Interim: 09/2009

ACUTE EXPOSURE GUIDELINE LEVELS (AEGLs)

FOR

1,2-BUTYLENE OXIDE

(CAS Reg. No. 106-88-7)

C_4H_8O

Interim

Oak Ridge National Laboratory, managed by UT-Battelle, LLC, for the U.S. Dept. of Energy under contract DE-AC05-00OR22725.

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

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SUMMARY

1,2-Butylene oxide (C_4H_8O; CAS No. 106-88-7) is a clear, colorless, highly flammable liquid with a pungent odor. The 1,2-isomer is used as a stabilizer in chlorinated hydrocarbon solvents and for the production of the corresponding butylene glycols and their derivatives. Butylene oxides are also used to make butanolamines, surface active agents, and gasoline additives. Annual U.S. production was reported as 8 million pounds in 1988 (NTP 1988). Recent production data were not available in the open literature.

No information on human exposure was located. Acute, repeat-exposure, and carcinogenicity studies were available for the rat and mouse. The target tissue of 1,2-butylene oxide is the respiratory tract, and it is a direct-acting irritant. Metabolism is via glutathione conjugation. In studies with laboratory rodents, systemic effects were either not observed or were minor. Following acute and repeat-exposures, inflammation and lesions of the rodent nasal mucosa were observed. Chronic exposure at sufficiently high concentrations resulted in clear evidence of carcinogenicity in male rats (alveolar/bronchiolar neoplasms), equivocal evidence in female rats, and no evidence of a carcinogenic response in male and female mice. AEGL values were based on acute studies with support from two well-conducted repeat-exposure studies (Miller et al. 1981; NTP 1988).

A level of distinct odor awareness (LOA) of 0.15 ppm was calculated for 1,2-butylene oxide. 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, and about 10% of the population will experience a strong odor intensity.

The point of departure for the AEGL-1 was the 4-hour exposure of rats to 721 ppm 1,2-butylene oxide (NTP 1988), considered a NOAEL for eye irritation. The next highest concentration, 1420 ppm for 4 hours, resulted in signs of eye irritation. No clinical signs and no lesions of the nasal epithelium were observed in either rats or mice exposed to 400 ppm in a 2-week repeat-exposure study. Therefore, the consequences of exposure to 400 ppm are below the definition of an AEGL-1. Identification of the 721 ppm value as the point of departure is supported by observations at the 7-hour exposure to 1000 ppm in which signs of moderate irritation, as evidenced by lower respiratory parameters, were observed (Reitz et al. 1983). Interspecies and intraspecies uncertainty factors of 3 each for a total of 10 were applied as slight irritation is not expected to differ greatly between species or among humans. Application of a greater uncertainty factor (10 and 3 for a total of 30), would bring the 4-hour value to 24 ppm, a value approximately 16-fold less than the no-effect concentration of 400 ppm in repeat-exposure studies with the rat and mouse (Miller et al. 1981; NTP 1988). The 4-hour 72 ppm value was not time-scaled as there is adaptation to the slight irritation that defines the AEGL-1.

The point of departure for calculation of the AEGL-2 was the 4-hour exposure of rats to 1420 ppm during which signs of eye irritation without tearing were seen (NTP 1988). Choice of the 1420 ppm value is supported by the 7-hour exposure to 1000 ppm in which signs of moderate irritation, as evidenced by lower respiratory parameters, were observed (Reitz et al. 1983). Interspecies and intraspecies uncertainty factors of 3 each for a total of 10 were applied. Moderate irritation is not expected to differ greatly between species or among humans. Furthermore, application of larger uncertainty factors (10 and 3 for a total of 30) would bring the

4-hour AEGL-2 value to 47 ppm, a factor of 10 less than the no-effect concentration of 400 ppm in repeat-exposure studies with the mouse and rat (Miller et al. 1981; NTP 1988). Because the irritation was considered moderate and because of the long (4-hour) exposure, the resulting 140 ppm value was not time-scaled.

The point of departure for the AEGL-3 was the 4-hour exposure of rats to the highest non-lethal concentration, 2050 ppm. A benchmark concentration could not be calculated because all rats died at the next highest concentration of 6550 ppm. The mouse was not chosen as the test species because mice appear to be unusually sensitive to respiratory irritants (NRC 1991) and to glutathione-depleting chemicals (U.S. EPA 2007). The 4-hour 2050-ppm concentration was scaled using interspecies and intraspecies uncertainty factors of 3 each (total of 10). Inter-and intraspecies uncertainty factors of 3 are sufficient for chemicals whose mode of action is direct contact irritation. Application of larger uncertainty factors, for example a total of 30, would lower the 4-hour value to 68 ppm, far below the 400 ppm no-effect concentration in repeat-exposure studies with both the rat and mouse. The resulting 4-hour concentration is 210 ppm. In the absence of information on concentration-exposure duration relationships, the 210 ppm value was time-scaled to the 30-minute and 1-hour exposure durations ($C^n \times t = k$) using an n value of 3 (NRC 2001). Because of uncertainty in time scaling from a 4-hour exposure to a 10-minute exposure, the 10-minute value was set equal to the 30-minute value. Based on the no-effect 13-week study in which rats and mice inhaled 150 ppm (Miller et al. 1981), the same value of 210 ppm was considered appropriate for the 8-hour AEGL-3.

The calculated values are listed in the table below.

S 1. **Summary of AEGL Values for 1,2-Buthylene Oxide** [1]

Classification	10-min	30-min	1-h	4-h	8-h	Endpoint (Reference)
AEGLB1 (Nondisabling)	72 ppm (210 mg/m^3)	72 ppm (210 mg/m^3)	72 ppm (210 mg/m^3)	72 ppm (210 mg/m^3)	72 ppm (210 mg/m^3)	NOAEL for eye irritation – rat – (NTP 1988)
AEGLB2 (Disabling)	140 ppm (410 mg/m^3)	140 ppm (410 mg/m^3)	140 ppm (410 mg/m^3)	140 ppm (410 mg/m^3)	140 ppm (410 mg/m^3)	Moderate eye irritation – rat – (NTP 1988)
AEGLB3 (Lethal)	410 ppm (1200 mg/m^3)	410 ppm (1200 mg/m^3)	330 ppm (970 mg/m^3)	210 ppm (620 mg/m^3)	210 ppm (620 mg/m^3)	Highest non-lethal concentration – rat (NTP 1988)

[1]A Level of Distinct Odor Awareness (LOA) of 0.15 ppm was calculated for 1,2-butylene oxide, as shown in Appendix A. The LOA is defined as the concentration above which it is predicted that more than half of the exposed population will experience at least a distinct odor intensity, and about 10% of the population will experience a strong odor intensity.

A cancer assessment based upon the carcinogenic potential of 1,2-butylene oxide revealed that AEGL values for a theoretical excess lifetime 10^{-4} carcinogenic risk were lower than AEGL values developed from noncancer endpoints. Available data indicate that the observed tumorigenic response to 1,2-butylene oxide is the result of repeated long-term exposure causing repetitive tissue damage. Because AEGLs are applicable to rare events or single once-in-a lifetime-exposure and because of the uncertainty in assessing excess cancer risk following a single acute exposure of 8 hours or less, the acute toxicity values were used to set AEGL levels.

1. INTRODUCTION

1,2-Butylene oxide (C_4H_8O; CAS No. 106-88-7) is a clear, colorless liquid with a pungent odor (Dow Chemical Co. 1988). It is highly flammable and reactive. The liquid is relatively stable but may react with materials having a labile hydrogen. Chemical and physical properties are listed in Table 1. Butylene oxide is available commercially as the single isomer or as a mixture of the 1,2- (80-90%) and 2,3-butylene oxide (10-20%) (Waechter et al. 2001). The present analysis addresses the 1,2-isomer.

1,2-Butylene oxide is a stabilizer in chlorinated hydrocarbons including 1,1,1-trichloroethane, trichloroethylene, and dichloromethane (NTP 1988; IARC 1999; Waechter et al. 2001). The butylene oxides are used for the production of the corresponding butylene glycols and their derivatives such as polybutylene glycols, mixed polyglycols, and glycol ethers and esters. They are also used to make butanolamines, surface active agents, and gasoline additives.

1,2-Butylene oxide is produced commercially from butylene through the intermediate butylene chlorohydrin. It may also be prepared by the epoxidation of 1-butene with peroxyacetic acid (Waechter et al. 2001; HSDB 2003). 1,2-Butylene oxide is listed in high-production volume inventories (European Commission 2000) but recent production data were not located.

TABLE 1. Chemical and Physical Properties

Parameter	Value	Reference
Synonyms	1,2-Butylene oxide; 1,2-epoxybutane; ethyloxirane; 1-butene oxide; 1,2-butene oxide; 1,2-butylene epoxide; α-butylene oxide; 1-butylene oxide; epoxybutane; ethyl ethylene oxide; 2-ethyloxirane	IARC 1999
Chemical formula	C_4H_8O	Waechter et al. 2001
Molecular weight	72.12	Waechter et al. 2001
CAS Reg. No.	106-88-7	HSDB 2003
Physical state	Clear, colorless liquid	Waechter et al. 2001
Solubility in water	82.4 mg/L @ 25°C	Waechter et al. 2001
Vapor pressure	176 mm Hg 18.6 kPa @ 20°C	NTP 1988 IARC 1999
Vapor density (air =1)	2.49	IARC 1999
Liquid density (water =1)	0.83	Waechter et al. 2001
Melting point	–60°C	Waechter et al. 2001
Boiling point	63.3°C	Waechter et al. 2001
Flammability limits in air	Extremely flammable Lower flammable limit: 1.7% v/v Upper flammable limit: 19% v/v	IARC 1999 HSDB 2003; Waechter et al. 2001
Conversion factors	1 ppm = 2.95 mg/m^3 1 mg/m^3 = 0.34 ppm	AIHA 2003

2. HUMAN TOXICITY DATA

No information addressing the toxicity of 1,2-butylene oxide to humans was located. Odor thresholds range from 0.07 to 0.70 ppm (Ruth 1986). Using the data of Hellman and Small, a level of distinct odor awareness (LOA) of 0.15 ppm was calculated for 1,2-butylene oxide (Appendix A). 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, and about 10% of the population will experience a strong odor intensity.

3. ANIMAL TOXICITY DATA

3.1. Acute Lethality

Lethality data are summarized in Table 2. The chemical was not a skin sensitizer in guinea pigs, but elicited marked skin irritation when applied topically and the material occluded in rabbits. Marked eye irritation with corneal injury was observed when the neat chemical was instilled in the eye of rabbits (Waechter et al. 2001).

3.1.1. Rats

A 4-hour inhalation study in Wistar rats found 100% mortality at 8000 ppm and a lowest lethal concentration of 4000 ppm (1 of 6 dead). No further details of the study were provided (Smyth et al. 1962).

Groups of 5 male and 5 female F-344 rats, 7-8 weeks old, inhaled 398, 721, 1420, 2050, or 6550 ppm 1,2-butylene oxide for 4 hours (NTP 1988). Concurrent controls were not included in the protocol and necropsies were not performed. The post-exposure observation period was 14 days. All rats exposed to 6550 ppm died during exposure. No other deaths occurred. Clinical signs observed in both sexes at the 2050 and 6550 ppm exposure included ocular discharge and dyspnea. Signs of eye irritation (no ocular discharge) were observed during the exposure to 1420 ppm. No further details were provided.

