ACUTE EXPOSURE GUIDELINE LEVELS (AEGLs)

FOR

CHLOROTRIFLUOROETHYLENE

(CAS Reg. No. 79-38-9)

$CF_2 = CFCl$

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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SUMMARY

Chlorotrifluoroethylene (CTFE, CAS Reg. No. 79-38-9) is a colorless gas at ambient temperature and pressure. It has a faint ethereal odor. The gas is flammable and may pose an explosion hazard. Production takes place in enclosed systems. The gas is used as a monomer for various fluoropolymers. In 2000, worldwide production was 1000-5000 tons.

No clinical data were located, but multiple studies with laboratory animals were available for development of AEGL values. These studies included acute, repeat-dose, subchronic, developmental, and cardiac sensitization studies. Although exposure durations in acute studies ranged from 5-15 minutes to 8 hours, no reliable empirical information was available for time scaling.

The target organ of CTFE toxicity is the kidney. Exposure of rats and mice resulted in concentration-dependent proximal tubular necrosis. Necrosis is mediated via metabolic bioactivation - conjugation with hepatic glutathione, the primary route of metabolism. The CTFE-glutathione metabolite is transported to the kidney where it is metabolized to a cysteine metabolite. Renal bioactivation of the cysteine metabolite by β-lyase yields an unstable thiolate metabolite that reacts with cellular constituents. In all cases where recovery was evaluated, kidney lesions in surviving animals showed evidence of recovery. At lethal concentrations, animals die of pulmonary congestion and edema.

The AEGL-1 value is based on a 4-hour, 102 ppm NOAEL for kidney lesions in the well-conducted study of Potter et al. (1981). Compared with humans, rodents have a higher respiratory rate and cardiac output, two determinants of chemical uptake. Blood:air partition coefficients for related chemicals such as tetrachloroethylene, are higher in rodents than humans. Thus, at similar concentrations chemical uptake is greater in rodents than in humans. Based on this information, an interspecies uncertainty factor of 1 might be considered. However, because no human toxicity data were available for comparison of uptake and metabolism, the 102 ppm concentration was adjusted by an interspecies uncertainty factor of 3. The choice of an interspecies uncertainty factor less than 10 is supported by the fact that rodents have higher tissue levels of glutathione transferase enzymes (Griem et al. 2002) and therefore may accumulate the toxic cysteine metabolite faster than humans.

Metabolism by glutathione conjugation varies among the human population (some humans are non-conjugators and theoretically would be at lower risk for nephrotoxicity). Based on other chemicals that are metabolized by conjugation with glutathione, the difference among individuals that metabolize CTFE is expected to be no greater than three-fold (Nolan et al. 1985; Mulder et al. 1999). Therefore, an intraspecies uncertainty factor of 3 was applied. The total uncertainty factor is 10. The resulting 4-hour value is 10 ppm. The 4-hour value of 10 ppm was time scaled to the shorter and longer exposure durations ($C^n \times t = k$) using n values of 3 and 1, respectively (NRC 2001). Because the time-scaled 8-hour value of 5 ppm was considered inconsistent with the monitoring data of Ryan (1991; no-effect chronic exposures of #20 ppm), the 8-hour value was set equal to the 4-hour value.

The threshold for irreversible kidney lesions following a single exposure was chosen as the basis for the AEGL-2. The point of departure was the 4-hour exposure of rats to 540 ppm

(Potter et al. 1981) which resulted in reversible kidney lesions and was considered a NOAEL for irreversible kidney lesions. Interspecies and intraspecies uncertainty factors of 3 and 3 (for a total of 10) were applied. The reasoning for selecting these values is the same as the reasoning for the AEGL-1 above. The 4-hour adjusted value of 54 ppm was time scaled to the shorter exposure durations (C^n x t = k) using an n value of 3 (NRC 2001). Because the time-scaled 8-hour value of 27 ppm would be inconsistent with the NOAEL of #20 ppm in monitoring studies (Ryan 1991), the 8-hour value was set equal to the 4-hour value.

Data on the highest non-lethal values and data for benchmark dose development were not available for the rat. The AEGL-3 values are based on a study with the mouse (Walther and Fischer 1968). The probit-analysis based dose-response program of ten Berge (2006) was used to calculate the threshold for lethality at each AEGL-3 exposure duration. The calculated value of n in the concentration-exposure duration relationship (C^n x t = k) was 1.37. Although LC_{50} data show that the mouse is not as sensitive to the effects of CTFE as the rat, the mouse has high levels of GST compared with humans, likely resulting in more rapid conjugation with glutathione and production of the toxic cysteine metabolite. Based on higher respiratory rate and cardiac output and more rapid metabolism to the toxic metabolite, the mouse is predicted to be more sensitive than humans. Therefore, an interspecies uncertainty factor of 3 was applied. Using the same reasoning as for the AEGL-1, an intraspecies uncertainty factor of 3 was applied for a total uncertainty factor of 10.

The calculated values are listed in the tables below.

S 1. **Summary of AEGL Values for Chlorotrifluoroethylene**

Classification	10-min	30-min	1-h	4-h	8-h	Endpoint (Reference)
AEGL–1[a] (Nondisabling)	29 ppm (138 mg/m^3)	20 ppm (95 mg/m^3)	16 ppm (76 mg/m^3)	10 ppm (48 mg/m^3)	10 ppm (48 mg/m^3)	NOAEL for kidney effects - rat (Potter et al. 1981)
AEGL–2 (Disabling)	160 ppm (760 mg/m^3)	110 ppm (523 mg/m^3)	86 ppm (409 mg/m^3)	54 ppm (266 mg/m^3)	54 ppm (266 mg/m^3)	Reversible kidney lesions - rat (Potter et al. 1981)
AEGL–3 (Lethal)	1500 ppm (7100 mg/m^3)	690 ppm (3300 mg/m^3)	420 ppm (2000 mg/m^3)	150 ppm (710 mg/m^3)	91 ppm (430 mg/m^3)	Highest non-lethal concentration - mouse (Walther and Fischer 1968)

[a] CTFE has a faint ethereal odor; no data on the odor threshold were available.

1. INTRODUCTION

Chlorotrifluoroethylene (CTFE) is a colorless gas with a faint ethereal odor. The vapor pressure is 4500 mm Hg at 25EC. It is soluble in organic solvents and slightly soluble in water (HSDB 2005). The gas is flammable and may pose an explosion hazard. Chemical and physical properties are listed in Table 1.

Chlorotrifluoroethylene is produced commercially in enclosed systems by dechlorination of 1,1,2-trichloro-1,2,2-trifluoroethane in methanol with a zinc catalyst. Dechlorination can also take place with an aluminum fluoride-nickel phosphate catalyst (HSDB 2005). Worldwide

production was 1000-5000 tons in 2000 (IUCLID 2002). The major use of CTFE is as a monomer for chlorotrifluoroethylene resins. It is also used in the manufacture of fire-extinguishing agents and pharmaceuticals (Kennedy 1990). The liquified gas (99.9% purity) is shipped in 140-lb and ton cylinders (IUCLID 2002).

