1	INTERIM 1: 08/2007
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6	BUTYL ACRYLATE
7	(CAS Reg. No. 141-32-2)
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12	INTERIM ACUTE EXPOSURE GUIDELINE LEVELS
13	(AEGLs)
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17	For
18	NAS/COT Subcommittee for AEGLs
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29 30 31 32 33 34	Oak Ridge National Laboratory, managed by UT-Battelle, LLC., for the U.S. Dept. of Energy under contract DE-AC05-00OR22725

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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. Three levels — AEGL-1,
 AEGL-2 and AEGL-3 — are developed for each of five exposure periods (10 and 30 minutes, 1
 hour, 4 hours, and 8 hours) and are distinguished by varying degrees of severity of toxic effects.
 The three AEGLs are defined as follows:

AEGL-1 is the airborne concentration (expressed as parts per million or milligrams per
 cubic meter [ppm or mg/m<sup>3</sup>]) 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<sup>3</sup>) 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<sup>3</sup>) of a substance above which it is predicted that the general population, including susceptible individuals, could experience life-threatening health effects or death.

30 Airborne concentrations below the AEGL-1 represent exposure levels that could produce 31 mild and progressively increasing but transient and nondisabling odor, taste, and sensory 32 irritation or certain asymptomatic, non-sensory effects. With increasing airborne concentrations 33 above each AEGL, there is a progressive increase in the likelihood of occurrence and the 34 severity of effects described for each corresponding AEGL. Although the AEGL values 35 represent threshold levels for the general public, including susceptible subpopulations, such as 36 infants, children, the elderly, persons with asthma, and those with other illnesses, it is recognized 37 that individuals, subject to unique or idiosyncratic responses, could experience the effects 38 described at concentrations below the corresponding AEGL.

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### SUMMARY

n-Butyl acrylate (BA) is a flammable liquid that is slightly soluble in water and miscible with
most organic solvents (ECETOC 1994). BA is an acrylate monomer used to prepare
homopolymers and copolymers with other monomers. The chemical reacts readily with
numerous organic and inorganic compounds so it is used as a starting product for chemical
synthesis (ECETOC 1994). BA is also used in surface coatings, leather finishes, adhesives,
paper coatings, fibers, plastics, and resins (Bisesi 2001; ECETOC 1994). BA is the largestvolume production commodity acrylate ester (Lacson et al. 2001).

Few data were available concerning human exposures to BA and none of the data were suitable for derivation of any AEGL values. Worker monitoring studies reported up to 10.5 ppm as a short-term exposure average concentration (Rohm and Haas, Co. 1987), but no health effects were included.

16 Few animal data were available for derivation of AEGL-1 values. In a developmental 17 toxicity study (Rohm and Haas Co. 1992; Merkle and Klimisch 1983), no clinical signs were 18 reported for rats exposed repeatedly to 25 ppm. Clinical signs reported in other studies were too 19 severe for AEGL-1 (concentrations of 135 ppm and higher resulted in eye and nasal discharge, 20 dyspnea, gasping). The no-effect level for respiratory depression in mice was 30 ppm 21 (Kirkpatrick 2003). A concentration of 25 ppm was chosen as a concentration below AEGL-1 22 effects. Extrapolations were not performed. A total uncertainty factor of 3 was used including a 23 1 for interspecies extrapolation and 3 for intraspecies extrapolation. Use of greater uncertainty 24 factors was not necessary because the mechanism of irritation is not expected to differ between 25 individuals.

27 The best animal data relevant to derivation of AEGL-2 are from a subchronic study in which 28 male and female Sprague-Dawley rats (n = 20) were exposed to 0, 21, 108, 211, or 546 ppm BA 29 for 6 hours/day, 5 days/week, for 13 weeks (Klimisch et al. 1978). At the highest concentration, 30 mortality, reduced body weight gain, and clinical signs of bloody ocular and nasal discharges 31 and rhinitis were observed; marked lesions of the respiratory tract were found at necropsy. At 32 211 ppm all animals survived but had reduced body weight gain and showed bloody ocular and 33 nasal discharges; slight edema and erosion of the nasal mucosa were observed histologically in a 34 few individuals. Slight decreases in weight gain but no histopathological changes were observed 35 in animals exposed to 108 ppm. The NOAEL was 21 ppm. In other studies, no maternal or developmental toxicity was seen in rats repeatedly exposed to 25 or 100 ppm during gestation 36 37 (Rohm and Haas Co. 1992; Merkle and Klimisch 1983; Saillenfait et al. 1999).

39 The concentration of 211 ppm for 6 hours/day was used as the basis for AEGL-2 derivation. 40 Values were scaled using the equation  $C^n \times t = k$  where n ranges from 0.8 to 3.5 (ten Berge et al. 41 1986). In the absence of an empirically derived, chemical-specific exponent, scaling was performed using n = 3 for extrapolating to the 30-minute and 1- and 4-hour time points and n = 142 43 for the 8-hour time point. A total uncertainty factor of 3 was used including 1 for interspecies 44 extrapolation and 3 for intraspecies extrapolation. Use of greater uncertainty factors was not 45 necessary because the mechanism of irritation is not expected to differ between individuals. According to Section 2.7 of the Standing Operating Procedures for Developing Acute Exposure 46

Guideline Levels for Hazardous Chemicals (NRC 2001), 10-minute values are not to be scaled 2 from an experimental exposure time of  $\geq$ 4 hours. Therefore, the 30-minute AEGL-2 value was also adopted as the 10-minute value.

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5 The best animal data relevant to derivation of AEGL-3 values is the Oberly and Tansy (1985) 4-hour LC<sub>50</sub> study in rats. This was a well conducted study with a wide range of 6 7 analytically determined exposure concentrations. Clinical signs of irritation were observed in 8 animals during exposure and death was attributed to cardiopulmonary collapse. The calculated 4-hour  $LC_{50}$  value was 2730 ppm. From these data a 4-hour  $BMCL_{05}$  value was calculated by a 9 log-probit analysis using US EPA Benchmark Dose Software version 1.3.2. The resulting 4-10 hour BMCL<sub>05</sub> of 1652 ppm was used to derive the 30-minute, and 1-, 4- and 8-hour AEGL-3 11 values. Values were scaled using the equation  $C^n \times t = k$  where n ranges from 0.8 to 3.5 (ten 12 13 Berge et al. 1986). A value of n = 1.3 was calculated by combining 1- and 4- hour LC<sub>50</sub> data sets 14 from ethyl acrylate (NAC 2004) in a 3-dimensional probit analysis (Zwart et al. 1992). Use of 15 an n value calculated from a structurally related chemical was considered appropriate because the mechanism leading to death is similar for both compounds. A total uncertainty factor of 10 16 17 was used including 3 for interspecies extrapolation and 3 for intraspecies extrapolation. Use of 18 greater uncertainty factors was not necessary because the mechanism of toxicity (local damage 19 in the lower airways/lungs) is not expected to differ between individuals. According to Section 20 2.7 of the Standing Operating Procedures for Developing Acute Exposure Guideline Levels for 21 Hazardous Chemicals (NRC 2001), 10-minute values are not to be scaled from an experimental 22 exposure time of  $\geq$ 4 hours. Therefore, the 30-minute AEGL-3 value was also adopted as the 10-23 minute value. 24

The reported odor threshold concentrations are not sufficiently qualified to derive a level of odor awareness (LOA) according to van Doorn et al. (2002).

