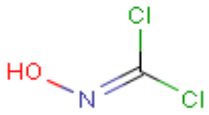
ACUTE EXPOSURE GUIDELINE LEVELS (AEGLs)

INTERIM

PHOSGENE OXIME (CAS Reg. No. 1794-86-1)



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

Phosgene oxime (CX) is an urticant or nettle agent causing instant intolerable pain, erythema, wheals and urticaria. It is very corrosive, capable of causing extensive tissue damage. Phosgene oxime was first produced by the Germans in 1929 as a possible warfare agent. The mechanism of action is not fully understood but the lesions produced in the skin are similar to those caused by a strong acid. Phosgene oxime will penetrate ordinary clothing and surgical gear.

Data regarding inhalation exposure of humans to phosgene oxime are limited to a controlled study with informed volunteers exposed for 1 minute (3 mg/m^3) or 10 minutes (1 mg/m^3); the former resulting in unpleasant irritation of the nose, eyes and skin during exposure, and the latter resulting in immediate detection of compound but no notable effects (Malatesta et al., 1983).

Inhalation toxicity data in animals are also limited. Results of experiments in dogs showed high mortality rates following 30-minute exposures to phosgene oxime concentrations of 1500-3000 mg/m^3. These studies also reported a latency period of up to three days between cessation of exposure and death. Exposure of mice, rabbits and guinea pigs for 30 minutes to 100-500 mg phosgene oxime/m^3 resulted in agitation, respiratory difficulty, and extreme lacrimation but no lethality. All of these reports lacked detail and provided no long-term follow-up, gross pathology, or histopathology findings.

No information is available regarding metabolism and disposition, mechanism of action, reproductive/developmental toxicity, mutagenicity or carcinogenicity of phosgene oxime.

AEGL-1 values for phosgene oxime were based upon awareness of the chemical as determined by ocular, nasal and dermal sensations by volunteers exposed for 10 minutes to 1 mg/m^3 (Malatesta et al., 1983). This sensory perception was not considered to be disabling. The use of data obtained from exposures of informed human volunteers eliminates the animal-to-human extrapolation concerns allowing an interspecies uncertainty factor of 1. Because the initial effects of phosgene oxime appear to be the result of direct-contact with exposed tissue (eyes, nasal mucosae, skin), an uncertainty factor of 3 was considered sufficient to account for possible individual variability. Metabolism and disposition processes would not be critical in such immediate responses. Rigorous empirical data regarding exposure concentration-duration relationship are not available for phosgene oxime, and more severe effects appear to occur with increasing concentration. Therefore, time scaling where $n = 1$ in the relationship $C^n \times t = k$ was applied to obtain AEGL values for time points greater that 10 minutes. A modifying factor of 2 was applied in derivation of the AEGL-1 values to account for limited information on the inhalation toxicity of phosgene oxime as well as the lack of methodologic detail in the Malatesta et al. (1983) report.

AEGL-2 values were based upon the same point-of-departure (POD) used for deriving AEGL-1 values; irritation (ocular, dermal, nasal) in volunteers exposed to phosgene oxime at a concentration of 1 mg/m^3 for 10 minute (Malatesta et al., 1983). No uncertainty factor for sensitive individuals was applied with the implication that the exposure may result in effects

approaching AEGL-2 severity for these individuals. This approach was considered more defensible than utilizing notable irritation reported by Malatesta et al. (1983) for volunteers exposed to 3 mg/m^3 for only 1 minute. Data from volunteers precluded the need for an interspecies uncertainty factor greater than 1. As for AEGL-1 derivation, a modifying factor of 2 was applied for overall data deficiencies as well as study deficiencies. Time scaling was applied as described for AEGL-1; $C^n \times t = k$, where n=1.

Lethality data for phosgene oxime were limited to animal studies reporting 100% lethality and were inappropriate for estimating a lethality threshold and derivation of AEGL-3 values. In lieu of lethality data, the highest nonlethal exposure (500 mg/m^3 for 30 minutes) reported by Malatesta et al. (1983) for mice, guinea pigs and rabbits was considered the POD for AEGL-3 derivation. Malatesta et al. (1983) observed agitation, respiratory difficulty, and intense lacrimation in these animals during the 30-minute exposure to phosgene oxime at concentrations of 100-500 mg/m^3. Total uncertainty factor application was 10. The uncertainty factor for interspecies extrapolation was limited to 3 because all of the species tested by Malatesta et al. (1983) exhibited a similar response. The uncertainty factor of 3 for individual variability was considered sufficient for direct-contact damage attributed to the actions of the parent molecule. A modifying factor of 2 was applied for data deficiencies (NRC, 2001).
In the absence of an empirically derived exponent (n), temporal scaling from the 30-minute experimental duration to AEGL-specific durations was performed using n = 3 when extrapolating to shorter time points and n = 1 when extrapolating to longer time points using the $C^n \times t = k$ equation (NRC, 2001).

