ACUTE EXPOSURE GUIDELINE LEVELS (AEGLs)

FOR

METHYL IODIDE

(CAS Reg. No. 74-88-4)

CH$_3$I

PROPOSED

1   **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 – AEGL-1,
11   AEGL-2 and AEGL-3 – are developed for each of five exposure periods (10 and 30 minutes, 1
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
21   AEGL-2 is the airborne concentration (expressed as ppm or mg/m^3) of a substance above
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
26   AEGL-3 is the airborne concentration (expressed as ppm or mg/m^3) of a substance above
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

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1   **SUMMARY**
2
3   Methyl iodide (CH_3I, CAS No. 74-88-4) is a colorless liquid that turns brown with
4   exposure to light or moisture due to the liberation of iodine. It has a sweet ethereal odor which
5   provides poor warning properties. Methyl iodide is a pre-plant biocide used to control insects,
6   plant parasitic nematodes, soil-born pathogens, and weed seeds. It is also used as a methylating
7   agent in inorganic synthesis; in microscopy, as an embedding material for examining diatoms;
8   and in testing for pyridine. Production data were not located.
9
10   Acute exposure to methyl iodide produces a number of effects in laboratory animals
11 including degeneration of the nasal epithelium and neurotoxicity in rats and fetal toxicity in
12 rabbits. Neurotoxicity has been observed in human accidental exposures. Absorption following
13 inhalation is rapid; retention in humans averages 72%. Methyl iodide is rapidly metabolized in
14 blood and tissue resulting in methylation products and release of inorganic iodide. Toxicity
15 appears linked to metabolism. Halomethanes are usually conjugated via glutathione-S-
16 transferase (GST) with glutathione (GSH), but the conjugation of methyl iodide with glutathione
17 may be non-enzymatic. Nasal lesions in rats are attributed to the sustained depletion of GSH
18 below critical levels due to metabolism. Depletion of GSH, likely renders tissues susceptible to
19 methylation and/or oxidative stress; in addition DNA repair processes may be inhibited. In the
20 nasal cavity of the rat, the olfactory epithelium is the target tissue of methyl iodide. Transient
21 neurotoxicity is attributed to the presence of the parent chemical in nerve cell membranes.
22 Fetotoxicity in rabbits (early fetal deaths) is attributed to the unregulated uptake of iodine by the
23 developing thyroid of the fetal rabbit. Accumulation of iodide in the rabbit fetus disrupts the
24 fetal hypothalamic-pituitary-thyroid axis at a critical time in the development of the fetal thyroid.
25   Fetal uptake of iodine is regulated in the rat and in humans. The data base for methyl iodide
26 includes repeat-exposure, genotoxicity, developmental, subchronic, and chronic studies.
27
28   The AEGL-1 values are based on a weight-of evidence approach. A 6-hour exposure to
29 27 ppm was a NOAEL for clinical signs that indicated neurotoxicity (U.S. EPA 2006). A 1-hour
30 exposure to 100 ppm was a no-effect concentration for lesions of the nasal passage in rats, and a
31 2-hour exposure to 100 ppm resulted in minimal lesions of the olfactory epithelium (Reed et al.
32 1995). Results of studies with longer exposure durations showed that the nasal lesions are
33 reversible. In a 4-week repeat-exposure study, 25 ppm was a no-effect level for irritation,
34 neurotoxic signs, and gross pathologic changes in rats (Monsanto Company 1983). In a 13-week
35 study, 21 ppm was a NOAEL for nasal degeneration in rats (U.S. EPA 2006).
36
37   Based on the acute studies of U.S. EPA (2006) and Reed et al. (1995) with support from
38 the repeat-exposure studies of Monsanto Company (1983) and U.S. EPA (2006), a weight-of
39 evidence approach shows that exposures of rats to 27 ppm for 6 hours and to 100 ppm for 30 or
40 60 minutes are NOAELs for both neurotoxicity and nasal lesions. The 6-hour 27 ppm
41 concentration was used as the point of departure for the AEGL-1. Based on a higher blood:air
42 partition coefficient for methyl iodide in rats compared with humans, resulting in greater uptake,
43 an interspecies uncertainty factor of 1 was applied. Metabolism via glutathione conjugation is
44 not expected to vary greatly among humans (Nolan et al. 1985). In addition, conjugation of
45 methyl iodide with glutathione, the primary route of metabolism, may be non-enzymatic, further
46 minimizing individual differences. Based on the neurotoxicity endpoint, Sweeney et al. (2009)
47 estimated that GSH conjugation with methyl iodide in a GSTT-1 null person would be a factor of

