological analysis revealed nasal lesions that were restricted to the olfactory epithelium lining the dorsal medial meatus at the level of the maxillary sinus in the proximal aspect of both nasal passages. The morphologic alterations consistently found in all acrylic acid-exposed monkeys were focal degeneration and necrosis of the olfactory epithelium with mild inflammation (influx of neutrophils and lymphocytes). No exposure-related lesions were present in the nasal respiratory, transitional or squamous epithelium in any of the monkeys examined. The extent and severity of the lesions were greater in monkeys exposed for 6 hours compared to those exposed for 3 hours (Rohm and Haas Co., 1995; Harkema, 2001; Harkema et al., 1997).

In a single exposure study, olfactory epithelial cell degeneration and sustentacular cell necrosis was observed in rats after exposure to 75 ppm acrylic acid vapor for 3 or 6 hours; additionally, limited respiratory epithelial cell degeneration was observed after the 6-hour exposure (Frederick et al., 1998).

Severe signs of irritation were observed in animals: in rabbits, blepharospasm was found during 6-hour exposures to 129 ppm or higher, but not at 77 and 61 ppm (Neeper-Bradley et al., 1997), eye lid closure was seen in rats during 6-hour exposures to 218 ppm, but not at 114 ppm (Klimisch and Hellwig, 1991).

6.3. Derivation of AEGL-2

Acrylic acid is a highly irritating chemical. Human data for effects more severe than odor recognition and slight to moderate irritative effects were not available. In studies in monkeys, rabbits, rats and mice, histopathological alteration of the nasal mucosa consistently was a more sensitive toxicological endpoint than the appearance of clinical signs of irritation. It was therefore considered appropriate to use the single inhalation exposure studies in monkeys (Rohm and Haas Co., 1995; Harkema, 2001; Harkema et al., 1997) as key study for the derivation of AEGL-2 values. Exposure to 75 ppm acrylic acid for 6 hours resulted in severe histopathological changes of the nasal epithelium (olfactory epithelial cell degeneration, sustentacular cell necrosis), while exposure for 3 hours resulted in less severe changes and a lesser area of the olfactory epithelium was affected. No obvious clinical symptoms were reported.

The regeneration of the olfactory epithelium will be incomplete if olfactory stem cells in the basal cell

layer are damaged. In this case, olfactory epithelium is permanently replaced by non-functional respiratory epithelium. Loss of olfactory epithelium could decrease the individuals sensitivity to odor (increase odor thresholds and reduce the number of different odors that can be recognized). The NAC/AEGL committee evaluated the histological damage (see photographs in Harkema, 2001 in Figure 1) and considered the effects after the 6-hour exposure as severe and probably irreversible, while the changes after the 3-hour exposure were considered reversible. Therefore, AEGL-2 values were derived on the basis of a 3-hour exposure to 75 ppm.

The studies in monkeys are supported by a single exposure study in rats, in which exposure to 75 ppm for 3 and 6 hours resulted in olfactory epithelial cell degeneration and sustentacular cell necrosis (Frederick et al., 1998).

The use of an exposure concentration of 75 ppm as the basis for the derivation of AEGL-2 values is supported by the observation that 77 ppm was the NOEL for blepharospasm in rabbits (Neeper-Bradley et al., 1997). Blepharospasm (involuntary eyelid closure) may be interpreted as a sign of impaired ability to escape. Similarly, eye lid closure in rats was found during a 6-hour exposure at 218 ppm, but not at 114 ppm (Klimisch and Hellwig, 1991).

The other exposure duration-specific values were derived by time scaling according to the dose-response regression equation $C^n * t = k$, using the default of n=3 for shorter exposure periods and n=1 for longer exposure periods, due to the lack of suitable experimental data for deriving the concentration exponent. The time extrapolation was continued to the 10-minute period because the resulting 10-minute AEGL-2 value was still below the threshold for blepharospasm in rabbits.

A total uncertainty factor of 3 was used. An uncertainty factor of 1 was applied for interspecies variability: for the toxicokinetic component a factor of 1 was used because a monkey inhalation study was used and because acrylic acid is a locally acting irritant not requiring metabolic activation. The toxicodynamic component of the uncertainty factor was reduced to 1 because single inhalation exposure of monkeys resulted in similar olfactory lesions than in rats (Rohm and Haas Co., 1995; Harkema, 2001; Harkema et al., 1997). An uncertainty factor of 3 was applied for intraspecies variability because tissue damage of the nasal mucosa by local cytotoxicity was considered not to vary considerably between individuals. The calculations of exposure concentrations for AEGL-2 time points are shown in Appendix A.

The derived values are supported by the findings of Renshaw (1988; personal communication), who reported that human exposure to concentrations of 4.5 - 23 ppm for 16 - 30 minutes resulted in eye irritation, but not in more severe effects.

TABLE 11: AEGL-2 VALUES FOR ACRYLIC ACID

AEGL Level	10 minutes	30 minutes	1 hour	4 hours	8 hours
AEGL-2	66 ppm (140 mg/m³)	45 ppm (140 mg/m³)	36 ppm (110 mg/m³)	19 ppm (56 mg/m³)	9.4 ppm (28 mg/m³)

7. DATA ANALYSIS FOR AEGL-3

7.1. Human Data Relevant to AEGL-3

Relevant human data for deriving AEGL-3 values are not available.

7.2. Animal Data Relevant to AEGL-3

BASF (1980) reported that exposure of 20 rats at 1705 ppm acrylic acid vapor for 4 hours did not result in deaths. No deaths occurred in rats after 1-hour exposure to 2142 ppm vapor (Hagan and Emmons, 1988). Union Carbide Co. (1977) found no deaths in 6 rats exposed to 3996 ppm vapor for 4 hours, while in the study of Carpenter et al. (1974) all of 6 rats died after a similar exposure.

In the study of Hagan and Emmons (1988), LC_{50} values of 1884 mg/m³ (equivalent to 5652 ppm) for 30 minutes, 1283 mg/m³ (equivalent to 3850 ppm) for 1 hour and 879 mg/m³ (equivalent to 2636 ppm) for 2 hours were derived for exposure to acrylic acid aerosol.

7.3. Derivation of AEGL-3

For the derivation of AEGL-3 values, the animal studies using vapor exposure were considered more relevant than the aerosol studies, because for emergency situations a vapor exposure was considered more likely than an aerosol exposure. The derivation was based on the study by BASF (1980) reporting no deaths of rats after exposure to 1705 ppm for 4 hours. This result is supported by the study of Hagan and Emmons (1988) which found no lethality in rats at 2142 ppm for 1 hour. While these studies did not report a LOEL for vapor lethality, the results of the study by Carpenter et al. (1974) indicated that a level of about 4000 ppm for 4 hours was clearly above the LOEL.

Time scaling using the equation $C^n \times t = k$ was carried out to derive exposure duration-specific values. Due to lack of a definitive data set, a default for n of 3 was used in the exponential function for extrapolation from the experimental period (4 hours) to shorter exposure periods and a default for n of 1 was used for extrapolation to longer exposure periods. For the 10-minute AEGL-3 the 30-minute value was applied because the derivation of AEGL values was based on a long experimental exposure period and no supporting studies using short exposure periods were available for characterizing the concentration-time-response relationship.

A total uncertainty factor of 10 was used. An uncertainty factor of 3 for interspecies variability and another uncertainty factor of 3 for intraspecies variability were applied based on the following reasoning: acrylic acid causes lethal effects by local tissue destruction in the lung with limited influence of systemic distribution, metabolism and elimination. Therefore, the toxicokinetic differences do not vary considerably within and between species. Also the toxicodynamic variability within and between species is considered to be limited because acrylic acid causes cell necrosis by reducing the pH and destroying mitochondria, which are unlikely to be influenced by species-specific differences. Overall these arguments support reduced interspecies and intraspecies uncertainty factors of 3 each. The calculations of exposure concentrations for AEGL-3 time points are shown in Appendix A.

The values are listed in Table 12 below.