	Summary of AEGL Values for Butyl Acrylate								
Classification	10-minute	30-minute	1-hour	4-hour	8-hour	Endpoint (Reference)			
AEGL-1 (Nondisabling)	8.3 ppm (44 mg/m <sup>3</sup> )	8.3 ppm (44 mg/m <sup>3</sup> )	8.3 ppm (44 mg/m <sup>3</sup> )	8.3 ppm (44 mg/m <sup>3</sup> )	8.3 ppm (44 mg/m <sup>3</sup> )	No clinical signs with repeated exposures (Rohm and Haas Co. 1992; Merkle and Klimisch 1983)			
AEGL–2 (Disabling)	160 ppm (850 mg/m <sup>3</sup> )	160 ppm (850 mg/m <sup>3</sup> )	130 ppm (690 mg/m <sup>3</sup> )	81 ppm (430 mg/m <sup>3</sup> )	53 ppm (280 mg/m <sup>3</sup> )	Clinical signs and histopathology with repeated exposure (Klimisch et al. 1978)			
AEGL–3 (Lethal)	820 ppm (4400 mg/m <sup>3</sup> )	820 ppm (4400 mg/m <sup>3</sup> )	480 ppm (2600 mg/m <sup>3</sup> )	170 ppm (906 mg/m <sup>3</sup> )	97 ppm (520 mg/m <sup>3</sup> )	Calculated BMCL <sub>05</sub> from LC <sub>50</sub> data (Oberly and Tansy 1985)			

The calculated values are listed in the tables below.

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### 1. INTRODUCTION

 F

n-Butyl acrylate (BA) is a flammable liquid that is slightly soluble in water and miscible with most organic solvents (ECETOC 1994). BA is an acrylate monomer used to prepare homopolymers and copolymers with other monomers. The chemical reacts readily with numerous organic and inorganic compounds so it is used as a starting product for chemical synthesis (ECETOC 1994). BA is also used in surface coatings, leather finishes, adhesives, paper coatings, fibers, plastics, and resins (Bisesi 2001; ECETOC 1994).

BA is the largest-volume production commodity acrylate ester (Lacson et al. 2001). In 1993, the United States produced 340 million kg BA (HSDB 2004) which increased to >454 million kg in 2002 (U.S. EPA 2004). The most common manufacturing process is by catalyzed esterification of acrylic acid with n-butanol (ECETOC 1994).

Parameter	Value	Reference
Synonyms	2-propenoic acid butyl ester	O'Neil et al. 2001
Chemical formula	$C_7 H_{12} O_2$	O'Neil et al. 2001
Molecular weight	128.17	O'Neil et al. 2001
CAS Reg. No.	141-32-5	
Physical state	liquid	O'Neil et al. 2001
Solubility in water	0.14 g/100 mL at 20°C	O'Neil et al. 2001
Vapor pressure	4.3 mmHg at 20°C	ECETOC 1994
Vapor density (air =1)	4.4	ECETOC 1994
Liquid density (water =1)	0.8986	O'Neil et al. 2001
Melting point	-64°C, approximately	ECETOC 1994
Boiling point	145°C	O'Neil et al. 2001
Auto-ignition	267°C	ECETOC 1994
Conversion factors	1 ppm = $5.33 \text{ mg/m}^3$ 1 mg/m <sup>3</sup> = $0.188 \text{ ppm}$	ECETOC 1994

Selected chemical and physical properties of BA are listed in Table 1.

# 2. HUMAN TOXICITY DATA

### 2.1. Acute Lethality

No reports of human fatalities from exposure to BA were found.

### 2.2. Nonlethal Toxicity

### 2.2.1. Odor Threshold/Odor Awareness

AIHA (1995a) listed the range of reported odor thresholds as 0.00096-0.10 ppm; however, all values were from either unpublished data or anonymous references.

### 2.2.2. Case Reports

Contact dermatitis to BA has been demonstrated with patch testing (Hambly and Wilkinson 1978), but no reports of respiratory sensitization were found.

### 2.2.3. Epidemiologic Studies/Occupational Exposures

No epidemiologic studies were found concerning human exposures to BA.

17 Tuček et al. (2002) conducted a prospective cohort study during 1992-1999 of workers 18 involved in the production of acrylic acid and its esters. Groups of 60 controls and 60 exposed individuals were followed with the average exposure period for the exposed group 13±5 years. 19 20 Exposures to up to eight chemicals, including BA, were determined by personal passive 21 dosimetry. Concentrations of all chemicals remained low, however, the maximum allowable 22 concentration for BA (not specified) was exceeded for 2% of the measurements. Throughout the 23 study chemical workers did not show any health-related changes as measured by interview, 24 general medical examination, hematology, clinical chemistry, serum immunity parameters, 25 selected tumor markers, and spirometry. Subjective complaints at the workplace of burning eyes 26 and throat, occasional irritating cough, headaches, and less frequently nausea or dizziness, and 27 fleeting dermatological complaints were reported by approximately 40% of the exposed workers; 28 the study authors did not correlate symptoms with exposure concentrations. In contrast only 29 20% of the controls reported subjective complaints with symptoms associated with ergonomics.

Rohm and Haas, Co. (1987) submitted employee exposure monitoring results for a number of
 operations during 1978-1987. Average concentrations of BA for full shift ranged from 0.1-1.0
 ppm and short-term exposure average concentrations ranged from 0.4-10.5 ppm. No other
 information was included in the report.

Time-weighted average concentrations of BA at four job sites in a polystyrene production plant were 12-93 ppb (range: not detected-270 ppb) in the breathing zone of workers and 1-93 ppb (range: not detected-525 ppb) in the atmosphere of the workplaces (Samimi and Falbo 1982). Samples were collected in charcoal tubes from 50 minutes to 7.5 hours and quantitated with a gas chromatograph. No information on worker health status was given.

### 2.2.4. Clinical Studies

Olfactory function was investigated in chemical workers exposed to acrylates and
 methacrylates (Schwartz et al. 1989; Rohm and Haas 1988). Specific chemicals were not
 identified. Workers were administered a standardized smell identification test consisting of an

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odorant strip and a questionnaire. A dose-responsive relationship was found between olfactory dysfunction and cumulative exposure scores (semi-quantitative indices of life-time exposures to the acrylates) with reversible effects shown with increasing duration since the last exposure.

A number of studies have shown positive results for skin sensitization with patch testing. In a summary of these studies (BIBRA 1991), it was emphasized that it was impossible to conclude whether the reactions were to primary sensitization to BA or to cross-reactivity to other acrylates.

### 2.3. Neurotoxicity

No reports of neurotoxicity in human from exposure to BA were found.

### 2.4. Developmental/Reproductive Toxicity

No information was found regarding the reproductive or developmental toxicity of BA in humans.

### 2.5. Genotoxicity

No information was found regarding the genotoxic effects of BA in humans.

### 2.6. Carcinogenicity

No information was found regarding the carcinogenicity of BA in humans. IARC (1999) lists BA as *not classifiable as to its carcinogenicity to humans* due to lack of data in humans and inadequate evidence in experimental animals.

### 2.7. Summary

Very little information is available concerning human exposure to BA. Symptoms of irritation were occasionally reported in chemical plant workers. Dermal sensitization has been reported but not respiratory sensitization.

# 3. ANIMAL TOXICITY DATA

### 3.1. Acute Lethality

### 3.1.1. Hamsters

Groups of 10 male and 10 female Chinese hamsters were exposed to a mean analytical
concentration of 817 ppm BA for 6 hours/day for 4 days (Engelhardt and Klimisch 1983). Four
males died during the exposure period. Clinical signs of toxicity were listed as dyspnea,
disequilibrium, and bloody discharge from the eyes and noses; no further details were given.

