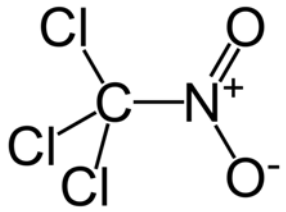
ACUTE EXPOSURE GUIDELINE LEVELS (AEGLs)

CHLOROPICRIN (CAS Reg. No. 76-06-2)

INTERIM



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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^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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EXECUTIVE SUMMARY

Chloropicrin is a slightly oily liquid used for disinfecting grains, as a fumigant, in the synthesis of crystal violet, and as a soil insecticide. It has also been used as a riot-control agent (PS).

The odor threshold is reportedly 0.78 ppm for chloropicrin. Exposure to chloropicrin vapor causes immediate cough, nausea, and vomiting in humans. At higher concentrations or exposures of longer duration more serious effects occur including dyspnea, cyanosis, weakness; unconsciousness and death.

Definitive exposure-response data for humans comes from sensory irritation studies conducted with human volunteers. More sensitive individuals exposed for 20-30 minutes reported chloropicrin concentration of 150 ppb (0.150 ppm) to be detectable as determined by notable ocular and nasal irritation. Exposure to 50 ppb (0.050 ppm) was reported as a No-Observed-Adverse-Effect-Level (NOAEL) for volunteer subjects (males and females; ages 18-35 years and including sensitive individuals). A quantitative analysis focusing on ocular irritation in human volunteers exposed for 1-hour/day for 4 days) provided a $BMCL_{10}$ of 73 ppb (0.073 ppm) for ocular irritation. (Reaves, 2006a). Human lethality data for chloropicrin are limited to earlier reports noting that exposure to 2.00 mg chloropicrin/L (300 ppm) for 10 minutes or 0.80 mg/L (120 ppm) for 30 minutes was lethal and that death due to infection may ensue several days following exposures that did not result in severe signs and symptoms. Nephritis also has been reported.

Lethality data for several species are available. Based upon signs of toxicity and necropsy findings, lethality appears to be a direct result of pulmonary damage and may be exhibit a latency period. Deaths occurring several days post exposure may be the result of infection following damage to respiratory tissues. Recent studies reported a 60-minute LC_{50} of 12 ppm and 240-minute LC_{50} values ranging from 12 to 19 ppm. For mice, 30-minute and 240 minute LC_{50} values of 56 ppm and 9.9 ppm, respectively, have been reported. Lethality data in other species from early studies were imprecise and not verifiable. Nonlethal toxicity data in animals are limited but indicate the respiratory tract as a primary target. No significant developmental or reproductive effects were observed in arts or rabbits following maternally nontoxic inhalation exposure to chloropicrin. Results of genotoxicity tests with chloropicrin were equivocal and no biologically significant carcinogenic potential was detected in cancer bioassays with mice and rats.

Studies with informed human volunteers showed that exposure to very low concentrations ($\leq$ 1 ppm) will result in ocular irritation that would likely exceed the severity criteria of AEGL-1 (Reaves, 2006a). The most reliable quantitative assessment applicable to AEGL-1 is the NOAEL of 50 ppb (0.050 ppm) for ocular irritation for human volunteers (Reaves, 2006a). Data for the human volunteer subjects indicated variability in detection of chloropicrin, exposure to 50 ppb (0.050 ppm) for 20 to 30 minutes was detected only by the more sensitive individuals (16 of 42 subjects). Therefore, uncertainty adjustment for sensitive individuals is not recommended. This would be protective for ocular irritation, the most sensitive critical effects for exposure to chloropicrin. Time scaling for AEGL-1 was not considered appropriate for the direct-contact irritation by chloropicrin and, therefore, the AEGL-1 values are the same for all AEGL-specific durations (NRC, 2001).

The studies with informed human volunteers (Reaves, 2006b) also provided the most appropriate data for AEGL-2 development. In addition to eliminating the uncertainties inherent with animal data, the studies in human volunteers assessed effects on the eye, the most sensitive target for chloropicrin vapor exposure. Severe ocular irritation reported by some volunteer participants in this study is considered an appropriate critical effect and the 150 ppm concentration is considered an appropriate POD for AEGL-2 derivation. Although all of the effects noted for exposure to 150 ppb chloropicrin were reversible upon cessation of exposure and the reported effects of less severity than those typically associated with the AEGL-2 tier, the ocular irritation was characterized as: "symptom hard to tolerate and can interfere with activities of daily living or sleeping". Because human volunteers were used, an interspecies uncertainty factor of 1 was applied. The intraspecies uncertainty factor is also limited to1 because some of the test subjects appeared to be representative of a sensitive population. Additionally, the effects occurring at 150 ppb were reversible and considered of minimal severity as a critical effect for AEGL-2 development. As for AEGL-1, no time scaling adjustment was applied.

Benchmark dose analysis (U.S. EPA, 2007) of the 240-minute exposure rat lethality data of Yoshida et al. (1987a; 1991) yielded a $BMCL_{05}$ of 7.9 ppm which served as the POD for AEGL-3 development. Exposure duration-exposure concentration analysis of rat data indicated an exponential relationship of $C^n \times t = k$, where $n = 2.3$. The interspecies uncertainty adjustment was limited to 3 because the toxic responses in multiple species (dogs, rats, and mice) were qualitatively equivalent; signs of respiratory tract damage (labored breathing, gasping, and nasal discharge) with histological findings affirming damage to the respiratory tract all of which are indicative of a direct-contact toxicity in all of the tested species. Quantitatively, comparison of 240-minute LC_{50} values in mice and rats varied less than 2-fold (9.9 ppm vs 18 ppm). Further, due to ventilatory rate-body size relationships, the dose to rodents would be greater than that to a human at any given air concentration of chloropicrin. Chloropicrin-induced respiratory tract damage and the hypothesized mode of action for chloropicrin (inhibition of pyruvate dehydrogenase and succinate dehydrogenase both of which are ubiquitous across mammalian species with respect to cellular metabolism) would also imply limited interspecies variability. In consideration of individual variability in the toxic response to chloropicrin, the direct-contact mechanism of chloropicrin on respiratory tract surfaces would be the same, although dosimetric variability among individuals may vary and is accounted for by an intraspecies uncertainty factor of 3. Further reduction of the AEGL-3 values by greater uncertainty factors would result in AEGL-3 values equivalent to the AEGL-2 values which are based upon data from carefully controlled studies in human volunteers. Time scaling the AEGL-3 values from the 60-minute POD to other AEGL-specific durations used the equation $C^n \times t = k$, where $n= 2.3$ was empirically determined from the concentration-time relationship of rat lethality data. Due to uncertainties in extrapolating from the 240-minute experimental exposure duration to the 10-minute AEGL time point, the 30-minute AEGL-3 was adopted for the 10-minute AEGL-3.

The AEGL values for chloropicrin are summarized in Table S-1.

S 1. AEGL Values for chloropicrin (expressed as ppm and [mg/m3])

Classification	10-min	30-min	1-h	4-h	8-h	Endpoint (Reference)
AEGL-1 (Nondisabling)	0.050 [0.34]	0.050 [0.34]	0.050 [0.34]	0.050 [0.34]	0.050 [0.34]	50 ppb NOAEL for ocular irritation in human subjects; UF = 1 x 1 (Reaves, 2006a)
AEGL-2 (Disabling)	0.15 [1.0]	0.15 [1.0]	0.15 [1.0]	0.15 [1.0]	0.15 [1.0]	150 ppb for 60 minutes as threshold for severe ocular irritation and possible respiratory effects in human volunteers (Reaves, 2006a); UF=1x1
AEGL-3 (Lethality)	2.0 [13]	2.0 [13]	1.4 [9.4]	0.79 [5.3]	0.58 [3.9]	$BMCL_{05}$ of 7.9 ppm for lethality in rats exposed for 240 min (Yoshida et al., 1987a; 1991); UF=3x3; n=2.3

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1. INTRODUCTION

Chloropicrin is a colorless slightly oily liquid used for disinfecting grains, as a fumigant, in the synthesis of crystal violet, and as a soil insecticide. It has also been used as a riot-control agent (PS) (Salem et al., 2001).

TABLE 1. Chemical and Physical Data for Chloropicrin

Parameter	Value	Reference
Synonyms	Nitrotrichloromethane; aquinite; trichloronitromethane; nitrochloroform; agent PS	Budavari et al., 1996; USACHPPM, 1996
Chemical formula	CCl_3NO_2	Budavari et al., 1996
Molecular weight	164.39	Budavari et al., 1996
CAS Registry No.	76-06-2	Budavari et al., 1996
Physical state	Liquid	Budavari et al., 1996
Solubility in water	0.16 g/100 mL @ 25°C	Budavari et al., 1996
Vapor pressure	20 mm Hg @ 20°C	USACHPPM, 1996
Relative vapor density	5.7	HSDB, 2007
Specific gravity	1.66 3.2 kPa @ 20°C	HSDB, 2007
Melting point/boiling point	-64°C/112°C	Budavari et al., 1996
Conversion factors in air	1 ppm = 6.7 mg/m^3 1 mg/m^3 = 0.15 ppm	

2. HUMAN TOXICITY DATA

2.1. Acute Lethality

Human lethality data for chloropicrin are limited. Vedder (1925), reported that exposure to 0.8 mg chloropicrin/L (120 ppm) for 30 minutes was lethal. Prentiss (1937) reported that exposure to 2.00 mg chloropicrin/L (300 ppm) for 10 minutes or 0.80 mg/L (120 ppm) for 30 minutes was lethal.

2.2. Nonlethal Toxicity

An odor threshold of 0.78 ppm for chloropicrin was reported by Speck et al., 1982. Inhalation exposure to chloropicrin reportedly causes immediate cough, nausea, and vomiting in humans. Exposure to higher concentrations or exposures of longer duration result in dyspnea, cyanosis, and weakness; unconsciousness and death may occur within a few hours. Several reports on acute inhalation exposure of humans are available (Table 2).

TABLE 2. Effects of Acute Chloropicrin Exposure in Humans

Exposure Duration	Exposure Concentration	LOAEL Concentration (ppm)	Comments	Reference
Immediate to 30 seconds	1, 2.5, 5.0, 7.5, 10.0, 15.0, 20.0, 25 ppm	1	Eyes remain open (as a measure of irritation); at 2.5 to 20 ppm eyes close within 3 to 30 seconds depending on concentration and individual susceptibility; eyes close immediately at 25 ppm	Fries and West 1921
Immediate	1 ppm	1	Immediate eye irritation	Fairhall 1957
Few seconds	26 mg/m^3 (3.9 ppm)	26	Unfit for combat	Flury and Zernick, 1931
Few seconds	100 mg/m^3 (15 ppm)	15	Non-specified injury to respiratory tract	
Unspecified (presumably immediate or within 10 min)	0.002 mg/L (0.30 ppm)	0.3	Lacrimation	Prentiss 1937
10 min	0.05 mg/L (7.4 ppm)	7.4	Intolerable ocular and respiratory tract irritation	
	2.00 mg/L (300 ppm)	300	Lethality; no further details	
30 min	0.80 mg/L (120 ppm)	120		
30 min	0.8 mg/L (120 ppm)	120	Lethality; no further details	Vedder 1925
1 h/d for 4 d	0, 0.1, 0.15 ppm	0.1	Ocular irritation at 0.1 ppm	Cain 2004 (summarized in Reaves 2004, 2006a,b)[a]

Note: age, gender, and number of subjects not reported except as footnoted.
[a] 15 males; 17 females

Fries and West (1921) reported that at exposure to concentrations less than 1 to 2 ppm (<6.7 to 13 mg/m^3), effects on the eyes are tolerable but considerable blinking may occur. Exposure to 2.5 to 20.0 ppm (17 to 130 mg/m^3) results in irritation and eye closure in 3 to 30 seconds depending on actual concentration and individual susceptibility while exposure to concentrations above 25 ppm (170 mg/m^3) results in immediate eye closure.

Exposure to a concentration of 26 mg/m^3 (3.9 ppm) for a few seconds was considered enough to render a soldier unfit for combat while 100 mg/m^3 (15 ppm) for a few seconds resulted in injury to the respiratory tract (Flury and Zernick, 1931).

