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4	ACUTE EXPOSURE GUIDELINE LEVELS (AEGLs)
5	FOR
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7	(CAS Reg. No. 7782-65-2)
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9	GeH <sub>4</sub>
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2	<b>ACUTE EXPOSURE GUIDELINE LEVELS (AEGLs)</b>
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# PREFACE

2 3 Under the authority of the Federal Advisory Committee Act (FACA) P. L. 92-463 of 4 1972, the National Advisory Committee for Acute Exposure Guideline Levels for Hazardous 5 Substances (NAC/AEGL Committee) has been established to identify, review and interpret 6 relevant toxicologic and other scientific data and develop AEGLs for high priority, acutely toxic 7 chemicals. 8 9 AEGLs represent threshold exposure limits for the general public and are applicable to 10 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 11 12 hour, 4 hours, and 8 hours) and are distinguished by varying degrees of severity of toxic effects. 13 The three AEGLs are defined as follows: 14 15 AEGL-1 is the airborne concentration (expressed as parts per million or milligrams per 16 cubic meter [ppm or  $mg/m^3$ ]) of a substance above which it is predicted that the general 17 population, including susceptible individuals, could experience notable discomfort, irritation, or 18 certain asymptomatic, non-sensory effects. However, the effects are not disabling and are 19 transient and reversible upon cessation of exposure. 20 AEGL-2 is the airborne concentration (expressed as ppm or  $mg/m^3$ ) of a substance above 21 22 which it is predicted that the general population, including susceptible individuals, could 23 experience irreversible or other serious, long-lasting adverse health effects or an impaired ability 24 to escape. 25 AEGL-3 is the airborne concentration (expressed as ppm or  $mg/m^3$ ) of a substance above 26 27 which it is predicted that the general population, including susceptible individuals, could 28 experience life-threatening health effects or death. 29 30 Airborne concentrations below the AEGL-1 represent exposure levels that could produce 31 mild and progressively increasing but transient and nondisabling odor, taste, and sensory 32 irritation or certain asymptomatic, non-sensory effects. With increasing airborne concentrations 33 above each AEGL, there is a progressive increase in the likelihood of occurrence and the severity 34 of effects described for each corresponding AEGL. Although the AEGL values represent 35 threshold levels for the general public, including susceptible subpopulations, such as infants, 36 children, the elderly, persons with asthma, and those with other illnesses, it is recognized that 37 individuals, subject to unique or idiosyncratic responses, could experience the effects described 38 at concentrations below the corresponding AEGL 39 40

PREFA	\CE	
LIST O	F TABLES	
SUMM	ARY	
1. IN	FRODUCTION	
2. HU	MAN TOXICITY DATA	
3. AN	IMAL TOXICITY DATA	
3.1.1.	Acute Toxicity	
3.1.2.	Repeated-exposure	
3.2.	Developmental/Reproductive Toxicity	
3.3. 2.4	Genoloxicity	
3.4. 3.5.	Summary	
4. SP	ECIAL CONSIDERATIONS	
4.1.	Metabolism and Disposition	
4.2.	Mechanism of Toxicity	
4.3.	Structure Activity Relationships	
4.4.	Other Relevant Information	
4.4	1. Species Variability	
4.4	2. Susceptible Populations	
5. DA	TA ANALYSIS FOR AEGL-1	
5.1.	Summary of Human Data Relevant to AEGL-1	
5.2.	Summary of Animal Data Relevant to AEGL-1	
5.3.	Derivation of AEGL-1	
6. DA	TA ANALYSIS FOR AEGL-2	
0.1.	Summary of Animal Data Relevant to AEGL-2	
6.3.	Derivation of AEGL-2	
7. DA	TA ANALYSIS FOR AEGL-3	
7.1.	Summary of Human Data Relevant to AEGL-3	
7.2.	Summary of Animal Data Relevant to AEGL-3	
7.3.	Derivation of AEGL-3	
8. SU	MMARY OF AEGLS	
8.1. o o	AEGL Values and Toxicity Endpoints	
ð.2. 8 2	Comparison with Other Standards and Guidelines	
0.3.	Data Aucquacy and Rescarch Needs	
9. RE	FERENCES	

1	APPENDIX B: DERIVATION SUMMARY FOR GERMANE AEGLS	19
2	APPENDIX C: CATEGORY PLOT FOR GERMANE	23
3 4 5	APPENDIX D: DERIVATION SUMMARY TABLES AND DERIVATION OF 10- MINUTE AEGL VALUES FOR ARSINE	26

