ACUTE EXPOSURE GUIDELINE LEVELS (AEGLs)
FOR
CHLOROSULFONIC ACID (CSA)
(CAS Reg. No. 7790-94-5)

INTERIM

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/m3]) 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/m3) 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/m3) 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

Chlorosulfonic acid (CSA), also called chlorosulfuric acid, is a highly reactive and corrosive acid with a pungent odor. It is a high production volume chemical that is manufactured worldwide. CSA decomposes instantaneously and exothermically in water to form one mole of HCl and one mole of H_2SO_4, and CSA fumes react with air vapor to form dense mists of HCl and H_2SO_4 (Kapias and Griffiths 2001).

CSA fumes are severely irritating to the mucous membranes of the eyes, skin, and respiratory passages. No human CSA inhalation studies were available. Rats and mice exposed to lethal concentrations have also had toxic effects on the liver, kidneys, myocardium, spleen, thymus, and CNS.

No CSA data were available to determine AEGL-1 values. These were instead based by structure-analogy on the H_2SO_4 AEGL-1 values (NAC/AEGL 2004). This approach is considered valid because H_2SO_4 is a rapid hydrolysis product of, and is structurally related to, CSA, and the two compounds have a similar mode of toxicity (eye and respiratory irritation). The H_2SO_4 AEGL-1 values were based on extensive human data (see Appendix D). A modifying factor (MF) of 2 was applied because CSA is believed to be approximately 2-fold more toxic than H_2SO_4. This is because one molecule of CSA yields a molecule of H_2SO_4 as well as a molecule of HCl and heat, and removes a molecule of water upon hydrolysis in tissues. A consistent picture of the relative toxicities of CSA and H_2SO_4 was not evident from the animal toxicity studies.

The CSA AEGL-2 values were based by structure-analogy to H_2SO_4 AEGL-2 values, which were based on an occupational study (NAC/AEGL 2004) (see Appendix D). As for AEGL-1, the H_2SO_4 AEGL-2 values were divided by a MF of 2 because CSA is believed to be approximately 2-fold more toxic than H_2SO_4. A rat CSA study (Katz 1987) in which exposure to ~287 mg/m^3 for 1 hour was a no-effect level for neurological and respiratory toxicity was also considered for AEGL-2 derivation. This study was not used, however, because it yielded AEGL-2 values greater than those of H_2SO_4 for 10, 30, and 60 minutes, and was thus considered inconsistent with the human exposure data.

The AEGL-3 was based on a 1-hour acute toxicity rat study in which sialorrhea, unkempt fur, and wheezing (males) occurred at 379 mg/m^3 in males and 735 mg/m^3 in females (target concentration was 563 mg/m^3 for both sexes; 5/sex), whereas 1539-3096 mg/m^3 caused the death of all except one female at 1539 mg/m^3 (Katz 1987). The POD was the highest non-lethal concentration of 735 mg/m^3 as an estimate of the 60-minute lethality threshold. An interspecies UF of 10 was applied because sufficient studies were not available to determine species variability, and there were inconsistencies among the animal studies. An intraspecies UF of 3 was applied because the dose-response for animal lethality was very steep, suggesting that human variability would be small. Concentration-time scaling was performed using the ten Berge et al. (1986) relationship $C^n \times t = k$. Default values of n=3 and n=1 were used to extrapolate to durations less than, and greater than, respectively, the key study exposure duration, because no reliable data were available to derive the value of n. The 4-hour value was adopted as the 8-hour value because the scaled 8-hour AEGL-3 value was below the 8-hour AEGL-2 value, i.e., was expected to cause only reversible, non-lethal effects.

The derived AEGL values are summarized in Table 1.

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TABLE 1. Summary of AEGL Values for Chlorosulfonic Acid						
Classification	**10-min**	**30-min**	**1-h**	**4-h**	**8-h**	**Endpoint (Reference)**
AEGL−1 (Nondisabling)	0.10 mg/m^3	0.10 mg/m^3	0.10 mg/m^3	0.10 mg/m^3	0.10 mg/m^3	By analogy, AEGL-1 for H_2SO_4 (NAC/AEGL 2004) divided by a modifying factor of 2
AEGL−2 (Disabling)	4.4 mg/m^3	4.4 mg/m^3	4.4 mg/m^3	4.4 mg/m^3	4.4 mg/m^3	By analogy, AEGL-2 for H_2SO_4 (NAC/AEGL 2004) divided by a modifying factor of 2
AEGL−3 (Lethal)	45 mg/m^3	31 mg/m^3	25 mg/m^3	6.1 mg/m^3	6.1 mg/m^3	Lethality threshold in rats (Katz 1987)

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1. INTRODUCTION

Chlorosulfonic acid (CSA), also commonly called chlorosulfuric acid, is a highly reactive and corrosive acid with a pungent odor. CSA is a strong oxidant and evolves hydrogen on contact with moist metals (HSDB 2007). CSA decomposes violently and exothermically in water instantaneously to form equimolar quantities of HCl and H_2SO_4 (Kapias and Griffiths 2001). Since a molecule of water is used for every molecule of hydrolyzed CSA, it is also a dehydrating agent. CSA fumes upon contact with air, and the fumes can react with air moisture to form dense mists of HCl and H_2SO_4 (McDonald 2001). Modeling of CSA behavior upon release from containment indicates that CSA will form liquid pools (primarily on the ground) that react with accessible water and water vapor to generate HCl gas and H_2SO_4 liquid, as well as aerosols of CSA and H_2SO_4 (Kapias and Griffiths 2001).

CSA is primarily manufactured by reaction of hydrochloric acid with sulfur trioxide. It is a strong sulfating and sulfonating agent, and is used as an intermediate in the synthesis of detergents, dyes, pharmaceuticals, and sulfate surfactants (McDonald 2001; HSDB 2007). CSA is a high-production volume chemical that is manufactured worldwide at sites in the U.S., Mexico, Australia, Europe and Asia. CSA use in the U.S. and Canada was about 27,000 tons/year in 2000 (McDonald 2001).

CSA fumes are severely irritating to the mucous membranes of the eyes, skin, and respiratory passages (HSDB 2007). Rat and mouse inhalation studies have shown that, in addition to its irritating effects on the respiratory tract, CSA can cause toxic effects on the liver, kidneys, myocardium, spleen, thymus, and CNS (see Section 3.1.1., 3.1.2.).

Selected chemical and physical properties of CSA are shown in Table 2.

TABLE 2. Chemical and Physical Properties of Chlorosulfonic Acid

Parameter	Value	References
Synonyms	Sulfuric chlorohydrin, chlorosulfuric acid	O'Neil et al. 2001
Chemical formula	Cl SO_3H	McDonald 2001
Molecular weight	116.53	O'Neil et al. 2001
CAS Reg. No.	7790-94-5	McDonald 2001
Physical state	Colorless or yellowish liquid	O'Neil et al. 2001
Solubility in water	Decomposes violently and exothermically to form HCl and H_2SO_4	O'Neil et al. 2001
Vapor pressure	1.1 mm Hg at 25°C	AIHA 2002a
Vapor density (air =1)	4.02	IPCS 2001
Liquid density (water =1)	1.75 at 20°C	AIHA 2002b
Melting point	- 80°C	O'Neil et al. 2001
Boiling point	151-152°C at 755 mm Hg	O'Neil et al. 2001
Flammability limits	3.3% (lower) - 37.7% (upper)	AIHA 2002b
Conversion factors	1 ppm = 4.77 mg/m^3; 1 mg/m^3 = 0.210 ppm	AIHA 2002a

2. HUMAN TOXICITY DATA

2.1. Acute Lethality

No human acute lethality studies were located. Secondary sources indicate that CSA vapor is severely irritating to the respiratory tract, and sufficiently high air concentration may lead to bronchitis and potentially fatal lung edema (IUCLID 2000; HSDB 2007).

2.2. Nonlethal Toxicity

Human nonlethal toxicity studies with CSA were not located in the available literature. Severe irritation of the eyes and respiratory tract, coughing, and a choking sensation have been attributed to CSA vapor of unspecified concentration (IUCLID 2000; HSDB 2007).