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

S- 1. AEGL Values for phosgene oxime expressed as mg/m^3 [ppm]

Classification	10-min	30-min	1-h	4-h	8-h	Endpoint (Reference)
AEGL-1 (Nondisabling)	0.17 [0.036]	0.056 [0.012]	0.028 [0.0059]	0.0069 [0.0014]	0.0035 [0.00074]	Awareness (ocular, nasal, dermal sensation) by human volunteers; 1 mg/m^3 for 10 min.; UF=1 x 3; MF=2; n=1 (Malatesta et al., 1983)
AEGL-2 (Disabling)	0.50 [0.011]	0.17 [0.036]	0.083 [0.017]	0.021 [0.0044]	0.010 [0.0021]	Awareness (ocular, nasal, dermal sensation) by human volunteers; 1 mg/m^3 for 10 min.; UF=1 x 1; MF=2; n=1 (Malatesta et al., 1983)
AEGL-3 (Lethality)	36 [7.6]	25 [5.3]	13 [2.7]	3.1 [0.65]	1.6 [0.34]	Highest nonlethal exposure in animals (500 mg/m^3 for 30 min.; UF= 3 x 3; MF=2; n=1 or 3 (Malatesta et al., 1983)

References

1 Malatesta, P., B. Bianchi and C. Malatesta. 1983. Contributo allo studio delle sostanze orticanti: Nota 1.
2 Boll. Chim. Farm 122: 96-103. (Translated from Italian)

1. INTRODUCTION

Phosgene oxime (CX) is an urticant or nettle agent causing instant intolerable pain, erythema, wheals and urticaria (USACHPPM, 1996). Due to its corrosive properties, damage to tissue is extensive. Phosgene oxime was first produced by the Germans in 1929 as a possible warfare agent. The precise mechanism of action is not fully understood but the lesions produced in the skin are similar to those made by a strong acid. Phosgene oxime penetrates ordinary clothing and surgical gear. The physical/chemical properties of phosgene oxime are summarized in Table 1.

TABLE 1. Chemical and Physical Data for Phosgene Oxime

Parameter	Value	Reference
Synonyms	CX; dichloroformoxime	Sidell et al., 1997
Chemical formula	$CHCl_2NOH$	Sidell et al., 1997
Molecular weight	113.9	USACHPPM, 1996
CAS Registry No.	1794-86-1	
Physical state	Colorless solid; yellowish-brown in liquid form Solid form can sublime	Sidell et al., 1997
Solubility in water	70% in water and very soluble in most organic solvents	Sidell et al., 1997
Vapor pressure	11.2 mm Hg at 25°C (solid) 13 mm Hg at 40°C (liquid)	Sidell et al., 1997
Density	<3.9	Sidell et al., 1997
Boiling point/Freezing point	53-54 °C/35- 40 °C	USACHPPM, 1996
Conversion factors in air	1 ppm = 4.66 mg/m^3 1 mg/m^3 = 0.21 ppm	

2. HUMAN TOXICITY DATA

2.1. Acute Lethality

An estimated LCt_{50} of 3200 mg•min/m^3 (based upon a 10-minute exposure) for phosgene oxime vapor has been reported by the U.S. Army (2005).

2.2 Nonlethal Toxicity

Phosgene oxime has been described as having a disagreeable, intensely irritating odor (Sidell et al., 1997). The U.S. Armed Forces (U.S. Army, 2005) report a provisional odor detection ECt_{50} of 1 mg•min/m^3 (10 minutes). A provisional inhalation exposure value of 3 mg•min/m^3 for 1 minute was considered an incapacitating/intolerable exposure (U.S. Army, 2005).

Malatesta et al. (1983) conducted a study in which six informed adults, including the investigators, were exposed to phosgene oxime. The exposure chamber was described as a hermetically sealed room (with precisely calculated capacity) that was equipped with a fan to enhance homogeneity of the test atmosphere. Phosgene oxime was introduced by high-pressure (200 atm) nebulization using gas cylinders and stainless steel cylinders. Methods for determination of exposure concentrations were not specified. A “threshold of physiologic

sensitivity" of 1 mg/m^3 (0.21 ppm) was reported which was also the minimal concentration achieved in the closed environment over a 10-minute period. The physiological response apparently referred to awareness of the chemical by ocular sensitivity, taste, and odor. The author also reported a "threshold of pathologic sensitivity" of ~3 mg/m^3 (0.63 ppm). This value was defined as the minimal concentration causing an unpleasant or irritating sensation on the conjunctiva, nose (assumed to refer to nasal passage surfaces), or intact skin after one minute of exposure.

2.3. Developmental/Reproductive Effects

Data on potential developmental/reproductive toxicity of phosgene oxime in humans were not available.

2.4. Genotoxicity

No information regarding potential genotoxicity of phosgene oxime in humans was available.

2.5. Carcinogenicity

No information regarding the carcinogenic potential of phosgene oxime in humans was available.

2.6. Summary

No information regarding inhalation toxicity of phosgene oxime in humans was available.

3. ANIMAL TOXICITY DATA

3.1. Acute Lethality

3.1.1 Dogs

In a Bulgarian study, dogs (breed, number, and sex not provided) were exposed to 1.5-3 mg phosgene oxime/L air (1500-3000 mg/m^3) for 30 minutes (Balev and Andreev, 1957). Cage-side observations included: general behavior, weight, body temperature, blood (no further details), pulse (rhythm, frequency and "fullness"), respiration (frequency, rhythm and "deepness"), and urination. Assessments were performed at pre-exposure, every 10-15 minutes during the 3-4 hours following exposure, and once daily until the animals died. Dogs in the study held their breath upon entering the chamber after which respiration became rapid and shallow. Animals appeared distressed and exhibited frequent movement. Increased lacrimation, salivation and coughing were observed. The oral mucosae and the skin turned red and, later during the exposure, became violet. Upon removal from the chamber, the dogs remained agitated and continuously rubbed their eyes. At a later (unspecified) time, the dogs became calmer, exhibited more normal coloration of the oral mucosae, and resumed normal breathing for 30 minutes to 24 hours (rarely), after which their condition deteriorated. This second phase was characterized by increased pulse, increased respiration, foaming of the mouth, cyanosis, and death 2-3 days post-exposure. Based upon these findings, the investigators defined three main

stages of phosgene oxime toxicity: reflective, latent and manifest. These same stages were observed after phosgene oxime was administered intravenously at 10 mg/kg bw.

