ACUTE EXPOSURE GUIDELINE LEVELS (AEGLs)

FOR

NITROGEN MUSTARDS
(HN1 CAS Reg. No. 538-07-8)
(HN2 CAS Reg. No. 51-75-2)
(HN3 CAS Reg. No. 555-77-1)

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/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.

TABLE OF CONTENTS

LIST OF TABLES

SUMMARY

Nitrogen mustards are tertiary *bis*(β-chloroethyl)amines with vesicant activity. All are active alkylating agents and ocular injurants as well. Although HN2 and HN3 were specifically developed as military agents, HN1 was originally developed as a pharmaceutical. HN2 (mechlorethamine) later found use as a pharmaceutical. Both HN1 and HN3 are among the chemical agents found in Chemical Agent Identification Sets (CAIS) that are considered a component of non-stockpiled material. Development of AEGL values is limited to the nitrogen mustards referred to as HN1, HN2, and HN3.

Because of the nature of the chemicals under review, military literature is a major source of the relevant toxicity data.. Consequently, much of the data sources possess "limited distribution", which is a separate issue from "classification". For various reasons, sources may possess a restricted distribution because of treaty restrictions on data access with allies, concerns regarding distribution of engineering information characterizing agent dissemination or generation in other sections of the same document, and related issues. To ensure public access to pertinent toxicity data originating from "limited distribution" materials, pertinent data from those sources have been incorporated into the technical support document.

All human exposure studies presented in this evaluation meet the criteria for acceptance for use in the AEGL process (e.g., there is evidence that subjects provided informed consent and that the studies were performed under appropriate clinical supervision) (NRC, 2001).

Toxicologic information on nitrogen mustard vapors focuses primarily upon assessment of dermal blistering/erythema thresholds and ocular irritation thresholds in human volunteer subjects. Lethality data are available for several laboratory species (monkeys, dogs, rats, mice, rabbits, guinea pigs). Most of these data were based upon analytical determinations of vapor concentrations and post exposure observations periods of approximately two weeks.

Human exposure data has provided information regarding absence of adverse effects as well as thresholds for ocular irritation/impairment, and dermal blistering and erythema formation. Vapor concentrations of 0.012 mg/m^3 averaged over 273-minutes (0.036 mg/m^3 for 20 minutes) during therapeutic use of HN2 were without effect. The median blistering Ct (10-minute exposure) for humans was >21,170 mg-min/m^3 (HN1), 5800 mg-min/m^3 (HN2), and 1800 mg-min/m^3 (HN3) for nonsweating subjects at 80-95% relative humidity. The median blistering Ct for HN3 (20-minute exposure) was 1300 mg-min/m^3 volunteers sweating as the result of exercise and 1800 mg-min/m^3 for nonsweating subjects. Thresholds for ocular impairment in human volunteer subjects were 37-90, 40-55, and 20-42 mg-min/m^3, respectively, for HN1, HN2, and HN3. Impairment was assessed based upon operational effectiveness in military tasks. Signs and symptoms of tended to develop after the short-term exposures (0.5-67 minutes), included effects such as lacrimation, pain, photophobia, blepharospasm, conjunctival injection, and tended to resolve several days later.

Extensive lethality data were available for animals exposed to nitrogen mustard vapors. These studies provided LCt_{50} values for exposure durations ranging from 0.25 to 510 minutes, although most experiments were conducted in the 2- to 10-minute range. Lethal responses did not vary greatly among the species tested nor did lethal toxicity of the nitrogen mustards vary greatly.

Latency periods of several days were often observed. Data regarding pathological findings and cause of death were unavailable for review.

No exposure-response data were available regarding AEGL-1 type effects following exposure of human or animals to nitrogen mustard vapors. A characteristic of nitrogen mustards exploited for their development as warfare agents was the absence of detection at exposures capable of causing toxic responses. For these reasons, no AEGL-1 values have been recommended.

The AEGL-2 values for HN1, HN2, and HN3 were developed based upon the lower limits of the previously noted eye injury thresholds from studies with human volunteer subjects; 37, 40, and 20 mg-min/m^3, respectively, for HN1, HN2, and HN3. Ocular effects appeared to be the most sensitive indicator of nitrogen mustard exposure. Although reversible, the identified thresholds represent a response consistent with the overall continuum of nitrogen mustard toxicity and were considered appropriate as a critical effect and point-of-departure for AEGL-2 development for all three agents. For HN1 and HN3, these effect were considered a NOAEL for the AEGL-2 tier while for HN2, the effects were of somewhat greater severity and considered a LOAEL. The ocular response is likely independent of dosimetric processes that would be relevant to systemically-mediated toxicity. Therefore, the uncertainty factor for individual variability was limited to 3. Some of the tests were apparently performed using volunteers with oronasal masks which would have precluded development of respiratory tract effects. A modifying factor of 3 was applied to account for possible effects on the respiratory tract (The modifying factor was increased to 10 for HN2 AEGL-2 derivation due to more severed effects (NOAEL-to-LOAEL adjustment) and uncertainties regarding the number of volunteer subjects in the test. Where AEGL-2 time points coincided with the exposure duration range used to establish the threshold Ct, time-specific exposure concentrations for AEGLs were calculated from the Ct value. Consistent with AEGL methodologies (NRC, 2001), an *n* of 1 or 3 was used in the equation, $C^n \times t = k$, for extrapolating to AEGL time periods not within the range of experimental exposure duration.

Lethality thresholds (LCt_{50}) for rats were used as the basis for AEGL-3 values; 860, 2000, and 670 mg-min/m^3 for HN1, HN2, and HN3, respectively. These specific LCt_{50} values were based upon experimental exposure durations ranging from 20-100 minutes (HN1), 120-360 minutes (HN2), and 10-100 minutes (HN3) and, therefore considered suitable for AEGL development. Consistent with AEGL methodology (NRC, 2001), a three-fold reduction of these lethality values was used as an estimate of the lethality threshold and the point-of-departure for AEGL-3 development. A total uncertainty factor of 10 was applied. Adjustment for interspecies variability was limited to 3 because LCt_{50} values among multiple species (including nonhuman primates) did not appear to vary by more than three-fold for each agent. Furthermore, the rat was somewhat more sensitive. Adjustment for individual variability was limited to 3 because the action of nitrogen mustards on cellular components would not be expected to greatly differ, and because additional downward adjustment would result in AEGL-3 values inconsistent with AEGL-2 values and available human data (ocular and dermal response data and monitoring data for therapeutic use of nitrogen mustard). Where AEGL-3 time points coincided with the exposure duration range used to establish the threshold Ct, time-specific exposure concentrations for AEGLs were calculated from the Ct value. Consistent with AEGL methodologies (NRC, 2001), an *n* of 1 or 3 was used in the equation, $C^n \times t = k$, for extrapolating to AEGL time periods not within the range of experimental exposure duration.

Although the nitrogen mustards are alkylating agents with known mutagenicity, there are no animal cancer bioassays for inhalation exposure and no human carcinogenicity data. IARC (1990) classified HN3 as *possibly carcinogenic to humans* (Group 2B). Carcinogenic potential was not a determinant for AEGL development.

By consensus, the National Advisory Committee for Acute Exposure Guideline Levels chose the AEGL-2 values for HN2 to represent AEGL-2 values for all of the reviewed nitrogen mustards and the AEGL-3 values for HN3 as representative of AEGL-3 values for all of the reviewed nitrogen mustards. Individual AEGL-2 and AEGL-3 values for HN1, HN2, and HN3 are presented in the text body of Technical Support Document and in Appendices A and C. Category plots for which AEGL values are compared to experimental data are presented in Appendix D.

Summary of AEGL Values (mg/m^3) for Nitrogen Mustards

Classification	10-minute	30-minute	1-hour	4-hour	8-hour	Endpoint (Reference)
AEGL-1 (Nondisabling)	NR[a]	NR[a]	NR[a]	NR[a]	NR[a]	Not recommended
AEGL-2 (Disabling) HN1, HN2, HN3	0.13[b]	0.044[b]	0.022[b]	0.0056[b]	0.0028[b]	Threshold for ocular irritation in humans sufficient to compromise operational effectiveness (Porton Report 1942a, 1943d; U.S. Army Med. Div. 1945c, d.)
AEGL-3 (Lethality) HN1, HN2, HN3	2.2[b]	0.74[b]	0.37[b]	0.093[b]	0.047[b]	Lethality threshold in rats estimated as 3-fold reduction of LCt_{50} values (Porton Report. 1943b,c; U.S. Army Med. Div., 1945a)

[a] NR: not recommended due to insufficient data and because adverse effects are know to occur in the absence of detection.

[b] By consensus vote, the AEGL-2 values for HN2 and AEGL-3 values for HN3 are representative of all nitrogen mustards reviewed.

References

NRC (National Research Council). 2001. Standing operating procedures for developing acute exposure guideline levels for hazardous chemicals. Committee on Toxicology, Board on Toxicology and Environmental Health Hazards, Commission on Life Sciences, National Research Council. National Academy Press, Washington, DC.

Porton Report. 1942a. On the action of S on the eye; its comparison with allied compounds and with H. No. 2402. August 7, 1942. Cited in NDRC, 1946.

Porton Report. 1943b. Toxicity of S vapour. Further experiments on the exposure of animals to S vapour. No. 2464. February 9, 1943. Cited in NDRC, 1946.

Porton Report. 1943c. Toxicity and pathology of HN-3. No. 2548. November 18, 1944. Cited in NDRC, 1946

Porton Report. 1943d. The effects of HN-1 vapour on human and rabbit eyes. No. 2563. November 18, 1943. Cited in NDRC, 1946.

U.S. Army Medical Division. 1945a. Medical Division monthly progress report. September, 1945. Cited in NRDC, 1946.

U.S. Army Medical Division. 1945c. Medical Division monthly progress report. March, 1945. Cited in NRDC, 1946.

U.S. Army Medical Division. 1945d. Medical Division monthly progress report. February, 1945. Cited in NRDC, 1946.

1. INTRODUCTION

Nitrogen mustards are tertiary *bis*(β-chloroethyl)amines with vesicant activity (NDRC, 1946). Exposure to vapors or aerosols may also cause eye injury. As such, they were developed as warfare agents and are often referred to as blister agents. All are active alkylating agents. This document is limited to the nitrogen mustards referred to as HN1, HN2, and HN3, the chemical and physical properties of which are summarized in Tables 1-3. Due to their toxicity and various physical-chemical properties, initial interest in these chemicals as warfare agents came about shortly before or during World War II. Although HN2 and HN3 were specifically developed as military agents, HN1 was originally developed as a pharmaceutical. HN2 (mechlorethamine) later found use as a pharmaceutical. Nitrogen mustards and derivatives such as melphalan, chlorambucil, and cyclophosphamide are alkylating agents used as cancer therapeutic agents (Somani, 1992). Both HN1 and HN3 are among the chemical agents found in Chemical Agent Identification Sets (CAIS) that are considered a component of non-stockpiled material.

TABLE 1. Chemical and Physical Data for HN1

Parameter	Value	Reference
Synonyms	ethyl-*bis*(β-chloroethyl)amine; *bis*-(2-chloroethyl)ethylamine	NDRC, 1946
Chemical formula	$(ClCH_2CH_2)_2NC_2H_5$	USACHPPM, 1996
Molecular weight	170.08	USACHPPM, 1996
CAS Registry No.	538-07-8	USACHPPM, 1996
Physical state	oily liquid	USACHPPM, 1996
Solubility in water	Limited; miscible in organic solvents	NDRC, 1946
Vapor pressure	0.25 mm Hg @ 25EC	USACHPPM, 1996
Density		
Boiling*/freezing point	194EC*/-34EC	USACHPPM, 1996
Conversion factors in air	1 ppm = 6.94 mg/m^3 1 mg/m^3 = 0.14 ppm	

* Boiling point is calculated; HN1 decomposes prior to reaching boiling point.

TABLE 2. Chemical and Physical Data for HN2

Parameter	Value	Reference
Synonyms	methyl-*bis*(β-chloroethyl)amine; 2,2'-dichloro-N-methyldiethylamine; "S"; mechlorethamine	NDRC, 1946
Chemical formula	$(ClCH_2CH_2)_2NCH_3$	USACHPPM, 1996
Molecular weight	156.07	USACHPPM, 1996
CAS Registry No.	51-75-2	USACHPPM, 1996
Physical state	oily liquid	USACHPPM, 1996
Solubility in water	Limited; miscible in organic solvents	NDRC, 1946
Vapor pressure	0.427 mm Hg @ 25EC	USACHPPM, 1996
Density	liquid: 1.09 @ 20EC vapor: 5.9	USACHPPM, 1996
Boiling*/freezing point	75EC*/-60EC	USACHPPM, 1996
Conversion factors in air	1 ppm = 6.37 mg/m^3 1 mg/m^3 = 0.16 ppm	

* Boiling point is calculated; HN2 decomposes prior to reaching boiling point.

TABLE 3. Chemical and Physical Data for HN3

Parameter	Value	Reference
Synonyms	*tris*(β-chloroethyl)amine; [*tris*(2-chloroethyl)amine hydrochloride]	NDRC, 1946
Chemical formula	$N(CH_2CH_2Cl)_3$	USACHPPM, 1996
Molecular weight	204.54	USACHPPM, 1996
CAS Registry No.	555-77-1	USACHPPM, 1996
Physical state	liquid	USACHPPM, 1996
Solubility in water	Limited; miscible in organic solvents	NDRC, 1946
Vapor pressure	0.0109 mm Hg @ 20EC	USACHPPM, 1996
Density	liquid: 1.15 g/cc @ 20EC vapor: 5.4	USACHPPM, 1996
Boiling*/freezing point	256EC*/-3.7EC	USACHPPM, 1996
Conversion factors in air	1 ppm = 8.35 mg/m^3 1 mg/m^3 = 0.12 ppm	

* Boiling point is calculated; HN3 decomposes prior to reaching boiling point.