1	LIST OF TABLES	
2		
3	TABLE 1. SUMMARY OF AEGL VALUES FOR GERMANE	7
4	TABLE 2. CHEMICAL AND PHYSICAL PROPERTIES	8
5	TABLE 3. EXPOSURE OF MICE, GUINEA PIGS AND RABBITS TO GERMANE (PANETH AND	
6	JOACHIMOGLU, 1924)	8
7	TABLE 4. COMPARATIVE TOXICITY OF GERMANE AND ARSINE (PANETH AND JOACHIMOGLU,	
8	1924)	10
9	TABLE 5. AEGL-1 VALUES FOR GERMANE	11
10	TABLE 6. AEGL-2 VALUES FOR GERMANE	12
11	TABLE 7. AEGL-3 VALUES FOR GERMANE	12
12	TABLE 8. SUMMARY OF AEGL VALUES	13
13	TABLE 9. EXTANT STANDARDS AND GUIDELINES FOR GERMANE	14
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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.

11 Chemical-specific germane data are insufficient for derivation of AEGL-2 or AEGL-3 12 values for germane. However, Paneth and Joachimoglu (1924) compared the acute inhalation 13 toxicity of germane with the acute inhalation toxicity of arsine and concluded that both are 14 hemolytic toxins and germane is less toxic than arsine. A mouse exposed to 207 ppm arsine for 15 1 hour exhibited difficulty breathing within 55 minutes and died within 1 hr, 48 minutes. A 16 mouse exposed to 185 ppm germane for 1 hour exhibited dyspnea during exposure, no clinical 17 signs 7 and 11 days post-exposure, and the animal died 13 days post-exposure. A guinea pig 18 exposed to 207 ppm arsine exhibited increased respiratory rate within 55 minutes; hemoglobin 19 was noted in the urine, and the animal died 4 days post-exposure (total exposure 2 hours). A 20 guinea pig exposed to 185 ppm germane for 1 hour exhibited hemoglobin and protein in the 21 urine, and the animal died 4 days post-exposure. Although these data are limited, the studies 22 were conducted in the same laboratory; therefore, the relative toxicity data are considered 23 acceptable. These data suggest that germane is less toxic than arsine in the mouse and no more 24 toxic in the guinea pig. Therefore, the AEGL-2 values for arsine will be adopted as AEGL-2 25 values for germane, and the AEGL-3 values for arsine will be adopted as AEGL-3 values for 26 germane.

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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 <sup>3</sup>	0.21 ppm 0.67 mg/m <sup>3</sup>	0.17 ppm 0.54 mg/m <sup>3</sup>	0.040 ppm 0.13 mg/m <sup>3</sup>	0.020 ppm 0.064 mg/m <sup>3</sup>	Arsine AEGL-2 values adopted as Germane AEGL-2 values (NRC, 2000; NRC, 2007)		
AEGL-3 (Lethal)	0.91 ppm 2.9 mg/m <sup>3</sup>	0.63 ppm 2.0 mg/m <sup>3</sup>	0.50 ppm 1.6 mg/m <sup>3</sup>	0.13 ppm 0.42 mg/m <sup>3</sup>	0.060 ppm 0.19 mg/m <sup>3</sup>	Arsine AEGL-3 values adopted as Germane AEGL-3 values (NRC, 2000: NRC, 2007)		

30 NR: Not Recommended due to insufficient data. Absence of an AEGL-1 value does not imply that concentrations

31 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 <sub>4</sub>	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 = $3.2 \text{ mg/m}^3$ 1 mg/m <sup>3</sup> = $0.32 \text{ ppm}$	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			

1 2 3 4 5 6		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.
7 8	3.1.2.	Repeated-exposure
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10 11 12		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.
12 13 14	3.2.	Developmental/Reproductive Toxicity
14 15 16		No data on developmental/reproductive toxicity were located.
10 17 18	3.3.	Genotoxicity
19 20		No genotoxicity data were located.
21 22	3.4.	Chronic Toxicity/Carcinogenicity
23 24		No data on chronic toxicity/carcinogenicity were located.
25 26	3.5.	Summary
27 28 29		Animal toxicity data are sparse and studies are poorly reported. No data on developmental/reproductive toxicity, genotoxicity, or chronic toxicity/carcinogenicity were located.
30 31	4.	SPECIAL CONSIDERATIONS
32 33	4.1.	Metabolism and Disposition
34 35		No information was located concerning the metabolism and disposition of germane.
36 37	4.2.	Mechanism of Toxicity
38 39 40		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.
41 42	4.3.	Structure Activity Relationships
43		
44 45		Paneth and Joachimoglu (1924) compared the effects of germane (GeH <sub>4</sub> ) and arsine (AsH <sub>3</sub> ), and concluded that germane was a hemolytic gas less toxic than arsine. Data are
46		summarized in Table 4.
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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	NĂ	1 day post- exposure	
Arsine	Guinea Pig (1)	550	2 hours	1 hr. Increased	1 day post-	
mone	Guinea I ig (1)	550	2 110415	respiratory rate	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	

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#### 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.