Human non-lethal inhalation studies were available for the CSA hydrolysis products HCl and H_2SO_4, which are both eye and respiratory irritants. Human data were used to derive the AEGL-1 and AEGL-2 values for H_2SO_4 (NAC/AEGL 2004), and the AEGL-1 values for HCl (NRC 2004).

2.2.1. Odor Threshold/Odor Awareness

CSA odor has been characterized as strong and pungent (HSDB 2007), but no information was found regarding the threshold of awareness or recognition. The odor thresholds of the CSA hydrolysis products HCl and H_2SO_4 have been reported as 1.0 ppm (1.4 mg/m^3) and 1.0 mg/m^3, respectively (AIHA 2002a).

2.3. Neurotoxicity

No human studies were located that addressed CSA neurotoxicity.

2.4. Developmental/Reproductive Toxicity

No human studies were located that evaluated CSA developmental or reproductive toxicity.

2.5. Genotoxicity

No human genotoxicity studies that tested CSA were located. Workers exposed to 0.34-11.97 mg/m^3 sulfur dioxide in a sulfuric acid factory had increased incidences of cultured lymphocyte sister chromatid exchanges, micronuclei, and chromosomal aberrations (Meng and Zhang 1990a,b).

2.6. Carcinogenicity

No human studies were found that evaluated CSA carcinogenicity. IARC (1992) reviewed the body of available data on occupational exposure to mists and vapors from strong inorganic acids. IARC (1992) concluded that there was inadequate evidence for the carcinogenicity of HCl in humans (or in experimental animals), and that HCl is not classifiable as to its carcinogenicity in humans, placing it in carcinogenicity Group 3. Conversely, IARC (1992) determined that there was sufficient evidence that occupational exposure to strong-

inorganic-acid mists containing H_2SO_4 is carcinogenic, causing cancer of the larynx and lung (carcinogenicity Group 1). It is notable that the occupational studies involved exposure to other chemicals in addition to H_2SO_4.

2.7. Summary

No quantitative human CSA toxicity studies, or an odor threshold, were located. Secondary sources indicate that CSA vapor is severely irritating to the eyes and respiratory tract, and can cause coughing, bronchitis, and potentially fatal lung edema, but the CSA concentrations were not specified. Human toxicity studies for the CSA hydrolysis products HCl and H_2SO_4 were available, and had been used to determine HCl and H_2SO_4 AEGL-1 and/or AEGL-2 values.

No human studies were located that evaluated CSA neurotoxicity, developmental or reproductive toxicity, genotoxicity, or carcinogenicity. Occupational exposure to strong inorganic mists containing sulfuric acid is associated with cancer of the larynx and lung, but a direct link with CSA or its hydrolysis products has not been established.

3. ANIMAL TOXICITY DATA

3.1. Acute Lethality

3.1.1. Rats

Mamleeva and Bakhtizina (1976) exposed white rats (rat strain, number and sex not specified) by inhalation for 4 hours to CSA. How the CSA atmosphere was generated, the concentrations tested, and the study observation period were not specified. [The same report also describes the exposure of mice to CSA, but does not always differentiate which species experienced a given toxic effect.] The stainless steel exposure chamber air was noted to contain a light mist during exposure. The CSA exposure concentration was measured analytically, although the sample collection method and frequency were not stated. CSA respiratory tract irritation was determined by its effects on the frequency and manner of breathing, the absorption of dye by the lungs, and by the animals' oxygen consumption. General whole animal toxicity was evaluated by the effects on organ weight and pathology. An LC_{50} of 38.5 mg/m^3 was determined, but neither individual nor group animal toxicity or mortality data were provided, nor was the method of obtaining the LC_{50}. The animals had marked irritation of the eyes and respiratory tract, a shaky gait, clonic convulsions, and stained fur. Gross and microscopic pathology revealed enlarged lungs and liver, lung edema, severe irritation of the trachea, bronchi, and lungs, brain perivascular and pericellular edema, myocaldial hemorrhage, edema, and necrosis, hepatocyte fatty depletion, necrotic foci and duct discomplexation, and kidney nephrosis. The weight of the liver and lungs was increased and spleen weight was decreased. The threshold concentration for general acute toxicity (Lim_{ac}) was estimated as 8.1-10.4 mg/m^3, and the irritation threshold (Lim_{ir}) as 8.1 mg/m^3.

To compare CSA toxicity to that of its hydrolysis products, Mamleeva and Bakhtizina (1976) exposed rats to a mixture of H_2SO_4 and HCl at concentrations 4 to 5 times the potential levels formed at the CSA LC_{50} (133 mg/m^3 H_2SO_4 and 32 mg/m^3 HCl; 1.5:1 molar ratio). The exposure duration was not specified but may have been 4 hours since the LC_{50} experiment reported in the same article used a 4-hour exposure. Rats "easily endured" this exposure (details not provided), and the authors concluded that intact CSA was significantly more toxic than its hydrolysis products H_2SO_4 and HCl.

Groups of Crl:CD BR rats (10/sex/group) were exposed for 4 hours nose-only to dynamically generated CSA aerosol of 0, 1765, 2768, or 5864 mg/m^3 (Hagan and Fisher 1987). The 1765 and 2768 mg/m^3 groups were exposed 6 days before the 5864 mg/m^3 group. The test chamber (stainless steel and glass) was 240 L, the air flow was 150 L/minute, and CSA aerosol was generated by blowing dry compressed air over the test fluid in a nebulizer. The aerosol particle size was not determined. Test concentrations were measured hourly by sorbent tube sampling and HPLC analysis, and were lower than the nominal concentrations (0, 4100, 3800, and 10,000 mg/m^3, respectively) due to reaction of the aerosol with the chamber walls. No sex-related differences were seen in the animal responses. During exposure and the ensuing 14-day observation period, the CSA-treated animals had bradypnea, dyspnea, apnea, rales, gasping, red-stained muzzles and eyes, yellow-stained fur, mucoid feces, and ataxia or prostration. The authors state that the signs increased in incidence and severity with increasing concentration, but the incidence data were not provided. During exposure, one animal died at 1765 mg/m^3, 5 died at 2768 mg/m^3, and 5 at 5864 mg/m^3. The 14-day mortality was not proportional to the measured CSA levels, being 0/20, 8/20, 13/20, and 9/20 at 0, 1765, 2768, and 5864 mg/m^3, respectively. Body weight gains were decreased primarily in the males, but there was no dose-response, and the greatest decrease was seen at 2768 mg/m^3. Necropsy revealed no clearly treatment-related gross pathology; all of the premature decedents had various degrees of autolysis and all their internal organs were dark red.

Katz (1987) conducted two one-hour inhalation exposure experiments 3 weeks apart with ~8-week-old Crl:CD BR rats (5/sex/group). Rats were exposed dynamically in a 20 L glass bell jar to target concentrations of 1500, 2250, or 3400 mg/m^3 in the first experiment and to 70, 282, or 563 mg/m^3 in the second experiment. The CSA aerosol/vapor atmosphere was generated by passing dried compressed oil-free air over liquid CSA dropped on a heated glass bead column. The investigators noted that upon entering the exposure chamber, the CSA hydrolyzed to form HCl and H_2SO_4 mists and vapors, and aerosol droplets were clearly visible. CSA concentration was measured twice/hour by collecting the chamber air with midget impingers and analysis for chloride ion by HPLC ion chromatography. The analytical concentrations for 70-3400 mg/m^3 were, respectively: 102, 285, 379, 1777, 2638, and 3096 mg/m^3 for males, and 61, 289, 735, 1539, 2091, and 2743 mg/m^3 for females. Particle size analysis of the 563, 282, and 70 mg/m^3 atmospheres with an Anderson mini-impactor showed that >91% of the particles were respirable, i.e. (≤4.7 μm diameter) in 5 of 6 measurements (other value was 77%). Deaths occurred only at the three higher concentrations. All males and all but one female (1539 mg/m^3) died during the 14-day observation period, with no clear relationship between time to death and test concentration. Probit analysis (by study authors) estimated a combined LC_{10} of 926 mg/m^3 (630 mg/m^3 for males and 1066 mg/m^3 for females).

