ACUTE EXPOSURE GUIDELINE LEVELS (AEGLs) FOR

CHLOROACETYL CHLORIDE (CAS Reg. No. 79-04-9)

and

DICHLOROACETYL CHLORIDE (CAS Reg. No. 79-36-7)

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

Chloroacetyl chloride (CAC) is a liquid with a pungent odor. It is corrosive to tissues and causes irritation of the eyes, skin, and respiratory system. It decomposes exothermally in water to produce chloroacetic acid and HCl. CAC major uses are as an intermediate in the synthesis of tear gas, chloracetamide herbicides, and pharamceuticals. Dichloroacetyl chloride (DCAC) is a clear, fuming liquid with an acrid, penetrating odor. It is irritating to the eyes and mucous membranes. DCAC is insoluble in water, but decomposes to form HCl and dichloroacetic acid. DCAC production in the U.S. exceeds 1 million pounds annually, and it is mainly used as a reactive intermediate. Because the database for DCAC was very limited, and the available data indicated that DCAC was less toxic than CAC, all AEGL values developed for CAC were adopted for DCAC.

AEGL-1 values were derived from a multiple-exposure study in which rats, mice, and hamsters received 18-20 exposures for 6 hours/day to nominal concentrations of 0.5, 1, 2.5 or 5 ppm CAC (Dow 1982). Eye irritation occurred in all dose groups, but rats were noted to have conjunctival redness after the initial exposure to ≥0.5 ppm. After 18-20 exposures, various nasal and/or lung lesions occurred in rats and mice (hamsters not examined) and death occurred at 2.5 and 5 ppm starting the second treatment week. AEGL-1 values were derived using a single 6-hour exposure to ~1 ppm (0.84 ± 0.51 ppm) because this is the highest concentration that caused conjunctival redness but no other more serious effects after one exposure. A modifying factor of 2 was applied to estimate no-effect level concentration for conjunctivitis. The same AEGL value is adopted for 10 minutes to 8 hours because mild irritant effects do not vary greatly over time. A total uncertainty factor of 10 was applied: 3 for interspecies variability and 3 for intraspecies variability, because the NOEL for eye conjunctivitis due to local contact irritation is not expected to vary greatly among animals or humans. The resulting AEGL-1 of 0.04 ppm is consistent with the limited human data in which exposure to 0.023 ppm for an undefined period was "barely detectable" but 0.140 ppm was "strong" (Dow 1988b), and exposure to 0.05 ppm was associated with odor that was "objectionable" but no adverse health effects were reported (Monsanto 1987).

The AEGL-2 values were derived using a study in which rats inhaled 32, 208, 522, or 747 ppm CAC for 1 hour (Dow 1986). Rats exposed to 32, 208, 522, or 747 ppm CAC (analytical) for 1 hour and observed for 14 days had eye squinting, lacrimation, urine stains, and initially lost weight; at ≥208 ppm, rats also displayed shallow breathing, lethargy, and reddish stains near the eyes, at ≥522 ppm, rats also had labored breathing, gasping, and salivation, and at 747 ppm, 5/6 males and 1/6 females died (days 2,7, 8, and 13). Necropsy revealed lung pathology, nasal congestion, and enlarged adrenals. The AEGL-2 endpoint was the NOEL for impaired ability to escape due to lacrimation and eye squinting, which was estimated by applying a modifying factor of 2 to the lowest concentration tested of 32 ppm. Data were not available to determine the CAC toxicity concentration-time relationship, which for many irritant and systemically acting vapors and gases may be described by $C^n \times t = k$, where the exponent n ranges from 0.8 to 3.5 (ten Berge et al. 1986). To obtain protective AEGL-2 values, scaling across time was performed using n=3 to extrapolate to exposure times < 1 hour (exposure duration in the key study), and n=1 to extrapolate to exposure times >1 hour. A total uncertainty factor of 10 was applied, consisting of 3 for interspecies variability and 3 for intraspecies

variability, because the AEGL-2 endpoint (NOEL for eye irritation sufficient to cause lacrimation and squinting) is a direct surface contact effect that is not likely to vary in severity among animals or humans.

The AEGL-3 values were also based on the Dow (1986) 1-hour inhalation rat study in which exposure was to 32, 208, 522, or 747 ppm CAC. The AEGL-3 toxic endpoint was the lethality threshold, which was taken as the highest concentration tested that caused no deaths (522 ppm). An LC_{01} or $BMDL_{05}$ were not used for the lethality threshold because mortality occurred in only one test group. Data were not available to determine the CAC toxicity concentration-time relationship, which for many irritant and systemically acting vapors and gases may be described by $C^n \times t = k$, where the exponent n ranges from 0.8 to 3.5 (ten Berge et al. 1986). To obtain protective AEGL-3 values, scaling across time was performed using n=3 to extrapolate to exposure times < 1 hour (exposure duration in the key study), and n=1 to extrapolate to exposure times >1 hour. A total uncertainty factor of 10 was applied: 3 for interspecies variability (lethality resulting from respiratory lesions and having a steep dose-response was seen in several studies with rats and mice, at CAC concentrations within a factor of 2-3), and 3 for intraspecies uncertainty (the threshold for lethality from direct destruction of respiratory tissue is not expected to vary greatly among humans, based on the steep dose-response seen in the animal studies).

The AEGL values for CAC (and adopted for DCAC) are listed in Table 1.

TABLE 1. Summary of AEGL Values for Chloroacetyl Chloride (and adopted for the related compound Dichloroacetyl Chloride)

Classification	10-minute	30-minute	1-hour	4-hour	8-hour	Endpoint (Reference)
AEGL–1[a] (Non-disabling)	0.04 ppm (0.19 mg/m^3)	0.04 ppm (0.19 mg/m^3)	0.04 ppm (0.19 mg/m^3)	0.04 ppm (0.19 mg/m^3)	0.04 ppm (0.19 mg/m^3)	NOEL for conjunctivitis in rats (Dow 1982)
AEGL–2 (Disabling)	2.9 ppm (13 mg/m^3)	2.0 ppm (9.2 mg/m^3)	1.6 ppm (7.4 mg/m^3)	0.40 ppm (1.8 mg/m^3)	0.20 ppm (0.92 mg/m^3)	NOEL for inability to escape due to eye irritation in rats (Dow 1986)
AEGL–3 (Lethal)	95 ppm (440 mg/m^3)	66 ppm (300 mg/m^3)	52 ppm (240 mg/m^3)	13 ppm (60 mg/m^3)	6.5 ppm (30 mg/m^3)	Threshold for lethality in male rats (Dow 1986)

[a] Odor of 0.023 ppm chloroacetyl chloride was reported to be barely detectable (Dow 1988b).

1. INTRODUCTION

CAC: Chloroacetyl chloride (CAC) is a colorless or slightly yellow liquid with a pungent odor. It is corrosive to tissues and causes irritation of the eyes, skin, and respiratory system. It is initially insoluble in water, but at the water-chloracetyl chloride interface, a slow (not specified) reaction produces chloroacetic acid that solubilizes the two phases, and a violent exothermal reaction forming chloroacetic acid and HCl ensues (Morris and Bost 2002). The decomposition in water to form hydrochloric acid and chloroacetic acid has a $t_{1/2}$ of <30 minutes, although in the gas phase, the hydrolysis of CAC in water vapor is slow ($t_{1/2}$ not stated) (Dow 2001). It is synthesized by a variety of methods including chloroacetic acid and benzoyl chloride, chlorination of ketene, chloroacetic acid and $POCl_2$ or pyrocatechyl phosphorus trichloride (O'Neil et al. 2001). CAC major uses are as an intermediate in the synthesis of tear gas (cloracetophenone), chloracetamide herbicides such as alachlor, and pharmaceuticals (adrenalin, diazepam, lidocaine-type anesthetics) (HSDB 2003a). It is estimated that in 1992, >45,000 metric tons of chloroacetyl chloride were used to manufacture alachlor and butachlor (Abaecherli and Miller 2000).

DCAC: Dichloroacetyl chloride (DCAC) is a clear, fuming liquid with an acrid, penetrating odor. It is irritating to the eyes and mucous membranes (HSDB 2003b). DCAC is insoluble in water, but decomposes quickly to form HCl and dichloroacetic acid ($t_{1/2}$ of hydrolysis of 0.0023 seconds in water at 25°C, and 0.2 seconds in 89.1:10.9 water-acetone at -20°C (Prager et al. 2001, Ugi and Beck 1961). DCAC is not known to occur naturally, but is synthesized from pentachloroethane by a patented method or from chloroform and carbon monoxide at high pressure (HSDB 2003b; O'Neil et al. 2001). DCAC major uses are as a reactive intermediate (HSDB 2003b). DCAC production in the U.S. exceeds 1 million pounds annually, and it is included on the U.S. EPA HPV Challenge Program Chemical List (U.S. EPA 2003a).

Selected chemical and physical properties of CAC and DCAC are listed in Table 2.

TABLE 2. Chemical and Physical Properties of CAC and DCAC

Parameter	CAC Value (Reference)	DCAC Value (Reference)
Synonyms	Chloroacetic acid chloride, chloroacetic chloride, monochloroacetyl chloride, chloracetyl chloride (NIOSH 1995)	2,2,-dichloroacetyl chloride, alpha, alpha-dichloroacetyl chloride, dichloroethanoyl chloride (NTP 2001)
Chemical formula	$C_2H_2Cl_2O$ (O'Neil et al. 2001)	C_2HCl_3O (O'Neil et al. 2001)
Molecular weight	112.94 (O'Neil et al. 2001)	147.39 (O'Neil et al. 2001)
CAS Reg. No.	79-04-9 (O'Neil et al. 2001)	79-36-7 (O'Neil et al. 2001)
Physical state	Liquid (O'Neil et al. 2001)	Liquid (O'Neil et al. 2001)
Solubility in water	Insoluble, but decomposes to form chloroacetic acid and HCl (Morris and Bost 2002)	Insoluble, but decomposes to form dichloroacetic acid and HCl (O'Neil et al. 2001)
Vapor pressure	20 mm Hg @ 21°C (NIOSH 1995)	23.0 mm Hg @ 25°C (Howard and Meylan 1997)
Vapor density (air =1)	3.9 (IPCS 2003)	5.1 (HSDB 2003b)
Liquid density (water =1)	1.42 @ 20°C (O'Neil et al. 2001)	1.5315 @ 16°C/4°C (O'Neil et al. 2001)
Melting point	-21.77°C (O'Neil et al. 2001)	not found
Boiling point	106°C (O'Neil et al. 2001)	107-108°C (O'Neil et al. 2001)
Flammability limits	not combustible (NIOSH 1995)	not found
Conversion factors	1 mg/m^3 = 0.216 ppm; 1 ppm = 4.62 mg/m^3 (NIOSH 2003)	1 mg/m^3 = 0.166 ppm; 1 ppm = 6.03 mg/m^3 [Calculated as: ppm=(24.45/MW)mg/m^3]

2. HUMAN TOXICITY DATA

2.1. Acute Lethality

CAC: No reports of death resulting from inhalation of CAC were located. Based on the adverse effects of inhalation exposure in humans, it is likely that exposure to sufficiently high concentrations of CAC would result in death. Reported effects include chest tightness, laryngospasm, pulmonary edema, bronchospasm, and bronchopneumonia (HSDB 2003a).

DCAC: No reports of death resulting from inhalation of DCAC were located.

2.2. Nonlethal Toxicity

2.2.1. Odor Threshold/Odor Awareness

CAC: Exposure for an undefined period of time (likely few minutes) to an air concentration of 0.011 ppm CAC was undetectable by odor, 0.023 ppm was "barely detectable," and 0.140 ppm was "strong" odor to an industrial hygienist (Dow, 1988b). Ocular irritation was not experienced at these concentrations, but 0.910 ppm was painful to the eyes and caused lacrimation (Dow 1988b).