Inhalation exposure to chloropicrin at concentrations of 2.00 mg/L (2,000 mg/m^3; 300 ppm) for 10 minutes or 0.80 mg/L (800 mg/m^3, 120 ppm) for 30 minutes was reportedly lethal (Prentiss, 1937). Prentiss (1937) also reported that exposure to 0.05 mg/L (50 mg/m^3, 7.4 ppm) for 10 minutes was intolerable, and exposure to 0.002 mg/L (2 mg/m^3, 0.30 ppm) for an unspecified period of time resulted in lacrimation. Although not specifically stated, due to the context of the study (assessment of low-level exposure to potential warfare agents), it is assumed that the reported nonlethal effects were based on observations in humans.

A study (reviewed and evaluated by Reaves, 2004) consisting of three phases, each phase varying in duration and exposure concentration, examined chloropicrin-induced sensory irritation in informed human volunteers. The apparatus and techniques utilized in this testing are the same as that used for studies with gluteraldehyde and are described by Cain et al. (2007). For the chloropicrin study, chloropicrin (>99.0% purity)/n-heptane solution was heated and the vapor swept by a nitrogen stream into a vapor delivery device (VDD). Actual vapor concentrations were within 1% of nominal. Healthy, informed, human volunteers (males and females aged 18-35 years) participated in the study. On a given day, a test subject would perform either odor detection, ocular detection or nasal localization. In Phase 1 identification of chloropicrin was assessed using odor, eye feel, and/or nasal feel, by subjects exposed to a single sniff of the chemical (odor detection), for 25 seconds (eye feel), or 7 seconds (nasal feel) to concentrations of 0, 356, 533, 800, or 1,200 ppb (0, 0.36, 0.53, 0.80, and, 1.2 ppm, respectively). For nasal localization, the vapor was directed to eight stations each equipped with a yoke that allowed controlled direction of vapor to either nostril. For odor detection, a subject was required to differentiate between two blanks and one active port. For ocular detection, the test subjects (wearing nose clips to prevent odor detection) would place an eye onto a cone and note any response. In Phase 2, positive detection was assessed as irritation of the eyes, nose, or throat, in subjects exposed for 20-30 minutes to 0, 50, 75, 100, or 150 ppb (0, 0.05, 0.10, and 0.15 ppm, respectively) in a walk-in chamber. Phase 3 was similar but also assessed clinical signs and changes in pulmonary function in subjects exposed for 60 min on each of 4 consecutive days to 0, 100, or 150 ppb (0, 0.10, and 0.15 ppm, respectively). Table 3 is a summary of the results of the three study phases.

TABLE 3. Summary of Human Sensory Irritation Testing with Chloropicrin

Test Phase	Concentration	Exposure Duration	Results
Phase I	0, 356, 533, 800, or 1200 ppb	"sniff"	Median odor detection: 700 ppb (males 590 ppb; females 810 ppb Median eye detection: 900 ppb (males790 ppb; females 1010 ppb)
Phase II	0, 50, 75, 100, or 150 ppb	20-30 minutes	1 Female subject left at 75 ppb 4 Subjects (2 of each gender) left at 150 ppb 16 of 42 Subjects detected chloropicrin at 50 ppb Ocular and nasal detection by sensitive individuals
Phase III	100 or 150 ppb	60 min./day; 4 consecutive days	NOAEL: not established <100 ppb LOAL: 100 ppb; ocular irritation, differential ventilatory flow; time for recognition at either concentration was 5 minutes

Results of the Phase 3 experiments were the most comprehensive assessment of sensory, clinical, and physiological responses. The assessments included sensory perception while in the chamber, clinical examination of the eyes, nose, and throat, tests of pulmonary function; and measurement of pulmonary, nasal, and lung nitric oxide. The only notable results were those pertaining to irritation and nitric oxide. While in the chamber, the subjects (15 males and 17 females) rated sensory perception symptoms at 30 seconds and every minute until the end of the 60 minute exposure using the following scale: 0, no symptom; 1, mild (symptom present but easily tolerated); 2, moderate (symptom definite and bothersome, but easily tolerated); and 3, severe (symptom hard to tolerate, could interfere with daily activities or sleeping). The sensory perception results for the eyes, nose, and throat are summarized in Table 4. The average symptom ratings ranged from 0.1 to 1 although there was considerable variability in the scores (some subjects sporadically reported severity ratings up to level 3 over the exposure duration while others reported no symptoms).

TABLE 4. Human Subject Response to Chloropicrin During a 1-h Exposure[a]

Concentration	Eyes			Nose		Throat	
	Average Symptom Rating	Individual Rating	Time for Recognition	Average Symptom Rating	Time for Recognition	Average Symptom Rating	Time for Recognition
0 ppb (0 mg/m^3)	0.1	Not available in summary report	NA	0.1	5 min	0.1	5 min
100 ppb (0.67 mg/m^3)	0.5	Sporadic "severe" irritation in 8/32 subjects (25%) over the 60-min exposure duration	30 min	0.1	5 min	0.1	5 min
150 ppb (1.0 mg/m^3)	1	Sporadic "severe" eye irritation scores in 7/32 subjects (22%) over the 60-min exposure duration	20 min	0.2	5 min	0.1	5 min

[a] Assessments made while subjects were in exposure chamber, with ratings given 30 seconds from initial exposure and every minute thereafter for the 60-minutes exposure duration.

U.S. EPA evaluations (Reaves 2004, 2006a, 2006b) of this study reported no change in pulmonary function testing (forced vital capacity [FVC] or forced expiratory volume [FEV1], lung nitric oxide, cytology (nose and eye), or nasal congestion or irritation. Change in nasal nitric oxide was significant; nitric oxide concentrations were 399 ppb before exposure and 425 ppb after exposure ($p = 0.012$). Nasal nitric oxide increased 1% after exposure to the blank, 10% at 0.67 mg/m^3, and 8% at 1.0 mg/m^3. Ocular irritation, however, was considered to be the most sensitive endpoint for exposure to chloropicrin vapors.

The U.S. EPA (Reaves, 2006a) evaluated a Benchmark Dose analysis for chloropicrin conducted by the Toxicology Excellence for Risk Assessment (TERA) organization. The analysis focused on the phase 3 data (1-hour/day for 4 days) of the previously described sensory irritation study. Based upon ocular irritation in the human volunteers, a $BMCL_{10}$ of 73 ppb (0.073 ppm) was calculated based upon the ocular irritation scores from Phase 3 of the aforementioned study.

2.3. Case Reports

An incident in which chloropicrin used as a soil fumigant drifted offsite into a residential area of Kern County, California over a 2-day period resulted in 165 persons experiencing symptoms consistent with chloropicrin exposure (CDC, 2004). Of the affected individuals, 150 were community residents, 2 were day care workers, and 9 were first responders. The remaining 4 persons were applicators or growers. The median age was 16 years (range: 3 months to 63 years). Most (99%) of the 165 affected individuals reported eye or upper respiratory tract irritation. Ocular symptoms included

lacrimation, pain, and burning. Gastrointestinal symptoms were reported in 47% of the affected individuals and included vomiting, nausea, abdominal pain, and diarrhea. Respiratory symptoms occurring in 51% of the people included cough, dyspnea, upper respiratory irritation, chest pain, and asthma exacerbation. Nine individuals received medical evaluations and 7 experienced persistent respiratory symptoms when interviewed 11 days later. Chloropicrin concentrations were not reported.

2.4. Developmental/Reproductive Effects

Data on the developmental/reproductive toxicity of chloropicrin in humans were not available.

2.5. Genotoxicity

No information regarding the genotoxicity of chloropicrin in humans was available.

2.6. Carcinogenicity

No information was available regarding the carcinogenicity of chloropicrin in humans.

2.7. Summary

Inhalation of chloropicrin causes immediate cough, nausea, and vomiting in humans. Exposure to higher concentrations or exposures of longer duration result in dyspnea, cyanosis, weakness, unconsciousness and death. Most human exposure data with definitive exposure-response data pertain to sensory irritation studies conducted with human volunteers. Human lethality data for chloropicrin are limited to the report by Prentiss (1937) stating that exposure to 2.00 mg chloropicrin/L (300 ppm) for 10 minutes or 0.80 mg/L (120 ppm) for 30 minutes was lethal. Lambert and Jackson (1920) stated that death due to infection may ensue several days following exposures that did not result in severe signs and symptoms. Nephritis has also been reported (Lambert and Jackson 1920).

3. ANIMAL TOXICITY DATA

3.1. Acute Lethality

3.1.1. Rats

Yoshida et al. 1987a reported a 4-hour LC_{50} value 11.9 ppm for groups of 6-8 male F-344 rats. Rats were exposed to 8.8, 11.0, 11.4, 12.1, 13.6, or 16.0 ppm (analytical) for 4 hours, or to 21.7 or 45.5 ppm (analytical) for 30 minutes. Exposed animals exhibited labored breathing, cyanosis, diffuse pulmonary edema, and increases in absolute lung weight. The chloropicrin (99.6% purity) vapor was generated by a well-described vapor generation system with chamber concentration analysis being conducted by gas chromatography 7 times during the 4-hour exposure and 3 times during the 30-minute exposure. Yoshida et al. (1987a) also reported that lethal responses exhibited a biphasic pattern with deaths occurring within 24 hours or with a latency period of 8 to 10 days during the 14-day post-exposure observation period. Table 5 summarizes information on incidences of mortality and gross pathology of the respiratory system from the whole-body 4-hour exposure study by Yoshida et al. (1987a). For the 30-minute

exposures, there were no deaths at 21.7 ppm and 100% mortality (deaths at 6 and 7 days post exposure) at 45.5 ppm.

TABLE 5. Toxicity of Chloropicrin Vapor in Male Fischer Rats (4-hr Exposure)[a]

Effect	Dose in ppm[b]				
	8.8	11.0	11.4	12.1	13.6
Mortality	0/8	2/8	3/8	5/8	7/8
Pathology					
Hydrothorax	0/8	0/8	0/8	3/8	5/8
Lung					
Edema	3/8	6/8	6/8	7/8	7/8
Emphysema	3/8	7/8	2/8	3/8	4/8
Dark red patches	0/8	1/8	3/8	2/8	1/8

Yoshida et al. 1987a.

[a]All rats in the 16.0 ppm group died within 24 hours and all exhibited hydrothorax, pulmonary edema, emphysema, and gaseous distention of the stomach. [b] Mean analytical concentration of chloropicrin vapor.

In a follow-up study assessing the effect of mode of exposure effects, Yoshida et al. (1991) exposed groups of 8 male F-344 rats exposed to chloropicrin (99.7%) vapor for 4 hours and observed for 14 days. The exposure system was as described in the preceding study with gas chromatographic analysis of the chamber atmospheres. The 4-hour LC_{50} values were 14.4 ppm (whole body exposure) and 6.6 ppm (nose-only exposure). The whole-body exposures resulted in a biphasic presentation of effects, the first phase lasting about 3 days and the second phase at 6-14 days post exposure. There was evidence of respiratory tract irritation and damage throughout the post exposure period but most deaths occurred within 24 hours. For the nose-only exposures, only the first phase effects were evident with deaths occurring within 24 hours. Results of dermal exposure experiments indicated that toxicity resulting from this exposure route was minimal; neither deaths nor toxic effects were noted at exposures equivalent to 2 to 4 times the 4-hr LC_{50} values. Results are summarized in Table 6.

TABLE 6. Lethality in rats exposed for 4 hours to chloropicrin.