#### GERMANE

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#### 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).

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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.

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#### 15 6. DATA ANALYSIS FOR AEGL-2

#### 16 6.1. Summary of Human Data Relevant to AEGL-2

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

## 20 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).

## 26 6.3. Derivation of AEGL-2

27 28 The animal data consistent with the definition of AEGL-2 were from only one guinea pig 29 and one rabbit, and the study was poorly described (Paneth and Joachimoglu, 1924). However, 30 in the same study report, Paneth and Joachimoglu (1924) compared the acute inhalation toxicity 31 of germane with the acute inhalation toxicity of arsine and concluded that both are hemolytic 32 toxins and germane is less toxic than arsine. A mouse exposed to 207 ppm arsine for 1 hour 33 exhibited difficulty breathing within 55 minutes and died within 1 hr, 48 minutes. A mouse 34 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 35 36 207 ppm arsine exhibited increased respiratory rate within 55 minutes; hemoglobin was noted in 37 the urine, and the animal died 4 days post-exposure (total exposure 2 hours). A guinea pig 38 exposed to 185 ppm germane for 1 hour exhibited hemoglobin and protein in the urine, and the 39 animal died 4 days post-exposure. Although these data are limited and not well described, the 40 studies were conducted in the same laboratory; therefore, the relative toxicity data are considered 41 acceptable. These data suggest that germane is less toxic than arsine in the mouse and no more 42 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 43 44 be protective. AEGL-2 values are presented in Table 6, and calculations are presented in 45 Appendix A. The derivation summary for Arsine is presented in Appendix D.

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

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#### 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.

#### 17 7.3. Derivation of AEGL-3

19 The animal data showing no mortality and thus consistent with the definition of AEGL-3 20 were from only one guinea pig and one rabbit, and the study was poorly described (Paneth and 21 Joachimoglu, 1924). However, in the same study report, Paneth and Joachimoglu (1924) 22 compared the acute inhalation toxicity of germane with the acute inhalation toxicity of arsine and 23 concluded that both are hemolytic toxins and germane is less toxic than arsine. A mouse 24 exposed to 207 ppm arsine for 1 hour exhibited difficulty breathing within 55 minutes and died 25 within 1 hr, 48 minutes. A mouse exposed to 185 ppm germane for 1 hour exhibited dyspnea 26 during exposure, no clinical signs 7 and 11 days post-exposure, and the animal died 13 days 27 post-exposure. A guinea pig exposed to 207 ppm arsine exhibited increased respiratory rate 28 within 55 minutes; hemoglobin was noted in the urine, and the animal died 4 days post-exposure 29 (total exposure was 2 hours). A guinea pig exposed to 185 ppm germane for 1 hour exhibited 30 hemoglobin and protein in the urine, and the animal died 4 days post-exposure. Although these 31 data are limited and not well described, the studies were conducted in the same laboratory; 32 therefore, the relative toxicity data are considered acceptable. These data suggest that germane is 33 less toxic than arsine in the mouse and no more toxic in the guinea pig. Therefore, the AEGL-3 34 values for arsine will be adopted as AEGL-3 values for germane. In the absence of chemical-35 specific data for germane, these values should be protective. AEGL-3 values are presented in 36 Table 7, and calculations are presented in Appendix A. The derivation summary for Arsine is 37 presented in Appendix D.

TABLE 7. AEGL-3 Values for Germane					
10-min	30-min	1-h	<b>4-h</b>	8-h	
0.91  ppm 2.9 mg/m <sup>3</sup>	0.63  ppm 2.0 mg/m <sup>3</sup>	$0.50 \text{ ppm} \\ 1.6 \text{ mg/m}^3$	$0.13 \text{ ppm} \\ 0.42 \text{ mg/m}^3$	0.060  ppm $0.19 \text{ mg/m}^3$	

#### 8. SUMMARY OF AEGLS

# 4 8.1. AEGL Values and Toxicity Endpoints5

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.