TABLE 1. Chemical and Physical Properties

Parameter	Value	Reference
Synonyms	Trifluorochoroethylene; CTFE; 2-chloro-1,1,2-trifluoroethylene; 1,1,2-trifluoro-2-chloroethylene; Trifluorovinylchloride; Trifluorochloroethene; Fluorocarbon 1113; Genetron® 1113	AIHA 2005 Honeywell 2005
Chemical formula	$CClFCF_2$	Honeywell 2005
Molecular weight	116.5	Honeywell 2005
CAS Reg. No.	79-38-9	Honeywell 2005
Physical state	Colorless gas at ambient temperature	Honeywell 2005
Solubility in water	4.5 g/L at 25EC	Howard and Meylan 1997
Vapor pressure	4500 mm Hg at 25EC 70 psia @ 70EF	Howard and Meylan 1997 Honeywell 2005
Vapor density (air =1)	~4	Honeywell 2005
Liquid density (water =1)	1.3 @ 21EC	Honeywell 2005
Freezing point	−157.5EC	Honeywell 2005
Boiling point	−27.9EC	Honeywell 2005
Flammability limits in air	Lower explosive limit: 14.2% upper explosive limit: 43.7%	Honeywell 2005
Conversion factors	1 ppm = 4.75 mg/m^3 1 mg/m^3 = 0.21 ppm	AIHA 2005

2. HUMAN TOXICITY DATA

Chlorotrifluoroethylene has a faint ethereal odor (Honeywell 2005); no information on the odor threshold was located.

No human toxicity data were located. According to a chemical company memorandum (Ryan 1991), CTFE has been produced for over 35 years. Workplace exposure levels have generally been at or below 20 ppm on a time-weighted average. No adverse effects have been reported.

3. ANIMAL TOXICITY DATA

Data on fluoroalkenes including CTFE were reviewed by Clayton (1967; 1977), Kennedy (1990), the American Industrial Hygiene Association (AIHA 2005), and the Organization for Economic Cooperative Development (IUCLID 2002). Acute lethality data are summarized in Table 2 and sublethal inhalation data are summarized in Table 3.

3.1. Acute Lethality

3.1.1. Rats

Early range-finding studies performed by Haskell Laboratory (DuPont 1946) are not summarized here because exposures were to nominal concentrations and were usually repeated; not all organs were examined microscopically.

Male albino rats (unspecified strain) inhaled 800, 900, 1000, or 1200 ppm for 4 hours (Hood et al. 1956). The LC_{50} was 1000 ppm. Rats that died showed progressive weakness leading to death in 1 to 11 days postexposure. Examination of decedents revealed pulmonary congestion, edema, and effusion and acute necrosis of the kidney tubules. Doses characterized as "high sublethal" caused a polyuria which reached a peak within 2-4 days after exposure. The polyuria gradually diminished by 14 days after exposure. Examination of these rats at 14 days after exposure revealed severe kidney nephrosis with beginning fibrosis. The highest non-lethal concentration was not reported.

Kochanov (1958) exposed rats (sex and strain not reported) to several concentrations of CTFE. A 2-hour lethal concentration of 5040 ppm was reported. This was also the reported LC_{50} for rabbits. All rats exposed to 7560 ppm died. Clinical signs preceding death included agitation, apathy, dyspnea, inactivity, and impairment of coordination. Animals that died exhibited organ congestion, changes in the brain, and necrosis of the kidney tubules. The highest non-lethal concentration was not reported.

Sakharova and Tolgskaya (1977) exposed albino rats (sex and strain unspecified) to CTFE concentrations for 4 hours. They reported an LC_{50} of approximately 1550 ppm (males, 1491 ppm [C.L. 1312-1703 ppm]; females, 1617" 9 ppm). The exposures resulted in lesions of the liver, kidney (degeneration and necrosis of the convoluted tubules), and brain. No further details were reported.

3.1.2. Mice

Sakharova and Tolgskaya (1977) exposed albino mice (number and strain unspecified) to CTFE concentrations for 4 hours. They reported an LC_{50} of 1800 ppm.

Walther and Fischer (1968) investigated the acute toxicity of CTFE to male white mice (groups of 10, strain unspecified). Concentrations were 1000, 3000, and 8000 ppm and exposure durations ranged from 2 to 36 hours. The authors calculated LC_{50} values based on deaths during and immediately following exposure. Apparently there was no post-exposure observation period for the reported LC_{50} values. Additional groups of mice were exposed to the same concentrations for shorter durations in order to report "late effects, " i.e., deaths in mice held for 6 days and, in one case, up to 29 days after exposure. In order to include a post-treatment observation period, only the latter data are reported here. Following an 8-hour exposure to 1000 ppm, no deaths occurred within a 6-day observation period. When the exposure was lengthened to 12 hours, mortality was 40% at 6 days. Following exposure to 3000 ppm for 2 and 3.5 hours, mortality rates were 10% and 80%, respectively. Following 1 and 1.5-hour exposure to 8000 ppm, mortality rates were 75 and 100%, respectively. The authors note that motor coordination was disrupted after 1 hour of exposure to 1000 ppm. Data are summarized in Table 2. In a

separate study, Walther et al. (1969) reported effects on the kidney following a 0.5-hour exposure to 3000 ppm. They found enzyme changes which rapidly progressed into a necrotizing nephrosis and uremia. Regeneration of the kidney tubules was observed in animals that survived.

TABLE 2. Summary of Acute Lethal Inhalation Data in Laboratory Animals

Species	Concentration (ppm)	Exposure Time	Effect[a]	Reference
Rat	1000	4 hours	LC_{50}	Hood et al. 1956
Rat	5040 7560	2 hours 2 hours	LC_{50} 100% mortality	Kochanov 1958
Rat	1550	4 hours	LC_{50}	Sakharova and Tolgskaya 1977
Mouse	1800	4 hours	LC_{50}	Sakharova and Tolgskaya 1977
Mouse	1000 3000 8000	8 hours 12 hours 2 hours 3.5 hours 1 hour 1.5 hours	No mortality 40% mortality 10% mortality 80% mortality 75% mortality 100% mortality	Walther and Fischer 1968

3.2. Nonlethal Acute Toxicity

Data are summarized in Table 3. Included in Table 3 are acute exposures of rats during neurotoxicity testing (see Section 3.4) and of dogs during cardiac sensitization tests (see Section 3.5). A study that employed repeat exposures but described damage to the kidneys following a single 4-hour exposure to CTFE at 395 ppm (Buckley et al. 1982) is summarized in Section 3.3.

3.2.1. Dogs

A single dog (sex and strain unspecified) was exposed to 1000 ppm for 4 hours (Hood et al. 1956). There were no clinical signs. There was a transient drop in white blood cell count, from 7100 to 2200 on the day following exposure. Pathologic examination at sacrifice revealed degenerative neural changes. Compared to the changes in a dog that had undergone multiple exposures (see Section 3.3, Repeat-Dose Studies), the degenerative changes were not as pronounced.

3.2.2. Rats

Groups of 10 male F344 rats inhaled analytically-determined concentrations of 0, 102, 222, 330, or 540 ppm for 4 hours (Potter et al. 1981). Rats were immediately placed in metabolism cages, and time courses of renal functional and morphological change were examined. Rats were sacrificed on days 1, 2, 3, 8, and 14 after exposure. Within two days after exposure, rats exhibited dose-related proximal tubular necrosis (limited to the pars recta) and diuresis and increases in urinary fluoride, urinary lactic dehydrogenase activity, serum creatinine, and blood urea nitrogen. Regeneration of tubule epithelial cells usually appeared by

Day 3. Full regeneration was apparent within two weeks. Rats exposed to 102 ppm exhibited only mild diuresis (no necrosis).

TABLE 3. Summary of Nonlethal Inhalation Data in laboratory Animals

Species	Concentration (ppm)	Exposure Time	Effect	Reference
Dog	1000	4 hours	Hematological changes; degenerative neurological changes	Hood et al. 1956
Dog	250,000-500,000	5-15 minutes	Anesthetic effect; cardiac sensitization	Burgison et al. 1955
Rat	0, 102, 222, 330, or 540	4 hours	Mild diuresis (no kidney necrosis) at 102 ppm; reversible, concentration-related kidney necrosis at higher concentrations	Potter et al. 1981

3.3. Repeat Dose Studies

Repeat-dose studies are summarized in Table 4.