1   1.4 lower than that derived for a person with full GST activity. Therefore, the intraspecies
2   uncertainty factor was lowered from the default of 10 to 3.
3
4   Development of nasal lesions and neurotoxicity are systemic effects; methyl iodide is not
5   an irritant at these concentrations. Therefore the AEGL-1 values were time-scaled. The 6-hour
6   NOAEL for nasal lesions and neurotoxicity value of 9 ppm (27 ppm/3) was time scaled using C^n
7   x t = k. Because neurotoxicity is on a continuum with lethality, time scaling was based on the rat
8   lethality data sets of Eastman Kodak Co. (1987), Reed et al. (1995), and U.S. EPA (2006). The
9   time scaling value was 2 (C^2 x t = k). The 6-hour value was time scaled to 10 minutes because
10 one of the key studies (Reed et al. 1995) utilized a 0.5-hour exposure. Because the 8-hour time-
11 scaled value of less than 10 ppm appears unrealistic in light of no-effect concentrations of 10
12 ppm and 20 ppm in subchronic and chronic studies reported by Blank et al. (1984) and U.S. EPA
13 (2006), respectively, the 8-hour value was set equal to the 4-hour value of 11 ppm.
14
15   The AEGL-2 values were based on reversible lesions of the olfactory epithelium of rats,
16 i.e., a NOAEL for irreversible lesions (Reed et al. 1995). The point of departure was the 6-hour
17 exposure to 100 ppm. This concentration (100 ppm for 6 hours) had no effect on breathing
18 frequency in rats (DeLorme et al. 2009), and is the threshold for neurotoxicity that might impede
19 the ability to escape (93 ppm for 6 hours) (U.S. EPA 2006). Based on a higher blood:air partition
20 coefficient for methyl iodide in rats compared with humans, an interspecies uncertainty factor of
21 1 was applied. Metabolism via glutathione conjugation is not expected to vary greatly among
22 humans (Nolan et al. 1985). In addition, conjugation of methyl iodide with glutathione, the
23 primary route of metabolism, may be non-enzymatic, further minimizing individual differences.
24 Based on the neurotoxicity endpoint, Sweeney et al. (2009) estimated that GSH conjugation with
25 methyl iodide in a GSTT-1 null person would be a factor of 1.4 lower than that derived for a
26 person with full GST activity. Therefore, the intraspecies default uncertainty factor of 10 was
27 lowered to 3. Values were time-scaled using C^2 x t = k. The fetotoxic effects of iodine liberated
28 from methyl iodide were considered in the derivation of AEGL-2 values. Based on historical
29 evidence of medical prescription of iodine to pregnant women, the inhaled dose at the 8-hour
30 AEGL-2 is considered of minimal health risk for the developing fetus.
31
32   The following data sets were considered in derivation of AEGL-3 values. Mortality rates
33 for male and female rats inhaling 1190, 1554, or 1973 ppm for 1 hour were 20, 60, and 90%,
34 respectively (Eastman Kodak Co. 1987). No mortality was observed in rats inhaling 100 ppm for
35 0.5 to 6 hours (Reed et al. 1995). Mortality rates of male and female rats inhaling 581, 710, 797,
36 or 1198 ppm for 4 hours were 0, 80, 80, and 100%, respectively (U.S. EPA 2006), and mortality
37 rates of rats inhaling 27, 93, or 401 ppm for 6 hours were 0, 0, and 4% (U.S. EPA 2006). Using
38 all data sets, the threshold for lethality was calculated at each AEGL-3 exposure duration using
39 the probit-analysis based dose-response program of ten Berge (2006). The threshold for lethality
40 was set at the lower limit of the 95% confidence limit. The data indicated a time-scaling value of
41 2 (C^2 x t = k). Based on a higher blood:air partition coefficient for methyl iodide in rats
42 compared with humans, resulting in greater uptake, an interspecies uncertainty factor of 1 was
43 applied. Although humans vary in the rate at which they metabolize halomethanes, the
44 difference is not expected to be greater than three-fold (Nolan et al. 1985). Furthermore, the
45 conjugation of methyl iodide with glutathione may be non-enzymatic, further minimizing
46 differences in metabolism rates. Based on the neurotoxicity endpoint, Sweeney et al. (2009)
47 estimated that GSH conjugation with methyl iodide in a GSTT-1 null person would be a factor of
48 1.4 lower than that of a person with full GST activity. Therefore, the intraspecies uncertainty