Test Group	Days post exposure							
	0[a]	1	2-7	8	9	10	11-14	Total
Whole-body								
12.3 ppm	1	0	0	0	0	0	0	1/8
13.9 ppm	2	0	0	0	0	0	0	2/8
15.4 ppm	5	0	0	0	2	0	0	7/8
Nose-only								
5.3 ppm	0	0	0	0	0	0	0	0/8
5.9 ppm	1	0	0	0	0	0	0	1/8
6.6 ppm	6	0	0	0	0	0	0	6/8
8.1 ppm	6	0	0	0	0	0	0	6/8

[a] Represents 0-24 hrs.
Yoshida et al., 1991

In an unpublished study (Hoffman 1999), 5 Sprague-Dawley rats/gender/group were exposed (whole body) to 0, 10.6, 18.0, or 28.5 ppm (analytical; determined by gas chromatography) aerosolized chloropicrin (>99% purity) for 4 hours and observed for 2 days. Particle sizes had mass median aerodynamic diameters ranging from 4.85 microns to 6.1 microns. Lethality was observed at the two highest concentrations (4/10 and 9/10,

respectively) with deaths occurring on both days. The 4-hr LC_{50} was 17 ppm for males and 20 ppm for females (19 ppm sexes combined). There was no evidence of gender-related difference in the toxic response to the chloropicrin. Clinical signs were similar at all dose levels and included labored breathing, gasping, and nasal discharge. Histological changes in the respiratory tract were observed in rats of all exposure groups.

The lethality of chloropicrin in a variety of species (rat, rabbit, dog, cat, monkey, and/or guinea pig) was reported by Lambert and Jackson (1920). The lethal concentrations were reported as 7.4 mg/L (7,400 mg/m^3; 1,100 ppm) for a 3-minute exposure; 1.0 to 3.7 mg/m^3 (1,000 to 3,700 mg/m^3; 150 to 550 ppm) for a 15-minute exposure; and 0.5 to 0.74 mg/L (500 to 740 mg/m^3; 74 to 110 ppm) for a 30-minute exposure. However, no experimental protocol details (e.g., number of test animals, number of exposure concentrations in each test, or species-specific responses) were provided.

3.1.2. Mice

Lethality in mice (30/group) 10 days following a 15-minute exposure to 50 ppm chloropicrin (purity not reported) was reported by Ritlop (1939). At 125 ppm, lethality occurred in 3-24 hours post exposure. The actual lethality rate was not specified and no additional details were available.

Kawai (1973) reported a 4-hour LC_{50} for chloropicrin (aerosol) in mice of 66.0 mg/m^3 (9.9 ppm) and a 30-minute LC_{50} (gas) of 370 mg/m^3 (56 ppm). Kane et al. (1979) reported an RD_{50} of 7.98 ppm (54 mg/m^3) for chloropicrin in mice following a 10-minute exposure.

3.1.3. Dogs

The lethality of chloropicrin in dogs was reported by Lambert and Jackson (1920). The lethal concentrations were reported as 7.4 mg/L (7,400 mg/m^3; 1,100 ppm) for a 3-minute exposure; 1.0 to 3.7 mg/m^3 (1,000 to 3,700 mg/m^3; 150 to 550 ppm) for a 15-minute exposure; and 0.5 to 0.74 mg/L (500 to 740 mg/m^3; 74 to 110 ppm) for a 30-minute exposure. However, no experimental protocol details (e.g., number of test animals, number of exposure concentrations in each test) were provided. Microscopic evaluation of dogs exposed to 1.035 mg/L (1,035 mg/m^3; 150 ppm) for 30 minutes showed extreme lung edema, severe necrosis of the bronchi, congestion of the lung, and dilation of the heart (Lambert and Jackson, 1920).

Ritlop (1939) reported 43% lethality in dogs (12/group) exposed for 30 minutes to 117-140 ppm (nominal) chloropicrin. No further details were available.

3.1.4. Rabbits

York et al. (1994) reported on developmental toxicity study using groups of 20 pregnant New Zealand White rabbits. The rabbits were exposed by inhalation (whole body) to 0, 0.4, 1.2, or 2 ppm of chloropicrin for 6 hours/day on gestation days 6-18 (rabbits) or 6-15 (rats). Two does died in the 1.2-ppm exposure group and 10 died in the 2-ppm group. Although the times of death were not reported, all deaths were attributed to the treatment.

3.1.5. Summary of Animal Lethality Data

Lethality data for several species are available. Based upon signs of toxicity and necropsy findings, lethality appears to be a direct result of pulmonary damage and may be exhibit a latency period. Deaths occurring several days post exposure may be the result of infection following damage to respiratory tissues. Animal toxicity data (both lethal and nonlethal) are summarized in Table 7.

TABLE 7. Summary of inhalation toxicity in animals exposed to chloropicrin						
Species Tested	**Exposure**	**Exposure Duration (min)**	**Exposure Concentrations**	**Effect**	**Comments**	**Reference**
Mice (Swiss-Webster), number per group not provided	Inhalation	10	7.98 ppm	RD_{50}: 8.1 ppm (54 mg/m^3)		Kane et al. 1979
Rat, rabbit, dog, cat, monkey, guinea pig (no details provided)	Inhalation	3	Not specified	LC: 1,110 ppm (7,400 mg/m^3)	Report specifies neither level of lethality nor species specificity	Lambert and Jackson 1920
		15		LC: 150-555 ppm (1,000-3,700 mg/m^3)		
		30		LC: 75-111 ppm (500-740 mg/m^3)		
Mice	Inhalation (gas)	30	118, 207, 284,406, 568, 893 mg/m^3	NOAEL: 18 ppm (118 mg/m^3) LC_{50}: 56 ppm (370 mg/m^3) LC_{100}: 134 ppm (893 mg/m^3)		Kawai 1973
	Inhalation (aerosol)	240	31, 32, 48, 72, 106, 171 mg/m^3	NOAEL: 31 mg/m^3 (4.7 ppm) LC_{50}: 66 mg/m^3 (9.9 ppm) LC_{100}: 171 mg/m^3 (26 ppm)		
Rat (species and number not specified in secondary reference)	Inhalation	60	Not specified	LC_{50}: 25.5 ppm (171 mg/m^3)	Lethality assessed up to 14 days post exposure	U.S. Testing Co., Inc. 1976
Rats (male Fischer 344) 8/group	Inhalation (whole body)	30	0, 21.7, 45.5 ppm (analytical)	LC_{100} : 45.5 ppm LOAEL: 21.7 ppm	100% lethality at highest concentration; increased absolute lung weights. No lethality at the lowest concentration; eyelid closure, decreased motor activity, labored breathing, and decreased body weight	Yoshida et al. 1987a
		240	0, 8.8, 11.0, 11.4, 12.1, 13.6, 16.0 ppm (analytical)	NOAEL: 8.8 ppm LC_{lo}11.0 ppm LC_{50}: 12.1 ppm $LC_{100:}$ 16.0 ppm	NOAEL for lethality characterized by labored breathing, cyanosis, diffuse pulmonary edema, increase in absolute lung weight.	
Rats (Sprague Dawley) 5/gender/group	Inhalation/ Aerosol (whole body)	240	0, 10.5, 18.0, 28.5 ppm (analytical)	NOAEL: 10.5 ppm LC_{50}: 18.0 ppm	NOAEL for lethality Animals were observed only 2 days post-exposure	Hoffman 1999
Rats (male Fischer 344), 8/group	Inhalation (whole body)	240	0, 12.3, 13.9, 15.4 ppm	LC_{50}: 14.4 ppm	Lethality assessed up to 14 days post exposure; most deaths within 24 h	Yoshida et al. 1991
	Inhalation (nose-only)	240	0, 5.3, 5.9, 6.6, 8.1 ppm	6.6 ppm LC_{50}: 14.4 ppm	NOAEL for lethality Lethality assessed up to 14 days; most deaths within 24 hrs	

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3.2. Nonlethal Toxicity

3.2.1. Rats

In the study by Yoshida et al. (1987a), no lethality was observed in rats exposed to 21.7 ppm for30 minutes. These rats exhibited gaseous distention of the stomach (2 of 7 rats) and dark red patches in the lungs (4 of 7 rats) but no evidence of edema, emphysema or hydrothorax. In later study by Yoshida et al. (1991), there were no deaths among 8 male rats exposed nosed-only to 5.3 ppm chloropicrin for 4 hours (Table 8). Hoffman (1999) reported that a 4 hour a whole-body inhalation exposure of rats to a chloropicrin aerosol (395 mg/m^3) was without lethality.

3.2.2. Mice

Mice (30/group) reportedly tolerated a 15-minute exposure to 25 ppm (Ritlop, 1939). Buckley et al. (1984) exposed groups of 16-24 male Swiss-Webster mice 6 hours/days for 5 days to 0 or 54 mg/m^3 (8.1 ppm) chloropicrin. Effects were assessed in one half of the mice immediately after the last exposure and at 72 hours post exposure in the remaining mice. Exfoliation, erosion, and necrosis of the olfactory and pulmonary epithelia were observed as well as severe fibrosing bronchitis and peribronchitis.

3.2.3. Dogs

Ritlop (1939) reported that dogs (12/group) tolerated a 15-minute exposure to 48 ppm chloropicrin (nominal; purity not reported) and became ill following a 12-minute exposure to 155 ppm.

3.2.4. Cats

Ritlop (1939) also reported no lethality in cats (12/group; no further details) up to 7 days following a 38-minute exposure to 21 ppm chloropicrin.

3.2.5. Summary of Nonlethal Toxicity in Animals

Table 8 (Section 3.1.4) includes a summary of nonlethal inhalation data for animals. Results of lethality studies show that animals exposed by inhalation to chloropicrin exhibit signs consistent those of a contact irritant: eye closure, decreased activity, labored ventilation, cyanosis, with gross pathology findings of pulmonary edema and increased lung weight. However, the exposure-response relationship for these nonlethal effects is not well characterized. A mouse RD_{50} of 8.1 ppm for a 1-minute exposure has been reported. The nonlethal effects appear to be consistent with a continuum of effects ultimately resulting in death due to pulmonary damage. Qualitatively, all species appear to exhibit similar responses.

3.3. Developmental/Reproductive Effects

In an unpublished developmental toxicity study, pregnant Charles River Crl:CD VAF/Plus rats (30/group) were exposed to chloropicrin in air at concentrations of 0, 0.4, 1.2, or 3.5 ppm by whole body inhalation for 6 hours/day from gestation day (GD) 6 through 15 (Schardein, 1993). The maternal NOAEL was 0.4 ppm. The LOAEL was 1.2 ppm based upon decreased food consumption, body weight, and body weight gain, and increased clinical signs.

There was a significant increase in total fetal skeletal variations in pups of the 1.2 ppm and 3.5 ppm groups. On a per-litter-basis, no statistically significant increase was observed. The developmental NOAEL was identified as 1.2 ppm.

York et al (1994) reported on developmental; toxicity study in which groups of 20 pregnant New Zealand White rabbits were exposed by inhalation (whole body) to 0, 0.4, 1.2, or 2 ppm of chloropicrin (99% purity)for 6 hours/day on gestation days 6-18 (rabbits) (Table 8). The maternal NOAEL was 0.4 ppm. Two does died in the 1.2-ppm exposure group and 10 died in the 2-ppm group. Abortions, pulmonary edema, and decreases in body weight and food consumption were observed at 1.2 ppm and higher. Dyspnea, nasal staining, salivation, and decreased activity occurred in a dose-related manner. The maternal LOAEL was 1.2 ppm based upon decreased body weight and food consumption. The developmental NOAEL and LOAEL were 0.4 ppm and 1.2 ppm, respectively, the latter being based upon increased developmental variations, abortions, and reduced fetal and uterine weights noted at the highest concentration.

In a multigeneration reproductive/fertility study (Schardein, 1994), Charles River Crl:CD VAF/Plus rats (26/gender/group) were exposed by whole body inhalation to chloropicrin at concentrations of 0, 0.5, 1.0, or 1.5 ppm (0, 3.4, 6.7, or 10 mg/m^3) for two generations through the weaning of the second generation F_2 pups. Slight inflammatory changes occurred in the lungs at 11.5 ppm in the F_1 adult females. There were no treatment-related effects in pups or reproductive effects in dams at any exposure concentration. In a review of this study report by the U.S. EPA, it was noted that effects were expected at the doses administered and questioned whether the reported dose levels had been achieved.

TABLE 8. Developmental toxicity of chloropicrin in rabbits following inhalation exposure.

