ACUTE EXPOSURE GUIDELINE LEVELS (AEGLs)
FOR
GERMANE
(CAS Reg. No. 7782-65-2)

GeH_4

INTERIM

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PREFACE

Under the authority of the Federal Advisory Committee Act (FACA) P. L. 92-463 of 1972, the National Advisory Committee for Acute Exposure Guideline Levels for Hazardous Substances (NAC/AEGL Committee) has been established to identify, review and interpret relevant toxicologic and other scientific data and develop AEGLs for high priority, acutely toxic chemicals.

AEGLs represent threshold exposure limits for the general public and are applicable to emergency exposure periods ranging from 10 minutes to 8 hours. Three levels C AEGL-1, AEGL-2 and AEGL-3 C are developed for each of five exposure periods (10 and 30 minutes, 1 hour, 4 hours, and 8 hours) and are distinguished by varying degrees of severity of toxic effects. The three AEGLs are defined as follows:

AEGL-1 is the airborne concentration (expressed as parts per million or milligrams per cubic meter [ppm or mg/m^3]) of a substance above which it is predicted that the general population, including susceptible individuals, could experience notable discomfort, irritation, or certain asymptomatic, non-sensory effects. However, the effects are not disabling and are transient and reversible upon cessation of exposure.

AEGL-2 is the airborne concentration (expressed as ppm or mg/m^3) of a substance above which it is predicted that the general population, including susceptible individuals, could experience irreversible or other serious, long-lasting adverse health effects or an impaired ability to escape.

AEGL-3 is the airborne concentration (expressed as ppm or mg/m^3) of a substance above which it is predicted that the general population, including susceptible individuals, could experience life-threatening health effects or death.

Airborne concentrations below the AEGL-1 represent exposure levels that could produce mild and progressively increasing but transient and nondisabling odor, taste, and sensory irritation or certain asymptomatic, non-sensory effects. With increasing airborne concentrations above each AEGL, there is a progressive increase in the likelihood of occurrence and the severity of effects described for each corresponding AEGL. Although the AEGL values represent threshold levels for the general public, including susceptible subpopulations, such as infants, children, the elderly, persons with asthma, and those with other illnesses, it is recognized that individuals, subject to unique or idiosyncratic responses, could experience the effects described at concentrations below the corresponding AEGL

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SUMMARY

Germane is a colorless gas with a pungent odor (NIOSH, 2005). It is used as a doping agent for solid-state electronic components (ACGIH, 2001). Inhalation exposure may result in malaise, headache, dizziness, fainting, dyspnea, nausea, vomiting, kidney injury, and hemolytic effects (NIOSH, 2005).

Data were insufficient to derive AEGL-1 values for germane. Therefore, AEGL-1 values are not recommended.

Chemical-specific germane data are insufficient for derivation of AEGL-2 or AEGL-3 values for germane. However, Paneth and Joachimoglu (1924) compared the acute inhalation toxicity of germane with the acute inhalation toxicity of arsine and concluded that both are hemolytic toxins and germane is less toxic than arsine. A mouse exposed to 207 ppm arsine for 1 hour exhibited difficulty breathing within 55 minutes and died within 1 hr, 48 minutes. A mouse exposed to 185 ppm germane for 1 hour exhibited dyspnea during exposure, no clinical signs 7 and 11 days post-exposure, and the animal died 13 days post-exposure. A guinea pig exposed to 207 ppm arsine exhibited increased respiratory rate within 55 minutes; hemoglobin was noted in the urine, and the animal died 4 days post-exposure (total exposure 2 hours). A guinea pig exposed to 185 ppm germane for 1 hour exhibited hemoglobin and protein in the urine, and the animal died 4 days post-exposure. Although these data are limited, the studies were conducted in the same laboratory; therefore, the relative toxicity data are considered acceptable. These data suggest that germane is less toxic than arsine in the mouse and no more toxic in the guinea pig. Therefore, the AEGL-2 values for arsine will be adopted as AEGL-2 values for germane, and the AEGL-3 values for arsine will be adopted as AEGL-3 values for germane.

The calculated values are listed in the table below.

TABLE 1. Summary of AEGL Values for Germane

Classification	10-mim	30-min	1-h	4-h	8-h	Endpoint (Reference)
AEGL-1 (Nondisabling)	NR	NR	NR	NR	NR	Insufficient data
AEGL-2 (Disabling)	0.30 ppm 0.96 mg/m^3	0.21 ppm 0.67 mg/m^3	0.17 ppm 0.54 mg/m^3	0.040 ppm 0.13 mg/m^3	0.020 ppm 0.064 mg/m^3	Arsine AEGL-2 values adopted as Germane AEGL-2 values (NRC, 2000; NRC, 2007)
AEGL-3 (Lethal)	0.91 ppm 2.9 mg/m^3	0.63 ppm 2.0 mg/m^3	0.50 ppm 1.6 mg/m^3	0.13 ppm 0.42 mg/m^3	0.060 ppm 0.19 mg/m^3	Arsine AEGL-3 values adopted as Germane AEGL-3 values (NRC, 2000; NRC, 2007)

NR: Not Recommended due to insufficient data. Absence of an AEGL-1 value does not imply that concentrations below the AEGL-2 are without effect.

1. INTRODUCTION

Germane is a colorless gas with a pungent odor (NIOSH, 2005). It is used as a doping agent for solid-state electronic components (ACGIH, 2001). Inhalation exposure may result in malaise, headache, dizziness, fainting, dyspnea, nausea, vomiting, kidney injury, and hemolytic effects (NIOSH, 2005). Chemical and physical properties are listed in Table 2.

TABLE 2. Chemical and Physical Properties

Parameter	Value	References
Synonyms	Germanium tetrahydride; Germanium hydride; Germanomethane; Monogermane	ACGIH, 2001 NIOSH, 2005
Chemical formula	GeH_4	ACGIH, 2001
Molecular weight	76.63	ACGIH, 2001
CAS Reg. No.	7782-65-2	ACGIH, 2001
Physical state	Colorless gas	ACGIH, 2001
Solubility in water	Insoluble	ACGIH, 2001
Melting point	-165 °C	ACGIH, 2001
Boiling point	-90 °C	ACGIH, 2001
Conversion factors	1 ppm = 3.2 mg/m^3 1 mg/m^3 = 0.32 ppm	ACGIH, 2001

2. HUMAN TOXICITY DATA

No human toxicity data or odor threshold data were located.