BASF (1979a) reported 4-hour  $LC_{50}$  values for male and female Chinese hamsters (n = 10/sex/group) of 1201-1654 ppm. No further study details were given.

### 3.1.2. Rats

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Male Sprague-Dawley rats (n = 10/group) were exposed whole body for 4 hours to 1990, 6 7 2035, 2500, 2828, or 3041 ppm BA followed by a 14-day observation period (Oberly and Tansy 1985). Atmospheres were generated by constant infusion of liquid monomer into a heated 8 9 reaction vessel through which room air was passed at a known constant rate. Vapor 10 concentration was determined by gas chromatography. During exposures animals had normal behavior during the first few minutes then exhibited irritation of the eyes, nose, and respiratory 11 12 tract and labored breathing. All deaths occurred within 24 hours and were attributed to 13 cardiopulmonary collapse. The number of deaths at each concentration was 0, 1, 3, 5, and 7, respectively. The 4-hour  $LC_{50}$  was calculated as 2730 ppm. 14

16 BASF (1979b,c, 1980) reported 4-hour LC<sub>50</sub> values for male and female Sprague-Dawley rats 17 (n = 10/sex/group) of 2140-2415 and 2405-2685 ppm, respectively, following whole body 18 exposure and 2140 and 1910 ppm, respectively, following nose-only exposure. Atmospheres 19 were generated by using a permanent infusion pump to add a constant concentration of the 20 testing substance to a heated vaporizer; the vapor was then mixed with fresh air. The analytical 21 method was not described. Clinical signs indicative of severe irritation were observed in animals 22 at concentrations of 677 ppm and above and deaths occurred at concentrations of 1278 ppm and 23 above.

Two older sources list lethality in rats exposed to 1000 ppm BA for 4 hours as 5/6 (Smyth et al. 1951) and 1/6 (Carpenter et al. 1974). No further information was available in either reference.

### 3.1.3. Mice

BASF (1979d,e) reported 4-hour  $LC_{50}$  values for male and female NMRI mice (n = 10/sex/group) of 1290 and 1285 ppm, respectively, for fed animals and 1315 and 1415 ppm, respectively, for fasted animals. Animals were exposed whole body in dynamic chambers. Atmospheres were generated by using a permanent infusion pump to add a constant concentration of the testing substance to a heated vaporizer; the vapor was then mixed with fresh air. The analytical method was not described. Clinical signs indicative of irritation included lacrimation, nasal discharge, and dyspnea.

3.2. Nonlethal Toxicity

### 3.2.1. Rats

Groups of 10 male and 10 female Sprague-Dawley rats were exposed by whole body to a
mean analytically determined concentration of 820 ppm BA for 6 hours/day for 4 days
(Engelhardt and Klimisch 1983). No deaths were reported. Clinical signs of toxicity were listed

as dyspnea, disequilibrium, and bloody discharge from the eyes and noses; no further details were given.

### 3.2.2. Mice

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Groups of male Swiss Webster mice (n = 8/group) were exposed head-only to 30-900 ppm 7 BA for 30 minutes (Kirkpatrick 2003). Test atmospheres were generated by mixing chemical 8 vapor with fresh air using a calibrated rotameter-type flowmeter. Concentrations were measured 9 by gas chromatography. No treatment-related deaths occurred during exposure to any 10 concentration and clinical signs were not reported. The calculated RD<sub>50</sub> was 340 ppm. The lowest effect level for respiratory depression was 100 ppm (-9%) and the no effect level was 30 12 ppm. 13

### 3.3. Neurotoxicity

No information was found on the neurotoxicity of BA in animals following inhalation exposure.

### 3.4. Developmental/Reproductive Toxicity

21 Groups of 30 female Sprague-Dawley rats were administered BA at concentrations of 0, 25, 22 135, or 250 ppm for 6 hrs/day, on gestation days 6-15 (Rohm and Haas Co. 1992, Merkle and 23 Klimisch 1983). Mean analytically determined concentrations during the study were 25, 137, 24 and 251 ppm, respectively. All dams survived to scheduled sacrifice on GD 20. During 25 exposure to 135 ppm, animals had pronounced eye and nasal discharge and ruffled fur; these 26 signs were more pronounced during exposure to 250 ppm and also included closed eyes and 27 matted fur. Concentration-related decreases in maternal body weight gain were observed during 28 the exposure interval at the two highest concentrations. Maternal necropsy revealed loss of fatty 29 tissue in two mid- and nine high-concentration animals. No differences between the treated and 30 control groups were found for numbers of corpora lutea and implantations or fetal and placental weights. Concentration-related decreases in live fetuses and subsequent increases in resorptions 31 32 occurred at the two highest concentrations. In the control, low-, mid-, and high-concentration 33 groups, the mean number of live fetuses/dam was 11.5, 10.6, 8.8, and 8.4, respectively, and the 34 mean percent resorptions per dam was 11.6, 13.8, 23.6, and 31.0, respectively. No treatment-35 related external, visceral, or skeletal malformations were observed in any fetus.

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37 In another study, Sprague-Dawley rats (n = 24-25) were administered 0, 100, 200, or 300 38 ppm BA, 6 hr/day on GD 6-20 (Saillenfait et al. 1999). Mean analytically determined 39 concentrations were 103.3, 202.8, and 302.5 ppm, respectively. All animals survived to 40 scheduled sacrifice; clinical signs of toxicity were not reported. Maternal body weight gain was 41 markedly reduced in the mid- and high-concentration groups during the exposure interval to 56% 42 and 13%, respectively, of the control group level. Food consumption was also decreased for 43 these treated groups. In contrast to the study described above, the numbers of implantation sites, 44 live fetuses, and resoprtions per litter were not affected. Fetal body weights were significantly 45 reduced in the 200 and 300 ppm groups. No treatment-related external, visceral, or skeletal 46 malformations were found in any fetus.

### 3.5. Genotoxicity

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BA, at concentrations up to 2000  $\mu$ g/plate, was not mutagenic in *Salmonella typhimurium* (TA1535, TA1537, TA1538, TA98, TA100) with and without metabolic activation (Waegemaekers and Bensink 1984). With Syrian hamster embryo cells, the chemical was negative in *in vitro* tests for micronucleus formation (Wiegand et al. 1989; Fritzenschaf et al. 1993) and unscheduled DNA synthesis (Wiegand et al. 1989).

Male and female Sprague-Dawley rats and Chinese hamsters were exposed to mean
concentrations of 820 ppm or 817 ppm, respectively, for 6 hours/day for 4 days. Cytogenetic
analysis of bone marrow did not show any indication of increased chromosomal aberrations
(Engelhardt and Klimisch 1983).

### 3.6. Subchronic and Chronic Toxicity/Carcinogenicity

16 Male and female Sprague-Dawley rats (n = 20) were exposed to 0, 21, 108, 211, or 546 ppm BA for 6 hours/day, 5 days/week, for 13 weeks (Klimisch et al. 1978). At the highest 17 18 concentration, 31/40 animals died during weeks 3-13 following reduced body weight gain and 19 clinical signs of bloody ocular and nasal discharges and rhinitis. Necropsy of these animals 20 revealed hyperemic nasal mucosa, edematous nasal epithelium, metaplasia of the olfactory 21 epithelium, extensive and advanced necrosis of the lungs associated with bacteria, cornification 22 of the epithelium of the trachea and bronchi, pulmonary hyperemia, and pneumonia. At 211 ppm 23 all animals survived but had reduced body weight gain and showed bloody ocular and nasal 24 discharges; slight edema and erosion of the nasal mucosa were observed histologically in a few 25 individuals. Slight decreases in weight gain but no histopathological changes were observed in 26 animals exposed to 108 ppm. The NOAEL was 21 ppm.