Three dogs (sex and strain unspecified) inhaled 300 ppm for 4 hours/day, 5 days a week for a total of 18 exposures (Hood et al. 1956). There were no clinical signs of toxicity (blood pressure and pulse rate were monitored). Daily hematology examinations revealed mild transient leukopenia, granulocytopenia, and occasional atypical cells. These effects were most pronounced on the third day of the first week, improving by the end of the week and over the weekend. The effects occurred weekly, but to a lesser extent each week. Two dogs sacrificed after the 18^{th} exposure showed mild encephalopathy. The third dog was further exposed to 300 ppm (three times), 400 ppm (seven times), 500 ppm (two times), 600 ppm (one time), 800 ppm (three times), and 1000 ppm (one time). Time between exposures was not clearly stated, but the authors reported that each exposure was followed by temporary leukopenia, and the next exposure was initiated when the white blood cell count recovered. Following the 1000 ppm exposure, the dog was subjected to a treadmill test (for simulation of muscular exertion associated with exposure). On the treadmill, the dog became weak and unable to complete a standard exercise regime. Heart rate was elevated to 200 beats/minute, but cardiac rhythm remained unchanged. Recovery to base line heart rate was slowed compared with unexposed dogs subjected to the treadmill test. Examination of tissues at sacrifice revealed mild degenerative changes in the brain, spinal cord, and nerves.

TABLE 4. Summary of Repeat-Dose Studies

Species	Concentration (ppm)	Exposure Time	Effect	Reference
Dog	300	4 hours/day, 5 days/week, 18 exposures	Hematological changes; mild encephalopathy	Hood et al. 1956
Rat	395	4 hours/day, 5 days	No clinical signs; renal tubular necrosis with regeneration	Buckley et al. 1982
Rat	0, 33, 61, 119, 241	6 hours/day, 5 days/week, 2 weeks	No clinical signs; lower body weight and nephrosis at 241 ppm; no kidney effects described at lower concentrations	Gad et al. 1988
Rat	0, 100, 200	5 hours/day, 5 days/week, 17 weeks	Necrosis and degenerative changes in the kidney tubules accompanied by clinical chemistry changes	Zhou et al. 1980
Rat	0, 29, 62, 121	6 hours/day, 5 days/week, 13 weeks	No clinical signs; dose-related kidney changes at 62 and 121 ppm; no kidney effects at 29 ppm	Gad et al. 1988
Rabbit	500 ppm	4 hours/day, 6 days/week, 58 days	Three deaths, days 16, 29, and 30	Kochanov 1958

Similar studies with rats, guinea pigs, and rabbits are not summarized in Table 4, but are briefly described here. Groups of ten adult male and female rats (unspecified strain) inhaled 300 ppm for 4 hours/day, 5 days a week for a total of 18 exposures (Hood et al. 1956). Except for a slight weight loss, there were no clinical signs over the treatment period. Microscopic examination of the tissues after the last exposure revealed “moderate cellular changes” in the kidney tubules.

Groups of ten adult male and female guinea pigs and ten male and female rabbits were exposed under the same regime as above (Hood et al. 1956). Guinea pigs exhibited weight loss and one guinea pig (sex unspecified) died after the sixth exposure. One of 10 rabbits died after the fourth exposure and another after five. Examination of tissues did not reveal any specific treatment-related causes of death.

Male F344 rats inhaled 395 ppm for 4 hours/day for 5 consecutive days (Buckley et al. 1982). The total number of animals was not stated, but numbers were sufficient for daily sacrifices of 4 to 8 animals during and after the exposure period. Except for flecks of dried blood around the mouth and nares of some animals, the general appearance of the animals was unremarkable during and following the exposure period. Within the first day, rats exhibited diuresis, increased water intake, decreased urine osmolality, increased urinary lactic dehydrogenase activity, and increased plasma creatinine and urea nitrogen. During days subsequent to exposure, these parameters declined or returned to control levels in a manner comparable to rats treated with a single exposure (following a single exposure, these parameters returned to normal by day 7). Renal tubular necrosis was present after one exposure and reached a peak of severity after the third exposure day. Regeneration was apparent by 24 hours after the third exposure, resulting in minimal additional necrosis with further exposures.

In a two-week inhalation study, groups of five male and five female CD rats inhaled analytically-determined concentrations of 0, 33, 61, 119, or 241 ppm for 6 hours/day, 5 days/week, for 2 weeks (Gad et al. 1988). There were no clinical signs attributed to treatment, and no effect on hematology parameters. Final body weight was reduced only at the highest concentration: males, -10%; females, -7%. Microscopic examination of tissues revealed toxic nephrosis in both sexes in the 241-ppm exposure group. Necrosis was characterized by the presence of tubular epithelial cell degeneration with luminal debris. In addition, testicular weight was reduced in the 241 ppm group males, along with an increase in testicular and epididymal luminal debris.

Male rats (strain unidentified) inhaled 0, 100, or 200 ppm for 5 hours/day, 5 days/week for 17 weeks (Zhou et al. 1980). Lowered body weight and proteinuria, elevated lactic acid dehydrogenase activity and urinary fluoride were observed at both concentrations. Necrosis and degenerative changes were observed in the kidney tubules. No further details were available in the English language abstract.

In a subchronic study, groups of 20 male and 20 female F344 rats inhaled 0, 29, 62, or 121 ppm for 6 hours/day, 5 days/week, for 13 weeks (Gad et al. 1988). Five animals/sex/group were held for a two-week recovery period. The study followed U.S. EPA guidelines for subchronic studies in that body weight was monitored, blood was collected to monitor effects on hematology and clinical chemistry, and urine was collected for urinalysis. Following exposure, major organs were weighed and tissues were examined microscopically. There were no treatment-related clinical signs during exposure, and there were no toxicologically significant effects on body weight or hematology parameters. Effects on the kidneys included increased weight, alterations in clinical chemistry, and alterations in microscopic structure. Microscopic kidney changes consisted of large, dilated tubules, and epithelial cells with enlarged nuclei. These finding were observed primarily in the 121 ppm exposure group, and to a lesser extent in the 62 ppm exposure group. No definitive kidney toxicity was observed in the 29 ppm exposure group. Liver weight was increased in all exposed male groups. Animals held for two weeks after the completion of exposure showed marked remission of the observed effects.

Mattie et al. (1998) exposed male and female F344 rats to 0, 50, 100, or 200 ppm for 6 hours/day, 5 days/week for 90 days. Only the effect on the liver was described. Exposure resulted in increased liver weight in both sexes. Hepatocyte hypertrophy as a result of induction of smooth endoplasmic reticulum and peroxisomal proliferation correlated with the increased liver weight. Livers of male rats were more sensitive to inhaled CTFE than livers of female rats. Severity of this effect in response to exposure concentration was not discussed. No further details were provided in the available abstract. This study is not summarized in Table 4 because effects on the target organ, the kidney, were not investigated.

Clayton (1977) summarized studies performed by Kochanov (1958). Seven rabbits (sex and strain not identified) were exposed 4 hours daily except Sundays and holidays for 58 days to 500 ppm. Three rabbits died at days 16, 29, and 30. At 59 days, the exposure concentration was lowered to 250 ppm and the daily exposure was increased to 6 hours. At this time, rabbits exhibited a reduction in motor activity and respiratory rate. Body weight gain was decreased compared to a control group, alkaline phosphatase activity dropped steadily (days 81-130), and

cholinesterase activity increased. Histological examination revealed widespread congestion of the liver, spleen, and kidneys. No further details were available in the summary.