TABLE 12: AEGL-3 VALUES FOR ACRYLIC ACID					
AEGL Level	**10 minutes**	**30 minutes**	**1 hour**	**4 hours**	**8 hours**
AEGL-3	340 ppm (1000 mg/m³)	340 ppm (1000 mg/m³)	270 ppm (810 mg/m³)	170 ppm (510 mg/m³)	85 ppm (260 mg/m³)

8. SUMMARY OF AEGLs

8.1. AEGL Values and Toxicity Endpoints

The AEGL values for various levels of effects and various time periods are summarized in Table 13. They were derived using the following key studies and methods.

The AEGL-1 was based on the study of Renshaw (1988; personal communication) reporting eye irritation during occupational exposure to concentrations of 4.5 ppm and higher. An intraspecies uncertainty factor of 3 was applied. Since slight irritative effects depend mostly on exposure concentration, the derived concentration was applied to all exposure periods (flat line for time scaling).

The AEGL-2 was based on histopathological changes in the upper respiratory tract (olfactory and respiratory epithelium degeneration) observed in monkeys after a single exposure to 75 ppm for 3 hours. The total uncertainty factor of 3 comprises an interspecies factor of 1 and an intraspecies factor of 3. Time scaling using the equation $C^n \times t = k$ was done to derive the exposure duration-specific values, using a default n of 3 for longer and 1 for shorter exposure periods. The time extrapolation was continued to the 10-minute period because the resulting 10-minute AEGL-2 value was still below the threshold for blepharospasm in rabbits.

The AEGL-3 was based on a vapor study in rats reporting no mortality at 1705 ppm for 4 hours(BASF, 1980). The total uncertainty factor of 10 comprises an interspecies factor of 3 and an intraspecies factor of 3. Time scaling using the equation $C^n \times t = k$ was done to derive the exposure duration-specific values, using a default n of 3 for longer and 1 for shorter exposure periods. For the 10-minute AEGL-3 the 30-minute value was applied because the derivation of AEGL values was based on a long experimental exposure period and no supporting studies using short exposure periods were available for characterizing the concentration-time-response relationship.

TABLE 13: SUMMARY/RELATIONSHIP OF AEGL VALUES					
Classification	**10-Minute**	**30-Minute**	**1-Hour**	**4-Hour**	**8-Hour**
AEGL-1 (Nondisabling)	1.5 ppm (4.5 mg/m³)	1.5 ppm (4.5 mg/m³)	1.5 ppm (4.5 mg/m³)	1.5 ppm (4.5 mg/m³)	1.5 ppm (4.5 mg/m³)
AEGL-2 (Disabling)	66 ppm (140 mg/m³)	45 ppm (140 mg/m³)	36 ppm (110 mg/m³)	19 ppm (56 mg/m³)	9.4 ppm (28 mg/m³)
AEGL-3 (Lethal)	430 ppm (1000 mg/m³)	340 ppm (1000 mg/m³)	270 ppm (810 mg/m³)	170 ppm (510 mg/m³)	85 ppm (260 mg/m³)

All inhalation data are summarized in Figure 3 below. The data were classified into severity categories chosen to fit into definitions of the AEGL level health effects. The category severity definitions are "No effect"; "Discomfort"; "Disabling"; "Some lethality"; and “Lethal". Note that the AEGL values are designated as triangles.

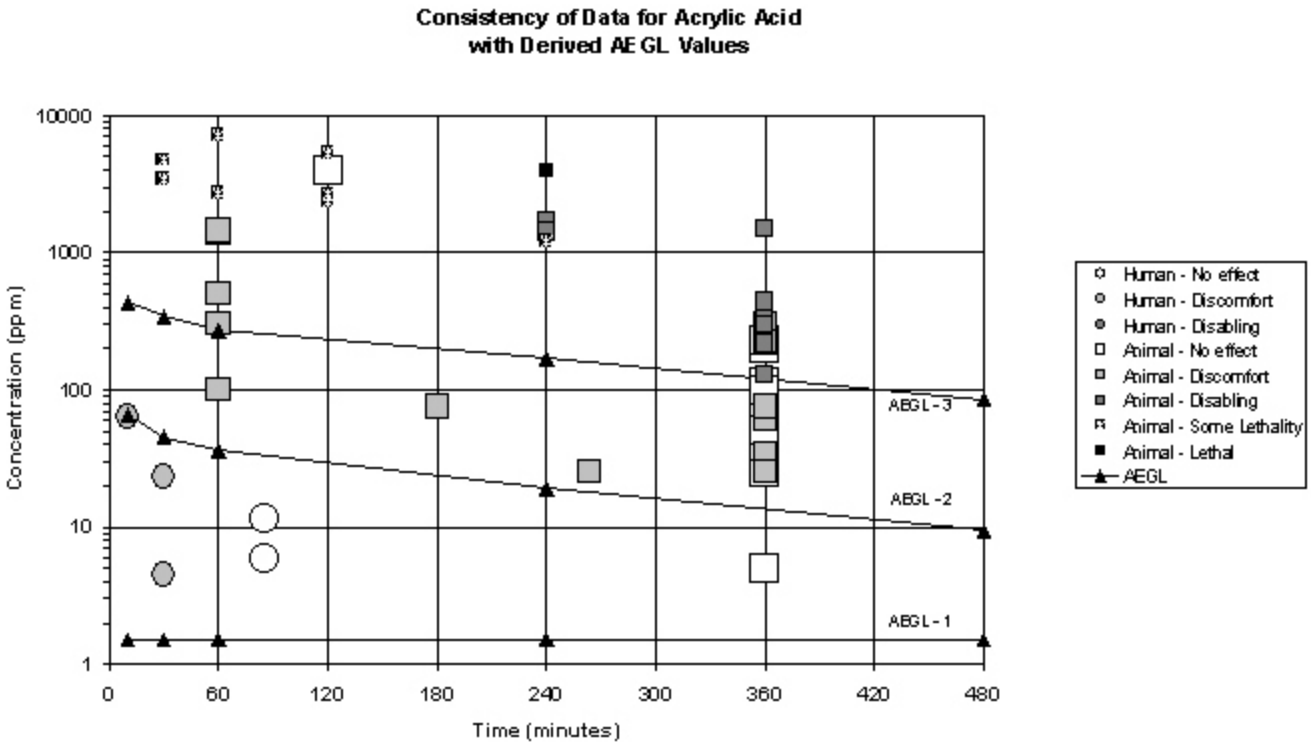


FIGURE 3: CATEGORICAL REPRESENTATION OF ALL ACRYLIC ACID INHALATION DATA

8.2. Comparison with Other Standards and Criteria

Standards and guidance levels for workplace and community exposures are listed in Table 14.

TABLE 14: EXTANT STANDARDS AND CRITERIA FOR ACRYLIC ACID

Guideline	Exposure Duration				
	10 minutes	30 minutes	1 hour	4 hours	8 hours
AEGL-1	1.5 ppm	1.5 ppm	1.5 ppm	1.5 ppm	1.5 ppm
AEGL-2	66 ppm	45 ppm	36 ppm	19 ppm	9.4 ppm
AEGL-3	340 ppm	340 ppm	270 ppm	170 ppm	85 ppm
ERPG-1 (AIHA)[a]			2 ppm		
ERPG-2 (AIHA)			50 ppm		
ERPG-3 (AIHA)			750 ppm		
TLV-TWA (ACGIH)[b]					2 ppm
REL-TWA (NIOSH)[c]					2 ppm
MAC (The Netherlands)[d]					2 ppm

[a] **ERPG (Emergency Response Planning Guidelines, American Industrial Hygiene Association)** (AIHA, 1991)

The ERPG-1 is the maximum airborne concentration below which it is believed nearly all individuals could be exposed for up to one hour without experiencing other than mild, transient adverse health effects or without perceiving a clearly defined objectionable odor. The ERPG-1 for acrylic acid is based on the odor threshold of 0.09 - 1.04 ppm (Hellman and Small, 1974). At the guideline level, the odor should be clearly recognizable and a very mild transient eye irritation may occur.