In a 2-year inhalation study followed by a 6-month recovery, male and female Sprague-Dawley rats (n = 86) were exposed to 0, 15, 45, or 135 ppm BA for 6 hours/day, 5 days/week; the concentrations were 0, 5, 15, and 45 ppm for the first 13 weeks (Reininghaus et al. 1991). No clinical signs or systemic toxicity were observed and no evidence of carcinogenicity was found. Histopathological lesions attributable to chronic irritation were seen in the nasal mucosa (concentration-related increases in all groups) and cornea (135-ppm groups).

### 3.7. Summary

BA caused clinical signs of irritation in all species tested.  $LC_{50}$  values were not substantially different between hamsters, rats, and mice; however in one study (Engelhardt and Klimisch 1983) hamsters appeared to be more sensitive than rats to the lethal effects of BA. Animal toxicity data are summarized in Table 2.

Embryolethality was found in one developmental toxicity study but not in another study; the reason for the difference in these results is unknown. 

TABLE 2. Summary of toxicity data in laboratory animals exposed to BA						
Species, duration	LC <sub>50</sub>	Lethal conc.	Reference			
Hamster (10/sex), 4 h	1201-1654 ppm		BASF 1979a			
Hamster (10/sex), 6 h/day, 4 days		817 ppm; 4/10 males	Engelhardt and Klimisch 1983			
Rat (10 m), 4 h	2730 ppm		Oberly and Tansy 1985			
Rat (10/sex), 4 h	1936-2500 ppm		BASF 1979b,c, 1980			
Rat (10/sex), 6 h/day, 4 days		820 ppm; 0/20	Engelhardt and Klimisch 1983			
Mouse (10/sex), 4 h	1278-1354 ppm		BASF 1979d,e			

### 4. SPECIAL CONSIDERATIONS

### 4.1. Metabolism and Disposition

Male Fischer 344 rats were administered 4, 40, or 400 mg/kg of [2,3-<sup>14</sup>C]-radiolabeled BA by gavage or 40 mg/kg by intravenous injection (Sanders et al. 1988). The results of this study showed that BA was rapidly absorbed from the gastrointestinal tract and completely metabolized following either route of administration. Gastrointestinal absorption and metabolism were similar over the range of doses used. BA-derived radioactivity was found in all major tissues sampled (blood, liver, kidney, skin, adipose, muscle) with peak concentrations within 15 minutes followed by rapid decline over the next 2 hours; elimination from the tissues was negligible between 2 hours and 3 days. Of the fraction measured in blood, 70% was associated with the red blood cells. BA was completely metabolized and no parent compound was detected in urine, bile, or tissues. BA was mainly hydrolyzed by carboxylesterases to acrylic acid and butanol, with a small portion being directly conjugated with glutathione. The acrylic acid moiety entered intermediary metabolism with 65-78% of the oral dose subsequently excreted as CO<sub>2</sub>. Small amounts of the mercapturic acids N-acetyl-S-(2-carboxyethyl)cysteine-S-oxide and N-acetyl-S-(2-carboxyethyl)cysteine were detected in urine. Comparisons by route of administration showed a slightly greater portion distributed to adipose tissue, less CO<sub>2</sub> excretion, and greater amounts of urinary metabolites following intravenous injection versus oral dosing (Sanders et al. 1988). 

A similar metabolic profile was found in female Wistar rats administered 1 mmol/kg of [3 <sup>13</sup>C]-labeled BA by intraperitoneal injection (Linhart et al. 1994a). The major urinary
 metabolites were 3-hydroxypropanoic acid and the murcapturic acids noted above. Metabolites
 indicative of metabolic activation of BA were not found. In other work by these authors (Linhart

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et al. 1994b), quantitation of the mercapturic acids showed that the absolute amount remained
relatively constant while the proportion conjugated decreased with increasing dose (3.6% at 0.5
mmol/kg to 1.6% at 3 mmol/kg). In addition, characterization of the carboxylic acids found in
urine indicated that the acrylic acid entered intermediary metabolism via propanoic acid
catabolism and the tricarboxylic acid cycle (Linhart et al. 1994a,b).

Following a 6-hour inhalation exposure of male Wistar rats to 188-752 ppm BA, <3% of the</li>
dose was excreted in the urine as thioethers (Vodička et al. 1990). However total tissue
sulfhydryl groups were significantly decreased in the liver following exposure to 752 ppm. Nonprotein sulfhydryl groups were also decreased in liver and to a lesser extent in blood, brain, and
lung.

The activity of carboxylesterase recovered from nasal mucosal tissue of B6C3F1/CrlBr mice was studied with BA (Stott and McKenna 1985). Under subsaturating concentrations, BA was hydrolyzed under first-order kinetics with a  $V_{MAX}$  of  $0.141 \times 10^{-3}$  M/min and a  $K_M$  of  $1.41 \times 10^{-3}$ M. Loss of enzymatic activity occurred at concentrations in excess of 5 mM. Carboxylesterase specific activity was approximately equivalent in the nasal mucosa and liver of mice with ethylene glycol monomethyl ether acetate as substrate. *In vitro* nasal enzyme activity was shown to be similar between mice and dogs, slightly less in rats, and nearly sevenfold less in rabbits.

Another *in vitro* study measured the hydrolysis rate in rat liver homogenate and disappearance from whole blood (Miller et al. 1981). The rate of hydrolysis of BA (23.6 nmole•min<sup>-1</sup>) in liver homogenate directly correlated with the appearance of acrylic acid (26 nmoles•min<sup>-1</sup>) in the medium. In contrast the rate of hydrolysis in whole blood (9.4 nmoles•min<sup>-1</sup>) was much greater than the production of acrylic acid (4.6 nmoles•min<sup>-1</sup>) suggesting a different mechanism. This is supported by results with ethyl acrylate in which the ester was shown to bind with non-protein sulfhydryls in red blood cells.

### 4.2. Mechanism of Toxicity

Stott and McKenna (1985) concluded from *in vitro* experiments that hydrolysis of BA by carboxylesterase activity in nasal mucosa produces acid metabolites which result in the nasal lesions. Subsequently, little BA is available for systemic absorption.

### 4.3. Structure Activity Relationships

37 The low molecular weight acrylic acid ester monomers are lacrimators and irritants to the eyes, skin, and mucus membranes (Bisesi 2001, Autian 1975). Acute toxicity based on  $LC_{50}$ 38 values for a number of chemicals was determined to be methyl acrylate (1350 ppm) > ethyl 39 40 acrylate (2180 ppm)> butyl acrylate (2730 ppm) > butyl methacrylate (4910 ppm) > methyl 41 methacrylate (7093 ppm) > ethyl methacrylate (8300 ppm) (Oberly and Tansy 1985). For all the acrylate esters tested by Oberly and Tansy (1985), rats showed signs of irritation of the eyes, 42 43 nose, and respiratory tract. The rapid metabolism and elimination of the low molecular weight 44 esters suggests that cumulative effects will not occur (Autian 1975).

The target within the respiratory tract was shown to be the olfactory epithelium lining the dorsal meatus following exposure to several acrylate esters. Similar nasal lesions were observed in laboratory animals after exposure to ethyl acrylate (NAC 2004a), methacrylic acid (NAC 2004b), methyl methacrylate (NAC 2004c), and acrylic acid (NAC 2004d).