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TABLE 8. Summary of AEGL Values						
Classification	Exposure Duration					
Classification	10-min 30-min 1-h 4-h 8-h					
AEGL-1	NR	NR	NR	NR	NR	
(Nondisabling)	INK	I	I	I	IUK	
AEGL-2	0.30 ppm	0.21 ppm	0.17 ppm	0.040 ppm	0.020 ppm	
(Disabling)	$0.96 \text{ mg/m}^3$	$0.67 \text{ mg/m}^3$	$0.54 \text{ mg/m}^3$	$0.13 \text{ mg/m}^3$	$0.064 \text{ mg/m}^3$	
AEGL-3	0.91 ppm	0.63 ppm	0.50 ppm	0.13 ppm	0.060 ppm	
(Lethal)	$2.9 \text{ mg/m}^3$	$2.0 \text{ mg/m}^3$	$1.6 \text{ mg/m}^3$	$0.42 \text{ mg/m}^3$	$0.19 \text{ mg/m}^3$	

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.

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#### 13 8.2. Comparison with Other Standards and Guidelines

15 Other standards and guidelines are presented in Table 9. The ACGIH TLV-TWA was 16 derived by analogy to stibine which was derived by analogy to arsine. In a Health-based 17 Reassessment of Administrative Occupational Exposure limits (Health Council of the 18 Netherlands, 2000), the committee concluded that the toxicological data base in germane was 19 too poor to justify recommendation of a health-based occupational exposure limit. The 20 committee concluded that there is insufficient information to comment on the level of the 21 present MAC value.

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23 Germane is described as a hemolytic agent, similar in properties to arsine and stibine 24 (ACGIH, 2001), and the ACGIH TLV-TWA value was derived by analogy to stibine. AEGL 25 values exist for both arsine and stibine; however, AEGL values for germane are derived by 26 analogy to arsine, not stibine, because the arsine AEGL values are more conservative than 27 the stibine AEGL values. [Stibine AEGL values are: AEGL-1 = NR at all time points. 28 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 29 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 30 ppm for 4-hr, and 1.2 ppm for 8-hr.] Given the very sparse data set for germane, this 31 conservatism is warranted.

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TABLE 9. Extant Standards and Guidelines for Germane								
		Exposure Duration						
Guideline	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) <sup>a</sup>					0.2 ppm			
TLV-TWA (ACGIH) <sup>b</sup>					0.2 ppm			
TLV-STEL (ACGIH) <sup>c</sup>	Deleted							
MAC (The Netherlands) <sup>d</sup>					0.2 ppm			

<sup>a</sup>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.

<sup>b</sup>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.

<sup>c</sup>ACGIH TLV-STEL (Threshold Limit Value - Short Term Exposure Limit) (ACGIH 2001) is defined as a 15minute 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.

<sup>c</sup>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.

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**APPENDIX A: Derivation of AEGL Values** 

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## **Derivation of AEGL-1 for Germane**

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

5 recommended.

GERMANE

#### **Derivation of AEGL-2 for Germane** 1 2 3 Arsine AEGL-2 values adopted as AEGL-2 values for Germane. 4 5 Paneth and Joachimoglu (1924) compared the acute inhalation toxicity of germane with the acute 6 inhalation toxicity of arsine and concluded that both are hemolytic toxins and germane is less 7 toxic than arsine. A mouse exposed to 207 ppm arsine for 1 hour exhibited difficulty breathing 8 within 55 minutes and died within 1 hr, 48 minutes. A mouse exposed to 185 ppm germane for 1 9 hour exhibited dyspnea during exposure, no clinical signs 7 and 11 days post-exposure, and the 10 animal died 13 days post-exposure. A guinea pig exposed to 207 ppm arsine exhibited increased 11 respiratory rate within 55 minutes; hemoglobin was noted in the urine, and the animal died 4 12 days post-exposure (total exposure 2 hours). A guinea pig exposed to 185 ppm germane for 1 13 hour exhibited hemoglobin and protein in the urine, and the animal died 4 days post-exposure. 14 Although these data are limited and not well described, the studies were conducted in the same 15 laboratory; therefore, the relative toxicity data are considered acceptable. These data suggest 16 that germane is less toxic than arsine in the mouse and no more toxic in the guinea pig. 17 18 19 20 **Derivation of AEGL-3 Germane** 21 22 Arsine AEGL-3 values adopted as AEGL-3 values for Germane. 23 24 Paneth and Joachimoglu (1924) compared the acute inhalation toxicity of germane with the acute 25 inhalation toxicity of arsine and concluded that both are hemolytic toxins and germane is less 26 toxic than arsine. A mouse exposed to 207 ppm arsine for 1 hour exhibited difficulty breathing 27 within 55 minutes and died within 1 hr, 48 minutes. A mouse exposed to 185 ppm germane for 1 28 hour exhibited dyspnea during exposure, no clinical signs 7 and 11 days post-exposure, and the 29 animal died 13 days post-exposure. A guinea pig exposed to 207 ppm arsine exhibited increased 30 respiratory rate within 55 minutes; hemoglobin was noted in the urine, and the animal died 4 31 days post-exposure (total exposure 2 hours). A guinea pig exposed to 185 ppm germane for 1 32 hour exhibited hemoglobin and protein in the urine, and the animal died 4 days post-exposure. 33 Although these data are limited and not well described, the studies were conducted in the same 34 laboratory; therefore, the relative toxicity data are considered acceptable. These data suggest 35 that germane is less toxic than arsine in the mouse and no more toxic in the guinea pig. 36