2. HUMAN TOXICITY DATA

2.1. Acute Lethality

No data are available regarding lethality in humans following exposure to nitrogen mustard vapors.

2.2. Nonlethal Toxicity

Eye injury and dermal vesication are the most prevalent effects in humans following vapor exposure to nitrogen mustards. A study of air concentrations of HN2 during treatment of mycosis fungoides revealed that mean room concentration during the complete treatment process (20 minutes total and within one meter of patient and nurse) was 0.036 mg/m^3 (Van Vloten et al., 1993). The concentration dropped immediately after treatment (0.004 mg/m^3) and was 0.012 mg/m^3 over the 273-minute experimental time.

2.2.1 Dermal Effects

In an attempt to determine the relative vesicant effect of vapors of HN1, HN2, and HN3 on human skin, a study was conducted in which naval volunteers (17-38 years old) were exposed via vapor cups for 10 minutes to various concentrations of the test articles applied to an 8-mm diameter area of the flexor surface of the forearm (NDRC, 1944). The vapors were generated by passing dry air (or nitrogen) through the agent. The container with vesicant was kept in a water bath to maintain constant temperature. Both nominal concentrations (calculated using weight loss of agent and air flow) and analytical concentrations (sampling at multiple points in vapor stream with subsequent analysis via hydrolysis and measurement of released chloride ion by the Volhard method) were reported. Agent purity was approximately 99%. The median blistering Ct (10-minute exposure) for HN1, HN2 and HN3 were >21,170 $mg\text{-}min/m^3$, 5800 $mg\text{-}min/m^3$, and 1800 $mg\text{-}min/m^3$, respectively for nonsweating subjects at 80-95% relative humidity. Assessments were made over 48 hours following exposure. A median blistering Ct value of 1300 $mg\text{-}min/m^3$ was determined for exposure of volunteers sweating as the result of exercise, and exposed to HN3 for 20 minutes. The Ct for 20-minute exposure of nonsweating subjects was the same as that for the 10-minute exposure. Results are summarized in Table 4.

Table 4. Vesicant action of nitrogen mustard vapors on forearm skin of human volunteer subjects following 10-min. or 20-min. exposures[a]

Compound/Concentration (mg-min/m^3)[b]	Total erythemas	Total blisters
HN1 (10-min)		
234	1/12	0/12
1400	0/11	0/11
2480	0/4	0/4
2660	6/12	0/12
3990	5/7	0/7
5000	7/8	0/8
7100	8/12	0/12
10,320	10/12	2/12
15,060	12/12	0/12
17,400	12/12	0/12
21,170	9/10	2/10
HN2 (10-min)		
1070	3/12	0/12
1450	11/12	0/12
2030	11/11	0/11
2400	12/12	1/12
3060	8/8	1/8
3180	8/8	0/8
3350	8/8	0/8
3700	11/11	1/11
4270	12/12	2/12
4550	12/12	2/12
5000	8/8	5/8
5200	7/7	5/7
6070	12/12	7/12
6450	7/7	4/7
6950	8/8	7/8
7300	7/7	5/7
7510	12/12	5/12
10,100	12/12	11/12

Table 4 (Cont.). Vesicant action of nitrogen mustard vapors on forearm skin of human volunteer subjects following 10-min. or 20-min. exposures[a]

Compound/Concentration (mg-min/m^3)[b]	Total erythemas	Total blisters
HN3 (10-min)		
135	0/12	0/12
287	4/12	0/12
515	8/12	0/12
820	4/4	0/4
1035	8/8	0/8
1280	9/11	0/11
1290	11/12	0/12
1380	9/12	1/12
1420	16/16	4/16
1470	8/8	0/8
1590	11/11	1/11
1620	8/8	7/8
1650	4/4	1/4
HN3 (20-min)		
1200	8/8	3/8
1280	8/8	0/8
1360	8/8	3/8
1420	6/8	3/8
1600	12/12	7/12
1620	8/8	4/8
1900	4/4	2/4
1940	8/8	6/8
2000	8/8	6/8
2060	12/12	12/12
2400	8/8	7/8
3060	12/12	10/12
3280	12/12	10/12
3640	12/12	10/12

NDRC, 1944. [a] 80-95% rel. humidity of air with test article; [b] analytical determinations

The relative vesicant activity of nitrogen mustards was also reported by Hunt et al. (1943). These experiments also involved application of the test articles via vapor cups attached to the flexor surface of the forearm. Exposures were for five minutes with saturated vapor concentrations. The results of these experiments are summarized in Table 5.

Table 5. Vesicant action of nitrogen mustard vapors on forearm skin of human volunteer subjects following 5-min. exposures[a]			
Agent	**Ct (mg-min/m^3)**	**Erythemas**	**Blisters**
HN1	8,000 11,500	4/5 8/10	2/5 0/10
HN2	12,500 17,000	4/5 10/10	1/5 7/10
HN3	350 550	1/5 5/10	1/5 0/10

[a] Ct values calculated by NDRC (1944) based upon volatility, temperature, and exposure duration data.

Additional studies summarized in NDRC (1946) provided information regarding whole-body exposure of human volunteer subjects to HN1 and HN3. Results are summarized in Table 6.

Table 6. Response of human volunteer subjects to whole-body exposure to nitrogen mustards[a].			
Compound	**Exposure (mg-min/m^3)**	**Duration (min)**	**Response**
HN1	107	11	no effect
	211	22	no effect
	285	30	possible erythema on neck
	520	34	mild erythema on neck and back
	689	41	mild erythema on neck and body
	940	44	mild erythema on upper body
	1030	29	mild erythema on neck, upper back, and axillary folds
HN3	90	15	minimal to marked erythema on exposed skin
	150	25	marked erythema at 20 hrs, decreasing by 96 hrs
	200	NA	slight to moderate erythema on exposed areas
	250	NA	slight to moderate erythema on exposed areas
	300	NA	slight to moderate erythema on exposed areas
	350	NA	marked erythema with areas of vesication
	350	NA	slight erythema and vesication on neck

NDRC, 1946.
[a]Subjects (2-8 per group) wore gas masks, shoes, socks, and protective clothing around the genital area.
NA: not available; noted in NDRC report as unknown.

2.2.2 Ocular Effects

HN1

Early studies examined eye injury following exposure to nitrogen mustards (summarized in NDRC, 1946). In tests where one eye of each of 21 subjects was exposed to HN1 (5 L/min for 5 to 67 minutes; Ct of 37 to 90 mg-min/m^3), three subjects receiving a cumulative exposure of 41, 56, and 90 mg-min/m^3 reported that their vision was impaired sufficiently to compromise efficient use of a firearm (Porton Report, 1943d). Symptoms and signs which included gritty feeling in the eyes, lacrimation, photophobia, blepherospasm, headache, and conjunctival hyperemia developed with an average latency of 12 hours and persisted up to 24 days. Not all

effects occurred in all test subjects. The investigators considered the 90 mg-min/m^3 as a threshold for human casualty.

HN2

Cumulative exposures of 40-55 mg-min HN2/m^3 (exposure durations of 0.5 to 10 minutes) were considered as the lowest limit for disablement (operationally ineffective) of human subjects (Porton Report, 1942a). These tests involved subjects (non-specified number of men) wearing oronasal masks and exposed to HN2 at concentrations of 10 to 55 mg/m^3. No symptoms were reported during exposure but at 8 to 15 minutes post exposure lacrimation and a feeling of grittiness in the eyes were reported. At 6 to 10 hours post exposure additional effects developed (e.g., photophobia, blepharospasm, pain severe enough to prevent sleep). At 24 hours, these effects continued but pain decreased. It was concluded that a cumulative exposure of 70 mg-min/m^3 be considered a minimum exposure for offensive purposes. Exposure to HN2 at 55 mg-min/m^3 was considered a limit for disablement based upon operational effectiveness.

HN3

Results of experiments with HN3 and four human volunteer subjects showed that exposure to 20 mg-min/m^3 (duration not specified) produced moderate conjunctival injection and corneal edema with no symptoms being reported by the subjects (U.S. Army Med. Div., 1945c,d). Three subjects exposed to 42 mg-min/m^3 (7-minutes exposure duration) experienced lacrimation, photophobia, and grittiness, and exhibited marked conjunctival injection.

2.3. Developmental/Reproductive Effects

No human developmental/reproductive toxicity data were available for the nitrogen mustards on concern.

2.4. Genotoxicity

The genotoxicity of nitrogen mustards has been extensively reviewed (Fox and Scott, 1980). Data are insufficient for assessing risk of genetic damage in humans.

2.5. Carcinogenicity

There is no information available on the carcinogenicity of nitrogen mustard (HN1, HN2, HN3) in humans. Based upon sufficient evidence of carcinogenicity in animals (see Section 3.5), IARC (1990) classified HN3 as *possibly carcinogenic to humans* (Group 2B). Studies in both mice (Boyland and Horning, 1949) and rats (Sýkora et al., 1981) involved multiple subcutaneous injections of HN3. Results of the former study were inconclusive while results of the latter showed decreased survival in male rats, increased spindle sarcomas at the injection site and intestinal adenocarcinomas.

2.6. Summary

Data regarding the response of human volunteer subjects comes from early studies (primarily the 1940s) investigating the effects the nitrogen mustards as chemical warfare agent candidates. As vesicants, the relative potency is HN3> HN1> HN2 although the differences are not great. Dermal effects appear to be enhanced by moisture (as from sweating). Estimated thresholds for vesicant activity and eye injury are summarized in Table 7. Ocular injury (irritation resulting in compromised operational effectiveness of military personnel) appears to occur at exposures much lower than those causing dermal responses (Table 7). All of the toxic effects of nitrogen

mustard appear to involve a latency period; several hours for ocular responses and several days for dermal blistering. Furthermore, effects may occur in the absence of detection. Although the nitrogen mustards are alkylating agents with known mutagenicity, there are no animal cancer bioassays for inhalation exposure and no human carcinogenicity data.

Table 7. Estimated effects thresholds in humans exposed to nitrogen mustard vapors.

HN1	HN2	HN3	Effect
-	0.012 mg-min/m^3	-	No observable effect level during therapeutic use of HN2 (Van Vloten et al., 1993)
90 mg-min/m^3	70 mg-min/m^3	42 mg-min/m^3	Moderate but reversible ocular effects (Porton report, 1942a, 1943d; U.S. Army Med. Div., 1945c,d; NDRC, 1946)
>21,170 mg-min/m^3	5800 mg-min/m^3	1800 mg-min/m^3 1300 mg-min/m^3	Median blistering Ct (10-min or 20-min exposure) for normal skin Median blistering Ct (20-min exposure) for sweating skin (NDRC, 1944)

3. ANIMAL TOXICITY DATA

3.1. Acute Lethality

Numerous acute lethality values for nitrogen mustards in several species have been reported. These data are primarily from older studies for which experimental protocol details are not readily available. Further, many experiments were specifically designed to assess lethal exposure parameters, especially in terms of cumulative exposure, and generally provide little information on nonlethal responses. Lethality in laboratory species appears to be delayed for one day to two weeks depending on exposure severity. Acute lethality data for HN1, HN2, and HN3 in animals are summarized in Tables 8-10.

Table 8. Lethal toxicity in laboratory species following inhalation exposure to HN1.

Species	LCt_{50} ($mg \cdot min/m^3$)	Duration (min)	No. animals	Comments	Reference
Monkey	1500	10	6	estimated LCt_{50} from nominal exposure values; low-flow chamber; 15-day observation	OSRD, 1945
Dog	800	10	14	estimated LCt_{50} from nominal exposure values; low-flow chamber; 10 to 30-day observation	OSRD, 1945
Rat	750	10	10	estimated LCt_{50} from nominal exposure values; low-flow chamber; 30-day observation	OSRD, 1945
	860	20-100	84	LCt_{50}; analytical exposure values; large chamber; 90EF 10 & 15-day observation; circulation ("wind speed") of no consequence	U.S. Army Med. Div., 1945a
	<1200	30	34	LCt_{50}; analytical exposure values; static chamber; 15-day observation	Porton Report, 1944
Mouse	900	10	280	LCt_{50}; analytical exposure values in low-flow chamber; 15-day observation	OSRD, 1945
	900	10	89	LCt_{50}; analytical exposure values in high-flow chamber; 15-day observation	OSRD, 1945
	960	20-100	140	LCt_{50}; analytical exposure values; large chamber; 90EF 15-day observation; circulation ("wind speed") of no consequence	U.S. Army Med. Div., 1945a
	1100	20-100	140	LCt_{50}; analytical exposure values; large chamber; 90EF 10-day observation; circulation ("wind speed") of no consequence	U.S. Army Med. Div., 1945a
	<1200	30	30	LCt_{50}; analytical exposure values in static chamber; 15-day observation	Porton Report, 1944
	1300	10	140	LCt_{50} estimated from nominal exposure values in low-flow chamber; 10-day observation	U.S. Army, 1942

Table 8. (Cont.). Lethal toxicity in laboratory species following inhalation exposure to HN1.