3. ANIMAL TOXICITY DATA

3.1.1. Acute Toxicity

Paneth and Joachimoglu (1924) exposed single mice (average weight 20 g), guinea pigs (average weight 200 g), or rabbits (weight 1500 g) to germane by placing the animals in glass jars and releasing the gas. The study states that "the test atmospheres were prepared by changing the germane from gas to condensate by using liquid air. Care was taken so as not to lose any of the test material." No further experimental details were provided. Exposure parameters and results are presented in Table 3.

TABLE 3. Exposure of Mice, Guinea pigs and Rabbits to Germane (Paneth and Joachimoglu, 1924)

Species (No. of animals)	Concentration (ppm)	Duration	Effect
Mouse (1)	2170	1 hour	Mouse sick; died 1 day after exposure
Mouse (1)	195	30 min	Slight dyspnea during exposure; No clinical signs 4 days after exposure; died 8 days after exposure
Mouse (1)	185	1 hour	Dyspnea during exposure; No clinical signs 7 and 11 days after exposure; died 13 days after exposure
Mouse (1)	153	1 hour	Died 1 day after exposure
Guinea pig (1)	185	1 hour	Hemoglobin and protein in urine 1 and 3 days after exposure; died 4 days after exposure; pneumonia at necropsy
Guinea pig (1)	153	1 hour	Animal appeared sick; hemoglobinuria
Rabbit (1)	100	1 hour	Slight dyspnea; No other effects through 1 month after exposure

A 2-hour LC_{50} of approximately 440 ppm was reported for white mice (Guskova, 1974). Clinical signs included excitation at the onset of exposure, motor coordination difficulties, jerking of extremities, convulsions, disrupted breathing pattern, and bloody discharge from the nose. Animals died at the end of exposure and the day following exposure. Vascular damage and liver and kidney histopathology were noted in decedents. No other details were provided.

3.1.2. Repeated-exposure

White rats exposed to 4 or 25 ppm germane 4 hours/day for 30 days showed no clinical signs (Ivanov et al., 1976). No further details were provided.

3.2. Developmental/Reproductive Toxicity

No data on developmental/reproductive toxicity were located.

3.3. Genotoxicity

No genotoxicity data were located.

3.4. Chronic Toxicity/Carcinogenicity

No data on chronic toxicity/carcinogenicity were located.

3.5. Summary

Animal toxicity data are sparse and studies are poorly reported. No data on developmental/reproductive toxicity, genotoxicity, or chronic toxicity/carcinogenicity were located.

4. SPECIAL CONSIDERATIONS

4.1. Metabolism and Disposition

No information was located concerning the metabolism and disposition of germane.

4.2. Mechanism of Toxicity

Germane is described as a hemolytic agent, similar in properties to arsine and stibine (ACGIH, 2001). Hemoglobinuria noted in mice and guinea pigs (Paneth and Joachimoglu, 1924) is consistent with hemolysis.

4.3. Structure Activity Relationships

Paneth and Joachimoglu (1924) compared the effects of germane (GeH_4) and arsine (AsH_3), and concluded that germane was a hemolytic gas less toxic than arsine. Data are summarized in Table 4.

TABLE 4. Comparative toxicity of Germane and Arsine (Paneth and Joachimoglu, 1924)

Compound	Species (No. of animals)	Concentration (ppm)	Duration	Clinical Signs	Death
Germane	Mouse (1)	2170	1 hour	Mouse sick	1 day post-exposure
Arsine	*Mouse (1)*	*1300*	*42 minutes*	*20 min: nervous 35 min: lying on side 40 min: Seizures*	*42 min*
Arsine	*Mouse (1)*	*550*	*1 hr*	*15 min:dyspnea 1 hr: Seizures*	*1 hr, 4 min*
Arsine	*Mouse (1)*	*440*	*47 minutes*	*40 min: Seizures 45 min: breathing difficulty, twitching*	*47 min*
Arsine	*Mouse (1)*	*207*	*1 hr*	*55 min: breathing difficulty*	*1 hr, 48 min*
Germane	Mouse (1)	195	30 min	Slight dyspnea during exposure; No clinical signs 4 days after exposure	8 days post-exposure
Germane	Mouse (1)	185	1 hour	Dyspnea during exposure; No clinical signs 7 and 11 days after exposure	13 days post-exposure
Germane	Mouse (1)	153	1 hour	NA	1 day post-exposure
Arsine	*Guinea Pig (1)*	*550*	*2 hours*	*1 hr: Increased respiratory rate*	*1 day post-exposure*
Arsine	*Guinea Pig (1)*	*440*	*2 hours*	*49 min: nervous 1 hr 33 min: Lying on side 1 hr 38 min: Seizures*	*1 hr, 48 min*
Arsine	*Guinea Pig (1)*	*207*	*2 hours*	*55 min: Increased respiratory rate; hemoglobin in urine*	4 days post-exposure
Germane	Guinea pig (1)	185	1 hour	1 & 3 days post exposure: Hemoglobin and protein in urine	4 days post-exposure
Germane	Guinea pig (1)	153	1 hour	Animal appeared sick; hemoglobinuria	NA

4.4. Other Relevant Information

4.4.1. Species Variability

Data are insufficient to determine species variability for germane.

4.4.2. Susceptible Populations

No information was available on populations especially sensitive to germane.

5. DATA ANALYSIS FOR AEGL-1

5.1. Summary of Human Data Relevant to AEGL-1

No human data relevant to development of AEGL-1 values were identified.

5.2. Summary of Animal Data Relevant to AEGL-1

No animal data relevant to development of AEGL-1 values were identified.

5.3. Derivation of AEGL-1

No human or animal data were available for derivation of AEGL-1 values for germane. Therefore, AEGL-1 values are not recommended (Table 5).