Two dogs/treatment group (breed, age, and gender not specified) were exposed to 1.5-2.0 mg phosgene oxime/L of air for 30 minutes in four treatment groups (Tschanatschev and Dronzin, 1957). In each of the four groups, one dog was administered a pre-exposure treatment to assess the effects on phosgene oxime-induced toxicity, while an untreated dog was exposed to phosgene oxime (designated as "control" in the study report). The treatment protocols included using a combination of Novacain neck blocks, calcium, glucose, Vitamin K and oxygen. Animals were placed in a dynamic flow chamber. No further detail was provided. Prior to and during the exposure, the dogs were monitored for body temperature, pulse, respiratory rate/pattern, blood chemistry and general behavior. Once exposures started, all dogs demonstrated anxiety, lacrimation, salivation, moving or shaking the head, coughing and increased respiration. Out of all four groups, only 1 of 8 dogs survived. The dog was treated with a vagosympathetic neck block using novacaine, a 2% sodium bicarbonate solution rinse in the eyes, oxygen, Cardiazol/Lobelin, calcium chloratum, Vitamin K, glucose supplementation and a tannic acid enema after exposure. The "control dog" exposed in this scenario died 10 hours post-exposure. The study demonstrated that aggressive supportive care post-exposure to phosgene oxime, possibly in combination with the pre-exposure treatment, could prevent mortality at this concentration.

3.2. Nonlethal Toxicity

3.2.1. Mice, Guinea Pigs, Rabbits

In a study by Malatesta et al. (1983), mice, guinea pigs and rabbits (number of animals, species and gender were not provided) were exposed by inhalation to phosgene oxime at concentrations of 100 to 500 mg/m^3 (only the range was provided). The experiments were conducted with an aqueous solution of phosgene oxime which was nebulized at 200 atm. using gas cylinders and stainless steel sprayers. The experiments were carried out in a tightly closed room with a precisely calculated capacity. Homogeneity of the test atmosphere was attempted using fans, although actual concentration and homogeneity of the vapor within the chamber were not confirmed analytically. No further details were provided. No deaths occurred at any concentration. Agitation, respiratory difficulty, and intense lacrimation during exposure were reported. No signs of phosgene oxime toxicity were observed in any animals at 3 days following exposure.

3.3 Summary of Toxicity in Animals

The limited inhalation toxicity data for phosgene oxime in animals is summarized in Table 2.

TABLE 2. Summary of inhalation toxicity of phosgene oxime in animals

Concentration	Exposure Duration	Species	Effect	Reference
100-500 mg/m^3	30 min.	Mice, guinea pigs, rabbits	All concentrations: no deaths; lacrimation, agitation and respiratory difficulty resolved by day 3 post-exposure	Malatesta et al., 1983
1.5- 2.0 mg/L (1,500-2,000 mg/m^3)	30 min.	Dogs (n =8)	7 of 8 dogs died; survivor received intensive support therapy	Tschanatschev and Dronzin, 1957
1.5-3 mg/L (1,500-3,000 mg/m^3)	30 min.	Dogs	100% lethality	Balev and Andreev, 1957

3.4. Developmental/Reproductive Effects

No information is available in the open literature regarding potential developmental and reproductive toxicity of phosgene oxime following inhalation exposure.

3.5. Genotoxicity

Information regarding the potential genotoxicity of phosgene oxime following inhalation exposure is not available.

3.6. Carcinogenicity

Information regarding the potential carcinogenicity of phosgene oxime following inhalation exposure is not available.

4. SPECIAL CONSIDERATIONS

4.1. Metabolism and Disposition

There are no data regarding the metabolism and disposition of phosgene oxime.

4.2. Mechanism of Toxicity

The mechanism of phosgene oxime toxicity is unknown. Damage is often instantaneous and may be the result of the necrotizing effects of the chlorine, direct effect of the oxime, or associated with the carbonyl group (Sidell et al., 1997). The tissue damage is very similar to that caused by a concentrated mineral acid. Within 5-30 minutes of exposure, edema develops at the initial site of contact and the tissues become necrotic. Over the course of 24 hours, the edema regresses and the blanched area becomes pigmented with an eschar forming over the next 7 days. In some cases, healing may require more than 6 months. Ocular exposure results in pain, conjunctivitis, and keratitis. Phosgene oxime appears to affect the first capillary bed encountered. With the exception of supportive care, there is no antidote or recommended therapeutic regimen once exposure has occurred.

4.3. Structure-Activity Relationships

There are no data with which to assess structure-activity relationships with respect to development of AEGL values. There is no evidence that phosgene is involved in the toxicity of phosgene oxime.

4.4. Other Relevant Information

4.4.1. Species Variability

Because the most significant and immediate effects of acute exposure to phosgene oxime are the result of direct-contact with ocular and respiratory tract tissue, variability across species is expected to be limited. These tissues represent the most sensitive targets for phosgene oxime vapor exposure.

4.4.2. Susceptible Populations

Phosgene oxime toxicity occurs after direct contact with the skin, eyes or respiratory tract, which would not vary between healthy individuals. However, those with compromised respiratory function such as asthma or COPD experience more severe responses to phosgene oxime exposure than otherwise healthy people. As the vapor is heavier than air, phosgene oxime can accumulate in low-lying areas and enclosed spaces.

4.4.3. Concurrent Exposure Issues

Concurrent exposure to other irritant chemicals affecting the eyes or respiratory tract may be of concern regarding exposure to phosgene oxime. No data are available with which to quantify such exposure with respect to development of AEGL values for phosgene oxime.