3.1.2. Mice

Groups of 5 male and 5 female B6C3F1 mice, 7-9 weeks old, inhaled 398, 721, 1420, or 2050 ppm 1,2-butylene oxide for 4 hours (NTP 1988). Concurrent controls were not included in the protocol and necropsies were not carried out. The post-exposure observation period was 14 days. All mice exposed at 2050 ppm died within 40 minutes of the end of exposure. One of four males in the 398-ppm group, and one male and one female in the 1420-ppm group died shortly after exposure. No deaths occurred in mice exposed to 721 ppm. Dyspnea developed in mice exposed to 2050 ppm. Mice exposed to 1420 ppm appeared restless and showed signs of eye irritation. The study authors calculated four-hour LC_{50} values of 944 ppm (C.L. 540-1516 ppm) and 1234 ppm (C.L. 915-1379 ppm) by probit analysis and the Spearman-Karber rank method, respectively.

TABLE 2. Summary of Acute Inhalation Data in Laboratory Animals

Species	Concentration (ppm)	Exposure Time	Effect[a]	Reference
Rat	4000 8000	4 hours	17% mortality 100% mortality	Smyth et al. 1962
Rat	398 721 1420 2050 6550	4 hours	No signs reported No signs reported Signs of eye irritation Ocular discharge, dyspnea Dyspnea; death, 10/10 animals	NTP 1988
Rat	50 1000	6 hours	No effect Moderate respiratory irritation	Reitz et al. 1983
Mouse	398 721 1420 2050	4 hours	Death, 1/10 animals No deaths Signs of eye irritation; death of 8/10 animals Dyspnea, death of 10/10	NTP 1988

3.2. Nonlethal Acute Toxicity

Other than the study conducted by NTP (1988), no data on acute non-lethal concentrations of 1,2-butylene oxide were located. In the NTP (1988) study, the highest non-lethal 4-hour concentration was 2050 ppm for the rat. Although a highest non-lethal value for the mouse was not reported in the acute study, the absence of effects at 400 ppm in repeat-dose studies with the same strain (Section 3.3) indicates that 721 ppm may be consistent with the highest non-lethal concentration for mice.

As part of a metabolism study, Reitz et al. (1983) measured respiratory parameters of male F-344 rats inhaling 1000 ppm and compared results to rats inhaling 50 ppm. Each group consisted of 5 rats. A plethysmograph/head-only exposure device was employed. Respiratory frequency, tidal volume, and minute volume were reduced by 16%, 17%, and 30%, respectively in rats inhaling 1000 ppm compared with those inhaling 50 ppm. Control values were not provided. The exposure duration was 6 hours. Rats were sacrificed 66 hours post-exposure. Decreases in respiratory rate in the range of 20-50% correspond to moderate irritation (ASTM 1991).

3.3. Repeat Exposure Studies

Repeat-exposure studies are summarized in Table 3. In all cases, animals were sacrificed within a few days post-exposure.

3.3.1. Rats

Groups of 5 male and 5 female F-344 rats, 6-8 weeks of age, inhaled 0, 400, 800, or 1600 ppm 1,2-butylene oxide (>99% pure), 6 hours/day, 5 days/week for a total of 9 days over a 2-week period (Miller et al. 1981). Animals were observed daily for clinical signs and body weights were monitored throughout the study. Hematology, clinical chemistry, and urinalyses

were conducted. At necropsy, organ weights were recorded, and organs and tissues were examined microscopically. Rats exposed to 1600 ppm showed no clinical signs, but body weight was significantly reduced at study termination (by 21% in males and 25% in females). Growth was also impaired in male rats in the 800-ppm group (11%). Rats that inhaled 800 or 1600 ppm groups developed an increased incidence of focal corneal cloudiness. Inflammatory and degenerative changes were observed in both the olfactory and respiratory portions of the nasal turbinates of rats exposed to 800 or 1600 ppm but no such changes were seen in animals that inhaled 400 ppm. No treatment-related changes were seen in the trachea or lungs. Myeloid hyperplasia in the vertebral bone marrow of rats in the 800 and 1600 ppm groups along with elevated white blood cell counts in the 1600-ppm group were considered secondary to inflammation of the nasal passages. No treatment-related lesions were observed in male or female rats exposed to 400 ppm for 9 days.

Groups of 5 male and 5 female F-344 rats, 8-9 weeks old, inhaled 0, 400, 800, 1600, 3200, or 6400 ppm, 6 hours/day, 5 days/week for 14 days (NTP 1988). Animals were observed three times daily and body weights were measured at one and two weeks. Necropsies were performed on all animals. All rats exposed at 3200 or 6400 ppm died before termination of the study, and two of five female rats that inhaled 1600 ppm died before the end of the study. Clinical signs observed in both sexes at 1600 ppm included increased physical activity and piloerection; final mean body weight was less than that of concurrent controls (by 33 and 17% in males and females, respectively). At necropsy, moderate multifocal pulmonary hemorrhage and moderate acute suppurative rhinitis were observed. Final body weight of both sexes was reduced by 12% in the 800 ppm group. No histologic lesions were reported in the 400 ppm group.

Groups of 15 F-344 rats/sex inhaled 0, 75, 150, or 600 ppm for 6 hours/day, 5 days/week for 13 weeks (Miller et al. 1981). The experimental protocol was the same as that reported for the 2-week study. No treatment-related deaths were observed. Slight body weight reductions were observed in females exposed to 600 ppm. Histopathologic examinations revealed treatment-related lesions of the nasal mucosa in both sexes in the 600-ppm group. The changes were attributed to primary upper respiratory irritation. Histologic changes in the nasal turbinates were considered minimal and were characterized by flattening of the olfactory and respiratory epithelia with some focal thickening of the respiratory epithelium. Increased inflammatory infiltrate was present in the nasal mucosa and within the lumen of the nasal cavity. The trachea and lungs remained unaffected. There were no lesions in the 75 or 150 ppm groups that were considered treatment related.

Groups of 10 male and 10 female F-344 rats were exposed to 0, 50, 100, 200, 400, or 800 ppm 1,2-butylene oxide, 6 hours/day and 5 days/week for 13 weeks (Dunnick 1981; NTP 1998). Necropsies were performed and tissues were examined histologically. No treatment-related deaths occurred, and no clinical signs were observed. Body weight of males and females in the 800-ppm groups were reduced at study termination by 23 and 16%, respectively. Inflammation was observed in the nasal cavities of all rats that received 800 ppm, but not at lower concentrations.

TABLE 3. Summary of Repeat-Exposure Studies

Species	Concentration (ppm)	Exposure Time	Effect	Reference
Rat	400 800 1600	6 hours/day, 9 days over 2-week period	No lesions in any tissue or organ Reduced growth (males); inflammatory/ degenerative changes in nasal passages No clinical signs; reduced body weight; inflammatory/degenerative changes in nasal passages	Miller et al. 1981
Rat	400 800 1600 3200 6400	6 hours/day, 5 days/week, 14 days	No lesions in any tissue or organ Reduced body weight (12%) 20% mortality 100% mortality 100% mortality	NTP 1988
Rat	75 150 600	6 hours/day, 5 days/week, 13 weeks	No lesions in any tissue or organ No lesions in any tissue or organ Lesions of the nasal mucosa (minimal)	Miller et al. 1981
Rat	50 100 200 400 800	6 hours/day, 5 days/week, 13 weeks	No clinical signs, no nasal lesions No clinical signs, no nasal lesions No clinical signs, no nasal lesions No clinical signs, no nasal lesions Inflammation of nasal cavity	Dunnick 1981; NTP 1988
Rat	2000	6 hours/day, 4 times/week, 5 months	Mild ataxia of the hindleg in 5th month of exposure; degeneration of myelinated fibers of fasciculus gracilis	Ohnishi and Murai 1993
Mouse	400 800 1600	6 hours/day, 9 days over 2-week period	No lesions in any tissue or organ Reduced growth; inflammatory/ degenerative changes in nasal passages 100% mortality	Miller et al. 1981
Mouse	400 800 1600 3200 6400	6 hours/day, 5 days/week, 14 days	No signs or lesions reported Dyspnea, death of 1 of 5 males 100% mortality 100% mortality 100% mortality	NTP 1988
Mouse	75 150 600	6 hours/day, 5 days/week, 13 weeks	No in lesions in any tissue or organ No lesions in any tissue or organ Reduced growth; nasal lesions	Miller et al. 1981
Mouse	50 100 200 400 800	6 hours/day, 5 days/week, 13 weeks	No lesions in any tissue or organ Nasal lesions (females) Inflammation of nasal turbinates Inflammation of nasal turbinates 100% mortality	Dunnick 1981; NTP 1988

Groups of 5 Wistar rats inhaled 0 or 2000 ppm 1,2-butylene oxide, 4 times/week, for 5 months (Ohnishi and Murai 1993). Treated rats developed mild ataxia of the hindleg in the second and third week of the fifth month of exposure. Histological examination revealed degeneration of myelinated fibers of the fasciculus gracilis at the third cervical segment. Lesions were not observed in other nerve fibers.

3.3.2. Mice

Groups of 5 male and 5 female B6C3F1 mice, 6-8 weeks of age, inhaled 0, 400, 800, or 1600 ppm 1,2-butylene oxide (>99% pure), 6 hours/day, 5 days/week for a total of 9 days over a 2-week period (Miller et al. 1981). The protocol was the same as in the 9-day study with rats. All mice in the 1600-ppm group died prior to the third day of exposure. All mice in the 400 and 800-ppm groups appeared normal and survived until scheduled sacrifice. Growth of both sexes of mice in the 800-ppm group was impaired (body weight 90% of controls). Inflammatory and degenerative changes were observed in both the olfactory and respiratory portions of the nasal turbinates of mice exposed to 800 ppm but not in mice exposed to 400 ppm. No treatment-related changes were seen in the trachea or lungs. Myeloid hyperplasia in the vertebral bone marrow of some mice in the 800-ppm group along with elevated white blood cell counts was considered secondary to inflammation of the tissues in the nasal passages. No treatment-related lesions were observed in male and female mice exposed to 400 ppm for 9 days.

Groups of 5 male and 5 female B6C3F1 mice, 11-12 weeks old, inhaled 0, 400, 800, 1600, 3200, or 6400 ppm butylene oxide, 6 hours/day, 5 days/week for 14 days (NTP 1988). All mice exposed to 1600 ppm or higher and one of five males exposed at 800 ppm died. Clinical signs observed at 800 ppm included dyspnea and listlessness on the first day of exposure. No clinical signs or lesions were reported in mice that inhaled 400 ppm. At necropsy, nephrosis was observed in some animals in the 1600- and 800-ppm groups.