1 factor was lowered from the default of 10 to 3. A total uncertainty factor of 3 was applied to the
2 time-scaled values of the ten Berge program.
3
4   The calculated values are listed in the table below.
5

S 1. **Summary of AEGL Values for Methyl Iodide**						
Classification	**10-min**	**30-min**	**1-h**	**4-h**	**8-h**	**Endpoint (Reference)**
AEGL–1 (Nondisabling)	54 ppm (310 mg/m^3)	31 ppm (180 mg/m^3)	22 ppm (130 mg/m^3)	11 ppm (64 mg/m^3)	11 ppm (64 mg/m^3)	Weight of evidence NOAEL for clinical signs/effects -rat (U.S. EPA 2006; Reed et al. 1995)
AEGL–2 (Disabling)	200 ppm (1200 mg/m^3)	120 ppm (700 mg/m^3)	82 ppm (480 mg/m^3)	41 ppm (240 mg/m^3)	29 ppm (170 mg/m^3)	Reversible lesions of the nasal passages – rat (Reed et al. 1995)
AEGL–3 (Lethal)	670 ppm (3900 mg/m^3)	400 ppm (2300 mg/m^3)	290 ppm (1700 mg/m^3)	150 ppm (870 mg/m^3)	98 ppm (570 mg/m^3)	Lower limit of the 95% CL based on the rat toxicity data of Eastman Kodak Co. (1987), Reed et al. (1995), and U.S. EPA (2006), calculated using the probit-analysis, dose-response program of ten Berge (2006)

6
7
8 **1. INTRODUCTION**
9
10   Methyl iodide (CH$_3$I, CAS No. 74-88-4) is a colorless liquid that turns brown with
11 exposure to light or moisture due to the liberation of iodine. It has a sweet ethereal odor which
12 provides poor warning properties. It is applied to soil used to grow crops such a strawberries,
13 tomatoes, peppers, and ornamentals. Liquid methyl iodide injected into soil rapidly volatilizes.
14 Methyl iodide is an alternative to methyl bromide, an ozone-depleting fumigant. The vapor
15 pressure is 375 mm Hg at 20°C. Solubility is 1 part in 50 parts of water (O'Neil et al. 2001;
16 ACGIH 1992; Gargas et al. 2009). Additional chemical and physical properties are listed in
17 Table 1.
18
19   The major sources of methyl iodide in the environment are the oceans. Near oceanic
20 regions characterized by high biomass productivity, atmospheric levels range from 40-128 ng/m^3
21 (IARC 1986).
22
23   Methyl iodide is produced commercially by any of the following methods: (1) reaction of
24 methanol and iodine in the presence of phosphorous, (2) the reduction of an aqueous solution of
25 iodine with bisulfate to yield hydriodic acid, which reacts with dimethyl sulfate to form methyl
26 iodide, (3) the reaction of hydrogen gas, elemental iodine, and aqueous methanol, (4) reaction of
27 methanol, iodine, and diborane (NIOSH 1984; Lauterbach and Ober 2001). Recent production
28 data were not found. In the past, the major uses of methyl iodide were as a methylation agent in