3.4. Neurotoxicity

Burgison et al. (1955) reported that dogs exposed to CTFE at concentrations of 25% to 50% (250,000 to 500,000 ppm) for 5-15 minutes, exhibited anesthetic effects. This study is deficient in methodology: it used a limited number of dogs, likely used nominal concentrations, and the results have not been replicated in more recent studies. Walther and Fisher (1968) observed that motor coordination in mice was disrupted after a 1-hour of exposure to 1000 ppm, but Sakharova and Tolgskaya (1977), in studies with rats, reported that CTFE did not possess typical narcotic action.

3.5. Cardiac Sensitization

Four unanesthized dogs were exposed to concentrations of CTFE ranging from 25% to 50% (250,000 to 500,000 ppm) with oxygen added to maintain oxygen levels at 20% (Burgison et al. 1955). After inhaling the test compound for 5 to 15 minutes, the dogs were injected with epinephrine hydrochoride solution (adrenalin) at a dose of 0.01 mg/kg. Under these test conditions, all four dogs exhibited focal ectopic ventricular beats, presumably at the lowest tested concentration.

3.6. Developmental/Reproductive Toxicity

In a probe developmental study (using a limited number of animals), groups of five pregnant Sprague-Dawley rats were exposed whole-body for 6 hours/day on days 6-19 of gestation (total of 14 days) (Gad et al. 1988). This study was conducted concurrently with the two-week study described above. Analytically-determined concentrations were 0, 33, 61, 119, and 241 ppm. Concentrations were selected on the basis that CTFE was a known renal toxicant at 241 ppm. Maternal toxicity was seen at 119 and 241 ppm, as indicated by reduced body weight (4% at 119 ppm and 16% at 241 ppm) and nephrosis. No effects were observed in adult animals at 33 or 61 ppm. The number of viable and nonviable fetuses, early and late resorptions, total implantations, and corpora lutea were recorded. Fetuses were examined individually for malformations. There were no indications of fetotoxicity, embryotoxicity, or increases in malformations among the treated groups.

In a definitive study, groups of 25 pregnant Sprague Dawley CD rats inhaled concentrations of 0, 31, 89, or 187 ppm for 6 hours/day, on days 6 through 19 of gestation (Huntingdon Life Sciences 2005). There was no effect of treatment on survival. Clinical signs were limited to the 89 and 187 ppm groups. These included some eye closure, piloerection and lethargy in the 187 ppm group during exposure-day 7 (prior to termination of exposures for that group), and red nasal discharge (a sign of irritation) in the 89 ppm exposure group following removal from the exposure on days 13-20 of gestation. In rats exposed to 187 ppm, treatment was discontinued after the 7^{th} day due to weight loss during the first four days of exposure. The animals were held for the full gestation period and the offspring were evaluated with the other groups. Body weight was also lower in the 89 ppm group (15% less than controls on gestation days 6-10). Pups were delivered by caesarean section, weighed, and examined for soft tissue and

skeletal abnormalities. There were no effects of exposure on corpora lutea numbers, pre- or post-implantation loss, litter size, or gravid uterine weight. There was a reduction in fetal weight (13%) and evidence of delayed ossification (slight) in pups from the 187-ppm exposure group. There was no indication of an increased incidence of fetal variants or abnormalities. The no-observed-effect level for developmental effects was 89 ppm.

3.7. Genotoxicity

CTFE was nonmutagenic in *Salmonella typhimurium* strains TA 98, TA 100, TA 1535, and TA 1537 at vapor concentrations of 25-50% in the atmosphere (Stetka et al. 1982). Assays were run with and without metabolic activation. A concentration of 50% was cytotoxic.

In *in vivo* tests, the frequency of sister chromatid exchanges was not increased by exposure of New Zealand white rabbits or male Sprague-Dawley rats to concentrations of 10, 30, or 100 ppm for nine days (Stetka et al. 1982; 1983).

3.8. Chronic Toxicity/Carcinogenicity

A group of animals consisting of dogs, rats, rabbits, and guinea pigs was exposed to progressively higher concentrations of CTFE over a period of 14 months (Hood et al. 1956). Exposures were for 5 hours/day, 5 days/week. Four dogs were exposed successively to 15 ppm (38 exposures), 30 ppm (28 exposures), and 50 ppm (72 exposures). Two dogs were sacrificed immediately after exposure. The remaining two dogs were exposed to 50 ppm for 21 exposures. Two additional dogs were added to the system and the concentration was raised to 100 ppm for 56 exposures. The exposure concentration was then raised to 150 ppm. After 54 exposures, one of the newer dogs died and the other became irritable. The remaining dogs were exposed to 150 ppm a total of 104 times; then, two were sacrificed and the third was maintained for 18 weeks. Clinical signs were not observed in dogs at concentrations #100 ppm. Blood pressure was affected at 50 ppm, hematological changes were seen at 100 ppm, and neurological changes and degenerative changes in the nervous system were observed at 150 ppm.

Rats exposed in a similar manner (Hood et al. 1956) showed no clinical signs, but severe tubular necrosis was found at sacrifice at 14 months. Rabbits and guinea pigs treated with the same exposures showed neither clinical signs nor pathological lesions.

3.9. Summary

Data on lethal effects were available for the rat and mouse. In the rat, the 2-hour LC_{50} was 5040 ppm (Kochanov 1958) and the 4-hour LC_{50} was 1000 ppm (Hood et al. 1956). Few data were available on the highest nonlethal concentrations. These two studies are quite old, and few details were reported. Mortality rates in mice following exposure to 1000, 3000, or 8000 for 8, 2, or 1 hours were 0%, 10%, and 75%, respectively (Walther and Fischer 1968).

The most frequently reported finding in both rats and mice after acute exposure was damage to the tubular epithelium of the kidney. Evidence of recovery was seen following a 4-hour exposure of rats to 395 ppm (Buckley et al. 1982) and a 4-hour exposure of rats to 540 ppm (Potter et al. 1981). Repeat-dose studies also showed the reversibility of the kidney lesion.

4. SPECIAL CONSIDERATIONS

4.1. Metabolism and Disposition

No information was located on the absorption, distribution, metabolism, or excretion of CTFE by humans.

A series of papers on metabolism indicate that CTFE is initially conjugated with glutathione (GSH) via glutathione transferases (GST) in the liver to form S-(2-chloro-1,1,2-trifluoroethyl) glutathione. This reaction proceeds *in vitro* in rat and human liver sections (Tanaka and Anders 1995). Translocation of the glutathione metabolite to the kidney where it is metabolized to the cysteine metabolite [S-(2-chloro-1,1,2-trifluoroethyl)cysteine] is followed by renal bioactivation by β-lyase to yield the unstable thiolate metabolite. The thiolate metabolite reacts with cellular constituents (Bonhaus and Gandolfi 1981; Dohn and Anders 1982; Hassall et al. 1984; Dohn et al. 1985; Anders et al. 1988; Boogaard et al. 1989; Harris et al. 1992; Tanaka and Anders 1995).

Some CTFE may be further metabolized as indicated by increases in fluoride excretion following CTFE exposure of rats (Zhou et al. 1980; Potter et al. 1981; Buckley et al. 1982). Morel et al. (2005), in studies with the rat, showed that liver CYP-450 may be involved in a detoxification pathway of CTFE. Induction of CYP-450 with β-naphthoflavone or phenobarbital afforded some protection against the nephrotoxicity of inhaled CTFE. In an *in vitro* system, rat liver microsomes metabolized CTFE as indicated by the release of fluorine (Baker et al. 1987). CTFE also inactivated CYP-450.