Groups of 15 B6C3F1 mice/sex inhaled 0, 75, 150, or 600 ppm 1,2-butylene oxide for 6 hours/day, 5 days/week for 13 weeks (Miller et al. 1981). The experimental protocol was the same as that reported for the 2-week study. No treatment-related deaths were observed. Significant reductions in body weight were observed for both sexes in the 600 ppm group. Histopathologic examinations revealed treatment-related lesions in the nasal mucosa in both sexes in the 600 ppm group. Microscopic changes in the nasal turbinates were minimal and were characterized by flattening of the olfactory and respiratory epithelia with some focal thickening of the respiratory epithelium. Increased numbers of inflammatory cells were present in the nasal mucosa and within the lumen of the nasal cavity. The trachea and lungs were unaffected. There were no lesions in the 75- or 150-ppm groups that were considered treatment-related. Other lesions and changes in hematology values were not considered treatment-related.

Groups of 10 male and 10 female B6C3F1 mice inhaled 0, 50, 100, 200, 400, or 800 ppm 1,2-butylene oxide, 6 hours/day, 5 days/week for 13 weeks (Dunnick 1981; NTP 1988). Necropsies were performed and tissues and organs were examined microscopically. All mice in the 800-ppm group died; the only clinical sign was listlessness. No clinical signs were observed at lower concentrations. Body weight was unaffected at ≤400 ppm. Renal tubular necrosis was observed only in the 800-ppm group. Inflammation of the nasal turbinates was observed in all mice exposed to 200 ppm or higher and in 0/10 males and 7/10 females exposed at 100 ppm.

Wolf (1961) exposed groups of 10 rats, 8 guinea pigs, and 2 rabbits/sex to 0, 400, or 800 ppm mixed butylene oxide isomers. The blend consisted of 70% 1,2-butylene oxide, 15% 2,3-butylene oxide, and 10% isobutylene oxide. The exposure was for 7 hours/day over a period of 198 days. Mortality and body weight were monitored. Results were only partially reported. Mortality was increased among male rats, but empirical data were not reported. No adverse

effects were observed in any animals at the 400-ppm exposure level. Evaluation of mixed isomers of butylene oxide and poorly described methods and results make this study of reduced relevance to AEGL development.

3.4. Developmental/Reproductive Toxicity

Sikov et al. (1981; Hardin et al. 1981) exposed groups of 38-45 Wistar rats to (1) filtered air for 3 weeks prior to and during gestation, (2) filtered air for 3 weeks prior to gestation followed by exposure to 250 ppm 1,2-butylene oxide for 7 hours/day, 5 days/week during days 1-19 of gestation, (3) filtered air for 3 weeks prior to gestation followed by exposure to 1000 ppm 1,2-butylene oxide for 7 hours/day, 5 days/week during days 1-19 of gestation, (4) 250 ppm 1,2-butylene oxide for 7 hours/day, 5 days/week for 3 weeks prior to gestation followed by exposure to filtered air during days 1-19 of gestation, (5), 250 ppm 1,2-butylene oxide for 7 hours/day, 5 days/week for 3 weeks prior to pregnancy followed by the same exposure during days 1-19 of gestation, (6) 1000 ppm 1,2-butylene oxide for 7 hours/day, 5 days/week for 3 weeks prior to pregnancy followed by filtered air during days 1-19 of gestation, and (7) 1000 ppm 1,2-butylene oxide for 7 hours/day, 5 days/week for 3 weeks prior to pregnancy followed by the same exposure during days 1-19 of gestation. Maternal body weight was reduced 10% in the group exposed to 1000 ppm during days 1-19 of gestation (group 3) and in the group exposed to 1000 ppm 1,2-butylene oxide both prior to and during gestation (group 7). One of 142 dams died pre-gestational in group 7. Fetuses were examined on day 21 of gestation. Fetal growth, viability, and development were unaffected by exposure.

Sikov et al. (1981; Hardin et al. 1981) exposed groups of 24-49 New Zealand white rabbits to 0, 250, or 1000 ppm, 7 hours/day, on gestation days 1 to 24. Pre-gestational exposure was not included as part of the protocol. Maternal deaths occurred in both treated groups (mortalities of 0/49, 6/48, and 14/24, respectively), and post-implantation loss was observed in the 1000-ppm group. The high dose was maternally as well as embryotoxic. Fetal length and weight were reduced in the two surviving litters in the 1000 ppm group, but no abnormalities were observed.

3.5. Genotoxicity

1,2-Butylene oxide is a direct-acting alkylating agent and has been shown to be genotoxic in standard *in vitro* bacterial and mammalian cell assays and *in vivo* in *Drosophila melanogaster* (IARC 1999; Waechter et al. 2001). A series of genetic toxicity tests was conducted by NTP (1988); 1,2-butylene oxide was mutagenic in *Salmonella typhimurium* strains TA100 and TA1535 when tested with a preincubation protocol with and without rat liver S9. *In vitro* 1,2-butylene oxide failed to elicit gene reversion in strains TA1537 or TA98. 1,2-Butylene oxide induced forward mutations at the TK locus of cultured mouse L5178Y lymphoma cells with and without metabolic activation. Both chromosomal aberrations and sister chromatid exchanges were induced in cultured Chinese hamster ovary cells with and without metabolic activation. When fed to male *Drosophila melanogaster*, 1,2-butylene oxide increased significantly the number of sex-linked recessive lethal mutations and reciprocal translocations in the germ cells. These studies with *Salmonella typhimurium* were repeated by Canter and Zeiger (1995). 1,2-Butylene oxide was mutagenic in strains TA100 and TA1535 with or without metabolic

activation. It was not mutagenic in strains TA95 or TA1537 with or without metabolic activation.

1,2-Butylene oxide was subject to mutagenicity screening that included unscheduled DNA synthesis in human diploid fibroblasts, dominant lethal test in male rats (exposures to 250 or 1000 ppm for 7 hours/day for 5 days), sperm abnormality test in male mice (same exposure as dominant lethal test), cytogenetic test in male and female rat bone marrow cells (same exposure as dominant lethal test), and sex-linked recessive lethal test in *Drosophila melanogaster* (1000 ppm) (McGregor 1981). All of the results failed to show any evidence of genotoxicity.

3.6. Chronic Toxicity/Carcinogenicity

Groups of 50 male and 50 female F-344 rats inhaled 0, 200, or 400 ppm 1,2-butylene oxide for 6 hours/day, 5 days/week, for 103 weeks (NTP 1988). The purity of the 1,2-butylene oxide was reported as >99% (Dunnick et al. 1988; NTP 1988). Necropsies were performed and tissues and organs were examined microscopically. Survival of both sexes was similar to that of the concurrent controls until week 50; thereafter, survival in both dosed groups was reduced. Final body weight of all treated groups was reduced by ≤10%. Nasal cavity lesions of rats that inhaled 1,2-butylene oxide included inflammation, epithelial hyperplasia, squamous metaplasia, hyperostosis of the nasal turbinate bone, and atrophy of the olfactory epithelium. Papillary adenomas of the nasal cavity were seen in 7/50 males and 2/50 females in the high dose group. The incidences of alveolar/bronchiolar adenomas or carcinomas (combined) in the control, low-, and high-dose groups of males were 0/50, 2/50, and 5/49, respectively. No carcinomas were observed in female rats.

Groups of 50 male and 50 female B6C3F1 mice inhaled 0, 50, or 100 ppm 1,2-butylene oxide for 6 hours/day, 5 days/week for 102 weeks (NTP 1988). Necropsies were performed and tissues and organs were examined microscopically. Survival was reduced only in females in the high-dose group. Reduced survival was associated with suppurative inflammation of the ovary and uterus. Body weight was reduced in a concentration-related manner for both sexes in both treated groups. Nasal cavity lesions of dosed mice included suppurative inflammation, epithelial hyperplasia, erosion, regeneration, and squamous metaplasia. Lesions were also observed in the olfactory epithelium and nasolacrimal duct. There was no significant increase in total neoplastic lesions in mice.

The NTP (1988) concluded that there was *clear evidence* of carcinogenic activity in male F-344 rats and *equivocal evidence* of carcinogenic activity in female F-344 rats. There was no evidence of carcinogenic activity in male or female B6C3F1 mice. IARC (1999) stated there is *limited* evidence of carcinogenicity in experimental animals. The overall IARC evaluation of 1,2-butylene oxide was that the material is *possibly carcinogenic to humans (Group 2B).* No evidence of carcinogenicity was observed in a topical application study with mice (Van Duuren et al. 1967). Female ICR/Ha mice received applications of 10% 1,2-butylene oxide in acetone on the shaved dorsal skin three times per week for 77 weeks. A cancer assessment based upon the carcinogenic potential of 1,2-butylene oxide as reported by NTP (1988) is in Appendix D.

3.7. Summary

Lethality studies were conducted with rats and mice. The highest non-lethal value following a 4-hour exposure of rats was 2050 ppm 1,2-butylene oxide (NTP 1988). For mice, deaths occurred at all exposures and a highest non-lethal value could not be ascertained (NTP 1988). However, based on the absence of mortality, clinical signs, or lesions in the same strain of mice following 9- and 14-day and 13-week exposures to 400 ppm (NTP 1988), it is unlikely that the single mouse death at 398 ppm following acute exposure is treatment-related. Highest non-lethal concentrations for rats in 9-day, 14-day, and 13-week studies were 1600 ppm, 800 ppm, and 800 ppm, respectively (Miller et al. 1981; NTP 1988). The mouse was more sensitive than the rat. Highest non-lethal concentrations for mice in 9-day, 14-day, and 13-week studies were 800 ppm, 400 ppm, and 600 ppm, respectively (Miller et al. 1981; NTP 1988).

1,2-Butylene oxide was not considered a developmental toxicant at maternally toxic concentrations (Sikov et al. 1981). 1,2-butylene oxide is a direct-acting alkylating agent (IARC 1999). Reverse mutations (base-pair substitutions) were induced in *Salmonella typhimurium* strains TA100 and TA1535 in the presence and absence of metabolic activation. It was mutagenic or genotoxic in a variety of other test systems with and without metabolic activation. 1,2-butylene oxide produced nasal papillary adenomas in rats of both sexes and pulmonary alveolar/bronchiolar tumors in male rats.

4. SPECIAL CONSIDERATIONS

4.1. Metabolism and Disposition

Reitz et al. (1983) studied the fate of 1,2-butylene oxide in rats following inhalation of 50 or 1000 ppm (6 hours) or gavage administration (20 mg/kg in corn oil) to male F-344 rats. Following either route of administration, 1,2-butylene oxide was rapidly absorbed, metabolized, and eliminated. 1,2-butylene was eliminated as unidentified nonvolatile urinary metabolites or as expired carbon dioxide. Radiolabeling on different carbon atoms determined that urinary metabolites are composed of breakdown products rather than the conjugated parent material. Similar percentages of the radiolabel were recovered in the urine and expired air, regardless of inhalation concentration. Steady state was achieved within 30-45 minutes. Steady state uptake rates were 0.0433 mg/kg/min at 50 ppm and 0.720 mg/kg/min at 1000 ppm. Uptakes were estimated at 15.6 and 252 mg/kg during the 6-hour exposure. Absorption, metabolism, and elimination at these concentrations appeared to be linear.