The ERPG-2 is the maximum airborne concentration below which it is believed nearly all individuals could be exposed for up to one hour without experiencing or developing irreversible or other serious health effects or symptoms that could impair an individual's ability to take protective action. The ERPG-2 for acrylic acid is based on a study showing no effects at 75 ppm for 10 days in rats (Miller et al., 1981); the eye and respiratory irritation at the guideline level is not expected to interfere with an individual's ability to escape.

The ERPG-3 is the maximum airborne concentration below which it is believed nearly all individuals could be exposed for up to one hour without experiencing or developing life-threatening health effects. The ERPG-3 for acrylic acid is based on the 1-hour LC_{01} for acrylic acid aerosol of 2180 ppm in rats (Hagan and Emmons, 1988).

[b] **ACGIH TLV-TWA (American Conference of Governmental Industrial Hygienists, Threshold Limit Value - Time Weighted Average)** (ACGIH, 1996)

The time-weighted average concentration for a normal 8-hour workday and a 40-hour workweek, to which nearly all workers may be repeatedly exposed, day after day, without adverse effect.

[c] **NIOSH REL-TWA (National Institute of Occupational Safety and Health, Recommended Exposure Limits - Time Weighted Average)** (NIOSH, 1992), is defined analogous to the ACGIH-TLV-TWA.

[d] **MAC ([Maximum Workplace Concentration], Dutch Expert Committee for Occupational Standards, The Netherlands)** (MSZW, 1999)
is defined analogous to the ACGIH-TLV-TWA.

8.3. Data Adequacy and Research Needs

Since human data were considered most relevant for AEGL derivation, a report on irritation during occupational exposure was used for derivation of AEGL-1 values, although the report format as well as the data had several shortcomings. An inhalation study in mice investigating histopathological alterations of the nasal mucosa was used as supportive evidence. Definitive exposure-response data for irritation in humans are not available. Other qualitative information on the human experience affirms that acrylic acid vapor is highly irritating.

Data from earlier animal studies were often compromised by uncertain quantitation of exposure atmospheres: due to adsorption and deposition on the tubing and walls of the exposure system nominal exposure concentrations would always have needed confirmation by analytical measurement of the actual exposure concentration. Many acute lethality studies used only a small number of animals and thus only poorly characterized exposure-response relationships.

More recent studies in laboratory animals, however, utilized accurate and reliable methods for characterizing exposure concentrations. For the derivation of AEGL-2 values, histopathological alteration of the nasal mucosa was used as the endpoint of local irritative effects of acrylic acid. Data from these studies allowed for development of AEGL values consistent with the methodologies described in the Standing Operating Procedures of the National Advisory Committee for AEGLs.

For the derivation of AEGL-3 values, lethality data in rats were used. Since the available vapor exposure studies used either very small numbers of animals or did not observe mortality, a study using exposure to acrylic acid aerosol was used as key study. Comparison of the aerosol with the vapor studies did not reveal fundamental differences in the type of effects or lethal concentrations.

The AEGL-1 could be strengthened by determination of the irritation threshold in non-acclimatized humans under controlled experimental conditions. Research aiming at better characterization of the toxicodynamic differences between humans and animals with regard to histopathologic effects on the olfactory mucosa could support the basis for the derivation of AEGL-2 values. In view of the lack of definitive data for humans, quantitative lethality data in several animal species would serve to reduce the uncertainty in interspecies variability in the AEGL-3 derivation. This research could also provide further evidence that lethality after inhalation is caused by local effects in the lungs.

9. REFERENCES

ACGIH, American Conference of Governmental Industrial Hygienists, 1996. Documentation of the Threshold Limit Values and Biological Exposure Indices. Cincinnati, OH, USA, pp.26-29.

AIHA, American Industrial Hygiene Association, 1989. Odor thresholds for chemicals with established occupational health standards. American Industrial Hygiene Association, Fairfax, VA, USA, 1989.

1283 AIHA, American Industrial Hygiene Association, 1991. Emergency Response Planning Guidelines, Acrylic acid. AIHA,
1284 Akron, OH, USA.

1285 Barrow, C.S., L.A. Buckley, R.A. James, W.H. Steinhagen and J.C.F. Chang, 1986. Sensory irritation: studies of
1286 correlation to pathology, structure-activity, tolerance development, and prediction of species differences to nasal injury.
1287 In: Toxicology of the Nasal Passages, C.S. Barrow (Ed.), Hemisphere Publishing Corporation, Washington, New York,
1288 London, 1986, pp. 101-122.

1289 Black K.A., L. Finch and C.B. Frederick, 1993. Metabolism of acrylic acid to carbon dioxide in mouse tissues. Fund.
1290 Appl. Toxicol. 21, 97-104.

1291 BASF AG, 1980. Bestimmung der akuten Inhalationstoxizität LC_{50} von Acrylsäure rein als Dampf bei 4stündiger
1292 Exposition an Sprague-Dawley-Ratten. Unpublished report, BASF AG, Ludwigshafen, Germany, 1980.

1293 Black K.A., J.L. Beskitt, L. Finch, M.J. Tallant, J.R. Udinsky and S.W. Frantz, 1995. Disposition and metabolism of
1294 acrylic acid in C3H mice and Fischer 344 rats after oral or cutaneous administration. J. Toxicol. Environ. Health 45, 291-
1295 311.

1296 BG Chemie, Berufsgenossenschaft der chemischen Industrie, 1990. Acrylsäure. Toxikologische Bewertungen, Nr. 157.
1297 Heidelberg, Germany.

1298 Buckley, L.A., R.A. James, and C.S. Barrow. 1984. Differences in nasal cavity toxicity between rats and mice exposed
1299 to acrylic acid vapor. Toxicologist. 4, 1 (abstract); cited in EPA, 2003.

1300 Bush M.L., C.B. Frederick, J.S. Kimbell and J.S. Ultman, 1998. A CFD-PBPK hybrid model for simulating gas and vapor
1301 uptake in the rat nose. Toxicol. Appl. Pharmacol. 150, 133-145.

1302 Carpenter C.P., C.S. Weil and H.F. Smyth, 1974. Range-finding toxicity data: List VIII. Toxicol. Appl. Pharmacol. 28,
1303 313-319.

1304 Cascieri, T. and J. Clary, 1993. Acrylic Acid Health Effects Overview. In: T.R. Tyler, S.R. Murphy and E.K. Hunt (Eds.),
1305 Health Assessment of the Basic Acrylates. CRC Press, Boca Raton, Ann Arbor, London and Tokyo, pp. 9-31.

1306 Custodio J.B., C.M. Palmeira, A.J. Moreno and K.B. Wallace, 1998. Acrylic acid induces the glutathione-independent
1307 mitochondrial permeability transition in vitro. Toxicol. Sci. 43, 19-27.

1308 Daecke, C., S. Schaller, J. Schaller and M. Goos, 1993. Contact urticaria from acrylic acid in Fixomull tape. Contact
1309 Dermatitis 29, 216-217, cited in PubMed database at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=PubMed.

1310 DeBethizy J.D., J.R. Udinsky, H.E. Scribner and C.B. Frederick, 1987. The disposition and metabolism of acrylic acid
1311 and ethyl acrylate in male Sprague-Dawley rats. Fund. Appl. Toxicol. 8, 549-561.

1312 DHHS, Department ofHealth and Human Services, 2004 . Toxmap. Specialized Information Services. National Institutes
1313 of Health, DHHS. Available on the internet at http://toxmap.nlm.nih.gov/toxmap/main/index.jsp. Accessed 7 March 2005.

1314 ECB, European Chemicals Bureau, 2002. European Union Risk Assessment Report. Acrylic acid. European Chemicals
1315 Bureau, Joint Research Centre, Ispra, Italy. Available on the internet at http://ecb.jrc.it.

1316 EPA, Environmental Protection Agency, 1988. Recommendations and Documentation of Biological Values for Use in

1317 Risk Assessment. U.S. Environmental Protection Agency, Washington, DC, 1988.

1318 EPA, Environmental Protection Agency, 2003. Acrylic acid. Integrated Risk Information System (IRIS). U.S.
1319 Environmental Protection Agency, Washington, DC, 2003. Available on the internet at http://www.epa.gov/iris/.