4.2. Mechanism of Toxicity

CTFE is nephrotoxic. Metabolism results in a thiol metabolite that can react with cellular constituents of the kidney. The mechanism of action of CTFE is believed to proceed through inhibition of reabsorption of glucose in the proximal tubules of the kidney (Dohn et al. 1985). Deaths reported during or immediately following acute exposure to high concentrations may be attributed to pulmonary congestion; whereas, delayed deaths at lower concentrations may be attributed to nephrotoxicity (Hood et al. 1956).

4.3. Structure Activity Relationships

Carbon-fluorine compounds are generally less toxic than their chlorinated counterparts because of the stability of the C-F bond (Odum and Green 1984). Toxicity increases with the substitution of chlorine atoms for fluorine. For example, the rat 4-hour LC_{50} for CTFE is 1000 ppm whereas the 4-hour LC_{50} for tetrafluoroethylene is 40,000 ppm (Clayton 1967). Both compounds are nephrotoxic.

4.4. Other Relevant Information

4.4.1. Species Variability

Although toxicity values for the same species differed among laboratories (Table 2), LC_{50} values for rats and mice reported from the same laboratory (Sakharova and Tolgskaya 1977)

were comparable. The rat appears to be more susceptible to the toxic effects of CTFE than the mouse.

Data on relative uptake of CTFE by rodents and humans were not available. However, blood:air partition coefficients for many such chemicals including the related chemical tetrachloroethylene are higher for rat blood than for human blood. For tetrachloroethylene, blood:air partition coefficients for rats, mice, and humans were 19, 18, and 10, respectively (Gargas et al. 1989). Relative to body weight, humans have a much lower respiratory rate and cardiac output than rodents. These are the two primary determinants of systemic uptake of volatile chemicals. Therefore, at similar nominal concentrations, rodents absorb substantially more of a chemical than primates.

When CTFE was added to rat and human liver preparations, conjugation with GSH was faster in rat liver cytosol preparations (52 nmol/mg protein/min) than in human liver cytosol (5 nmol/mg protein/min) (Tanaka and Anders 1995). In a study of methyl chloride metabolism (metabolized by both glutathione conjugation and CYP-450), reaction rates of GST-methyl chloride conjugation by liver tissue preparations were in the order mouse > rat > hamster = human (Andersen et al. 1987; Reitz et al. 1989). These comparisons indicate that levels of GST enzymes are much lower in human tissues than mouse and rat liver tissue. The data are consistent with the hypotheses that the rate of activation of some chemicals, e.g., mono- and dihalomethanes to toxic metabolites by the GST pathway occurs much more slowly in humans than in rodents. Griem et al. (2002) compiled rodent:human ratios of GST activity in various tissues. Ratios of mouse:human and rat:human GST activity in liver were 7.64 and 3.95, respectively.

4.4.2. Susceptible Populations

Due to the genetic polymorphism of GSH-transferases, humans may conjugate CTFE at different rates. For the chemical methyl chloride, also metabolized by conjugation with glutathione, humans were classified into “fast, “slow,” or non-conjugators (Nolan et al. 1985; see U.S. EPA 2005). Fast metabolism may lead to rapid production of the toxic cysteine metabolite, making this population more susceptible to kidney damage. However, metabolism rates for glutathione conjugation among humans are expected to be within a three-fold difference (Nolan et al. 1985; Mulder et al. 1999). As an example, Tanaka and Anders (1995) found that cytosol preparations of hepatocytes from three normal human livers (donors for tissue transplantation) conjugated CTFE at the rate of 3.7, 4.7, and 7.4 nmol/mg protein/minute).

CTFE damages the kidneys. Therefore, persons with kidney disease may be more susceptible to the effects of CTFE than healthy individuals. CTFE has been reported to induce cardiac sensitization to epinephrine (Burgison et al. 1955), but only at extremely high exposure levels (5 to 15 minutes at levels of 25 to 50% CTFE). As this study used only a few dogs and was conducted at levels that were in the anticipated lethal range for CTFE, the results cannot be used to estimate risk to humans.

4.4.3. Concentration-Exposure Duration Relationship

No empirical data on the relationship between concentration and exposure duration for endpoints defined by the AEGL-1 or AEGL-2 were found. When such data are lacking, time scaling ($C^n \times t = k$) is used, with default values of n = 3 and n = 1 for scaling to shorter and longer exposure durations, respectively (NRC 2001). Although halogenated hydrocarbons rapidly reach steady-state in the blood, and blood concentrations do not greatly increase as exposure duration is increased (NRC 1996; Bakshi 1998), there is likely a time component to the development of kidney lesions.

For the AEGL-3, the probit-analysis dose-response program of ten Berge (2006) was used to estimate the threshold for lethality and to determine the relationship between concentration and exposure duration. Data from Walther and Fischer (1968) - concentrations, exposure durations, and percent mortality of male mice - were amenable to program calculations (see Table 2 for data).

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 clinical studies were available for development of AEGL-1 values. Workplace experience over 35 years indicates that a time-weighed average exposure at or below 20 ppm is a NOAEL for any adverse effects (Ryan 1991).

5.2. Summary of Animal Data Relevant to AEGL-1

No kidney lesions were observed in rats exposed to 102 ppm for 4 hours (Potter et al. 1981). In repeat-dose studies, 61 ppm was a NOAEL for adult rats in a developmental toxicity study (Gad et al. 1988), and no definitive toxicity was observed in rats at 29 ppm in a subchronic study (Gad et al. 1988). Irritation was not reported in the Gad et al. (1988) study, but pulmonary congestion was reported in rats at much higher concentrations (Hood et al. 1956) and nasal irritation was reported following repeat exposures to 89 ppm (Huntingdon Life Sciences 2005).

5.3. Derivation of AEGL-1

For CTFE, the kidney is the target organ. Irritation was not reported in studies that used low concentrations (Potter et al. 1981), but was seen in another acute study at a higher exposure level (Hood et al. 1956). The 4-hour, 102 ppm NOAEL for reversible kidney effects in rats in the well-conducted study of Potter et al. (1981) was used as the basis for the AEGL-1. Compared with humans, rodents have a higher respiratory rate and cardiac output. Blood:air partition coefficients for related chemicals such as tetrachloroethylene, are higher in rodents than humans. At similar concentrations, chemical uptake is greater in rodents than in humans. This information would argue for an interspecies uncertainty factor of 1. However, because no human data are available on comparative uptake and metabolism, an interspecies uncertainty

factor of 3 was applied. The interspecies uncertainty factor of 3 is supported by the fact that rodents have higher tissue levels of GST enzymes (Griem et al. 2002) and therefore may accumulate the toxic cysteine metabolite faster than humans.

Metabolism by glutathione conjugation varies among the human population (some humans are non-conjugators and theoretically would be at lower risk of nephrotoxicity). Based on other chemicals that are metabolized by conjugation with glutathione, the difference among individuals that metabolize CTFE is expected to be no greater than three-fold (Nolan et al. 1985; Mulder et al. 1999). Therefore, an intraspecies uncertainty factor of 3 was applied. The total uncertainty factor is 10. The resulting 4-hour value is 10 ppm. This value is one-sixth of the NOAEL of 61 ppm in the repeat-dose study of Gad et al. (1988) and is half of the #20 ppm workplace chronic NOAEL for humans (Ryan 1991). Because data were unavailable on time scaling, the default values of n = 3 and n = 1 for shorter and longer exposure durations, respectively (NRC 2001), were applied. Although there are uncertainties in extrapolating from a 4-hour value to 10 minutes, the 10-minute time-scaled value of 29 ppm is considered appropriate based on the extensive data base including a monitoring study (Ryan 1991) and acute and repeat-dose animal studies. Because the time-scaled 8-hour value of 5 ppm would be low in comparison to the chronic NOAEL of Ryan (1991), the 8-hour value was set equal to the 4-hour value. Calculations are in Appendix A and values are summarized in Table 5 below. A category graph of the AEGL-1 values in relation to animal toxicity data is in Appendix B.