Acute vapor exposure of F-344 male rats to 400, 1000, or 2000 ppm 1,2-butylene oxide caused a dose-related depletion of glutathione (approximated as nonprotein sulfhydryl groups) in liver and kidney tissue (Reitz et al. 1983). Compared to the control, depletions in liver and kidney were 10-11%, 30-36%, and 61-65% at the respective concentrations. Following a single gavage dose to rats (180 mg/kg), 11% of the dose was excreted in the urine as 2-hydroxybutyl mercapturic acid, indicating conjugation with glutathione (James et al. 1968). It is not clear from the Reitz et al. (1983) study that conjugation with glutathione is the only route of metabolism.

4.2. Mechanism of Toxicity

Butylene oxides are moderately acutely toxic and are substantial irritants that react with portal of entry tissues such as the nasal epithelium and lung (Waechter et al. 2001). Both the Miller et al. (1981) and NTP (1988) studies confirm that the nasal mucosa is the target of 1,2-butylene oxide in both rats and mice. The absence of lesions in other organs and tissues as well as the absence of reproductive and developmental effects indicates that the action of 1,2-butylene oxide is a direct effect on the target organ (U.S. EPA 1992).

4.3. Structure Activity Relationships

Lethality studies with the rat are available for the related chemicals, ethylene oxide and propylene oxide. Based on 4-hour LC_{50} values, ethylene oxide (1741 ppm) is more toxic than propylene oxide (3205 ppm) (Nachreiner 1991; NTP 1985). An LC_{50} for 1,2-butylene oxide could not be calculated with the available data, but would be between 2050 and 6550 ppm (NTP 1988).

The mechanism of action for both 1,2-butylene oxide and propylene oxide is that of a direct-acting irritant. Interim AEGL values have been derived for the related chemical, propylene oxide (Table 4). AEGL-1, -2, and -3 values were based on human irritation, dyspnea in mice, and a 4-hour $BMCL_{05}$ in rats, respectively (U.S. EPA 2001).

TABLE 4. AEGL Values for Propylene Oxide

Classification	Exposure Duration				
	10-min	30-min	1-h	4-h	8-h
AEGL-1	73 ppm	73 ppm	73 ppm	73 ppm	73 ppm
AEGL-2	440 ppm	440 ppm	290 ppm	130 ppm	86 ppm
AEGL-3	1300 ppm	1300 ppm	870 ppm	390 ppm	260 ppm

Data from studies on structural analogs of 1,2-butylene oxide indicate that neoplasms in organ systems other than the nasal cavity are present with exposure to the 2-carbon analog (ethylene oxide), but absent with exposure to the 3-carbon analog (propylene oxide) or the 4-carbon analog (1,2-butylene oxide) (U.S. EPA 1992).

4.4. Other Relevant Information

4.4.1. Species Variability

The available studies conducted with rats and mice indicate that mice are more susceptible to the toxicity of 1,2-butylene oxide than rats. According to the NRC (1991), for some respiratory irritants such as hydrogen chloride, the mouse may not be a good model for extrapolation to humans. Mice have been shown to be more sensitive to glutathione depletion when inhaling chemicals metabolized via glutathione conjugation (Csanady et al. 2003; U.S. EPA 2007). Mice were approximately two-fold more sensitive than rats to inhaled methyl chloride, a chemical also conjugated via glutathione. For inhaled styrene, modeled values indicate relative reductions of pulmonary glutathione in the order: mouse>>rat>human. Depletion of glutathione may impair the ability of tissues to suppress lipid peroxidation reactions

(Kornbrust and Bus 1984). Mice also have higher levels of glutathione-S-transferase in their tissues than rats or humans (Griem et al. 2002).

4.4.2. Susceptible Populations

No information on susceptible populations was located. Humans differ in their response to irritant chemicals, and asthmatics would be more sensitive than healthy individuals. Although humans differ in the rate at which they metabolize other chemicals via glutathione conjugation (e.g., methyl chloride), the difference does not appear to be toxicologically significant (Nolan et al. 1985).

4.4.3. Concentration-Exposure Duration Relationship

No information on a concentration-exposure duration relationship was located. All acute rodent studies were conducted for 4 hours. The concentration-exposure duration relationship for many irritant and systemically-acting vapors and gases has been described by $C^n \times t = k$ where the exponent n values range from 0.8 to 3.5 (ten Berge et al. 1986). In the absence of a chemical-specific, empirically described exponent, default values of n = 3 and n = 1 when extrapolating to shorter and longer time periods is used (NRC 2001). This method will yield the most conservative AEGL estimates.

4.4.4. Concurrent Exposure Issues

No information relevant to concurrent exposure issues was located.

5. DATA ANALYSIS FOR AEGL-1

5.1. Summary of Human Data Relevant to AEGL-1

No human studies were available for development of AEGL-1 values.

5.2. Summary of Animal Data Relevant to AEGL-1

No signs were reported in rats exposed to 398 or 721 ppm 1,2-butylene oxide for 4 hours (NTP 1988). Eye irritation (severity not described) was reported at the next highest concentration, 1420 ppm. In repeat-exposure studies of 9 and 14 days, 6 hours/day, no lesions were reported in either rats or mice exposed to 400 ppm (Miller et al. 1981; NTP 1988). A 7-hour exposure of rats to 1000 ppm resulted in decreases in respiratory parameters of 10-30%, indicating moderate irritation (Reitz et al. 1983). Animals were sacrificed at 2.75 days post-exposure. Further details including deaths were not reported.

5.3. Derivation of AEGL-1

The point of departure for the AEGL-1 is the 4-hour exposure of rats to 721 ppm 1,2-butylene oxide (NTP 1988), considered a NOAEL for eye irritation. The next highest concentration, 1420 ppm for 4 hours, resulted in signs of eye irritation. No clinical signs and no lesions were observed in either rats or mice exposed to 400 ppm in a repeat-exposure study.

Therefore, effects of exposure to 400 ppm are below the definition of an AEGL-1. Choice of the 721 ppm value is supported by the 7-hour exposure to 1000 ppm in which signs of moderate irritation, as evidenced by lower respiratory parameters, were observed (Reitz et al. 1983). Interspecies and intraspecies uncertainty factors of 3 each for a total of 10 were applied as slight irritation is not expected to differ greatly between species or among humans. Application of a greater uncertainty factor (10 and 3 for a total of 30), would bring the 4-hour value to 24 ppm, a value approximately 16-fold less than the no-effect concentration of 400 ppm in repeat-exposure studies with the rat and mouse (Miller et al. 1981; NTP 1988). The 4-hour 72 ppm value was not time-scaled as there is adaptation to the slight irritation that defines the AEGL-1. AEGL-1 values are summarized in Table 5 and calculations are in Appendix B. A graph of AEGL values in relation to toxicity data is in Appendix C.

TABLE 5. AEGL-1 Values for 1,2-Butylene Oxide

10-min	30-min	1-h	4-h	8-hour
72 ppm (210 mg/m^3)	72 ppm (210 mg/m^3)	72 ppm (210 mg/m^3)	72 ppm (210 mg/m^3)	72 ppm (210 mg/m^3)

6. DATA ANALYSIS FOR AEGL-2

6.1. Summary of Human Data Relevant to AEGL-2

No human studies were available for development of AEGL-2 values.

6.2. Summary of Animal Data Relevant to AEGL-2

Studies addressing irritation and reversible lesions were available for the rat and mouse (NTP 1988). Following an acute 4-hour exposure to 1420 ppm, signs of eye irritation were seen in the rat. The next highest concentration, 2050 ppm for 6 hours was the highest non-lethal value; ocular discharge and dyspnea were observed. These effects are greater than those defined by the AEGL-2. A 7-hour exposure of rats to 1000 ppm resulted in decreases in respiratory parameters of 10-30%, indicating moderate irritation (Reitz et al. 1983). Animals were sacrificed at 2.75 days post-exposure. Further details including deaths were not reported.

6.3. Derivation of AEGL-2

The point of departure for the AEGL-2 is the 4-hour exposure of rats to 1420 ppm during which eye irritation was seen (NTP 1988). There was no report of lacrimation which might impair the ability to escape. Choice of the 1420 ppm value is supported by the 7-hour exposure to 1000 ppm in which signs of moderate irritation, as evidenced by lower respiratory parameters, were observed (Reitz et al. 1983). Interspecies and intraspecies uncertainty factors of 3 each for a total of 10 were applied. Moderate irritation is not expected to differ greatly between species or among humans. Furthermore, application of larger uncertainty factors (10 and 3 for a total of 30) would bring the 4-hour AEGL-2 value to 47 ppm, a factor of 10 less than the no-effect concentration of 400 ppm in repeat-exposure studies with the mouse and rat (Miller et al. 1981; NTP 1988). Because the irritation was considered moderate and because of the long (4-hour) exposure, the resulting 140 ppm value was not time-scaled. AEGL-2 values are summarized in

Table 6 and calculations are in Appendix B. A graph of AEGL values in relation to toxicity data is in Appendix C.

TABLE 6. AEGL-2 Values for 1,2-Butylene Oxide

10-min	30-min	1-h	4-h	8-h
140 ppm (410 mg/m^3)	140 ppm (410 mg/m^3)	140 ppm (410 mg/m^3)	140 ppm (410 mg/m^3)	140 ppm (410 mg/m^3)

Holding the AEGL-2 value constant across exposure durations is supported by the Interim AEGL-2 values for acrolein which were also based on irritation (http://www.epa.gov/oppt/aegl/). In that clinical study, prolonged exposure to acrolein was not expected to result in a greatly enhanced effect.

7. DATA ANALYSIS FOR AEGL-3

7.1. Summary of Human Data Relevant to AEGL-3

No human studies were available for development of AEGL-3 values.

7.2. Summary of Animal Data Relevant to AEGL-3

Studies addressing lethality and highest non-lethal concentrations were available for the rat and mouse (NTP 1988). Following an acute 4-hour exposure, the highest nonlethal concentration for the rat was 2050 ppm. The next highest concentration, 6550 ppm resulted in 100% morality. A highest non-lethal value for the mouse could not be ascertained, but based on results of repeat-dose studies, is estimated at 721 ppm. Highest non-lethal concentrations in 9-day repeat-dose studies were 1600 and 800 ppm for the rat and mouse, respectively (Miller et al. 1981).

7.3. Derivation of AEGL-3

The point of departure for the AEGL-3 is the 4-hour exposure of rats to the highest non-lethal concentration, 2050 ppm. A benchmark concentration could not be calculated because all rats died at the next highest concentration of 6550 ppm. The mouse was not chosen as the test species because mice appear to be unusually sensitive to respiratory irritants (NRC 1991) and to glutathione-depleting chemicals (Csanady et al. 2003; U.S. EPA 2007). The 4-hour 2050-ppm concentration was divided by interspecies and intraspecies uncertainty factors of 3 each for a total of 10. Interspecies and intraspecies uncertainty factors of 3 each are sufficient for chemicals whose mode of action is direct contact irritation. Application of larger uncertainty factors, for example a total of 30, would lower the 4-hour value to 68 ppm, far below the 400 ppm no-effect concentration in repeat-exposure studies with both the rat and mouse. The resulting 4-hour concentration is 210 ppm. In the absence of information on concentration-exposure duration relationships, the 210 ppm value was time-scaled to the 30-minute and 1-hour exposure durations ($C^n \times t = k$) using an n value of 3 (NRC 2001). Because of uncertainty in extrapolating from a 4-hour exposure to a 10-minute exposure, the 10-minute value was set equal to the 30-minute value. Based on the no-effect repeat-exposure concentration for rats and mice of 400 ppm (Miller et al. 1981; NTP 1988) and on the 13-week study in which rats inhaled up to

800 pm without mortality (NTP 1988), the same value of 210 ppm was considered appropriate for the 8-hour AEGL-3. AEGL-3 values are summarized in Table 7 and calculations are in Appendix B. A graph of AEGL values in relation to toxicity data is in Appendix C.