No clinical signs were seen at 70 or 282 mg/m^3. Body weight gains were comparable to those of the controls at 70, 282, and 563 mg/m^3. At 563 mg/m^3, rats exhibited excessive salivation, unkempt fur, and males wheezed, although these signs resolved after 24-48 hours. At ≥1500 mg/m^3, rats additionally had wheezing, gasping, lacrimation, gait disturbance during exposure, "porphyrin-like" nasal discharge, and hypothermia. Gross and microscopic changes were seen at only ≥1500 mg/m^3. Necropsy revealed lung hemorrhage, enlarged liver, small spleens, small thymuses, wet facial fur, and nasal discharge. Microscopic changes consisted of respiratory tract degeneration and inflammation, most notably tracheal erosion, hemorrhage, necrosis, and cero-cellular exudate. Rats that survived "longest" (not defined) also had squamous metaplasia, hypertrophy, and focal mineralization of the respiratory epithelium; atrophy of the spleen and thymus; hepatocyte hypertrophy and liver sinusoidal dilation. The

incidence of the tissue lesions was not provided, although the author stated that there was no clear dose-response. Death was considered due to airway obstruction caused by tissues sloughed off at the tracheal lesions.

In a pulmonary function study, male ~8-week-old Crl:CD BR rats (4/dose) were exposed for 1 hour to target concentrations of 563, 750, or 1125 mg/m^3 CSA aerosol (Gordon 1987). The test atmospheres were generated as by Katz (1987). The calculated nominal concentrations were 700, 1002, and 1266 mg/m^3. The analytical concentrations and particle size were not reported. Animals were weighed prior to exposure and on post-test day 6, and were observed for mortality for 13 days but were not necropsied. On the day before and after exposure, the rats were anesthetized and intubated and subjected to pulmonary function analysis. Each rat served as its own control. Parameters tested included lung volume and capacity, ventilation force and pressure, dynamic compliance, and airway resistance. One low-dose rat survived to day 13; the others died on days 7-11 except one mid-dose rat died just after the pulmonary testing. No effects were noted on body weight gain. Clinical signs included gasping (mid and high dose) and sialorrhea (all doses) during exposure, unkempt fur after exposure, and pallor and increased recovery time during pulmonary testing in all groups. The pulmonary function analysis revealed increases in the total lung capacity (TLC), respiratory volume (RV)/TLC, and dynamic compliance in one or more animals of all groups. The high-dose animals also had increased forced vital capacity (FVC) at 0.2 seconds, peak forced expiratory flow (PFEF), and PFEF of vital capacity/second, and the mid-dose rats had increased VC/kg body weight. The authors considered only the increases in the TLC, dynamic compliance, and the RV/TLC ratio to be toxicologically significant and indicative of lung air trapping hyperinflation, as is seen in obstructive pulmonary disease. The reliability of these lethality results is confounded by the fact that the animals were additionally stressed by the anesthesia and intubation in the pulmonary function studies.

3.1.2. Mice

Mamleeva and Bakhtizina (1976) exposed mice (strain, number, and sex not stated) by inhalation for 2 hours to CSA. The report did not specify how the CSA atmosphere was generated, the concentrations tested, or the observation period. [The same report also describes the exposure of rats to CSA, and does not always specify which species experienced a given effect.] The stainless steel exposure chamber air was noted to contain a light mist during exposure. The CSA exposure concentration was measured analytically, although the sample collection method and frequency were not stated. The authors noted that fluctuations in the chamber temperature and humidity drastically affected the CSA concentration, and it was frequently necessary to re-examine the air concentration. CSA respiratory tract irritation was determined by its effects on the frequency and manner of breathing, the absorption of dye by the lungs, and by the animals' oxygen consumption. General whole animal toxicity was evaluated by the effects on motor activity. An LC_{50} of 25 mg/m^3 was obtained, although neither individual nor group animal toxicity and mortality data were provided, nor was the method of obtaining the LC_{50}. The animals had marked irritation of the eyes and respiratory tract, a shaky gait, clonic convulsions, and stained fur. The threshold concentration for general acute toxicity (Lim_{ac}) was estimated as 8.1-10.4 mg/m^3, and the irritation threshold (Lim_{ir}) as 8.1 mg/m^3.

The CSA acute lethality animal studies are summarized in Table 3.

TABLE 3. Summary of CSA Acute Lethal Inhalation Data in Laboratory Animals

Species	Exposure time	Aerosol conc. (mg/m^3)	Effect	Reference
Rat	4 hr	1765 2768 5864	Bradypnea, apnea, rales, gasping, red-stained muzzles and eyes, mucoid feces, and ataxia or prostration; 14-day mortality was 8/20, 13/20, and 9/20. Males had decreased weight gain.	Hagan and Fisher 1987
Rat	4 hr	Unknown test concentrations	LC_{50} =38.5 mg/m^3; irritation threshold (Lim_{ir}) = 8.1 mg/m^3; had marked eye irritation, shaky gait, clonic convulsions, stained fur; lesions of trachea, bronchi, lungs, brain, myocardium, liver, bile duct, kidneys, and decreased spleen weight.	Mamleeva and Bakhtizina 1976
Rat	1 hr	70 [102-M; 61-F] [1] 282 [285-M; 289-F] [1]	No effects noted No effects noted	Katz 1987
		563 [379-M; 735-F] [1]	Drooling, unkempt fur, wheezing (males) for 24-48 hr	
		1500 [1777-M; 1539-F] [1] 2250 [2638-M; 2091-F] [1] 3400 [3096-M; 2743-F] [1]	All died but one F at 1539 mg/m^3; had drooling, unkempt fur, wheezing, gasping, lacrimation, nasal discharge, abnormal gait during exposure, hypothermia, lesions of the respiratory tract, spleen, thymus, and liver.	
Rat	1 hr	700 [2]	3/4 die by day 11; sialorrhea; altered pulmonary function	Gordon 1987
		1002 [2], 1266 [2]	4/4 (each conc.) died by day 11; effects as above plus gasping during exposure	
Mouse	2 hr	Unknown test concentrations	LC_{50} =25 mg/m^3; irritation threshold (Lim_{ir}) = 8.1 mg/m^3. Mice had marked eye and respiratory tract irritation, shaky gait, clonic convulsions, and stained fur.	Mamleeva and Bakhtizina 1976

[1] The target concentration precedes the analytical levels for males (M) and females (F), shown in brackets.
[2]The rats were anesthetized and intubated for pulmonary function analysis before and after exposure.

3.2. Nonlethal Toxicity

3.2.1. Rats

Only one study was available that tested non-lethal CSA concentrations, that of Katz (1987), which is described in Section 3.1.1. In this one-hour inhalation study, no clinical signs were seen at the target concentrations of 70 or 282 mg/m^3, whereas at 563 mg/m^3, rats exhibited excessive salivation, unkempt fur, and males wheezed. At the next higher test concentration (1500 mg/m^3) the rats had more serious signs of toxicity (gasping, lacrimation, gait disturbance), pathological changes of the lungs, liver, spleen, and thymus, and 9/10 animals died.

3.3. Neurotoxicity

CNS effects were seen in most of the CSA animal studies, and were manifested as ataxia, prostration, abnormal gait, and clonic convulsions (Hagan and Fisher 1987, Mamleeva and Bakhtizina 1976, Katz 1987). In each case, however, the effects were seen at concentrations that caused severe respiratory toxicity and mortality, and it is unclear which was the most sensitive endpoint.

3.4. Developmental/Reproductive Toxicity

No animal data were available that evaluated CSA developmental or reproductive toxicity. The limited studies with the CSA hydrolysis products HCl and H_2SO_4 provided little evidence of either being a potent developmental or reproductive toxicant. Fetal mortality was increased in female Wistar rats exposed to 302 ppm HCl for 1 hour on gestation day (GD) 9, however, one third of the dams died with lung lesions (Pavlova 1976). Conversely, maternal toxicity was only minor in mouse and rabbit dams that inhaled 5.7 or 19.3 mg/m^3 H_2SO_4 for 7 hours/day from GD 6-15 (mice; reduced liver weight) or GD 6-18 (rabbits; nasal and tracheal lesions) (Murray et al. 1979). Neither species had an increase in embryotoxicity or malformations, although the rabbit pups had a statistical increase in the incidence of a minor skeletal variation (small non-ossified areas in the skull bones).