Species	LCt_{50} (mg·min/m^3)	Duration (min)	No. animals	Comments	Reference
Rabbit	900	30	66	LCt_{50} estimated from nominal exposure values in low-flow chamber at 90EF; 15-day observation	U.S. Army Med. Div., 1945b
	900	20-100	84	LCt_{50}; analytical exposure values; large chamber; 90EF 15-day observation; circulation ("wind speed") of no consequence	U.S. Army Med. Div., 1945a
	910	360	54	LCt_{50}; analytical exposure values in low-flow chamber; 90EF 15-day observation; circulation ("wind speed") of no consequence	U.S. Army Med. Div., 1945b
	1000	30	18	LCt_{50}; analytical exposure values in low-flow chamber; 73EF 15-day observation	U.S. Army Med. Div., 1945b
	1100	20-100	84	LCt_{50}; analytical exposure values in low-flow chamber; 90EF 15-day observation; circulation ("wind speed") of no consequence	U.S. Army Med. Div., 1945b
	1000-3000	10	5	LCt_{50} estimated from nominal exposure values in low-flow chamber; 30-day observation	OSRD, 1945
	>4000	30	15	LCt_{50}; analytical exposure values in static chamber; 15-day observation	Porton Report, 1943a
Guinea pig	1500-3000	30	36	LCt_{50}; analytical exposure values in static chamber; 15-day observation	OSRD, 1945
	2500	10	18	LCt_{50} estimated from nominal exposure values in low-flow chamber; 30-day observation	OSRD, 1945
Cat	400	10	12	LCt_{50} estimated from nominal exposure values in low-flow chamber; 10-30 day observation	OSRD, 1945

NDRC, 1946

Table 9. Lethal toxicity in laboratory species following inhalation exposure to HN2.

Species	LCt_{50} (mg·min/m^3)	Duration (min)	No. animals	Comments	Reference
Dog	2000	10	4	LCt_{50} estimated from nominal exposure values in low-flow chamber; 10 to 30-day observation	OSRD, 1943b
Rat	600-1200	2	24	LCt_{50} based upon analytically measured concentrations in static chamber; 18-day observation	Porton Report, 1942b
	1500	5	40	LCt_{50} based upon analytically measured concentrations in static chamber; <10-day observation	Porton Report, 1942b
	1750	10	24	LCt_{50} estimated from nominal exposure values in static chamber; 10-day (uncertain) observation	CETS, 1942
	<1800	20	30	LCt_{50} based upon analytically measured concentrations in static chamber; <10-day observation	Porton Report, 1942b
	1000-3000	30	30	LCt_{50} based upon analytically measured concentrations in static chamber; <10-day observation	Porton Report, 1942b
	#2000	10	30	LCt_{50} based upon analytically measured concentrations in static chamber; <10-day observation	Porton Report, 1942b
	2000	120-360	56	LCt_{50} based upon analytically measured concentrations in low-flow chamber; 14-day observation	Porton Report, 1943b
	2000-3000	60-120	26	LCt_{50} based upon analytically measured concentrations in low-flow chamber; no observation time specified	Porton Report, 1943b
	2000-3000	240-510	40	LCt_{50} based upon analytically measured concentrations in low-flow chamber; 14-day observation time	Porton Report, 1943b
	2000-4000	240-450	38	LCt_{50} based upon analytically measured concentrations in low-flow chamber; no observation time specified	Porton Report, 1943b

Table 9 (Cont.). Lethal toxicity in laboratory species following inhalation exposure to HN2.

Species	LCt_{50} (mg·min/m^3)	Duration (min)	No. animals	Comments	Reference
Mouse	1500	30	50	LCt_{50} estimated from nominal exposure values in static chamber; >25-day observation	Porton Report, 1942b
	2000	20	40	LCt_{50} based upon analytically measured concentrations in static chamber; >25-day observation time	Porton Report, 1942b
	2600	10	138	LCt_{50} based upon analytically measured concentrations in low-flow chamber; 15-day observation time	OSRD, 1944
	2000-6000	10	30	LCt_{50} based upon analytically measured concentrations in static chamber; >25-day observation time	Porton Report, 1942b
	2000-7000	10	40	LCt_{50} estimated from nominal exposure values in static chamber; 10-day observation	CETS, 1942
	3000-4000	60-120	36	LCt_{50} based upon analytically measured concentrations in low-flow chamber; no observation time specified	Porton Report, 1943b
	4000-5000	240-450	54	LCt_{50} based upon analytically measured concentrations in low-flow chamber; no observation time specified	Porton Report, 1943b
	5100	2	200	LCt_{50} estimated from nominal exposure values in low-flow chamber; 10-day observation	U.S. Army, 1942
	5600	10	240	LCt_{50} estimated from nominal exposure values in low-flow chamber; 10-day observation	U.S. Army, 1942
	5700	30	160	LCt_{50} estimated from nominal exposure values in low-flow chamber; 10-day observation	U.S. Army, 1942
	6000	2	40	LCt_{50} based upon analytically measured concentrations in static chamber; <25-day observation period.	Porton Report, 1942b

Table 9 (Cont.). Lethal toxicity in laboratory species following inhalation exposure to HN2.

Species	LCt_{50} ($mg \cdot min/m^3$)	Duration (min)	No. animals	Comments	Reference
Rabbit	1000-3500	5	24	LCt_{50} based upon analytically measured concentrations in static chamber; 26-day observation period	Porton Report, 1942b
	>1200	2	24	LCt_{50} based upon analytically measured concentrations in static chamber; 25-day observation period	Porton Report, 1942b
	3000	10	19	LCt_{50} based upon analytically measured concentrations in static chamber; 15-day observation period	Porton Report, 1942b
	3000-6000	30	29	LCt_{50} based upon analytically measured concentrations in static chamber; 26-day observation period	Porton Report, 1942b
	2000-8000	20	30	LCt_{50} based upon analytically measured concentrations in static chamber; 26-day observation period	Porton Report, 1942b
	4400	10	4	LCt_{50} estimated from nominal exposure values in static chamber; 15-day observation	Porton Report, 1942b
Guinea pig	>1200	2	24	LCt_{50} based upon analytically measured concentrations in static chamber; non-specified observation period	Porton Report, 1942b
	3000	5	24	LCt_{50} based upon analytically measured concentrations in static chamber; 19-day observation period	Porton Report, 1942b
	2500-5000	240-450	14	LCt_{50} based upon analytically measured concentrations in low-flow chamber; non-specified observation period	Porton Report, 1943b
	>3800	60-120	8	LCt_{50} based upon analytically measured concentrations in low-flow chamber; non-specified observation period	Porton Report, 1943b
	3000-6000	10	20	LCt_{50} based upon analytically measured concentrations in static chamber; 5-day observation period	Porton Report, 1942b
	3000-6000	30	30	LCt_{50} based upon analytically measured concentrations in static chamber; 7-day observation period	Porton Report, 1942b
	5500	10	12	LCt_{50} estimated from nominal exposure values low-flow chamber; 15-day observation	OSRD, 1943b
	3500-7000	10	16	LCt_{50} estimated from nominal exposure values in static chamber; 10-day observation	CETS, 1942
	4000-8000	20	30	LCt_{50} based upon analytically measured concentrations in static chamber; 19-day observation period	Porton Report, 1942b

Table 10. Lethal toxicity in laboratory species following inhalation exposure to HN3.

Species	LCt_{50} (mg·min/m^3)	Duration (min)	No. animals	Comments	Reference
Dog	400-1500	10	36	LCt_{50} based upon analytically measured concentrations in low-flow chamber; non-specified observation period	OSRD, 1945
Rat	670	10-100	69	LCt_{50} based upon analytically measured concentrations in static chamber at 85EF; 15-day observation period	Porton Report, 1943c
	800	0.25-2	104	LCt_{50} based upon analytically measured concentration of fine aerosol; 20-day observation period	Porton Report, 1944
	$1000	30	50	LCt_{50} based upon analytically measured concentrations in static chamber at 85EF; non-specified observation period	Porton Report, 1943c
	800-1500	10	18	LCt_{50} based upon analytically measured concentrations in low-flow chamber; 15-day observation period	OSRD, 1945
	1700	10	28	LCt_{50} estimated from nominal exposure values in low-flow chamber; 15-day observation	Smith, 1943
Mouse	165	10	20	LCt_{50} based upon analytically measured concentrations in wind tunnel, 95EF	OSRD, 1945
	300	10	60	LCt_{50} based upon analytically measured concentrations in high-flow chamber (aerosol present); 15-day observation period	OSRD, 1945
	570	10-100	139	LCt_{50} based upon analytically measured concentrations; 90EF, 85% humidity; 15-day observation period	U.S. Army Med. Div. 1945c
	590	10	230	LCt_{50} based upon analytically measured concentrations in low-flow chamber; 15-day observation period	OSRD, 1945
	500-600	10	58	LCt_{50} based upon analytically measured aerosol-free vapor	U.S. Army Med. Div., 1944

Table 10 (Cont.). Lethal toxicity in laboratory species following inhalation exposure to HN3.

Species	LCt_{50} (mg·min/m^3)	Duration (min)	No. animals	Comments	Reference
Rabbit	500	10-18	8	LCt_{50} based upon analytically measured concentrations in low-flow chamber at 100EF; 15-day observation period	OSRD, 1945
	635	10-100	70	LCt_{50} based upon analytically measured concentrations; 90EF, 85% humidity; 15-day observation period	U. S. Army Med. Div., 1945c
	830	18-50	30	LCt_{50} based upon analytically measured concentrations in low-flow chamber at 72EF; 15-day observation period	OSRD, 1945
	>1000	30	31	LCt_{50} based upon analytically measured concentrations in static chamber at 85EF; non-specified observation period	Porton Report, 1943c
	1000-3000	10	11	LCt_{50} estimated from nominal exposure values in low-flow chamber; 10-day observation	OSRD, 1945
Guinea pig	>1000	30	45	LCt_{50} based upon analytically measured concentrations in static chamber at 85EF; non-specified observation period	Porton Report, 1943c
	>2300	10	10	LCt_{50} estimated from nominal exposure values in low-flow chamber; non-specified observation period	OSRD, 1945

NDRC, 1946

3.2. Nonlethal Toxicity

Nitrogen mustards are reportedly non-irritating at exposure concentrations lower than those resulting in vesicant effects (NDRC, 1945). Reports available for review focused on lethal responses and provided no information on nonlethal effects.

3.3. Developmental/Reproductive Toxicity

No developmental/reproductive toxicity data in animals were available.

3.4. Genotoxicity

The genotoxicity of nitrogen mustards has been extensively reviewed (Fox and Scott, 1980). Nitrogen mustards are known to produce deletions and chromosomal structural aberrations in multiple test systems, and are have been shown to induce sister chromatid exchanges. Assessment of genetic damage in humans is reportedly difficult due to the absence of sufficient dose-response data in laboratory species.

3.5. Carcinogenicity

No studies are available regarding carcinogenicity in animals following inhalation exposure to nitrogen mustards. A high incidence of spindle-cell sarcomas was observed in male and female rats given subcutaneous injections of HN3 (0.1 or 0.25 mg/kg/day or 1.0 mk/kg/wk for 6 months) but no such tumors were detected in controls (Sýkora et al., 1981).

3.6. Summary

Variability in the lethal response among several species of animals appears to approximately 2 to 3-fold with rats tending to be somewhat more sensitive. Results of lethality studies in several species affirm a latency period of at least several days. Higher temperatures and moisture on the skin appear to enhance the vesicant activity of nitrogen mustards. Secondary infection may account for variability in toxicity especially relative to this latency period (NDRC, 1945).

4. SPECIAL CONSIDERATIONS

4.1. Metabolism and Disposition

Vapor penetration studies provided information on the effects of time, temperature and humidity on penetration of HN1 and HN3 into the forearm skin of human male volunteers (NDRC, 1945). Results of this study revealed that penetration of HN1 and HN3 was linear with time (5 to 20 minutes for HN1 and 30-60 minutes for HN3). At 71-72EF and 50-52% relative humidity, HN1 penetration rate was 2.8 Fg/cm^2/min and that of HN3 was 0.18 Fg/cm^2/ min at 72-73 EF and 45-48% relative humidity. At 86-87EF and 47-49% relative humidity, HN1 penetration rate increased to 5.2 Fg/cm^2/min and HN3 penetration rate increased to 0.3 Fg/cm^2/min at 85EF and47-48% relative humidity. The immonium ion (see below) being water soluble is excreted via the urine.

4.2. Mechanism of Toxicity

A key reaction that is likely important to the biological activity of nitrogen mustard is the formation of a cyclic onium cation (immonium for nitrogen mustards) in the presence of polar solvents such as water (Somani, 1992). The immonium ion can react with nucleophiles such as nitrogen in the base components of nucleic acids and sulfur in SH-groups in proteins and peptides. The precise mechanism of nitrogen mustards is unclear but may involve any or all of the following molecular mechanisms: DNA/RNA alkylation and resultant effects, effects on

glutathione, membrane effects (protein cross-linking, ion transport effects), and cytoplasmic effects (release of lysosomal enzymes). The possible mechanisms of nitrogen mustard have been reviewed by Gray (1989)

4.3. Structure-Activity Relationships

Sulfur mustard also forms onium ion (sulfonium) and exhibits a similar toxicologic profile (vesication/blistering, ocular and respiratory tract injury). Sulfur mustard, unlike nitrogen mustards, is readily detectable by odor and sensory irritation.

5. DATA ANALYSIS FOR AEGL-1

5.1. Human Data Relevant to AEGL-1

A study by Van Vloten et al. (1993) found that treatment of mycosis fungoides with HN2 resulted in mean air concentrations of 0.036 mg HN2/m^3 within one meter of the patient over a 20-minute period. Immediately following treatment, the HN2 concentration dropped to 0.004 mg/m^3. Mean concentration over the 273-minute monitor time was 0.012 mg/m^3. No adverse effects were reported to have resulted from these exposures.