1320 Finney, D.J., 1977. Probit Analysis. Cambridge University Press, London, 1977.

1321 Fowler, J.F. Jr., 1990. Immediate contact hypersensitivity to acrylic acid. Dermatol. Clin. 8, 193-195, cited in PubMed
1322 database at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=PubMed.

1323 Frederick C.B., M.L. Bush, L.G. Lomax, K.A. Black, L. Finch, J.S. Kimbell, K.T. Morgan, R.P. Subramaniam, J.B.
1324 Morris and J.S. Ultman, 1998. Application of a hybrid computational fluid dynamics and physiologically based inhalation
1325 model for interspecies dosimetry extrapolation of acidic vapors in the upper airways. Toxicol. Appl. Pharmacol. 152, 211-
1326 231.

1327 Gage J.C., 1970. The subacute inhalation toxicity of 109 industrial chemicals. Brit. J. Ind. Med. 27, 1-18.

1328 Grudzinskii, U.J., 1988. Substantiation of single maximum permissible levels of acrylic acid in the air of populated regions
1329 (in Russian). Gig. I. Sanit. 9, 64-65.

1330 Hagan, J.V. and H.F. Emmons, 1988. Acrylic acid - acute inhalation toxicity study in rats. Unpublished report No. 87R-
1331 106, Rohm and Haas Company, Spring House, PA, USA, 1988.

1332 Harkema, 2001. Single Dose Inhalation Toxicity Study of Ethyl Acrylate And Acrylic Acid in Nonhuman Primates:
1333 Histopathology Report. Letter of Dr. Jack R. Harkema, Michigan State University, East Lansing to BAMM, dated
1334 November 26, 2001.

1335 Harkema, J.R., J.K. Lee, K.T. Morgan and C.B. Frederick, 1997. Olfactory Epithelial Injury in Monkeys After Acute
1336 Inhalation Exposure to Acrylic Monomers, The Toxicologist, 36, No. 1, Part 2, abstract No. 576.

1337 Hellman, T.M. and F.H. Small, 1974. Characterization of the odor properties of 101 petrochemicals using sensory
1338 methods. J. Air Pollution Control Assoc. 24, 979-982.

1339 Hellwig J., K. Deckardt and K.O. Freisberg, 1993. Subchronic and chronic studies of the effects of oral administration
1340 of acrylic acid to rats. Food Chem. Toxicol. 31, 1-18.

1341 Hellwig J., C. Gembardt and S.R. Murphy, 1997. Acrylic acid: two-generation reproduction toxicity study in Wistar rats
1342 with continous administration in the drinking water. Food Chem. Toxicol. 35, 859-868.

1343 HSDB, Hazardous Substances Databank. Accessed November 2004. NLM, U.S. National Library of Medicine. Available
1344 on the internet at http://toxnet.nlm.nih.gov.

1345 IUCLID (International Uniform Chemical Information Database) CD-ROM data base(1996), European Commission,
1346 European Chemicals Bureau, Joint Research Centre, Ispra, Italy.

1347 Izmerov N.F., I.V. Sanotsky andK.K. Sidorov, 1982. In: Toxicometric parameters of industrial toxic chemicals under
1348 single exposure, Centre of Internatinal Projects, GKNT, Moscow.

1349 Klimisch H.-J. and J. Hellwig, 1991. The prenatal inhalation toxicity of acrylic acid in rats. Fund. Appl. Toxicol. 16, 656-

666.

Kutzman R.S., G.J. Meyer and A.P. Wolff, 1982. The biodistribution and metabolic fate of 11C-acrylic acid in the rat after acute inhalation exposure or stomach intubation. J. Toxicol. Environ. Health 10, 969-979.

Lide, D.R. (Ed.), 1995. CRC Handbook of Chemistry and Physics. 76th Ed., CRC Press Inc., Boca Raton, FL, 1995-1996., pp. 3-290.

Lomax, L.G., D.W. Brown and C.B. Frederick, 1994. Regional histopathology of the mouse nasal cavity following two weeks of exposure to acrylic acid for either 6 or 22 h per day. Abstract presented at a Meeting on Nasal Toxicity and dosimetry of Inhaled Xenobiotics: Implications for human health, Durham, North Carolina, 20-22 September 1993, Inhal. Toxicol. 6 (Suppl.), 445-449.

Majka J., K. Knobloch and J. Stetkiewicz, 1974. Evaluation of acute and subacute toxicity of acrylic acid. Medycyna Pracy 25, 427-435, study description in English in ECB (2002).

McCarthy, K.L., W.C. Thomas, M.J. Aardema, J.L. Seymour, D.L. Putman, L.L. Yang, R.D. Curren, and R. Valencia R (1992). Genetic toxicology of acrylic acid. Food Chem. Toxicol. 30, 505-515.

McLaughlin J.E., J. Parno, F.M. Garner, J.J. Clary, W.C. Thomas and S.R. Murphy, 1995. Comparison of the maximum tolerated dose (MTD) dermal response in three strains of mice following repeated exposure to acrylic acid. Food Chem. Toxicol. 33, 507-513.

Miller R.R., J.A. Ayres, G.C. Jersey and M.J. McKenna, 1981. Inhalation toxicity of acrylic acid. Fund. Appl. Toxicol. 1, 271-277.

Morris J.B. and C.B. Frederick, 1995. Upper respiratory tract uptake of acrylate ester and acid vapors. Inh. Toxicol. 7, 557-574.

MSZW, Ministerie van Sociale Zaken en Werkgelegenheid, 1999. Nationale MAC-lijst 2000. Sdu Vitgeers, Den Haag, 1999.

Nachreiner, D.J. and D.E. Dodd, 1988. Acrylic acid: acute vapor inhalation toxicity test in rats. Bushy Run Research Center, Project Report 51-577, cited in BG Chemie, 1990.

Neeper-Bradley T.L., E.H. Fowler, I.M. Pritts and T.R. Tyler, 1997. Developmental toxicity study of inhaled acrylic acid in New Zealand White rabbits. Food Chem. Toxicol. 35, 869-880.

NIOSH, National Institute of Occupational Safety and Health, 1992. NIOSH Pocket Guide to Chemical Hazards. Http://www.cdc.gov/niosh/npg/npgd0013.html.

Renshaw, F.M., 1988. F.M. Renshaw, Rohm & Haas Company, personal communication cited in AIHA, 1991 and provided by fax by Dr. J.E. McLaughlin, Rohm & Haas Co. on 18 July 2000.

Rohm and Haas Co., 1995. Single Dose Inhalation Toxicity Study of Ethyl Acrylate (EA) And Acrylic Acid (AA). Unpublished study report, dated September 12, 1995.

Saillenfait A.M., P. Bonnet, F. Gallissot, J.C. Protois, A. Peltier and J.F. Fabriès, 1999. Relative developmental toxicities of acrylates in rats following inhalation exposure. Toxicol. Sci. 48, 240-254.

Silver, E.H., D.E. Leith and S.D. Murphy, 1981. Potentiation by triorthotolyl phosphate of acrylate ester-induced alterations in respiration. Toxicol. 22, 193-203.

Ten Berge W.F., A. Zwart and L.M. Appelman, 1986. Concentration-time mortality response relationship of irritant and systemically acting vapours and gases. J. Haz. Mat. 13, 301-309.

Union Carbide Co., 1977. Toxicological studies: acrylic acid glacial. Union Carbide Corporation, Industrial and Toxicology Department, unpublished report, cited in WHO (1997)

Van Doorn, R., M. Ruijten and T. Van Harreveld (2002). Guidance for the application of odor in chemical emergency response. Version 2.1, 29.08.2002.

Vodicka P., I. Gut and L. Vodickova, 1986. Effects of selected derivatives of acrylic acid in six-hour inhalation exposure of rats: elimination of thioethers and modification of glycemia. Pracovni Lékarstvi 38, 407-413.