TABLE 5. AEGL-1 Values for Chlorotrifluoroethylene

10-min	30-min	1-h	4-h	8-hour
29 ppm (138 mg/m^3)	20 ppm (95 mg/m^3)	16 ppm (76 mg/m^3)	10 ppm (48 mg/m^3)	10 ppm (48 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

Kidney lesions were observed in rats following single 4-hour exposures to 222-540 ppm (Potter et al. 1981; Buckley et al. 1982). As noted above, the next lower concentration of 102 ppm was a NOAEL for kidney lesions (Potter et al. 1981). Kidney lesions were also observed following repeat exposures to 241 ppm, 6 hours/day, 5 days/week for 2 weeks (Gad et al. 1988) and 395 ppm for 4 hours/day for 5 consecutive days (Buckley et al. 1982). In all cases where recovery was evaluated, kidney lesions in surviving rats showed evidence of recovery. Potter et al. (1981) noted that full regeneration was apparent within 2 weeks of acute exposure to 222-540 ppm, and Buckley noted regeneration during repeat exposure. In a developmental toxicity study with the rat, the no-observed effect level for developmental effects was 90 ppm (Huntingdon Life Sciences 2005). Maternal exposure was for 6 hours/day on gestation days 6-19.

6.3. Derivation of AEGL-2

The threshold for irreversible kidney lesions following a single exposure was chosen as the basis for the AEGL-2. The 4-hour exposure of rats to 540 ppm (Potter et al. 1981), considered a NOAEL for irreversible kidney lesions, was chosen as the point of departure. Based on higher respiratory rates and cardiac output and as evidenced by higher blood:air partition coefficients for related chemicals such as tetrachloroethylene, chemical uptake is greater in rodents than in humans. Higher chemical uptake in rodents might argue for an interspecies factor of 1. However, because no human data that address effects defined by the AEGL-2 were available, the 4-hour 540 ppm concentration was adjusted by an interspecies uncertainty factor of 3. The interspecies uncertainty factor of 3 is supported by the fact that rodents have higher tissue levels of GST enzymes (Griem et al. 2002) and therefore will likely accumulate the toxic cysteine metabolite faster than humans.

Metabolism by glutathione conjugation varies among the human population (some humans are non-conjugators and theoretically would be at lower risk of nephrotoxicity). Based on other chemicals that are metabolized by conjugation with glutathione, the difference among individuals that metabolize CTFE is expected to be no greater than three-fold (Nolan et al. 1985; Mulder et al. 1999). Therefore, an intraspecies uncertainty factor of 3 was applied. The total uncertainty factor is 10. The resulting 4-hour value is 54 ppm. In the absence of empirical data on time scaling, the default values of n = 3 and n = 1 for shorter and longer exposure durations, respectively (NRC 2001), were applied. Calculations are in Appendix A and values are summarized in Table 6. There is uncertainty in time-scaling from a 4-hour exposure to 10 minutes. Based on the comprehensive data base of animal studies, and in light of the fact that repeated 4-hour exposures of rats to 395 ppm do not greatly intensify kidney necrosis and lesions are still reversible (Buckley et al. 1982), the 4-hour exposure was time scaled to 10 minutes. The 8-hour value was set equal to the 4-hour value because the time scaled 8-hour value of 27 ppm is similar to the #20 ppm chronic NOAEL in the monitoring data of Ryan (1991). See Appendix B for the relationship between AEGL-2 values and toxicity data.

TABLE 6. AEGL-2 Values for Chlorotrifluoroethylene

10-min	30-min	1-h	4-h	8-h
160 ppm (760 mg/m^3)	110 ppm (523 mg/m^3)	86 ppm (409 mg/m^3)	54 ppm (266 mg/m^3)	54 ppm (266 mg/m^3)

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

Data on lethal effects were available for the rat and mouse. In the rat, the 2-hour LC_{50} was 5040 ppm (Kochanov 1958) and 4-hour LC_{50} values were 1000 ppm (Hood et al. 1956) and 1550 ppm (Sakharova and Tolgskaya 1977). Few data were available on highest nonlethal concentrations. Mortality rates of mice following exposure to 1000, 3000, or 8000 for 8, 2, or 1

hours were 0%, 10%, and 75%, respectively (Walther and Fischer 1968). Sakharova and Tolgskaya (1977) reported a 4-hour LC_{50} of 1800 ppm for the mouse.

7.3. Derivation of AEGL-3

Data on the rat were not used because only LC_{50} values were available (Table 2). In addition, some of these data are quite old and presumably used nominal concentrations. If, in accordance with NRC (2001) guidelines, the 4-hour mouse LC_{50} value of 1550 ppm is reduced 3-fold to reach a non-lethal level, and interspecies and intraspecies uncertainty factors of 3 and 3, respectively, are applied for a total reduction/uncertainty factor of 30, the resulting 4-hour value of 52 ppm is inconsistent with AEGL-2 values. The AEGL-2 values are based on a more recent, well-conducted study.

Using the data of Walther and Fischer (1968), the probit-analysis based dose-response program of ten Berge (2006) was used to calculate the threshold for lethality at each AEGL-3 exposure duration. The program incorporated all of the data of #8 hours duration of Walther and Fischer (1968) in Table 2. The calculated value of n in the concentration-exposure duration relationship ($C^n \times t = k$) was 1.37. Although LC_{50} data show that the mouse is not as sensitive to the effects of CTFE as the rat, the mouse has high levels of GST compared with humans, likely resulting in more rapid conjugation with glutathione and production of the toxic cysteine metabolite. Based on higher respiratory rate and cardiac output and more rapid metabolism to the toxic metabolite, the mouse is predicted to be more sensitive than humans. Therefore, an interspecies uncertainty factor of 3 was applied. Using the same reasoning as for the AEGL-1 above, an intraspecies uncertainty factor of 3 was applied. The total uncertainty factor was 10.

Calculations are in Appendix A and values are summarized in Table 7. Appendix B is a graph of the relationship between AEGL-3 values and toxicity data.

TABLE 7. AEGL-3 Values for Chlorotrifluoroethylene

10-min	30-min	1-h	4-h	8-h
1500 ppm (7100 mg/m^3)	690 ppm (3300 mg/m^3)	420 ppm (2000 mg/m^3)	150 ppm (710 mg/m^3)	91 ppm (430 mg/m^3)

Repeat-dose and short-term acute studies can be used to support the AEGL-3 values. Although the study of Hood et al. (1956) with dogs and rodents is relatively old and used nominal concentrations, it indicates that repeat exposures to approximately 300 ppm for 4 hours a day are not lethal to dogs, rats, guinea pigs, or rabbits. Successively increasing concentrations up to 1000 ppm (one time) were not lethal to dogs.

8. SUMMARY OF AEGLs

8.1. AEGL Values and Toxicity Endpoints

Data are summarized in Table 8.

TABLE 8. Summary of AEGL Values					
Classification	Exposure Duration				
	10-min	30-min	1-h	4-h	8-h
AEGL-1 (Nondisabling)	29 ppm	20 ppm	16 ppm	10 ppm	10 ppm
AEGL-2 (Disabling)	160 ppm	110 ppm	86 ppm	54 ppm	54 ppm
AEGL-3 (Lethal)	1500 ppm	690 ppm	420 ppm	150 ppm	91 ppm

8.2. Comparison with Other Standards and Guidelines

CTFE is manufactured and used in enclosed systems. The American Industrial Hygiene Association has developed workplace guidelines (Table 9). The AIHA 8-hour TWA Workplace Environmental Exposure Level (WEEL) is 5 ppm (AIHA 2005). According to a chemical company memorandum (Ryan 1991), CTFE has been produced for over 35 years. Workplace exposure levels have generally remained at or below 20 ppm on a time-weighted average. No adverse effects have been reported.