5.2. Animal Data Relevant to AEGL-1

No exposure-response data are available regarding AEGL-1 severity effects in animals exposed to nitrogen mustards.

5.3. Derivation of AEGL-1

AEGL-1 values for nitrogen mustards are not recommended (Table 11) due to insufficient data and because adverse effects are reported to occur in the absence of detection of the agents (NDRC, 1946). The monitoring data provided by Van Vloten et al. (1993) referenced no health effects upon which to base an AEGL determination. The exposure data do, however, serve as reference point for other AEGL values.

TABLE 11. AEGL-1 Values For HN1, HN2, and HN3

Classification	10-min	30-min	1-hr	4-hr	8-hr
AEGL-1					
HN1	NR	NR	NR	NR	NR
HN2	NR	NR	NR	NR	NR
HN3	NR	NR	NR	NR	NR

NR: not recommended due to insufficient data. Absence of AEGL-1 values does not imply that exposure below AEGL-2 is without adverse effects.

6. DATA ANALYSIS FOR AEGL-2

6.1. Human Data Relevant to AEGL-2

Ocular irritation and formation of dermal erythemas and blistering are the most prevalent nonlethal effects in humans exposed to vapors of nitrogen mustards. Based upon results of military studies in which human volunteers were exposed to nitrogen mustards, ocular effects manifest at notably lower Cts than do the dermal effects (Table 7). The ocular effects characterized by lacrimation, feeling of grittiness, photophobia, blepharospasm, conjunctival injection are reversible and appear to develop post exposure. Using operational effectiveness with rifles as the criterion, “casualty” thresholds for the volunteer subjects were developed for

HN1 (90 mg-min/m^3) and HN3 (42 mg-min/m^3) (Porton Report, 1943d; U.S. Army Med. Div. 1945c,d). For HN2, 70 mg-min/m^3 as considered a target for minimum offensive purposes (Porton Report, 1942a). Exposure to HN2 at 55 mg-min/m^3 was considered a lowest limit for disablement based upon operational effectiveness. For some of the volunteer subjects, these exposures were associated with pain and persisted for hours or days (up to 24 days for HN1).

Based on 10 to 20-minute exposures of the forearms of human volunteers, median dermal blistering threshold of >21,170 mg-min/m^3, 5800 mg-min/m^3, and 1300-1800 mg-min/m^3 were estimated, respectively, for HN1, HN2, and HN3 (NDRC, 1944).

6.2. Animal Data Relevant to AEGL-2

Exposure-response data for nonlethal responses of animals exposed to nitrogen mustard vapors were not available in the reviewed reports. Available animal data focused on lethal responses. There are no data currently available applicable to development of AEGL-2 values for nitrogen mustards.

6.3. Derivation of AEGL-2

The most appropriate data for development of AEGL-2 values for nitrogen mustards are the data generated for estimating thresholds for military personnel "casualties" as determined by ocular irritation. The threshold values were based upon reversible effects following vapor exposures of relatively short maximum durations (7-67 minutes) but included post exposure observation up to 24 days. "Casualty" tended to be defined in terms of compromised efficiency in military type tasks, e.g., use of firearms. In this context, eye injury thresholds of 90 mg-min/m^3, 55 mg-min/m^3 (70 mg-min/m^3 for an offensive application) and 42 mg-min/m^3 were developed for HN1, HN2, and HN3, respectively (Porton Report 1942a, 1943d, U.S. Army Med. Div. 1945c,d). These thresholds were, however, associated with effects (photophobia, lacrimation, feeling of grittiness in the eyes, and ocular pain) some of which persisted up to 24 days. To avoid possibility of ocular responses that would adversely affect egress from an emergency situation, the lower range of the Ct product for these threshold estimates for military personnel (see Section 2.2.2) was selected as the point-of-departure (POD) for AEGL-2 derivation.

Although thresholds for dermal effects (erythema and blistering) following exposure to nitrogen mustard vapors were also developed, they were considerably greater than those for ocular irritation. These thresholds were based upon effects that are reversible and not of a severity that would preclude escape. Therefore, these ocular irritation thresholds were considered NOAELs for AEGL-2 severity and were considered appropriate for development of AEGL-2 values.

HN1

The lower range of the ocular effects Ct product of 37-90 mg-min/m^3 based upon exposure durations of 5 to 67 minutes was used as the point-of-departure for the AEGL-2 values for HN1. This cumulative exposure would result in exposure concentrations of 3.7 mg/m^3, 1.2 mg/m^3, and 0.62 mg/m^3, respectively, for 10, 30, and 60 minutes, all of which are within the experimental exposure duration. The exposure time-response relationship for longer durations (e.g., the 4-hr and 8-hr AEGL time points) is uncertain and an empirically-derived value for the exponent, *n*, in the equation $C^n \times t = k$ could not be developed. Consistent with AEGL methodologies (NRC, 2001), an *n* of 1 was used in extrapolating from the 60-minute experimental exposure of 0.62

mg/m^3 period to the 4-hour and 8-hour AEGL-2 time periods resulting in exposures of 0.15 mg/m^3 and 0.077 mg/m^3.

The test subjects were from a population of military personnel for which it was assumed had no compromising ophthalmic conditions and were in good health. Definitive assessment of individual variability in the toxic response to HN1 is not possible. However, the ocular response is likely the result of direct-contact with the nitrogen mustard vapors rather than a systemically-mediated process. Therefore, the uncertainty factor for individual variability was limited to 3. Some of the tests were apparently performed using volunteers with oronasal masks which would have precluded development of respiratory tract effects. A modifying factor of 3 was applied to account for possible latent effects on the respiratory tract. The resulting AEGL-2 values for HN1 are shown in Table 12.

HN2

For HN2, the ocular effects threshold of 40 mg-min/m^3 (based on exposure durations up to 10 minutes) was the lower limit of the cumulative exposure resulting in compromised military effectiveness and was used as the POD. For a 10-minute exposure, this is equivalent to an exposure concentration of 4.0 mg/m^3. The exposure time-response relationship for longer durations (30-min., 1-hr, 4-hr and 8-hr AEGL time points) is uncertain and an empirically-derived value for the exponent, *n*, in the equation $C^n \times t = k$ could not be developed. Consistent with AEGL methodologies (NRC, 2001), an *n* of 1 was used in extrapolating from the 10-minute experimental exposure of 40 mg/m^3 period to the 30-minute, 1-hour, 4-hour and 8-hour AEGL-2 time periods resulting in exposures of 4.0 mg/m^3, 1.3 mg/m^3, 0.67 mg/m^3, 0.17 mg/m^3, and 0.083 mg/m^3.

An uncertainty factor of 3 was applied to account for individual variability in the ocular response (mediated by direct-contact mechanisms which would not be expected to vary greatly among individuals) and for possible latent effects on the respiratory tract; the latter is especially relevant to HN2 for which test results were from volunteers wearing oronasal masks. The modifying factor was increased to10 (as opposed to 3 for the other nitrogen mustards) to account for a deficient database (as for HN1 and HN3), to estimate an AEGL-2 no-effect level as the POD (the observed effects following HN2 exposure appeared to be of a severity such that there may be impairment of escape from a situation), and for uncertainties regarding the number of test subjects. The resulting AEGL-2 values for HN2 are shown in Table 12.

HN3

Ocular effects (conjunctival injection, lacrimation, photophobia, ocular irritation) occurred in human volunteers exposed to 20-42 mg-min/m^3 (7-minute exposure duration). Similar to HN1, the lower range of this cumulative exposure was selected as the POD for HN2 AEGL-2 derivation. For the 7-minute exposure, this is equivalent to an exposure concentration of 2.9 mg/m^3. The exposure time-response relationship for longer durations (10-min., 30-min., 1-hr, 4-hr and 8-hr AEGL time points) is uncertain and an empirically-derived value for the exponent, *n*, in the equation $C^n \times t = k$ could not be developed. Consistent with AEGL methodologies (NRC, 2001), an *n* of 1 was used in extrapolating from the 7-minute experimental exposure of 2.9 mg/m^3 period to the 10-min., 30-minute, 1-hour, 4-hour and 8-hour AEGL-2 time periods resulting in exposures of 2.0 mg/m^3, 0.67 mg/m^3, 0.33 mg/m^3, 0.083 mg/m^3, and 0.042 mg/m^3. Although the short exposure duration results in extensive extrapolation, an *n* of 1 was applied to

provide more conservative exposure concentration estimates. Furthermore, the critical effect is a conservative point-of-departure for AEGL-2 severity effects.

Similar to HN1, the combined uncertainty factor and modifying factor adjustment was 10 to account for individual variability in the ocular response and uncertainties regarding possible respiratory tract effects. The resulting AEGL-2 values for HN3 are shown in Table 12. More details regarding AEGL-2 derivations for HN1, HN2, and HN3, are provided in Appendix A.

Table 12. AEGL-2 Values (mg/m^3) For Nitrogen Mustards (HN1, HN2, and HN3)[a]

Classification	10-min	30-min	1-hr	4-hr	8-hr
AEGL-2					
HN1	0.37	0.12	0.062	0.015	0.0077
HN2	0.13	0.044	0.022	0.0056	0.0028
HN3	0.20	0.067	0.033	0.0083	0.0042

[a] By consensus vote, the AEGL-2 values for HN2 are representative of all nitrogen mustards reviewed.

7. DATA ANALYSIS FOR AEGL-3

7.1. Human Data Relevant to AEGL-3

No human lethality data were reviewed.

7.2. Animal Data Relevant to AEGL-3

There are numerous military reports regarding lethality of laboratory species exposed to HN1, HN2, and HN3 vapors. These reports provided LCt_{50} values generally representing short duration (<1 hour) exposures although some studies exposed animals for 100-510 minutes. Most studies observed animals for up to 15 days post exposure due to the know latency period associated with nitrogen mustard toxicity. Based upon LCt_{50} values, the rat appeared to be somewhat more sensitive to all three nitrogen mustards than did other species (monkey, dog, mouse, rabbit, guinea pig, cat).

7.3. Derivation of AEGL-3

For all three nitrogen mustards, the lethality threshold was estimated as a three-fold reduction of the rat LCt_{50} for the specific agent. For all three nitrogen mustards, the lowest LCt_{50} values were those for the rat. Lethal exposure values (LCt_{50} values) did not, however, appear to vary more than three-fold among the species tested. Histopathologic findings were not available for review. Most lethality studies utilized observation periods of sufficient duration to address the known latency period for nitrogen mustard-induced effects.

HN1

The rat LCt_{50} of 860 mg-min/m^3 was the basis for development of AEGL-3 values for HN1. This value was derived based upon the lethal response of rats exposed for periods of 20 to 100 minutes. Exposures were analytically determined and conducted at 90EF (a worst-case scenario) and mortality assessed over a 10 to 15-day observation period. A threshold for lethality (287 mg-min/m^3) was estimated as a three-fold reduction of the LCt_{50} which served as the point-of-departure for AEGL-3 development (NRC, 2001).

The exposure time-response relationship for exposure durations shorter than the experimental range of 20 to 100 minutes (i.e., 10-min. AEGL-3) and longer than the experimental periods (i.e., 4-hr and 8-hr AEGL-3) is uncertain and an empirically-derived value for the exponent, *n*, in the equation $C^n \times t = k$ could not be developed. Consistent with AEGL methodologies (NRC, 2001), an *n* of 3 was used in extrapolating from the 20-minute experimental exposure (equivalent to 14.4 mg/m^3) to the 10-min. AEGL-3 time period. An *n* of 1 was used to extrapolate to the 4- and 8-hour AEGL time periods. Adjustment for uncertainty regarding interspecies variability was limited to 3 because LCt_{50} values among seven species (including nonhuman primates) did not appear to vary by more than three-fold; the rat being somewhat more sensitive. Adjustment regarding individual variability was also limited to 3 because of the action of nitrogen mustards on cellular components would not be expected to greatly differ, and because additional downward adjustment would result in AEGL-3 values inconsistent with AEGL-2 values and available human data (ocular and dermal response data and monitoring data for therapeutic use of nitrogen mustard). The AEGL-3 values for HN1 are shown in Table 13 and their derivation summarized in Appendix A.

HN2

The point of departure for HN2 AEGL-3 development was an LCt_{50} of 2000 mg-min/m^3 for rats exposed to HN2 vapors for 120-360 minutes (Porton Report, 1943b). Exposures were analytically determined and mortality assessed over a 14-day observation period. A threshold for lethality (667 mg-min/m^3) was estimated as a three-fold reduction of the LCt_{50} which served as the point-of-departure for AEGL-3 development (NRC, 2001).

The exposure time-response relationship for exposure durations shorter than the experimental range of 120 to 360 minutes (i.e., 10-min., 30-min, and 1-hr. AEGL-3) and longer than the experimental periods (i.e., 4-hr and 8-hr AEGL-3) is uncertain and an empirically-derived value for the exponent, *n*, in the equation $C^n \times t = k$ could not be developed. Consistent with AEGL methodologies (NRC, 2001), an *n* of 3 was used in extrapolating from the 120-minute experimental exposure (equivalent to 5.6 mg/m^3) to the 10-min., 30-min. and 1-hr AEGL-3 time period. An *n* of 1 was used to extrapolate to the remaining AEGL time periods. Total uncertainty adjustment was 10 as described for HN1. The AEGL-3 values for HN2 are shown in Table 13 and their derivation summarized in Appendix A.