	Effect	**Exposure concentration (ppm)**			
		0	**0.4**	**1.2**	**2.0**
Maternal	Mortality	0/20	0/20	2/20	10/20
	Pulmonary edema	0/20	0/20	1/20	7/20
	Lung – discolored	NR	NR	3/20	10/20
	Eyes (redness in area around eyes/eyelids) during exposure	0/20	0/20	0/20	4/20
	Excessive lacrimation during exposure	0/20	0/20	0/20	3/20
	Body weight gain/loss (g) Dosing period (GD 7-29) GD 0-29	 51 269	 142 335	 -119 137	 **-320*** **-59***
	Food consumption during dosing period (g/animal/d)	135	149	**93***	**42***
	Abortions	0/20	0/20	**1/20**	**2/20**
	Post-implantation loss (%)	2.9%	12.5%	7.6%	9.1%
Fetal	Body weight	43.0 ± 7.92	45.2 ± 6.38	43.8 ± 8.66	**39.4 ± 8.87**
	No treatment-related increased incidences of fetal malformations were reported				

$p \leq 0.05$
York 1993

3.4. Genotoxicity

A positive mutagenic response was obtained with and without metabolic activation in the Ames *Salmonella* test (Moriya et al. 1983, San and Wagner 1990) and in *Escherichia coli* (WP2 hcr) (Moriya et al. 1983). Using the Chinese hamster ovary cell assay, a significant increase in

chromosomal aberrations in the absence of a metabolic activation system was observed (Putman and Morris 1990). No increase in forward mutation frequency was seen using the mouse lymphoma mutagenicity assay with L5178Y mouse lymphoma cells (San and Sigler 1990). Curren (1990) found no increase in unscheduled DNA synthesis in rat primary hepatocytes.

3.5. Carcinogenicity

In an unpublished study, CD-1 mice (50/gender/group) were exposed to chloropicrin in air at concentrations of 0, 0.1, 0.5, or 1.0 ppm for 6 hours/day, 5 days/week for 78 weeks (Burleigh-Flayer et al. 1995a). Exposure to 0.5 ppm and higher resulted in significantly decreased body weight and body weight gain in both sexes. For the 0.5 ppm group, an increase in absolute and relative lung weight was also observed. Microscopic evaluation showed histopathological alterations of the nasal cavity, including serous exudate, hyaline epithelial inclusions, rhinitis, and atrophy of olfactory epithelium. At 0.1 ppm and higher, there were significantly increased incidences of peribronchial lymphocyte infiltrates and at 0.5 ppm incidences of alveolar histiocytosis, bronchiectasis, bronchial submucosal fibrosis, and/or bronchiolalveolar cell hyperplasia were significantly increased (Table 9).

In a study reported by Burleigh-Flayer and Benson (1995b), Sprague-Dawley CD rats (50/gender/group) were exposed to chloropicrin (0, 0.1, 0.5, or 1.0 ppm) for 6 hours/day, 5 days/week up to 108 weeks. The 0.1 ppm was a noncancer NOAEL based upon assessment of clinical signs, food consumption, ophthalmologic findings, hematology, organ weights, and gross pathology. At 0.5 ppm, effects included decreased survival time in males and transient decreases in body weight gain in both genders as well as increased mortality rate at week 108.

TABLE 9. Toxicity of Chloropicrin Vapor in Mice (78-week Study)

Effect	0 ppm		0.1 ppm		0.5 ppm		1.0 ppm	
	M	F	M	F	M	F	M	F
	N=36	N=34	N=27	N=34	N=30	N=31	N=41	N=32
Nasal Cavity								
Serous exudate	4	3	3	2	12**	24**	30**	30**
Epithelial hyalin inclusions	3	3	4	8	7	18**	12*	25**
Rhinitis	5	2	3	4	11*	11**	28**	18**
Olfactory epithelial atrophy	3	7	1	11	5	26**	34**	25**
Lungs								
Alveolar histiocytosis	NR	9	NR	12	NR	13	NR	22**
Peribronchial lymphocite infiltrates	1	4	6*	9	8**	14**	12**	23**
Bronchiectasis	0	0	3	4	22**	19**	35**	30**
Bronchial submucosal fibrosis	0	0	0	0	11**	10**	16**	17**
Bronchio alveolar cell hyperplasia	NR	0	NR	1	NR	2	NR	5*

* $p<0.05$; ** $p<0.01$; NR: not reported

Burleigh-Flayer et al. 1995a.

4. SPECIAL CONSIDERATIONS

4.1. Metabolism and Disposition

Definitive metabolism and disposition data for chloropicrin in humans or animals were not available. The possible involvement of glutathione conjugates is discussed briefly in the following section.

4.2. Mechanism of Toxicity

Exposure to chloropicrin produces lacrimation, skin irritation, and pulmonary edema, but the mode of action is not fully understood. Chloropicrin reportedly reacts with sulfhydryl groups of hemoglobin resulting in compromised oxygen transport (Liebecq 1946, Cal/EPA 1999b). Although it has been hypothesized that glutathione-mediated formation dechlorinated metabolites may be instrumental in toxicity, results of metabolism studies in mice and subsequent analysis of urinary metabolite profiles do not support the hypothesis (Sparks et al. 1997). In a subsequent study, Sparks et al. (2000) provided data indicating that the parent compound was directly responsible for observed toxicity. This contention was based upon data from several lines of experimentation including (1) inhibition of pyruvate dehydrogenase (PDH) activity in porcine heart and succinate dehydrogenase (SDH) activity in mouse liver, (2) evaluation of the cytotoxicity of chloropicrin in human peripheral blood cells (HL-60), mouse hepatoma cells (Hepa 1c1c7), and human lung fibroblasts (IMR-90), and (3) evaluation of potential effects on hemoproteins, liver hemoglobin, and total hemoglobin *in vitro* in mouse blood and methemoglobin *in vivo* in mice. Based upon the results of these experiments, Sparks and colleagues concluded that acute toxicity results from the parent compound due to inhibition of PDH, and to a lesser extent, SDH activity, and that elevated oxyhemoglobin may also play a role. In an early report, Mackworth (1948) had suggested that inhibition of PDH and SDH activity by chloropicrin may be involved with chloropicrin-induced lacrimation.

4.3. Structure-Activity Relationships

There are no structure activity data instrumental in developing or refining the AEGL values for chloropicrin.

4.4. Species Variability

Animal lethality data suggest minimal variability among the species tested.

4.5. Concurrent Exposure Issues

Chloropicrin is frequently used in conjunction with soil fumigants such as methyl iodide. When chloropicrin is detected in agricultural situations it is likely that soil fumigants may be represent as well and vice versa. Any simultaneous exposure to a chemical that targets the eyes or respiratory system would logically be of concern.

5. DATA ANALYSIS FOR AEGL-1

5.1. Human Data Relevant to AEGL-1

The irritant properties of inhaled chloropicrin are well documented. Ocular irritation has been shown to occur in human volunteers at chloropicrin concentrations as low as 0.9 ppm following very brief (seconds) exposure to the chemical. Fries and West (1921) reported that ocular irritation following exposure to 1 or 2 ppm (duration not specified but assumedly less than 1 minute) are tolerable but that 3 to 30-second exposure to 2.5 ppm produces notable irritation. In a human study reviewed by Reaves (2004a) a median odor detection level of 0.70 ppm and a median ocular detection level of 0.90 ppm was reported for male and female volunteers taking a single “sniff” of chloropicrin. A 20 to 30-minute exposure to 0.050 ppm was detected by most

(16 of 42) volunteers based upon ocular and nasal sensation, while 0.075 to 0.15 ppm was intolerable to some subjects. A concentration of 0.10 ppm was considered a LOAEL for ocular irritation and recognition of the chemical following 4 1-hr/day exposures to 0.10 or 0.15 ppm.

Based upon ocular irritation scores in human volunteers (Phase 3 of the study reviewed by Reaves [2004a] , see Table 3, Section 2.2), a $BMCL_{10}$ of 73 ppb (0.073 ppm) was determined by the Toxicology Excellence for Risk Assessment (TERA) organization. The analysis was evaluated by U.S. EPA (Reaves, 2006a) and considered a biologically and statistically robust 1-hour exposure limit for chloropicrin.

5.2. Animal Data Relevant to AEGL-1

Ritlop (1939) reported that 15-minute exposure to 48 ppm or 25 ppm was tolerated by dogs and mice, respectively. No further details were available, the exposure values were nominal, and purity of the chloropicrin was not reported. Other reports have indicated exposures that were not lethal but provided no information on what, if any, toxic responses occurred. Animal data pertaining to AEGL-1 tier effects are lacking.

5.3. Derivation of AEGL-1 Values

The most appropriate data for the development of AEGL-1 values for chloropicrin are from the study using informed human volunteers (reviewed by Reaves, 2006a). It is evident from the human experience information that exposure to very low concentrations ($\leq$ 1 ppm) will result in ocular irritation that would likely exceed the severity criteria of AEGL-1. The most reliable quantitative assessment applicable to AEGL-1 is the $BMCL_{10}$ analysis of the Cain (2004) data on ocular irritation in human volunteers (Reaves, 2006a). This lower bound estimate of 73 ppb (0.073 ppm) was considered by the U.S. EPA (Reaves, 2006a) appropriate as a point-of-departure for a 1-hour acute inhalation exposure risk assessment.

Time scaling was not applied in the development of the AEGL-1 values. The critical effect (ocular irritation) is a function of direct contact with the chloropicrin vapors and not likely to increase with duration of exposure (NRC, 2001). Cain et al. (2007) have shown this for gluteraldehyde in a study with human volunteers similar to that conducted for chloropicrin. Although the data for human volunteer subjects indicated variability in detection of chloropicrin (Phase II of the human subject study reviewed by Reaves, 2006a; see Table 4, Section 2.2), exposure to 50 ppb (0.050 ppm) for 20 to 30 minutes was detected only by the more sensitive individuals (16 of 42 subjects) suggesting this exposure to be near a NOAEL. Therefore, uncertainty adjustment for sensitive individuals is not recommended. The AEGL-1 values for chloropicrin are shown in Table 10 and their derivation presented in Appendix A.

TABLE 10. AEGL-1 Values for Chloropicrin

Classification	10-min	30-min	1-h	4-h	8-h
AEGL-1	0.050 ppm 0.34 mg/m^3	0.050 ppm 0.34 mg/m^3	0.050 ppm 0.34 mg/m^3	0.050 ppm 0.34 mg/m^3	0.050 ppm 0.34 mg/m^3

6. DATA ANALYSIS FOR AEGL-2

6.1. Human Data Relevant to AEGL-2

Data from exposure of informed human volunteers indicate that irritation of the eyes and respiratory tract are the initial critical effects resulting from chloropicrin vapor exposure. Older reports (Fries and West, 1921; Prentiss, 1937; Fairhall, 1957) indicated that very short exposures (a few seconds to <1 minute) to concentrations as low as 1 to 2.5 ppm resulted in immediate eye irritation and that higher concentrations (7-26 ppm) were intolerable. Cain (2004) and Reaves (2006b) reported that the more sensitive of the 42 human volunteers found 20 to 30-minute exposure to 75 to 150 ppb (0.075-0.15 ppm) to be intolerable. Similarly, 60-minute exposure produced eye irritation considered severe by some individuals.

6.2. Animal Data Relevant to AEGL-2

Some lethality studies in animals indicated nonlethal exposures but often lacked details regarding specific effects other than the exposure being nonlethal. Exposure of rats for 240 minutes to 10.8 ppm (Hoffman, 1999) or 8.8 ppm were not lethal (Yoshida et al., 1987a) but resulted in severe effects (e.g., labored breathing, cyanosis, pulmonary edema). A 240-minute exposure of rats to 6.6 ppm (nose-only) was not lethal. An RD_{50} of 8.1 ppm (10-minute exposure) was reported for Swiss-Webster mice by Kane et al. (1979).