### 4.4. Other Relevant Information

### 4.4.1. Species Variability

Little evidence for species variation was seen in the available data. Clinical signs were similar between hamsters, rats, and mice following exposure to BA.

### 4.4.2. Susceptible Populations

Little data were available that identified susceptible populations. Developmental toxicity studies show that the fetus is affected at maternally toxic concentrations.

### 4.4.3. Concentration-Exposure Duration Relationship

The concentration-exposure duration relationship for an irritant gas such as BA can be described by the equation  $C^n \times t = k$ , where the exponent n ranges from 0.8 to 3.5 (ten Berge et al. 1986). In the absence of a chemical-specific, empirically derived exponent, a default value of n = 1 can be used when extrapolating to longer timepoints and a default value of n = 3 can be used when extrapolating to shorter timepoints. This method will yield the most conservative AEGL estimates and was used for extrapolation of AEGL-2 values.

Different n values were used in the extrapolation of AEGL-2 and -3. This approach was considered to be appropriate because the mechanism of toxicity for AEGL-2 endpoints differs from that of AEGL-3 endpoints. Under the definition of AEGL-2, lesions in the upper respiratory tract were caused by irritation of the chemical due to direct contact with mucus membranes in conjunction with enzymatic hydrolysis. In contrast, lethality as the basis for AEGL-3 was due to cardiopulmonary collapse as a result of the chemical reaching the lower respiratory tract and the systemic circulation. A value of n = 1.3 was calculated by combining 1-and 4- hour LC<sub>50</sub> data sets from ethyl acrylate (NAC 2004a) in a 3-dimensional probit analysis (Zwart et al. 1992). Use of an n value calculated from a structurally related chemical was considered appropriate because the mechanism leading to death is similar for both compounds.

### 5. DATA ANALYSIS FOR AEGL-1

5.1. Summary of Human Data Relevant to AEGL-1

No human data relevant to derivation of AEGL-1 values were found. Worker monitoring
studies reported up to 10.5 ppm as a short-term exposure average concentration (Rohm and
Haas, Co. 1987), but no health effects were included.

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# 5.2. Summary of Animal Data Relevant to AEGL-1

Few animal data were available for derivation of AEGL-1 values. In a developmental toxicity study (Rohm and Haas Co. 1992; Merkle and Klimisch 1983), no clinical signs were reported for rats exposed repeatedly to 25 ppm. Clinical signs reported in other studies were too severe for AEGL-1 (concentrations of 135 ppm and higher resulted in eye and nasal discharge, dyspnea, gasping). The no-effect level for respiratory depression in mice was 30 ppm (Kirkpatrick 2003).

10 **5.3. Derivation of AEGL-1** 

Limited data were available upon which to base AEGL-1 values. A concentration of 25 ppm, which did not result in any effects in pregnant rats following repeated exposures, was chosen as a concentration below the threshold for AEGL-1 effects. Extrapolations were not performed. A total uncertainty factor of 3 was used including 1 for interspecies extrapolation and 3 for intraspecies extrapolation. Use of greater uncertainty factors was not necessary because the mechanism of irritation is not expected to differ between individuals. AEGL-1 values are given in Table 3.

TABLE 3. AEGL-1 Values for Butyl Acrylate								
10-minute	10-minute 30-minute 1-hour 4-hour 8-hour							
8.3 ppm (44 mg/m <sup>3</sup> )	8.3 ppm (44 mg/m <sup>3</sup> )	8.3 ppm (44 mg/m <sup>3</sup> )	8.3 ppm (44 mg/m <sup>3</sup> )	8.3 ppm (44 mg/m <sup>3</sup> )				

The reported odor threshold concentrations are not sufficiently qualified to derive a level of odor awareness (LOA) according to van Doorn et al. (2002).

# 6. DATA ANALYSIS FOR AEGL-2

# 6.1. Summary of Human Data Relevant to AEGL-2

Data in humans relevant to derivation of AEGL-2 values were not found.

# 6.2. Summary of Animal Data Relevant to AEGL-2

The best animal data relevant to derivation of AEGL-2 are from the subchronic study in which male and female Sprague-Dawley rats (n = 20) were exposed to 0, 21, 108, 211, or 546 ppm BA for 6 hours/day, 5 days/week, for 13 weeks (Klimisch et al. 1978). At the highest concentration, mortality, reduced body weight gain, and clinical signs of bloody ocular and nasal discharges and rhinitis were observed; marked lesions of the respiratory tract were found at necropsy. At 211 ppm all animals survived but had reduced body weight gain and showed bloody ocular and nasal discharges; slight edema and erosion of the nasal mucosa were observed

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histologically in a few individuals. Slight decreases in weight gain but no histopathological changes were observed in animals exposed to 108 ppm. The NOAEL was 21 ppm.

No maternal or developmental toxicity was seen in rats repeatedly exposed to 25 or 100 ppm during gestation (Rohm and Haas Co. 1992; Merkle and Klimisch 1983; Saillenfait et al. 1999).

### 6.3. Derivation of AEGL-2

The subchronic study by Klimisch et al. (1978) was used to derive AEGL-2 values. 9 Repeated exposure to a concentration of 211 ppm for 6 hours/day resulted in clinical signs of 10 toxicity including nasal irritation but no mortality. Slight lesions of the nasal mucosa were seen 11 histologically. Values were scaled using the equation  $C^n \times t = k$  where n ranges from 0.8 to 3.5 12 13 (ten Berge et al. 1986). In the absence of an empirically derived, chemical-specific exponent, 14 scaling was performed using n = 3 for extrapolating to the 30-minute and 1- and 4-hour time points and n = 1 for the 8-hour time point. A total uncertainty factor of 3 was used including 1 15 16 for interspecies extrapolation and 3 for intraspecies extrapolation. Use of greater uncertainty 17 factors was not necessary because the mechanism of irritation is not expected to differ between 18 individuals. According to Section 2.7 of the Standing Operating Procedures for Developing 19 Acute Exposure Guideline Levels for Hazardous Chemicals (NRC 2001), 10-minute values are 20 not to be scaled from an experimental exposure time of  $\geq 4$  hours. Therefore, the 30-minute 21 AEGL-2 value was also adopted as the 10-minute value. AEGL-2 values are given in Table 4.

TABLE 4. AEGL-2 Values for Butyl Acrylate								
10-minute	10-minute30-minute1-hour4-hour8-hour							
160 ppm (850 mg/m <sup>3</sup> )	160 ppm (850 mg/m <sup>3</sup> )	130 ppm (690 mg/m <sup>3</sup> )	81 ppm (430 mg/m <sup>3</sup> )	53 ppm (280 mg/m <sup>3</sup> )				

### 7. DATA ANALYSIS FOR AEGL-3

### 7.1. Summary of Human Data Relevant to AEGL-3

Human exposure data relevant to derivation of AEGL-3 values were not available. No reports of human lethality from exposure to EA were found in the literature.

### 7.2. Summary of Animal Data Relevant to AEGL-3

The best animal data relevant to derivation of AEGL-3 values is the Oberly and Tansy (1985) 4-hour  $LC_{50}$  study in rats. This was a well conducted study with a wide range of analytically determined exposure concentrations. Clinical signs of irritation were observed in animals during exposure and death was attributed to cardiopulmonary collapse. The calculated 43 4-hour  $LC_{50}$  value was 2730 ppm.