5. DATA ANALYSIS FOR AEGL-1

5.1. Human Data Relevant to AEGL-1

Data regarding AEGL-1 tier effects in humans following vapor exposure to phosgene oxime are limited.

Malatesta et al. (1983) conducted a study in which six informed volunteers, including the investigator, were exposed to phosgene oxime. A concentration of 1 mg/m^3 (0.21 ppm) was considered the “threshold of physiologic sensitivity”; this was also the minimal concentration achieved in the closed environment over a 10-minute period. Higher concentrations resulted in the identification/characterization of a “threshold of pathologic sensitivity” of ~3 mg/m^3 (0.63 ppm). This was defined as the minimal concentration causing an unpleasant or irritating sensation on the conjunctiva, nose, or skin after one minute of exposure.

5.2. Animal Data Relevant to AEGL-1

The responses of mice, guinea pigs, and rabbits described by Malatesta et al. (1983) included agitation, respiratory difficulty, and intense lacrimation, all of which are of greater severity than that consistent with the AEGL-1 definition.

5.3. Derivation of AEGL-1 Values

The most appropriate data for derivation of AEGL-1 values for phosgene oxime are the responses of the human volunteers exposed for 10 minutes to phosgene oxime at a concentration of 1 mg/m^3 (Malatesta et al., 1983). The physiological responses (awareness based upon ocular, nasal and dermal responses) over a 10-minute exposure to 1 mg/m^3 were considered an appropriate point-of-departure (POD) and the critical endpoint for AEGL-1 development. Although deficient in details regarding the analysis of the test atmosphere these findings provide the only information regarding exposure-response data for AEGL-1 tier effects following acute inhalation exposure to phosgene oxime. Further, the information comes from humans, thereby eliminating the need for animal-to-human extrapolation. Because the initial effects of phosgene oxime result from direct-contact with exposed tissues (eyes, nasal mucosae, skin), an uncertainty factor of 3 to account for possible individual variability is appropriate. Metabolism and disposition processes would not be critical in such responses.

Because rigorous empirical data regarding exposure concentration-duration relationship were not available for phosgene oxime, and because more severe effects appear to occur with increasing concentration, time scaling (where n =1 in the relationship $C^n \times t = k$) was applied to obtain AEGL values for time points greater than 10 minutes (NRC, 2001). A modifying factor of 2 has also been applied in the derivation of the AEGL-1 values to account for limited information on the inhalation toxicity of phosgene oxime as well as the recognized deficiencies in the Malatesta et al. (1983) report. The AEGL-1 values for phosgene oxime are presented in Table 3 and the derivation summarized in Appendices A and C.

TABLE 3. AEGL-1 values for phosgene oxime

Classification	10-min	30-min	1-h	4-h	8-h
AEGL-1	0.17 mg/m^3 0.036 ppm	0.056 mg/m^3 0.012 ppm	0.028 mg/m^3 0.0059 ppm	0.0069 mg/m^3 0.0014 ppm	0.0035 mg/m^3 0.00074 ppm

6. DATA ANALYSIS FOR AEGL-2

6.1. Human Data Relevant to AEGL-2

In a study using six informed volunteers, Malatesta et al. (1983) reported that a 1-minute exposure to phosgene oxime at 3 mg/m^3 resulted in unpleasant or irritating sensations in the eyes (conjunctiva), nose (assumedly nasal epithelium), and skin (termed threshold of pathologic sensitivity by the investigators). The U.S. Army (2005) reported a provisional inhalation exposure value of 3 mg•min/m^3 (derived based upon 1-minute exposure duration) which was considered incapacitating/intolerable, but the U.S. Army assessment appears to have been based upon the Malatesta et al. (1983) study.

6.2. Animal Data Relevant to AEGL-2

Mice guinea pigs and rabbits exposed to phosgene oxime at concentrations of 100 to 500 mg/m^3 (21 to 105 ppm) for 30 minutes displayed agitation, respiratory difficulty, and intense lacrimation during exposure (Malatesta et al., 1983). Although these changes occurred during

exposure and resolved within 3 days following cessation of exposure, no gross pathology or histopathology findings were reported.

6.3. Derivation of AEGL-2 Values

AEGL-2 values were based upon the same point-of-departure (POD) used for deriving AEGL-1 values; irritation (ocular, dermal, nasal) in volunteers exposed to phosgene oxime at a concentration of 1 mg/m^3 for 10 minutes (Malatesta et al., 1983). No uncertainty factor for sensitive individuals was applied with the implication that the exposure may result in effects approaching AEGL-2 severity for these individuals. This approach was considered more defensible than utilizing notable irritation reported by Malatesta et al. (1983) for volunteers exposed to 3 mg/m^3 for only 1 minute. Data from human volunteers precluded the need for an interspecies uncertainty factor greater than 1. As for AEGL-1 derivation, a modifying factor of 2 was applied for overall data deficiencies as well as study deficiencies. Time scaling was applied as described for AEGL-1; $C^n \times t = k$, where n=1.

The AEGL-2 values for phosgene oxime are presented in Table 4 and the derivation summarized in Appendices A and C.

TABLE 4. AEGL-2 values for phosgene oxime

Classification	10-min	30-min	1-h	4-h	8-h
AEGL-2	0.50 mg/m^3 0.011 ppm	0.17 mg/m^3 0.036 ppm	0.083 mg/m^3 0.017 ppm	0.021 mg/m^3 0.0044 ppm	0.010 mg/m^3 0.0021 ppm

7. DATA ANALYSIS FOR AEGL-3

7.1. Human Data Relevant to AEGL-3

No human data were available for derivation of AEGL-3 values for phosgene oxime.