6.3. Derivation of AEGL-2 Values

Results of studies with informed human volunteers (reviewed by Reaves, 2006b) provide the most appropriate data for AEGL-2 development. In addition to eliminating the uncertainties inherent with animal data, the studies in human volunteers assess effects on the eye, the most sensitive target for chloropicrin vapor exposure. Severe ocular irritation reported by some volunteer participants in this study is considered an appropriate critical effect and the 150 ppm concentration is considered an appropriate point-of departure (POD) for AEGL-2 derivation. Although all of the effects noted for exposure to 150 ppb chloropicrin were reversible upon cessation of exposure and the reported effects of less severity than that typically associated with the AEGL-2 tier, the ocular irritation was characterized as: “symptom hard to tolerate and can interfere with activities of daily living or sleeping”. The exposure duration of 60 minutes in Phase III of this key study versus 1 minute or less in the early studies limit extensive extrapolations required if using the data from earlier reports. In Phase II of the study, 4 of the more sensitive of 42 human volunteers found a 20 to 30-minute exposure to 150 ppb (0.15 ppm) to be intolerable. In a multiple-day exposure experiment (Phase III), human volunteers were exposed to 100 or 150 ppb for 60 minutes on 4 consecutive days with some participants reporting severe eye irritation during the first exposure.

Because human volunteers were used, an interspecies uncertainty factor of 1 is appropriate. The intraspecies uncertainty factor is also limited to1 because some of the test subjects appeared to be representative of a sensitive population. Additionally, the effects occurring at 150 ppb were reversible and considered of minimal severity as a critical effect for AEGL-2 development. Because the AEGL-2 is also based upon ocular irritation, time scaling was not applied (see section 5.3) resulting in the same concentration for all AEGL-specific exposure durations.

The AEGL-2 values for chloropicrin are shown in Table 11 and their derivation summarized in Appendix A.

TABLE 11. AEGL-2 Values for Chloropicrin

Classification	10-min	30-min	1-h	4-h	8-h
AEGL-2	0.15 ppm 1.0 mg/m^3	0.15 ppm 1.0 mg/m^3	0.15 ppm 1.0 mg/m^3	0.15 ppm 1.0 mg/m^3	0.15 ppm 1.0 mg/m^3

7. DATA ANALYSIS FOR AEGL-3

7.1. Human Data Relevant to AEGL-3

Human lethality data for chloropicrin are limited to non-verifiable reports of Vedder (1925), who reported that exposure to 0.8 mg chloropicrin/L (120 ppm) for 30 minutes was lethal. Prentiss (1937) reported that exposure to 2.00 mg chloropicrin/L (300 ppm) for 10 minutes or 0.80 mg/L (120 ppm) for 30 minutes was lethal.

7.2. Animal Data Relevant to AEGL-3

Animal lethality data are available for rats, mice, dogs, rabbits, and guinea pigs although only the study reports for rats and mice have sufficient information for AEGL-3 development. The most definitive data come from studies by Yoshida et al. (1987a; 1991) in which rats were exposed (whole-body or nose-only) to chloropicrin for 30 or 240 minutes. The 240-minute LC_{50} values ranged from 12.1 to 18.9 ppm. The 30-minute exposure study provided only a LOAEL for lethality (21.7 ppm) and 100% lethality at 45.5 ppm. U.S. Testing Co., Inc (1976) reported a 60-minute LC_{50} of 26 ppm for rats and Hoffman (1999) reported a 240-minute LC_{50} of 18.9 ppm. Kawai (1973) reported 30-minute LC_{50} of 56 ppm (vapor) and a 240-minute LC_{50} of 9.9 ppm (aerosol) for mice. Lethality data are summarized in Table 7.

7.3. Derivation of AEGL-3 Values

Benchmark dose analysis (U.S. EPA, 2007) of the 240-minute exposure rat lethality data of Yoshida et al. (1987a;1991) yielded a $BMCL_{05}$ of 7.9 ppm and a BMC_{01} of 8.4 ppm. Analysis of these data by the method of Litchfield and Wilcoxon (1949) showed an LC_{01} of 8.3 ppm. All of the estimates of a lethality threshold are remarkably similar (Appendix D). Consistent with the AEGL Standing Operating Procedures (NRC, 2001), the $BMCL_{05}$ of 7.9 ppm was selected as the POD for derivation of AEGL-3 values. Exposure duration-exposure concentration analysis of rat data indicated an exponential relationship of $C^n \times t = k$, where n = 2.3 (Appendix B). Due to uncertainties in extrapolating from the 240-minute experimental exposure duration to the 10-minute AEGL time point, the 30-minute AEGL-3 was adopted for the 10-minute AEGL-3. The interspecies uncertainty adjustment was limited to 3 because the toxic responses in multiple species (dogs, rats, and mice) were qualitatively equivalent; signs of respiratory tract damage (labored breathing, gasping, and nasal discharge) with histological findings affirming damage to the respiratory tract all of which are indicative of a direct-contact toxicity in all of the tested species. Quantitatively, comparison of 240-minute LC_{50} values in mice and rats varied less than 2-fold (9.9 ppm vs 18 ppm). Further, due to ventilatory rate-body size relationships, the dose to rodents would be greater than that to a human at any given air concentration of chloropicrin. Chloropicrin-induced respiratory tract damage and the

hypothesized mode of action for chloropicrin (inhibition of pyruvate dehydrogenase and succinate dehydrogenase both of which are ubiquitous across mammalian species with respect to cellular metabolism) would also imply limited interspecies variability. In consideration of individual variability in the toxic response to chloropicrin, the direct-contact mechanism of chloropicrin on respiratory tract surfaces would be the same, although dosimetric variability among individuals may vary and is accounted for by an intraspecies uncertainty factor of 3. Further reduction of the AEGL-3 values by greater uncertainty factors would result in AEGL-3 values equivalent to the AEGL-2 values which are based upon data from carefully controlled studies in human volunteers.

The resulting AEGL-3 values are shown in Table 12 and their derivation summarized in Appendix A.

TABLE 12. AEGL-3 Values for Chloropicrin

Classification	10-min	30-min	1-h	4-h	8-h
AEGL-3	2.0 ppm 13 mg/m^3	2.0 ppm 13 mg/m^3	1.4 ppm 9.4 mg/m^3	0.79 ppm 5.3 mg/m^3	0.58 ppm 3.9 mg/m^3

8. SUMMARY OF AEGLs

8.1. AEGL Values and Toxicity Endpoints

Both the AEGL-1 and AEGL-2 values are based upon data from a controlled study using informed human volunteers and critical effects typical for chloropicrin exposures. The results observed in these studies suggested some individuals to be more sensitive responders. The AEGL values for these two tiers were derived using PODs for critical effects of lesser severity than the respective AEGL tier definition. The AEGL-3 values are based upon benchmark analysis of animal data from well-conducted recent experiments.

TABLE 13. AEGL Values for Chloropicrin

Classification	10-min	30-min	1-h	4-h	8-h
AEGL-1 (Nondisabling)	0.050 ppm 0.34 mg/m^3	0.050 ppm 0.34 mg/m^3	0.050ppm 0.34 mg/m^3	0.050 ppm 0.34 mg/m^3	0.050 ppm 0.34 mg/m^3
AEGL-2 (Disabling)	0.15 ppm 1.0 mg/m^3	0.15 ppm 1.0 mg/m^3	0.15 ppm 1.0 mg/m^3	0.15 ppm 1.0 mg/m^3	0.15 ppm 1.0 mg/m^3
AEGL-3 (Lethality)	2.0 ppm 13 mg/m^3	2.0 ppm 13 mg/m^3	1.4 ppm 9.4 mg/m^3	0.79 ppm 5.3 mg/m^3	0.58 ppm 3.9 mg/m^3

8.2. Comparisons with Other Standards and Guidelines

A summary of currently available standards and guidelines is shown in Table 14. The AEGL values are derived using more recent data and are remarkably consistent with existing guidelines and standards.

TABLE 14. Extant Standards and Guidelines for Chloropicrin

Guideline	Exposure Duration				
	10 min	**30 min**	**1 h**	**4 h**	**8 h**
AEGL-1	0.050 ppm 0.34 mg/m^3	0.050 ppm 0.34 mg/m^3	0.050 ppm 0.34 mg/m^3	0.050 ppm 0.34 mg/m^3	0.050 ppm 0.34 mg/m^3
AEGL-2	0.15 ppm 1.0 mg/m^3	0.15 ppm 1.0 mg/m^3	0.15 ppm 1.0 mg/m^3	0.15 ppm 1.0 mg/m^3	0.15 ppm 1.0 mg/m^3
AEGL-3	2.0 ppm 13 mg/m^3	2.0 ppm 13 mg/m^3	1.4 ppm 9.4 mg/m^3	0.79 ppm 5.3 mg/m^3	0.58 ppm 3.9 mg/m^3
ERPG-1 (AIHA)[a]			0.1 ppm		
ERPG-2 (AIHA)			0.3 ppm		
ERPG-3 (AIHA)			1.5 ppm		
EEGL (NRC)[b]					
PEL-TWA (OSHA)[c]					0.1 ppm
PEL-STEL (OSHA)[d]					
IDLH (NIOSH)[e]					
REL-TWA (NIOSH)[f]					
TLV-TWA (ACGIH)[h]					0.1 ppm
TLV-STEL (ACGIH)[i]					
MAC[j] (the Netherlands)					0.1 ppm
MAK (Germany)[k]					0.1 ppm (0.68 mg/m^3)
MAK Spitzenbegrenzung (Germany)[l]					
Einsaztoleranzwert (Germany)[m]					

[a] **ERPG (Emergency Response Planning Guidelines, American Industrial Hygiene Association)** (AIHA, 2006)
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 protective 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.

[b] **EEGL (Emergency Exposure Guidance Levels, National Research Council)** (NRC, 1985)
is the concentration of contaminants that can cause discomfort or other evidence of irritation or intoxication in or around the workplace, but avoids death, other severe acute effects and long-term or chronic injury.

[c] **OSHA PEL-TWA (Occupational Health and Safety Administration, Permissible Exposure Limits - Time Weighted Average)** (OSHA, 2007) is defined analogous to the ACGIH-TLV-TWA, but is for exposures of no more than 10 hours/day, 40 hours/week.

[d] **OSHA PEL-STEL (Permissible Exposure Limits - Short Term Exposure Limit)** (OSHA, 1993) is defined analogous to the ACGIH-TLV-STEL.

[e] **IDLH (Immediately Dangerous to Life and Health, National Institute of Occupational Safety and Health)** (NIOSH, 1996) represents the maximum concentration from which one could escape within 30 minutes without any escape-impairing symptoms, or any irreversible health effects.

[f] **NIOSH REL-TWA (National Institute of Occupational Safety and Health, Recommended Exposure Limits - Time Weighted Average)** (NIOSH, 2005) is defined analogous to the ACGIH-TLV-TWA.

[g] **NIOSH REL-STEL (Recommended Exposure Limits - Short Term Exposure Limit)** (NIOSH, 2005) is defined analogous to the ACGIH-TLV-STEL.

[h] **ACGIH TLV-TWA (American Conference of Governmental Industrial Hygienists, Threshold Limit Value - Time Weighted Average)** (ACGIH, 2007) is the time-weighted average concentration for a normal 8-hour workday and a 40-hour work week, to which nearly all workers may be repeatedly exposed, day after day, without adverse effect. Expressed as osmium.

[i] **ACGIH TLV-STEL (Threshold Limit Value - Short Term Exposure Limit)** (ACGIH, 2007) is defined as a 15-minute TWA exposure which should not be exceeded at any time during the workday even if the 8-hour TWA is within the TLV-TWA. Exposures above the TLV-TWA up to the STEL should not be longer than 15 minutes and should not occur more than 4 times per day. There should be at least 60 minutes between successive exposures in this range. Expressed as osmium.

[j] **MAC (Maximaal Aanvaaarde Concentratie [Maximal Accepted Concentration])** Nationale MAC List (2000). (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.

[k] **MAK (Maximale Arbeitsplatzkonzentration [Maximum Workplace Concentration], Deutsche Forschungs-gemeinschaft [German Research Association], Germany)** (DFG, 2006) is defined analogous to the ACGIH-TLV-TWA.