Young, J.T., 1981. Histopathologic examination of the rat nasal cavity. Fund. Appl. Toxicol. 1, 309-312, cited in Frederick et al., 1998.

WHO WorldHealthOrganization, 1997. In: Environmental Health Criteria 191, Acrylic Acid, IPCS, International Programme on Chemical Safety; World Health Organization, Geneva.

References evaluated but not cited (for reasons indicated in brackets)

Andersen, M., R. Sarangapani, R. Gentry, H. Clewell, T. Covington and C.B. Frederick, 2000. Application of a hybrid CFD-PBPK nasal dosimetry model in an inhalation risk assessment: an example with acrylic acid. Toxicol. Sci. 57, 312-325. (Methodological consideration on how to derive reference concentrations for long exposure times by incorporating computational fluid dynamic models)

Morris, J.B. and C.B Frederick, 1995. Upper respiratory tract uptake of acrylate ester and acid vapors. Inhal. Toxicol. 7, 557-574. (Reports that deposition efficiencies in surgically isolated rat upper respiratory tract of acrylic acid and methacrylic acid are higher than that of the respective esters)

Granstrand P., L. Nylander-French and M. Holmström, 1998. Biomarkers of nasal inflammation in wood-surface coating industry workers. Am. J. Ind. Med. 33, 392-399. (Reports nasal inflammation in wood-curing workers exposed to mixtures of acrylate prepolymers and monomers, but not acrylic acid, wood dust and UV light)

Parker D. and J.L. Turk, 1983. Contact sensitivity to acrylate compounds in guinea pigs. Contact Dermatitis 9, 55-60. (The sensitization capacity is not relevant to derivation of AEGL values and thus was only summarized without citation of original studies)

Oberly R. and M.F. Tansey, 1985. LC50 values for rats acutely exposed to vapors of acrylic and methacrylic acid esters. J. Toxicol. Environ. Health 16, 811-822. (Comparison of LC_{50} for different esters of acrylic acid and methacrylic acid, but not the free acids)

De Pass L.R., M.D. Woodside, R.H. Garman and C.S. Weil, 1983. Subchronic and reproductive toxicology studies on acrylic acid in the drinking water of the rat. Drug Chem. Toxicol. 6, 1-20. (Oral study not providing usefull information to local toxic effects after inhalation)

Schwartz B.S., R.L. Doty, C. Moroe, R. Frye and S. Barker, 1989. Olfactory function in chemical workers exposed to acrylate and methacrylate vapors. Am. J. Public Health 79, 613-618. (A negative effect on olfactory function (smelling of different odors) was found in workers exposed to mixtures of acrylic acid, methacrylic acid, acrylates and methacrylates (exposures did not exceed current threshold limit values))

Singh, A.R., W.H. Lawrence and J. Autian, 1972. Embryonic-fetal toxicity and teratogenic effects of a group of methacrylate esters in rats. (Describes developmental toxic effects for acrylic acid and acrylates after repeated intraperitoneal injection)

1425 **APPENDIX A**

1426 **Time Scaling Calculations for AEGLs**

AEGL-1

Key study:	Renshaw (1988)
Toxicity endpoint:	Eye irritation was noted after exposure to concentrations of 4.5 - 23 ppm for 16 - 30 minutes (other workers exposed to the same concentration for up to 1.5 hours did not report any symptoms). Measurements were done by personal sampling. The lowest concentration of the given range, 4.5 ppm, was used for AEGL derivation.
Scaling:	Flat line for extrapolation to 8 hours, 4 hours, 1 hour, 30 minutes and 10 minutes
Uncertainty factors:	Combined uncertainty factor of 3 3 for intraspecies variability
Calculations:	
10-minute AEGL-1	C = 4.5 ppm 10-minute AEGL-1 = 4.5 ppm/3 = 1.5 ppm (4.5 mg/m^3)
30-minute AEGL-1	C = 4.5 ppm 30-minute AEGL-1 = 4.5 ppm/3 = 1.5 ppm (4.5 mg/m^3)
1-hour AEGL-1	C = 4.5 ppm 1-hour AEGL-1 = 4.5 ppm/3 = 1.5 ppm (4.5 mg/m^3)
4-hour AEGL-1	C = 4.5 ppm 4-hour AEGL-1 = 4.5 ppm/3 = 1.5 ppm (4.5 mg/m^3)
8-hour AEGL-1	C = 4.5 ppm 8-hour AEGL-1 = 4.5 ppm/3 = 1.5 ppm (4.5 mg/m^3)

AEGL-2

Key study:	Frederick et al. (1998); Rohm and Haas Co. (1995); Harkema (2001); Harkema et al. (1997)
Toxicity endpoint:	Single exposure of monkeys and rats to 75 ppm acrylic acid for 3 and 6 hours resulted in histopathological changes of the nasal epithelium (olfactory epithelial cell degeneration, sustentacular cell necrosis; severity of effects increased with exposure time). Since the changes were more severe at 6 hours and considered irreversible, the exposure for 3 hours to 75 ppm was used as a basis for AEGL derivation.
Scaling:	$C^3 * t = k$ for extrapolation to 1 hours and 30 and 10 minutes $k = 75^3$ ppm^3 * 180 min = $7.59 * 10^7$ ppm^3 min $C^1 * t = k$ for extrapolation to 4 and 8 hours $k = 75^1$ ppm * 180 min = $1.35 * 10^4$ ppm min
Uncertainty factors:	Combined uncertainty factor of 3 1 for interspecies variability 3 for intraspecies variability
Calculations:	
10-minute AEGL-2	C^3 x 10 min = $7.59 * 10^7$ ppm^3 min C = 197 ppm 30-min AEGL-2 = 197 ppm/3 = 66 ppm (200 mg/m^3)
30-minute AEGL-2	C^3 x 30 min = $7.59 * 10^7$ ppm^3 min C = 136 ppm 30-min AEGL-2 = 136 ppm/3 = 45 ppm (140 mg/m^3)
1-hour AEGL-2	C^3 x 60 min = $7.59 * 10^7$ ppm^3 min C = 108 ppm 1-hour AEGL-2 = 108 ppm/3 = 36 ppm (110 mg/m^3)
4-hour AEGL-2	C^1 x 240 min = $1.35 * 10^4$ ppm min C = 56 ppm 4-hour AEGL-2 = 56 ppm/3 = 19 ppm (56 mg/m^3)
8-hour AEGL-2	C^1 x 480 min = $1.35 * 10^4$ ppm min C = 28 ppm 8-hour AEGL-2 = 28 ppm/3 = 9.4 ppm (28 mg/m^3)

AEGL-3

Key study: BASF (1980)

Toxicity endpoint: Exposure of 20 rats at 1705 ppm acrylic acid vapor for 4 hours did not result in deaths.

Probit Calculation: Using Probit analysis, maximum likelihood estimates for LC_{50} and LC_{01} values as well as the lower 95 % confidence limit of LC_{05} values were calculated for 10 min, 30 min, 1 h, 2 h, 4 h and 8 h (see Appendix B). MLE of LC_{01} values, which were close to the 95 % C.I. of LC_{05} values were used for the derivation of AEGL-3 values.