3.5. Genotoxicity

No CSA genotoxicity studies were located. Genetoxicity data for the CSA hydrolysis products HCl and H_2SO_4 were mixed, each chemical generally yielding positive results in mammalian systems and negative results in bacterial assays (IARC 1992).

3.6. Chronic Toxicity/Carcinogenicity

CSA chronic toxicity or carcinogenicity animal studies were not available. Syrian golden hamsters exposed for their lifetime to 100 mg/m^3 H_2SO_4 mist, in some cases after 1 or 15 intratracheal exposures to 10-40 mg benzo[a]pyrene, developed moderate bronchial, laryngeal, and/or tracheal hyperplasia, but no tumors (Laskin and Sellakumar 1978). Rats exposed to 10 ppm HCl 6 hours/day, 5 days/week for their lifetime (Sellakumar et al. 1985) or over a 588-day period (Albert et al. 1982) developed tracheal and laryngeal hyperplasia but no cancerous lesions.

IARC (1992) determined that there was inadequate evidence for the carcinogenicity of HCl in experimental animals (or humans), and placed it in carcinogenicity Group 3 (not classifiable as to its carcinogenicity to humans). No H_2SO_4 animals studies were available to the IARC working group to evaluate its carcinogenic potential, but occupational data were considered sufficient to place strong-inorganic-acid mists containing sulfuric acid in carcinogenicity Group 1 (carcinogenic to humans) (IARC 1992).

3.7. Summary

Non-lethal CSA concentrations were tested in only one study (Katz 1987). In this study, no effects were seen in rats exposed to 61-289 mg/m^3 for 1 hour, whereas sialorrhea, unkempt fur, and/or wheezing resulted from exposure of male rats to 379 mg/m^3 or female rats to 735 mg/m^3 CSA, and exposure to ≥1500 mg/m^3 caused serious signs of toxicity, pathological changes in several organs, and most animals died. Mamleeva and Bakhtizina (1976) estimated an acute toxicity threshold of 8.1-10.4 mg/m^3 and an irritation threshold of 8.1 mg/m^3 for mice and rats, although the CSA concentrations tested and resulting effects were not provided.

CSA acute exposure animal studies showed a consistent toxicity profile that included eye irritation, breathing difficulties, lesions of the respiratory tract and/or changes in pulmonary function, and CNS effects. The myocardium, liver, bile duct, spleen, and/or thymus were also

adversely affected in some studies. There was considerable variation among the studies, however, in the exposure concentrations causing lethality. This is likely due at least in part to the difficulty of achieving and maintaining target CSA aerosol concentrations, which were highly dependent on the chamber humidity and temperature. CSA is very hygroscopic, indeed, several of the studies noted the formation of condensate on the chamber walls and/or formation of mists despite use of dry air.

No animal data were found that evaluated CSA developmental or reproductive toxicity, or genotoxicity. The CSA hydrolysis products HCl and H_2SO_4 do not appear to have significant developmental or reproductive toxicity, but both have some genotoxic potential. CSA multiple-exposure studies were unavailable and its carcinogenicity has not been evaluated. Long-term rat studies with 10 ppm HCl and golden hamster studies with 100 mg/m^3 H_2SO_4 mist found tracheal and laryngeal hyperplasia but no cancerous lesions. However, based on occupational data, IARC (1992) concluded that strong-inorganic-acid mists containing sulfuric acid are carcinogenic to humans (IARC 1992).

4. SPECIAL CONSIDERATIONS

4.1. Metabolism and Disposition

No studies were located that specifically addressed the metabolism or disposition of CSA. Airborne CSA can be hydrolyzed in water vapor in the air, or in the moisture of tissues to form HCl and H_2SO_4 *in situ*, releasing heat and taking up a molecule of water. Upon inhalation, the particles are initially deposited in the nose and upper respiratory tract, where they are scrubbed by the epithelial mucosa until that capacity is exceeded, allowing the particles to penetrate deeper into the respiratory tract and to the lungs. Smaller aerosol particle size, higher ventilation rate, and mouth breathing also promote deeper penetration of the aerosol particles (Jarabek et al. 1989). Ammonia produced by the mucous lining of the respiratory tract can partially neutralize acid aerosols, small particles being neutralized more efficiently than large particles (Larson et al. 1982; Utell et al. 1989). The absorption and distribution of CSA and/or its hydrolysis product is evidenced by the systemic effects seen in animal studies, in which toxicity occurred in the CNS and numerous internal organs including the lungs, liver, kidneys, thymus, spleen, and myocardium. The metabolism and disposition of acids and chloride ions from intentional dosing is believed to be similar in humans and other mammals (IARC 1992).

4.2. Mechanism of Toxicity

Studies examining the mechanism of CSA toxicity were not found. CSA is a strong corrosive acid, and hydrolyzes exothermically *in situ* upon contact with moist mucous membranes to form equimolar amounts of the strong corrosive acids HCl and H_2SO_4. It is unknown to what degree CSA and/or its hydrolysis products contribute to CSA toxicity, although each is capable of lowering tissue pH at the contact site and causing cellular destruction. Consistent with contact-site toxicity, the respiratory system was the initial target organ for CSA, HCl, and H_2SO_4 in animal inhalation studies. However, since CSA hydrolysis also produces heat and uses a molecule of water for each molecule of hydrolyzed CSA, it is likely that there are some differences in the toxicity of CSA, HCl, and H_2SO_4. Animal studies indicated that CSA is more acutely toxic than HCl or H_2SO_4, or a mixture of HCl + H_2SO_4 (see Section 4.3.).

The mechanism by which CSA is toxic to non-respiratory organs is unknown, but likely involves the disruption of the body's acid-base balance. Despite finding lesions in numerous

organs in rats exposed to CSA, Katz (1987) concluded that death was due to airway obstruction caused by sloughed-off tracheal tissues.

4.3. Structure-Activity Relationships

No quantitative toxicity data were found for the structurally related compound fluorosulfonic acid, which is also an extremely corrosive strong acid. Both human and animal toxicity data were, however, available for the CSA hydrolysis products HCl and H_2SO_4. CSA is structurally very similar to H_2SO_4, but a chlorine atom substitutes for one of the two hydroxyl groups. Because the CSA toxicity database is small and includes no human studies, it is of particular interest to examine the relative toxicity of CSA, H_2SO_4, and HCl.

A comparison of the toxicity of H_2SO_4 and HCl can be made based on their AEGL values (NAC/AEGL 2004; NRC 2004), as shown in Table 4. This indicates that H_2SO_4 is more toxic at non-lethal concentrations (i.e., AEGL-1 and AEGL-2), and for exposures of an hour or less at lethal concentrations (i.e., AEGL-3).

TABLE 4. Comparison of AEGL values for H_2SO_4 and HCl
(NAC/AEGL 2004; NRC 2004)

Level	Exposure Duration, in mg/m^3 and [ppm equivalents]				
	10 minute	30 minute	1 hour	4 hour	8 hour
AEGL-1	H_2SO_4: 0.20 [0.061] HCl: 2.7 [1.8]	H_2SO_4: 0.20 [0.061] HCl: 2.7 [1.8]	H_2SO_4: 0.20 [0.061] HCl: 2.7 [1.8]	H_2SO_4: 0.20 [0.061] HCl: 2.7 [1.8]	H_2SO_4: 0.20 [0.061] HCl: 2.7 [1.8]
AEGL-2	H_2SO_4: 8.7 [2.7] HCl: 156 [100]	H_2SO_4: 8.7 [2.7] HCl: 65 [43]	H_2SO_4: 8.7 [2.7] HCl: 33 [22]	H_2SO_4: 8.7 [2.7] HCl: 17 [11]	H_2SO_4: 8.7 [2.7] HCl: 17 [11]
AEGL-3	H_2SO_4: 260 [80] HCl: 937 [620]	H_2SO_4: 200 [61] HCl: 313 [210]	H_2SO_4: 160 [49] HCl: 155 [100]	H_2SO_4: 110 [34] HCl: 39 [26]	H_2SO_4: 93 [28] HCl: 39 [26]