1 inorganic synthesis, in microscopy (because of its high refractive index), as an embedding
2 material for examining diatoms, and in testing for pyridine (Lauterbach and Ober 2001). Methyl
3 iodide is a pre-plant biocide used to control insects, plant parasitic nematodes, soil born
4 pathogens, and weed seeds (U.S. EPA 2006). Although stored as a liquid under pressure, it
5 volatilizes rapidly following soil injection as a pesticide.
6

TABLE 1. Chemical and Physical Properties		
Parameter	**Value**	**Reference**
Synonyms	Iodomethane	O'Neil et al. 2001
Chemical formula	CH_3I	O'Neil et al. 2001
Molecular weight	141.95	O'Neil et al. 2001
CAS Reg. No.	74-88-4	ACGIH 1992
Physical state	Liquid	O'Neil et al. 2001
Solubility in water	1 part/50 parts	O'Neil et al. 2001
Vapor pressure	375 mm Hg at 20ºC	ACGIH 1992
Vapor density (air =1)	4.9	HSDB 2007
Liquid density (water =1)	2.28 at 20ºC	O'Neil et al. 2001
Melting point	–66.5ºC	O'Neil et al. 2001
Boiling point	42.5ºC; decomposes at 270ºC	O'Neil et al. 2001
Flammability limits in air	Nonflammable	NIOSH 1984
Conversion factors	1 ppm = 5.81 mg/m^3 1 mg/m^3 = 0.172 ppm	Calculated

7
8
9 **2. HUMAN TOXICITY DATA**
10 **2.1.   Clinical Studies**
11
12   At high concentrations, methyl iodide has a sweet, ethereal odor. No odor threshold data
13 were available. A concentration of 3700 ppm was reported as irritating (ACGIH 1992; Ruth
14 1986), but the source of the data was not provided. Two metabolism studies were conducted
15 with methyl iodide. These studies are summarized in Section 4.1, Metabolism and Disposition.
16
17 **2.2.   Case Studies**
18
19   Schwartz et al. (2005) reviewed 11 case reports of methyl iodide poisoning. Six of the
20 patients experienced a chronic neurological syndrome characterized by delayed psychiatric,
21 behavioral, and cognitive sequelae. Acute symptoms in a fatal case included nausea, vomiting,
22 diarrhea and oliguria, vertigo, slurred speech, visual disturbances, ataxia, tremor, irritability,
23 drowsiness, and coma (Garland and Camps 1945). In a non-fatal case (Appel et al. 1975),
24 symptoms were delayed, but included systemic, motor, and psychotic changes. Recovery of
25 motor and memory skills was slow, with some symptoms present after 9 months. Air sampling
26 was reported in only one study (Hermouet et al. 1996). Following repeated exposure of an
27 unprotected worker which resulted in motor and sensory disturbances, air samples were taken at
28 the work site where methyl iodide was decanted in open containers. The three sample
29 concentrations were 16, 22, and 24 ppm (analysis method and air sampling time were not
30 provided).
31