Scaling:
$C^3 * t = k$ for extrapolation to 1 hours and 30 minutes
$k = 1705^3$ ppm^3 * 240 min = $1.19 * 10^{12}$ ppm^3 min
$C^1 * t = k$ for extrapolation to 8 hours
$k = 1705^1$ ppm * 240 min = $4.09 * 10^5$ ppm min

Uncertainty factors: Combined uncertainty factor of 10
3 for interspecies variability
3 for intraspecies variability

Calculations:

10-minute AEGL-3: 10-min AEGL-3 = 30-min AEGL-3 = 340 ppm (1000 mg/m^3)

30-minute AEGL-3:
$C^3 * 30$ min = $4.333 * 1.19 * 10^{12}$ ppm^3 min
C = 3410 ppm
30-min AEGL-3 = 3410 ppm/10 = 340 ppm (1000 mg/m^3)

1-hour AEGL-3:
$C^3 * 60$ min = $1.19 * 10^{12}$ ppm^3 min
C = 2707 ppm
1-hour AEGL-3 = 2707 ppm/10 = 270 ppm (810 mg/m^3)

4-hour AEGL-3: 4-hour AEGL-3 = 1705 ppm/10 = 170 ppm (510 mg/m^3)

8-hour AEGL-3:
$C^1 * 480$ min = $4.09 * 10^5$ ppm min
C = 853 ppm
8-hour AEGL-3 = 853 ppm/10 = 85 ppm (260 mg/m^3)

1507 **APPENDIX B**

1508 **Probit Analysis**

Probit Analysis of Rat Mortality Data

Study providing experimental data: Hagan and Emmons (1988)

Data: Mortality data for rats exposed whole-body to acrylic acid aerosols for 30, 60 or 120 minutes, as shown in Table 15 were used for analysis. Since the authors reported the acrylic acid concentration in ppm, probit analysis was done using the ppm figures.

The authors used Probit analysis on the data for whole-body exposure to acrylic acid aerosol and calculated maximum likelihood estimates for LC_{50} and LC_{01} values as shown in Table 16. Since some inconsistencies occurred in the summary tables of the study (see footnotes to Table 15), the values were recalculated as shown in Table 16.

TABLE 15: LETHAL EFFECTS OF ACRYLIC ACID IN RATS AFTER ACUTE INHALATION EXPOSURE; adopted from Hagan and Emmons (1988)

Exposure				Number of rats exposed			Number of dead rats		
Physical state of acrylic acid	Condition	Time (min)	Analytical concentration mg/m³ (equivalent in ppm)	Male	Female	Total	Male	Female	Total
aerosol	whole-body	30	975 (2925)	5	5	10	0	0	0
aerosol	whole-body	30	1151 (3452)	5	5	10	2	0	2
aerosol	whole-body	30	1218 (3654)	5	5	10	1	0	1
aerosol	whole-body	30	1318 (3954) [a]	5	5	10	3	0	3
aerosol	whole-body	30	1342 (4025)	5	5	10	2	0	2
aerosol	whole-body	30	1359 (4076)	5	5	10	2	1	3
aerosol	whole-body	30	1461 (4384)	5	5	10	2	0	2
aerosol	whole-body	30	1480 (4441) [a]	5	5	10	0	0	0
aerosol	whole-body	30	1562 (4687)	5	5	10	2	2 [b]	4
aerosol	whole-body	30	1572 /(4715)	5	5	10	1	0	1
aerosol	whole-body	60	904 (2713)	3	3	6	2	2	4
aerosol	whole-body	60	922 (2767)	6	6	12	0	1	1
aerosol	whole-body	60	924 (2773)	6	6	12	0	0	0

Exposure				Number of rats exposed			Number of dead rats		
Physical state of acrylic acid	Condition	Time (min)	Analytical concentration mg/m³ (equivalent in ppm)	Male	Female	Total	Male	Female	Total
aerosol	whole-body	60	949 (2848)	6	6	12	1	0	1
aerosol	whole-body	60	1011 (3032)	6	6	12	1	0	1
aerosol	whole-body	60	1066 (3197)	6	6	12	1 [b]	0	1
aerosol	whole-body	60	1403 (4208)	3	3	6	2	3	5
aerosol	whole-body	120	408 (1224) [a]	5	5	10	0	0	0
aerosol	whole-body	120	788 (2363) [a]	5	5	10	5	3	8
aerosol	whole-body	120	880 (2641)	4	4	8	3	0	3
aerosol	whole-body	120	951 (2852)	6	6	12	2	3	5
aerosol	whole-body	120	971 (2913)	6	6	12	3	2	5
aerosol	whole-body	120	1102 (3305)	4	4	8	4	3	7
aerosol	whole-body	120	1138 (3413)	5	5	10	5	5	10
aerosol	nose-only	30	252 (757)	2	3	5	0	0	0
aerosol	nose-only	30	350 (1051)	3	2	5	0	0	0
aerosol	nose-only	30	358 (1075)	3	2	5	0	0	0
aerosol	nose-only	30	398 (1195)	2	3	5	0	0	0
aerosol	nose-only	30	572 (1717)	5	5	10	0	0	0
aerosol	nose-only	30	971 (2912)	5	5	10	0	0	0
aerosol	nose-only	30	1164 (3493)	5	5	10	0	0	0
aerosol	nose-only	30	950 (3850)	5	5	10	0	0	0
aerosol	nose-only	60	363 (1088)	2	3	5	0	0	0
aerosol	nose-only	60	408 (1225)	3	2	5	0	0	0
aerosol	nose-only	60	733 (2200)	3	2	5	0	0	0
aerosol	nose-only	60	1076 (3228)	3	2	5	0	0	0
aerosol	nose-only	60	1189 (3568)	3	2	5	0	0	0

Exposure				Number of rats exposed			Number of dead rats		
Physical state of acrylic acid	Condition	Time (min)	Analytical concentration mg/m³ (equivalent in ppm)	Male	Female	Total	Male	Female	Total
aerosol	nose-only	60	1294 (3882)	3	2	5	0	0	0
aerosol	nose-only	120	408 (1223)	5	5	10	0	0	0
aerosol	nose-only	120	787 (2362)	2	2	4	0	0	0
aerosol	nose-only	120	977 (2931)	2	2	4	0	0	0
aerosol	nose-only	120	1171 (3512)	2	2	4	0	0	0
aerosol	nose-only	120	1307 (3922)	2	2	4	0	0	0
vapor	whole-body	60	928	10	10	20	0	0	0
vapor	whole-body	60	932	5	5	10	0	0	0
vapor	whole-body	60	1165	10	10	20	0	0	0
vapor	whole-body	60	1439	5	5	10	0	0	0
vapor	whole-body	60	2142	5	5	10	0	0	0

[a] for these groups, slightly different concentrations (3943, 4411, 1223 and 2362 ppm, respectively) were given in several tables, but not consistently throughout the study; used here were the calculated mean values from the concentrations given for individual sorbent tube measurements in Appendix B1 of the study.

[b] these values were given differently in " Summary of Mortality", Tables 7 A and 7 B, respectively, of the report; used here were the values given in the post-exposure observations table for the respective concentration. (Tables 3 R and 4 L of the study).

Probit analysis: According to ten Berge et al. (Ten Berge et al., 1986) based on Finney (1977) using a computer program (Ten Berge et al., 1986; kindly provided by the Dr. ten Berge, Heerlen, Netherlands)

Probit equation: $Y = b_0 + b_1 \ln C + b_2 \ln T$ with b_0, b_1, b_2 regression coefficients; C exposure concentration; T exposure time

Calculation of the time scaling exponent n: Rearrangement of the Probit equation into the following equation:

$Y = b_0 + b_2 \ln (C^n \times T)$ with $n = b_1/b_2$

allows calculation of n from the maximum likelihood estimates of regression coefficients produced by Probit analysis. Regression coefficients and n were calculated according to Ten Berge et al. (1986) as:

b0 = -27.25
b1 = 3.07
b2 = 1.68
n = 1.8

Hagan and Emmons (1988) calculated an n of 1.7.