[l] **MAK Spitzenbegrenzung (Kategorie II,2) [Peak Limit Category II,2]** (DFG, 2006) constitutes the maximum average concentration to which workers can be exposed for a period up to 30 minutes, with no more than 2 exposure periods per work shift; total exposure may not exceed 8-hour MAK. Cat. III indicates possible significant contribution to cancer risk.

[m] **Einsatztoleranzwert [Action Tolerance Levels] (Vereinigung zur Förderung des deutschen Brandschutzes e.V. [Federation for the Advancement of German Fire Prevention])** constitutes a concentration to which unprotected firemen and the general population can be exposed to for up to 4 hours without any health risks.

8.3. Data Adequacy and Research Needs

Data are adequate for development of scientifically defensible AEGL values for chloropicrin. Human data from controlled studies are the foundation of nonlethal toxicity values while several well-conducted studies is animals define the lethal response to inhaled chloropicrin.

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APPENDIX A: Derivation of AEGL Values

Derivation of AEGL-1 Values for Chloropicrin

Key study: Cain, W. 2004. Human Sensory Irritation Testing for Chloropicrin. Chemosensory Perception Laboratory, University of California, San Diego. Unpubl. (summarized in Reaves 2004, 2006a, and 2006b).

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Critical effect: The point-of-departure for deriving AEGL-1 is 50 ppb (0.050 ppm) which represents a NOAEL for ocular irritation but is a detection level for sensitive individuals. This is supported by a $BMCL_{10}$ of 73 ppb (0.073 ppm) based on the analysis of the Cain (2004) data on ocular irritation in human volunteers (Reaves, 2006a).

Time scaling: None applied. Time scaling for AEGL-1 was not considered appropriate for the direct-contact irritation by chloropicrin and, therefore, the AEGL-1 values are the same for all AEGL-specific durations (NRC, 2001).

Uncertainty factors: Total uncertainty factor adjustment was 1.
Interspecies: 1; human data
Intraspecies: 1; test group included individuals who appeared to be sensitive responders

Modifying factor: None applied

AEGL-1 for all exposure durations is 0.050 ppm.

Derivation of AEGL-2 Values for Chloropicrin

Key study: Cain, W. 2004. Human Sensory Irritation Testing for Chloropicrin. Chemosensory Perception Laboratory, University of California, San Diego. Unpubl. (summarized in Reaves 2004, 2006a, and 2006b).

Reaves, E. 2006b. Memorandum from Elissa Reaves, Ph.D., Toxicologist, USEPA Health Effects Division, to Tina Levine, Ph.D., Director, US EPA Health Effects Division, "Human Studies Review Board: Weight of Evidence Discussion for Trichloronitromethane (Chloropicrin.)." June 7.

Critical effect:	Eye irritation; threshold for respiratory/ventilatory effects in human volunteers exposed to 150 ppb (0.15 ppm) for 60 minutes.
Time scaling:	None applied. Time scaling for AEGL-2 was not considered appropriate for the direct-contact effects of chloropicrin and, therefore, the AEGL-2 values are the same for all AEGL-specific durations (NRC, 2001).
Uncertainty factors:	Total uncertainty factor adjustment was 1. Interspecies: 1; response data are from human volunteers Intraspecies: 1; some of the test subjects represented sensitive responders; additionally, the POD represents minimal effects for AEGL-2 tier severity.
Modifying factor:	None applied

AEGL-2 for all exposure durations is 0.15 ppm.

Derivation of AEGL-3 Values for Chloropicrin

Key studies: Yoshida M., Ikeda, T., Iwasaki, M., Tsuda, S., Shirasu, Y. 1987a. Acute inhalation toxicity of chloropicrin vapor in rats. J. Pesticide Sci. 12:237-244.

Yoshida, M., Murao, N., Tsuda, S., Shirasu, Y. 1991. Effects of mode of exposure on acute inhalation toxicity of chloropicrin vapor in rats. Nippon Noyaku Gakkaishi (Journal of the Pesticide Science Society of Japan) 16:63-69.

Critical effect: Lethality; 4-hr $BMCL_{05}$ of 7.9 ppm

Time scaling: $C^n \times t = k$, where n=2.3 based upon exposure concentration-exposure duration analysis of rat lethality data using the software of ten Berge (2006) (see Appendix B).

Uncertainty factors: Total uncertainty factor adjustment was 10.
Interspecies: 3; interspecies uncertainty adjustment was limited to 3 because the toxic responses in multiple species (dogs, rats, and mice) were qualitatively equivalent; signs of respiratory tract damage (labored breathing, gasping, and nasal discharge) with histological findings affirming damage to the respiratory tract all of which are indicative of a direct-contact toxicity in all of the tested species. Quantitatively, comparison of 240-minute LC_{50} values in mice and rats varied less than 2-fold (9.9 ppm vs 18 ppm). Further, due to ventilatory rate-body size relationships, the dose to rodents would be greater than that to a human at any given air concentration of chloropicrin. Chloropicrin-induced respiratory tract damage and the hypothesized mode of action for chloropicrin (inhibition of pyruvate dehydrogenase and succinate dehydrogenase both of which are ubiquitous across mammalian species with respect to cellular metabolism) would also imply limited interspecies variability.
Intraspecies: 3; the direct-contact mechanism of chloropicrin on respiratory tract surfaces would be the same, although dosimetric variability among individuals may vary and is accounted for by an intraspecies uncertainty factor of 3. Further reduction of the AEGL-3 values by greater uncertainty factors would result in AEGL-3 values equivalent to the AEGL-2 values which are based upon data from carefully controlled studies in human volunteers.

Modifying Factor: None applied

Calculation: $(7.9 \text{ ppm})^{2.3} \times 4 \text{ hrs} = 464.1 \text{ ppm}^{2.3} \cdot \text{hrs}$

10-minute AEGL-3	Due to uncertainties in extrapolating from the 4-hr experimental epxosure duration, the 30-minute AEGL-3 is adopted for the 10-minute AEGL-3 (NRC, 2001).
30-minute AEGL-3	$C^{2.3}$ x 0.5 hr = 464.1 $ppm^{2.3}$ · hrs $C^{2.3}$ = 91.5 ppm C = 19.5 ppm/10 = 1.95 ppm (rounded to 2.0 ppm)
1-hour AEGL-3	$C^{2.3}$ x 1 hr = 464.1 $ppm^{2.3}$ · hrs $C^{2.3}$ = 14.4 ppm C = 14.4 ppm/10 = 1.4 ppm
4-hour AEGL-3	$C^{2.3}$ x 4 hrs = 464.1 $ppm^{2.3}$ · hrs $C^{2.3}$ = 7.9 ppm C = 7.9 ppm/10 = 0.79 ppm
8-hour AEGL-3	$C^{2.3}$ x 8 hrs = 464.1 $ppm^{2.3}$ · hrs $C^{2.3}$ = 5.8 ppm C = 5.8 ppm/10 = 0.58 ppm

APPENDIX B: Time Scaling Calculations

The relationship between dose and time for any given chemical is a function of the physical and chemical properties of the substance and the unique toxicological and pharmacological properties of the individual substance. Historically, the relationship according to Haber (1924), commonly called Haber's Law or Haber's Rule (i.e., $C \times t = k$, where C = exposure concentration, t = exposure duration, and k = a constant) has been used to relate exposure concentration and duration to effect (Rinehart and Hatch, 1964). This concept states that exposure concentration and exposure duration may be reciprocally adjusted to maintain a cumulative exposure constant (k) and that this cumulative exposure constant will always reflect a specific quantitative and qualitative response. This inverse relationship of concentration and time may be valid when the toxic response to a chemical is equally dependent upon the concentration and the exposure duration. However, an assessment by ten Berge et al. (1986) of LC_{50} data for certain chemicals revealed chemical-specific relationships between exposure concentration and exposure duration that were often exponential. This relationship can be expressed by the equation $C^n \times t = k$, where n represents a chemical specific, and even a toxic endpoint specific, exponent. The relationship described by this equation is basically the form of a linear regression analysis of the log-log transformation of a plot of C vs t. ten Berge et al. (1986) examined the airborne concentration (C) and short-term exposure duration (t) relationship relative to death for approximately 20 chemicals and found that the empirically derived value of n ranged from 0.8 to 3.5 among this group of chemicals. Hence, the value of the exponent (n) in the equation $C^n \times t = k$ quantitatively defines the relationship between exposure concentration and exposure duration for a given chemical and for a specific health effect endpoint. Haber's Rule is the special case where $n = 1$. As the value of n increases, the plot of concentration vs time yields a progressive decrease in the slope of the curve.

An n of 2.4 was obtained following analysis of lethality data in rats Yoshida et al., 1987a) using the software of the ten Berge. This exposure-time relationship for lethality was considered appropriate for AEGL-3 development but because chloropicrin-induced ocular irritation is the results of direct-contact irritation, no time scaling was applied in the development of AEGL-1 and AEGL-2 values.

Filename: Chloropicrin for Log Probit Model
Date: 04 January 2008 Time: 10:36:15

Seq.Nr	conc ppm	minutes	exposed	responded
1	9	240	8	0
2	11	240	8	2
3	11	240	8	3
4	12	240	8	5
5	14	240	8	7
6	12	240	8	1
7	14	240	8	2
8	15	240	8	7
9	22	30	7	0
10	46	30	6	6

Observations 1 through 10 considered!

Seq.nr	conc ppm	minutes	exposed	responded
1	9	240	8	0
2	11	240	8	2
3	11	240	8	3
4	12	240	8	5
5	14	240	8	7
6	12	240	8	1
7	14	240	8	2
8	15	240	8	7
9	22	30	7	0
10	46	30	6	6

Used Probit Equation Y = B0 + B1*X1 + B2*X2
X1 = conc ppm, ln-transformed
X2 = minutes, ln-transformed

ChiSquare = 14.33
Degrees of freedom = 7
Probability Model = 4.56E-02

Ln(Likelihood) = -15.24

B 0 = -2.1221E+01 Student t = -2.4191
B 1 = 5.3210E+00 Student t = 3.1638
B 2 = 2.3046E+00 Student t = 2.5409

variance B 0 0 = 7.6948E+01
covariance B 0 1 = -1.3952E+01
covariance B 0 2 = -7.6155E+00
variance B 1 1 = 2.8286E+00
covariance B 1 2 = 1.2394E+00
variance B 2 2 = 8.2266E-01

Estimation ratio between regression coefficients of ln(conc) and ln(minutes)
Point estimate = 2.309
Lower limit (95% CL) = 1.059
Upper limit (95% CL) = 3.559

APPENDIX C: Derivation Summary Tables

ACUTE EXPOSURE GUIDELINE LEVELS FOR CHLOROPICRIN DERIVATION SUMMARY

AEGL-1 VALUES FOR CHLOROPICRIN				
10 min	**30 min**	**1 h**	**4 h**	**8 h**
0.050 ppm 0.34 mg/m^3	0.050 ppm 0.34 mg/m^3	0.050 ppm 0.34 mg/m^3	0.050 ppm 0.34 mg/m^3	0.050 ppm 0.34 mg/m^3
Reference: Cain, W. 2004. Human Sensory Irritation Testing for Chloropicrin. Chemosensory Perception Laboratory, University of California, San Diego. Unpubl. (summarized in Reaves 2004, 2006a, and 2006b). Reaves, E. 2006a. Memorandum from Elissa Reaves, Ph.D., US EPA Health Effects Division to Nathan Mottl, Chemical Review Manager, Special Review and Reregistration Division. Review of the TERA Document: "Use of Benchmark Concentration Modeling and Categorical Regression to Evaluate the Effects of Acute Exposure to Chloropicrin Vapor. MRID 46614801."				
Test Species/Strain/Number: Informed human volunteer subjects (male and female; aged 18-35 years); 42 total subjects				
Exposure Route/Concentrations/Durations: vapor exposure (up to 30 minutes)				
Effects: detection by sensitive individuals, ocular irritation NOAEL				
Endpoint/Concentration/Rationale: 0.50 ppb (0.050 ppm) NOAEL for ocular irritation				
Uncertainty Factors/Rationale: none; $BMCL_{10}$ determined from response of a group of individuals including sensitive responders; POD is sufficiently protective				
Modifying Factor: None applied				
Animal to Human Dosimetric Adjustment: no adjustments				
Time Scaling: none applied; direct-contact				
Data Adequacy: Sufficient for AEGL-1 development; human data were used to estimated a protective threshold for ocular irritation, the most sensitive critical effect.				