Shift sample CAC air concentrations of 0.05 ppm, taken over a period of ≥7 hours, were associated with CAC odor that was "readily apparent and objectionable throughout the shift" for

workers at two CAC manufacturing sites (Monsanto 1987). The air monitoring method was not specified but had a detection limit of <0.01 ppm.

The CAC threshold of irritation (Lim_{ir}) for a group of human volunteers (number, ages, sex not reported) "using subjective indicators" was 0.43 ppm (Germanova et al. 1988). The nature of the subjective indicators was not stated. The duration of exposure was not reported, but may have been 1 minute, per the definition of Lim_{ir} as stated by Izmerov et al. (1982).

Dow (2001) reported that CAC vapor can dull the sense of smell and be difficult to detect.

DCAC: DCAC has an acrid, penetrating odor that is recognized at 0.1 ppm (HSDB 2003b; Dahlberg and Myrin 1971; see Section 2.2.2.).

2.2.2. Case Reports

CAC: The medical department of a chemical company reported that six workers receiving "mild" inhalation exposures of CAC experienced dyspnea and cough, whereas 3 workers that received "moderate" inhalation exposures had cyanosis and cough (Dow 1988a). CAC air concentrations and exposure durations were not stated.

DCAC: Exposure to approximately 10 ppm DCAC causes immediate coughing and eye irritation and "is not endurable for very long, " and exposure to 13 ppm DCAC "could certainly not be endured for as long as 1 hour" by welders (Dahlberg and Myrin 1971; see Section 2.2.2.).

A secondary source reported that acute exposure by humans to DCAC may cause dyspnea, chest pain, upper airway and pulmonary edema, bronchospasm, pneumonitis, airway hyper-reactivity, and chronic lung function abnormalities (HSDB 2003b). A delay of several hours may occur before the symptoms appear (HSDB 2003b).

Dahlberg and Myrin (1971) described scenarios in 10 welding shops in which welders were exposed to DCAC formed from the welding arc in air containing trichloroethylene (TCE). Phosgene was also produced in this reaction, albeit at 5-fold lower amounts than DCAC. Gas-liquid chromatography was used to measure levels of air DCAC, phosgene, and TCE. Exposure durations for specific time periods were generally not reported, but it was stated that the welding took place during a "minor" part of the working hours. Maximum air DCAC concentrations were reached at the end of each "short" welding operation (which appeared to last only a few minutes, from the report text). Air samples were collected for a 3-minute period, typically ~30 cm from the arc in a horizontal direction. Air sampling began one minute after welding commenced, and always ended after welding had finished. The air sampling results and exposure scenario descriptions are summarized in Table 3. Note that the workers' responses were only provided for workshop scenarios #3 and #6. Based on data from the 10 welding shops, the investigators noted that (1) the odor of DCAC is recognized at 0.1 ppm, (2) exposures to DCAC above 0.5-1 ppm are not advisable, although workers may be able to tolerate it for a time (not defined) without complaining except of "bad smell," (3) exposure to ~10 ppm caused immediate coughing and eye irritation and "is not endurable for very long, " and (4) 13 ppm

DCAC "could certainly not be endured for as long as 1 hour" by welders (Dahlberg and Myrin 1971). Because the workers were simultaneously exposed to DCAC, TCE, and phosgene, the possibility exists that some of the toxic effects experienced by the welders were not due to DCAC.

TABLE 3. Exposure scenarios in 10 welding workshops
(Dahlberg and Myrin 1971)

Work-shop	DCAC (ppm)	Phosgene (ppm)	TCE (ppm)	Scenario description
1	<0.01	–	6	Degreasing apparatus (DA) was 13 m from ventilated welding booth. Carbon steel welded with metal and gas (80% Ar; 20% CO_2).
2	0.4	–	53	Degreased materials piled ~15 m from non-ventilated welding bench. Carbon steel welded with tungsten-Ar.
3 [Near welding site; near vent]	13 0.5	–	256 248	Carbon steel was welded 10 m from where ~10 L TCE was spilled and swept into a drain, simulating accident where worker was exposed for ~1 hr to DCAC. He noticed an unpleasant smell, left to vomit, came back and lost consciousness. He was hospitalized and revived. Afterwards, he had muscle pains and was unable to work for a "long time." The simulated samples were taken at the welding site and at a nearby vent.
4	0.03	0.01	11	DA was 20 m from unventilated welding booth. Carbon steel welded with metal and gas (80% Ar; 20% CO_2).
5	0.04	0.01	16	DA was 15 m from ventilated welding booth. Carbon steel welded using OK 55.00 covered electrodes.
6 [Before & after fan adjustment]	10.4 1.6	0.3 0.06	65 27	DA was 15-20 m from unventilated welding bench. During sampling, all bystanders noticed "very disagreeable smell" and the welder had several coughing attacks. Carbon steel welded with metal and CO_2. Air was sampled before and after adjustment of a ventilation fan.
7	0.04	0.003	4	Cold-cleaning with TCE was ~15 m from ventilated welding site. Carbon steel was welded with metal and CO_2.
8	0.3	–	1.4	DA was next to welding shop with slightly lower air pressure. Stainless steel was tungsten welded with Ar.
9	0.14	0.03	10	No DA was present but air contained "split" TCE. Welding bench was ventilated. Aluminum was tungsten welded with Ar.
10 [30 cm & 3.5 m from arc]	10 5	3 1.5	6 14	DA was 4 m from place aluminum was welded with metal and Ar (170 A). Air was intentionally contaminated with TCE, DCAC, and phosgene, and their levels were measured 30 cm and 3.5 m from the welding place.

TCE = trichloroethylene; DA = degreasing apparatus

2.3. Neurotoxicity

CAC: Neurological effects specific to CAC have not been reported in any human studies. Exposure to CAC has caused agitation and syncope due to panic (HSDB 2003a).

DCAC: Human studies specifically evaluating neurological effects were not located. A welder exposed to ~13 ppm DCAC for < 1 hour vomited and lost consciousness in a welding shop (Dahlberg and Myrin 1971; see section 2.2.2.). He was rushed to the hospital where he

soon regained consciousness, but afterwards had muscular pains and was "sick-listed" (i.e., unable to work) for a "long time."

2.4. Developmental/Reproductive Toxicity

No human developmental studies with CAC or DCAC were located.

2.5. Genotoxicity

Human genotoxicity studies were not located that tested either CAC or DCAC.

2.6. Carcinogenicity

No studies examining the carcinogenic activity of CAC or DCAC were located. Neither the U.S. EPA nor IARC currently have carcinogenicity guidelines for CAC or DCAC.

2.7. Summary

CAC: CAC has a strong, pungent odor and causes respiratory, ocular, and dermal irritation. Its odor was "barely detectable" at 0.023 ppm whereas 0.910 ppm was painful to the eyes and caused lacrimation (exposure duration not specified). Exposure by inhalation (concentrations and duration not specified) has also been reported to caused dyspnea, cough, cyanosis, chest tightness, laryngospasm, pulmonary edema, bronchospasm, and bronchopneumonia. Human neurological, developmental, genotoxicity, and carcinogenicity studies were not located.

DCAC: No reports of death resulting from inhalation of DCAC were located. Based on results of DCAC measurements in 10 welding workshops, Dahlberg and Myrin (1971) found that DCAC odor is recognized at 0.1 ppm, DCAC above 0.5-1 ppm may be tolerated for a short time (not defined) without complaints except for "bad smell,"~10 ppm DCAC caused immediate coughing and eye irritation and "is not endurable for very long, " and exposure to ~13 ppm DCAC for < 1 hour caused a worker to vomit and lose consciousness, and this concentration "could certainly not be endured for as long as 1 hour"(Dahlberg and Myrin 1971). Human studies specifically evaluating neurological, developmental, genotoxicity, and carcinogenicity endpoints were not located.

3. ANIMAL TOXICITY DATA

3.1. Acute Lethality

3.1.1. Rats

CAC: Treatment of male or female Sherman albino rats with 1000 ppm (range of 700-1390 ppm) CAC for 4 hours killed either 2/6, 3/6, or 4/6 animals after 14 days in a range-finding test (Carpenter et al. 1949). No further experimental results were provided. The atmosphere was generated by delivering the liquid into an evaporator through which metered air was forced into the 9-liter glass exposure chamber containing the rats on a desiccator grid. Analytical

concentrations were not measured but were believed to be "slightly" lower than the nominal concentrations (not further defined).

Herzog (1959) treated 80 rats for 2 hours with 0.5-30 mg/L (108-6494 ppm) chloroacetyl chloride concurrently with mice and guinea pigs in 72.7 or 74.1 L glass bottles using a static exposure method (sex, strain, number of animals/concentration not specified; see Sections 3.1.2. and 3.1.3.). It was not specified whether the air concentrations were analytical or nominal (assume nominal). Animals were observed during exposure and for the following five days. Results were not given other than that all animals inhaling ≥16 mg/L (3462 ppm) died on study, and that 5 rats inhaling 2381-6480 ppm died within the first 2-3 minutes of exposure.

Four male rats exposed to "concentrated" chloroacetyl chloride all died within two hours (Younger Labs 1969). The exposure concentration was not specified, although it was stated that 27.9 g liquid CAC was vaporized or left in the equipment, and that air was supplied at 4 L/min to a 35 L metal chamber (saturation is 25,000 ppm at 20°C, AIHA 2000). Immediately upon exposure, the rats showed signs of irritation including pawing at the face and mouth, and tightly shut eyes. Within 10 minutes, rats had reddened eyes with nasal and salivary excretion and gasping, and within 30 minutes they had opaque corneas, and death occurred after 90 (3/4 rats) or 120 (1/4) minutes. Severely hemorrhaging lungs were seen at necropsy.

Fischer 344 rats (6/sex/dose; 6-8 weeks old) were exposed whole-body to 32, 208, 522, or 747 ppm CAC for 1 hour, followed by observation for 14 days (Dow 1986). A control group was not included. The analytical concentrations were lower than the nominal concentrations (102, 598, 956, and 1366 ppm, respectively), possibly due to degradation of CAC in the air moisture to chloroacetic acid and HCl gas (these were not measured). Liquid CAC was vaporized into stainless steel and glass 112 L chambers, airflow was 30 L/minute, and analytical CAC concentrations were measured by drawing chamber air through a bubbler, derivatizing the CAC, and analysis by HPLC. All animals were observed daily, weighed on days 2, 4, 8, 11, and 15, and necropsied at death. Observations during exposure or later the same day included eye squinting, lacrimation, and urine stains in all groups, shallow breathing and lethargy at ≥208 ppm, and labored breathing, gasping, and salivation at ≥522 ppm. The urine stains, lethargy, and salivation may have been caused by stress. Effects on day 2 and/or later included urine stains at all doses, and reddish stains near the eyes (≥208 ppm) or muzzle (≥522 ppm). Animals initially lost weight in all groups but began to recover by day 4 (32 ppm), 8 (208 ppm) or 11 (≥522 ppm). The incidence and/or severity of the findings increased with dose. Death occurred at only 747 ppm, in 5/6 males (days 2, 7, 8) and 1/6 females (day 13), yielding an LC_{50} of 660 ppm for males, calculated by the moving average method (Thompson and Weil 1952). An LC_{50} of 645 ppm and an LC_{01} of 453 ppm were obtained with the male rat data by probit analysis (using the Number Cruncher Statistical System: Survival Analysis, Version 5.5, Published by Jerry L. Hintze, July 1991). The LC_{50} for females could not be calculated but was >747 ppm. Necropsy of rats that died revealed lung edema in males, failure of lungs to collapse in the females, nasal congestion in both sexes, and enlarged adrenals in most females and one male (possibly due to stress). Other changes at 747 ppm (decreased size of spleen and thymus in 1-2 males; decreased amount of fat in one female) were attributed to the animals' decreased body weights.