TABLE 7. AEGL-3 Values for 1,2-Butylene Oxide

10-min	30-min	1-h	4-h	8-h
410 ppm (1200 mg/m^3)	410 ppm (1200 mg/m^3)	330 ppm (970 mg/m^3)	210 ppm (620 mg/m^3)	210 ppm (620 mg/m^3)

8. SUMMARY OF AEGLs

8.1. AEGL Values and Toxicity Endpoints

AEGL values based on acute exposures are summarized in Table 8. An estimation of AEGLs based on carcinogenic potential resulting from a single, short-term exposure was conducted (Appendix D). The assessment showed that AEGL values derived from carcinogenic effects are lower than values for all AEGL levels. Available data indicate that the observed tumorigenic response to 1,2-butylene oxide is the result of repeated long-term exposure causing repetitive tissue damage. Because of the uncertainties inherent in assessing excess cancer risk following a single acute exposure of 8 hours or less duration, the acute toxicity values were used to set AEGL values.

TABLE 8. Summary of AEGL Values

Classification	Exposure Duration				
	10-min	30-min	1-h	4-h	8-h
AEGL-1 (Nondisabling)	72 ppm	72 ppm	72 ppm	72 ppm	72 ppm
AEGL-2 (Disabling)	140 ppm	140 ppm	140 ppm	140 ppm	140 ppm
AEGL-3 (Lethal)	410 ppm	410 ppm	330 ppm	210 ppm	210 ppm

8.2. Comparison with Other Standards and Guidelines

Guidelines for 1,2-butylene oxide are limited to the workplace (Table 9). The 8-hour TWA Workplace Environment Exposure Level (WEEL) is 2 ppm (AIHA 2003). An ACGIH TLV has not been established. Based on likely carcinogenicity, a German MAK has not been established (German Research Association 2006).

TABLE 9. Standards and Guidelines for 1,2-Butylene Oxide					
Guideline	Exposure Duration				
	10-min	30-min	1-h	4-h	8-h
AEGL-1	72 ppm	72 ppm	72 ppm	72 ppm	72 ppm
AEGL-2	140 ppm	140 ppm	140 ppm	140 ppm	140 ppm
AEGL-3	410 ppm	410 ppm	330 ppm	210 ppm	210 ppm
WEEL (AIHA)[a]					2 ppm

[a]**WEEL (Workplace Environmental Exposure Levels, American Industrial Hygiene Association** (AIHA 2003) The WEEL is the time-weighted average 8-hour occupational exposure concentration for chemical and physical agents that protects the health and safety of workers.

8.3. Data Adequacy and Research Needs

No information on human exposure was located. Acute, repeat-exposure, and carcinogenicity inhalation studies were available for the rat and mouse. Developmental and reproductive studies used two species, the rat and rabbit. Fetotoxicity was observed only at maternally toxic doses. The route of metabolism, conjugation with glutathione, is known. However, in studies with laboratory rodents, systemic effects were either not observed or were minor. The target tissue of 1,2-butylene oxide in both acute and chronic studies is the respiratory tract, and it is a direct-acting irritant. Adequate data were available to develop AEGL values based on acute studies with support from well-conducted repeat-exposure studies.

9. REFERENCES

AIHA (American Industrial Hygiene Association). 2003. Workplace Environmental Exposure Level Guide: 1,2-Epoxybutane. Fairfax, VA: AIHA.

ASTM (American Society for Testing and Materials). 1991. Method E981. Pp 610-619 in Standard Test Method for Estimating Sensory Irritancy of Airborne Chemicals, Volume 11.04. Philadelphia, PA: ASTM.

Canter, D.A. and E. Zeiger. 1995. Comparative mutagenicity of aliphatic epoxides in Salmonella. OTS 0522513. Available from the National Technical Service, Springfield, VA.

Csanady, Gy.A., W. Kessler, H.D. Hoffman, and J.G. Filser. 2003. A toxicokinetics model for styrene and its metabolite styrene-7,8-oxide in mouse, rat and human with special emphasis on the lung. Toxicol. Lett. 138:75-102.

Crump, K.S. and R.B. Howe. 1984. The multistage model with a time-dependent dose pattern: Applications to carcinogenic risk assessment. Risk Anal. 4:163-479.

Dow Chemical Company. 1988. Material Safety Data Sheet: 1,2-Epoxybutane. Midland, MI: Dow Chemical Company.

Dunnick, J.K. 1981. Prechronic Test Phase Review. OTS0509932.

Dunnick, J.K., S.L. Eustis, W.W. Pigorsch, and R.A. Miller. 1988. Respiratory tract lesions in F344/N rats and B6C3F1 mice after inhalation exposure to 1,2-epoxybutane. Toxicology 50:69-82.

European Commission. 2000. IUCLID Data Set: 1,2-Epoxybutane.

[German Research Association] Deutsche Forschungsgemeinschaft. 2006. List of MAK and BAT values: 2006. Germany: Wiley-VCH.

Griem, P., M. Hassauer, F. Kaberlah, J. Oltmanns, J. Scheibner, K. Schneider, and U. Schuhmacher-Wolz. 2002. Quantitative differences in xenobiotic metabolism between animals and humans. Federal Institute for Occupational Safety and Health Research Report, Dortmund, Germany. See also Schneider et al. 2002. Naunym.-Schmiedeberg's Arch. Pharmacol. 365:R163.

Hardin, B.D., G.P. Bond, M.R. Sikov, F.D. Andrews, R.P. Beliles, and R.W. Niemeier. 1981. Testing of selected workplace chemicals for teratogenic potential. Scand. J. Work Environ. Health 7 (Suppl. 4):66-75.

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

HSDB (Hazardous Substances Data Bank). 2003. 1-Butene Oxide. Available online: http://toxnet.nlm.nih.gov/cgi-bin/sis/download.txt, retrieved 7/2/2007.

IARC (International Agency for Research on Cancer). 1999. IARC Monographs on the Evaluation of Carcinogenic Risks to Hymans: Re-Evaluation of Some Organic Chemicals, Hydrazine and Hydrogen Peroxide (Part Two), Volume 71. Lyon France: World Health Organization.

James, S.P., D.A. Jeffery, R.H. Waring, and P.B. Wood. 1968. Some metabolites of 1-bromobutane in the rabbit and rat. Biochem. J. 109:727-736.

Kornbrust, D.J. and J.S. Bus. 1984. Glutathione depletion by methyl chloride and association with lipid peroxidation in mice and rats. Toxicol. Appl. Pharmacol. 72:388-399.

McGregor, D.B. 1981. Tier II Mutagenicity Screening of 13 NIOSH Priority Compounds: Individual Compound Report: Butylene Oxide. OTS05099930.

Miller, R.R., J.F. Quast, J.A. Ayres, and M.J. McKenna. 1981. Inhalation toxicity of butylene oxide. Fundam. Appl. Toxicol. 1:319-324.

Nachreiner, 1991. Ethylene oxide: Acute Vapor Inhalation Toxicity Test in Rats (Four-Hour Test). Bushy Run Research Center, Export, PA, Project ID 54-76.

Nolan, R.J., D.L. Dick, T.D. Landry, L.P. McCarty, G.L. Agin, and J.H. Saunders. 1985. Pharmacokinetics of inhaled methyl chloride (CH_3Cl) in male volunteers. Fund. Appl. Toxicol. 5:361-369.

NRC (National Research Council). 1985. Emergency and Continuous Exposure Guidance Levels for Selected Airborne Contaminants, Vol. 5. Washington, DC: National Academy Press.

NRC (National Research Council). 1991. Permissible Exposure Levels and Emergency Exposure Guidance Levels for Selected Airborne Contaminants. Washington, D.C.: National Academy Press.

NRC (National Research Council). 2001. Standing Operating Procedures for Developing Acute Exposure Guideline Levels for Hazardous Chemicals. Washington, DC: National Academy Press.

NTP (National Toxicology Program). 1985. Toxicology and Carcinogenesis Studies of Propylene Oxide (CAS No. 75-56-9) in F344/N Rats and B6C3F1 Mice (Inhalation Studies). Technical Report No. 267. Research Triangle Park, NC: U.S. Department of Health and Human Services.

NTP (National Toxicology Program). 1988. Toxicology and Carcinogenesis Studies of 1,2-Epoxybutane (CAS No. 106-88-7) in F344/N Rats and B6C3F1 Mice (Inhalation Studies). Technical Report No. 329. Research Triangle Park, NC: U.S. Department of Health and Human Services.

Ohnishi, A. and Y. Murai. 1993. Polyneuropathy due to ethylene oxide, propylene oxide, and butylene oxide. Environ. Res. 60:242-247.

Reitz, R.H., T.R. Fox, and E.A. Hermann. 1983. Fate of 1,2-butylene in male rats following inhalation exposure. EPA/OTS Document No. 878213688. Toxicology Research Laboratory, Health and Environmental Sciences, Dow Chemical Company, Midland, MI.

Ruth, J.H. 1986. Odor thresholds and irritation levels of several chemical substances: a review. Am. Ind. Hyg. Assoc. J. 47:A142-A151.

Sikov, M.R., W.C. Cannon, D.B. Carr, R.A. Miller, L.F. Montgomery, and D.W. Phelps. 1981. Teratologic Assessment of Butylene Oxide, Styrene Oxide, and Methyl Bromide. NIOSH Technical Report No. 81-124. Division of Biomedical and Behavioral Science, National Institute of Occupational Safety and Health.

Smyth, H.F., Jr., C.P. Carpenter, C.S. Weil, U.C. Pozzani, and J.A. Striegel. 1962. Range-finding toxicity data: List VI. Am. Ind. Hyg. Assoc. J. 23:95-107.

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

U.S. EPA (United States Environmental Protection Agency). 1992. 1,2-Epoxybutane (EBU) (CASRN 106-88-7). Integrated Risk Assessment System. Available online: http://www.epa.gov/iris/subst/0630.htm.

U.S. EPA (United States Environmental Protection Agency). 1994. Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry. EPA/600/8-90/066F. Available online: http://www.epa.gov/iris/backgr-d.htm.

U.S. EPA (United States Environmental Protection Agency). 2001. Interim Acute Exposure Guideline Levels for Propylene Oxide. Available online: http://www.epa.gov/oppt/aegl/pubs/results17.htm.

U.S. EPA (United States Environmental Protection Agency). 2005. Guidelines for Carcinogen Risk Assessment. Risk Assessment Forum, Washington, DC. EPA/630/P-03/001B. Available online: http://www.epa.gov/iris/backgr-d.htm.