**APPENDIX B: Derivation Summary for Germane AEGLs** 

10-min	30-min	1-h	<b>4-h</b>	8-h
NR	NR	NR	NR	NR
Key Reference:				
Test Species/Strain/I	Number:			
Exposure Route/Cor	ncentrations/Durations:			
Effects:				
Endpoint/Concentrat	tion/Rationale:			
Uncertainty Factors/	Rationale:			
Total uncertainty fac	ctor:			
Modifying Factor: N	IA			
Animal to Human D	osimetric Adjustment:			
Time Scaling:				
Data Adequacy: Da recommended for ge	ta are insufficient for der ermane.	ivation of AEGL-1 valu	es. Therefore, AEGL-1	values are not

AEGL-2	Values for	r Germane
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10-min	30-min	1-h	4-h	8-h		
0.30 ppm	) ppm 0.21 ppm 0.17 ppm 0.040 ppm 0.020 p					
<ul> <li>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.</li> <li>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.</li> </ul>						
Paneth, F. and Joach germanium hydride]	imoglu, G. 1924. [The . Ber. D. deut. Chem C	pharmacological charac Ges., 57: 1925-1930.	teristics of tin [IV] hydr	ide (stannane) and		
Test Species/Strain/I	Number:					
Exposure Route/Con	centrations/Durations					
Effects:						
Endpoint/Concentrat Joachimoglu (1924) and concluded that b arsine for 1 hour exh exposed to 185 ppm exposure, and the an increased respiratory exposure (total expo and protein in the uri described, the studie acceptable. These da pig.	tion/Rationale: Arsine A compared the acute inha oth are hemolytic toxins ibited difficulty breathin germane for 1 hour exh imal died 13 days post- rate within 55 minutes; sure 2 hours). A guinea ine, and the animal died s were conducted in the ata suggest that germane	EGL-2 values adopted a alation toxicity of germa: s and germane is less tox ng within 55 minutes and ibited dyspnea during ex exposure. A guinea pig e hemoglobin was noted is pig exposed to 185 ppm 4 days post-exposure. A same laboratory; therefore is less toxic than arsine	is AEGL-2 values for Go ne with the acute inhalat ic than arsine. A mouse d died within 1 hr, 48 mi posure, no clinical signs xposed to 207 ppm arsin in the urine, and the anin germane for 1 hour exh Although these data are I ore, the relative toxicity	ermane. Paneth and tion toxicity of arsine e exposed to 207 ppm inutes. A mouse s 7 and 11 days post- ne for exhibited mal died 4 days post- nibited hemoglobin limited and not well data are considered ore toxic in the guinea		
Uncertainty Factors/	Rationale:					
Total uncertainty fac	Total uncertainty factor:					
Modifying Factor:						
Animal to Human D	osimetric Adjustment:					
Data Adaguague Ser	and data ast for as					
Data Adequacy: Spa	arse data set for germane	2.				

2

I

### **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		
<ul> <li>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.</li> <li>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.</li> </ul>						
Paneth, F. and Joach germanium hydride]	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/N	Number:					
Exposure Route/Con	centrations/Durations					
Effects:						
Endpoint/Concentrat Joachimoglu (1924) and concluded that b arsine for 1 hour exh exposed to 185 ppm exposure, and the an respiratory rate withi (total exposure 2 hou in the urine, and the studies were conduct These data suggest th	ion/Rationale: Arsine A compared the acute inha oth are hemolytic toxins ibited difficulty breathir germane for 1 hour exhi imal died 13 days post- in 55 minutes; hemoglob urs). A guinea pig expos animal died 4 days post- ted in the same laborator hat germane is less toxic	EGL-3 values adopted a alation toxicity of german s and germane is less tox ng within 55 minutes and ibited dyspnea during ex exposure. A guinea pig e bin was noted in the urin sed to 185 ppm germane exposure. Although the ry; therefore, the relative than arsine in the moust	Is AEGL-3 values for Ge ne with the acute inhalat ic than arsine. A mouse d died within 1 hr, 48 mi posure, no clinical signs xposed to 207 ppm arsir e, and the animal died 4 for 1 hour exhibited her ese data are limited and r toxicity data are consid e and no more toxic in the	ermane. Paneth and ion toxicity of arsine exposed to 207 ppm nutes. A mouse 7 and 11 days post- ne exhibited increased days post-exposure noglobin and protein not well described, the ered acceptable. he guinea pig.		
Uncertainty Factors/	Rationale:					
I otal uncertainty fac	tor:					
A nimel to Human D	osimatria Adjustmenti					
Time Scaling	osinicule Aujusullelli.					
Data Adequacy: Spa	arse data set for germane	2				