The American Industrial Hygiene Association has developed Emergency Response Planning Guidelines (ERPGs) (AIHA 2005). The ERPG values (all based on one-hour exposure) are similar to the time-respective AEGL values. The ERPG-1 is based on the no-observable effect concentration of 29 ppm in the subchronic study of Gad et al. (1988) and the workplace NOAEL of 20 ppm cited by Ryan (1991). The ERPG-2 is based on the subacute and subchronic studies of Gad et al. (1988), particularly the 14-day exposure to 119 ppm that resulted in only slight weight loss in pregnant rats. The ERPG-3 is based on the reversible kidney changes that occurred at 200-400 ppm (Buckley et al. 1982; Gad et al. 1988). Protecting individuals with kidney disease was part of the consideration for establishment of the ERPG-3.

TABLE 9. Standards and Guidelines for Chlorotrifluoroethylene					
Guideline	Exposure Duration				
	10 min	30 min	1 h	4 h	8 h
AEGL-1	29 ppm	20 ppm	16 ppm	10 ppm	10 ppm
AEGL-2	160 ppm	110 ppm	86 ppm	54 ppm	54 ppm
AEGL-3	1500 ppm	690 ppm	420 ppm	150 ppm	91 ppm
ERPG-1 (AIHA)[a]			20 ppm		
ERPG-2 (AIHA)			100 ppm		
ERPG-3 (AIHA)			300 ppm		
WEEL (AIHA)[b]					5 ppm

[a]**ERPG (Emergency Response Planning Guidelines, American Industrial Hygiene Association** (AIHA 2005)
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]**WEEL (Workplace Environmental Exposure Levels, American Industrial Hygiene Association** (AIHA 2005)
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 human toxicity data were located. Data from studies with laboratory animals involving acute, repeat-dose, and subchronic exposure were sufficient for development of AEGL values. Exposure durations ranged from 5-15 minutes to 8 hours.

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APPENDIX A: Derivation of Chlorotrifluoroethylene AEGLs

Derivation of AEGL-1 Values

Key Study:	Potter et al. 1981
Toxicity endpoint:	NOAEL for kidney effects in rats (102 ppm for 4 hours)
Time scaling:	Default values of n = 3 and n = 1 for scaling to shorter and longer exposure durations, respectively (NRC 2001).
Uncertainty factors:	Total uncertainty factor: 10 Interspecies: 3, rodents are more sensitive than humans Intraspecies: 3, metabolism of CTFE by humans is not expected to vary greatly
Modifying factor:	None applied
Calculations:	The 102 ppm concentration was adjusted by a total uncertainty factor of 10: 102/10 ppm = 10 ppm $C^n \times t = k$, where n = 3 and n = 1 $C^3 \times t$: $10^3 \times 240$ minutes = 240,000 ppm^3•minutes; $C^1 \times t$: 10x 240 minutes = 2400 ppm•minutes
10-minute AEGL-1:	$C^3 \times 10$ minutes = 240,000 ppm^3•minutes C = 29 ppm
30-minute AEGL-1:	$C^3 \times 30$ minutes = 240,000 ppm^3•minutes C = 20 ppm
1-hour AEGL-1:	$C^3 \times 60$ minutes = 240,000 ppm^3•minutes C = 16 ppm
4-hour AEGL-1:	C = 10 ppm
8-hour AEGL-1:	$C^1 \times 480$ minutes = 2400 ppm•minutes C = 5 ppm; adjusted to 10 ppm based on Ryan (1991)

Derivation of AEGL-2 Values

Key Study:	Potter et al. 1981
Toxicity endpoints:	NOAEL for irreversible kidney lesions - rat (540 ppm for 4 hours)
Time scaling	Default values of n = 3 and n = 1 for scaling to shorter and longer exposure durations, respectively (NRC 2001)
Uncertainty factors:	Total uncertainty factor: 10 Interspecies: 3, rodents are more sensitive than humans Intraspecies: 3, metabolism of CTFE by humans is not expected to vary greatly
Modifying factor:	None applied
Calculations:	The 540 ppm concentration was adjusted by a total uncertainty factor of 10: 540 ppm/10 = 54 ppm $C^n \times t = k$, where n = 3 and n = 1 $C^3 \times t$: $54^3 \times 240$ minutes = 37,791,360 ppm^3minutes $C^1 \times t = 54 \times 240$ minutes = 12,960 ppmminutes
10-minute AEGL-2:	$C^3 \times 10$ = 37,791,360 ppm^3minutes C = 160 ppm
30-minute AEGL-2:	$C^3 \times 30$ = 37,791,360 ppm^3minutes C = 110 ppm
1-hour AEGL-2:	$C^3 \times 60$ = 37,791,360 ppm^3minutes C = 86 ppm
4-hour AEGL-2:	C = 54 ppm
8-hour AEGL-2:	$C^1 \times 480$ = 12,960 ppmminutes C = 27 ppm; set equal to 4-hour value of 54 ppm based on Ryan (1991)

Derivation of AEGL-3 Values

Key Study: Walther and Fischer 1968

Toxicity endpoints: Threshold for lethality at each AEGL exposure duration using the ten Berge (2006) probit-analysis dose-response program. All data of #8 hours duration were used (see Table 2).

Time scaling: ten Berge (2006) probit analysis dose-response program; the n value in $C^n \times t = k$ was 1.37

Uncertainty factors: Total uncertainty factor: 10
Interspecies: 3, rodents are more sensitive than humans
Intraspecies: 3, metabolism of CTFE by humans is not expected to vary greatly

Modifying factor: None applied

Data for calculations:

Concentration (ppm)/time (min)/no. exposed/no. responded

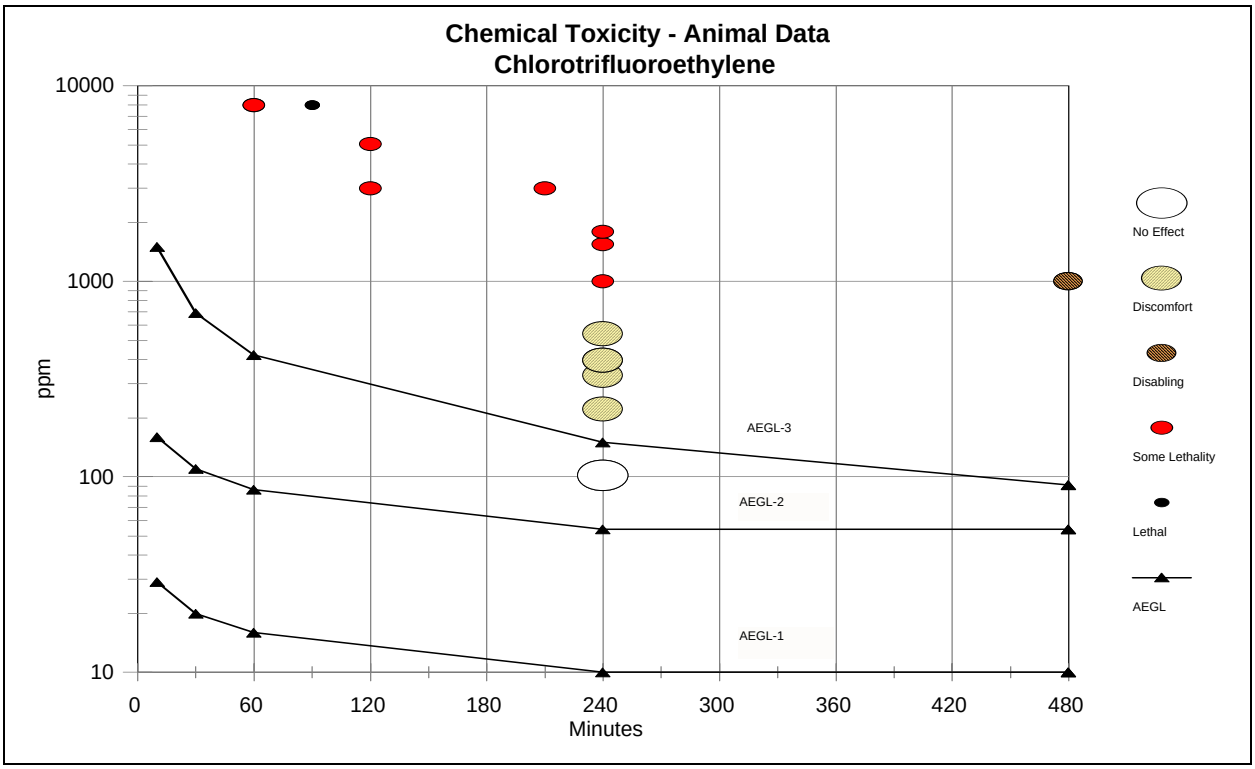
1000	480	10	0
1000	720	10	4
3000	120	10	1
3000	210	10	8
8000	60	12	9
8000	90	10	10