The animal toxicity data do not clearly determine the relative toxicities of CSA, H_2SO_4 and HCl, as can be seen by comparing the results of rat 1-hour acute inhalation studies (Table 5). The data suggest that CSA is the most toxic of the three, as for example, 100% mortality was caused by 1777 mg/m^3 CSA (Katz 1987), >3940 mg/m^3 H_2SO_4 (Zwart 1984), and 6638 mg/m^3 HCl (Wohlslagel et al. 1976). Another comparison, however, suggests that H_2SO_4 is more toxic than CSA: 0/5 rats died from 61-735 mg/m^3 CSA (Katz 1987), whereas 1/8 rats died after exposure to 470 or 730 mg/m^3 H_2SO_4 (Runkle and Hahn 1976). The latter study also points out another characteristic of the CSA and H_2SO_4 studies, that is, their inconsistent lethality dose-response. Thus, in the Runkle and Hahn (1976) study, although 1/8 rats died from 470 or 730 mg/m^3 H_2SO_4, none died at 800 or 1090 mg/m^3 H_2SO_4. Similarly, Katz (1987) found that ≥1777 mg/m^3 CSA caused 100% mortality in rats after 1 hour, whereas Hagan and Fisher (1987) obtained mortalities of 8/20-13/20 for a 4-hour exposure to 1765-5864 mg/m^3 CSA. As discussed in Section 3.7., the variability in the concentration-response is due at least in part to the difficulty of maintaining chamber CSA concentrations due to its hydrolysis to HCl and H_2SO_4 upon contact with liquid water or water vapor.

TABLE 5. Comparison of the 1-hour mortality of HCl, H_2SO_4, and CSA in rats		
Chemical	**Exposure concentration [mg/m^3] (Mortality)**	**Reference**
HCl	M: 2701 (0/10); 3852 (2/10); 4878 (6/10); 5873 (8/10); 6638 (10/10)	Wohlslagel et al. 1976
H_2SO_4	M+F: 240 (0/8); 470 (1/8); 730 (1/8); 800 (0/8); 1090 (0/8)	Runkle and Hahn 1976
	M: 3540 (5/10); 3940 (9/10)	Zwart 1984
CSA	M: 102 (0/5); 285 (0/5); 379 (0/5); 1777 (5/5); 2638 (5/5); 3096 (5/5) F: 61 (0/5); 289 (0/5); 735 (0/5); 1539 (4/5); 2091 (5/5); 2743 (5/5)	Katz 1987

M=males; F=females

4.4. Other Relevant Information

4.4.1. Species Variability

No CSA studies were available that could be used to evaluate interspecies variability at non-lethal exposure concentrations. Only one acute lethality CSA study tested a species other than rat (Mamleeva and Bakhtizina 1976). Rats were exposed for 4 hours and mice for 2 hours to unspecified CSA concentrations, yielding LC_{50} values of 38.5 mg/m^3 for rats and 25 mg/m^3 for mice. This indicated that mice were more sensitive than rats to acute CSA toxicity. There is some uncertainty in this interpretation, however, because the LC_{50} concentrations were much lower than those found by other investigators (see Table 3). However, it is expected that similar experimental conditions were present for both species, and that the study results reflect the variability between rats and mice to CSA exposure.

The acute lethality inhalation data for H_2SO_4 did not clearly discern whether rats or mice were more sensitive, but indicated that both species were much less sensitive than guinea pigs (NAC/AEGL 2004). HCl acute lethality studies determined that mice were approximately 3-fold and 4-fold more sensitive than rats and baboons, respectively (NRC 2004).

4.4.2. Susceptible Populations

No susceptible human populations were identified.

4.4.3. Concentration-Exposure Duration Relationship

Sufficient data were not available to evaluate the concentration-exposure duration relationship for CSA inhalation toxicity. Ten Berge et al. (1986) determined that the concentration-time relationship 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, and n ranged from 1 to 3 for 90% of the chemicals examined. To obtain protective AEGL values for systemically acting compounds, as was the case for the AEGL-3, scaling across time was performed using n=3 to extrapolate to shorter exposure times and n=1 to extrapolate to longer exposure times than in the key study, to provide AEGL values that would be protective of human health (NRC 2001).

The AEGL-1 and AEGL-2 for CSA were based on the AEGL-1 and AEGL-2 values derived for H_2SO_4.

5. DATA ANALYSIS FOR AEGL-1

5.1. Summary of Human Data Relevant to AEGL-1

No relevant human CSA studies were located.

5.2. Summary of Animal Data Relevant to AEGL-1

No CSA animal studies were available with an endpoint in the scope of AEGL-1.

5.3. Derivation of AEGL-1

Because no CSA human or animal studies were available, the AEGL-1 values were instead based by structure-analogy to the H_2SO_4 AEGL-1 values (NAC/AEGL 2004). This approach is considered valid because H_2SO_4 is a rapid hydrolysis product of, and is structurally related to, CSA, and the two compounds have a similar mode of toxicity (eye and respiratory irritants). The H_2SO_4 AEGL-1 values were based on extensive human data (see Appendix D). A modifying factor (MF) of 2 was applied because CSA is believed to be approximately 2-fold more toxic than H_2SO_4. This is because one molecule of CSA yields a molecule of H_2SO_4 as well as a molecule of HCl and heat, and removes a molecule of water upon hydrolysis in tissues. A consistent picture of the relative toxicities of CSA and H_2SO_4 was not evident from the animal toxicity studies. The resulting CSA AEGL-1 values are shown in Table 6, and calculations are detailed in Appendix A.

TABLE 6. AEGL-1 Values for Chlorosulfonic Acid

10-min	30-min	1-h	4-h	8-h
0.10 mg/m^3	0.10 mg/m^3	0.10 mg/m^3	0.10 mg/m^3	0.10 mg/m^3

6. DATA ANALYSIS FOR AEGL-2

6.1. Summary of Human Data Relevant to AEGL-2

No relevant human CSA studies were located.

6.2. Summary of Animal Data Relevant to AEGL-2

Only one study tested non-lethal CSA concentrations, and was conducted by Katz (1987). In this study, rats exposed to 61-289 mg/m^3 CSA had no obvious effects; 379 mg/m^3 (males) or 735 mg/m^3 (females) caused sialorrhea, unkempt fur, and/or wheezing; and all but one rat died from 1539-3096 mg/m^3 CSA. Exposure to 287 mg/m^3 for 1 hour (mean of the analytical concentration of 285 mg/m^3 for males and 289 mg/m^3 for females) could be the POD as a no-effect level for neurological and respiratory toxicity.

6.3. Derivation of AEGL-2

The CSA AEGL-2 values were based by structure-analogy to H_2SO_4 AEGL-2 values, which were based on an occupational study (NAC/AEGL 2004) (see Appendix D). A rat CSA

study (Katz 1987) in which exposure to ~287 mg/m^3 for 1 hour was a no-effect level for neurological and respiratory toxicity was also considered for AEGL-2 derivation. This study was not used, however, because it yielded AEGL-2 values greater than those of H_2SO_4 for 10, 30, and 60 minutes, and was thus considered inconsistent with the human exposure data. [Values of 17, 12, 9.6, 2.4, and 1.2 mg/m^3 CSA were obtained for 10, 30, 60, 240, and 480 minutes, respectively, if one uses the same uncertainty factors (total of 30) and values for n (default n=1 or 3) in the ten Berge equation as are used to derive the AEGL-3 values from the Katz (1987) study; see Section 6.4.]. As was the case for AEGL-1, the H_2SO_4 AEGL-2 values (NAC/AEGL 2004) were divided by a MF of 2 because CSA is believed to be approximately 2-fold more toxic than H_2SO_4. The resulting AEGL-2 values are shown in Table 7, and the calculations are detailed in Appendix A.

TABLE 7. AEGL-2 Values for Chlorosulfonic Acid

10-min	30-min	1-h	4-h	8-h
4.4 mg/m^3	4.4 mg/m^3	4.4 mg/m^3	4.4 mg/m^3	4.4 mg/m^3

7. DATA ANALYSIS FOR AEGL-3

7.1. Summary of Human Data Relevant to AEGL-3

No relevant human studies were located for CSA.