HN3

The point of departure for HN3 AEGL-3 development was an LCt_{50} of 670 mg-min/m^3 for rats exposed to HN3 vapors for 10-100 minutes (Porton Report, 1943c). Exposures were analytically determined and conducted at 85EF and mortality assessed over a 15-day observation period. A threshold for lethality (223 mg-min/m^3) was estimated as a three-fold reduction of the LCt_{50} which served as the point-of-departure for AEGL-3 development (NRC, 2001).

The point-of-departure for 10-min., 30-min. and 1-hr AEGL-3 values was determined directly from the estimated lethality threshold LCt (223 mg-min/m^3). The exposure time-response relationship for exposure durations longer than the experimental periods (i.e., 4-hr and 8-hr AEGL-3) is uncertain and an empirically-derived value for the exponent, *n*, in the equation $C^n \times t = k$ could not be developed. Consistent with AEGL methodologies (NRC, 2001) an *n* of 1 was used to extrapolate to the 4-hr and 8-hr AEGL-3 time periods. Total uncertainty adjustment was

10 as described for HN1. The AEGL-3 values for HN3 are shown in Table 13 and their derivation summarized in Appendix A.

Table 13. AEGL-3 Values (mg/m^3) for Nitrogen Mustards (HN1, HN2, and HN3)[a]

Classification	10-min	30-min	1-hr	4-hr	8-hr
AEGL-3	2.2	0.74	0.37	0.093	0.047

[a] By consensus vote, the AEGL-3 values for HN3 are representative of all nitrogen mustards reviewed.

8. SUMMARY OF AEGLs

8.1. AEGL Values and Toxicity Endpoints

AEGL-1 values were not recommended due to the absence of definitive dose-response data consistent with AEGL-1 type effects and because adverse effects (ocular irritation, dermal erythema and blistering) may occur at exposures below odor detection levels (NDRC, 1946). Monitoring data obtained during HN2 therapy referenced no health effects upon which to base an AEGL determination. The AEGL-2 values were based upon ocular irritation effects in human volunteer subjects and resulting estimated thresholds for compromised operational effectiveness. The AEGL-2 value took into consideration of sensitive responders and possible respiratory effects. The resulting AEGL-2 values are also relationally appropriate to therapeutic monitoring data. Animal LCt_{50} data used to develop AEGL-3 were generally based upon exposure durations encompassing the majority of the AEGL time points resulting in temporal extrapolation which was not unreasonable. The toxicity profiles of nitrogen mustards and sulfur mustard (HD) are qualitatively and quantitatively similar (NDRC, 1946). The AEGL values for nitrogen mustards are consistent with previously established AEGL values for agent HD (NRC, 2003). The AEGL values for nitrogen mustards (HN1, HN2, and HN3) are summarized in Table 14.

A comparison of the nitrogen mustard AEGL values to available human and animal data (Appendix D) suggests appropriateness of the AEGL values regarding accommodating uncertainties in human responses to nitrogen mustard vapors.

By consensus, the National Advisory Committee for Acute Exposure Guideline Levels chose the AEGL values for HN2 as representing the AEGLs for all of the reviewed nitrogen mustards.

Table 14. Summary of AEGL Values for Nitrogen Mustards(mg/m^3)

Classification	10-minute	30-minute	1-hour	4-hour	8-hour
AEGL-1 (Nondisabling)					
HN1	NR[a]	NR[a]	NR[a]	NR[a]	NR[a]
HN2	NR[a]	NR[a]	NR[a]	NR[a]	NR[a]
HN3	NR[a]	NR[a]	NR[a]	NR[a]	NR[a]
AEGL-2[a] (Disabling)					
HN1	0.37	0.12	0.062	0.015	0.0077
HN2	0.13	0.044	0.022	0.0056	0.0028
HN3	0.20	0.067	0.033	0.0083	0.0042
AEGL-3[b] (Lethality)					
HN1	2.9	0.96	0.48	0.12	0.060
HN2	6.7	2.2	1.1	0.28	0.14
HN3	2.2	0.74	0.37	0.093	0.047

[a] By consensus vote, the AEGL-2 values for HN2 are representative of all nitrogen mustards reviewed.
[b] By consensus vote, the AEGL-3 values for HN3 are representative of all nitrogen mustards reviewed.

8.2. Comparisons with Other Standards and Guidelines

Standards and guidance levels for workplace and community exposures are limited. Currently available values are listed in Table 15.

Table 15. Extant Standards and Guidelines for Nitrogen Mustards (HN1, HN2, HN3)

Guideline	Exposure Duration				
	10 minute	30 minute	1 hour	4 hour	8 hour
AEGL-1 (mg/m^3)					
HN1	NR[a]	NR[a]	NR[a]	NR[a]	NR[a]
HN2	NR[a]	NR[a]	NR[a]	NR[a]	NR[a]
HN3	NR[a]	NR[a]	NR[a]	NR[a]	NR[a]
AEGL-2 (mg/m^3)[b]					
HN1	0.37	0.12	0.062	0.015	0.0077
HN2	0.13	0.044	0.022	0.0056	0.0028
HN3	0.20	0.067	0.033	0.0083	0.0042
AEGL-3 (mg/m^3)[b]					
HN1	2.9	0.96	0.48	0.12	0.060
HN2	6.7	2.2	1.1	0.28	0.14
HN3	2.2	0.74	0.37	0.093	0.047
US Army					
WPL[c]					0.003 mg/m^3
GPL[d]					NR

[a] **NR**: Not Recommended or specified. Absence of an AEGL-1 does not imply that exposure below the AEGL-2 is without adverse effects. U.S. Army GPL not identified.
[b] By consensus vote, the AEGL-2 values for HN2 and AEGL-3 values for HN3 are representative for all nitrogen mustards reviewed.
[c] **U.S. Army WPL** (Worker Population Limit): 8-hr TWA, 5 days/wk (USACHPPM, 1996; USACHPPM, 2004).
[d] **U.S. Army GPL** (General Population Limit) (USACHPPM, 1996; USACHPPM, 2004).

8.3. Data Adequacy and Research Needs

Data consistent with AEGL-1 severity effects were unavailable. Serious effects (ocular and dermal injury) may occur at exposure levels insufficient to allow for detection. The know latency in manifestation of effects further precludes development of AEGL-1 values in the absence of validated markers of exposure. Data from human volunteer subjects indicate ocular effects to be a sensitive indicator of nitrogen mustard exposure. The AEGL-2 values are based upon human exposure data identifying cumulative exposures below those that would induce irreversible effects or that would result in compromising egress from an exposure situation. Lethality data in several species indicated species variability to be about 2 to-3-fold and provided a data base sufficient for development of AEGL-3 values.

9. REFERENCES

ACGIH (American Conference of Governmental Industrial Hygienists). 2003. Threshold Limit Values and Biological Exposure Indices. ACGIH, Cincinnati, OH.

AIHA (American Industrial Hygiene Association). 1996. The AIHA 1996 Emergency Response Planning Guidelines and Workplace Environmental Exposure Level Guidelines Handbook. AIHA, Fairfax VA.

Boyland, E., Horning, E.S. 1949. The induction of tumours with nitrogen mustards. Br. J. Cancer 3: 118-123.

CETS (Cambridge Extramural Testing Station). 1942. The toxicity of "S" by inhalation. XZ.98 (W.1712). April 20, 1942. Cited in NDRC, 1946.

Fox, M., Scott, D. 1980. The genetic toxicology of nitrogen and sulphur mustard. Mutation Research 75: 131-168.

Gray, P.J. 1989. A literature review on the mechanism of action of sulphur and nitrogen mustard. MRL Tech. Report MRL-TR-89-24. DSTO Materials Research Laboratory, Victoria, Australia.

HSDB (Hazardous Substances Data Bank). 2004. Nitrogen mustard. On-line retrieval. U.S. Natl. Library of Medicine, Natl. Inst. Of Health, Dept. of Health and Human Services

Hunt, C.M., Breazeale, E. L., Lowry, J.J., Lankford, E. 1943. Nitrogen mustards. Comparative vesicant action and cloth penetration. TDMR-656, Chemical Corps Technical Command, Army chemical Center, MD. Unclassified report AD B960 458. Cited in NDRC, 1944.

IARC (International Agency for Research on Cancer). 1990. Pharmaceutical drugs. IARC Monographs on the Evaluation of Carcinogenic Risks to Cancer. V. 50. Lyon. Pp. 143-149.

NDRC (National Defense Research Committee). 1944. A vapor-train study of the comparative vesicancy of mustard and several related amines and sulfides on human skin. Univ. of Chicago Toxicity Laboratory Report No. 34. OSRD Report No. 3944, August 30, 1944.

NDRC (National Defense Research Committee). 1945. The penetration of vesicant vapors into human skin. Rockefeller Inst. Med. Res. OSRD Report No. 4855, March 24, 1945.

NDRC (National Defense Research Committee). 1946. Chemical warfare agents and related chemical problems. Volume I, Parts I-VI. Summary Technical Report of Division 9, NDRC. Office of Scientific Research and Development, National Defense Research Committee. U.S. Department of Commerce National Technical Information Service. PB158507 and PB158508.

NIOSH (National Institute for Occupational Safety and Health). 2004. NIOSH Pocket Guide to Chemical Hazards. NIOSH Publication 94-116, U.S. Department of Health and Human Services; U.S. Government Printing Office, Washington, PB9419504 National Technical Information Service, Springfield, VA.

NIOSH (National Institute for Occupational Safety and Health). 1994. Documentation for Immediately Dangerous to Life or Health Concentrations (IDLHS). National Institute for Occupational Safety and Health, Cincinnati, OH; PB94195047, National Technical Information Service, Springfield, VA.

NRC (National Research Council). 2001. Standing operating procedures for developing acute exposure guideline levels for hazardous chemicals. Committee on Toxicology, Board on Toxicology and Environmental Health Hazards, Commission on Life Sciences, National Research Council. National Academy Press, Washington, DC.

OSHA. 1996. Limits for Air Contaminants. CFR, Title 29, Part 1910.1000, Table Z-1, p. 16.

OSRD (Office of Scientific Research and Development). 1943a. Status report on toxicity and vesicant tests of compounds referred to the University of Chicago Toxicity Laboratory. OSRD 4176. October 3, 1944.

OSRD (Office of Scientific Research and Development). 1943b. Toxicity of chemical warfare agents. Informal Progress Report No. 1. NDRC. 9:4:1. Div. 9-125-M2. Univ. of Chicago Toxicity Laboratory. February 10. Cited in NDRC, 1946.

OSRD (Office of Scientific Research and Development). 1945. The effect of flow rate on the toxicities of H, Q, HN1, HN3 and L by inhalation, by total exposure and by body exposure. OSRD 5000. Div. 9-360-M1. Univ. of Chicago Toxicity Laboratory. April 28. Cited in NDRC, 1946.

Porton Report. 1942a. On the action of S on the eye; its comparison with allied compounds and with H. No. 2402. August 7, 1942. Cited in NDRC, 1946.

Porton Report. 1942b. Pathological changes in animals exposed to S vapour. No. 2378. July 9, 1942. Cited in NDRC, 1946.

Porton Report. 1943a. Vapour toxicity and pathology of ethyl, n-propyl and iso-propyl analogues of HN2. No. 2565. December 10. Cited in NDRC, 1946.

Porton Report. 1943b. Toxicity of S vapour. Further experiments on the exposure of animals to S vapour. No. 2464. February 9, 1943. Cited in NDRC, 1946.

Porton Report. 1943c. Toxicity and pathology of HN3. No. 2548. November 18, 1944. Cited in NDRC, 1946

Porton Report. 1943d. The effects of HN1 vapour on human and rabbit eyes. No. 2563. November 18, 1943. Cited in NDRC, 1946.

Porton Report. 1944. The toxicity of aerosols of HN3. No. 2614. May 30, 1944. Cited in NDRC, 1946.

Somani, S. M. 1992. Toxicokinetics and toxicodynamics of mustard. In: Somani, S.M., ed. Chemical Warfare Agents. Academic Press, Inc. New York. Pp. 13-50.

Smith, H.W. 1943. Untitled Inf. Month Progress Report. New York Univ. Contract No. OEMsr-556. NDRC 9:5:1, No.11. December 10, 1943. Cited in NDRC, 1946.

Sýkora, I., Yortel, V., Marhan, O. Dynterová, A. 1981. Carcinogenicity of trichloromethine hydrochloride (TS-160 Spofa) and morphological damage after its intraamniotic injection. Neoplasma 28: 565-574. Cited in IARC 1990.

Ten Berge, W.F., Zwart, A., Appelman, L.M. 1986. Concentration-time mortality response relationship of irritant and systemically acting vapours and gases. J. Hazard Materials 13: 301-309.

USACHPPM (U.S. Army Center for Health Promotion and Preventive Medicine). 1996. Detailed and General Facts About Chemical Agents - TG 218. USACHPPM, Aberdeen Proving Ground, MD. USACHPPM TG No. 218. October 1996.

USACHPPM (U.S. Army Center for Health Promotion and Preventive Medicine). 2004. Acute Toxicity Estimation and Operational Risk Management of Chemical Warfare Agent Exposures. USACHPPM Report No. 47-EM-5863-04. USACHPPM, Aberdeen Proving Ground, MD. May 2004.

U.S. Army 1942. Bis(2-chloroethyl)methylamine ("S"). Median lethal concentration in mice. TDMR 397. June 20, 1942.. TDMR 521. December 26. Div. 9-300-M1. Cited in NDRC, 1945.

U.S. Army Medical Division. 1944. Medical Division monthly progress report. November, 1944. Cited in NRDC, 1946.

U.S. Army Medical Division. 1945a. Medical Division monthly progress report. September, 1945. Cited in NRDC, 1946.