1   **3. ANIMAL TOXICITY DATA**
2
3   Methyl iodide was tested for irritation in a study with rabbits (Monsanto Company
4   1982a). It was severely irritating to the skin (0.5 mL applied undiluted) and corrosive to the eye
5   (0.1 mL instilled undiluted). Data on methyl iodide toxicity were reviewed by Bolt and
6   Gansewendt (1993) and U.S. EPA (2006). The studies reviewed by U.S. EPA (2006) were
7   sponsor-submitted unpublished studies; original documents were not available. Recent, well
8   characterized studies with laboratory rodents are summarized in Table 2. Older studies that
9   generally used nominal concentrations are described only in the text. A single acute study that
10   addressed neurotoxicity is summarized in Table 2 and described in Section 3.4.
11
12   **3.1.   Acute Toxicity**
13   **3.1.1. Rats**
14
15   Deichmann and Gerarde (1969) reported a 4-hour LC_{50} in rats of 216 ppm, but details of
16   the exposure were not provided.
17
18   The approximate lethal concentration (ALC) was determined in male Wistar rats
19   (Comstock et al. 1950). Measured quantities of the gas were introduced into the chamber air
20   stream at a constant rate. Rats were tested one at a time for 15 minutes. At 14 days
21   postexposure, mortalities at concentrations of 1590 and 2760 ppm were 0/1 and 0/1. A rat
22   exposed to 3790 ppm for 15 minutes died after 11 days. This concentration-exposure duration
23   was considered the ALC. At higher concentrations, the survival time shortened in a
24   concentration-dependent manner. The two rats that survived for 14 days post-exposure (15-
25   minute exposures to 1590 or 2760 ppm) showed no remarkable lesions when tissues were
26   examined grossly and microscopically (MacNamee 1950). Following a 15-minute lethal
27   exposure to 32,100 ppm, the trachea and lungs were severely eroded, with severe pulmonary
28   edema and hemorrhage.
29
30   Groups of 5 male and 5 female Crl:CD rats were exposed to measured concentrations of
31   1190, 1554, or 1973 ppm for one hour (Eastman Kodak Co. 1987) and were observed for 14 days
32   post-exposure. Concentration-related mortality was observed post-exposure (days 1 and 2) in all
33   groups: males, 0/5, 2/5, and 4/5; and females, 2/5, 4/5, and 5/5. The 1-hour LC_{10} was 1347 ppm
34   for males and 976 ppm for females. The 1-hour LC_{10} for males and females combined was 1074
35   ppm with 95% confidence limits of 565-1266 ppm. Concentration-related clinical signs
36   observed during the exposure included lethargy, gait disturbance, gasping, and excessive tearing.
37   At necropsy, edema and necrosis of the nasal passages, hemorrhage in the lungs, and enlarged
38   livers with focal necrosis were observed.
39
40   In a recent study, groups of Sprague-Dawley rats (4 to 5/sex) inhaled 581, 710, 797, or
41   1198 ppm for 4 hours (U.S. EPA 2006). Animals were observed for 14 days post-exposure and
42   terminal necropsy findings were recorded. No deaths were recorded at 581 ppm. Clinical signs
43   at all concentrations included gasping, ataxia, hypoactivity, nasal discharge, labored respiration,
44   rales and red material around the nose. Deaths occurred within two days at the highest
45   concentration. Following an initial weight loss, the surviving animals gained weight during the
46   rest of the study. A few decedents showed several of the following macroscopic lesions: dark
47   pituitary, dark red lungs, distended gas filled and congested stomach, hemorrhagic thymus, dark
48   red adrenal glands, and distended intestines.