7.2. Summary of Animal Data Relevant to AEGL-3

Three CSA animal studies were conducted in which lethality occurred, as well as respiratory and eye irritation, breathing difficulties, and CNS toxicity. These are (1) the 1-hour rat study in which no effects were seen at 61-289 mg/m^3 CSA, sialorrhea, unkempt fur, and wheezing (males) occurred at 379-735 mg/m^3, and all but one animal died after exposure to 1539-3096 mg/m^3 (Katz 1987); (2) the 4-hour rat study in which animals exposed to 1765, 2768, or 5864 mg/m^3 CSA had 14-day mortalities of 8/20, 13/20, and 9/20, respectively (Hagan and Fisher 1987); and (3) the 1-hour pulmonary function study where 700, 1002, and 1266 mg/m^3 caused 75-100% mortality and impaired pulmonary function. The Hagan and Fisher (1987) study was considered inappropriate for AEGL derivation because there was no dose-response, and the Gordon (1987) study was excluded because the rats were anesthetized and intubated for pulmonary function analysis before and after exposure, which likely made them more susceptible to pulmonary injury.

7.3. Derivation of AEGL-3

The AEGL-3 was based on a 1-hour acute toxicity rat study in which sialorrhea, unkempt fur, and wheezing (males) occurred at 379 mg/m^3 in males and 735 mg/m^3 in females (target concentration was 563 mg/m^3 for both sexes; 5/sex), whereas 1539-3096 mg/m^3 caused the death of all except one female at 1539 mg/m^3 (Katz 1987). The POD was the highest non-lethal concentration of 735 mg/m^3 in rats as an estimate of the 60-minute lethality threshold. An interspecies UF of 10 was applied because sufficient studies were not available to determine species variability, and there were inconsistencies among the animal studies. An intraspecies UF

of 3 was applied because the dose-response for animal lethality was very steep, suggesting that human variability would be small. Concentration-time scaling was performed using the ten Berge et al. (1986) relationship $C^n \times t = k$. Default values of n=3 and n=1 were used to extrapolate to durations less than, and greater than, respectively, the key study exposure duration, because no reliable data were available to derive the value of n. The 4-hour value was adopted as the 8-hour value because the scaled 8-hour AEGL-3 value was below the 8-hour AEGL-2 value, i.e., was expected to cause only reversible, non-lethal effects. The resulting AEGL-3 values are shown in Table 8, and the calculations are shown in Appendix A.

TABLE 8. AEGL-3 Values for Chlorosulfonic Acid

10-min	30-min	1-h	4-h	8-h
45 mg/m^3	31 mg/m^3	25 mg/m^3	6.1 mg/m^3	6.1 mg/m^3

8. SUMMARY OF AEGLS

8.1. AEGL Values and Toxicity Endpoints

Because no suitable human or animal CSA data were available, the CSA AEGL-1 and AEGL-2 were instead based by structure-analogy on the H_2SO_4 AEGL-1 and AEGL-2 values (NAC/AEGL 2004). H_2SO_4, like CSA, is an eye and respiratory irritant, and the H_2SO_4 AEGL-1 and AEGL-2 values were derived using human data. The AEGL-3 was derived from the highest empirical no-lethality level from a rat CSA acute lethality study (Katz 1987). The derived AEGL-1, AEGL-2, and AEGL-3 values and their relationship to one another are shown in Table 9 below. A category plot showing the animal experimental results for CSA as compared to the derived AEGL values is shown in Appendix B.

TABLE 9. Summary of AEGL Values for Chlorosulfonic Acid

Classification	Exposure Duration				
	10 minute	30 minute	1 hour	4 hour	8 hour
AEGL-1 (Nondisabling)	0.10 mg/m^3	0.10 mg/m^3	0.10 mg/m^3	0.10 mg/m^3	0.10 mg/m^3
AEGL-2 (Disabling)	4.4 mg/m^3	4.4 mg/m^3	4.4 mg/m^3	4.4 mg/m^3	4.4 mg/m^3
AEGL-3 (Lethal)	45 mg/m^3	31 mg/m^3	25 mg/m^3	6.1 mg/m^3	6.1 mg/m^3

8.2. Comparison with Other Standards and Guidelines

Standards and guidelines for workplace exposures to CSA are listed in Table 10. The ERPGs for CSA were based on protecting humans from the toxicity of its hydrolysis products HCl and H_2SO_4, and are the same as the ERPGs for H_2SO_4. The AIHA WEELs were based on the ACGIH TLV-TWA for H_2SO_4 (AIHA 2002b). The latter were adopted to protect workers from pulmonary changes observed in human studies, and impaired mucociliary clearance seen in

human and animal studies; the value was changed from 0.01 to 0.02 mg/m^3 in 2004. As of 2006, a MAK for CSA was under consideration by Germany (Deutsche Forschungsgemeinschaft 2006).

TABLE 10. Extant Standards and Guidelines for Chlorosulfonic Acid

Guideline	Exposure Duration (mg/m^3)				
	10 minute	30 minute	1 hour	4 hour	8 hour
AEGL-1	0.10 mg/m^3	0.10 mg/m^3	0.10 mg/m^3	0.10 mg/m^3	0.10 mg/m^3
AEGL-2	4.4 mg/m^3	4.4 mg/m^3	4.4 mg/m^3	4.4 mg/m^3	4.4 mg/m^3
AEGL-3	45 mg/m^3	31 mg/m^3	25 mg/m^3	6.1 mg/m^3	6.1 mg/m^3
ERPG-1 (AIHA) [a]			2 mg/m^3		
ERPG-2 (AIHA)			10 mg/m^3		
ERPG-3 (AIHA)			30 mg/m^3		
WEEL (AIHA) [b]					0.1 mg/m^3 (ceiling)
MAK (Germany) [c]					Under consideration

[a]ERPG (Emergency Response Planning Guidelines, American Industrial Hygiene Association (AIHA 2002a)
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 Level) ceiling (AIHA 2002b) is the American Industrial Hygiene Association's (AIHA) recommended ceiling limit for an airborne concentration of the chemical which should not be exceeded at any time (during a work day).

[c]MAK (Maximale Arbeitsplatzkonzentration [Maximum Workplace Concentration]) (German Research Association 2006) is defined 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. As of 2006, development of MAK values for CSA was under consideration.

8.3. Data Adequacy and Research

No human data were found for CSA, and there were no CSA animal data with an endpoint consistent with the definition of AEGL-1. One CSA study was available in which non-lethal exposure concentrations were tested, however, the AEGL-2 values it yielded were inconsistent with human studies with the CSA analog H_2SO_4. CSA animal lethality data were available, but there were inconsistencies among the study results. Thus additional data relevant for the derivation of AEGL-1, AEGL-2, and AEGL-3 are needed, that would optimally include several exposure durations to permit an estimate of the CSA concentration-exposure time relationship.

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APPENDIX A: Derivation of AEGL Values

Derivation of AEGL-1

Key Study: H_2SO_4 AEGL-1 Values (NAC/AEGL 2004). This approach is considered valid because H_2SO_4 is a rapid hydrolysis product of, and is structurally related to, CSA, and the two compounds have a similar mode of toxicity (eye and respiratory irritation). A modifying factor (MF) of 2 was applied because CSA is believed to be approximately 2-fold more toxic than H_2SO_4 (see below).

Modifying Factor: 2: CSA is believed to be approximately 2-fold more toxic than H_2SO_4, since one molecule of CSA yields a molecule of H_2SO_4 as well as a molecule of HCl and heat, and removes a molecule of water upon hydrolysis in tissues. A consistent picture of the relative toxicities of CSA and H_2SO_4 was not evident from the animal toxicity studies.

Calculations:

10-minute AEGL-1	0.20 mg/m^3 /2 = 0.10 mg/m^3
30-minute AEGL-1	0.20 mg/m^3 /2 = 0.10 mg/m^3
1-hour AEGL-1	0.20 mg/m^3 /2 = 0.10 mg/m^3
4-hour AEGL-1	0.20 mg/m^3 /2 = 0.10 mg/m^3
8-hour AEGL-1	0.20 mg/m^3 /2 = 0.10 mg/m^3

Derivation of AEGL-2

Key Study: H_2SO_4 AEGL-2 Values (NAC/AEGL 2004). This approach is considered valid because H_2SO_4 is a rapid hydrolysis product of, and is structurally related to, CSA, and the two compounds have a similar mode of toxicity (eye and respiratory irritation). A modifying factor (MF) of 2 was applied because CSA is believed to be approximately 2-fold more toxic than H_2SO_4 (see below).