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Other studies reporting 4-hour  $LC_{50}$  values in rats (BASF 1979b,c, 1980) are in good agreement with that of Oberly and Tansy (1985). These are also well conducted studies but lacked details of the experimental procedures.

# 7.3. Derivation of AEGL-3

The  $LC_{50}$  study by Oberly and Tansy (1985) was well conducted and included mortality ratios at all concentrations. From these data a 4-hour BMCL<sub>05</sub> value was calculated by a log-probit analysis using US EPA Benchmark Dose Software version 1.3.2. The resulting 4-hour BMCL<sub>05</sub> of 1652 ppm was used to derive the 30-minute, and 1-, 4- and 8-hour AEGL-3 values. Values were scaled using the equation  $C^n \times t = k$  where n ranges from 0.8 to 3.5 (ten Berge et al. 1986). A value of n = 1.3 was calculated by combining 1- and 4- hour LC<sub>50</sub> data sets from ethyl acrylate (NAC 2004a) in a 3-dimensional probit analysis (Zwart et al. 1992). Use of an n value calculated from a structurally related chemical was considered appropriate because the mechanism leading to death is similar for both compounds. A total uncertainty factor of 10 was used including 3 for interspecies extrapolation and 3 for intraspecies extrapolation. Use of greater uncertainty factors was not necessary because the mechanism of toxicity (local damage in the lower airways/lungs) is not expected to differ between individuals. According to Section 2.7 of the Standing Operating Procedures for Developing Acute Exposure Guideline Levels for Hazardous Chemicals (NRC 2001), 10-minute values are not to be scaled from an experimental exposure time of  $\geq$ 4 hours. Therefore, the 30-minute AEGL-3 value was also adopted as the 10minute value. AEGL-3 values are given in Table 5.

TABLE 5. AEGL-3 Values for Butyl Acrylate								
10-minute	10-minute30-minute1-hour4-hour8-hour							
820 ppm (4400 mg/m <sup>3</sup> )	820 ppm (4400 mg/m <sup>3</sup> )	480 ppm (2600 mg/m <sup>3</sup> )	170 ppm (906 mg/m <sup>3</sup> )	97 ppm (520 mg/m <sup>3</sup> )				

### 8. SUMMARY OF AEGLS

### 8.1. AEGL Values and Toxicity Endpoints

The derived AEGL values for various levels of effects and durations of exposure are summarized in Table 6. AEGL-1 was based on a no-effect level for sensory irritation in rats. AEGL-2 values were derived from a subchronic study resulting in clinical signs and microscopic lesions of the nasal mucosa. The basis for AEGL-3 was a calculated 4-hour BMCL<sub>05</sub> from lethality data in the rat.

TABLE 6. Summary of AEGL Values							
	Exposure Duration						
Classification	10-minute	30-minute	1-hour	4-hour	8-hour		
AEGL-1 (Nondisabling)	8.3 ppm (44 mg/m <sup>3</sup> )	8.3 ppm (44 mg/m <sup>3</sup> )	8.3 ppm (44 mg/m <sup>3</sup> )	8.3 ppm (44 mg/m <sup>3</sup> )	8.3 ppm (44 mg/m <sup>3</sup> )		
AEGL-2 (Disabling)	160 ppm (850 mg/m <sup>3</sup> )	160 ppm (850 mg/m <sup>3</sup> )	130 ppm (690 mg/m <sup>3</sup> )	81 ppm (430 mg/m <sup>3</sup> )	53 ppm (280 mg/m <sup>3</sup> )		
AEGL-3 (Lethal)	820 ppm (4400 mg/m <sup>3</sup> )	820 ppm (4400 mg/m <sup>3</sup> )	480 ppm (2600 mg/m <sup>3</sup> )	170 ppm (906 mg/m <sup>3</sup> )	97 ppm (520 mg/m <sup>3</sup> )		

### 8.2. Comparison with Other Standards and Guidelines

Standards and guidance levels for workplace and community exposures are listed in Table 7.
The ACGIH recommends a TLV of 2 ppm for workers (ACGIH 2003) while the NIOSH REL is
10 ppm (NIOSH, 2003). A NIOSH IDLH has not been established. ERPG-3 and -2 values were
based on no effect levels for lethality and developmental toxicity effects and the ERPG-1 is at or
below a moderate odor intensity level (AIHA 1995b). The occupational exposure limits from
ACGIH, Germany, The Netherlands, and Sweden are 2-10 ppm.

TABLE 7. Extant Standards and Guidelines for Butyl Acrylate							
~			Exposure Duratio	n			
Guideline	10 minute	30 minute	1 hour	4 hour	8 hour		
AEGL-1	8.3 ppm	8.3 ppm	8.3 ppm	8.3 ppm	8.3 ppm		
AEGL-2	160 ppm	160 ppm	130 ppm	81 ppm	53 ppm		
AEGL-3	820 ppm	820 ppm	480 ppm	170 ppm	97 ppm		
ERPG-1 (AIHA) <sup>a</sup>			0.05 ppm				
ERPG-2 (AIHA)			25 ppm				
ERPG-3 (AIHA)			250 ppm				
REL-TWA (NIOSH) <sup>b</sup>					10 ppm		
TLV-TWA (ACGIH) <sup>c</sup>					2 ppm (SEN		
MAK (Germany) <sup>d</sup>					2 ppm (Sh)		
MAK Peak Limit (Germany) <sup>e</sup>	21	opm					
MAC (The Netherlands) <sup>f</sup>					1 ppm		
OEL-TWA (Sweden) <sup>g</sup>					10 ppm		
OEL-STEL (Sweden) <sup>h</sup>	15	ppm					

<sup>a</sup>ERPG (Emergency Response Planning Guidelines, American Industrial Hygiene Association (AIHA 1995b, 2003) 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-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 protection action.

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.

<sup>b</sup>NIOSH REL-TWA (National Institute of Occupational Safety and Health, Recommended Exposure Limits -Time Weighted Average) (NIOSH 2003) is defined analogous to the ACGIH-TLV-TWA.

<sup>c</sup>ACGIH TLV-TWA (American Conference of Governmental Industrial Hygienists, Threshold Limit Value - Time Weighted Average) (ACGIH 2003) is 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. SEN:sensitizer

#### <sup>d</sup>MAK (Maximale Arbeitsplatzkonzentration [Maximum Workplace Concentration]) (Deutsche

Forschungsgemeinschaft [German Research Association] 2002) is defined analogous to the ACGIH-TLV-TWA. "Sh" designates substances which can cause allergic reactions of the skin and mucosa.

# <sup>f</sup>MAK Spitzenbegrenzung (Peak Limit [I(2)]) (German Research Association 2002)

constitutes the maximum average concentration to which workers can be exposed for a period up to 15 minutes with no more than 4 exposure periods per work shift; total exposure may not exceed 8-hour MAK.

- <sup>f</sup>MAC (Maximaal Aanvaaarde Concentratie [Maximal Accepted Concentration]) (SDU Uitgevers [under the auspices of the Ministry of Social Affairs and Employment], The Hague, The Netherlands 2000) is defined analogous to the ACGIH-TLV-TWA.
- <sup>g</sup>**OEL-TWA (Occupational Exposure Limits Time-weighted-average)** (IPCS 2003) is an occupational exposure limit value for exposure during one working day.

<sup>h</sup>OEL-STEL (Occupational Exposure Limits - Short-term exposure limit) (IPCS 2003) is an occupational exposure limit value for exposure during a reference period of fifteen minutes.