Fischer-344 (CDF) rats (10/sex/dose) were exposed to 0 (room air) or approximately 0.5, 1, 2.5, or 5 ppm CAC vapor for 6 hours/day, 5 days/week, for 4 weeks for a total of 18-20 exposures (Dow 1982). Mice and hamsters were treated concurrently (see Sections 3.1.3. and 3.2.4.). Treatment of the 0.5 ppm group began two weeks after the other groups, thus half the controls were kept for 4 weeks and half for 6 weeks. The analytical concentrations were 0.55 ± 0.61 (CAC was ≤0.1 ppm, the detection limit, for the last 8 exposures), 0.84 ± 0.51, 2.6 ±1.4, and 5.0 ± 2.3 ppm, respectively. Nominal concentrations were much higher due largely to incomplete CAC vaporization (1.35 ± 0.69, 4.5 ± 2.1, 11.7 ± 3.8, and 22.1 ± 4.7 ppm, respectively). Air CAC concentrations were measured by collecting air through methanol using glass midget impingers and detecting of the resulting methyl-2-chloroacetate by gas chromatography/mass spectrometry. All animals were necropsied, the brain, heart, liver, kidneys, and testes were weighed, and ≤5 survivors/dose/sex were examined microscopically. No deaths occurred at 0, 0.5, or 1 ppm, whereas 17/20 rats died at 2.5 ppm (8/10 males, 9/10 females) and 19/20 rats died at 5 ppm (10/10 males, 9/10 females). Deaths occurred after the first week of exposure. The 2.5 and 5 ppm rats had rough and discolored hair coats, were lethargic and irritable when handled, and had nasal exudate and eye conjunctival redness, lost weight and body fat, and had numerous respiratory lesions in the nasal turbinates, trachea, and lungs (inflammation, hypertrophy, hyperplasia, metaplasia, necrosis, atrophy, pneumonitis and/or bronchitis). The lesions were the most severe in the nasal turbinates. The 2.5 and 5 ppm rats also had alterations of the liver, uterus, thymus, spleen, and spermatogenesis that were due to the weight loss or poor health of the animals. Some 1 ppm rats had nasal exudate, roughened hair coats, eye conjunctivitis (incidence and severity decreased with time) and inflammation of the olfactory epithelium, poor weight gain, and lung lesions (pneumonitis, hypertrophy). Olfactory epithelium inflammation was also seen at 0.5 ppm.

CAC single-exposure animal inhalation studies are summarized in Table 4 and CAC multiple-exposure animal studies are summarized in Table 5.

TABLE 4. Chloracetyl Chloride Single-Exposure Animal Studies

Species	Exposure time (Reference)	Conc. [1] (ppm)	Mortality M	Mortality F	Effects, Comments
Rat, F344	1 hr (Dow 1986)	32 (A)	0/6	0/6	Observed 14 d (all groups); eye squinting and lacrimation during exposure; urine stains, initial weight loss Effects as at 32 ppm but inc increased incidence and/or severity; also shallow breathing; lethargy, periocular red stains
		208 (A)	0/6	0/6	Effects as at 208 ppm but increased incidence and/or severity; also labored breathing, gasping, salivation, reddish stains near muzzle
		522 (A)	0/6	0/6	LC_{50} = 660[2] or 645[3] ppm for males; death on days 2 (3), 7, 8 for M; day 13 for F; toxicity as for 522 ppm but increased incidence and/or severity, also lung edema or failure of lungs to collapse at necropsy, nasal congestion, enlarged adrenals
		747 (A)	5/6	1/6	
Rat	2 hrs (Herzog 1959)	108-6494 (N)	100% at ≥3462		80 animals tested and observed for 5 d.; sex, strain, number of animals/group, and specific results not given.
Rat, Sherman	4 hrs (Carpenter et al. 1949)	1000 (N)	2/6, 3/6, or 4/6		Observed 14 d; animal sex and further methods and results details were not provided.
Rat	7 hrs 5-10 min (Dow 1970a)	~2.5 (A) ~4 (A)	0/? 0/?		No visible effects; number and sex of rats not specified. Respiratory distress; number and sex of rats not specified
Mouse, white	2 hrs (Herzog 1959)	108...[4](N)	0/? [4]		LC_{50} = 1123[5] or 1066 ppm[3]; 220 mice tested, sex not stated; observed 5 d. All groups had symptoms of upper respiratory irritation. Mice were agitated, rubbed their mouths with their paws, did not eat or groom, had half-open and watery eyes, dyspnea, foamy pink liquid at the mouth, convulsions, apnea, and death. Severe effects after 2-5 min at ≥2164 ppm; at 433-1082 ppm had only mild dyspnea. Most lesions were in trachea and lungs, including edema, hemorrhage, and necrosis (caused most deaths). Some mice had mild hyperemia of heart and liver, glomerulonephritis, glomerular edema, and brain hemorrhage. Incidence and severity of lesions increased with dose, but did not specify which effects occurred at a given conc.
		649	0/10		
		866	3/10		
		1082	6/10		
		1299	7/10		
		1515	8/10		
		1732	9/10		
		1948	19/20		
		2164	20/20		
		2381	20/20		
		2597	10/10		
		2814	10/10		
		3030	10/10		
		[4]...6494	all/?[4]		
Guinea pig	2 hrs (Herzog 1959)	108-6494 (N)	100% at ≥3462		50 animals tested; observed for 5 d. Sex, strain, number animals per group, and specific results not given.

[1]Exposure concentrations presented are analytical (A) or nominal (N). If both A and N were available in the study report, analytical concentrations are presented in the table.
[2]Calculated by moving average method and presented in Dow (1986).
[3]Caculated by probit analysis using the Number Cruncher Statistical System for Survival Analysis.
[4]Concentrations and no. of mice/group not given between 108 and 649 ppm, and between 3030 and 6494 ppm.
[5]Calculated by integration method and presented in Herzog (1959).

TABLE 5. Chloracetyl Chloride Multiple-Exposure Animal Studies

Species	Exposure time (Reference)	Analytical Conc. (ppm)	Mortality M	Mortality F	Effects, Comments
Rat	7 hr [1]/d at 2-3 ppm for 4 wks + {12 wk rest} – OR –			0/5	No clinical signs or pathology in respiratory tract, liver, kidneys
	+ {4 wk rest + 7 hr/d [2] at 5-7 ppm for 5 d + 8 wk rest} (Dow 1970b)		0/2		Slight respiratory distress, alveolar and hepatic alterations
Rat	6 hr/d, 5 d/wk, 4 wks (Dow 1982)	0.5[2]	0/10	0/10	– Conjunctival redness after initial exposure, olfactory epithelium inflammation
		1.0	0/10	0/10	– Effects as for 0.5 ppm but increased incidence and/or severity; also nasal exudate, rough coats, poor weight gain, lung lesions
		2.5	8/10	9/10	– Effects as for 1 ppm but increased incidence and/or severity; also lethargy, body fat and weight loss, lesions in nasal turbinates, trachea, and/or lungs (inflammation, hypertrophy, hyperplasia, metaplasia, necrosis, atrophy, pneumonitis or
		5.0	10/10	9/10	bronchitis). No death during first week of exposure. – Effects as for 2.5 ppm but increased incidence and/or severity. No death during first week of exposure.
Mouse	6 hr/d, 5 d/wk, 4 wks (Dow 1982)	0.5[2]	0/10	0/10	– Rough coats, sneezing, and eye conjunctivitis, respiratory mucosa inflammation with large cytoplasmic eosinophilic inclusions in nasal turbinates, trachea, and bronchi
		1.0	0/10	0/10	– Effects as for 0.5 ppm but increased incidence and/or severity; also poor weight gain
		2.5	0/10	2/10	– Effects as for 1 ppm but increased incidence and/or severity; also, weight loss or poor gain, depleted fat reserves, mucosal hypertrophy and hyperplasia. No death first week of exposure.
		5.0	1/10	2/10	– Effects as for 2.5 ppm but increased incidence and/or severity, also rales, lethargy, nasal exudate, alveolar macrophages w. red cytoplasmic masses. No death during first week of exposure.
Hamster	6 hr/d, 5 d/wk, 4 wks (Dow 1982)	0.5[2]	0/10	0/10	– Sneezing and closed eyes
		1.0	0/10	0/10	– Effects as for 0.5 ppm but increased incidence and/or severity
		2.5	0/10	0/10	– Effects as for 1 ppm but increased incidence and/or severity; also poor weight gain
		5.0	0/10	0/10	– Effects as for 2.5 ppm but increased incidence and/or severity; also, weight loss; depleted fat reserves in females

[1]Exposure duration of 7 hr/d not stated but inferred from related preliminary study (Dow 1970a).
[2]Actual analytical concentrations for 0.5, 1, 2.5 and 5 ppm were 0.55 ± 0.61 ppm (CAC was ≤ 0.1 ppm, the detection limit, for the last 8 exposures), 0.84 ± 0.51 ppm, 2.6 ± 1.4 ppm, and 5.0 ± 2.3 ppm, respectively.

DCAC: Using the range-finding test that their laboratory developed, Smyth et al. (1951; 1954) reported that 2/6 Carworth-Wistar rats (probably males) exposed to 2000 ppm (nominal concentration) for 4 hours died. Since their methodology involves testing a logarithmic series of concentrations with a factor of two, it can be inferred that 1000 ppm (nominal) was also tested and caused no mortality. In their published range-finding lists, these investigators reported results for only "the concentration yielding fractional mortality among six rats within 14 days" (Smyth et al. 1954). Vapors are generated using flowing air streams and proportioning pumps, and the concentrations are not analytically confirmed. No results other than death were reported.

Smyth et al. (1951) also treated 6 male albino to a flowing stream of DCAC vapor approaching saturation concentration (~30,000 ppm for DCAC). Vapor was generated by passing dried air through a fritted disc bubbler at room temperature. The longest period that allowed all the rats to survive was 8 minutes.

3.1.2. Mice

CAC: CD-1 mice (10/sex/dose) were exposed to 0 (room air) or approximately 0.5, 1, 2.5, or 5 ppm CAC vapor for 6 hours/day, 5 days/week, for 4 weeks for a total of 18-20 exposures (Dow 1982). Treatment of the 0.5 ppm group began two weeks after the other groups, thus half the controls were kept for 4 weeks and half for 6 weeks. The actual CAC analytical air concentrations and the experimental methods were as listed for the concurrent rat study (see Section 3.1.1.). No mortality occurred at 0, 0.5, or 1 ppm, whereas 2/20 (2 females) and 3/20 (1 male, 2 females) died at 2.5 and 5 ppm, respectively. Deaths all occurred after the first treatment week. Mice had rough hair coats, sneezing, and eye conjunctival redness throughout the experiment, the incidence and severity increasing with dose. Animals exposed to 5 ppm also had rales, were lethargic, and had nasal exudate during the first week. Weight loss or poor weight gain occurred at ≥1 ppm in both sexes, and depleted fat reserves were evident at ≥2.5 ppm. All dose groups had numerous respiratory lesions including inflammation accompanied by large intracytoplasmic eosinophilic inclusions in the respiratory mucosa of the nasal turbinates, trachea, and bronchi. The lungs revealed mucosal hypertrophy and hyperplasia; the 2.5 and 5 ppm mice also had alveolar macrophages containing red cytoplasmic masses (believed to be hemoglobin and or its breakdown product(s)). The 2.5 and 5 ppm mice also had alterations of the liver and female reproductive organs attributed to the weight loss and poor health of the animals.