U.S. EPA (United States Environmental Protection Agency). 2007. Acute Exposure Guideline Values: Methyl Chloride. Washington, DC: U.S. EPA.

van Doorn, R., M. Ruijten and T. van Harreveld. 2002. Guidance for the Application of Odor in Chemical Emergency Responses, Unpublished report, Version 2.1, August 29, 2002.

Van Duuren, B.L., L. Langseth, B.M. Goldschmidt, and L. Orris. 1967. Carcinogenicity of epoxides, lactones, and peroxy compounds. VI. Structure and carcinogenic action. J. Natl. Cancer Inst. 39:1217-1228.

Waechter, J.M., L.H.. Pottenger, and G.E. Veenstra. 2001. Epoxy Compounds – Olefin Oxides, Aliphatic Glycidyl Ethers and Aromatic Monoglycidyl Ethers: 1,2-Butylene Oxide. Pp 1021-1025 in Patty's Toxicology, 5th Ed., Vol. 6. New York: John Wiley & Sons, Inc.

Wolf, M.A. 1961. Results of repeated exposures of laboratory animals to the vapors of butylene oxide(s) (mixed isomers). EPA/OTS Document No. 878211232. Dow Chemical Biochemical Research Department, Midland, MI.

APPENDIX A: Derivation of the Level of Distinct Odor Awareness

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, and 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}) for 1,2-butylene oxide, one study (Hellman and Small 1974) was available in which the odor threshold for the reference chemical n-butanol (odor detection threshold 0.04 ppm) was also determined:

Hellman and Small (1974):

odor detection threshold for 1,2-butylene oxide: 0.07 ppm

odor detection threshold for n-butanol: 0.3 ppm

corrected odor detection threshold (OT_{50}) for 1,2-butylene oxide:

0.07 ppm x 0.04 ppm / 0.3 ppm = 0.0093 ppm

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

$$I = kw \times \log (C / OT_{50}) + 0.5$$

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

$3 = 2.33 \times \log (C / 0.0093) + 0.5$ which can be rearranged to

$\log (C / 0.0093) = (3 - 0.5) / 2.33 = 1.07$ and results in

$C = (10^{1.07}) \times 0.0093 = 11.8 \times 0.0093 = 0.11$ 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

$$LOA = C \times 1.33 = 0.11 \text{ ppm} \times 1.33 = 0.15 \text{ ppm}$$

The LOA for 1,2-butylene oxide is 0.15 ppm.

APPENDIX B: Derivation of 1,2-Butylene Oxide AEGLs

Derivation of AEGL-1 Values

Key Study:	NTP 1988
Toxicity endpoint:	No clinical signs, no lesions following 4-hour exposure of rats to 721 ppm; moderate respiratory tract irritation at a higher concentration (1000 ppm) and longer exposure duration (6 hours) (Reitz et al. 1981)
Time scaling:	The 4-hour value was not time scaled as there is adaptation to the mild sensory irritation that defines the AEGL-1.
Uncertainty factors:	Total Uncertainty factor 10 Interspecies: 3, Response to a direct-acting irritant should not differ greatly Intraspecies: 3, Response to a direct-acting irritant should not differ greatly Application of larger uncertainty factors would bring the values down to less than the no-effect value of 400 ppm in repeat-dose studies.
Modifying factor:	None
Calculations:	The 721 ppm concentration was adjusted by a total uncertainty factor of 10. 721 ppm/10 = 72.1 ppm
10-minute AEGL-1:	Set equal to the 4-hour value = 72 ppm
30-minute AEGL-1:	Set equal to the 4-hour value = 72 ppm
1-hour AEGL-1:	Set equal to the 4-hour value = 72 ppm
4-hour AEGL-1:	C = 72 ppm
8-hour AEGL-1:	C = 72 ppm (adaptation to the slight irritation that defines the AEGL-1)

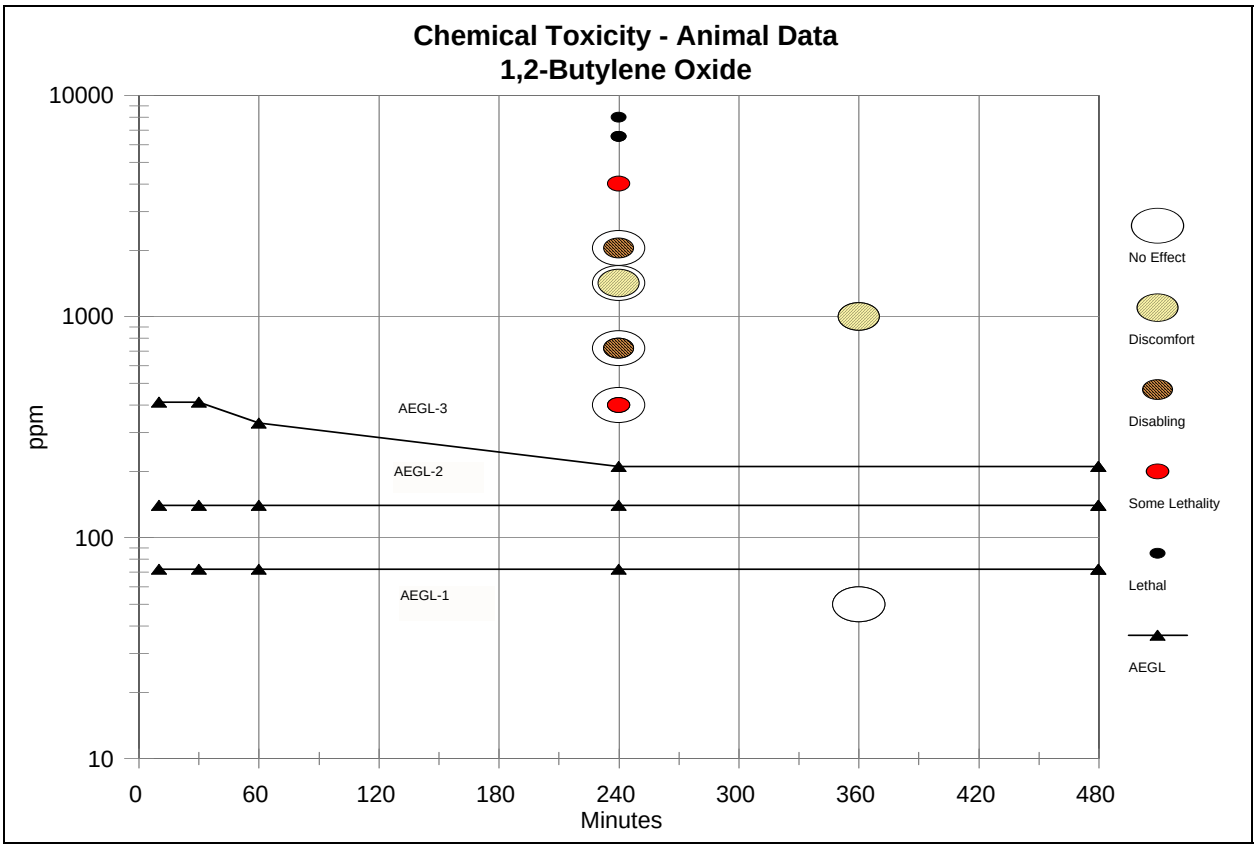
Derivation of AEGL-2 Values

Key Study:	NTP 1988
Toxicity endpoints:	Signs of eye irritation in rats during 4-hour exposure to 1420 ppm, with support from the study of Reitz et al. (1983) in which moderate respiratory tract irritation was observed during a 7-hour exposure to 1000 ppm.
Time scaling	None; there is adaptation to the moderate irritation that defines the AEGL-2; furthermore, the exposure duration was 4 hours.
Uncertainty factors:	Total uncertainty factor: 10 Interspecies: 3, Moderate irritation should not differ greatly between species Intraspecies: 3, Response to a direct-acting irritant should not differ greatly among individuals. Application of a larger uncertainty factor (30) would bring the 4-hour value to 47 ppm, a number 10-fold less than the no-effect level in repeat-exposure studies.
Modifying factor:	None applied
Calculations:	The 1420 ppm concentration was adjusted by a total uncertainty factor of 10: 1420 ppm/10 = 142.0 ppm
10-minute AEGL-2:	Set equal to the 4-hour value of 140 ppm
30-minute AEGL-2:	Set equal to the 4-hour value of 140 ppm
1-hour AEGL-2:	Set equal to the 4-hour value of 140 ppm
4-hour AEGL-2:	C = 140 ppm
8-hour AEGL-2:	Set equal to the 4-hour value of 140 ppm

Derivation of AEGL-3 Values

Key Study:	NTP 1988
Toxicity endpoints:	Highest non-lethal concentration in available 4-hour study with rat: 2050 ppm
Time scaling	Default value of n = 3 for scaling to shorter exposure durations (NRC 2001) The 8-hour value was set equal to the 4-hour value based on non-lethal effects in repeat-exposure studies [400 ppm for 2 weeks and 150 ppm for 13 weeks (Miller et al. 1981)].
Uncertainty factors:	Total uncertainty factor: 10 Interspecies: 3, severe effects from contact irritation should not differ greatly among species (NRC 2001). Intraspecies: 3, severe effects from contact irritation should not vary greatly among individuals (NRC 2001).
Modifying factor:	None applied
Calculations:	The 2050 ppm concentration was adjusted by a total uncertainty factor of 10: 2050 ppm/10 = 205 ppm $C^n \times t = k$, where n = 3 and n = 1 $C^3 \times t$: $205^3 \times 240$ minutes = 2.07×10^9 ppm^3Xminutes
10-minute AEGL-3:	Set equal to the 30-minute value of 410 ppm (NRC 2001).
30-minute AEGL-3:	$C^3 \times 30 = 2.07 \times 10^9$ ppm^3Xminutes C = 410 ppm
1-hour AEGL-3:	$C^3 \times 60 = 2.07 \times 10^9$ ppm^3Xminutes C = 330 ppm
4-hour AEGL-3:	C = 210 ppm
8-hour AEGL-3:	Set equal to the 4-hour value of 210 ppm

APPENDIX C: Category Graph of AEGL Values and Toxicity Data



Data:

For Category: 0 = No effect, 1 = Discomfort, 2 = Disabling, SL = Some Lethality, 3 = Lethal					
Source	**Species**	**ppm**	**Minutes**	**Category**	**Comments**
NAC/AEGL-1		72	10	AEGL	
NAC/AEGL-1		72	30	AEGL	
NAC/AEGL-1		72	60	AEGL	
NAC/AEGL-1		72	240	AEGL	
NAC/AEGL-1		72	480	AEGL	
NAC/AEGL-2		140	10	AEGL	
NAC/AEGL-2		140	30	AEGL	
NAC/AEGL-2		140	60	AEGL	
NAC/AEGL-2		140	240	AEGL	
NAC/AEGL-2		140	480	AEGL	
NAC/AEGL-3		410	10	AEGL	
NAC/AEGL-3		410	30	AEGL	
NAC/AEGL-3		330	60	AEGL	
NAC/AEGL-3		210	240	AEGL	
NAC/AEGL-3		210	480	AEGL	
Smyth et al. 1962	rat	4000	240	SL	17% mortality
	rat	8000	240	3	100% mortality
NTP 1988	rat	398	240	0	No signs reported
	rat	721	240	0	No signs reported
	rat	1420	240	1	Signs of eye irritation
	rat	2050	240	2	Ocular discharge, dyspnea
	rat	6550	240	3	100% mortality
NTP 1988	mouse	398	240	SL	10% mortality
	mouse	721	240	2	No deaths
	mouse	1420	240	SL	80% mortality
	mouse	2050	240	3	100% mortality
Reitz et al. 1983	rat	50	360	0	No effect
	rat	1000	360	1	Signs of irritation

APPENDIX D: Cancer Assessment for 1,2-Butylene Oxide

NTP (1988) has conducted cancer bioassays for 1,2-butylene oxide in F344 rats and B6C3F1 mice. There was clear evidence of carcinogenicity in male rats, equivocal evidence of carcinogenicity in females, and no evidence of carcinogenicity in male and female mice. EPA has not conducted a cancer assessment for 1,2-buylene oxide.