7.2. Animal Data Relevant to AEGL-3

Animal lethality data were limited to two studies in dogs (Balev and Andreev, 1957; Tschanatschev and Dronzin, 1957) that used very high exposure concentrations (1500-300 mg/m^3) for exposure durations of 30 minutes. These exposures caused death. The study reports provided no data with which to empirically determine a lethality threshold

7.3. Derivation of AEGL-3 Values

Lethality data for phosgene oxime were limited to animal studies reporting 100% lethality. In lieu of lethality data, the highest nonlethal exposure (500 mg/m^3 for 30 minutes) reported by Malatesta et al. (1983) for mice, guinea pigs and rabbits was considered the POD for AEGL-3 derivation. Malatesta et al. (1983) observed agitation, respiratory difficulty, and intense lacrimation in these animals during the 30-minute exposure to phosgene oxime at concentrations of 100-500 mg/m^3. In the absence of an empirically derived exponent (n), temporal scaling from the 30-minute experimental duration to AEGL-specific durations was performed using n = 3

when extrapolating to shorter time points and $n = 1$ when extrapolating to longer time points using the $C^n \times t = k$ equation (NRC, 2001). Total uncertainty factor application was 10. The uncertainty factor for interspecies extrapolation was limited to 3 because all of the species tested by Malatesta et al. (1983) exhibited a similar response. The uncertainty factor of 3 for individual variability was considered sufficient for direct-contact damage attributed to the actions of the parent molecule. A modifying factor of 2 was applied for data deficiencies (NRC, 2001).

The AEGL-3 values for phosgene oxime are presented in Table 5 and the derivation summarized in Appendices A and C.

TABLE 5. AEGL-3 values for phosgene oxime

Classification	10-min	30-min	1-h	4-h	8-h
AEGL-3	36 mg/m^3 7.6 ppm	25 mg/m^3 5.3 ppm	13 mg/m^3 2.7 ppm	3.1 mg/m^3 0.65 ppm	1.6 mg/m^3 0.34 ppm

8. SUMMARY OF AEGLs

8.1. AEGL Values and Toxicity Endpoints

Information regarding the toxicity of phosgene oxime following inhalation exposure is limited. A single study using informed volunteers provided data for very short exposure durations. These data were sufficient for deriving AEGL-1 and AEGL-2 values based upon the potent irritant effects of phosgene oxime. No data were available for empirical determination of a lethality threshold. AEGL-3 values were developed based upon the highest nonlethal concentration in several laboratory species. The AEGL values for phosgene oxime are summarized in Table 6.

TABLE 6. AEGL values for phosgene oxime expressed as mg/m^3 [ppm]

Classification	10-min	30-min	1-h	4-h	8-h
AEGL-1 (Nondisabling)	0.17 [0.036]	0.056 [0.012]	0.028 [0.0059]	0.0069 [0.0014]	0.0035 [0.00074]
AEGL-2 (Disabling)	0.50 [0.011]	0.17 [0.036]	0.083 [0.017]	0.021 [0.0044]	0.010 [0.0021]
AEGL-3 (Lethality)	36 [7.6]	25 [5.3]	13 [2.7]	3.1 [0.65]	1.6 [0.34]

8.2. Comparisons with Other Standards and Guidelines

There are no standards or guideline values for phosgene oxime.

8.3. Data Adequacy and Research Needs

Inhalation toxicity data for phosgene oxime are extremely limited. Additional studies examining low level exposure for longer exposure durations as well as data allowing for estimation of a lethality threshold are required for a more definitive assessment. At the present

time, no empirical data regarding the exposure concentration-time relationship for phosgene oxime are available.

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APPENDIX A: Derivation of AEGL Values

Derivation of AEGL-1 Values for Phosgene Oxime

Key Study: Malatesta, P., B. Bianchi and C. Malatesta. 1983. Contributo allo studio delle sostanze orticanti [Contributions to the study of oro-nasal irritants]: Nota 1. Boll. Chim. Farm 122: 96-103. (Translated from Italian)

Critical effect: Awareness of chemical by ocular, nasal, and dermal sensation following 10-minute exposure of 6 informed human volunteers to 1 mg phosgene oxime/m^3

Time scaling: Time scaling using $C^n \times t = k$, where $n = 1$ for extrapolating from the 10-minute experimental exposure duration to AEGL-specific exposure durations (NRC, 2001).

Uncertainty factors: Total uncertainty factor 3.
Interspecies: 1; informed volunteers

Intraspecies: 3; direct contact irritant (ocular, nasal, dermal contact) requiring no metabolism/disposition processes; initial awareness of this urticant/nettle agent is not expected to vary among individuals

Modifying Factor: 2; overall data set for phosgene oxime inhalation toxicity is limited; available studies lack analytical exposure terms; animal studies lack adequate post exposure follow-up, gross necropsy and histopathology findings

Calculation: 1 mg/m^3 x 10 min = 10 mg·min/m^3

10-min AEGL-1
C mg/m^3 x 10 min. = 10 mg·min/m^3
C = 1 mg/m^3
(1 mg/m^3)/6 = 0.17 mg/m^3

30-min AEGL-1
C mg/m^3 x 30 min. = 10 mg·min/m^3
C = 0.33 mg/m^3
(0.33 mg/m^3)/6 = 0.056 mg/m^3

1-hr AEGL-1
C mg/m^3 x 60 min. = 10 mg·min/m^3
C = 0.167 mg/m^3
(0.167 mg/m^3)/6 = 0.028 mg/m^3