Herzog (1959) exposed 220 white mice (sex not specified) for 2 hours to 0.5-30 mg/L (108-6494 ppm) CAC concurrently with rats and guinea pigs (see Sections 3.1.1 and 3.1.3). Control groups were not mentioned. The number of mice/dose were 10 or 20 at 3-14 mg/L; concentrations and/or the number of mice/group were not stated at < 3 mg/L and >14 mg/L (see Table 2). Animals were observed during exposure and for the following 5 days. No mice died at ≤ 649 ppm, all mice inhaling ≥3030 ppm died during the 2-hour exposure, and 18 mice inhaling 2381-6480 ppm died within the first 2-3 minutes of exposure. Over the 5-day period, all mice died at ≥10 mg/L (2164 ppm). Herzog (1959) calculated the mean lethal concentration, i.e., LC_{50}, over the 5-day period as 5.2 mg/L (1123 ppm) using the statistical integration method of Behrens (1929). An LC_{50} of 1066 ppm was obtained by probit analysis (using the Number Cruncher Statistical System). Symptoms of irritation of the upper respiratory passages were seen at ≥0.5 mg/L (108 ppm). The animals initially appeared agitated and had signs of eye and respiratory irritation (rubbed mouth with paws, scratched themselves, had half-open and watery eyes), profound dyspnea, foamy pink liquid at the mouth, and eventually cyanosis of the extremities, spastic convulsions, apnea, and death. Mice that died between days 2-5 in some cases no longer had dyspnea, but remained in a state of prostration, refused to eat, and did not groom themselves. Symptom severity was related to the exposure concentration, with severe effects occurring within 2-5 minutes at ≥10 mg/L (2164 ppm), whereas at 2-5 mg/L (433-1082 ppm), symptoms had a “slower evolution” and only mild dyspnea was seen at the end of the exposure period. Necropsy and histopathology revealed that the majority of the lesions were in

the trachea and lungs. Lesions in the trachea included lumen blocked with blood-soaked necrotic tissue, mucosal necrosis, hyperemia, edema, atrophy, detachment of mucosa. The lungs were enlarged and congested, and had lesions including dilated interalveolar capillaries, hemorrhagic alveolitis, bronchopneumonia, emphysema, and atelectasis. Lung congestion and pulmonary edema caused the death of most of the animals. Other less commonly seen lesions included mild hyperemia of the heart and liver, glomerular edema and glomerulonephritis, and mild brain hemorrhage. The incidence and severity of the lesions increased with dose, although it was not specified which effects occurred at a given test concentration. Based on the fact that upper respiratory irritation was seen in mice at 0.5 mg/L (108 ppm), Herzog (1959) suggested that the maximum workplace air concentration should remain below 0.01 mg/L (2.2 ppm).

Herzog (1959) also exposed 120 white mice (sex, strain, number/concentration not specified) for 5 minutes to 10-65 mg/L (2164-14,066 ppm) acetyl chloride similarly to the 2-hour exposure study. Details of the results were not stated other than that death occurred even within this (5-minute) period. Herzog (1959) theorized that deaths during exposure were due to inhibition of the respiratory center reflex, and those occurring post-exposure were due to pulmonary lesions (congestion and edema).

3.1.3. Guinea pigs

CAC: Herzog (1959) exposed 50 guinea pigs (sex, strain, number/concentration not specified) for 2 hours to 0.5-30 mg/L (108-6494) acetyl chloride, concurrently with the rats and mice (see Sections 3.1.1. and 3.1.2.). The only results given were that all animals inhaling ≥3462-3895 ppm died during the 5-day observation period, and that 3 animals inhaling 2381-6480 ppm died within the first 2-3 minutes of exposure.

3.2. Nonlethal Toxicity

3.2.1. Rats

CAC: Exposure to ~2.5 ppm CAC (analytical) for 7 hours did not induce any adverse effects in rats, but exposure to ~4 ppm for 5-10 minutes caused "respiratory embarrassment" (i.e. respiratory difficulty or distress) in a range-finding study (Dow 1970a). The number of rats tested, their sex, and the method of generating the chamber atmosphere were not reported. In the ensuing 4-week study (Dow 1970b), rats were exposed to 0 or 2-3 ppm CAC 7 hours/day for 4 weeks followed by either 12 weeks of recovery (no treatment) (5 females/group) or by 4 weeks recovery, then 5 days re-exposure to 5-7 ppm for 7 hours/day, then 8 weeks recovery (2 treated** and 5 control males). [**It is unclear whether there were actually 5 instead of 2 treated males, and if the other 3 males died, as stated in Dow 1982, but no mention of other animals is made in Dow 1970b.] The exposure duration of 7 hr/d was not stated in the study report, but was inferred from information in the related range finding study (Dow 1970a). No clinical signs or histopathology in the respiratory tract, liver, or kidneys were seen in the female group, whereas the two males re-exposed to 5-7 ppm for 5 days displayed signs of respiratory distress (further details not provided) and had minor focal alterations in the alveolar walls.

DCAC: Male Sprague-Dawley rats given 30 exposures of 0.5, 1.0, or 2.0 ppm DCAC for 6 hours/day, 5 days/week had no mortality during the treatment period in a carcinogenicity

study described in Section 3.6. (Sellakumar et al. 1987). Two of 50 animals exposed to 2.0 ppm developed nasal carcinomas (none in control group). Results not directly related to tumor development were not presented in the study report (e.g. cageside observations, gross pathology, body weights).

3.2.2. Hamsters

CAC: Syrian Golden hamsters (10/sex/dose) were exposed to 0 (room air) or approximately 0.5, 1, 2.5, or 5 ppm CAC vapor for 6 hours/day, 5 days/week, for 4 weeks for a total of 18-20 exposures (Dow 1982). Treatment of the 0.5 ppm group began two weeks after the other groups, thus half the controls were kept for 4 weeks and half for 6 weeks. The actual CAC analytical air concentrations and the experimental methods were as listed for the concurrent rat and mouse studies, except histopathological examination was not performed. (Dow 1982). No animals died on study. Sneezing and closed eyes were observed in all test groups, the incidence increasing with dose. At 5 ppm, animals typically lost weight and females had depleted fat reserves. Hamsters inhaling 2.5 ppm had poor weight gain during the study.

3.3. Neurotoxicity

CAC: Neurotoxicity was not a major toxic effect in the available CAC animal inhalation studies, although some neurologic endpoints were seen at test concentrations approaching lethality. Fischer 344 rats (6/sex/dose) exposed for 1 hour to CAC had eye squinting, lacrimation, and urine stains at $\geq$32 ppm, dyspnea and lethargy at $\geq$208 ppm, salivation at $\geq$522 ppm, and many died at $\geq$747 ppm (Dow 1986). Brain lesions occurred in some white mice exposed for 2 hours to 0.5-30 mg/L (108-6494 ppm) CAC, consisting of mild hemorrhage (9/153 mice) and hyperemia (15/153 mice) (Herzog 1959). However, the actual CAC concentrations at which the lesions occurred were not stated, and no control groups were mentioned. In both of these studies, respiratory irritation and lung lesions were the primary toxic finding.

DCAC: Neurotoxicity as an endpoint was not reported in any DCAC inhalation animal studies.

3.4. Developmental/Reproductive Toxicity

No animal studies were located that evaluated developmental and/or reproductive toxicity of CAC or DCAC.

3.5. Genotoxicity

CAC: CAC was not mutagenic in five strains of *Salmonella*, with or without metabolic activation (Simmon and Poole 1976). CAC tested up to the highest non-toxic dose (0.39 mg/mL) did not induce sister-chromatid exchange or chromosomal aberrations in Chinese hamster CHL cells, with or without metabolic activation (Sawada 1987).

DCAC: DCAC was mutagenic in the Ames test using *Salmonella typhimurium* TA100 without metabolic activation. However, negative results were obtained when *S. typhimurium*

TA100 was tested with metabolic activation, and when *S. typhimurium* TA98 was tested with or without metabolic activation (DeMarini et al. 1994; Zeiger et al. 1992). DCAC did not induce prophage lambda in *E. coli* in the Microscreen assay (DeMarini et al. 1994).

3.6. Chronic Toxicity/Carcinogenicity

CAC: CAC chronic toxicity or carcinogenicity animal studies were not found. Neither the U.S. EPA nor IARC have classified CAC as to its carcinogenicity.

DCAC: The carcinogenic potential of DCAC was evaluated in male Sprague-Dawley rats given 30 exposures of 0.5, 1.0, or 2.0 ppm DCAC for 6 hours/day, 5 days/week (actual concentrations were 0.53 ± 0.03, 1.03 ± 0.08, and 2.00 ± 0.12 ppm, respectively) (Sellakumar et al. 1987). The rats were 9-10 weeks old; 50/dose were tested and there were 98 controls. Liquid DCAC was vaporized in a generating flask, and the vapor was directed into a 1.0 m^3 or 1.3 m^3 dynamic exposure chamber. Air concentrations were measured every 30 minutes with an infrared gas analyzer. All rats were observed daily, weighed monthly, and necropsied when moribund or after spontaneous death. Histopathology was evaluated for each lobe of the lung, the trachea, larynx, liver, kidneys, testes and other organs with gross lesions. Unfortunately, the animal observations and body weights were not provided in the study report. Pathology data were not reported specifically for DCAC, but a summary was provided for results of testing a group of five water-reactive electrophilic (alkylating) compounds, including DCAC, β-propiolactone, methylmethane sulfonate, ethylchloroformate, and propylene oxide.

None of the rats died on study. The time of death was not stated but the first deaths appeared (from a text figure) to have occurred ~2 weeks after the end of exposure to 2 ppm. The main lesions were in the upper respiratory tract, involving the anterior respiratory epithelium (nasomaxillary turbinates, lateral walls, and nasal septum), and olfactory epithelium. The epithelium was the most severely affected, displaying necrosis, ulceration, acute inflammation, and in some cases squamous metaplasia and dysplasia, which led to tumorigenesis at 2 ppm. Two rats exposed to 2 ppm had nasal carcinomas (Zymbal gland squamous cell carcinoma and sebacious acinar carcinoma) and died 701 and 887 days after initial DCAC exposure. No carcinomas were found in controls and the non-respiratory tumor incidences were comparable to historical controls. The study authors speculated that the lower than expected tumor response for DCAC was due to its rapid hydrolysis ($t_{1/2}$= 0.004 minutes at -20°C) and reaction with other nucleophiles, preventing sufficient amounts to cross the nasal mucosa and react with DNA (Sellakumar et al. 1987).

The carcinogenicity of DCAC was also evaluated by the dermal route in female ICR/Ha Swiss mice treated by repeated skin application or subcutaneous injection for 18-22 months (van Duuren et al. 1987). A definitive increase in tumor incidence was not found.

Neither the U.S. EPA nor IARC have classified DCAC as to its carcinogenicity. Dichloroacetic acid, the hydrolysis product of DCAC, has been classified as "likely to be a carcinogen" in humans, based on no human data but sufficient evidence in at least two species of experimental animals (U.S. EPA 2003b). The animal data were obtained by exposure in the drinking water; no inhalation carcinogenicity studies were available.

3.7. Summary

CAC: In single-exposure studies, animals were exposed for 5-10 minutes to 7 hours to CAC ranging from 2.5 ppm to near saturation (~25,000 ppm). Inhalation of ~2.5 ppm CAC (analytical) for 7 hours did not cause adverse effects in a preliminary rat study, but inhalation of ~4 ppm for 5-10 minutes caused respiratory difficulty (Dow 1970a). Fischer 344 rats exposed to 32-747 ppm CAC (analytical) for 1 hour had respiratory and eye irritation, weight loss, dyspnea and/or lethargy that were dose-related in incidence and/or severity (Dow 1986). At 747 ppm, rats had lung edema, stomach erosion, and enlarged adrenals and 5/6 males and 1/6 females died (14-day LC_{50} of ~ 660 ppm and >747 ppm, respectively). Fractional mortality (2/6, 3/6, or 4/6) occurred in Sherman albino rats exposed to 1000 ppm (nominal) CAC for 4 hours and observed for 14 days (Carpenter et al. 1949).