1
2   In a study that addressed effects on the nasal cavity, Reed et al. (1995) exposed groups of
3   three male Alpk:APfsD (Wistar-derived) rats, nose-only, to a measured concentration of 100
4   ppm methyl iodide for 0.5, 1, 2, 3, 4, or 6 hours. Rats were sacrificed 24 hours later. Additional
5   groups inhaled 100 ppm for either 3 or 6 hours and were sacrificed either 0 to 6 hours or 2 weeks
6   later. Microscopic examination of the nasal epithelium showed that the olfactory epithelium was
7   the target tissue. At 24 hours postexposure, there were no observable changes in the nasal tissues
8   of the rats administered 100 ppm for 0.5 or 1 hour. With increasing exposure duration,
9   degeneration of the olfactory epithelium ranged from focal to complete destruction. The basal
10 cell layer remained intact as did nerve bundles and Bowman's glands in the lamina propria. The
11 lesions were characterized as minimal at 100 ppm for two hours, slight at 100 ppm for 3 hours,
12 moderate at 100 ppm for 4·hours and marked at 100 ppm for 6 hours. Following the 6-hour
13 exposure, the lesions included focal degeneration of the transitional epithelium in the anterior
14 nasal passages while the respiratory epithelium was unaffected. The earliest detected nasal
15 lesion, vacuolation of the olfactory epithelium, was observed in rats killed immediately after a 3-
16 hour exposure. In rats sacrificed 2 weeks after exposure for 3 or 6 hours, there was almost
17 complete regeneration of the nasal epithelium.
18
19   The respiratory frequency was measured in groups of 4 rats exposed to 0, 25, or 100 ppm
20 and in groups of 4 rabbits exposed to 0 or 20 ppm methyl iodide for 6 hours (DeLorme et al.
21 2005; 2009). No significant reductions in breathing frequency were observed in either rats or
22 rabbits. In rats, minute volume increased at 25 ppm but decreased at 100 ppm as did total
23 volume inhaled. At 20 ppm, rabbits demonstrated a 30% increase over controls in total volume
24 of air inhaled. According to the authors, neither species demonstrated a sensory irritant effect or
25 decreased inhalation uptake of test atmosphere.
26
27 **3.1.2. Mice**
28
29   Buckell (1950) determined the LC_{50} in an unreported strain of male white mice.
30 Concentrations ranged from approximately 86 to 14,600 ppm, and were determined by metering
31 a measured quantity of methyl iodide into the exposure chamber. Exposure durations were not
32 clearly stated. Air samples were collected in alcoholic potash and liberated iodine was measured
33 by titration. All mice exposed to approximately 900 ppm or greater died. Obvious signs of
34 toxicity included irritation of the eyes and increased general activity. Groups of 10 mice were
35 also exposed to 860 ppm for varying times and then observed for a week. Mortality was 0 after a
36 20-minute exposure and 100% after an 80-minute exposure. The LC_{50} time was estimated at 57
37 minutes, i.e. 57-minute LC_{50} of 860 ppm.

1

	Concentration	Exposure		
Species	(ppm)	Time	Effect[a]	Reference
Rat	1190	1 hour	20% mortality	Eastman Kodak Co.
	1554	1 hour	60% mortality	1987
	1973	1 hour	90% mortality	
	1074	1 hour	Calculated LC_{10}	
	1458	1 hour	Calculated LC_{50}	
Rat	581	4 hours	0% mortality	U.S. EPA 2006
	710	4 hours	80% mortality	
	797	4 hours	80% mortality	
	1198	4 hours	100% mortality	
	691	4 hours	Calculated LC_{50}	
			Clinical signs of gasping, ataxia, hypoactivity, nasal discharge, labored respiration, rales and red material around the nose at all concentrations	
Rat	27	6 hours	NOAEL for neurotoxicity	U.S. EPA 2006
	93	6 hours	Clonic convulsions; decreased body temperature, decreased motor activity	
	401	6 hours	Additional neurotoxicity, gasping, one death (4% mortality)	
Rat	100	0.5 hour	No observable change, nasal passages	Reed et al. 1995
		1 hour	No observable change, nasal passages	
		2 hours	Minimal lesions, olfactory epithelium	
		3 hours	Slight lesion, olfactory epithelium	
		4 hours	Moderate lesion, olfactory epithelium	
		6 hours	Marked lesion, olfactory epithelium; almost complete regeneration after 2 weeks	
Rat	0, 25, or 100	6 hours	No clear effect on respiratory parameters	DeLorme et al. 2005
Mouse	860	20 minutes	0/10 dead	Buckell 1950
	860	80 minutes	10/10 dead	
	860	57 minutes	LC_{50}	

TABLE 2. Summary of Acute Inhalation Data in Laboratory Animals

2
3
4   **3.2.   Repeat-Exposure Studies**

5
6   Repeat-dose studies are summarized in Table 3.