#### 8.3. Data Adequacy and Research Needs

No human data were available. Worker monitoring studies did not report potential individual exposure or effects. No animal data which matched the definition of AEGL-2 were available. However, AEGL-3 values were based on a well-conducted study with adequate information.

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**APPENDIX A: Derivation of AEGL Values** 

1		Derivation of AEGL-1
2		
3 4 5	Key Studies:	Rohm and Haas Co. 1992; Merkle and Klimisch 1983
6 7	Toxicity endpoint:	No fetal effects and no clinical signs of toxicity in dams exposed to 25 ppm, 6 hours/day on gestation days 6-15.
8 9 10	Time scaling:	None
10 11 12	Uncertainty factors:	3 (1 for intraspecies variability and 3 for interspecies variability)
13 14	Modifying factor:	None
15 16	Calculations:	C/UFs = 25  ppm/3 = 8.3  ppm
17 18	<u>10-minute AEGL-1</u> :	8.3 ppm
19 20	30-minute AEGL-1:	8.3 ppm
21 22	<u>1-hour AEGL-1</u> :	8.3 ppm
23 24	<u>4-hour AEGL-1</u> :	8.3 ppm
25 26 27	<u>8-hour AEGL-1</u> :	8.3 ppm

1 2		<b>Derivation of AEGL-2</b>			
2 3 4	Key Studies:	Klimisch et al. 1978			
5 6 7 8	Toxicity endpoints:	A concentration of 211 ppm for 6 h/d, 5 d/week, for 13 weeks resulted in clinical signs of toxicity and microscopic lesions of the nasal mucosa.			
9 10 11 12	Time scaling:	$C^n \times t = k$ (ten Berge et al. 1986) n = 3 for extrapolating to the 30-min and 1- and 4-hour time points; n = 1 for extrapolating to the 8-hr time point			
13 14	Uncertainty factors:	3 (3 for intraspecies variability and 1 for interspecies variability)			
15 16	Modifying factor:	None			
17 18 19 20 21 22 23 24	Calculations:	30-min and 1- and 4-hr time points $(C/UFs)^3 \times t = k$ $(211 \text{ ppm/3})^3 \times 6 \text{ hr} = 2.088 \times 10^6 \text{ ppm}^3 \cdot \text{hr}$ 8-hr time point $(C/UFs)^1 \times t = k$ $(211 \text{ ppm/3})^1 \times 6 \text{ hr} = 422 \text{ ppm}^1 \cdot \text{hr}$			
24 25 26	10-minute AEGL-2:	160 ppm			
27 28	30-minute AEGL-2:	$(2.088 \times 10^6 \text{ ppm}^3 \cdot \text{hr}/0.5 \text{ hr}) = 160 \text{ ppm}$			
29 30	<u>1-hour AEGL-2</u> :	$(2.088 \times 10^6 \text{ ppm}^3 \cdot \text{hr}/1 \text{ hr}) = 130 \text{ ppm}$			
31 32	4-hour AEGL-2:	$(2.088 \times 10^6 \text{ ppm}^3 \cdot \text{hr}/4 \text{ hr}) = 81 \text{ ppm}$			
33 34	8-hour AEGL-2:	$(422 \text{ ppm}^1 \cdot \text{hr}/8) = 53 \text{ ppm}$			

1 2		Derivation of AEGL-3
3 4 5	Key Study:	Oberly and Tansy 1985
6 7 8 9 10	Toxicity endpoint:	The 4-hour $LC_{50}$ value of 2730 ppm in rats was used for derivation of AEGL-3 values. From these data, a 4-hour BMCL <sub>05</sub> value was calculated by a log-probit analysis. The resulting 4-hour BMCL <sub>05</sub> of 1652 ppm was used to derive the 30-minute, 1-hour, 4-hour, and 8-hour AEGL-3 values.
12 13 14 15	Time scaling	$C^n \times t = k$ (ten Berge et al. 1986) n = 1.3; calculated by combining 1- and 4- hour LC <sub>50</sub> data sets from ethyl acrylate (NAC 2004a) in a 3-dimensional probit analysis (Zwart et al. 1992)
10 17 18	Uncertainty factors:	10 (3 for intraspecies variability and 3 for interspecies variability)
19 20	Modifying factor:	None
20 21 22 23	Calculations:	$(C/UFs)^{1.3} \times t = k$ (1652 ppm/10) <sup>1.3</sup> × 4 hr = 3058 ppm <sup>1.3</sup> ·hr
23 24 25	10-minute AEGL-3:	820 ppm
26 27	30-minute AEGL-3:	$(3058 \text{ ppm}^{1.3} \cdot \text{hr}/0.5 \text{ hr}) = 820 \text{ ppm}$
28 29	1-hour AEGL-3:	$(3058 \text{ ppm}^{1.3} \cdot \text{hr}/1 \text{ hr}) = 480 \text{ ppm}$
30 31	4-hour AEGL-3:	$(3058 \text{ ppm}^{1.3} \cdot \text{hr}/4 \text{ hr}) = 170 \text{ ppm}$
32 33 34 35	8-hour AEGL-3:	$(3058 \text{ ppm}^{1.3} \cdot \text{hr}/8 \text{ hr}) = 97 \text{ ppm}$

1

**APPENDIX B: Benchmark Calculations** 

#### **Benchmark Calculations** The benchmark calculations are based on the study by Oberly and Tansy (1985) using a range of five concentrations in rats to determine a 4-hour $LC_{50}$ . For the derivation of AEGL-3, a BMCL<sub>05</sub> of 1652 ppm, derived with the Log-Probit model, was used. $BMCL_{05} = 1652 \text{ ppm}$ $BMC_{01} = 1775 \text{ ppm}$ Probit Model with 0.95 Confidence Level Probit 0.8 0.6 Fraction Affected 0.4 0.2 BMDL BMD dose 13:04 08/03 2004 Probit Model \$Revision: 2.1 \$ \$Date: 2000/02/26 03:38:53 \$ Input Data File: C:\BMDS\DATA\BA-4HR.(d) Gnuplot Plotting File: C:\BMDS\DATA\BA-4HR.plt Tue Aug 03 13:04:20 2004 BMDS MODEL RUN The form of the probability function is: P[response] = Background + (1-Background) \* CumNorm(Intercept+Slope\*Log(Dose)), where CumNorm(.) is the cumulative normal distribution function

dependent variable = Conc.ope parameter is not restrictedotal number of observations = 6otal number of records with missing values = 0aximum number of iterations = 250elative Function Convergence has been set to: 1e-008rameter Convergence has been set to: 1e-008ser has chosen the log transformed modelefault Initial (and Specified) Parameter Valuesbackground = 0intercept = -37.3048slope = 4.7058symptotic Correlation Matrix of Parameter Estimates*** The model parameter(s) -background have been estimateen specified by the user, and do not appear in the correlationintercept 1lope -1lope	1	= Mortality		
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intercept         -41.1086         11.4106           slope         5.18388         1.44983	Variable	Parameter Estimate	es Std. Err.	
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A - Indicates that this parameter has hit a bound implied by s	Variable background intercept slope	Parameter Estimate Estimate 0 -41.1086 5.18388	es Std. Err. NA 11.4106 1.44983	

2

Analysis of Deviance Table						
Model	Log(likelihood)	Deviance	Test DF	P-value		
Full model	-22.3996					
Fitted model	-23.0385	1.27778	4	0.8651		
Reduced model	-34.7949	24.7906	5	0.0001529		