Mice, rats, and guinea pigs exposed for 2 hours to 108-6494 ppm CAC all died within 5 days at ≥3030 ppm (Herzog 1959). Of the early decedents, 18/220 mice, 5/80 rats, and 3/50 guinea pigs died during the first 2-3 minutes at 2381-6480 ppm. No mice died at ≤649 ppm and a 5-day LC_{50} of 1123 ppm was obtained (alternately calculated as 1066 ppm). The mice had signs of upper respiratory and eye irritation at all doses, dyspnea, and lesions in the trachea and lungs that increased with dose, although dose-response data were not provided. Male rats exposed to chloroacetyl chloride near saturation concentration (25,000 ppm) had severe eye and respiratory irritation leading to blindness, lung hemorrhage, and death within 2 hours (Younger Labs 1969).

Two multiple-exposure studies were conducted, which tested significantly lower concentrations than the single-exposure studies. Rats exposed to 2-3 ppm for 4 weeks, followed by 4 weeks recovery, then 5 days re-exposure to 5-7 ppm, then 8 weeks recovery had signs of respiratory distress and minor focal alterations in the alveolar walls. However, rats exposed to 2-3 ppm CAC 7 hours/day for 4 weeks followed by 12 weeks of recovery had no clinical signs or histopathology in the respiratory tract, liver, or kidneys (Dow 1970b). In a repeat-exposure study testing Fischer 344 rats, CD-1 mice, and Syrian Golden hamsters, rats had the highest death rates following 18-20 exposures to ~0.5, 1, 2.5, or 5 ppm CAC vapor 6 hours/day, 5 days/week, for 4 weeks (Dow 1982). No deaths occurred at 0, 0.5, or 1 ppm in rats or mice, or at any dose in hamsters. All groups of rats and mice had eye conjunctivitis and inflammation of the respiratory mucosa. At ≥1 ppm, rats and mice had poor weight gain and numerous nasal and/or lung lesions, which were dose-related. Death occurred at 2.5 ppm (17/20 rats, 2/20 mice) and 5 ppm (19/20 rats, 3/20 mice), starting during the second treatment week. Hamsters sneezed, had closed eyes, and had poor weight gain at ≥2.5 ppm, but were not examined microscopically.

Neurotoxicity was not a major CAC effect in the animal studies. CAC was not mutagenic in *Salmonella* (Simmon and Poole 1976) and did not induce sister-chromatid exchange or chromosomal aberrations in Chinese hamster CHL cells (Sawada 1987). No animal studies were located that evaluated CAC developmental and/or reproductive toxicity, chronic toxicity, or carcinogenicity.

DCAC: Lethality from acute exposure but no other results were reported in a range-finding test conducted by Smyth et al. (1951), in which 2/6 rats exposed to 2000 ppm (nominal

concentration) for 4 hours died within 14 days, and 0/6 died after 4 hours at 1000 ppm (nominal) (latter is inferred from the methodology description in Smyth et al. 1954). Smyth et al. (1951) also found that 8 minutes was the longest period survived by 6 rats exposed to near-saturated DCAC vapor (~30,000 ppm).

In a 6-week carcinogenicity study, male rats given 30 exposures (6 hours/day, 5 days/week) of 0.5, 1.0, or 2.0 ppm DCAC had no mortality during the treatment period or for 2 weeks thereafter. Two of 50 rats exposed to 2.0 ppm developed nasal carcinomas during their second year of life (0/50 controls; Sellakumar et al. 1987). Results such as cageside observations, complete gross pathology, and body weights were not reported. Skin carcinogenicity studies using female ICR/Ha Swiss did not show a definitive increase in tumor incidence from DCAC treatment (van Duuren et al. 1987). Neither the U.S. EPA nor IARC have classified DCAC as to its carcinogenicity (U.S. EPA 2003b). DCAC was mutagenic in one strain of *Salmonella* but did not induce prophage lambda in *E. coli* (DeMarini et al. 1994; Zeiger et al. 1992).

Neurotoxicity and developmental and/or reproductive toxicity were not evaluated in any DCAC inhalation animal studies.

4. SPECIAL CONSIDERATIONS

4.1. Metabolism and Disposition

CAC: No information was found addressing CAC metabolism and disposition. CAC decomposes in water to form hydrochloric acid and chloroacetic acid ($t_{1/2}$ <30 minutes) (Dow 2001).

DCAC: No information was found addressing DCAC metabolism and disposition. DCAC decomposes in water to form hydrochloric acid and dichloroacetic acid (HSDB 2003b). The water hydrolysis rate has been reported as having a $t_{1/2}$ of 0.004 minutes at -20°C (Sellakumar et al. 1987).

4.2. Mechanism of Toxicity

No studies were found that specifically addressed the mechanism of CAC or DCAC toxicity. Both compounds are known to be strong contact irritants to mucosal surfaces. Both decompose in water, CAC to form hydrochloric acid and chloroacetic acid, and DCAC to form hydrochloric acid and dichloroacetic acid, which are locally-acting irritants and likely contribute to CAC and DCAC toxicity.

4.3. Structure Activity Relationships

Chlorinated acetyl chlorides are hydrolyzed rapidly in water. The $t_{1/2}$ of hydrolysis for acetyl chloride, chloroacetyl chloride, dichloroacetyl chloride, and trichloroacetyl chloride (TCAC) were 0.002, 0.126, 0.0023, and < 0.002 seconds, respectively, in water at 25°C, and in 89.1:10.9 water-acetone at -20°C were 636, 34, 0.2, and <0.07 seconds, respectively (Prager et

al. 2001, Ugi and Beck 1961). Therefore it appears that at room temperature, hydrolysis rates are similar for three of the four acetyl chlorides.

A comparison of rat 4-hour LC_{50} values indicated that TCAC is more toxic than CAC, which is more toxic than DCAC (LC_{50} values of 64 ppm, 660 ppm, and >2000 ppm, respectively (Izmerov et al. 1982; Dow 1986; Smyth et al. 1954).

The relative toxicities of the chlorinated acetyl chlorides at non-lethal exposure concentrations could not be definitively established due to lack of data. The few available human and animal studies suggest that CAC, DCAC, and TCAC have approximately the same relative toxicities at non-lethal concentrations as they do at lethal concentrations, i.e., TCAC > CAC > DCAC. The threshold of irritation of mucous membranes of the upper airways and eyes for a 1-minute exposure (Lim_{ir}) in man was reported as 0.08 ppm for TCAC (Izmerov et al. 1982) and 0.43 ppm for CAC (Germanova et al. 1988). [This is consistent with the fact that the acid hydrolysis product of TCAC is stronger than of CAC (pKa 0.51 for TCAC and 2.87 for CAC).] Rats exposed to ~2.5 ppm CAC for 7 hours had no reported adverse effects, but ~4 ppm for 5-10 minutes caused respiratory difficulty or distress (Dow 1970a). Rats, mice, and hamsters exposed to ~0.5-5 ppm CAC vapor for 6 hours/day, 5 days/week, for 4 weeks had ocular and respiratory irritation at all test concentrations (Dow 1982). Rats inhaling 0.5-2.0 ppm DCAC (6 hours/day, 5 days/week, for 6 weeks) had no reported clinical signs or mortality during treatment, and those that died later had respiratory lesions (Sellakumar et al. 1987).

4.4. Other Relevant Information

4.4.1. Species Variability

CAC: Rats appeared to be the most sensitive to CAC in a multiple-exposure study in which rats, mice, and hamsters were exposed to ~ 0.5, 1, 2.5, or 5 ppm CAC vapor for 6 hours/day, 5 days/week, for 4 weeks for a total of 18-20 exposures (Dow 1982). Ocular and respiratory irritation occurred in all three species at all test concentrations. Rats had the most severe clinical signs and the highest mortality rate: 17/20 and 18/20 died at 2.5 and 5 ppm, respectively, whereas only 2/20 and 3/20 mice and no hamsters died at these concentrations. Pathological changes consistent with chronic irritation were seen in the respiratory system at necropsy in only rats and mice.

Interspecies variability between mice, rats, and guinea pigs in a 2-hour exposure study (108-6494 ppm CAC) could not be established because mortality for single exposure concentrations was only provided for mice (Herzog 1959). A comparison of the LC_{100} values, which were provided for all three species, suggests that interspecies variability was not great. All animals died within 5 days of exposure to ≥3030 ppm (mice), 3462 ppm (rats), or 3462-3895 ppm (guinea pigs).

DCAC: Species variability for DCAC toxicity could not be evaluated because only rat studies were available.

4.4.2. Susceptible Populations

No susceptible populations were identified for exposure to either CAC or DCAC.

4.4.3. Concentration-Exposure Duration Relationship

CAC: No data were available from which to determine the concentration-time relationship for CAC inhalation toxicity. Scaling across time was not performed for AEGL-1, because using the same value across time was considered appropriate since mild irritant effects do not vary greatly over time. For AEGL-2 and AEGL-3 values for 10, 30, 60, 240, and 480 minutes, scaling across time was performed using the ten Berge et al. (1986) equation, $C^n \times t = k$, using n=3 to extrapolate to shorter exposure times and n=1 to extrapolate to longer exposure times to obtain protective values. This equation describes the concentration-time relationship for many irritant and systemically acting vapors and gases, where the exponent n ranges from 0.8 to 3.5, and n ranged from 1 to 3 for 90% of the chemicals.

DCAC: No data were available from which to determine the concentration-time relationship for DCAC inhalation toxicity.

4.4.4. Concurrent Exposure Issues

CAC: The presence of CAC in the air can also result in inadvertent exposure of the skin, which is capable of absorbing sufficient CAC to result in death (Morris and Bost 2002). The minimal dermal dose causing lethality in rabbits was 316-501 mg/kg after exposure for 24 hours under a semi-occluded dressing (Younger Labs 1969). Necropsy showed that animals that died on study had enlarged gallbladders and hemorrhagic lungs and livers, and all treated animals had deep dermal lesions.

5. DATA ANALYSIS FOR AEGL-1

5.1. Summary of Human Data Relevant to AEGL-1

AEGL-1 values were developed using only the CAC data base. An industrial hygienist reported that CAC odor at an air concentration of 0.011 ppm CAC was undetectable, at 0.023 ppm was "barely detectable," and at 0.140 ppm was "strong" but not irritating to the eyes, whereas 0.910 ppm was painful to the eyes and caused lacrimation (Dow, 1988b). An exposure duration was not reported. Shift sample ($\geq$7 hours) air concentrations of 0.05 ppm was associated with odor that was "readily apparent and objectionable throughout the shift" for workers (Monsanto 1987).

5.2. Summary of Animal Data Relevant to AEGL-1

The following five animal studies are potentially useful for developing AEGL-1 values:
(1) inhalation of ~2.5 ppm CAC for 7 hours did not cause adverse effects, but exposure to ~4 ppm for 5-10 minutes caused respiratory difficulty in rats (Dow 1970a),
(2) female rats exposed to 2-3 ppm CAC for 7 hours/day for 4 weeks followed by 12 weeks of recovery had no clinical signs or histopathology, but male rats re-exposed for 5 days to 5-

7 ppm after a 4 week recovery had respiratory distress and alveolar lesions (Dow 1970b; 7 hours/day is assumed),

(3) rats, mice, and hamsters received 18-20 exposures to ~0.5, 1, 2.5 or 5 ppm for 6 hours/day over 4 weeks (5 days/week); rats were noted to have conjunctival redness after the initial exposure, and at unspecified times, eye irritation occurred in all groups of species; mice and hamsters sneezed, and mice and rats had rough hair coats. After 18-20 exposures, various nasal and/or lung lesions occurred at all doses in rats and mice (hamsters were not examined microscopically), and led to death at 2.5 and 5 ppm starting during week 2 (Dow 1982),

(4) rats inhaled 32, 208, 522, or 747 ppm CAC for 1 hour; all groups squinted, lacrimated, had urine stains, and initially lost weight. At ≥208 ppm, rats had shallow breathing, lethargy, and reddish stains near the eyes, and at 747 ppm, rats had labored breathing and gasping, lung and stomach lesions, and some died (Dow 1986), and

(5) mice exposed for 2 hours to 108-6494 ppm CAC had upper respiratory irritation that increased in severity with dose, although effects at a given test concentration were not generally provided (Herzog 1959).