U.S. Army Medical Division. 1945b. Evaluation of the rabbit for HN1 field bioassay: LC50 symptomatology, pathology, hematology and eye studies. Medical Division Report No. 40. July 7. Cited in NRDC, 1946.

U.S. Army Medical Division. 1945c. Medical Division monthly progress report. March, 1945. Cited in NRDC, 1946.

U.S. Army Medical Division. 1945d. Medical Division monthly progress report. February, 1945. Cited in NRDC, 1946.

Van Vloten, W.A., Cooijams, A.C.M., Poel, J., and Meulembelt, J. 1993. Concentrations of nitrogen mustard in the air during topical treatment of patients with mycosis fungoides. Brit. J. Dermatol. 128: 404-406.

APPENDIX A
Derivation of AEGL Values

Derivation of AEGL-1 for Nitrogen Mustards (HN1, HN2, HN3)

No AEGL-1 values were recommended for HN1, HN2, or HN3 due to lack of sufficient data and because adverse effects are known to occur in the absence of detection.

Derivation of AEGL-2 for Nitrogen Mustards

HN1

Key study:	Porton Report. 1943d. The effects of HN1 vapour on human and rabbit eyes. No. 2563. November 18, 1943. Cited in NDRC, 1946.
Critical effect:	Ocular irritation in human volunteer subjects; cumulative exposure threshold of 37 mg-min/m^3 based upon exposure durations of 5-67 minutes.
Time scaling:	For the 10-min., 30-min, and 1-hr AEGL-2, concentrations determined directly from cumulative exposure threshold value of 37 mg-min/m^3. The exposure concentration-time relationship for longer durations (e.g., the 4-hr and 8-hr AEGL time points) is uncertain and an empirically-derived value for the exponent, *n*, in the equation $C^n \times t = k$ could not be developed. Consistent with AEGL methodologies (NRC, 2001), an *n* of 1 was used in extrapolating from the 60-minute experimental exposure of 0.62 mg/m^3 period to the 4-hour and 8-hour AEGL-2 time periods resulting in exposures of 0.15 mg/m^3 and 0.077 mg/m^3.
Uncertainty factors:	Intraspecies adjustment was limited to 3 because the ocular response is considered the result of direct-contact with the nitrogen mustard vapors rather than a systemically-mediated process.
Modifying factor:	Because some of the tests were apparently performed using volunteers with oronasal masks which would have precluded development of respiratory tract effects, a modifying factor of 3 was applied to account for possible effects on the respiratory tract.
10-minute AEGL-2	$C^1 \times 10$ min. = 37 mg-min/m^3 C = 3.7 mg/m^3 10-min AEGL-2 = (3.7 mg/m^3)/10 = 0.37 mg/m^3
30-minute AEGL-2	$C^1 \times 30$ min. = 37 mg-min/m^3 C = 1.2 mg/m^3 30-min AEGL-2 = (1.2 mg/m^3)/10 = 0.12 mg/m^3
1-hour AEGL-2	$C^1 \times 60$ min. = 37 mg-min/m^3 C = 0.62 mg/m^3 60-min AEGL-2 = (0.62 mg/m^3)/10 = 0.062mg/m^3
4-hour AEGL-2	$C^1 \times 240$ min. = 37 mg-min/m^3 C = 0.15 mg/m^3 240-min AEGL-2 = (0.15 mg/m^3)/10 = 0.015 mg/m^3

8-hour AEGL-2 $C^1 \times 480$ min. = 37 mg-min/m^3
$C = 0.077$ mg/m^3
480-min AEGL-2 = (0.077 mg/m^3)/10 = 0.0077 mg/m^3

Derivation of AEGL-2 for Nitrogen Mustards

HN2

Key study:	Porton Report. 1942a. On the action of S on the eye; its comparison with allied compounds and with H. No. 2402. August 7, 1942. Cited in NDRC, 1946
Critical effect:	Ocular irritation in human volunteer subjects; cumulative exposure threshold of 40 mg-min/m^3 based upon exposure durations of 0.5-10 minutes.
Time scaling:	For the 10-min. AEGL-2, concentrations were determined directly from cumulative exposure threshold value of 40 mg-min/m^3. The exposure concentration- time relationship for remaining AEGL-specific time points durations is uncertain and an empirically-derived value for the exponent, n, in the equation $C^n \times t = k$ could not be developed. Consistent with AEGL methodologies (NRC, 2001), an n of 1 was used in extrapolating to these time points.
Uncertainty factors:	Intraspecies adjustment was limited to 3 because the ocular response is considered the result of direct-contact with the nitrogen mustard vapors rather than a systemically-mediated process.
Modifying factor:	10; because some of the tests were apparently performed using volunteers with oronasal masks which would have precluded development of respiratory tract effects, a modifying factor of 3 was justified to account for possible effects on the respiratory tract. However, because the number of subjects was unknown, and the HN2 exposure induced effects of notable severity that persisted for at least 24 hours, the total modifying factor adjustment was increased to 10.
10-minute AEGL-2	$C^1 \times 10$ min. = 40 mg-min/m^3 C = 4.0 mg/m^3 10-min AEGL-2 = (4.0 mg/m^3)/30 = 0.13 mg/m^3

30-minute AEGL-2 $C^1 \times 30 \text{ min.} = 40 \text{ mg-min/m}^3$
$C = 1.3 \text{ mg/m}^3$
30-min AEGL-2 $= (1.3 \text{ mg/m}^3)/30 = 0.044 \text{ mg/m}^3$

1-hour AEGL-2 $C^1 \times 60 \text{ min.} = 40 \text{ mg-min/m}^3$
$C = 0.67 \text{ mg/m}^3$
60-min AEGL-2 $= (0.67 \text{ mg/m}^3)/30 = 0.022 \text{ mg/m}^3$

4-hour AEGL-2 $C^1 \times 240 \text{ min.} = 40 \text{ mg-min/m}^3$
$C = 0.17 \text{ mg/m}^3$
240-min AEGL-2 $= (0.17 \text{ mg/m}^3)/30 = 0.0056 \text{ mg/m}^3$

8-hour AEGL-2 $C^1 \times 480 \text{ min.} = 40 \text{ mg-min/m}^3$
$C = 0.083 \text{ mg/m}^3$
480-min AEGL-2 $= (0.083 \text{ mg/m}^3)/30 = 0.0028 \text{ mg/m}^3$

Derivation of AEGL-2 for Nitrogen Mustards

HN3

Key studies:	U.S. Army Medical Division. 1945c. Medical Division monthly progress report. March, 1945. Cited in NRDC, 1946. U.S. Army Medical Division. 1945d. Medical Division monthly progress report. February, 1945. Cited in NRDC, 1946.
Critical effect:	Ocular irritation in human volunteer subjects; cumulative exposure threshold of 20 mg-min/m^3 based upon exposure durations of 7 minutes.
Time scaling:	The exposure concentration-time relationship for AEGL-specific time points durations is uncertain and an empirically-derived value for the exponent, *n*, in the equation $C^n \times t = k$ could not be developed. Consistent with AEGL methodologies (NRC, 2001), an *n* of 1 was used in extrapolating from the 7-minute experimental period to the AEGL-specific time points.
Uncertainty factors:	Intraspecies adjustment was limited to 3 because the ocular response is considered the result of direct-contact with the nitrogen mustard vapors rather than a systemically-mediated process.
Modifying factor:	Because some of the tests were apparently performed using volunteers with oronasal masks which would have precluded development of respiratory tract effects, a modifying factor of 3 was applied to account for possible effects on the respiratory tract
10-minute AEGL-2	$C^1 \times 10$ min. = 20 mg-min/m^3 C = 2.0 mg/m^3 10-min AEGL-2 = (2.0 mg/m^3)/10 = 0.20 mg/m^3

30-minute AEGL-2 $C^1 \times 30 \text{ min.} = 20 \text{ mg-min/m}^3$
$C = 0.67 \text{ mg/m}^3$
30-min AEGL-2 $= (0.67 \text{ mg/m}^3)/10 = 0.067 \text{ mg/m}^3$

1-hour AEGL-2 $C^1 \times 60 \text{ min.} = 20 \text{ mg-min/m}^3$
$C = 0.33 \text{ mg/m}^3$
60-min AEGL-2 $= (0.33 \text{ mg/m}^3)/10 = 0.0033 \text{ mg/m}^3$

4-hour AEGL-2 $C^1 \times 240 \text{ min.} = 20 \text{ mg-min/m}^3$
$C = 0.083 \text{ mg/m}^3$
240-min AEGL-2 $= (0.083 \text{ mg/m}^3)/10 = 0.0083 \text{ mg/m}^3$

8-hour AEGL-2 $C^1 \times 480 \text{ min.} = 20 \text{ mg-min/m}^3$
$C = 0.042 \text{ mg/m}^3$
480-min AEGL-2 $= (0.042 \text{ mg/m}^3)/10 = 0.0042 \text{ mg/m}^3$

Derivation of AEGL-3 for Nitrogen Mustards

HN1

Key study:	U.S. Army Medical Division. 1945a. Medical Division monthly progress report. September, 1945. Cited in NRDC, 1946.
Critical effect:	Lethality threshold of 287 mg-min/m^3 in rats estimated by 3-fold reduction of LCt_{50} of 860 mg-min/m^3; experimental exposure durations of 20-100 minutes.
Time scaling:	$C^n \times t = k$; data were unavailable for empirical derivation of a scaling factor. The exposure concentration-time relationship for many irritant and systemically acting vapors and gases may described by $C^n \times t = k$, where the exponent n ranges from 0.8 to 3.5. In the absence of chemical-specific data, temporal scaling 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).
Uncertainty factors:	Interspecies uncertainty adjustment was limited to 3 because LCt_{50} values among seven species (including nonhuman primates) did not appear to vary by more than three-fold; the rat being somewhat more sensitive. Intraspecies adjustment was also limited to 3 because of the direct action of nitrogen mustards on tissue and because additional downward adjustment would result in AEGL-3 values inconsistent with AEGL-2 values and available human data (ocular and dermal response data and monitoring data for therapeutic use of nitrogen mustard
Calculations:	For 10-min. AEGL-3: point-of-departure based upon estimated lethality threshold of 287 mg-min/m^3 resulting from 20-minute exposure (14.4 mg/m^3) (14.4 mg/m^3)^3 x 20 min. = 59,719 mg-min/m^3
10-minute AEGL-3	$C^3 \times 10$ min. = 59,719 mg-min/m^3 C = 18.14 mg/m^3 10-min AEGL-3 = (18.14 mg/m^3)/10 = 1.8 mg/m^3

30-minute AEGL-3 $C^1 \times 30 \text{ min.} = 287 \text{ mg-min/m}^3$
$C = 9.57 \text{ mg/m}^3$
30-min AEGL-3 $= (9.57 \text{ mg/m}^3)/10 = 0.96 \text{ mg/m}^3$

1-hour AEGL-3 $C^1 \times 60 \text{ min.} = 287 \text{ mg-min/m}^3$
$C = 4.78 \text{ mg/m}^3$
60-min AEGL-3 $= (4.78 \text{ mg/m}^3)/10 = 0.48 \text{ mg/m}^3$

4-hour AEGL-3 $C^1 \times 240 \text{ min.} = 287 \text{ mg-min/m}^3$
$C = 1.19 \text{ mg/m}^3$
240-min AEGL-3 $= (1.19 \text{ mg/m}^3)/10 = 0.12 \text{ mg/m}^3$

8-hour AEGL-3 $C^1 \times 480 \text{ min.} = 287 \text{ mg-min/m}^3$
$C = 0.598 \text{ mg/m}^3$
480-min AEGL-3 $= (0.598 \text{ mg/m}^3)/10 = 0.060 \text{ mg/m}^3$

Derivation of AEGL-3 for Nitrogen Mustards

HN2

Key study:	Porton Report. 1943b. Toxicity of S vapour. Further experiments on the exposure of animals to S vapour. No. 2464. February 9, 1943. Cited in NDRC, 1946.
Critical effect:	Lethality threshold of 667 mg-min/m^3 in rats estimated by 3-fold reduction of LCt_{50} of 2000 mg-min/m^3; experimental exposure durations of 120-360 minutes.
Time scaling:	$C^n \times t = k$; data were unavailable for empirical derivation of a scaling factor. The exposure concentration-time relationship for many irritant and systemically acting vapors and gases may described by $C^n \times t = k$, where the exponent n ranges from 0.8 to 3.5. In the absence of chemical-specific data, temporal scaling 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).
Uncertainty factors:	Interspecies uncertainty adjustment was limited to 3 because LCt_{50} values among seven species (including nonhuman primates) did not appear to vary by more than three-fold; the rat being somewhat more sensitive. Intraspecies adjustment was also limited to 3 because of the direct action of nitrogen mustards on tissue and because additional downward adjustment would result in AEGL-3 values inconsistent with AEGL-2 values and available human data (ocular and dermal response data and monitoring data for therapeutic use of nitrogen mustard
Calculations:	For 10-min., 30-min, and 1-hr AEGL-3: point-of-departure based upon estimated lethality threshold of 667 mg-min/m^3 resulting from 120-minute exposure (5.56 mg/m^3) (5.56 mg/m^3)^3 x 120 min. = 20,625.6 mg-min/m^3
10-minute AEGL-3	C^3 x 10 min. = 20,625.6 mg-min/m^3 C = 12.73 mg/m^3 10-min AEGL-3 = (12.73 mg/m^3)/10 = 1.3 mg/m^3

30-minute AEGL-3 $C^3 \times 30$ min. = 20,625.6 mg-min/m^3
$C = 8.83$ mg/m^3
30-min AEGL-3 = (8.83 mg/m^3)/10 = 0.88 mg/m^3