Program output:

Exposure Duration	AEGL-3 Value
10 minutes	1532 ppm (rounded to 1500 ppm)
30 minutes	690 ppm
60 minutes	420 ppm
4 hours	150 ppm
8 hours	91 ppm

n = 1.37
k = approximately 232,000 $ppm^{1.37}$minutes

APPENDIX B: Category Graph of AEGL Values and Toxicity Data



APPENDIX C: Derivation Summary for Chlorotrifluoroethylene AEGLs

ACUTE EXPOSURE GUIDELINE LEVELS FOR CHLOROTRIFLUOROETHYLENE (CAS Reg. No. 79-38-9)

AEGL-1 VALUES				
10-min	**30-min**	**1-h**	**4-h**	**8-hour**
29 ppm	**20 ppm**	**16 ppm**	**10 ppm**	**10 ppm**

Key Reference: Potter, C.L., A.J. Gandolfi, R. Nagle, and J.W. Clayton. 1981. Effects of inhaled chlorotrifluoroethylene and hexafluoropropene on the rat kidney. Toxicol. Appl. Pharmacol. 59:431-440.

Test Species/Strain/Number: Rat, male/F344/10 per group

Exposure Route/Concentration/Duration: Inhalation/0, 102, 222, 330, 540 ppm for 4 hours

Effects:
102 ppm: mild diuresis, no kidney necrosis
222, 330, 540 ppm: reversible, concentration-related kidney lesions

Endpoint/Concentration/Rationale: 4-hour exposure to 102 ppm was a NOAEL for kidney lesions; no evidence of irritation was reported.

Uncertainty Factors/Rationale:
Total uncertainty factor: 10
Interspecies: 3, considered sufficient as chemical uptake is greater in rodents than humans; also, higher tissue levels of glutathione in rodents, presumably resulting in higher concentrations of the toxic metabolite
Intraspecies: 3, considered sufficient to account for metabolism-mediated variability in production of the toxic metabolite

Modifying Factor: None applied

Animal to Human Dosimetric Adjustment: Not applicable

Time Scaling: $C^n \times t = k$, where n = 3 and 1 for shorter and longer exposure durations, respectively (NRC 2001). The 8-hour value was set equal to the 4-hour value because the time-scaled 8-hour value of 5 ppm appears inconsistent with the 20 ppm NOAEL reported for monitoring data (Ryan 1991).

Data Adequacy: There are no clinical data. Some of the rodent studies are old and poorly described. The NOAEL of 102 ppm is considered sufficiently protective.

AEGL-2 VALUES				
10-minute	**30-minute**	**1-hour**	**4-h**	**8-h**
160 ppm	**110 ppm**	**86 ppm**	**54 ppm**	**54 ppm**

Key Reference: Potter, C.L., A.J. Gandolfi, R. Nagle, and J.W. Clayton. 1981. Effects of inhaled chlorotrifluoroethylene and hexafluoropropene on the rat kidney. Toxicol. Appl. Pharmacol. 59:431-440.

Test Species/Strain/Number: Rat, male/F344/groups of 10

Exposure Route/Concentration/Duration: Inhalation/0, 102, 222, 330, 540 ppm for 4 hours

Effects:
102 ppm: mild diuresis, no kidney necrosis
222, 330, 540 ppm: reversible, concentration-related kidney lesions

Endpoint/Concentration/Rationale: 4-hour exposure to 540 ppm resulted in severe, reversible kidney lesions

Uncertainty Factors/Rationale:
Total uncertainty factor: 10
Interspecies: 3, considered sufficient as chemical uptake is greater in rodents than humans; also, higher tissue levels of glutathione are found in rodents, presumably resulting in higher concentrations of the toxic metabolite
Intraspecies: 3, considered sufficient to account for metabolism-mediated variability in production of the toxic metabolite

Modifying Factor: None applied

Animal to Human Dosimetric Adjustment: Not applicable

Time Scaling: $C^n \times t = k$, where n = 3 and 1 for shorter and longer exposure durations, respectively (NRC 2001). The 8-hour value was set equal to the 4-hour value because the time-scaled 8-hour value of 27 ppm appears inconsistent with the 20 ppm NOAEL reported for monitoring data (Ryan 1991).

Data Adequacy: There are no clinical data. Some of the rodent studies are old and poorly described. The data in the key study described a continuum of effects. In all studies where recovery was evaluated, kidney lesions in surviving animals showed evidence of recovery.

AEGL-3 VALUES				
10-min	**30-min**	**1-h**	**4-h**	**8-h**
1500 ppm	**690 ppm**	**420 ppm**	**150 ppm**	**91 ppm**

Key Reference: Walther, H. and H.D. Fischer. 1968. [On the toxicology of chlorotrifluoroethylene]. Acta Biol. Med. Germ. 21:377-384.

Test Species/Strain/Number: Mouse/unspecified/groups of 10

Exposure Route/Concentration/Duration: Inhalation/100, 3000, 8000 ppm/2-36 hours

Effects:
1000 ppm for 8 hours: No mortality
3000 ppm for 2 hours: 10% mortality
3000 ppm for 3.5 hours: 80% mortality
8000 ppm for 1 hour: 75% mortality
8000 ppm for 1.5 hours: 100% mortality

Endpoint/Concentration/Rationale: The threshold for mortality at each AEGL exposure duration was calculated using the ten Berge (2006) probit-analysis dose-response program.

Uncertainty Factors/Rationale:
Total uncertainty factor: 10
Interspecies: 3, considered sufficient as chemical uptake is greater in rodents than humans; also, higher tissue levels of glutathione are found in rodents, presumably resulting in higher concentrations of the toxic metabolite
Intraspecies: 3, considered sufficient to account for metabolism-mediated variability in production of the toxic metabolite

Modifying Factor: None applied

Animal to Human Dosimetric Adjustment: Not applicable

Time Scaling: Calculated using the ten Berge program (n in $C^n \times t = 1.37$)

Data Adequacy: There are no clinical data. Some of the rodent studies are old and poorly described. The data in the key study described mortality at several different concentrations and exposure durations.