TABLE 5. AEGL-1 Values for Germane

10-min	30-min	1-h	4-h	8-h
NR	NR	NR	NR	NR

NR: Not Recommended due to insufficient data. Absence of AEGL-1 values does not imply that concentrations below AEGL-2 are without effect.

6. DATA ANALYSIS FOR AEGL-2

6.1. Summary of Human Data Relevant to AEGL-2

No human data relevant to development of AEGL-2 values were identified.

6.2. Summary of Animal Data Relevant to AEGL-2

One guinea pig exposed to 153 ppm for 1 hour appeared sick and had hemoglobinuria, and one rabbit exposed to 100 ppm for 1 hour showed only slight dyspnea (Paneth and Joachimoglu, 1924).

6.3. Derivation of AEGL-2

The animal data consistent with the definition of AEGL-2 were from only one guinea pig and one rabbit, and the study was poorly described (Paneth and Joachimoglu, 1924). However, in the same study report, Paneth and Joachimoglu (1924) compared the acute inhalation toxicity of germane with the acute inhalation toxicity of arsine and concluded that both are hemolytic toxins and germane is less toxic than arsine. A mouse exposed to 207 ppm arsine for 1 hour exhibited difficulty breathing within 55 minutes and died within 1 hr, 48 minutes. A mouse exposed to 185 ppm germane for 1 hour exhibited dyspnea during exposure, no clinical signs 7 and 11 days post-exposure, and the animal died 13 days post-exposure. A guinea pig exposed to 207 ppm arsine exhibited increased respiratory rate within 55 minutes; hemoglobin was noted in the urine, and the animal died 4 days post-exposure (total exposure 2 hours). A guinea pig exposed to 185 ppm germane for 1 hour exhibited hemoglobin and protein in the urine, and the animal died 4 days post-exposure. Although these data are limited and not well described, the studies were conducted in the same laboratory; therefore, the relative toxicity data are considered acceptable. These data suggest that germane is less toxic than arsine in the mouse and no more toxic in the guinea pig. Therefore, the AEGL-2 values for arsine will be adopted as AEGL-2 values for germane. In the absence of chemical-specific data for germane, these values should be protective. AEGL-2 values are presented in Table 6, and calculations are presented in Appendix A. The derivation summary for Arsine is presented in Appendix D.

TABLE 6. AEGL-2 Values for Germane				
10-min	**30-min**	**1-h**	**4-h**	**8-h**
0.30 ppm 0.96 mg/m^3	0.21 ppm 0.67 mg/m^3	0.17 ppm 0.54 mg/m^3	0.040 ppm 0.13 mg/m^3	0.020 ppm 0.064 mg/m^3

7. DATA ANALYSIS FOR AEGL-3

7.1. Summary of Human Data Relevant to AEGL-3

No human data relevant to development of AEGL-3 values were identified.

7.2. Summary of Animal Data Relevant to AEGL-3

One guinea pig exposed to 153 ppm for 1 hour appeared sick and had hemoglobinuria, and one rabbit exposed to 100 ppm for 1 hour showed only slight dyspnea (Paneth and Joachimoglu, 1924). No mortality was noted.

7.3. Derivation of AEGL-3

The animal data showing no mortality and thus consistent with the definition of AEGL-3 were from only one guinea pig and one rabbit, and the study was poorly described (Paneth and Joachimoglu, 1924). However, in the same study report, Paneth and Joachimoglu (1924) compared the acute inhalation toxicity of germane with the acute inhalation toxicity of arsine and concluded that both are hemolytic toxins and germane is less toxic than arsine. A mouse exposed to 207 ppm arsine for 1 hour exhibited difficulty breathing within 55 minutes and died within 1 hr, 48 minutes. A mouse exposed to 185 ppm germane for 1 hour exhibited dyspnea during exposure, no clinical signs 7 and 11 days post-exposure, and the animal died 13 days post-exposure. A guinea pig exposed to 207 ppm arsine exhibited increased respiratory rate within 55 minutes; hemoglobin was noted in the urine, and the animal died 4 days post-exposure (total exposure was 2 hours). A guinea pig exposed to 185 ppm germane for 1 hour exhibited hemoglobin and protein in the urine, and the animal died 4 days post-exposure. Although these data are limited and not well described, the studies were conducted in the same laboratory; therefore, the relative toxicity data are considered acceptable. These data suggest that germane is less toxic than arsine in the mouse and no more toxic in the guinea pig. Therefore, the AEGL-3 values for arsine will be adopted as AEGL-3 values for germane. In the absence of chemical-specific data for germane, these values should be protective. AEGL-3 values are presented in Table 7, and calculations are presented in Appendix A. The derivation summary for Arsine is presented in Appendix D.

TABLE 7. AEGL-3 Values for Germane				
10-min	**30-min**	**1-h**	**4-h**	**8-h**
0.91 ppm 2.9 mg/m^3	0.63 ppm 2.0 mg/m^3	0.50 ppm 1.6 mg/m^3	0.13 ppm 0.42 mg/m^3	0.060 ppm 0.19 mg/m^3

8. SUMMARY OF AEGLS

8.1. AEGL Values and Toxicity Endpoints

AEGL values are summarized in Table 8. AEGL-1 values are not recommended due to insufficient data. The AEGL-2 and AEGL-3 values for arsine were adopted as AEGL-2 and AEGL-3 values for germane.

TABLE 8. Summary of AEGL Values

Classification	Exposure Duration				
	10-min	30-min	1-h	4-h	8-h
AEGL-1 (Nondisabling)	NR	NR	NR	NR	NR
AEGL-2 (Disabling)	0.30 ppm 0.96 mg/m^3	0.21 ppm 0.67 mg/m^3	0.17 ppm 0.54 mg/m^3	0.040 ppm 0.13 mg/m^3	0.020 ppm 0.064 mg/m^3
AEGL-3 (Lethal)	0.91 ppm 2.9 mg/m^3	0.63 ppm 2.0 mg/m^3	0.50 ppm 1.6 mg/m^3	0.13 ppm 0.42 mg/m^3	0.060 ppm 0.19 mg/m^3

NR: Not Recommended due to insufficient data. Absence of an AEGL-1 value does not imply that concentrations below the AEGL-2 are without effect.