1-hour AEGL-3 $C^3 \times 60$ min. = 20,625.6 mg-min/m^3
$C = 7.0$ mg/m^3
60-min AEGL-3 = (7.0 mg/m^3)/10 = 0.70 mg/m^3

4-hour AEGL-3 $C^1 \times 240$ min. = 667 mg-min/m^3
$C = 2.78$ mg/m^3
240-min AEGL-3 = (2.78 mg/m^3)/10 = 0.28 mg/m^3

8-hour AEGL-3 $C^1 \times 480$ min. = 667 mg-min/m^3
$C = 1.39$ mg/m^3
480-min AEGL-3 = (1.39 mg/m^3)/10 = 0.14 mg/m^3

Derivation of AEGL-3 for Nitrogen Mustards

HN3

Key study:	Porton Report, 1943c. Toxicity and pathology of HN3. No. 2548. November 18, 1944. Cited in NDRC, 1946
Critical effect:	Lethality threshold of 223.3 mg-min/m^3 in rats estimated by 3-fold reduction of LCt_{50} of 670 mg-min/m^3; experimental exposure durations of 10-100 minutes.
Time scaling:	Point-of-departure concentrations for each AEGL time point were determined directly from cumulative exposure threshold value of 223.3 mg-min/m^3. This is effectively the use of $n = 1$ for $C^n \times t = k$.
Uncertainty factors:	Interspecies uncertainty adjustment was limited to 3 because LCt_{50} values among seven species (including nonhuman primates) did not appear to vary by more than three-fold; the rat being somewhat more sensitive. Intraspecies adjustment was also limited to 3 because of the direct action of nitrogen mustards on tissue and because additional downward adjustment would result in AEGL-3 values inconsistent with AEGL-2 values and available human data (ocular and dermal response data and monitoring data for therapeutic use of nitrogen mustard
10-minute AEGL-3	$C^1 \times 10$ min. = 223.3 mg-min/m^3 C = 22.3 mg/m^3 10-min AEGL-3 = (22.3 mg/m^3)/10 = 2.2 mg/m^3

30-minute AEGL-3 $C^1 \times 30$ min. = 223.3 mg-min/m^3
$C = 7.44$ mg/m^3
30-min AEGL-3 = (7.44 mg/m^3)/10 = 0.74 mg/m^3

1-hour AEGL-3 $C^3 \times 60$ min. = 223.3 mg-min/m^3
$C = 3.72$ mg/m^3
60-min AEGL-3 = (3.72 mg/m^3)/10 = 0.37 mg/m^3

4-hour AEGL-3 $C^1 \times 240$ min. = 223.3 mg-min/m^3
$C = 0.93$ mg/m^3
240-min AEGL-3 = (0.93 mg/m^3)/10 = 0.093 mg/m^3

8-hour AEGL-3 $C^1 \times 480$ min. = 223.3 mg-min/m^3
$C = 0.47$ mg/m^3
480-min AEGL-3 = (0.47 mg/m^3)/10 = 0.047 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 (NRC, 1993) or Haber's Rule (i.e., $C \times t = k$, where C = exposure concentration, t = exposure duration, and k = a constant) has been used to relate exposure concentration and duration to effect (Rinehart and Hatch, 1964). This concept states that exposure concentration and exposure duration may be reciprocally adjusted to maintain a cumulative exposure constant (k) and that this cumulative exposure constant will always reflect a specific quantitative and qualitative response. This inverse relationship of concentration and time may be valid when the toxic response to a chemical is equally dependent upon the concentration and the exposure duration. However, an assessment by ten Berge et al. (1986) of LC_{50} data for certain chemicals revealed chemical-specific relationships between exposure concentration and exposure duration that were often exponential. This relationship can be expressed by the equation $C^n \times t = k$, where n represents a chemical specific, and even a toxic endpoint specific, exponent. The relationship described by this equation is basically the form of a linear regression analysis of the log-log transformation of a plot of C vs t ten Berge et al. (1986) examined the airborne concentration (C) and short-term exposure duration (t) relationship relative to death for approximately 20 chemicals and found that the empirically derived value of n ranged from 0.8 to 3.5 among this group of chemicals. Hence, these workers showed that 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.

For the nitrogen mustards, critical effect thresholds from various studies were expressed as cumulative exposures (Ct) along with exposure duration ranges from which they were developed. Where AEGL-specific time points coincided with the reported exposure duration ranges, starting points for the specific AEGL values were obtained by simply calculating the exposure concentration required to produce the Ct; essentially using an n of 1. In the absence of chemical-specific data, temporal scaling 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).

APPENDIX C
Derivation Summary Tables

AEGL-1 VALUES FOR HN1				
10 minutes	**30 minutes**	**1 hour**	**4 hours**	**8 hours**
Not recommended	**Not recommended**	**Not recommended**	**Not recommended**	**Not recommended**
Reference: Not applicable				
Test Species/Strain/Number: Not applicable				
Exposure Route/Concentrations/Durations: Not applicable				
Effects: Not applicable				
Endpoint/Concentration/Rationale: Not applicable				
Uncertainty Factors/Rationale: Not applicable				
Modifying Factor: Not applicable				
Animal to Human Dosimetric Adjustment: Not applicable				
Time Scaling: Not applicable				
Data Adequacy: Data were insufficient for developing AEGL-1 values for HN1. Absence of AEGL-1 values does not imply that exposures below AEGL-2 are without effects.				

AEGL-2 VALUES FOR HN1				
10 minutes	**30 minutes**	**1 hour**	**4 hours**	**8 hours**
0.90 mg/m^3	**0.30 mg/m^3**	**0.15 mg/m^3**	**0.038 mg/m^3**	**0.019 mg/m^3**

Reference: Porton Report. 1943d. The effects of HN1 vapour on human and rabbit eyes. No. 2563. November 18, 1943. Cited in NDRC, 1946.

Test Species/Strain/Sex/Number: Human volunteers/males/21

Exposure Route/Concentrations/Durations: ocular exposure to vapors; CT determined based upon exposure durations of 5 to 67 minutes.

Effects: Ocular irritation in human volunteer subjects; lacrimation, feeling of grittiness in eyes, belpharospasm, photophobia, conjunctival injection.

Endpoint/Concentration/Rationale: 37 mg-min/m^3 based upon exposure durations of 5-67 minutes.

Uncertainty Factors/Rationale:
Total uncertainty factor: 3
Interspecies: none; human subjects
Intraspecies: 3; intraspecies adjustment was limited to 3 because the ocular response is considered the result of direct-contact with the nitrogen mustard vapors rather than a systemically-mediated process.

Modifying Factor: 3; to account for an overall deficient database and because some of the tests were apparently performed using volunteers with oronasal masks which would have precluded development of respiratory tract effects. Therefore, a modifying factor of 3 was applied to account for possible effects on the respiratory tract.

Animal to Human Dosimetric Adjustment: Not applicable

Time Scaling: For the 10-min., 30-min, and 1-hr AEGL-2, concentrations determined directly from cumulative exposure threshold value of 37 mg-min/m^3. The exposure concentration-time relationship for longer durations (e.g., the 4-hr and 8-hr AEGL time points) is uncertain and an empirically-derived value for the exponent, *n*, in the equation $C^n \times t = k$ could not be developed. Consistent with AEGL methodologies (NRC, 2001), an *n* of 1 was used in extrapolating from the 60-minute experimental exposure of 0.62 mg/m^3 period to the 4-hour and 8-hour AEGL-2 time periods resulting in exposures of 0.15 mg/m^3 and 0.077 mg/m^3.

Data Adequacy: The available data provide exposure-response data characterizing a sensitive critical effect in human volunteer subjects. The effect is consistent with the continuum of effects observed for this class of compounds. The data are considered appropriate for setting AEGL-2 values for HN1.

AEGL-3 VALUES FOR HN1				
10 minutes	**30 minutes**	**1 hour**	**4 hours**	**8 hours**
1.8 mg/m^3	**0.96 mg/m^3**	**0.48 mg/m^3**	**0.12 mg/m^3**	**0.060 mg/m^3**

Reference: U.S. Army Medical Division. 1945a. Medical Division monthly progress report. September, 1945. Cited in NRDC, 1946.

Test Species/Strain/Sex/Number: 84 male rats

Exposure Route/Concentrations/Durations: inhalation/experimental exposure durations of 20-100 minutes/ analytically determined concentrations.; 90EF chamber temp., 10-15 day observation period

Effects: Lethality response data only

Endpoint/Concentration/Rationale: Lethality threshold of 287 mg-min/m^3 in rats estimated by 3-fold reduction of inhalation LCt_{50} of 860 mg-min/m^3

Uncertainty Factors/Rationale:
Total uncertainty factor: 10

Interspecies: Limited to 3 because LCt_{50} values among seven species (including nonhuman primates) did not appear to vary by more than three-fold; the rat being somewhat more sensitive.

Intraspecies: Limited to 3 because of the direct action of nitrogen mustards on tissue and because additional downward adjustment would result in AEGL-3 values inconsistent with AEGL-2 values and available human data (ocular and dermal response data and monitoring data for therapeutic use of nitrogen mustard).

Modifying Factor: Not applicable

Animal to Human Dosimetric Adjustment: Not applicable

Time Scaling: $C^n \times t = k$; data were unavailable for empirical derivation of a scaling factor. The exposure concentration-time relationship for many irritant and systemically acting vapors and gases may described by $C^n \times t = k$, where the exponent n ranges from 0.8 to 3.5. In the absence of chemical-specific data, temporal scaling 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).
For 10-min. AEGL-3: point-of-departure based upon estimated lethality threshold of 287 mg-min/m^3 resulting from 20-minute exposure (14.4 mg/m^3)
(14.4 mg/m^3)^3 x 20 min. = 59,719 mg-min/m^3

Data Adequacy: The AEGL-3 values were based upon lethality assessment (analytically determined concentrations) using the most sensitive species exposed to high temperature conditions optimal for enhancing HN1 activity (i.e., worst-case scenario). A 10 to15-day post exposure observation period accounted for kown latency in toxic responses to HN1

AEGL-1 VALUES FOR HN2				
10 minutes	**30 minutes**	**1 hour**	**4 hours**	**8 hours**
Not recommended	**Not recommended**	**Not recommended**	**Not recommended**	**Not recommended**
Reference: Not applicable				
Test Species/Strain/Number: Not applicable				
Exposure Route/Concentrations/Durations: Not applicable				
Effects: Not applicable				
Endpoint/Concentration/Rationale: Not applicable				
Uncertainty Factors/Rationale: Not applicable				
Modifying Factor: Not applicable				
Animal to Human Dosimetric Adjustment: Not applicable				
Time Scaling: Not applicable				
Data Adequacy: Data were insufficient for developing AEGL-1 values for HN2. Absence of AEGL-1 values does not imply that exposures below AEGL-2 are without effects.				

AEGL-2 VALUES FOR HN2				
10 minutes	**30 minutes**	**1 hour**	**4 hours**	**8 hours**
0.13 mg/m^3	**0.044 mg/m^3**	**0.022 mg/m^3**	**0.0056 mg/m^3**	**0.0028 mg/m^3**

Reference: Porton Report. 1942a. On the action of S on the eye; its comparison with allied compounds and with H. No. 2402. August 7, 1942. Cited in NDRC, 1946

Test Species/Strain/Sex/Number: Human male volunteers/number not specified

Exposure Route/Concentrations/Durations: 10-55 mg/m^3; exposure durations of 0.5 min to 10 min.; Ct values of 40-55 mg-min/m^3; subjects wore oronasal masks

Effects: ocular irritation following exposure (grittiness in eyes; photophobia, belpharospasm; ocular pain).

Endpoint/Concentration/Rationale: 40 mg-min/m^3 considered threshold for inducing military fine-skill operational ineffectiveness

Uncertainty Factors/Rationale:
Total uncertainty factor: 3
Interspecies: none; human subjects
Intraspecies: 3; intraspecies adjustment was limited to 3 because the ocular response is considered the result of direct-contact with the nitrogen mustard vapors rather than a systemically-mediated process.

Modifying Factor: 10. The modifying factor was increased to10 (as opposed to 3 for the other nitrogen mustards) to account for possible latent respiratory effects (as for HN1and HN3), and for estimating an AEGL-2 no-effect level as the POD (the observed effects following HN2 exposure appeared to be of a severity such that there may be impairment of escape from a situation) and uncertainties regarding the number of human volunteer subjects in the HN2 studies.

Animal to Human Dosimetric Adjustment: Not applicable

Time Scaling: For the 10-min. AEGL-2, concentrations were determined directly from cumulative exposure threshold value of 40 mg-min/m^3. The exposure concentration-time relationship for remaining AEGL-specific time points durations is uncertain and an empirically-derived value for the exponent, *n*, in the equation $C^n \times t = k$ could not be developed. Consistent with AEGL methodologies (NRC, 2001), an *n* of 1 was used in extrapolating to these time points.

Data Adequacy: The available data provide exposure-response data characterizing a sensitive critical effect in human volunteer subjects. The effect is consistent with the continuum of effects observed for this class of compounds. The data are considered appropriate for setting AEGL-2 values for HN2.

AEGL-3 VALUES FOR HN2				
10 minutes	**30 minutes**	**1 hour**	**4 hours**	**8 hours**
1.3 mg/m^3	**0.88 mg/m^3**	**0.70 mg/m^3**	**0.28 mg/m^3**	**0.14 mg/m^3**

Reference: Porton Report. 1943b. Toxicity of S vapour. Further experiments on the exposure of animals to S vapour. No. 2464. February 9, 1943. Cited in NDRC, 1946.