**APPENDIX C: Category Plot for Germane** 



1

## 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

1	<b>APPENDIX D: DERIVATION SUMMARY TABLES AND DERIVATION OF 10-</b>
2	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/Ratio	onale: 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.				

	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 of exposure response	, D.P., M.H. Bhattacharyya.	1985. Hematological responsional responsional responsion for the second	onses to arsine exposure: quantitatio
Test Species/Strain/S	ex/Number: Female B6C3F	F <sub>1</sub> mice, 8/group	
Exposure Route/Con	centrations/Durations: Inha	lation: 0, 5, 9, 11, 15, or 26	ppm for 1 hour
Effects: hematoc	rit level (as % of controls)		
5 ppm no significan	t effects (determinant for A	EGL-2)	
9 ppm 80.2 %			
11 ppm 79.7%			
15 ppm 61.4%	mortality at 1 days postar		
<u>20 ppiii 21.7% (100%</u> Endpoint/Concentrat	ion/Pationale: 5 ppm for 1	hour considered as no obse	arved affect level for decreased
hematocrit A NOFI	was used because of an ex	tremely steen dose-response	e curve and the fact that the ultimate
toxic effect renal fai	lure is delayed for several $\hat{c}$	lavs	e curve and the fact that the utilitat
Uncertainty Factors/	Rationale:	<i>uy</i> 5.	
Total uncertainty fac	tor: 30		
Interspecies: 10 -	The 10 minute LC <sub>50</sub> value f	or the monkey was about 6	0% of the rat value and one third the
rabbit value. The mo	use data were used to calcul	ate the AEGL levels because	se the data exhibited a good exposur
response curve and th	he endpoint of decreased he	matocrit can be considered	a sensitive indicator of arsine
toxicity. In addition,	arsine has an extremely ste	ep dose response curve givi	ing little margin between no effects
and lethality.			
Intraspecies: 3 - U	Incertainty regarding intrasp	becies variability was limite	d 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 in	at physiologic parameters (e	e.g., absorption, distribution	, metabolism, structure of the
such an extent that the	sponse to arsine, renai response severity to arsin	a would be altered by an or.	der of magnitude Individual
variability (i.e. varia	bility in erythrocyte structu	re/function or response of fl	he kidney to hemolysis) would not
likely have a signific	ant impact on any of the pro-	posed subcellular mechaniz	sms of arsine toxicity. The steep
exposure-response ci	rves from animal data also	affirm the limited variabilit	y in response. Further more, the
AEGL-2 values were	developed using a conservation		
hemolysis in mice ex	posed for 1 hour to 5 ppm a	ative estimate of a toxic res	ponse (no significant indication of
unwarranted.		ative estimate of a toxic res rsine) and additional reduc	ponse (no significant indication of tion of the values would seem
Modifying Factor: N		ative estimate of a toxic res rsine) and additional reduc	ponse (no significant indication of tion of the values would seem
	lot applicable	ative estimate of a toxic res rsine) and additional reduc	ponse (no significant indication of tion of the values would seem
Animal to Human Do	lot applicable	ative estimate of a toxic res rsine) and additional reduc applied, insufficient data	ponse (no significant indication of tion of the values would seem
Animal to Human De Time Scaling: C <sup>n</sup> x	Tot applicable psimetric Adjustment: None t = k where n = 1 or 3; The	ative estimate of a toxic res rsine) and additional reduct applied, insufficient data concentration exposure tim	ponse (no significant indication of tion of the values would seem e relationship for many irritant and
Animal to Human Do Time Scaling: C <sup>n</sup> x systemically acting v	Iot applicable osimetric Adjustment: None t = k where n = 1 or 3; The apors and gases may be des	ative estimate of a toxic res rsine) and additional reduct applied, insufficient data concentration exposure tim cribed by $C^n x t = k$ , where	ponse (no significant indication of tion of the values would seem e relationship for many irritant and the exponent, <i>n</i> , ranges from 0.8 to
Animal to Human Do Time Scaling: C <sup>n</sup> x systemically acting v 3.5 (ten Berge et al.,	Tot applicable Desimetric Adjustment: None t = k where n = 1 or 3; The apors and gases may be des 1986). To assure AEGL va	ative estimate of a toxic res rsine) and additional reduction applied, insufficient data concentration exposure tim cribed by $C^n x t = k$ , where lues that are protective of h	ponse (no significant indication of tion of the values would seem e relationship for many irritant and the exponent, <i>n</i> , ranges from 0.8 to uman health, temporal scaling was