8.2. Comparison with Other Standards and Guidelines

Other standards and guidelines are presented in Table 9. The ACGIH TLV-TWA was derived by analogy to stibine which was derived by analogy to arsine. In a Health-based Reassessment of Administrative Occupational Exposure limits (Health Council of the Netherlands, 2000), the committee concluded that the toxicological data base in germane was too poor to justify recommendation of a health-based occupational exposure limit. The committee concluded that there is insufficient information to comment on the level of the present MAC value.

Germane is described as a hemolytic agent, similar in properties to arsine and stibine (ACGIH, 2001), and the ACGIH TLV-TWA value was derived by analogy to stibine. AEGL values exist for both arsine and stibine; however, AEGL values for germane are derived by analogy to arsine, not stibine, because the arsine AEGL values are more conservative than the stibine AEGL values. [Stibine AEGL values are: AEGL-1 = NR at all time points. AEGL-2 = 4.2 ppm for 10-min, 2.9 ppm for 30-min, 1.5 ppm for 1-hr, 0.36 ppm for 4-hr, and 18 ppm for 8-hr. AEGL-3 = 28 ppm for 10-min, 19 ppm for 30-min, 9.6 ppm for 1-hr, 2.4 ppm for 4-hr, and 1.2 ppm for 8-hr.] Given the very sparse data set for germane, this conservatism is warranted.

TABLE 9. Extant Standards and Guidelines for Germane

Guideline	Exposure Duration				
	10 minute	30 minute	1 hour	4 hour	8 hour
AEGL-1	NR	NR	NR	NR	NR
AEGL-2	0.30 ppm	0.21 ppm	0.17 ppm	0.040 ppm	0.020 ppm
AEGL-3	0.91 ppm	0.63 ppm	0.50 ppm	0.13 ppm	0.060 ppm
REL-TWA (NIOSH)[a]					0.2 ppm
TLV-TWA (ACGIH)[b]					0.2 ppm
TLV-STEL (ACGIH)[c]	Deleted				
MAC (The Netherlands)[d]					0.2 ppm

[a]**NIOSH REL-TWA (National Institute of Occupational Safety and Health, Recommended Exposure Limits - Time Weighted Average)** (NIOSH, 2005) is defined analogous to the ACGIH-TLV-TWA.

[b]**ACGIH TLV-TWA (American Conference of Governmental Industrial Hygienists, Threshold Limit Value - Time Weighted Average)** (ACGIH 2001) is the time-weighted average concentration for a normal 8-hour workday and a 40-hour workweek, to which nearly all workers may be repeatedly exposed, day after day, without adverse effect.

[c]**ACGIH TLV-STEL (Threshold Limit Value - Short Term Exposure Limit)** (ACGIH 2001) is defined as a 15-minute TWA exposure which should not be exceeded at any time during the workday even if the 8-hour TWA is within the TLV-TWA. Exposures above the TLV-TWA up to the STEL should not be longer than 15 minutes and should not occur more than 4 times per day. There should be at least 60 minutes between successive exposures in this range. The value was deleted in 1986.

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

8.3. Data Adequacy and Research Needs

There are no human data, and animal data are extremely limited. Additional acute inhalation toxicity studies in animals would be helpful.

9. REFERENCES

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APPENDIX A: Derivation of AEGL Values

Derivation of AEGL-1 for Germane

Data are insufficient to derive AEGL-1 values for germane. Therefore, AEGL-1 values are not recommended.

Derivation of AEGL-2 for Germane

Arsine AEGL-2 values adopted as AEGL-2 values for Germane.

Paneth and Joachimoglu (1924) compared the acute inhalation toxicity of germane with the acute inhalation toxicity of arsine and concluded that both are hemolytic toxins and germane is less toxic than arsine. A mouse exposed to 207 ppm arsine for 1 hour exhibited difficulty breathing within 55 minutes and died within 1 hr, 48 minutes. A mouse exposed to 185 ppm germane for 1 hour exhibited dyspnea during exposure, no clinical signs 7 and 11 days post-exposure, and the animal died 13 days post-exposure. A guinea pig exposed to 207 ppm arsine exhibited increased respiratory rate within 55 minutes; hemoglobin was noted in the urine, and the animal died 4 days post-exposure (total exposure 2 hours). A guinea pig exposed to 185 ppm germane for 1 hour exhibited hemoglobin and protein in the urine, and the animal died 4 days post-exposure. Although these data are limited and not well described, the studies were conducted in the same laboratory; therefore, the relative toxicity data are considered acceptable. These data suggest that germane is less toxic than arsine in the mouse and no more toxic in the guinea pig.

Derivation of AEGL-3 Germane

Arsine AEGL-3 values adopted as AEGL-3 values for Germane.

Paneth and Joachimoglu (1924) compared the acute inhalation toxicity of germane with the acute inhalation toxicity of arsine and concluded that both are hemolytic toxins and germane is less toxic than arsine. A mouse exposed to 207 ppm arsine for 1 hour exhibited difficulty breathing within 55 minutes and died within 1 hr, 48 minutes. A mouse exposed to 185 ppm germane for 1 hour exhibited dyspnea during exposure, no clinical signs 7 and 11 days post-exposure, and the animal died 13 days post-exposure. A guinea pig exposed to 207 ppm arsine exhibited increased respiratory rate within 55 minutes; hemoglobin was noted in the urine, and the animal died 4 days post-exposure (total exposure 2 hours). A guinea pig exposed to 185 ppm germane for 1 hour exhibited hemoglobin and protein in the urine, and the animal died 4 days post-exposure. Although these data are limited and not well described, the studies were conducted in the same laboratory; therefore, the relative toxicity data are considered acceptable. These data suggest that germane is less toxic than arsine in the mouse and no more toxic in the guinea pig.