Animals were exposed to 0, 200, or 400 ppm for 6 hours/day and 5 days/week for 105 weeks. In male rats there was a statistically significant increase in papillary adenomas of the nasal cavity (0/50; 0/50; 7/50). There was also a statistically significant increase in alveolar/bronchiolar neoplasms (0/50; 2/50; 5/49). The average body weight after 105 weeks was 425 g.

The NAC used these data to derive an Inhalation Unit Risk for 1,2-butylene oxide using procedures consistent with U.S. EPA (1994) and U.S. EPA (2005). The multi-stage model (EPA Benchmark Dose Software, version 1.4.1) was used to calculate the lower 95% confidence limit to give a 10% tumor response ($BMCL_{10}$). The human equivalent concentration was calculated by adjusting to continuous exposure (24 hours/day and 7 days/week) and using $RGDR_{ET}$ (Regional Gas Deposition Ratio for the extrathoracic region) or $RGDR_{PU}$ (Regional Gas Deposition Ratio for the pulmonary region) (U.S. EPA, 1994).

$BMCL_{10\ HECET}$ = 284.17 x 6/24 x 5/7 x 0.063 = 3.196913 ppm

$BMCL_{10\ HECPU}$ = 245.768 x 6/24 x 5/7 x 0.065 = 2.852664 ppm

The Inhalation Unit Risk was calculated by dividing 0.1 by the ($BMCL_{10\ HEC}$) for nasal or alveolar/bronchiolar neoplasms. The Inhalation Unit Risk for nasal tumors is 0.031 ppm^{-1} (rounded to 0.03 ppm^{-1}). The Inhalation Unit Risk for alveolar/bronchiolar neoplasms is 0.035 ppm^{-1} (rounded to 0.04 ppm^{-1}). The higher value of 0.04 ppm^{-1} or 0.118 $(mg/m^3)^{-1}$ is used for subsequent calculations.

To convert to a level of 1,2-butylene oxide that would cause a theoretical excess cancer risk of 10^{-4}:

Risk of 1 x 10^{-4}: (1 x 10^{-4} risk) / 0.118 $(mg/m^3)^{-1}$ = 8.48 x 10^{-4} mg/m^3

To convert the 8.48 x 10^{-4} mg/m^3 dose from a 70-y exposure (25,600 hours) to a 24-h exposure:

24-h exposure = dose x 25,600
= (8.48 x 10^{-4} mg/m^3) x 25,600
= 21.71 mg/m^3

To account for uncertainty regarding the variability in the stage of the cancer process at which 1,2-butylene oxide may act, a multistage factor of 6 is applied (Crump and Howe 1984):

(21.71 mg/m^3)/6 = 3.62 mg/m^3 (1.23 ppm)

Therefore, based upon the potential carcinogenicity of 1,2-butylene oxide, an acceptable

24-h exposure would be 3.62 mg/m^3 (1.23 ppm).

If the exposure is limited to a fraction of a 24-h period, the fractional exposure becomes 1/fraction x 24 h (NRC 1985).

24-h exposure = 3.62 mg/m^3 (1.2 ppm)
8-h " = 10.86 mg/m^3 (3.7 ppm)
4-h " = 21.72 mg/m^3 (7.4 ppm)
1-h " = 86.88 mg/m^3 (29 ppm)
0.5-h " = 173.76 mg/m^3 (59 ppm)

For 10^{-5} or 10^{-6} risk levels, the 10^{-4} values are reduced by 10-fold or 100-fold, respectively.

Calculation of Cancer Slope Factor for Lung Tumors in Male Rats:

```
 ================================================================
        Multistage Cancer Model. (Version: 1.5;  Date: 02/20/2007)
        Input Data File: C:\BMDS\EPOXYBUTANE_LUNG.(d)
        Gnuplot Plotting File:  C:\BMDS\EPOXYBUTANE_LUNG.plt
                                          Thu Mar 20 13:59:31 2008
 ================================================================

 BMDS MODEL RUN
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(
                -beta1*dose^1-beta2*dose^2)]

   The parameter betas are restricted to be positive


   Dependent variable = COLUMN3
   Independent variable = COLUMN1

 Total number of observations = 3
 Total number of records with missing values = 0
 Total number of parameters in model = 3
 Total number of specified parameters = 0
 Degree of polynomial = 2


 Maximum number of iterations = 250
 Relative Function Convergence has been set to: 1e-008
 Parameter Convergence has been set to: 1e-008



                  Default Initial Parameter Values
                     Background = 1.46367e-017
                        Beta(1) =  0.000139143
                        Beta(2) = 3.24833e-007


           Asymptotic Correlation Matrix of Parameter Estimates

           ( *** The model parameter(s)  -Background
                 have been estimated at a boundary point, or have been
specified by the user,
                 and do not appear in the correlation matrix )

                Beta(1)      Beta(2)

   Beta(1)            1        -0.97

   Beta(2)        -0.97            1


                                Parameter Estimates

                                                        95.0% Wald Confidence
Interval
```

Variable	Estimate	Std. Err.	Lower Conf. Limit	Upper Conf. Limit
Background	0	*	*	*
Beta(1)	0.000139143	*	*	*
Beta(2)	3.24832e-007	*	*	*

* - Indicates that this value is not calculated.

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-24.5449	3			
Fitted model	-24.5449	2	5.18057e-011	1	1
Reduced model	-28.2392	1	7.38864	2	0.02486

AIC: 53.0897

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0000	0.000	0	50	-0.000
200.0000	0.0400	2.000	2	50	0.000
400.0000	0.1020	5.000	5	49	0.000

Chi^2 = 0.00 d.f. = 1 P-value = 1.0000

Benchmark Dose Computation

Specified effect = 0.1

Risk Type = Extra risk

Confidence level = 0.95

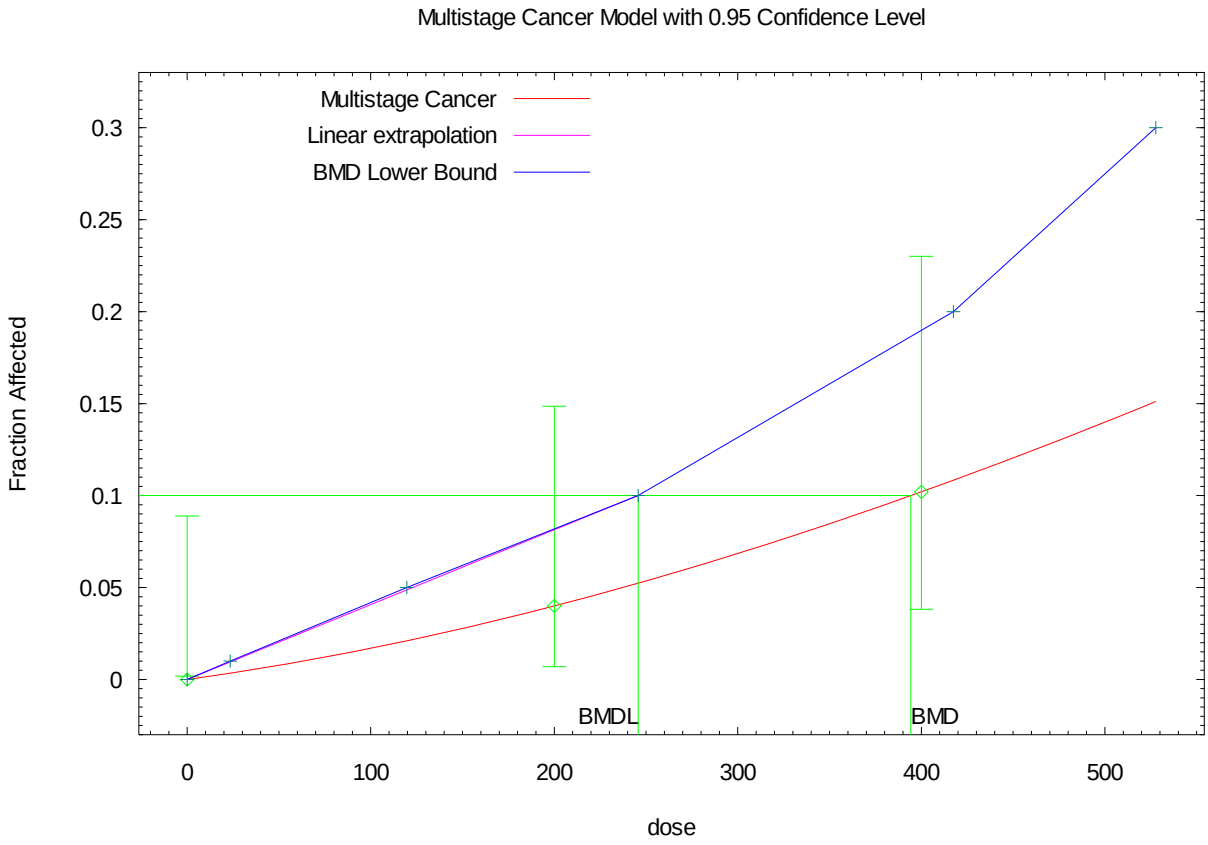
BMD = 394.285

BMDL = 245.768

BMDU = 892.919

Taken together, (245.768, 892.919) is a 90 % two-sided confidence interval for the BMD