Animal to Human Do Time Scaling: $C^n x$ systemically acting v 3.5 (ten Berge et al., performed using $n =$	Tot applicable posimetric Adjustment: None t = k where n = 1 or 3; The apors and gases may be des 1986). To assure AEGL va 3 when extrapolating to sho	ative estimate of a toxic res rsine) and additional reduct applied, insufficient data concentration exposure time cribed by $C^n x t = k$ , where lues that are protective of h rter time points and $n = 1$ w	ponse (no significant indication of tion of the values would seem the relationship for many irritant and the exponent, <i>n</i> , ranges from 0.8 to uman health, temporal scaling was when extrapolating to longer time
Animal to Human Do Time Scaling: $C^n x$ systemically acting v 3.5 (ten Berge et al., performed using $n =$ points using the $C^n x$	Not applicable Desimetric Adjustment: None t = k where $n = 1$ or 3; The apors and gases may be des 1986). To assure AEGL va 3 when extrapolating to sho t = k equation.	ative estimate of a toxic res rsine) and additional reduct applied, insufficient data concentration exposure tim cribed by $C^n x t = k$ , where lues that are protective of h rter time points and $n = 1$ w	ponse (no significant indication of tion of the values would seem re relationship for many irritant and the exponent, <i>n</i> , ranges from 0.8 to uman health, temporal scaling was when extrapolating to longer time
Animal to Human Do Time Scaling: $C^n x$ systemically acting v 3.5 (ten Berge et al., performed using $n =$ points using the $C^n x$ Data Quality and Sup	Not applicable Desimetric Adjustment: None t = k where $n = 1$ or 3; The apors and gases may be des 1986). To assure AEGL va 3 when extrapolating to sho t = k equation. poport for AEGL Levels: here the desire the function of the terms of t	ative estimate of a toxic res rsine) and additional reduction applied, insufficient data concentration exposure time cribed by $C^n x t = k$ , where lues that are protective of h rter time points and $n = 1$ w	ponse (no significant indication of tion of the values would seem the relationship for many irritant and the exponent, <i>n</i> , ranges from 0.8 to uman health, temporal scaling was when extrapolating to longer time
Animal to Human Do Time Scaling: $C^n x$ systemically acting v 3.5 (ten Berge et al., performed using $n =$ points using the $C^n x$ Data Quality and Sup The study was considered	Not applicable Desimetric Adjustment: None t = k where $n = 1$ or 3; The apors and gases may be des 1986). To assure AEGL va 3 when extrapolating to sho t = k equation. port for AEGL Levels: lered adequate for AEGL-2 animals, used an approximate	ative estimate of a toxic respective estimate of a toxic respective of a toxic respective of a toxic respective of a toxic respective of the state of the stateo	ponse (no significant indication of tion of the values would seem the relationship for many irritant and the exponent, <i>n</i> , ranges from 0.8 to uman health, temporal scaling was when extrapolating to longer time
Animal to Human Do Time Scaling: $C^n x$ systemically acting v 3.5 (ten Berge et al., performed using $n =$ points using the $C^n x$ Data Quality and Sup The study was conside adequate numbers of AEGL 2 definition of	Not applicable t = k where $n = 1$ or 3; The apors and gases may be des 1986). To assure AEGL va 3 when extrapolating to sho t = k equation. port for AEGL Levels: lered adequate for AEGL-2 animals, used an appropriate and with the known effects of	ative estimate of a toxic res rsine) and additional reduct applied, insufficient data concentration exposure tim cribed by $C^n x t = k$ , where lues that are protective of h rter time points and $n = 1$ w derivation. It was carefully the exposure regimen, and id for argine	ponse (no significant indication of tion of the values would seem re relationship for many irritant and the exponent, <i>n</i> , ranges from 0.8 to uman health, temporal scaling was when extrapolating to longer time y designed and performed, used entified an endpoint consistent with

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	
30 minutes1 hour4 hours8 hours0.63 ppm0.50 ppm0.13 ppm0.060 ppmReference: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 B6C3F1 mice, 8/groupExposure Route/Concentrations/Durations:Inhalation: 0, 5, 9, 11, 15, or 26 ppm for 1 hourEffects:hematocrit level (as % of controls) and lethality 5 ppm no significant effects 9 ppm 80.2 % (no mortality) 11 ppm 79.7% (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 <sub>50</sub> 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.				
Animal to Human Dosimetric Adjustment:				
Time Scaling: $C^n x t = k$ where n = 1 or 3; The concentration exposure time relationship for many irritant and systemically acting vapors and gases may be described by $C^n x t = k$ , where the exponent, <i>n</i> , 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 $C^n x t = k$ 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.				