APPENDIX B: Derivation Summary for Germane AEGLs

AEGL-1 Values for Germane

10-min	30-min	1-h	4-h	8-h
NR	**NR**	**NR**	**NR**	**NR**
Key Reference:				
Test Species/Strain/Number:				
Exposure Route/Concentrations/Durations:				
Effects:				
Endpoint/Concentration/Rationale:				
Uncertainty Factors/Rationale: Total uncertainty factor:				
Modifying Factor: NA				
Animal to Human Dosimetric Adjustment:				
Time Scaling:				
Data Adequacy: Data are insufficient for derivation of AEGL-1 values. Therefore, AEGL-1 values are not recommended for germane.				

AEGL-2 Values for Germane

10-min	30-min	1-h	4-h	8-h
0.30 ppm	**0.21 ppm**	**0.17 ppm**	**0.040 ppm**	**0.020 ppm**

Key References: NRC (National Research Council). 2000. Arsine. Acute Exposure Guideline Levels for Selected Airborne Chemicals. Volume 1. The National Academies Press, Washington, DC. pp. 65-112.

NRC (National Research Council). 2007. Arsine. Acute Exposure Guideline Levels for Selected Airborne Chemicals. Volume 6. Prepublication Copy. The National Academies Press, Washington, DC. pp. 89-91.

Paneth, F. and Joachimoglu, G. 1924. [The pharmacological characteristics of tin [IV] hydride (stannane) and germanium hydride]. Ber. D. deut. Chem.. Ges., 57: 1925-1930.

Test Species/Strain/Number:

Exposure Route/Concentrations/Durations

Effects:

Endpoint/Concentration/Rationale: Arsine AEGL-2 values adopted as AEGL-2 values for Germane. Paneth and Joachimoglu (1924) compared the acute inhalation toxicity of germane with the acute inhalation toxicity of arsine and concluded that both are hemolytic toxins and germane is less toxic than arsine. A mouse exposed to 207 ppm arsine for 1 hour exhibited difficulty breathing within 55 minutes and died within 1 hr, 48 minutes. A mouse exposed to 185 ppm germane for 1 hour exhibited dyspnea during exposure, no clinical signs 7 and 11 days post-exposure, and the animal died 13 days post-exposure. A guinea pig exposed to 207 ppm arsine for exhibited increased respiratory rate within 55 minutes; hemoglobin was noted in the urine, and the animal died 4 days post-exposure (total exposure 2 hours). A guinea pig exposed to 185 ppm germane for 1 hour exhibited hemoglobin and protein in the urine, and the animal died 4 days post-exposure. Although these data are limited and not well described, the studies were conducted in the same laboratory; therefore, the relative toxicity data are considered acceptable. These data suggest that germane is less toxic than arsine in the mouse and no more toxic in the guinea pig.

Uncertainty Factors/Rationale:
Total uncertainty factor:

Modifying Factor:

Animal to Human Dosimetric Adjustment:

Time Scaling

Data Adequacy: Sparse data set for germane.

1
2
3

AEGL-3 Values for Germane

10-min	30-min	1-h	4-h	8-h
0.91 ppm	**0.63 ppm**	**0.50 ppm**	**0.13 ppm**	**0.060 ppm**

Key References: NRC (National Research Council). 2000. Arsine. Acute Exposure Guideline Levels for Selected Airborne Chemicals. Volume 1. The National Academies Press, Washington, DC. pp. 65-112.

NRC (National Research Council). 2007. Arsine. Acute Exposure Guideline Levels for Selected Airborne Chemicals. Volume 6. Prepublication Copy. The National Academies Press, Washington, DC. pp. 89-91.

Paneth, F. and Joachimoglu, G. 1924. [The pharmacological characteristics of tin [IV] hydride (stannane) and germanium hydride]. Ber. D. deut. Chem.. Ges., 57: 1925-1930.

Test Species/Strain/Number:

Exposure Route/Concentrations/Durations

Effects:

Endpoint/Concentration/Rationale: Arsine AEGL-3 values adopted as AEGL-3 values for Germane. Paneth and Joachimoglu (1924) compared the acute inhalation toxicity of germane with the acute inhalation toxicity of arsine and concluded that both are hemolytic toxins and germane is less toxic than arsine. A mouse exposed to 207 ppm arsine for 1 hour exhibited difficulty breathing within 55 minutes and died within 1 hr, 48 minutes. A mouse exposed to 185 ppm germane for 1 hour exhibited dyspnea during exposure, no clinical signs 7 and 11 days post-exposure, and the animal died 13 days post-exposure. A guinea pig exposed to 207 ppm arsine exhibited increased respiratory rate within 55 minutes; hemoglobin was noted in the urine, and the animal died 4 days post-exposure (total exposure 2 hours). A guinea pig exposed to 185 ppm germane for 1 hour exhibited hemoglobin and protein in the urine, and the animal died 4 days post-exposure. Although these data are limited and not well described, the studies were conducted in the same laboratory; therefore, the relative toxicity data are considered acceptable. These data suggest that germane is less toxic than arsine in the mouse and no more toxic in the guinea pig.

Uncertainty Factors/Rationale:
Total uncertainty factor:

Modifying Factor:

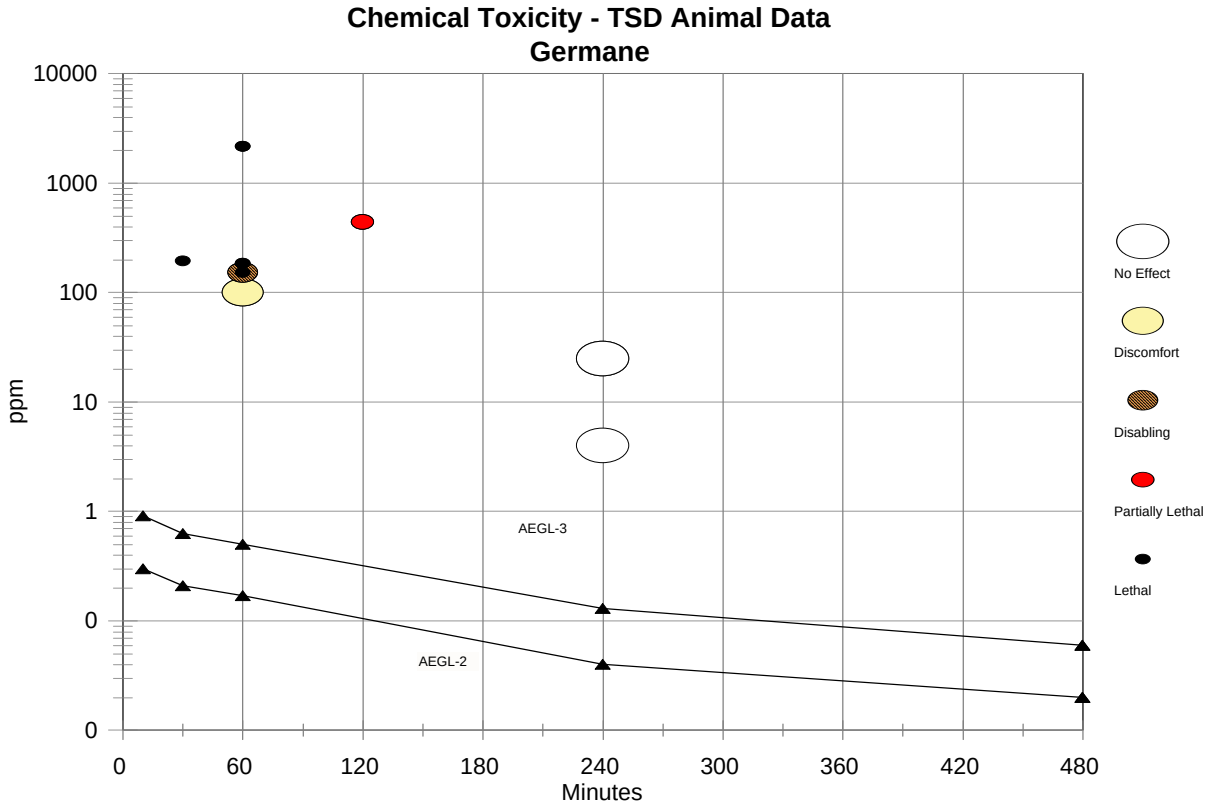
Animal to Human Dosimetric Adjustment:

Time Scaling

Data Adequacy: Sparse data set for germane.

APPENDIX C: Category Plot for Germane

1


Chemical Toxicity - TSD Animal Data
Germane
10000
1000
100
10
1
0
0
ppm
AEGL-3
AEGL-2
0
60
120
180
240
300
360
420
480
Minutes
No Effect
Discomfort
Disabling
Partially Lethal
Lethal

2

1
2

Germane

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

Source	Species	Sex	# Exposures	ppm	Minutes	Category	Effect
NAC/AEGL-1				NR	10	AEGL	
NAC/AEGL-1				NR	30	AEGL	
NAC/AEGL-1				NR	60	AEGL	
NAC/AEGL-1				NR	240	AEGL	
NAC/AEGL-1				NR	480	AEGL	
NAC/AEGL-2				0.30	10	AEGL	
NAC/AEGL-2				0.21	30	AEGL	
NAC/AEGL-2				0.17	60	AEGL	
NAC/AEGL-2				0.04	240	AEGL	
NAC/AEGL-2				0.02	480	AEGL	
NAC/AEGL-3				0.91	10	AEGL	
NAC/AEGL-3				0.63	30	AEGL	
NAC/AEGL-3				0.50	60	AEGL	
NAC/AEGL-3				0.13	240	AEGL	
NAC/AEGL-3				0.06	480	AEGL	
	mouse		1	2170	60	3	Mortality 1/1
	mouse		1	195	30	3	Mortality 1/1
	mouse		1	185	60	3	Mortality 1/1
	mouse		1	153	60	3	Mortality 1/1
	Gp		1	185	60	3	Mortality 1/1
	Gp		1	153	60	2	Hemoglobinuria, animal appeared sick
	rabbit		1	100	60	1	Dyspnea
	mouse		1	440	120	pl	Approximate LC50
	rat		30	4	240	0	No clinical signs
	rat		30	25	240	0	No clinical signs

APPENDIX D: DERIVATION SUMMARY TABLES AND DERIVATION OF 10-MINUTE AEGL VALUES FOR ARSINE

Derivation Summary Tables for Arsine (NRC, 2000)

AEGL-1 VALUES FOR ARSINE			
30 minutes	1 hour	4 hours	8 hours
Not recommended	Not recommended	Not recommended	Not recommended
Reference: The available human and animal data indicate that there is very little margin between seemingly inconsequential exposures and lethal exposures. The mechanism of arsine toxicity (hemolysis and subsequent renal failure) and the fact that toxicity has been demonstrated at or below the odor threshold justify the inappropriateness of AEGL-1 values for any exposure period.			
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 (1)			
Animal to Human Dosimetric Adjustment: Not applicable			
Time Scaling: Not applicable			
Data Quality and Support for AEGL Levels: Numeric values for AEGL-1 are not recommended because (1) the lack of available data, (2) an inadequate margin of safety exists between the derived AEGL-1 and the AEGL-2, or (3) the derived AEGL-1 is greater than the AEGL-2. Absence of an AEGL-1 does not imply that exposure below the AEGL-2 is without adverse effects.			

1

AEGL-2 VALUES FOR ARSINE			
30 minutes	1 hour	4 hours	8 hours
0.21 ppm	0.17 ppm	0.040 ppm	0.020 ppm

Reference: Peterson, D.P., M.H. Bhattacharyya. 1985. Hematological responses to arsine exposure: quantitation of exposure response in mice. Fundam. Appl. Toxicol. 5: 499-505.

Test Species/Strain/Sex/Number: Female $B6C3F_1$ mice, 8/group

Exposure Route/Concentrations/Durations: Inhalation: 0, 5, 9, 11, 15, or 26 ppm for 1 hour

Effects: hematocrit level (as % of controls)
5 ppm no significant effects (determinant for AEGL-2)
9 ppm 80.2 %
11 ppm 79.7%
15 ppm 61.4%
26 ppm 21.7% (100% mortality at 4 days postexposure)

Endpoint/Concentration/Rationale: 5 ppm for 1 hour considered as no-observed-effect-level for decreased hematocrit. A NOEL was used because of an extremely steep dose-response curve and the fact that the ultimate toxic effect, renal failure, is delayed for several days.