Modifying Factor: 2: CSA is believed to be approximately 2-fold more toxic than H_2SO_4, since one molecule of CSA yields a molecule of H_2SO_4 as well as a molecule of HCl and heat, and removes a molecule of water upon hydrolysis in tissues. A consistent picture of the relative toxicities of CSA and H_2SO_4 was not evident from the animal toxicity studies.

Calculations:

10-minute AEGL-2	8.7 mg/m^3 /2 = 4.4 mg/m^3
30-minute AEGL-2	8.7 mg/m^3 /2 = 4.4 mg/m^3
1-hour AEGL-2	8.7 mg/m^3 /2 = 4.4 mg/m^3
4-hour AEGL-2	8.7 mg/m^3 /2 = 4.4 mg/m^3
8-hour AEGL-2	8.7 mg/m^3 /2 = 4.4 mg/m^3

Derivation of AEGL-3

Key study: Katz (1987). Rats (5/sex/group) exposed for 1 hour to 61-289 mg/m^3 CSA had no effects; sialorrhea, unkempt fur, and wheezing (males) occurred at 379-735 mg/m^3, and all but one animal died after exposure to 1539-3096 mg/m^3. The POD was a 1-hour exposure to 735 mg/m^3, which was the highest non-lethal exposure concentration, as an empirical estimate of the threshold for lethality.

Toxicity endpoint: Lethality threshold in rats

Scaling: $C^n \times t = k$ (ten Berge et al. 1986), using default values of n=3 to extrapolate to <1 hour, and n=1 to extrapolate to > 1 hour, because no reliable data were available to derive n. The 4-hour value was adopted as the 8-hour value because the scaled 8-hour AEGL-3 value was below the 8-hour AEGL-2 value, i.e., was expected to cause only reversible, non-lethal effects.

Uncertainty Factors: Total uncertainty factor: 30
Interspecies: 10: Sufficient studies were not available to determine species variability, and there were inconsistencies among the animal studies.
Intraspecies: 3: The dose-response for animal lethality was very steep, suggesting human variability is small.

Modifying Factor: None

Calculations:

10-min AEGL-3

$C^3 \times t = k = (735 \text{ mg/m}^3)^3 \times 60 \text{ min} = 2.38 \times 10^{10} \text{ mg/m}^3\text{-min}$

$C^3 \times 10 \text{ min} = 2.38 \times 10^{10} \text{ mg/m}^3\text{-min}$; $C = 1336 \text{ mg/m}^3$

$1336 \text{ mg/m}^3 / 30 =$ **45 mg/m^3**

30-min AEGL-3

$C^3 \times 30 \text{ min} = 2.38 \times 10^{10} \text{ mg/m}^3\text{-min}$; $C = 926 \text{ mg/m}^3$

$926 \text{ mg/m}^3 / 30 =$ **31 mg/m^3**

1-hour AEGL-3

$C = 735 \text{ mg/m}^3$

$735 \text{ mg/m}^3 / 30 =$ **25 mg/m^3**

4-hour AEGL-3

$C^1 \times t = k = (735 \text{ mg/m}^3)^1 \times 60 \text{ min} = 44100 \text{ mg/m}^3\text{-min}$

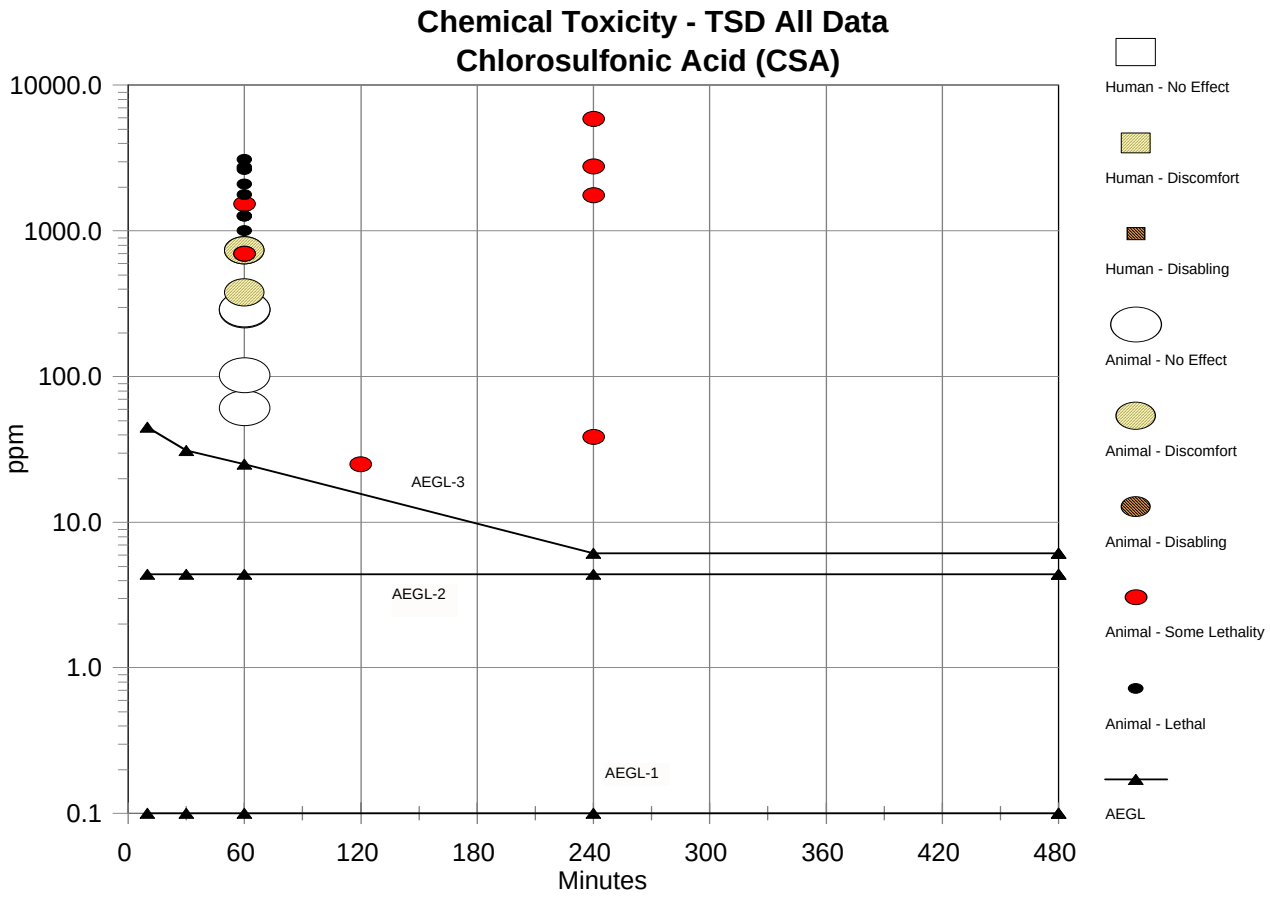
$C^1 \times 240 \text{ min} = 44100 \text{ mg/m}^3\text{-min}$; $C = 184 \text{ mg/m}^3$

$184 \text{ mg/m}^3 / 30 =$ **6.1 mg/m^3**

8-hour AEGL-3

Adopted the 4-hour value of **6.1 mg/m^3**

APPENDIX B: Category Plot for Chlorosulfonic Acid (CSA)



Note that the animal studies in which lethality occurred close to the AEGL-3 levels were considered outliers in the CSA data set and not used directly for AEGL derivation.

APPENDIX C: Derivation Summary of AEGLs for Chlorosulfonic Acid

AEGL-1 Values				
10-minute	**30-minute**	**1-hour**	**4-hour**	**8-hour**
0.10 mg/m^3	0.10 mg/m^3	0.10 mg/m^3	0.10 mg/m^3	0.10 mg/m^3

Key Reference: NAC/AEGL (National Advisory Committee/Acute Exposure Guideline levels). 2004. Acute Exposure Guideline Levels for Sulfuric Acid, Sulfurtrioxide, and Oleum. Interim Draft 1. October, 2004.