4-hr AEGL-1
C mg/m^3 x 240 min. = 10 mg·min/m^3
C = 0.0416 mg/m^3
(0.0416 mg/m^3)/6 = 0.0069 mg/m^3

8-hr AEGL-1
C mg/m^3 x 480 min. = 10 mg·min/m^3
C = 0.0208 mg/m^3
(0.0208 mg/m^3)/6 = 0.0035 mg/m^3

Derivation of AEGL-2 Values for Phosgene Oxime

Key Study: Malatesta, P., B. Bianchi and C. Malatesta. 1983. Contributo allo studio delle sostanze orticanti [Contributions to the study of oro-nasal irritants]: Nota 1. Boll. Chim. Farm 122: 96-103. (Translated from Italian)

Critical effect: Awareness of chemical by ocular, nasal, and dermal sensation following 10-minute exposure of 6 informed human volunteers to 1 mg phosgene oxime/m^3.

Time scaling: Time scaling using $C^n \times t = k$, where $n = 1$ for extrapolating from the 10-minute experimental exposure duration to AEGL-specific exposure durations (NRC, 2001).

Uncertainty factors: Total uncertainty factor: 1

Interspecies: 1; informed human volunteers

Intraspecies: 1; no uncertainty factor for sensitive individuals was applied with the implication that the 10-min. exposure to 1 mg/m^3 would result in effects approaching AEGL-2 severity for these individuals. This approach was considered more defensible than utilizing notable irritation reported by Malatesta et al. (1983) for volunteers exposed to 3 mg/m^3 for only 1 minute.

Modifying Factor: 2; overall data set for phosgene oxime inhalation toxicity is limited; available studies lack analytical exposure terms; animal studies lack adequate post exposure follow-up, gross necropsy and histopathology findings

Calculation: 1 mg/m^3 x 10 min = 10 mg·mg/m^3

10-min AEGL-2
C mg/m^3 x 10 min. = 10 mg·min/m^3
C = 1 mg/m^3
(1 mg/m^3)/2 = 0.50 mg/m^3

30-min AEGL-2
C mg/m^3 x 30 min. = 10 mg·min/m^3
C = 0.33 mg/m^3
(0.33 mg/m^3)/2 = 0.17 mg/m^3

1-hr AEGL-2
C mg/m^3 x 60 min. = 10 mg·min/m^3
C = 0.167 mg/m^3
(0.167 mg/m^3)/2 = 0.083 mg/m^3

4-hr AEGL-2 C mg/m^3 x 240 min. = 10 mg·min/m^3
C = 0.0416 mg/m^3
(0.0416 mg/m^3)/2 = 0.021 mg/m^3

8-hr AEGL-2 C mg/m^3 x 480 min. = 10 mg·min/m^3
C = 0.0208 mg/m^3
(0.0208 mg/m^3)/2 = 0.010 mg/m^3

Derivation of AEGL-3 Values for Phosgene Oxime

Key Study: Malatesta, P., B. Bianchi and C. Malatesta. 1983. Contributo allo studio delle sostanze orticanti: Nota 1. Boll. Chim. Farm 122: 96-103. (Translated from Italian)

Critical effect: 30-minute exposure to 500 mg/m^3 was the highest nonlethal exposure for mice guinea pigs and rabbits; responses included lacrimation, agitation and respiratory difficulty which resolved by day 3 post-exposure

Time scaling: Time scaling using $C^n \times t = k$, where $n = 1$ for extrapolating from the 10-minute experimental exposure duration to longer AEGL-specific exposure durations and $n = 3$ for extrapolating to the 10-min AEGL duration (NRC, 2001).

Uncertainty factors: Total uncertainty factor: 10

Interspecies: 3; all three test species exhibited the same signs of toxicity

Intraspecies: 3; direct contact irritant (ocular, nasal, dermal contact) requiring no metabolism/disposition processes; effects are due to interaction of parent molecule with any tissues.

Modifying Factor: 2; overall data set for phosgene oxime inhalation toxicity is limited; available studies lack analytical exposure terms; animal studies lack adequate post exposure follow-up, gross necropsy and histopathology findings

Calculation:
500 mg/m^3 x 0.5 hr = 250 mg·hr/m^3
(500 mg/m^3)^3 x 0.5 hr min = 62,500,000 mg·hr/m^3

10-min AEGL-3
(C mg/m^3)^3 x 0.1667 hr = 62,500,000 mg·hr/m^3
C = 721 mg/m^3
(721 mg/m^3)/20 = 36 mg/m^3

30-min AEGL-3
C mg/m^3 x 0.5 hr = 250 mg·hr/m^3
C = 500 mg/m^3
(500 mg/m^3)/20 = 25 mg/m^3

1-hr AEGL-3
C mg/m^3 x 1 hr = 250 mg·hr/m^3
C = 250 mg/m^3
(250 mg/m^3)/20 = 13 mg/m^3

4-hr AEGL-3 C mg/m^3 x 4 hrs = 250 mg·hr/m^3
C = 62.5 mg/m^3
(62.5 mg/m^3)/20 = 3.1 mg/m^3

8-hr AEGL-3 C mg/m^3 x 8 hrs = 250 mg·min/m^3
C = 31.25 mg/m^3
(31.25 mg/m^3)/20 = 1.6 mg/m^3

APPENDIX B: Time Scaling Calculations

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

The available data do not allow for empirical derivation of a temporal scaling factor (n) for phosgene oxime. The concentration-exposure 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 (ten Berge et al. 1986). Data are unavailable with which to evaluate the exposure time-exposure concentration relationship and empirical derivation of the exponent, n, for the relationship $C^n \times t = k$ is not possible. In the absence of definitive data, temporal scaling default exponents of $n = 3$ are typically applied when extrapolating to shorter time points and $n = 1$ when extrapolating to longer time points (NRC 2001).