Uncertainty Factors/Rationale:
Total uncertainty factor: 30
Interspecies: 10 - The 10 minute LC_{50} value for the monkey was about 60% of the rat value and one third the rabbit value. The mouse data were used to calculate the AEGL levels because the data exhibited a good exposure response curve and the endpoint of decreased hematocrit can be considered a sensitive indicator of arsine toxicity. In addition, arsine has an extremely steep dose response curve giving little margin between no effects and lethality.
Intraspecies: 3 - Uncertainty regarding intraspecies variability was limited to 3 because the hemolytic response is likely to occur to a similar extent and with similar susceptibility in most individuals. This was based on the assumption that physiologic parameters (e.g., absorption, distribution, metabolism, structure of the erythrocyte and its response to arsine, renal responses) would not vary among individuals of the same species to such an extent that the response severity to arsine would be altered by an order of magnitude. Individual variability (i.e., variability in erythrocyte structure/function or response of the kidney to hemolysis) would not likely have a significant impact on any of the proposed subcellular mechanisms of arsine toxicity. The steep exposure-response curves from animal data also affirm the limited variability in response. Further more, the AEGL-2 values were developed using a conservative estimate of a toxic response (no significant indication of hemolysis in mice exposed for 1 hour to 5 ppm arsine) and additional reduction of the values would seem unwarranted.

Modifying Factor: Not applicable

Animal to Human Dosimetric Adjustment: None applied, insufficient data

Time Scaling: $C^n \times t = k$ where n = 1 or 3; The concentration exposure time relationship for many irritant and systemically acting vapors and gases may be described by $C^n \times t = k$, where the exponent, n, ranges from 0.8 to 3.5 (ten Berge et al., 1986). To assure AEGL values that are protective of human health, 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.

Data Quality and Support for AEGL Levels:
The study was considered adequate for AEGL-2 derivation. It was carefully designed and performed, used adequate numbers of animals, used an appropriate exposure regimen, and identified an endpoint consistent with AEGL-2 definition and with the known effects of arsine.

AEGL-3 VALUES FOR ARSINE			
30 minutes	1 hour	4 hours	8 hours
0.63 ppm	0.50 ppm	0.13 ppm	0.060 ppm

Reference: Peterson, D.P., M.H. Bhattacharyya. 1985. Hematological responses to arsine exposure: quantitation of exposure response in mice. Fundam. Appl. Toxicol. 5: 499-505.

Test Species/Strain/Sex/Number: Female $B6C3F_1$ mice, 8/group

Exposure Route/Concentrations/Durations: Inhalation: 0, 5, 9, 11, 15, or 26 ppm for 1 hour

Effects: hematocrit level (as % of controls) and lethality
5 ppm no significant effects
9 ppm 80.2 % (no mortality)
11 ppm 79.7% (no mortality)
15 ppm 61.4% (no mortality) (determinant for AEGL-3)
26 ppm 21.7% (3/8 immediately following exposures;
100% mortality at 4 days post-exposure)

Endpoint/Concentration/Rationale: 15 ppm for 1 hour induced a significant decrease in hematocrit that may be approaching a degree of hemolysis that can lead to renal failure. Given the steepness of the dose response curve this is justified as an estimate of the lethality threshold. An exposure of 26 ppm for 1 hour resulted in 100% lethality.

Uncertainty Factors/Rationale:
Total uncertainty factor: 30
Interspecies: 10 - The 10 minute LC_{50} value for the monkey was about 60% of the rat value and one third the rabbit value. The mouse data were used to calculate the AEGL levels because the data exhibited a good exposure response curve and the endpoint of decreased hematocrit can be considered a sensitive indicator of arsine toxicity. In addition, arsine has an extremely steep dose response curve giving little margin between no effects and lethality.
Intraspecies: 3 - Uncertainty regarding intraspecies variability was limited to 3 because the hemolytic response is likely to occur to a similar extent and with similar susceptibility in most individuals. This was based on the assumption that physiologic parameters (e.g., absorption, distribution, metabolism, structure of the erythrocyte and its response to arsine, renal responses) would not vary among individuals of the same species to such an extent that the response severity to arsine would be altered by an order of magnitude. Individual variability (i.e., variability in erythrocyte structure/function or response of the kidney to hemolysis) would not likely have a significant impact on any of the proposed subcellular mechanisms of arsine toxicity. The steep exposure-response curves from animal data also affirm the limited variability in response. Further more, the AEGL-2 values were developed using a conservative estimate of a toxic response (no significant indication of hemolysis in mice exposed for 1 hour to 5 ppm arsine) and additional reduction of the values would seem unwarranted.

Modifying Factor: Not applicable

Animal to Human Dosimetric Adjustment:

Time Scaling: $C^n \times t = k$ where n = 1 or 3; The concentration exposure time relationship for many irritant and systemically acting vapors and gases may be described by $C^n \times t = k$, where the exponent, n, ranges from 0.8 to 3.5 (ten Berge et al., 1986). To assure AEGL values that are protective of human health, 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.

Data Quality and Support for AEGL Levels:
The study was considered adequate for AEGL-3 derivation. It was carefully designed and performed, used adequate numbers of animals, used an appropriate exposure regimen, and identified an endpoint consistent with AEGL-3 definition and with the known effects of arsine. The available data indicate that the exposure-response relationship for arsine is very steep, thereby justifying a conservative approach to deriving AEGL values.

UPDATE OF ARSINE AEGLS TO INCLUDE 10-MINUTE VALUES (NRC, 2007)

In Volume 1 of the Acute Exposure Guideline Levels for Selected Airborne Chemicals Series (NRC, 2000) AEGL values were developed for 30 minute, and 1, 4, and 8 hours. Since that timeAEGL values have also been developed for 10 minute exposures. This article updates NRC (2000) to include 10 minute values. The summary below is from the NRC (2000) reference with additional discussion to address the development of 10 minute values.

SUMMARY

Arsine is a colorless gas used in the semiconductor industry. Arsine also is used in mining and manufacturing processes involving arsenicals, and from paints and herbicides containing arsenicals.