1

AEGL-2 VALUES FOR CHLOROPICRIN				
10 min	**30 min**	**1 h**	**4 h**	**8 h**
0.15 ppm 1.0 mg/m^3	0.15 ppm 1.0 mg/m^3	0.15 ppm 1.0 mg/m^3	0.15 ppm 1.0 mg/m^3	0.15 ppm 1.0 mg/m^3
Reference: Cain, W. 2004. Human Sensory Irritation Testing for Chloropicrin. Chemosensory Perception Laboratory, University of California, San Diego. Unpubl. (summarized in Reaves, 2006b).				
Test Species/Strain/Sex/Number: : Informed human volunteer subjects (male and female; aged 18-35 years); 42 total subjects				
Exposure Route/Concentrations/Durations: 60 minutes				
Effects: intolerable eye irritation; threshold for ventilatory effects				
Endpoint/Concentration/Rationale: 150 ppb (0.15 ppm)				
Uncertainty Factors/Rationale: Total UF= 1 Interspecies: 1; informed human volunteer subjects Intraspecies: 1; sensitive individuals (some of the test subjects were sensitive responders)				
Modifying Factor: none applied				
Animal to Human Dosimetric Adjustment:				
Time Scaling: : none applied; direct-contact				
Data Adequacy: Human data were available with which to estimate a threshold for intolerable eye irritation serving as a POD for AEGL-2 tier effects (i.e., threshold for escape-impairing response).				

AEGL-3 VALUES FOR CHLOROPICRIN				
10 min	**30 min**	**1 h**	**4 h**	**8 h**
2.0 ppm 13 mg/m^3	2.0 ppm 13 mg/m^3	1.4 ppm 9.4 mg/m^3	0.79 ppm 5.3 mg/m^3	0.58 ppm 3.9 mg/m^3

Reference:
Yoshida M., Ikeda, T., Iwasaki, M., Tsuda, S., Shirasu, Y. 1987a. Acute inhalation toxicity of chloropicrin vapor in rats. J. Pesticide Sci. 12:237-244.
Yoshida, M., Murao, N., Tsuda, S., Shirasu, Y. 1991. Effects of mode of exposure on acute inhalation toxicity of chloropicrin vapor in rats. Nippon Noyaku Gakkaishi (Journal of the Pesticide Science Society of Japan) 16:63-69.

Test Species/Strain/Sex/Number: rat/Fischer 344/male/8 per group

Exposure Route/Concentrations/Durations: inhalation exposure: 8.8, 11.0, 11.4, 12.1, 13.6, 16.0 ppm whole-body for 240 min (Yoshida et al., 1987a); 12.3 , 13.9, 15.4 ppm nose-only for 240 min. or 5.3, 5.9, 6.6, 81. ppm (whole-body) (Yoshida et al., 1991)

Effects: lethality
Yoshida et al. (1987a)Yoshida et al. (1991)

Dose	Lethality	Dose	Lethality
8.8	0/8	12.3	1/8 nose-only
11.0	2/8	13.9	2/8 nose-only
11.4	3/8	15.4	7/8 nose-only
12.1	5/8	5.3	0/8 whole-body
13.6	7/8	5.9	1/8 whole-body
16.0	8/8	6.6	6/8 whole-body
		8.1	6/8 whole-body

Endpoint/Concentration/Rationale: $BMCL_{05}$ of 7.9 ppm used as estimate of lethality threshold in rats exposed for 240 minutes as per AEGL Standing Operating Procedures (NRC, 2001).

Uncertainty Factors/Rationale: Total uncertainty factor adjustment was 10.

Interspecies: 3; interspecies uncertainty adjustment was limited to 3 because the toxic responses in multiple species (dogs, rats, and mice) were qualitatively equivalent; signs of respiratory tract damage (labored breathing, gasping, and nasal discharge) with histological findings affirming damage to the respiratory tract all of which are indicative of a direct-contact toxicity in all of the tested species. Quantitatively, comparison of 240-minute LC_{50} values in mice and rats varied less than 2-fold (9.9 ppm vs 18 ppm). Further, due to ventilatory rate-body size relationships, the dose to rodents would be greater than that to a human at any given air concentration of chloropicrin. Chloropicrin-induced respiratory tract damage and the hypothesized mode of action for chloropicrin (inhibition of pyruvate dehydrogenase and succinate dehydrogenase both of which are ubiquitous across mammalian species with respect to cellular metabolism) would also imply limited interspecies variability.

Intraspecies: 3; the direct-contact mechanism of chloropicrin on respiratory tract surfaces would be the same, although dosimetric variability among individuals may vary and is accounted for by an intraspecies uncertainty factor of 3. Further reduction of the AEGL-3 values by greater uncertainty factors would result in AEGL-3 values equivalent to the AEGL-2 values which are based upon data from carefully controlled studies in human volunteers.

Modifying Factor: None applied

Animal to Human Dosimetric Adjustment: Not applicable

Time Scaling: $C^n \times t = k$, where n=2.3 as determined by analysis of rat lethality data using ten Berge, 2006 software.

Data Adequacy: Several well-conducted lethality assays in rats are available; lethality data in laboratory species appear to be consistent and are sufficient for benchmark analysis and development of AEGL-3 values.

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APPENDIX D: BENCHMARK CONCENTRATION AND LC_{50} CALCULATION FOR CHLOROPICRIN

Yoshida et al. 1987a; 1991; rat whole-body 240-minute inhalation exposure to chloropicrin

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Probit Model. (Version: 2.8; Date: 02/20/2007)
Input Data File: C:\BMDS\UNSAVED1.(d)
Gnuplot Plotting File: C:\BMDS\UNSAVED1.plt
Thu Sep 13 13:06:26 2007

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BMDS MODEL RUN

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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 = COLUMN3
Independent variable = COLUMN1
Slope parameter is not restricted
Total number of observations = 9
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

User has chosen the log transformed model

Default Initial (and Specified) Parameter Values
background = 0
intercept = -12.4956
slope = 4.93287

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)

	Intercept	slope
Intercept	1	-1
slope	-1	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
Background	0	NA		
Intercept	-14.1155	3.3469	-20.6753	-7.55566
Slope	5.54777	1.3127	2.97493	8.1206

NA - Indicates that this parameter has hit a bound implied by some inequality constraint and thus has no standard error.
~~~~~~~~~~

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-28.6249	9			
Fitted model	-36.8585	2	16.4673	7	0.02117
Reduced model	-49.8788	1	42.5079	8	<.0001

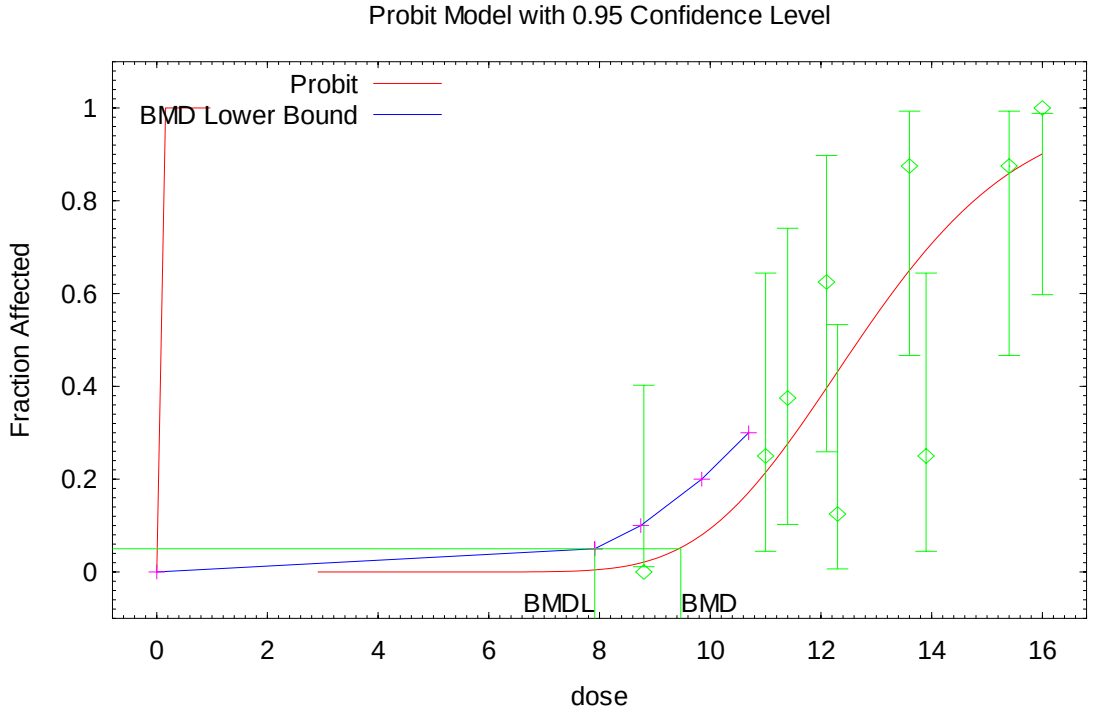
AIC: 77.717

Goodness of Fit

Dose	Est._Prob.	Scaled Expected	Observed	Size	Residual
8.8000	0.0202	0.161	0	8	-0.406
11.0000	0.2083	1.666	2	8	0.291
11.4000	0.2695	2.156	3	8	0.673
12.1000	0.3883	3.106	5	8	1.374
13.6000	0.6423	5.138	7	8	1.373
16.0000	0.8973	7.178	8	8	0.957
12.3000	0.4236	3.389	1	8	-1.709
13.9000	0.6864	5.491	2	8	-2.660
15.4000	0.8541	6.833	7	8	0.167

Chi^2 = 15.42 d.f. = 7 P-value = 0.2320

Benchmark Dose Computation
Specified effect = 0.05
Risk Type = Extra risk
Confidence level = 0.95
BMC = 9.46745
BMCL = 7.9137



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Yoshida et al. 1987a; 1991; rat whole-body 240-minute inhalation exposure to chloropicrin BMC01

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Probit Model. (Version: 2.8; Date: 02/20/2007)
Input Data File: C:\BMDS\UNSAVED1.(d)
Gnuplot Plotting File: C:\BMDS\UNSAVED1.plt
Thu Sep 13 13:14:40 2007

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BMDS MODEL RUN

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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 = COLUMN3
Independent variable = COLUMN1
Slope parameter is not restricted

Total number of observations = 9
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

User has chosen the log transformed model

Default Initial (and Specified) Parameter Values
background = 0
intercept = -12.4956
slope = 4.93287

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)

	intercept	slope
intercept	1	-1
slope	-1	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
background	0	NA		
intercept	-14.1155	3.3469	-20.6753	-7.55566
slope	5.54777	1.3127	2.97493	8.1206

NA - Indicates that this parameter has hit a bound
implied by some inequality constraint and thus
has no standard error.
~~~~~~~~~~

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-28.6249	9			
Fitted model	-36.8585	2	16.4673	7	0.02117
Reduced model	-49.8788	1	42.5079	8	<.0001