Multistage Cancer Slope Factor = 0.000406887

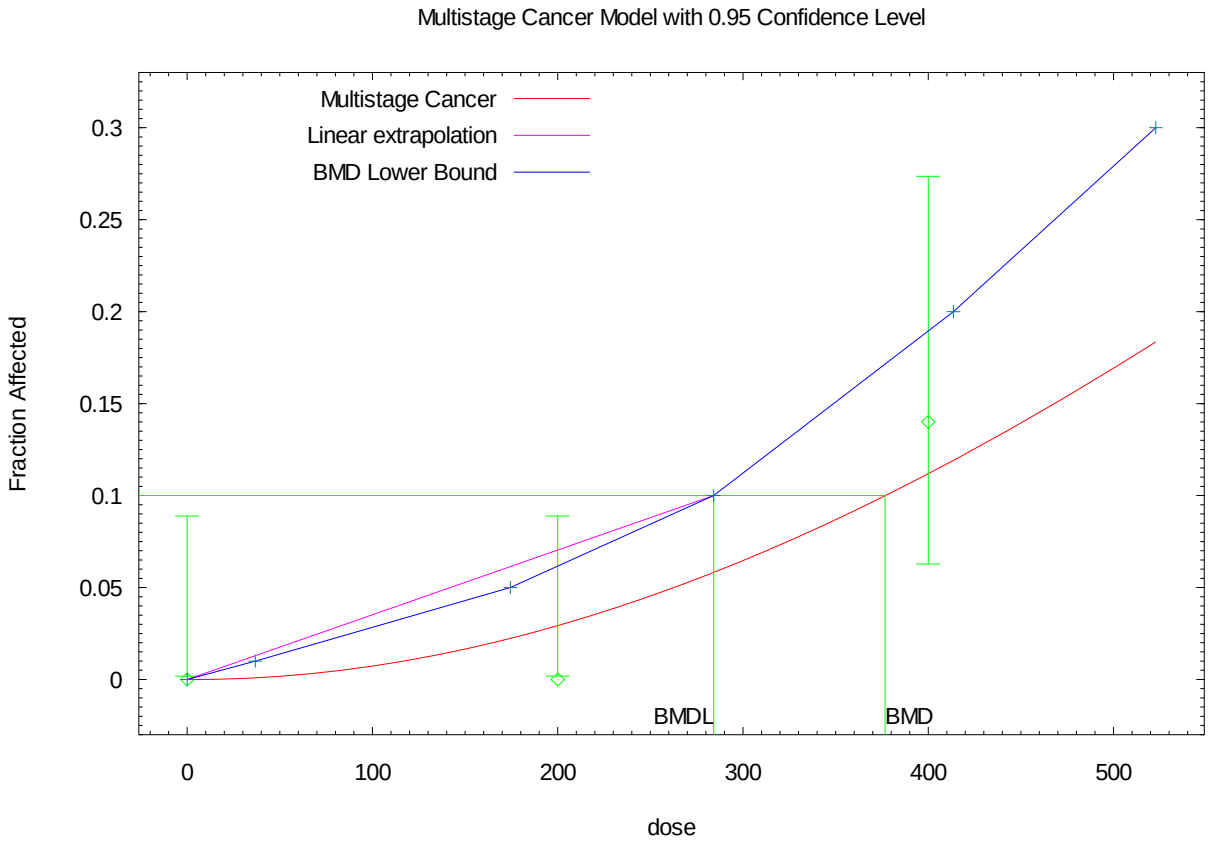

Multistage Cancer Model with 0.95 Confidence Level
Multistage Cancer
Linear extrapolation
BMD Lower Bound
Fraction Affected
0.3
0.25
0.2
0.15
0.1
0.05
0
BMDL
BMD
0
100
200
300
400
500
dose
13:59 03/20 2008

1
2

Calculation of Cancer Slope Factor for Nasal Tumors in Male Rats:

```
 ================================================================
        Multistage Cancer Model. (Version: 1.5;  Date: 02/20/2007)
        Input Data File: C:\BMDS\EPOXYBUTANE_NASAL.(d)
        Gnuplot Plotting File:  C:\BMDS\EPOXYBUTANE_NASAL.plt
                                          Thu Mar 20 13:56:06 2008
 ================================================================

 BMDS MODEL RUN
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(
                -beta1*dose^1-beta2*dose^2)]

   The parameter betas are restricted to be positive


   Dependent variable = COLUMN3
   Independent variable = COLUMN1

 Total number of observations = 3
 Total number of records with missing values = 0
 Total number of parameters in model = 3
 Total number of specified parameters = 0
 Degree of polynomial = 2


 Maximum number of iterations = 250
 Relative Function Convergence has been set to: 1e-008
 Parameter Convergence has been set to: 1e-008



                  Default Initial Parameter Values
                     Background =            0
                        Beta(1) =            0
                        Beta(2) = 1.01515e-006


           Asymptotic Correlation Matrix of Parameter Estimates

           ( *** The model parameter(s)  -Background    -Beta(1)
                 have been estimated at a boundary point, or have been
specified by the user,
                 and do not appear in the correlation matrix )

                Beta(2)

   Beta(2)           1



                                Parameter Estimates

                                                      95.0% Wald Confidence
Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit
Upper Conf. Limit
```

```
      Background                0           *               *
  *
           Beta(1)              0           *               *
  *
           Beta(2)     7.42398e-007         *               *
  *

* - Indicates that this value is not calculated.


                        Analysis of Deviance Table

        Model      Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
      Full model         -20.2482         3
     Fitted model        -21.9173         1       3.33821      2          0.1884
    Reduced model        -28.2871         1       16.0779      2       0.0003226

             AIC:         45.8346


                                  Goodness  of  Fit
                                                                        Scaled
      Dose     Est._Prob.    Expected    Observed     Size       Residual
    ----------------------------------------------------------------------
       0.0000     0.0000         0.000         0          50        0.000
     200.0000     0.0293         1.463         0          50       -1.228
     400.0000     0.1120         5.600         7          50        0.628

  Chi^2 = 1.90      d.f. = 2        P-value = 0.3865


     Benchmark Dose Computation

Specified effect =            0.1

Risk Type        =      Extra risk

Confidence level =           0.95

              BMD =        376.722

             BMDL =         284.17

             BMDU =         535.06

Taken together, (284.17 , 535.06 ) is a 90     % two-sided confidence
interval for the BMD

Multistage Cancer Slope Factor =   0.000351902
```


Multistage Cancer Model with 0.95 Confidence Level
Multistage Cancer
Linear extrapolation
BMD Lower Bound
Fraction Affected
0.3
0.25
0.2
0.15
0.1
0.05
0
BMDL
BMD
0
100
200
300
400
500
dose
13:56 03/20 2008

1
2
3

APPENDIX E: Derivation Summary for 1,2-Butylene Oxide AEGLs

Acute Exposure Guideline Levels for 1,2-Butylene Oxide (CAS Reg. No. 106-88-7)

AEGL-1 VALUES				
10-min	**30-min**	**1-h**	**4-h**	**8-hour**
72 ppm	**72 ppm**	**72 ppm**	**72 ppm**	**72 ppm**

Key Reference: NTP (National Toxicology Program). 1988. Toxicology and Carcinogenesis Studies of 1,2-Epoxybutane (CAS No. 106-88-7) in F344/N Rats and B6C3F1 Mice (Inhalation Studies). Technical Report No. 329. Research Triangle Park, NC: U.S. Department of Health and Human Services.

Test Species/Strain/Number: Rat/F-344/Groups of 5 per sex

Exposure Route/Concentration/Duration: Inhalation/398, 721, 1420, or 2050 ppm for 4 hours

Effects:
398 ppm: no signs reported
721 ppm: no signs reported
1420 ppm: signs of eye irritation
2050 ppm: ocular discharge, dyspnea
6550 ppm: 100% mortality

Endpoint/Concentration/Rationale: 4-hour exposure to 721 ppm/NOAEL for eye irritation

Uncertainty Factors/Rationale:
Total uncertainty factor: 10
Interspecies: 3, considered sufficient; slight irritation should not vary greatly between species.
Intraspecies: 3, considered sufficient; slight irritation should not vary greatly among humans.

Modifying Factor: None applied

Animal to Human Dosimetric Adjustment: Not applicable

Time Scaling: Same value applied across 10-minute to 8 hours as there is adaptation to the slight irritation that defines the AEGL-1.

Data Adequacy: There are no clinical data. The animal studies were well-conducted. Results of acute exposure studies with rats and mice conducted in two different laboratories were consistent.

AEGL-2 VALUES				
10-minute	**30-minute**	**1-hour**	**4-h**	**8-h**
140 ppm	**140 ppm**	**140 ppm**	**140 ppm**	**140 ppm**
Key Reference: NTP (National Toxicology Program). 1988. Toxicology and Carcinogenesis Studies of 1,2-Epoxybutane (CAS No. 106-88-7) in F344/N Rats and B6C3F1 Mice (Inhalation Studies). Technical Report No. 329. Research Triangle Park, NC: U.S. Department of Health and Human Services.				
Test Species/Strain/Number: Rat/F-344/5 per sex per group				
Exposure Route/Concentration/Duration: Inhalation/ 398, 721, 1420, 2050, or 6550 ppm for 4 hours				
Effects: 398 ppm: no signs reported 721 ppm: no signs reported 1420 ppm: signs of eye irritation 2050 ppm: ocular discharge, dyspnea 6550 ppm: 100% mortality				
Endpoint/Concentration/Rationale: 4-hour exposure to 1420 ppm resulted in eye irritation				
Uncertainty Factors/Rationale: Total uncertainty factor: 10 Interspecies: 3, considered sufficient; moderate irritation should not vary greatly between species. Intraspecies: 3, considered sufficient; moderate irritation should not vary greatly among humans.				
Modifying Factor: None applied				
Animal to Human Dosimetric Adjustment: Not applicable				
Time Scaling: Based on the fact that the irritation was considered moderate and the exposure duration was 4 hours, the same value was applied across 10 minutes to 8 hours.				
Data Adequacy: There are no clinical data. The animal studies were well-conducted. Results of acute exposure studies with rats and mice conducted in two different laboratories were consistent.				

AEGL-3 VALUES				
10-min	**30-min**	**1-h**	**4-h**	**8-h**
410 ppm	**410 ppm**	**330 ppm**	**210 ppm**	**210 ppm**
Key Reference: NTP (National Toxicology Program). 1988. Toxicology and Carcinogenesis Studies of 1,2-Epoxybutane (CAS No. 106-88-7) in F344/N Rats and B6C3F1 Mice (Inhalation Studies). Technical Report No. 329. Research Triangle Park, NC: U.S. Department of Health and Human Services.				
Test Species/Strain/Number: Rat/F-344/5 per sex per group				
Exposure Route/Concentration/Duration: Inhalation/398, 721, 1420, 2050, or 6550 ppm for 4 hours				
Effects: 398 ppm: no signs reported 721 ppm: no signs reported 1420 ppm: signs of eye irritation 2050 ppm: ocular discharge, dyspnea 6550 ppm: 100% mortality				
Endpoint/Concentration/Rationale: The highest non-lethal value of 2050 ppm.				
Uncertainty Factors/Rationale: Total uncertainty factor: 10 Interspecies: 3, considered sufficient; although the mouse was more sensitive than the rat in lethality studies, the difference was approximately 2-fold in repeat-exposure studies. Intraspecies: 3, considered sufficient; extreme irritation of the target tissue resulting in death should not vary greatly among humans.				
Modifying Factor: None applied				
Animal to Human Dosimetric Adjustment: Not applicable				
Time Scaling: $C^n \times t = k$, where n = 3 for shorter exposure durations (NRC 2001). The 10-minute value was set equal to the 30-minute value because of uncertainty in extrapolating from a 4-hour exposure to a 10-minute exposure. Because no deaths occurred in rats and mice repeatedly exposed to 150 or 400 ppm, the 4-hour value of 210 ppm was considered appropriate for the 8-hour value.				
Data Adequacy: There are no clinical data. The animal studies were well-conducted. Results of acute exposure studies with rats and mice conducted in two different laboratories were consistent.				

1