LC_{50} values reported: The following calculations were given by Hagan and Emmons (1988) using Probit analysis:

TABLE 16: RESULTS OF PROBIT CALCULATIONS BY HAGAN AND EMMONS (1988)

Exposure time	LC_{50} (ppm)	LC_{01} (ppm)
30 min	5565 (1855 mg/m³)	3005 (1002 mg/m³)
1 h	3745 (1248 mg/m³)	2020 (673 mg/m³)
2 h	2520 (840 mg/m³)	1360 (453 mg/m³)

Calculations: The following maximum likelihood estimates (MLE) for LC_{50} (MLE_{50}) and LC_{01} (MLE_{01}) values and the lower 95 % confidence limit for the LC_{05} value (BMC_{05}) were calculated using the computer program by Ten Berge:

TABLE 17: RESULTS OF MLE_{50}, MLE_{01} and BMC_{05} CALCULATIONS

Exposure time	All animals			Male animals			Female animals		
	MLE_{50} (ppm)	MLE_{01} (ppm)	BMC_{05} (ppm)	MLE_{50} (ppm)	MLE_{01} (ppm)	BMC_{05} (ppm)	MLE_{50} (ppm)	MLE_{01} (ppm)	BMC_{05} (ppm)
10 min	10260	4810	4469	9093	3946	2461	11680	6309	4930
30 min	5652	2638	2374	5122	2223	945	6169	3333	2216
1 h	3850	1806	1340	3566	1548	423	4125	2228	352
2 h	2636	1236	715	2483	1078	179	2758	1490	41
4 h	1804	846	375	1729	750	74	1844	996	4.6
8 h	1235	579	196	1204	522	30	1233	666	0.52

1619 **APPENDIX C**

1620 **Level of Distinct Odor Awareness**

Derivation of the Level of Distinct Odor Awareness (LOA)

The level of distinct odor awareness (LOA) represents the concentration above which it is predicted that more than half of the exposed population will experience at least a distinct odor intensity, about 10 % of the population will experience a strong odor intensity. The LOA should help chemical emergency responders in assessing the public awareness of the exposure due to odor perception. The LOA derivation follows the guidance given by van Doorn et al. (2002).

For derivation of the odor detection threshold (OT_{50}), a study is available in which the odor threshold for the reference chemical n-butanol (odor detection threshold 0.04 ppm) has also been determined:

Hellman and Small (1974):
odor detection threshold for acrylic acid: 0.094 ppm
odor detection threshold for n-butanol: 0.3 ppm
corrected odor detection threshold (OT_{50}) for acrylic acid: 0.094 ppm * 0.04 ppm / 0.3 ppm = 0.013 ppm

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

$I = k_w * \log (C / OT_{50}) + 0.5$

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

$3 = 2.33 * \log (C / 0.013) + 0.5$ which can be rearranged to

$\log (C / 0.013) = (3 - 0.5) / 2.33 = 1.07$ and results in

$C = (10^{1.07}) * 0.013 = 11.8 * 0.013 = 0.15$ ppm

The resulting concentration is multiplied by an empirical field correction factor. It takes into account that in every day life factors, such as sex, age, sleep, smoking, upper airway infections and allergy as well as distraction, increase the odor detection threshold by a factor of 4. In addition, it takes into account that odor perception is very fast (about 5 seconds) which leads to the perception of concentration peaks. Based on the current knowledge, a factor of 1/3 is applied to adjust for peak exposure. Adjustment for distraction and peak exposure lead to a correction factor of 4 / 3 = 1.33

LOA = C * 1.33 = 0.15 ppm * 1.33 = 0.20 ppm

The LOA for acrylic acid is 0.20 ppm.

1648 **APPENDIX D**

1649 **Derivation Summary for Acrylic Acid AEGLs**

ACUTE EXPOSURE GUIDELINES FOR ACRYLIC ACID
(CAS NO. 79-10-7)

AEGL-1 VALUES				
10 minutes	30 minutes	1 hour	4 hours	8 hours
1.5 ppm	1.5 ppm	1.5 ppm	1.5 ppm	1.5 ppm

Reference: Renshaw, F.M., 1988. F.M. Renshaw, Rohm & Haas Company, *personal communication* cited in *Emergency Response Planning Guidelines*, Acrylic acid. AIHA, American Industrial Hygiene Association, Akron, OH, USA, 1991 and provided by fax by Dr. J.E. McLaughlin, Rohm & Haas Co. on 18 July 2000.

Test Species/Strain/Number: a) human subjects / not applicable / not stated exactly, <11

Exposure Route/Concentrations/Durations:
Inhalation / 0.3 - 1.6 ppm for 30 minutes to 2.5 hours; 4.5 - 23 ppm for 16 - 30 minutes; 63 ppm for 10 minutes

Effects:
Slight eye irritation was experienced at exposure to 0.3 - 1.6 ppm for 30 minutes to 2.5 hours and eye irritation was noted at exposure to 4.5 - 23 ppm for 16 - 30 minutes. Exposure to 63 ppm for 10 minutes resulted in slight throat irritation in one individual.

Endpoint/Concentration/Rationale:
Irritation is the most relevant endpoint for deriving of AEGL-1 values. The data on irritative effects in humans by Renshaw (1988; personal communication) was used as key study because human data were considered most relevant for AEGL derivation. Renshaw (1988) reported that slight eye irritation was experienced at 0.3 - 1.6 ppm for 30 minutes to 2.5 hours. However, the exposure concentrations were measured by area sampling, which is unlikely to accurately reflect the breathing zone concentrations to which the workers were exposed. Therefore, the concentration of 4.5 ppm, which was the lowest personal sampling measurement at which eye irritation was observed, was used as a point of departure for AEGL-1 derivation.
Since the Renshaw (1988) study has obvious shortcomings, e.g. the limited number of subjects and lack of exact characterization of exposure time-exposure concentration combinations, the study by Lomax et al. (1994) investigating histopathological alterations in mice was used as supportive evidence (see Data Adequacy).

Uncertainty Factors/Rationale:
Total uncertainty factor: 1
Interspecies: not applicable
Intraspecies: 3 - because the intraspecies uncertainty factor is used to compensate for both, toxicokinetic and toxicodynamic differences between individuals. For local effects, the toxicokinetic differences between individuals are usually much smaller when compared to systemic effects. Therefore, a reduced uncertainty factor was retained to account for toxicodynamic differences between individuals.

Modifying Factor: Not applicable
Animal to Human Dosimetric Adjustment: Not applicable
Time Scaling: Since very slight irritative effects depend primarily on the actual exposure concentration and not much on exposure time, it was considered adequate to use the same exposure concentration for all exposure durations between 10 minutes and 8 hours (i.e. a flat line was used for time scaling).
Data Adequacy: The derived values are supported by the study of Lomax et al. (1994) investigating histopathological alterations in mice: an exposure to 5 ppm for 6 hours was considered the threshold for irritation in mice because 1) no histopathological alterations of the nasal mucosa were observed in experiments using repeated exposure to 5 ppm for 6 hours/day for 2 weeks, while atrophy, necrosis and desquamation of olfactory epithelium were observed after exposure to 5 ppm for 22 hours/day for 2 weeks, 2) olfactory lesions were observed after exposure to higher concentrations of acrylic acid at 25 ppm for 4.4 hours/day for 2 weeks permanent replacement of olfactory epithelium with respiratory epithelium was observed after exposure to 25 ppm for 22 hours/day for 2 weeks, but not after exposure to 25 ppm for 6 hours/day or 5 ppm for 22 hours/day. Application of a total uncertainty factor of 3 (see derivation of AEGL-2 for uncertainty factor rationale) would result in an exposure concentration of 1.7 ppm, which supports the level of 1.5 ppm derived from human observations. Since human data were considered most relevant for AEGL derivation, a report on irritation during occupational exposure was used for derivation of AEGL-1 values, although the report format as well as the data had several shortcomings, e.g. the limited number of subjects and lack of exact characterization of exposure time and exposure concentration.

ACUTE EXPOSURE GUIDELINES FOR ACRYLIC ACID (CAS NO. 79-10-7)

AEGL-2 VALUES				
10 minutes	30 minutes	1 hour	4 hours	8 hours
66 ppm	45 ppm	36 ppm	19 ppm	9.4 ppm

Reference: Rohm and Haas Co., 1995. Single Dose Inhalation Toxicity Study of Ethyl Acrylate (EA) And Acrylic Acid (AA). Unpublished study report, dated September 12, 1995; Harkema, 2001. Single Dose Inhalation Toxicity Study of Ethyl Acrylate And Acrylic Acid in Nonhuman Primates: Histopathology Report. Letter of Dr. Jack R. Harkema, Michigan State University, East Lansing to BAMM, dated November 26, 2001; Harkema, J.R., J.K. Lee, K.T. Morgan and C.B. Frederick, 1997. Olfactory Epithelial Injury in Monkeys After Acute Inhalation Exposure to Acrylic Monomers, The Toxicologist, 36, No. 1, Part 2, abstract No. 576.