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9 10

11

#### 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,

17 however, affirm the extreme toxicity and latency period for the toxic effects of arsine in humans.

18

19 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

24 The AEOE values for the various exposure periods of concern (10 min, 30 min, 1, 4, and 8 ms) were 25 scaled from the experimental exposure duration using exponential scaling ( $C^n x t = k$ , where C = exposure

26 concentration, t = exposure duration, and k = a constant). Data were unavailable to empirically derive a

27 scaling factor (*n*) for arsine. The concentration exposure time relationship for many irritant and

28 systemically acting vapors and gases may be described by  $C^n x t = k$ , where the exponent, *n*, ranges from

29 0.8 to 3.5 (ten Berge et al., 1986). In the absence of an empirically derived exponent (*n*), and to obtain

30 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  $C^n x t = k$ equation.

33

34 Based upon the available data, derivation of AEGL-1 values was considered inappropriate. The

35 continuum of arsine-induced toxicity does not appear to include effects consistent with the AEGL-1

36 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

38 (hemolysis that results in renal failure and death), and the fact that toxicity in humans and animals has

39 been reported at concentrations at or below odor detection levels (-0.5 ppm) also support such a

40 conclusion. The use of analytical detection limits (0.01 to 0.05 ppm) was considered as a basis for

41 AEGL-1 values but was considered to be inconsistent with the AEGL-1 definition.

42

43 The AEGL-2 values were based upon exposure levels that did not result in significant alterations in

44 hematologic parameters in mice exposed to arsine for 1 hour (Peterson and Bhattacharyya, 1985).

45 Uncertainty factor application included a factor of 10-fold interspecies variability because of uncertainties

46 regarding species-specific sensitivity to arsine-induced hemolysis. The 10 minute LC<sub>50</sub> value for the

47 monkey was about 60% of the rat value and one third the rabbit value. A less sensitive species, the rat,

48 was used to calculate the AEGL levels because the data exhibited a good exposure response curve and the

49 endpoint of decreased hematocrit can be considered a sensitive indicator of arsine toxicity. Uncertainty

50 regarding intraspecies variability was limited to a factor of 3-fold, because the hemolytic response is

51 likely to occur to a similar extent and with similar susceptibility in most individuals. This was based on

52 the assumption that physiologic parameters (e.g., absorption, distribution, metabolism, structure of the

#### GERMANE

1 erythrocyte and its response to arsine, renal responses) would not vary among individuals of the same

2 species to such an extent that the response severity to arsine would be altered by an order of magnitude.

3 Additionally, individual variability (i.e., variability in erythrocyte structure/function or response of the

4 kidney to hemolysis) is not likely to have a significant impact on any of the proposed subcellular

5 mechanisms of arsine toxicity. The steep exposure-response curves from animal data also affirm the

6 limited variability in response. Furthermore, the AEGL-2 values were developed using an exposure

7 resulting in no significant hemolysis in mice exposed to arsine at 5 ppm for 1 hr, and, therefore, additional

8 reduction of the values was unwarranted.9

10 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 applie

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

15 was warranted. The derivation of AEGL-3 values using limited data in monkeys affirmed the values

16 derived based upon the mouse data. Although the information on the human experience was of

17 qualitative value, the absence of definitive verifiable exposure terms severely limited its usefulness as a

18 valid quantitative measure for AEGL-3 development.

19

20 Time scaling was performed as previously described for the AEGL-2 tier. 21

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.

27 28

TABLE 4-1.       SUMMARY OF AEGL VALUES FOR ARSINE						
Classificati on	10-min	30-min	1-hour	4-hour	8-hour	Endpoint (Reference)
AEGL-1	NR <sup>a</sup>	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 <sup>3</sup>	0.21 ppm 0.7 mg/m3	0.17 ppm 0.5 mg/m <sup>3</sup>	0.040 ppm 0.1 mg/m <sup>3</sup>	0.020 ppm 0.06 mg/m <sup>3</sup>	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 <sup>3</sup>	0.63 ppm 2.0 mg/m3	0.50 ppm 1.6 mg/m <sup>3</sup>	0.13 ppm 0.4 mg/m <sup>3</sup>	0.060 ppm 0.2 mg/m <sup>3</sup>	Estimated threshold for lethality in mice (Peterson and Bhattacharyya, 1985)

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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.