Test Species/Strain/Sex/Number: rat/gender not specified/56

Exposure Route/Concentrations/Durations: inhalation/experimental exposure durations of 120-360 minutes resulting in cumulative exposures of 2000 mg-min/m^3

Effects: Lethality only

Endpoint/Concentration/Rationale: Lethality threshold of 667 mg-min/m^3 in rats estimated by 3-fold reduction of LCt_{50} of 2000 mg-min/m^3.

Uncertainty Factors/Rationale:
Total uncertainty factor: 10

Interspecies: Limited to 3 because LCt_{50} values among seven species (including nonhuman primates) did not appear to vary by more than three-fold; the rat being somewhat more sensitive.

Intraspecies: Limited to 3 because of the direct action of nitrogen mustards on tissue and because additional downward adjustment would result in AEGL-3 values inconsistent with AEGL-2 values and available human data (ocular and dermal response data and monitoring data for therapeutic use of nitrogen mustard).

Modifying Factor: Not applicable

Animal to Human Dosimetric Adjustment: Not applicable

Time Scaling: $C^n x\ t = k$; data were unavailable for empirical derivation of a scaling factor. The concentration-time relationship for many irritant and systemically acting vapors and gases may described by $C^n x\ t = k$, where the exponent n ranges from 0.8 to 3.5. In the absence of chemical-specific data, temporal scaling was performed using $n = 3$ when extrapolating to shorter time points and $n = 1$ when extrapolating to longer time points using the $Cn\ x\ t = k$ equation (NRC, 2001).

For 10-min., 30-min, and 1-hr AEGL-3: point-of-departure based upon estimated lethality threshold of 667 mg-min/m^3 resulting from 120-minute exposure (5.56 mg/m^3)
(5.56 mg/m^3)^3 x 120 min. = 20,625.6 mg-min/m^3

Data Adequacy: The AEGL-3 values were based upon lethality assessment (analytically determined concentrations) using the most sensitive species. A 14-day post exposure observation period accounted for kown latency in toxic responses to HN2.

AEGL-1 VALUES FOR HN3				
10 minutes	**30 minutes**	**1 hour**	**4 hours**	**8 hours**
Not recommended	**Not recommended**	**Not recommended**	**Not recommended**	**Not recommended**
Reference: Not applicable				
Test Species/Strain/Number: Not applicable				
Exposure Route/Concentrations/Durations: Not applicable				
Effects: Not applicable				
Endpoint/Concentration/Rationale: Not applicable				
Uncertainty Factors/Rationale: Not applicable				
Modifying Factor: Not applicable				
Animal to Human Dosimetric Adjustment: Not applicable				
Time Scaling: Not applicable				
Data Adequacy: Data were insufficient for developing AEGL-1 values for HN3. Absence of AEGL-1 values does not imply that exposures below AEGL-2 are without effects.				

AEGL-2 VALUES FOR HN3				
10 minutes	**30 minutes**	**1 hour**	**4 hours**	**8 hours**
0.42 mg/m^3	**0.14 mg/m^3**	**0.070 mg/m^3**	**0.018 mg/m^3**	**0.0088 mg/m^3**

Reference: U.S. Army Medical Division. 1945c. Medical Division monthly progress report. March, 1945. Cited in NRDC, 1946.
U.S. Army Medical Division. 1945d. Medical Division monthly progress report. February, 1945. Cited in NRDC, 1946.

Test Species/Strain/Sex/Number: Human volunteer subjects/male/7

Exposure Route/Concentrations/Durations: inhalation/20-40 mg-min/m^3; 7 min.

Effects: exposure to 20 mg-min/m^3 (duration not specified) resulted in conjunctival injection and corneal edema with no symptoms being reported by subjects
exposure to 40-mg-min/m^3 produced lacrimation, feeling of grittiness, photophobia, marked conjunctival injection

Endpoint/Concentration/Rationale:20-mg-min/m^3 considered threshold for compromised task efficiency.

Uncertainty Factors/Rationale:
Total uncertainty factor: 3
Interspecies: human subjects, none applied
Intraspecies: adjustment was limited to 3 because the ocular response is considered the result of direct-contact with the nitrogen mustard vapors rather than a systemically-mediated process.
Intraspecies:

Modifying Factor: 3; some of the tests may have been performed using volunteers with oronasal masks which would have precluded development of respiratory tract effects. Therefore, a modifying factor of 3 was applied to account for possible effects on the respiratory tract.

Animal to Human Dosimetric Adjustment: Not applicable

Time Scaling: The exposure-time response relationship for AEGL-specific time points durations is uncertain and an empirically-derived value for the exponent, n, in the equation $C^n \times t = k$ could not be developed. Consistent with AEGL methodologies (NRC, 2001), an n of 1 was used in extrapolating from the 7-minute experimental period to the AEGL-specific time points.

Data Adequacy: The available data provide exposure-response data characterizing a sensitive critical effect in human volunteer subjects. The effect is consistent with the continuum of effects observed for this class of compounds. Although the short exposure duration results in extensive extrapolation, an n of 1 was applied to provide more conservative exposure concentration estimates. Furthermore, the critical effect is a conservative point-of-departure for AEGL-2 severity effects. The data are considered appropriate for setting AEGL-2 values for HN3.

AEGL-3 VALUES FOR HN3				
10 minutes	**30 minutes**	**1 hour**	**4 hours**	**8 hours**
2.2 mg/m^3	**0.74 mg/m^3**	**0.37 mg/m^3**	**0.093 mg/m^3**	**0.047 mg/m^3**

Reference: Porton Report, 1943c. Toxicity and pathology of HN3. No. 2548. November 18, 1944. Cited in NDRC, 1946

Test Species/Strain/Sex/Number: 69 rats/gender not specified/exposure group

Exposure Route/Concentrations/Durations: inhalation LCt_{50} of 670 mg-min/m^3; exposure durations of 10-100 min.

Effects: Lethality response data only

Endpoint/Concentration/Rationale: Lethality threshold of 223.3 mg-min/m3 in rats estimated by 3-fold reduction of LCt_{50} of 670 mg-min/m3; experimental exposure durations of 10-100 minutes.

Uncertainty Factors/Rationale:
Total uncertainty factor: 10
- Interspecies: Limited to 3 because LCt_{50} values among seven species (including nonhuman primates) did not appear to vary by more than three-fold; the rat being somewhat more sensitive.
- Intraspecies: Limited to 3 because of the direct action of nitrogen mustards on tissue and because additional downward adjustment would result in AEGL-3 values inconsistent with AEGL-2 values and available human data (ocular and dermal response data and monitoring data for therapeutic use of nitrogen mustard).

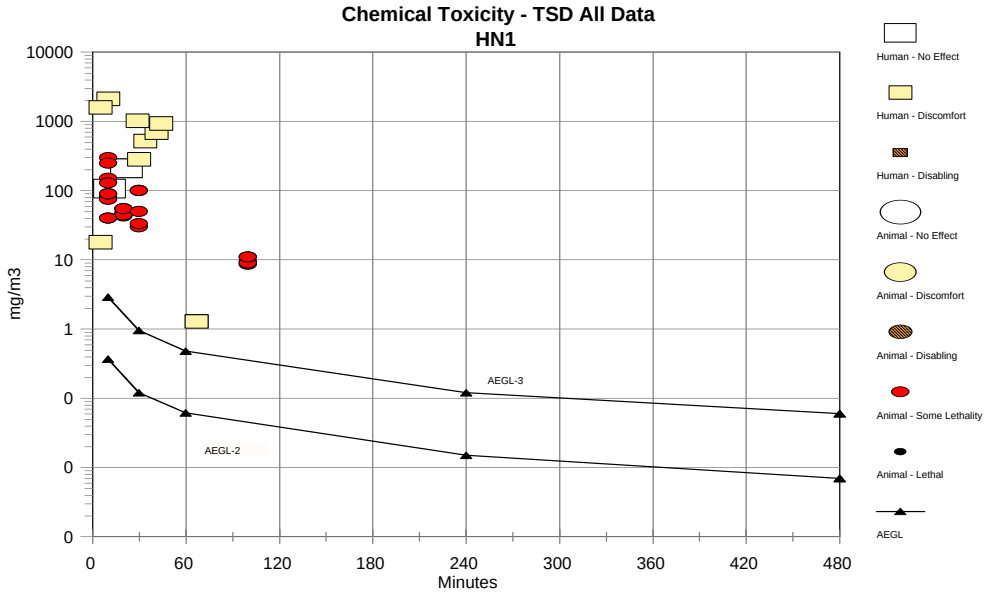
Modifying Factor: Not applicable

Animal to Human Dosimetric Adjustment: Not applicable

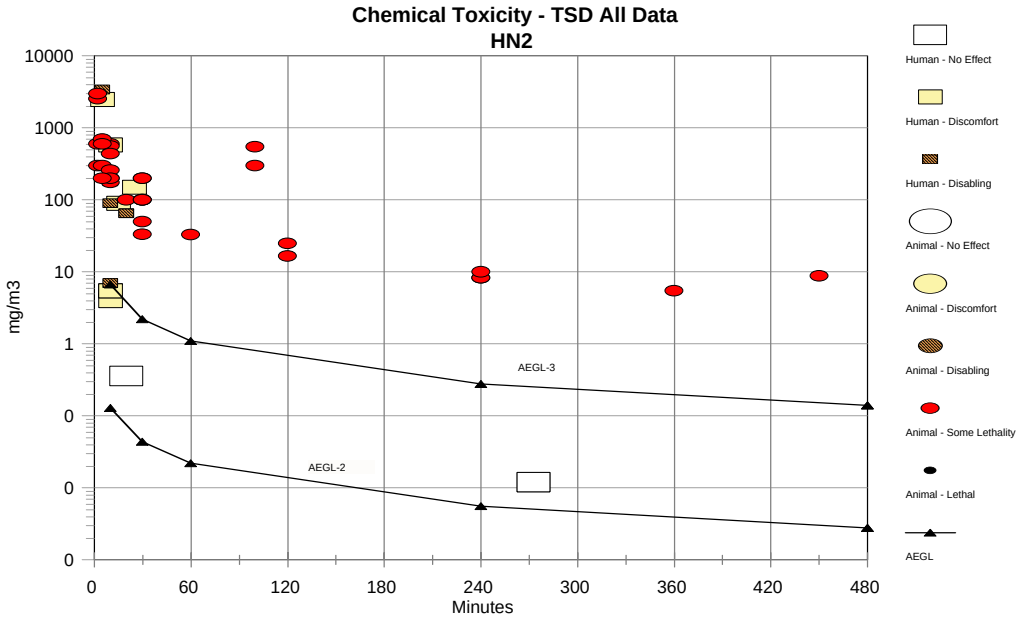
Time Scaling: Point-of-departure concentrations for each AEGL time point were determined directly from cumulative exposure threshold value of 223.3 mg-min/m^3. This is effectively the use of $n = 1$ for $C^n \times t = k$.

Data Adequacy: The AEGL-3 values were based upon lethality assessment (analytically determined concentrations) using the most sensitive species and a chamber temperature (85EF) which would represent a worst-case scenario. A 15-day post exposure observation period accounted for known latency in toxic responses to HN3.

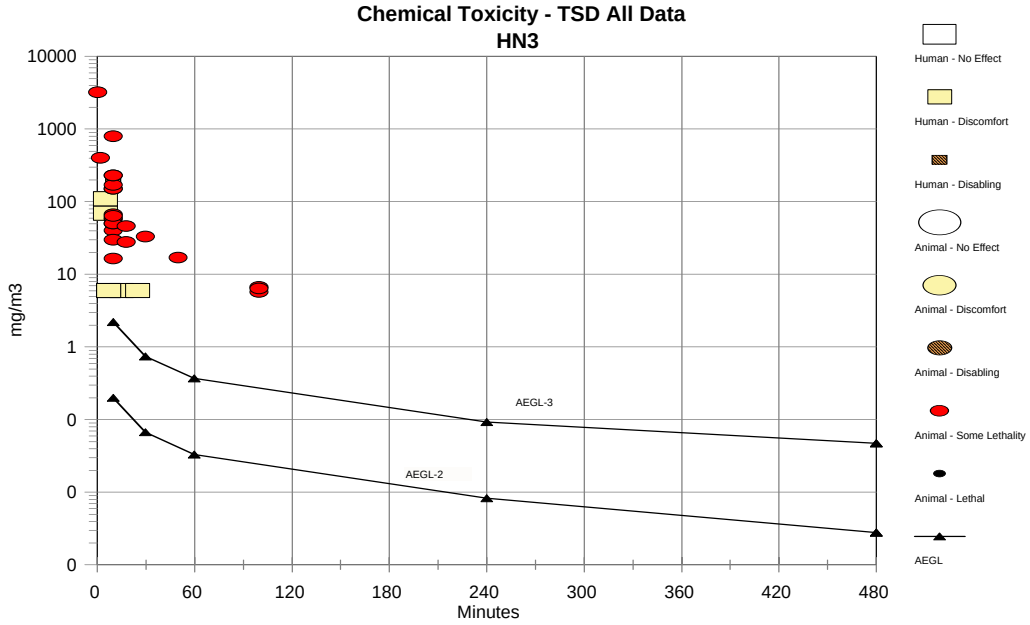
APPENDIX D
CATEGORY PLOTS FOR NITROGEN MUSTARDS (HN1, HN2, HN3)



AEGL-1 values for HN1 are not recommended due to insufficient data.



AEGL-1 values for HN2 are not recommended due to insufficient data.



AEGL-1 values for HN3 are not recommended due to insufficient data.