Test Species/Strain/Sex/Number: monkey / cynomolgus / mixed, males and females / 3/dose group

Exposure Route/Concentrations/Durations:
Monkeys: inhalation / 0 and 75 ppm / 3 and 6 hours; additional groups were exposed to 75 ppm ethyl acrylate for 3 and 6 hours

Effects:
Monkeys: no abnormal clinical observations were recorded. Nasal lesions were restricted to the olfactory epithelium lining the dorsal medial meatus at the level of the maxillary sinus in the proximal aspect of both nasal passages. The morphologic alterations consistently found in all acrylic acid-exposed monkeys were focal degeneration and necrosis of the olfactory epithelium with mild inflammation (influx of neutrophils and lymphocytes). No exposure-related lesions were present in the nasal respiratory, transitional or squamous epithelium in any of the monkeys examined. The Bowman's glands and olfactory nerves in the lamina propria underlying the degenerating olfactory epithelium were also histologically normal. The extent and severity of the lesions were greater in monkeys exposed for 6 hours compared to those exposed for 3 hours. The character, severity and distribution of the morphologic alterations induced by acrylic acid and ethyl acrylate were similar.

Endpoint/Concentration/Rationale: Acrylic acid is a highly irritating chemical. Human data for effects more severe than odor recognition and slight to moderate irritative effects were not available. In studies in monkeys, rabbits, rats and mice, histopathological alteration of the nasal mucosa consistently was a more sensitive toxicological endpoint than the appearance of clinical signs of irritation. It was therefore considered appropriate to use the single inhalation exposure studies in monkeys (Rohm and Haas Co., 1995; Harkema, 2001; Harkema et al., 1997) as key study for the derivation of AEGL-2 values. Exposure to 75 ppm acrylic acid for 6 hours resulted in severe histopathological changes of the nasal epithelium (olfactory epithelial cell degeneration, sustentacular cell necrosis), while exposure for 3 hours resulted in less severe changes and a lesser area of the olfactory epithelium was affected. No obvious clinical symptoms were reported. The regeneration of the olfactory epithelium will be incomplete if olfactory stem cells in the basal cell layer are damaged. In this case, olfactory epithelium is permanently replaced by non-functional respiratory epithelium. Loss of olfactory epithelium could decrease the individuals sensitivity to odor (increase odor thresholds and reduce the number of different odors that can be recognized). The NAC/AEGL committee evaluated the histological damage (see photographs in Harkema, 2001 in Figure 1) and considered the effects after the 6-hour exposure as severe and probably irreversible, while the changes after the 3-hour exposure were considered reversible. Therefore, AEGL-2 values were derived on the basis of a 3-hour exposure to 75 ppm. The studies in monkeys are supported by a single exposure study in rats, in which exposure to 75 ppm for 3 and 6 hours resulted in olfactory epithelial cell degeneration and sustentacular cell necrosis (Frederick et al., 1998). The use of an exposure concentration of 75 ppm as the basis for the derivation of AEGL-2 values is supported by the observation that 77 ppm was the NOEL for blepharospasm in rabbits (Neeper-Bradley et al., 1997). Blepharospasm (involuntary eyelid closure) may be interpreted as a sign of impaired ability to escape. Similarly, eye lid closure in rats was found during a 6-hour exposure at 218 ppm, but not at 114 ppm (Klimisch and Hellwig, 1991).
Uncertainty Factors/Rationale: Total uncertainty factor: 3 Interspecies: 1 - For the toxicokinetic component a factor of 1 was used because a monkey inhalation study was used and because acrylic acid is a locally acting irritant not requiring metabolic activation. The toxicodynamic component of the uncertainty factor was reduced to 1 because single inhalation exposure of monkeys resulted in similar olfactory lesions than in rats (Frederick et al., 1998). Intraspecies: 3 - because tissue damage of the nasal mucosa by local cytotoxicity was considered not to vary considerably between individuals.
Modifying Factor: Not applicable
Animal to Human Dosimetric Adjustment: Not applicable, local irritative effect

Time Scaling: Time scaling using the equation $C^n \times t = k$ was carried out to derive exposure duration-specific values. Due to lack of a definitive data set, a default for n of 3 was used in the exponential function for extrapolation from the experimental period (3 hours) to shorter exposure periods and a default for n of 1 was used for extrapolation to longer exposure periods. The time extrapolation was continued to the 10-minute period because the resulting 10-minute AEGL-2 value was still below the threshold for blepharospasm in rabbits.
Data Adequacy: The overall quality of the key studies is medium to high. No data on severe irritation effects in humans are available. The derived values are supported by the personal communication by Renshaw (1988) who reported that exposure of humans to concentrations of 4.5 - 23 ppm for 16 - 30 minutes resulted in eye irritation, but not in more severe effects.

ACUTE EXPOSURE GUIDELINES FOR ACRYLIC ACID (CAS NO. 79-10-7)

AEGL-3 VALUES				
10 minutes	30 minutes	1 hour	4 hours	8 hours
340 ppm	340 ppm	270 ppm	170 ppm	85 ppm

Reference: BASF AG, 1980. Bestimmung der akuten Inhalationstoxizität LC_{50} von Acrylsäure rein als Dampf bei 4stündiger Exposition an Sprague-Dawley-Ratten. Unpublished report, BASF AG, Ludwigshafen, Germany, 1980.

Test Species/Strain/Sex/Number: rat / Sprague-dawley / 10 male and 10 female perconcentration

Exposure Route/Concentrations/Durations: Whole-body inhalation exposure to acrylic acid vapor / 1705 or 1415 ppm / 4 hours

Effects:
No deaths occurred during the 14-day observation period. During and up to 4 days after the exposure, the following symptoms were observed: clear to slightly reddish discharge from eyes and nose, salivation, eye lid closure, dyspnea and rough/clotted hair. No symptoms were observed after 5 days or later.

Endpoint/Concentration/Rationale:
For the derivation of AEGL-3 values, the animal studies using vapor exposure were considered more relevant than the aerosol studies, because for emergency situations a vapor exposure was considered more likely than an aerosol exposure. The derivation was based on the study by BASF (1980) reporting no deaths of rats after exposure to 1705 ppm for 4 hours. This result is supported by the study of Hagan and Emmons (1988) which found no lethality in rats at 2142 ppm for 1 hour. While these studies did not report a LOEL for vapor lethality, the results of the study by Carpenter et al. (1974) indicated that a level of about 4000 ppm for 4 hours was clearly above the LOEL.

Uncertainty Factors/Rationale:
Total uncertainty factor: 10
Interspecies: 3
Intraspecies: 3
acrylic acid causes lethal effects by local tissue destruction in the lung with limited influence of systemic distribution, metabolism and elimination. Therefore, the toxicokinetic differences do not vary considerably within and between species. Also the toxicodynamic variability within and between species is considered to be limited because acrylic acid causes cell necrosis by reducing the pH and destroying mitochondria, which are unlikely to be influenced by species-specific differences. Overall these arguments support reduced interspecies and intraspecies uncertainty factors of 3 each.

Modifying Factor: Not applicable

Animal to Human Dosimetric Adjustment: Insufficient data

Time Scaling: Time scaling using the equation $C^n \times t = k$ was carried out to derive exposure duration-specific values. Due to lack of a definitive data set, a default for n of 3 was used in the exponential function for extrapolation from the experimental period (4 hours) to shorter exposure periods and a default for n of 1 was used for extrapolation to longer exposure periods. For the 10-minute AEGL-3 the 30-minute value was applied because the derivation of AEGL values was based on a long experimental exposure period and no supporting studies using short exposure periods were available for characterizing the concentration-time-response relationship.
Data Adequacy: Although the key study did not report a LOEL for lethality, the derivation basis was supported by other studies in rats. Adequate lethality data for other animal species are lacking.