5.3. Derivation of AEGL-1

AEGL-1 values were derived only for CAC. The CAC AEGL-1 values were derived from the Dow (1982) multiple-exposure study in which conjunctival redness was reported in rats after the initial 6-hour exposure to ≥0.5 ppm. This study was chosen because it was well-conducted, both an exposure duration and the analytical concentration were determined, and the endpoint (eye irritation) was consistent with the definition of AEGL-1. The human data were not used because either the exposure duration was not given (Dow 1988b) or an adverse health effect did not occur (Monsanto 1987). AEGL-1 values were derived using a single 6-hour exposure to ~1 ppm (0.84 ± 0.51 ppm) because this is the highest concentration that caused conjunctival redness but no other more serious effects after one exposure. A modifying factor of 2 was applied to estimate a no-effect level concentration for conjunctivitis. The same AEGL value is adopted for 10 minutes to 8 hours because mild irritant effects do not vary greatly over time. A total uncertainty factor of 10 was applied: 3 for interspecies variability and 3 for intraspecies variability, because the NOEL for eye conjunctivitis due to local contact irritation is not expected to vary greatly among animals or humans. The resulting AEGL-1 of 0.04 ppm is consistent with the limited human data in which exposure to 0.023 ppm for an undefined period was "barely detectable" but 0.140 ppm was "strong"(Dow 1988b), and exposure to 0.05 ppm was associated with odor that was "objectionable" but no adverse health effects were reported (Monsanto 1987). The AEGL-1 values are shown in Table 6 and calculations are detailed in Appendix A.

TABLE 6. AEGL-1 Values for Chloroacetyl Chloride (and Dichloroacetyl Chloride)

10-minute	30-minute	1-hour	4-hour	8-hour
0.04 ppm (0.19 mg/m^3)	0.04 ppm (0.19 mg/m^3)	0.04 ppm (0.19 mg/m^3)	0.04 ppm (0.19 mg/m^3)	0.04 ppm (0.19 mg/m^3)

6. DATA ANALYSIS FOR AEGL-2

6.1. Summary of Human Data Relevant to AEGL-2

AEGL-1 values were developed using only the CAC data base. The only CAC human data within the scope of AEGL-2 is a report by an industrial hygienist that CAC odor at 0.140 ppm was "strong" but not irritating to the eyes, whereas 0.910 ppm was painful to the eyes and caused lacrimation (exposure time not reported; likely few minutes) (Dow, 1988b).

6.2. Summary of Animal Data Relevant to AEGL-2

AEGL-2 values can be derived from the same five studies, albeit using different endpoints, considered for developing AEGL-1 values (see Section 5.2.).

6.3. Derivation of AEGL-2

AEGL-2 values were developed using only the CAC data base. An The Dow (1986) 1-hour inhalation rat study (32, 208, 522, or 747 ppm CAC) was chosen for AEGL-2 derivation because it was the only well-conducted study in which effects within the scope of AEGL-2 occurred from a single exposure. All test groups squinted, lacrimated, had urine stains, and initially lost weight. At ≥208 ppm, rats had shallow breathing, lethargy, and reddish stains near the eyes, at ≥522 ppm, rats also had labored breathing, gasping, and salivation, and at 747 ppm, 5/6 males and 1/6 females died and necropsy revealed lung pathology, nasal congestion, and enlarged adrenals. The AEGL-2 endpoint was the NOEL for impaired ability to escape due to lacrimation and eye squinting, which was estimated by applying a modifying factor of 2 to the lowest concentration tested of 32 ppm. Data were not available to determine the CAC toxicity concentration-time relationship, which for many irritant and systemically acting vapors and gases may be described by $C^n \times t = k$, where the exponent n ranges from 0.8 to 3.5 (ten Berge et al. 1986). To obtain protective AEGL-2 values, scaling across time was performed using n=3 to extrapolate to exposure times < 1 hour (exposure duration in the key study), and n=1 to extrapolate to exposure times >1 hour. A total uncertainty factor of 10 was applied, consisting of 3 for interspecies variability and 3 for intraspecies variability, because the AEGL-2 endpoint (NOEL for eye irritation sufficient to cause lacrimation and squinting) is a direct surface contact effect that is not likely to vary in severity among animals or humans. The AEGL-1 values are shown in Table 7 and calculations are detailed in Appendix A.

TABLE 7. AEGL-2 Values for Chloroacetyl Chloride (and Dichloroacetyl Chloride)

10-minute	30-minute	1-hour	4-hour	8-hour
2.9 ppm (13 mg/m^3)	2.0 ppm (9.2 mg/m^3)	1.6 ppm (7.4 mg/m^3)	0.40 ppm (1.8 mg/m^3)	0.20 ppm (0.92 mg/m^3)

7. DATA ANALYSIS FOR AEGL-3

7.1. Summary of Human Data Relevant to AEGL-3

AEGL-3 values were developed using only the CAC data base. No quantitative human information on lethal CAC exposure was located.

7.2. Summary of Animal Data Relevant to AEGL-3

Animal studies potentially useful for AEGL-3 derivation include:

(1) 2/6, 3/6, or 4/6 (not specified) rats died within 14 days of inhaling 1000 ppm (nominal) CAC for 4 hours in a range-finding test, but no further results were provided (Carpenter et al. 1949),

(2) rats exposed to 32, 208, 522, or 747 ppm CAC (analytical) for 1 hour and observed for 14 days had eye squinting, lacrimation, urine stains, and initially lost weight; at ≥208 ppm, rats also displayed shallow breathing, lethargy, and reddish stains near the eyes, and at ≥522 ppm, rats additionally had labored breathing, gasping, and salivation. The incidence and/or severity of the findings increased with dose. Necropsy of rats that died at 747 ppm (5/6 males, 1/6 females) revealed lung pathology, nasal congestion, and enlarged adrenals (Dow 1986),

(3) white mice that inhaled 0.5-30 mg/L (108-6494 ppm) CAC for 2 hours had dose-related eye and respiratory irritation, and at unspecified doses had dyspnea, foamy pink liquid at the mouth, lesions in the trachea and lungs; mortality occurred at ≥866 ppm during the 5-day observation period (Herzog 1959).

7.3. Derivation of AEGL-3

AEGL-3 values were developed only for CAC. An The Dow (1986) 1-hour inhalation rat study (32, 208, 522, or 747 ppm CAC) was chosen for AEGL-3 derivation. This study was considered the best conducted of the candidate acute lethality studies: the observation period was sufficiently long, analytical CAC concentrations were determined, and toxicity was described at specific test concentrations. The AEGL-3 toxic endpoint was the lethality threshold, which was taken as the highest concentration tested that caused no deaths (522 ppm). An LC_{01} or $BMDL_{05}$ were not used for the lethality threshold because mortality occurred in only one test group. Data were not available to determine the CAC toxicity concentration-time relationship, which for many irritant and systemically acting vapors and gases may be described by $C^n \times t = k$, where the exponent n ranges from 0.8 to 3.5 (ten Berge et al. 1986). To obtain protective AEGL-3 values, scaling across time was performed using n=3 to extrapolate to exposure times < 1 hour (exposure duration in the key study), and n=1 to extrapolate to exposure times >1 hour. A total uncertainty factor of 10 was applied. An interspecies uncertainty factor of 3 was used because lethality resulting from respiratory lesions and having a steep dose-response was seen in several studies with rats and mice, at CAC concentrations within a factor of 2-3. An intraspecies uncertainty factor of 3 was applied because the threshold for lethality from direct destruction of respiratory tissue is not expected to vary greatly among humans, based on the steep dose-response seen in the animal studies. The resulting AEGL-3 values are shown in Table 8 and calculations are detailed in Appendix A.

TABLE 8. AEGL-3 Values for Chloroacetyl Chloride (and Dichloroacetyl Chloride)

10-minute	30-minute	1-hour	4-hour	8-hour
95 ppm (440 mg/m^3)	66 ppm (300 mg/m^3)	52 ppm (240 mg/m^3)	13 ppm (60 mg/m^3)	6.5 ppm (30 mg/m^3)

8. SUMMARY OF AEGLS

8.1. AEGL Values and Toxicity Endpoints

AEGL-1, AEGL-2, and AEGL-3 values were developed only for CAC because the database for DCAC was very limited. Since the available data indicated that DCAC was less toxic than the related compound CAC, all AEGL values developed for CAC were adopted for DCAC.

AEGL-1 values for CAC were derived from a multiple-exposure study in which rats, mice, and hamsters received 18-20 exposures for 6 hours/day to nominal concentrations of 0.5, 1, 2.5 or 5 ppm (Dow 1982). At unspecified times, eye irritation occurred in all dose groups, but rats were noted to have conjunctival redness after the initial 6-hour exposure to ≥0.5 ppm. After 18-20 exposures, various nasal and/or lung lesions occurred in rats and mice (hamsters were not examined microscopically), and led to death at 2.5 and 5 ppm starting during the second treatment week. AEGL-1 values were derived using a single 6-hour exposure to ~1 ppm (0.84 ± 0.51 ppm) because this is the highest concentration that caused conjunctival redness but no other more serious effects after one exposure. A modifying factor of 2 was applied to estimate a NOEL for conjunctivitis. The same AEGL value is adopted for 10 minutes to 8 hours because mild irritant effects do not vary greatly over time. A total uncertainty factor of 10 was applied: 3 for interspecies variability and 3 for intraspecies variability, because the NOEL for eye conjunctivitis due to local contact irritation is not expected to vary greatly among animals or humans. The resulting AEGL-1 of 0.04 ppm is consistent with the limited human data.

AEGL-2 values for CAC were derived using a study in which rats inhaled 32, 208, 522, or 747 ppm CAC for 1 hour (Dow 1986). All groups squinted, lacrimated, had urine stains, and initially lost weight. At ≥208 ppm, rats also displayed shallow breathing, lethargy, and reddish stains near the eyes, at ≥522 ppm, rats had labored breathing, gasping, and salivation, and at 747 ppm, 5/6 males and 1/6 females died (days 2,7, 8, and 13) and necropsy revealed lung pathology, nasal congestion, and enlarged adrenals. The AEGL-2 endpoint was the NOEL for impaired ability to escape due to lacrimation and eye squinting, which was estimated by applying a modifying factor of 2 to the lowest concentration tested of 32 ppm. Data were not available to determine the CAC toxicity concentration-time relationship, which for many irritant and systemically acting vapors and gases may be described by $C^n \times t = k$, where the exponent n ranges from 0.8 to 3.5 (ten Berge et al. 1986). To obtain protective AEGL-2 values, scaling across time was performed using n=3 to extrapolate to exposure times < 1 hour (exposure duration in the key study), and n=1 to extrapolate to exposure times >1 hour. A total uncertainty factor of 10 was applied, consisting of 3 for interspecies variability and 3 for intraspecies variability, because the AEGL-2 endpoint (NOEL for eye irritation sufficient to cause lacrimation and squinting) is a direct surface contact effect that is not likely to vary in severity among animals or humans.

The AEGL-3 values for CAC were also based on the Dow (1986) 1-hour inhalation rat study (32, 208, 522, or 747 ppm CAC). The AEGL-3 toxic endpoint was the lethality threshold, which was taken as the highest concentration tested that caused no deaths (522 ppm). An LC_{01} or $BMDL_{05}$ were not used for the lethality threshold because mortality occurred in only one test group. Data were not available to determine the CAC toxicity concentration-time relationship,

and scaling across time was performed using n=3 to extrapolate to exposure times < 1 hour (exposure duration in the key study), and n=1 to extrapolate to exposure times >1 hour per Section 4.4.3. A total uncertainty factor of 10 was applied: 3 for interspecies variability (lethality resulting from respiratory lesions and having a steep dose-response was seen in several studies with rats and mice, at CAC concentrations within a factor of 2-3), and 3 for intraspecies uncertainty (the threshold for lethality from direct destruction of respiratory tissue is not expected to vary greatly among humans, based on the steep dose-response in the animal studies).