APPENDIX C: Derivation Summary Tables

1

AEGL-1 VALUES FOR PHOSGENE OXIME (ppm)				
10 min	**30 min**	**1 h**	**4 h**	**8 h**
0.17 mg/m^3	**0.056 mg/m^3**	**0.028 mg/m^3**	**0.0069 mg/m^3**	**0.0035 mg/m^3**
Reference: Malatesta, P., B. Bianchi and C. Malatesta. 1983. Contributo allo studio delle sostanze orticanti [Contributions to the study of oro-nasal irritants]: Nota 1. Boll. Chim. Farm 122: 96-103. (Translated from Italian)				
Test Species/Strain/Number: Informed volunteers/ 6				
Exposure Route/Concentrations/Durations : 1 mg /m^3 for 10-min ; 3 mg/m^3 for 1 min				
Effects: 1 mg/m^3: Awareness of chemical based upon ocular, nasal, and dermal sensations following 10-min exposure (POD for AEGL-1 derivation) 3 mg/m^3 : unpleasant irritation ; 1-min exposure duration				
Endpoint/Concentration/Rationale: Awareness of chemical based upon ocular, nasal, and dermal sensations following 10-min exposure to 1 mg/m^3				
Uncertainty Factors/Rationale: **Interspecies**: 1; Human volunteers **Intraspecies**: 3; Direct contact irritant (ocular, nasal, dermal contact) requiring no metabolism/disposition processes; initial awareness of this urticant/nettle agent is not expected to vary significantly among individuals				
Modifying Factor: 2 ; A modifying factor of 2 was applied to account for the overall limited data on this chemical as well as deficiencies (no analytical determination of concentrations ; limited exposure durations and concentrations) in the available studies				
Animal to Human Dosimetric Adjustment: not applicable				
Time Scaling: $C^n \times t = k$, where $n = 1$				
Data Adequacy: Data are sufficient for derivation of AEGL-1 values for phosgene oxime. Although the overall data set is very limited, the AEGL-1 values are based upon controlled exposure studies with informed volunteers.				

2

1

AEGL-2 VALUES FOR PHOSGENE OXIME (mg/m^3)				
10 min	**30 min**	**1 h**	**4 h**	**8 h**
0.50 mg/m^3	**0.17 mg/m^3**	**0.083 mg/m^3**	**0.021 mg/m^3**	**0.010 mg/m^3**
Reference: Malatesta, P., B. Bianchi and C. Malatesta. 1983. Contributo allo studio delle sostanze orticanti [Contributions to the study of oro-nasal irritants]: Nota 1. Boll. Chim. Farm 122: 96-103. (Translated from Italian)				
Test Species/Strain/Number: Informed volunteers/6				
Exposure Route/Concentrations/Durations: 1 mg /m^3 for 10-min ; 3 mg/m^3 for 1 min				
Effects: 1 mg/m^3: Awareness of chemical based upon ocular, nasal, and dermal sensations following 10-min exposure to 3 mg/m^3 : unpleasant irritation ; 1-min exposure duration (POD for AEGL-2 derivation)				
Endpoint/Concentration/Rationale: Awareness of chemical based upon ocular, nasal, and dermal sensations following 10-min exposure to 1 mg/m^3				
Uncertainty Factors/Rationale: **Interspecies**: 1; Human volunteers **Intraspecies**: 1; no uncertainty factor for sensitive individuals was applied with the implication that the 10-min. exposure to 1 mg/m^3 would result in effects approaching AEGL-2 severity for these individuals. This approach was considered more defensible than utilizing notable irritation reported by Malatesta et al. (1983) for volunteers exposed to 3 mg/m^3 for only 1 minute.				
Modifying Factor: 2 ; A modifying factor of 2 was applied to account for the overall limited data on this chemical as well as deficiencies (no analytical determination of concentrations ; limited exposure durations and concentrations) in the available studies				
Animal to Human Dosimetric Adjustment: not applicable				
Time Scaling: $C^n \times t = k$, where $n = 1$				
Data Adequacy: Data are marginally sufficient for derivation of AEGL-2 values for phosgene oxime. Although the overall data set is very limited, the AEGL-2 values are based upon controlled exposure studies with informed human volunteers.				