AIC: 50.077

9								
10		Goodness of Fit						
11	Dose	Est. Prob.	Expected	Observed	Size	Scaled Residual		
12	0.0000	0.0000	0.0000	0	10	0		
13	1990.0000	0.0416	0.416	0	10	-0.6588		
14	2035.0000	0.0530	0.530	1	10	0.6636		
15	2500.0000	0.2913	2.913	3	10	0.06083		
16	2828.0000	0.5356	5.356	5	10	-0.2257		
17	3041.0000	0.6793	6.793	7	10	0.1401		
18	Chi-square = 0	.95	DF = 4		P-value = 0.9175			
19								

Benchmark Dose Computation

Specified effect = 0.05 Risk Type = Extra risk Confidence level = 0.95 

BMC = 2023.91 BMDL = 1651.9

**APPENDIX C: Derivation Summary for Butyl Acrylate AEGLs** 

# ACUTE EXPOSURE GUIDELINE LEVELS FOR *n*-BUTYL ACRYLATE (CAS Reg. No. 141-32-5) DERIVATION SUMMARY

AEGL-1 VALUES							
10-minute	30-minute	1-hour	4-hour	8-hour			
8.3 ppm	8.3 ppm	8.3 ppm	8.3 ppm	8.3 ppm			
<ul> <li>Key Reference:</li> <li>Rohm and Haas, Co. 1992. Initial submission: 2-Propenoic acid, butyl ester: translation of German article on industrial hygiene and toxicology describing studies in rats with cover letter dated 081292. Doc ID 88-920005597.</li> <li>Merkle, J. and HJ. Klimisch. 1983. N-Butyl acrylate: prenatal inhalation toxicity in the rat. Fundam. Appl. Toxicol. 3:443-447.</li> </ul>							
Test Species/Strai	n/Number:	Rat/Sprague-Dawle	ey/30				
Exposure Route/C 6-15.	Concentrations/Dura	ations: Inhalation: 2	5-250 ppm, 6 hr/day	y, gestation days			
Effects: 25 ppm: no m 135 and 250 p number of live	Effects: 25 ppm: no maternal effects or clinical signs. 135 and 250 ppm: decreased maternal body weight, clinical signs of irritation, reduced number of live fetuses and increased resorptions.						
Endpoint/Concent clinical signs.	Endpoint/Concentration/Rationale: No-observed-effect level/25 ppm/below threshold for clinical signs.						
Uncertainty Factors/Rationale: Total uncertainty factor: 3 Interspecies: 1, clinical signs similar among different species. Intraspecies: 3, mechanism of irritation is not expected to differ between individuals.							
Modifying Factor: None							
Animal to Human	Animal to Human Dosimetric Adjustment: Not applicable						
Time Scaling: Extrapolation to time points was not done.							
Data Adequacy: No human data and only limited animal data were available.							

AEGL-2 VALUES					
10-minute	30-minute	1-hour	4-hour	8-hour	
160 ppm	160 ppm	130 ppm	81 ppm	53 ppm	
Key Reference: H der subakuten tox	Klimisch, HJ., K. E kizität von <i>n</i> -butylac	Deckardt, and D. Mi rylat. BASF, Ludw	rea. 1978. Bericht <sup>,</sup> igshafen.	über die prüft	
Test Species/Stra	in/Number: Rat/Spr	ague-Dawley/20/se	x/group		
Exposure Route/ 5 d/week, 13 wee	Concentrations/Dura ks.	ations: Inhalation/ 0	, 21, 108, 211, or 54	46 ppm/6 hr/d	
10 21 54 m Endpoint/Concer	08 ppm: decreased w 1 ppm: decreased w 6 ppm: mortality, de ucosa and necrosis o ntration/Rationale: C	veight gain veight gain, clinical ecreased weight gai of lungs Clinical signs and his	signs, lesions on na n, clinical signs, les stopathology/211 pj	sal mucosa ions on nasal	
Uncertainty Factors/Rationale: Total uncertainty factor: 3 Interspecies: 1, clinical signs similar among different species. Intraspecies: 3, mechanism of irritation is not expected to differ between individuals.					
Modifying Factor	r: None				
Animal to Human Dosimetric Adjustment: Not applicable Time Scaling: $C^n \times t = k$ where n ranges from 0.8 to 3.5 (ten Berge et al. 1986). In the absence of an empirically derived, chemical-specific exponent, scaling was performed using n = 3 for extrapolating to the 30-minute and 1- and 4-hour time points and n = 1 for the 8-hour time point. According to Section 2.7 of the Standing Operating Procedures for Developing Acute Exposure Guideline Levels for Hazardous Chemicals (NRC 2001), 10-minute values are not to be scaled from an experimental exposure time of $\geq$ 4 hours. Therefore, the 30- minute AEGL-2 value was also adopted as the 10-minute value.					
Data Adequacy: No acute exposure data were available for derivation of AEGL-2; values were derived from a subchronic study.					
	<u></u>				

	AEGL-3 VALUES					
10-minute	30-minute	1-hour	4-hour	8-hour		
820 ppm	820 ppm	480 ppm	170 ppm	97 ppm		
Key Reference:	Oberly, R. and exposed to va Toxicol. Envir	1 M.F. Tansy. 1983 pors of acrylic and ron. Health 16:811	5. LC50 values methacrylic acie -822.	for rats acutely d esters. J.		
Test Species/Strai	n/Number: Rat/Sprag	ue-Dawley/10				
Exposure Route/C ppm/4 hr.	Concentrations/Duratio	ons: Inhalation/199	0, 2035, 2500, 2	2828, or 3041		
Effects: 27	30 ppm: 4-hour $LC_{50}$					
Clinical signs of	f irritation during exp	osures; death due to	o cardiopulmona	ary collapse.		
Endpoint/Concent analysis. The resu minute, 1-hour, an	tration/Rationale: A 4 alting 4-hour BMCL <sub>0:</sub> and 8-hour AEGL-3 va	-hour BMCL <sub>05</sub> valu 5 of 1652 ppm was lues.	e was calculate used to derive th	d by a log-probit he 10-minute, 30		
Uncertainty Factor Total uncertaint Interspecies: 3 Intraspecies: 3	Uncertainty Factors/Rationale: Total uncertainty factor: 10 Interspecies: 3, little species variation. Intraspecies: 3, mechanism of lethality is not expected to differ between individuals.					
Modifying Factor	: None					
Animal to Human	Dosimetric Adjustme	ent: Not applicable				
Fime Scaling: $C^n \times t = k$ where n ranges from 0.8 to 3.5 (ten Berge et al. 1986). A value of n = 1.3 was calculated by combining 1- and 4- hour LC <sub>50</sub> data sets from ethyl acrylate (NAC 2004a) in a 3-dimensional probit analysis (Zwart et al. 1992). According to Section 2.7 of he Standing Operating Procedures for Developing Acute Exposure Guideline Levels for Hazardous Chemicals (NRC 2001), 10-minute values are not to be scaled from an experimental exposure time of $\geq$ 4 hours. Therefore, the 30-minute AEGL-3 value was also adopted as the 10-minute value.						
Data Adequacy: ' concentrations. C in good agreemen	The key LC <sub>50</sub> study w Other studies reporting t with that of Oberly a	as well conducted as $4$ -hour LC <sub>50</sub> value and Tansy (1985).	and included mo s in rats (BASF	ortality ratios at a 1979b,c, 1980)		

**APPENDIX D: Time-scaling Category Plot for Butyl Acrylate** 



- 27 Some lethality = Some, but not all, exposed animals died
- 28 Lethal = All exposed animals died