The resulting AEGL-1, AEGL-2, and AEGL-3 values are summarized in Table 9.

TABLE 9. Summary of AEGL Values for Chloroacetyl Chloride (and Dichloroacetyl Chloride)

Classification	Exposure Duration				
	10-minute	30-minute	1-hour	4-hour	8-hour
AEGL-1 (Nondisabling)	0.04 ppm (0.19 mg/m^3)	0.04 ppm (0.19 mg/m^3)	0.04 ppm (0.19 mg/m^3)	0.04 ppm (0.19 mg/m^3)	0.04 ppm (0.19 mg/m^3)
AEGL-2 (Disabling)	2.9 ppm (13 mg/m^3)	2.0 ppm (9.2 mg/m^3)	1.6 ppm (7.4 mg/m^3)	0.40 ppm (1.8 mg/m^3)	0.20 ppm (0.92 mg/m^3)
AEGL-3 (Lethal)	95 ppm (440 mg/m^3)	66 ppm (300 mg/m^3)	52 ppm (240 mg/m^3)	13 ppm (60 mg/m^3)	6.5 ppm (30 mg/m^3)

8.2. Comparison with Other Standards and Guidelines

No standards or guidelines currently exist for DCAC inhalation exposure.

The existing standards and guidelines for CAC are shown in Table 10. The NIOSH TWA-REL is based on avoiding eye, skin and respiratory irritation from exposure to CAC by inhalation, ingestion, and skin and eye contact (NIOSH 1995). The ACGIH TLV-TWA is intended to prevent irritative effects, and the TLV-STEL is recommended to prevent irritation to eyes and other organs, and includes a skin notation based on human case reports (ACGIH 2001).

The ERPG-1 is based on workplace exposure reports that "exposure to 0.05 ppm for 1 hour may be objectionable" (Monsanto, 1987; Dow 1988b). The ERPG-2 was based on the rat and mouse multiple-exposure study where exposure to 5 ppm for 6 hours/day for 4 weeks caused slight nasal lesions (Dow 1982) and the human report that painful eye irritation and lacrimation occurred around 1 ppm (Dow 1988b). The ERPG-3 was based on the one-hour exposure acute lethality study in which the LC_{50} for males was 660 ppm (Dow 1986), the rat and mouse 4-week study (Dow 1982), and the limited human data (Monsanto, 1987; Dow 1988b).

TABLE 10. Extant Standards and Guidelines for Chloroacetyl Chloride

Guideline	Exposure Duration				
	10 minute	**30 minute**	**1 hour**	**4 hour**	**8 hour**
AEGL-1	0.04 ppm	0.04 ppm	0.04 ppm	0.04 ppm	0.04 ppm
AEGL-2	2.9 ppm	2.0 ppm	1.6 ppm	0.40 ppm	0.20 ppm
AEGL-3	95 ppm	66 ppm	52 ppm	13 ppm	6.5 ppm
ERPG-1 (AIHA)[a]			0.05 ppm		
ERPG-2 (AIHA)			0.5 ppm		
ERPG-3 (AIHA)			10 ppm		
REL-TWA (NIOSH)[b]					0.05 ppm
TLV-TWA (ACGIH)[c]					0.05 ppm
TLV-STEL (ACGIH)[d] (15 min)	0.15 ppm (skin)				
MAC (The Netherlands)[e]					0.05 ppm

[a]**ERPG (Emergency Response Planning Guidelines, American Industrial Hygiene Association** (AIHA 2000)
The ERPG-1 is the maximum airborne concentration below which it is believed nearly all individuals could be exposed for up to one hour without experiencing other than mild, transient adverse health effects or without perceiving a clearly defined objectionable odor.
The ERPG-2 is the maximum airborne concentration below which it is believed nearly all individuals could be exposed for up to one hour without experiencing or developing irreversible or other serious health effects or symptoms that could impair an individual's ability to take protection action.
The ERPG-3 is the maximum airborne concentration below which it is believed nearly all individuals could be exposed for up to one hour without experiencing or developing life-threatening health effects.

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

[c]**ACGIH TLV-TWA (American Conference of Governmental Industrial Hygienists, Threshold Limit Value - Time Weighted Average)** (ACGIH 2002; established 1980) is the time-weighted average concentration for a normal 8-hour workday and a 40-hour workweek, to which nearly all workers may be repeatedly exposed, day after day, without adverse effect. A skin designation is indicated. Designed to minimize the potential for eye irritation, lacrimation, skin erythema and burns, respiratory effects including dyspnea, cyanosis, cough, and gastrointestinal effects.

[d]**ACGIH TLV-STEL (Threshold Limit Value - Short Term Exposure Limit)** (ACGIH 2002; established 1991) 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.

[e]**MAC (Maximaal Aanvaaarde Concentratie [Maximal Accepted Concentration])** (SDU Uitgevers [under the auspices of the Ministry of Social Affairs and Employment], The Hague, The Netherlands 2000) is defined analogous to the ACGIH-TLV-TWA.

8.3. Data Adequacy and Research Needs

CAC: No human data were adequate to derive AEGL-1 values because either the exposure duration was not given (Dow 1988b) or an adverse health effect did not occur (Monsanto 1987). However, the human data were useful in supporting the AEGL-1 and AEGL-2 values derived from the animal data. No human lethality studies were available, but the animal data clearly indicated that respiratory lesions were the main cause of death in animals, and is expected to act similarly in humans since CAC is a direct-acting irritant. Additional human irritation studies and acute lethality data would be helpful to confirm the findings in the animal studies.

DCAC: The database for DCAC was too limited to permit the derivation of AEGL-1, AEGL-2, or AEGL-3 values with a reasonable degree of confidence. Additional human and animal data for all three AEGL levels are needed.

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APPENDIX A: Derivation of AEGL Values

Derivation of AEGL-1

Key Study: Dow 1982. Rats, mice, and hamsters received 18-20 exposures to nominal concentrations of 0.5, 1, 2.5 or 5 ppm. At unspecified times, eye irritation occurred in all dose groups, mice and hamsters sneezed, and mice and rats had rough hair coats. Rats were noted to have conjunctival redness after the initial exposure to ≥0.5 ppm. After 18-20 exposures, various nasal and/or lung lesions occurred at all doses in rats and mice (hamsters were not examined microscopically), and led to death at 2.5 and 5 ppm starting during the second week of treatment. A modifying factor of 2 was applied to estimate a NOEL for conjunctivitis of 0.42 ppm.

Toxicity endpoint: NOEL for (eye) conjunctivitis

Scaling: None; using the same value across time was considered appropriate since mild irritant effects do not vary greatly over time

Uncertainty factors:
Total Uncertainty Factor: 10
Interspecies: 3: The NOEL for conjunctivitis due to local contact irritation is not expected to vary greatly among animals
Intraspecies: 3: The NOEL for conjunctivitis due to local contact irritation is not expected to vary greatly among humans

Modifying factor: 2: To estimate a NOEL for conjunctivitis

Calculations:

10-minute AEGL-1 = 0.42 ppm/10 = 0.04 ppm [0.19 mg/m^3]

30-minute AEGL-1 = 0.42 ppm/10 = 0.04 ppm [0.19 mg/m^3]

1-hour AEGL-1 = 0.42 ppm/10 = 0.04 ppm [0.19 mg/m^3]

4-hour AEGL-1 = 0.42 ppm/10 = 0.04 ppm [0.19 mg/m^3]

8-hour AEGL-1 = 0.42 ppm/10 = 0.04 ppm [0.19 mg/m^3]

Derivation of AEGL-2

Key Study: Dow 1986. Rats exposed to 32, 208, 522, or 747 ppm CAC (analytical) for 1 hour and observed for 14 days had eye squinting, lacrimation, urine stains, and initially lost weight; at ≥208 ppm, rats also displayed shallow breathing, lethargy, and reddish stains near the eyes, at ≥522 ppm, rats additionally had labored breathing, gasping, and salivation, and at 747 ppm, 5/6 males and 1/6 females died (days 2,7, 8, and 13) and necropsy revealed lung pathology, nasal congestion, and enlarged adrenals.

Toxicity endpoint: NOEL for impaired ability to escape due to lacrimation and eye squinting, which was estimated by applying a modifying factor of 2 to the lowest concentration tested of 32 ppm.

Time scaling: $C^n \times t = k$ (ten Berge et al. 1986); no data to derive n; scaled using n=3 for <1 hr (key study exposure) and n=1 for >1 hr to obtain protective AEGL values.

Uncertainty factors: Total Uncertainty Factor: 10

Interspecies: 3: The AEGL-2 endpoint is a direct surface contact effect that is not likely to vary in severity among animals

Intraspecies: 3: The AEGL-2 endpoint is a direct surface contact effect that is not likely to vary in severity among humans

Modifying factor: 2: Applied to the lowest concentration tested (LOEL) to estimate a NOEL for the critical endpoint

Calculations for 10 and 30 min: $(32 \text{ ppm} / 20)^3 \times 1 \text{ hour} = k = 4.096 \text{ ppm}^3\text{-hrs}$

$C^3 \times 0.167 \text{ hr} = 4.096 \text{ ppm}^3\text{-hrs}$

10-minute AEGL-2 = C = 2.9 ppm [13 mg/m^3]

$C^3 \times 0.5 \text{ hr} = 4.096 \text{ ppm}^3\text{-hrs}$

30-minute AEGL-2 = C = 2.0 ppm [9.2 mg/m^3]

Calculations for 1 hour: No scaling: 1-hour AEGL-2 = C = 1.6 ppm [7.4 mg/m^3]

Calculations for 4 and 8 hrs: $(32 \text{ ppm} / 20)^1 \times 1 \text{ hour} = k = 1.6 \text{ ppm-hrs}$

$C^1 \times 4 \text{ hr} = 1.6 \text{ ppm-hrs}$

4-hour AEGL-2 = C = 0.40 ppm [1.8 mg/m^3]

$C^1 \times 8 \text{ hr} = 1.6 \text{ ppm-hrs}$

8-hour AEGL-2 = C = 0.20 ppm [0.92 mg/m^3]

Derivation of AEGL-3

Key Study: Dow 1986. Rats exposed to 32, 208, 522, or 747 ppm CAC (analytical) for 1 hour and observed for 14 days had eye squinting, lacrimation, urine stains, and initially lost weight; at ≥208 ppm, rats also displayed shallow breathing, lethargy, and reddish stains near the eyes, at ≥522 ppm, rats additionally had labored breathing, gasping, and salivation, and at 747 ppm, 5/6 males and 1/6 females died (days 2,7, 8, and 13) and necropsy revealed lung pathology, nasal congestion, and enlarged adrenals.

Toxicity endpoint: The lethality threshold (522 ppm)

Time scaling: $C^n \times t = k$ (ten Berge et al. 1986); no data to derive n; scaled using n=3 for <1 hr (key study exposure) and n=1 for >1 hr to obtain protective AEGL values.