Arsine is an extremely toxic potent hemolytic agent, ultimately causing death via renal failure. Numerous human case reports are available but these reports lack definitive quantitative exposure data. The reports, however, affirm the extreme toxicity and latency period for the toxic effects of arsine in humans.

Exposure-response data from animal studies were used to derive acute exposure guideline level (AEGL) values for arsine. AEGL values derived with animal data which had complete exposure data were more scientifically valid than AEGLs estimated from limited anecdotal human data.. The greater conservatism afforded by the animal data is justified by the incomplete and often equivocal data for human exposures, the documented extreme toxicity of arsine, and the known latency involved in arsine-induced lethality. The AEGL values for the various exposure periods of concern (10 min, 30 min, 1, 4, and 8 hrs) were scaled from the experimental exposure duration using exponential scaling ($C^n \times t = k$, where C = exposure concentration, t = exposure duration, and k = a constant). Data were unavailable to empirically derive a scaling factor (*n*) for arsine. The concentration exposure time relationship for many irritant and systemically acting vapors and gases may be described by $C^n \times t = k$, where the exponent, *n*, ranges from 0.8 to 3.5 (ten Berge et al., 1986). In the absence of an empirically derived exponent (*n*), and to obtain conservative and protective AEGL values, 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.

Based upon the available data, derivation of AEGL-1 values was considered inappropriate. The continuum of arsine-induced toxicity does not appear to include effects consistent with the AEGL-1 definition. The available human and animal data affirm that there is little margin between exposures that result in little or no signs of toxicity and those that result in lethality. The mechanism of arsine toxicity (hemolysis that results in renal failure and death), and the fact that toxicity in humans and animals has been reported at concentrations at or below odor detection levels (–0.5 ppm) also support such a conclusion. The use of analytical detection limits (0.01 to 0.05 ppm) was considered as a basis for AEGL-1 values but was considered to be inconsistent with the AEGL-1 definition.

The AEGL-2 values were based upon exposure levels that did not result in significant alterations in hematologic parameters in mice exposed to arsine for 1 hour (Peterson and Bhattacharyya, 1985). Uncertainty factor application included a factor of 10-fold interspecies variability because of uncertainties regarding species-specific sensitivity to arsine-induced hemolysis. The 10 minute LC_{50} value for the monkey was about 60% of the rat value and one third the rabbit value. A less sensitive species, the rat, was used to calculate the AEGL levels because the data exhibited a good exposure response curve and the endpoint of decreased hematocrit can be considered a sensitive indicator of arsine toxicity. Uncertainty regarding intraspecies variability was limited to a factor of 3-fold, because the hemolytic response is likely to occur to a similar extent and with similar susceptibility in most individuals. This was based on the assumption that physiologic parameters (e.g., absorption, distribution, metabolism, structure of the

erythrocyte and its response to arsine, renal responses) would not vary among individuals of the same species to such an extent that the response severity to arsine would be altered by an order of magnitude. Additionally, individual variability (i.e., variability in erythrocyte structure/function or response of the kidney to hemolysis) is not likely to have a significant impact on any of the proposed subcellular mechanisms of arsine toxicity. The steep exposure-response curves from animal data also affirm the limited variability in response. Furthermore, the AEGL-2 values were developed using an exposure resulting in no significant hemolysis in mice exposed to arsine at 5 ppm for 1 hr, and, therefore, additional reduction of the values was unwarranted.

The AEGL-3 values were based upon lethality and hemolysis in mice exposed to arsine for 1 hr (Peterson and Bhattacharyya, 1985). A 1-hr exposure to 15 ppm, resulted in significant hemolysis, and a 1-hr exposure at 26 ppm produced 100% lethality. A total uncertainty factor application of 30 was applied as was done for AEGL-2 values using identical rationale. Because the AEGL-3 values were developed based upon an exposure producing hemolysis but no lethality in mice, no further reduction in the values was warranted. The derivation of AEGL-3 values using limited data in monkeys affirmed the values derived based upon the mouse data. Although the information on the human experience was of qualitative value, the absence of definitive verifiable exposure terms severely limited its usefulness as a valid quantitative measure for AEGL-3 development.

Time scaling was performed as previously described for the AEGL-2 tier.

The three AEGL exposure levels reflect the narrow range between exposures resulting in minor effects and those producing lethality. A conservative approach in the development of AEGLs for arsine was justified by the confirmed steep dose-response curve, the induction of hemolysis by arsine at extremely low concentrations, and the potential of hemolysis to progress to life-threatening renal failure. It is also noted that all of the AEGL values are near or below the odor threshold for arsine. A summary of AEGL values is shown in Table 4-1.

TABLE 4-1. SUMMARY OF AEGL VALUES FOR ARSINE

Classification	10-min	30-min	1-hour	4-hour	8-hour	Endpoint (Reference)
AEGL-1	NR[a]	NR	NR	NR	NR	Not recommended due to steep dose-response relationship, mechanism of toxicity, and because toxicity occurs at or below the odor threshold
AEGL-2	0.30 ppm 0.9 mg/m^3	0.21 ppm 0.7 mg/m3	0.17 ppm 0.5 mg/m^3	0.040 ppm 0.1 mg/m^3	0.020 ppm 0.06 mg/m^3	Absence of significant hematological alterations in mice consistent with the known continuum of arsine toxicity (Peterson and Bhattacharyya, 1985)
AEGL-3	0.91 ppm 2.9 mg/m^3	0.63 ppm 2.0 mg/m3	0.50 ppm 1.6 mg/m^3	0.13 ppm 0.4 mg/m^3	0.060 ppm 0.2 mg/m^3	Estimated threshold for lethality in mice (Peterson and Bhattacharyya, 1985)

NR: Not recommended. Numeric values for AEGL-1 are not recommended because (1) the lack of available data, (2) an inadequate margin of safety exists between the derived AEGL-1 and the AEGL-2, or (3) the derived AEGL-1 is greater than the AEGL-2. Absence of an AEGL-1 does not imply that exposure below the AEGL-2 is without adverse effects.