Test species/Strain/Sex/Number:

Exposure Route/Concentrations/Duration:

Effects:

Endpoint/Concentration/Rationale: AEGL-1 values for chlorosulfonic acid (CSA) were derived by analogy to the H_2SO_4 AEGL-1 values. This approach is considered valid because H_2SO_4 is a rapid hydrolysis product of, and is structurally related to, CSA, and the two compounds have a similar mode of toxicity. A modifying factor (MF) of 2 was applied because CSA is believed to be approximately 2-fold more toxic than H_2SO_4 (see below).

Uncertainty Factors/Rationale:
Interspecies:
Intraspecies:

Modifying Factor: 2: CSA is believed to be approximately 2-fold more toxic than H_2SO_4, since one molecule of CSA yields a molecule of H_2SO_4 as well as a molecule of HCl and heat, and removes a molecule of water upon hydrolysis in tissues. A consistent picture of the relative toxicities of CSA and H_2SO_4 was not evident from the animal toxicity studies.

Animal to Human Dosimetric Adjustment:

Time Scaling:

Data Adequacy: AEGL-1 values for CSA were derived by analogy to H_2SO_4 AEGL-1 values, which were based on an extensive database of human studies. Assuming that the MF of 2 adequately accounts for the differential toxicity of the two chemicals, confidence in the AEGL-1 values is very good.

AEGL-2 Values				
10-minute	**30-minute**	**1-hour**	**4-hour**	**8-hour**
4.4 mg/m^3	4.4 mg/m^3	4.4 mg/m^3	4.4 mg/m^3	4.4 mg/m^3

Key reference: NAC/AEGL (National Advisory Committee/Acute Exposure Guideline levels). 2004. Acute Exposure Guideline Levels for Sulfuric Acid, Sulfurtrioxide, and Oleum. Interim Draft 1. October, 2004.

Tested species/Strains/Number:

Exposure Route/Concentrations/Duration:

Effects:

Endpoint/Concentration/Rationale: AEGL-2 values for chlorosulfonic acid (CSA) were derived by analogy to the H_2SO_4 AEGL-2 values. This approach is considered valid because H_2SO_4 is a rapid hydrolysis product of, and is structurally related to, CSA, and the two compounds have a similar mode of toxicity. A modifying factor (MF) of 2 was applied because CSA is believed to be approximately 2-fold more toxic than H_2SO_4 (see below).

Uncertainty Factors/Rationale:
Interspecies:
Intraspecies:

Modifying Factor: 2: CSA is believed to be approximately 2-fold more toxic than H_2SO_4, since one molecule of CSA yields a molecule of H_2SO_4 as well as a molecule of HCl and heat, and removes a molecule of water upon hydrolysis in tissues. A consistent picture of the relative toxicities of CSA and H_2SO_4 was not evident from the animal toxicity studies.

Animal to Human Dosimetric Adjustment:

Time Scaling:

Data Adequacy: AEGL-2 values for CSA were derived by analogy to H_2SO_4 AEGL-2 values, which were based on a human occupational study. Assuming that the MF of 2 adequately accounts for the differential toxicity of the two chemicals, confidence in the AEGL-2 values is good.

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AEGL-3 Values				
10-minute	**30-minute**	**1-hour**	**4-hour**	**8-hour**
45 mg/m^3	31 mg/m^3	25 mg/m^3	6.1 mg/m^3	6.1 mg/m^3
Key reference: Katz, G.V. 1987. Acute inhalation toxicity and one-hour LC_{10} value of chlorosulfonic acid in the rat. Eastman Kodak Company Health and Environment Laboratories, Rochester, NY. Accession no. 900669, Study no. 86-0128-3.				
Tested species/Strains/Number: Crl:CD BR rats, 5/group/sex				
Exposure Route/Concentrations/Duration: Inhalation for 60 minutes of 102, 285, 379, 1777, 2638, or 3096 mg/m^3 for males, and 61, 289, 735, 1539, 2091, or 2743 mg/m^3 for females				
Effects: 61 - 289 mg/m^3: No effects noted 379 mg/m^3 (M); 735 mg/m^3 (F): Sialorrhea, unkempt fur, wheezing (males) for 24-48 hr 1539 - 3096 mg/m^3: All died but one F at 1539 mg/m^3; effects as above plus gasping, lacrimation, nasal discharge, abnormal gait during exposure, hypothermia, lesions of the respiratory tract, spleen, thymus, and liver.				
Endpoint/Concentration/Rationale: The highest non-lethal exposure concentration of 735 mg/m^3 for female rats was used as an estimate of the 60-minute lethality threshold.				
Uncertainty Factors/Rationale: Total uncertainty factor: 30 Interspecies: 10: Sufficient studies were not available to determine species variability, and there were inconsistencies among the animal studies. Intraspecies: 3: The dose-response for animal lethality was very steep, suggesting human variability is small.				
Modifying factor: None				
Animal to Human Dosimetric Adjustment: Not applied				
Time Scaling: $C^n \times t = k$ (ten Berge et al. 1986), using default values n=3 and n=1 to extrapolate to <1 hour and >1 hour, respectively, because no reliable data were available to derive n.				
Data Adequacy: The chlorosulfonic data were sparse and somewhat inconsistent, prompting use of an interspecies UF of 10. The data did indicate that the lethality dose-response was very steep, thus the intraspecies UF of 3 was considered adequate to provide protective values.				

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APPENDIX D: Derivation Summary of AEGL-1 and AEGL-2 for H_2SO_4

ACUTE EXPOSURE GUIDELINE LEVELS FOR SULFURIC ACID AND SULFURTRIOXIDE (CAS Reg. No. 7664-93-9, 7446-11-9, 8014-95-7) DERIVATION SUMMARY

AEGL-1 VALUES for H_2SO_4 [Adopted from NAC/AEGL (2004)]				
10-minute	**30-minute**	**1-hour**	**4-hour**	**8-hour**
0.20 mg/m^3	0.20 mg/m^3	0.20 mg/m^3	0.20 mg/m^3	0.20 mg/m^3
Key Reference: Various studies				
Test Species/Strain/Number: Humans				
Exposure Route/Concentrations/Durations: Inhalation of 0.01-39.4 mg/m^3 for up to 390 minutes				
Effects: Respiratory irritation above 0.2 mg/m^3				
Endpoint/Concentration/Rationale: Respiratory irritation // 0.2 mg/m^3 // all human data (more than 600 volunteers tested for irritation) of healthy and asthmatic subjects were combined and showed that some respiratory irritation started at levels above 0.2 mg/m^3.				
Uncertainty Factors/Rationale: Total uncertainty factor: 1 Interspecies: Not applicable Intraspecies: 1: There was a very large database of controlled human experiments that included exercising asthmatics				
Modifying Factor: None				
Animal to Human Dosimetric Adjustment: Not applied.				
Time Scaling: None				
Data Adequacy: Very good				

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AEGL-2 VALUES for H_2SO_4 [Adopted from NAC/AEGL (2004)]				
10-minute	**30-minute**	**1-hour**	**4-hour**	**8-hour**
8.7 mg/m^3	8.7 mg/m^3	8.7 mg/m^3	8.7 mg/m^3	8.7 mg/m^3
Key Reference: El-Sadik, Y.M., H.A. Osman, and R.M. El-Gazzar. 1972. Exposure to sulfuric acid in manufacture of storage batteries. JOM 14: 224-226.				
Test Species/Strain/Number: Human workers				
Exposure Route/Concentrations/Durations: Inhalation of 26-35 mg/m^3 for 8-h work shifts for a long period				
Effects: Typical long term effects like tooth erosion. No acute effects relevant to AEGL-2				
Endpoint/Concentration/Rationale: Absence of acute severe or disabling effects at 26 mg/m^3. Human data were used because the human database was large (n >1000) and animal to human extrapolation was difficult due to complex factors of deposition.				
Uncertainty Factors/Rationale: Total uncertainty factor: 3 Interspecies: Not applicable Intraspecies: 3: To account for human variation in susceptibility				
Modifying Factor: 1				
Animal to Human Dosimetric Adjustment: Not applied.				
Time Scaling: None				
Data Adequacy: Quantity very good, but usefulness for AEGL-2 was poor.				

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