Uncertainty factors: Total Uncertainty Factor: 10
Interspecies: 3: Lethality resulting from respiratory lesions and having a steep dose-response was seen in several studies with rats and mice at CAC concentrations within a factor of 2-3
Intraspecies: 3: Steep dose-response in animal studies indicates that the threshold for lethality from direct destruction of respiratory tissue will not vary greatly among humans.
Modifying factor: None

Calculations for 10 and 30 min: $(522 \text{ ppm} / 10)^3 \times 1 \text{ hour} = k = 142237 \text{ ppm}^3\text{-hrs}$

$C^3 \times 0.167 \text{ hr} = 142237 \text{ ppm}^3\text{-hrs}$

10-minute AEGL-3 = C = 95 ppm [440 mg/m^3]

$C^3 \times 0.5 \text{ hr} = 142237 \text{ ppm}^3\text{-hrs}$

30-minute AEGL-3 = C = 66 ppm [300 mg/m^3]

Calculations for 1 hour: No scaling: 1-hour AEGL-3 = C = 52 ppm [240 mg/m^3]

Calculations for 4 and 8 hrs: $(522 \text{ ppm} / 10)^1 \times 1 \text{ hour} = k = 52.2 \text{ ppm-hrs}$

$C^1 \times 4 \text{ hr} = 52.2 \text{ ppm-hrs}$

4-hour AEGL-3 = C = 13 ppm [60 mg/m^3]

$C^1 \times 8 \text{ hr} = 52.2 \text{ ppm-hrs}$

8-hour AEGL-3 = C = 6.5 ppm [30 mg/m^3]

APPENDIX B: Derivation Summary for Chloroacetyl Chloride AEGLs

AEGL-1 VALUES				
10-minute	**30-minute**	**1-hour**	**4-hour**	**8-hour**
0.04 ppm	0.04 ppm	0.04 ppm	0.04 ppm	0.04 ppm

Key Reference: Dow (Dow Chemical Company). 1982. Dow Chemical Company Initial Submission: Chloroacetyl Chloride: A four-week inhalation toxicity study in rats, mice, and hamsters with cover sheet & letter dated 04/21/92 (sanitized). Study report written by Henck, J.W., K.D. Nitschke, G.C. Jersey et al.; issued 6/28/82. NTIS/OTS 0536493; EPA Doc. #88-920002593S. Additional study details provided by Dow Chemical Company, September 2003.

Test Species/Strain/Number: Fischer 344 rats, CD-1 mice, and Syrian Golden hamsters, 10/sex/dose/species

Exposure Route/Concentrations/Durations: 18-20 inhalation exposures to ~0.5, 1, 2.5, or 5 ppm CAC vapor 6 hrs/day, 5 days/week, for 4 weeks [actual conc. (ppm): 0.55 ± 0.61, 0.84 ± 0.51, 2.6 ± 1.4, 5.0 ± 2.3]

Effects: Rats were noted to have conjunctival redness after the initial 6-hour exposure to ≥0.5 ppm. At unspecified times, eye irritation occurred in all dose groups, mice and hamsters sneezed, and mice and rats had rough hair coats. After 18-20 exposures, various nasal and/or lung lesions occurred at all doses in rats and mice (hamsters were not examined microscopically), and led to death at 2.5 and 5 ppm starting during the second week of exposure.

Endpoint/Concentration/Rationale: NOEL for (eye) conjunctivitis

Uncertainty Factors/Rationale:
Total Uncertainty Factor: 10
Interspecies: 3: Eye conjunctivitis due to local contact irritation is not expected to vary greatly among animals
Intraspecies: 3: Eye conjunctivitis due to local contact irritation is not expected to vary greatly among humans

Modifying Factor: None

Animal to Human Dosimetric Adjustment: Not performed.

Time Scaling: None; using the same value across time was considered appropriate since mild irritant effects do not vary greatly over time

Data Adequacy: The resulting AEGL-1 of 0.04 ppm is consistent with the limited human data in which exposure to 0.023 ppm for an undefined period was "barely detectable" but 0.140 ppm was "strong"(Dow 1988b), and exposure to 0.05 ppm was associated with odor that was "objectionable" but no adverse health effects were reported (Monsanto 1987).

AEGL-2 VALUES				
10-minute	**30-minute**	**1-hour**	**4-hour**	**8-hour**
2.9 ppm	2.0 ppm	1.6 ppm	0.40 ppm	0.20 ppm

Key Reference: Dow (Dow Chemical Company). 1986. Chloroacetyl chloride: an acute vapor inhalation study with rats. Final report by C.M. Streeter, J.E. Battjes, and M.A. Zimmer, December 29, 1986, Mammalian and Environmental Toxicology Research Laboratory, Dow Chemical Company, Midland, MI.

Test Species/Strain/Number: Fischer 344 rats, 6/sex/dose

Exposure Route/Concentrations/Durations: Inhalation of 32, 208, 522, or 747 ppm for 1 hour

Effects:
32 ppm: Eye squinting and lacrimation during exposure; urine stains, initial weight loss
208 ppm: As at 32 ppm but increased incidence and/or severity; also shallow breathing; lethargy, periocular reddish stains
522 ppm: As at 208 ppm but increased incidence and/or severity; also labored breathing, gasping, salivation, reddish stains near muzzle
747 ppm: As for 522 ppm but inc incidence and/or severity, also lung edema or failure of lungs to collapse, nasal congestion, enlarged adrenals; death on days 2 (3), 7, 8 for M; day 13 for F

Endpoint/Concentration/Rationale: NOEL for impaired ability to escape due to lacrimation and eye squinting, (estimated by applying a modifying factor of 2 to the lowest concentration tested of 32 ppm)

Uncertainty Factors/Rationale:
Total Uncertainty Factor: 10
Interspecies: 3: The AEGL-2 endpoint is a direct surface contact effect that is not likely to vary in severity among animals
Intraspecies: 3: The AEGL-2 endpoint is a direct surface contact effect that is not likely to vary in severity among humans

Modifying factor: 2: Applied to the lowest concentration tested (LOEL) to estimate a NOEL for the critical endpoint

Animal to Human Dosimetric Adjustment: Not performed.

Time Scaling: $C^n \times t = k$ (ten Berge et al. 1986); no data were available to derive n; scaled using n=3 for <1 hr (key study exposure) and n=1 for >1 hr.

Data Adequacy: The animal data were sufficient to derive AEGL values. Great variability in the human response is not expected because the endpoint is a direct surface-contact effect.

1

AEGL-3 VALUES				
10-minute	**30-minute**	**1-hour**	**4-hour**	**8-hour**
95 ppm	66 ppm	52 ppm	13 ppm	6.5 ppm

Key Reference: Dow (Dow Chemical Company). 1986. Chloroacetyl chloride: an acute vapor inhalation study with rats. Final report by C.M. Streeter, J.E. Battjes, and M.A. Zimmer, December 29, 1986, Mammalian and Environmental Toxicology Research Laboratory, Dow Chemical Company, Midland, MI.

Test Species/Strain/Number: Fischer 344 rats, 6/sex/dose

Exposure Route/Concentrations/Durations: Inhalation of 32, 208, 522, or 747 ppm for 1 hour

Effects:
32 ppm: Eye squinting and lacrimation during exposure; urine stains, initial weight loss
208 ppm: As at 32 ppm but inc incidence and/or severity; also shallow breathing; lethargy, periocular reddish stains
522 ppm: As at 208 ppm but inc incidence and/or severity; also labored breathing, gasping, salivation, reddish stains near muzzle
747 ppm: As for 522 ppm but inc incidence and/or severity, also lung edema or failure of lungs to collapse, nasal congestion, enlarged adrenals; death on days 2 (3), 7, 8 for M; day 13 for F

Endpoint/Concentration/Rationale: Rat lethality threshold (522 ppm)

Uncertainty Factors/Rationale:
Total Uncertainty Factor: 10
Interspecies: 3: Lethality resulting from respiratory lesions and having a steep dose-response was seen in several studies with rats and mice, at CAC concentrations within a factor of 2-3
Intraspecies: 3: The threshold for lethality from direct destruction of respiratory tissue is not expected to vary greatly among humans, based on the steep dose-response seen in the animal studies.

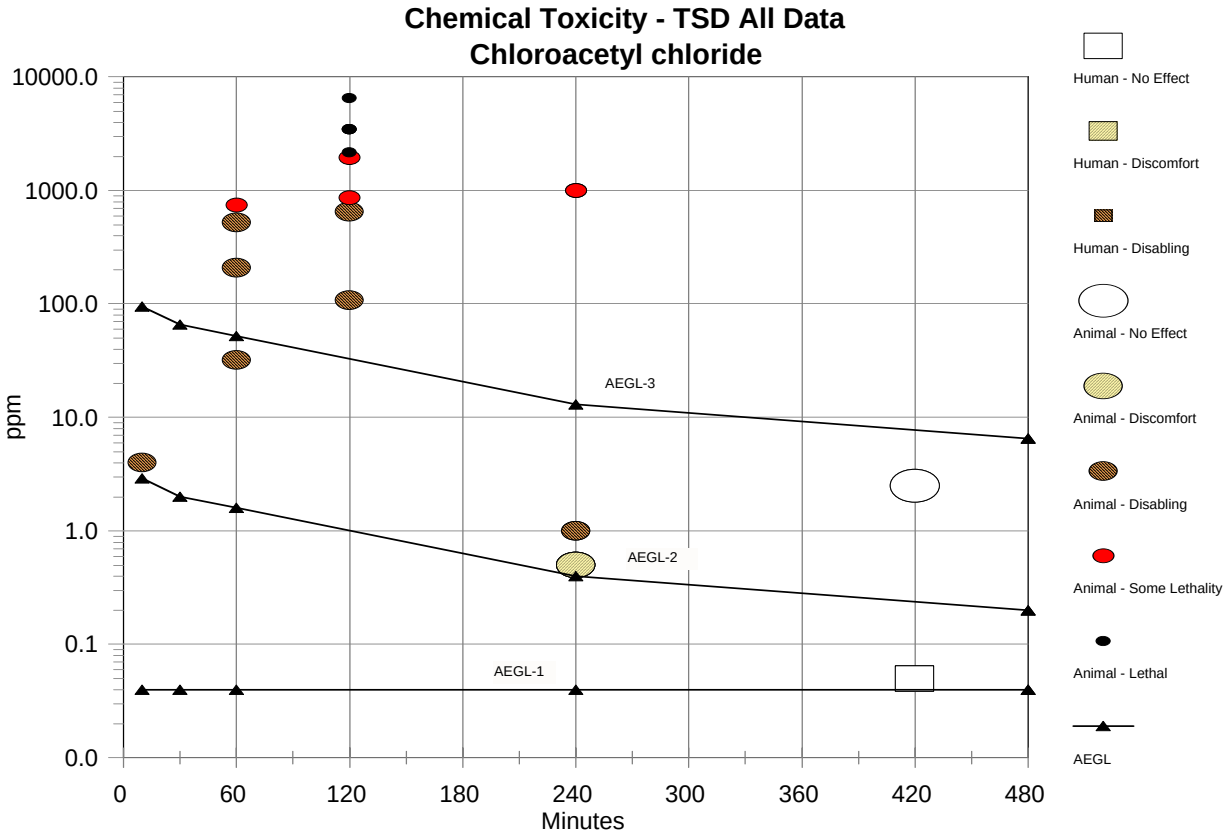
Modifying Factor: None

Animal to Human Dosimetric Adjustment: Not performed.

Time Scaling: $C^n \times t = k$ (ten Berge et al. 1986); no data were available to derive n; scaled using n=3 for <1 hr (key study exposure) and n=1 for >1 hr

Data Adequacy: The animal data were sufficient to derive AEGL values. Great variability in the human response is not expected based on the steep dose-response seen in animal studies. The AEGL-3 toxic endpoint was the lethality threshold, which was taken as the highest concentration tested that caused no deaths (522 ppm). An LC_{01} or $BMDL_{05}$ were not used for the lethality threshold because mortality occurred in only one test group.

APPENDIX C: Category Plot for Chloroacetyl Chloride



Notes:

1. For the Dow 1982 multiple-exposure study, a single 6-hour exposure to 0.5 ppm was entered as Category 1 (discomfort) for rats, mice, and hamsters. A single 6-hour exposure to 1 ppm was entered as Category 1 only for rats.

2. Concentrations are presented as analytical, if available, otherwise they are presented as nominal without adjustment for possible discrepancies between nominal and analytical concentrations.