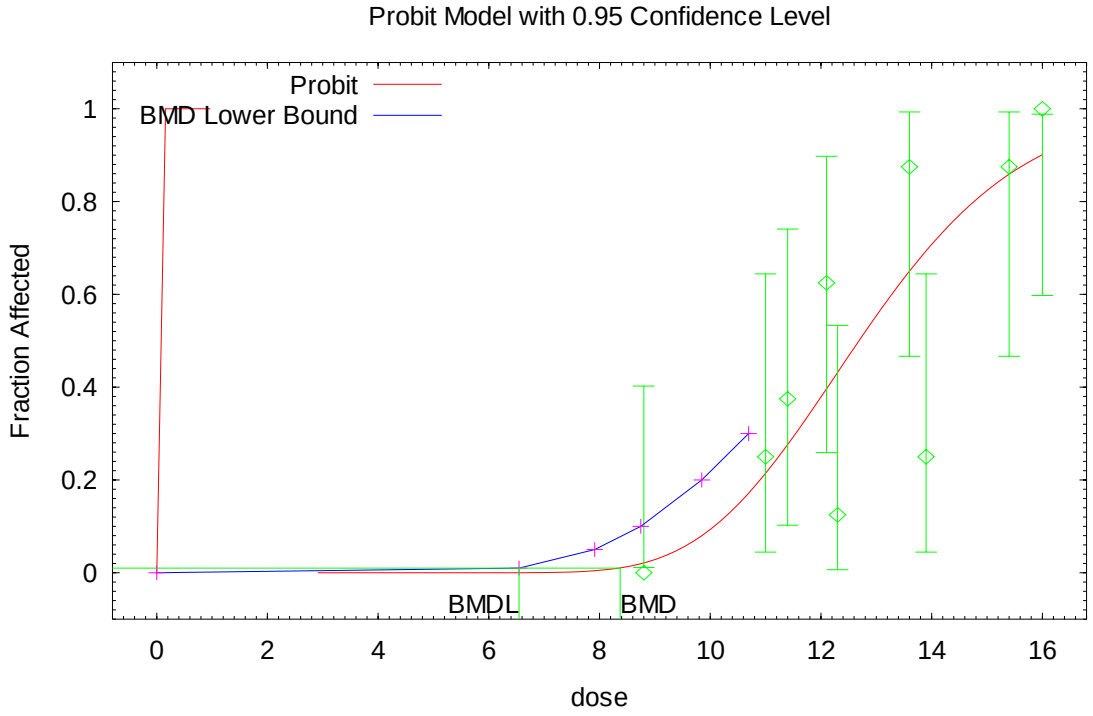
AIC: 77.717

Goodness of Fit

Dose	Est._Prob.	Expected	Scaled Observed	Size	Residual
8.8000	0.0202	0.161	0	8	-0.406
11.0000	0.2083	1.666	2	8	0.291
11.4000	0.2695	2.156	3	8	0.673
12.1000	0.3883	3.106	5	8	1.374
13.6000	0.6423	5.138	7	8	1.373
16.0000	0.8973	7.178	8	8	0.957
12.3000	0.4236	3.389	1	8	-1.709
13.9000	0.6864	5.491	2	8	-2.660
15.4000	0.8541	6.833	7	8	0.167

Chi^2 = 15.42 d.f. = 7 P-value = 0.0310

Benchmark Dose Computation
Specified effect = 0.01
Risk Type = Extra risk
Confidence level = 0.95
BMC = 8.37305
BMCL = 6.54615



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Litchfield and Wilcoxon analysis of rat lethality data for chloropicrin

Yoshida et al. (1987a; 1991) 240-minute rat data. Lethal response levels estimated using the method of Litchfield and Wilcoxon (1949).

Dose	Mortality	Observed%	Expected%	Observed-Expected	Chi-Square
8.000	0/ 8	0(0.70)	0.75	-0.05	0.0000
11.000	2/ 8	25.00	16.66	8.34	0.0501
11.400	3/ 8	37.50	22.39	15.11	0.1313
12.100	5/ 8	62.50	34.75	27.75	0.3396
12.300	1/ 8	12.50	38.67	-26.17	0.2887
13.600	7/ 8	87.50	63.92	23.58	0.2411
13.900	2/ 8	25.00	68.92	-43.92	0.9004
15.400	7/ 8	87.50	86.41	1.09	0.0010
16.000	8/ 8	100(95.30)	90.41	4.89	0.0276

Values in parentheses are corrected for 0 or 100 percent Total = 1.9798

LC_{50} = 12.864(11.558 - 14.318)*
Slope = 1.17(1.08 - 1.28)*

* These values are 95 percent confidence limits

Total animals = 72 Total doses = 9 Animals/dose = 8.00
Chi-square = total chi-square X animals/dose = 15.8385

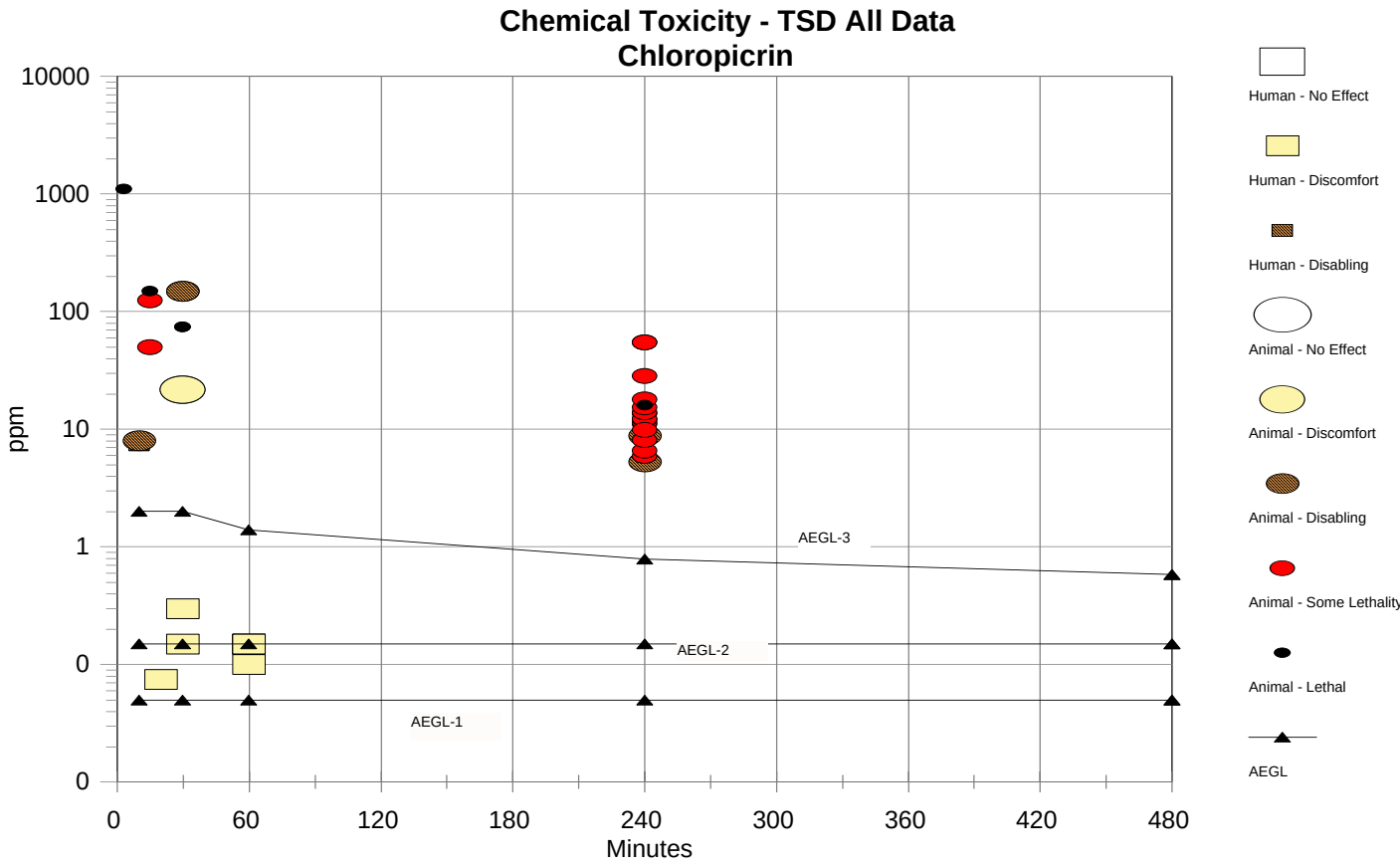
Table value for Chi-square with 7 Degrees of Freedom = 14.0700

LC_{84} = 15.115 LC_{16} = 10.949 FED = 1.11 FS = 1.09 A = 1.04

Expected Lethal Dose Values

$LC_{0.1}$	6.572
$LC_{1.0}$	**8.229**
$LC_{5.0}$	9.662
LC_{10}	10.390
LC_{25}	11.561
LC_{50}	12.864
LC_{75}	14.315
LC_{90}	15.929
LC_{99}	20.

APPENDIX E: CATEGORY PLOT FOR CHLOROPICRIN



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Source	Species	Sex	# Exposures	Ppm	Minutes	Category	Comments
NAC/AEGL-1				0.05	10	AEGL	NOAEL for ocular irritation; detection by sensitive individuals
NAC/AEGL-1				0.05	30	AEGL	NOAEL for ocular irritation
NAC/AEGL-1				0.05	60	AEGL	NOAEL for ocular irritation
NAC/AEGL-1				0.05	240	AEGL	NOAEL for ocular irritation
NAC/AEGL-1				0.05	480	AEGL	NOAEL for ocular irritation
NAC/AEGL-2				0.15	10	AEGL	Threshold for severe ocular irritation; threshold for ventilatory effects
NAC/AEGL-2				0.15	30	AEGL	
NAC/AEGL-2				0.15	60	AEGL	
NAC/AEGL-2				0.15	240	AEGL	
NAC/AEGL-2				0.15	480	AEGL	
NAC/AEGL-3				2	10	AEGL	Estimated lethality threshold in rats
NAC/AEGL-3				2	30	AEGL	
NAC/AEGL-3				1.4	60	AEGL	
NAC/AEGL-3				0.79	240	AEGL	
NAC/AEGL-3				0.58	480	AEGL	
	human		1	7.4	10	2	intolerable eye/resp. tract irritation (Prentiss, 1937)
	human		1	300	10	3	lethal; no details (Prentiss, 1937)
	human		1	120	30	3	lethal; no details (Prentiss, 1937)
	human	f	1	0.075	20	1	eye irritation (Cain, 2004; Reaves, 2006a)
	human	b	1	0.15	30	1	eye irritation (Cain, 2004; Reaves, 2006a)
	human	b	1	0.3	30	1	detection (Cain, 2004; Reaves, 2006a)
	human	b	1	0.15	60	1	eye irritation (Cain, 2004; Reaves, 2006a)
	human	b	1	0.1	60	1	severe eye irritation (Cain 2004; Reaves, 2006a)
	human	b	1	0.15	60	1	severe eye irritation (Cain 2004; Reaves, 2006a)
	rat	m	1	8.8	240	2	pulmonary edema, emphysema (Yoshida et al., 1987a)
	rat	m	1	11	240	PL	Yoshida et al., 1987a
	rat	m	1	11.4	240	PL	Yoshida et al., 1987a
	rat	m	1	12.1	240	PL	Yoshida et al., 1987a
	rat	m	1	13.6	240	PL	Yoshida et al., 1987a
	rat	m	1	16	240	3	Yoshida et al., 1987a
	rat	m	1	12.3	240	PL	Yoshida et al., 1991
	rat	m	1	13.9	240	PL	Yoshida et al., 1991
	rat	m	1	15.4	240	PL	Yoshida et al., 1991
	rat	m	1	5.3	240	2	Yoshida et al., 1991
	rat	m	1	5.9	240	PL	Yoshida et al., 1991
	rat	m	1	6.6	240	PL	Yoshida et al., 1991
	rat	m	1	8.1	240	PL	Yoshida et al., 1991
	rat	b	1	18	240	PL	Hoffman, 1999
	rat	b	1	28.5	240	PL	Hoffman, 1999
	mice		1	50	15	PL	Ritlop, 1939
	mice		1	125	15	PL	Ritlop, 1939
	mice		1	9.9	240	PL	LC50 (Kawai (1973)
	mice		1	55	240	PL	LC50 (Kawai (1973)
	mice		1	8	10	2	RD50 (Kawai, 1973)
	dog		1	1100	3	3	Lambert and Jackson (1920)
	dog		1	150	15	3	Lambert and Jackson (1920)

dog	1	74	30	3	Lambert and Jackson (1920)
dog	1	150	30	2	severe lung edema, necrosis (Lambert and Jackson, 1920)
rat	1	21.7	30	1	pulmonary irritation minor damage (Yoshida et al., 1987a)

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