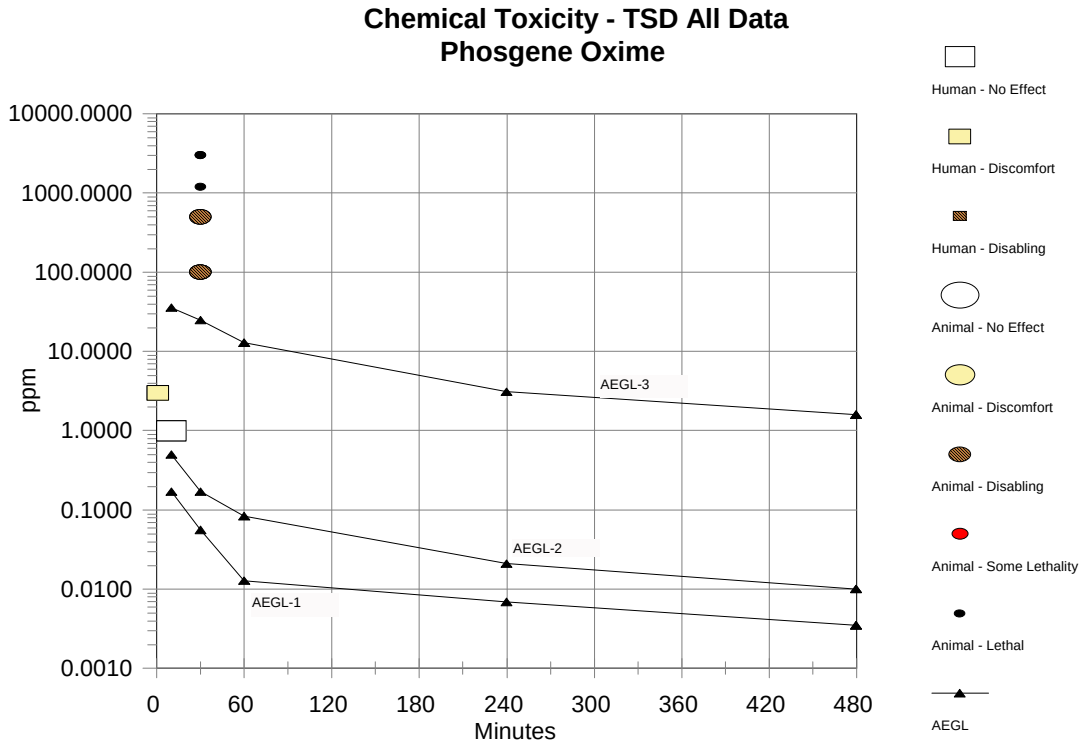
2

1

AEGL-3 VALUES PHOSGENE OXIME (mg/m^3)				
10 min	**30 min**	**1 h**	**4 h**	**8 h**
36 mg/m^3	**25 mg/m^3**	**13 mg/m^3**	**3.1 mg/m^3**	**1.6 mg/m^3**
Key Study: Malatesta, P., B. Bianchi and C. Malatesta. 1983. Contributo allo studio delle sostanze orticanti: Nota 1. Boll. Chim. Farm 122: 96-103. (Translated from Italian)				
Test Species/Strain/Sex/Number: mice, guinea pigs and rabbits (number of animals, species or gender were not provided) were exposed by inhalation to phosgene oxime at concentrations of 100 to 500 mg/m^3 (only the range was provided)				
Exposure Route/Concentrations/Durations: inhalation/ 100-500 mg/m^3/30 minutes				
Effects: For all concentrations: no deaths; lacrimation, agitation and respiratory difficulty resolved by day 3 post-exposure				
Endpoint/Concentration/Rationale: 30-min. exposure to 500 mg/m^3 was highest nonlethal exposure and selected as POD for AEGL-3 derivation				
Uncertainty Factors/Rationale: 10 Interspecies: 3; all three test species exhibited the same signs of toxicity Intraspecies: 3; direct contact irritant (ocular, nasal, dermal contact) requiring no metabolism/disposition processes; effects are due to interaction of parent molecule with any tissue				
Modifying Factor: 2; deficient overall database				
Animal to Human Dosimetric Adjustment: not applicable				
Time Scaling: $C^n \times t = k$, where $n = 1$ or 3				
Data Adequacy: marginal; assessment of a lethality threshold using empirical data not possible.				

2

APPENDIX D: Category Plot


Chemical Toxicity - TSD All Data
Phosgene Oxime
10000.0000
1000.0000
100.0000
10.0000
1.0000
0.1000
0.0100
0.0010
ppm
0
60
120
180
240
300
360
420
480
Minutes
AEGL-3
AEGL-2
AEGL-1
Human - No Effect
Human - Discomfort
Human - Disabling
Animal - No Effect
Animal - Discomfort
Animal - Disabling
Animal - Some Lethality
Animal - Lethal
AEGL

1

Phosgene oxime

For Category 0 = No effect, 1 = Discomfort, 2 = Disabling, PL = Partially Lethal, 3 = Lethal

Source	Species	Sex	# Exposures	ppm	Minutes	Category	Comments
NAC/AEGL-1				0.17	10	AEGL	
NAC/AEGL-1				0.056	30	AEGL	
NAC/AEGL-1				0.028	60	AEGL	
NAC/AEGL-1				0.0069	240	AEGL	
NAC/AEGL-1				0.0035	480	AEGL	
NAC/AEGL-2				0.5 0	10	AEGL	
NAC/AEGL-2				0.17	30	AEGL	
NAC/AEGL-2				0.083	60	AEGL	
NAC/AEGL-2				0.021	240	AEGL	
NAC/AEGL-2				0.010	480	AEGL	
NAC/AEGL-3				36	10	AEGL	
NAC/AEGL-3				25	30	AEGL	
NAC/AEGL-3				13	60	AEGL	
NAC/AEGL-3				3.1	240	AEGL	
NAC/AEGL-3				1.6	480	AEGL	
	human	m	1	1	10	0	awareness but no irritation (Malatesta et al., 1983)
	human	m	1	3	1	1	unpleasant irritation (Malatesta et al., 1983)
	mouse		1	100	30	2	extreme lacrimation, agitation, labored breathing (Malatesta et al., 1983)
	guinea pig		1	100	30	2	extreme lacrimation, agitation, labored breathing (Malatesta et al., 1983)
	rabbit		1	100	30	2	extreme lacrimation, agitation, labored breathing (Malatesta et al., 1983)
	dog		1	1200	30	3	lethality in dogs (Tschanatschev and Dronzin, 1957)
	dog		1	3000	30	3	lethality in dogs (Balev and Andreev , 1957)
				500	30	2	extreme lacrimation, agiatation, labored breathing (Malatesta et al., 1983)

2