7
8   Groups of 5 male and 5 female Sprague-Dawley rats inhaled 150 ppm methyl iodide for 6
9   hours/day for 3 days (Monsanto Co. 1982b). Clinical signs included eye irritation and sneezing
10 in all animals. Tremors were observed in one female on the third day. No deaths were reported.

11
12   Groups of 10 male and 10 female Sprague-Dawley rats inhaled 0, 25, 74, or 140 ppm for
13 6 hours/day, 5 days/week for 4 weeks (Monsanto Company 1983; Blank et al. 1984). Exposure-
14 related signs in the 74- and 143-ppm groups included irritation of the eyes, nasal discharge,
15 tremors, disturbances of the fur, poor general physical condition, and lowered mean body weight
16 compared with controls. Five animals, 2 males and 3 females in the 140-ppm group died or were
17 sacrificed moribund during the last week of exposure. No gross lesions were observed. The "no-
18 effect" level was 25 ppm.

1

2   Additional groups of 10 male and 10 female Sprague-Dawley rats inhaled 0, 10, 30, or 60
3   ppm for 14 weeks (Blank et al. 1984). Ocular irritation and lower mean body weight were
4   observed in the "higher" exposure groups. Microscopic examination of tissues in the 60-ppm
5   exposure groups failed to reveal gross or microscopic lesions. The NOAEL was 10 ppm. No
6   further details were reported in the published abstract.

7

8   In a subchronic inhalation toxicity study, described in U.S. EPA (2006), methyl iodide
9   (99.7% pure) was administered whole-body to groups of 20 male and 20 female Crl:CD (SD)IGS
10 BR rats for 6 hours/day, 5 days/week for 13 weeks. Analytically-determined concentrations were
11 0, 5, 21, and 70 ppm. Ten rats/sex/concentration were sacrificed after 4 weeks, and the
12 remaining rats were sacrificed after 13 weeks. There were no effects of treatment on mortality,
13 ophthalmology, urinalysis, hematology, organ weights, or gross pathology. There was an initial
14 decrease in body weight, body weight gain, and food consumption in males that received 70 ppm
15 for 13 weeks. At 70 ppm, there was degeneration of the olfactory epithelium (not further
16 described). The NOAEL for olfactory degeneration was 21 ppm.

17

18   In a range-finding study, groups of three New Zealand rabbits inhaled 0, 30, 100, or 300
19 ppm methyl iodide for 6 hours/day for 5 days (Nemec et al. 2009). No clinical signs were
20 reported in the group exposed to 30 ppm. At 100 ppm, food consumption and body weight
21 deficits were observed. At 300 ppm, all rabbits died or were euthanized *in extremis* prior to
22 scheduled termination. Toxicity described as behavioral/central nervous system and
23 cardiopulmonary signs were accompanied by reduced food intake and loss of body weight.

24

TABLE 3. Summary of Repeat-Dose Studies				
Species	Concentration (ppm)	Exposure Time	Effect	Reference
Rat	150	6 hours/day, 3 days	No deaths, eye irritation and sneezing; slight tremors in one of 5 females	Monsanto Company 1982b
Rat	0, 25, 74, 140	6 hours/day, 5 days/week, 4 weeks	Exposure–related signs of eye irritation, nasal discharge, tremors, lower mean body weight; mortality 20% at 143 ppm No clinical signs at 25 ppm.	Monsanto Company 1983; Blank et al. 1984
Rat	0, 10, 30, 60	6 hours/day, 5 days/week, 14 weeks	Ocular irritation and decrease in mean body weight in 30 and 60 ppm groups; no lesions observable microscopically; 10 ppm – no effect concentration	Blank et al. 1984
Rat	0, 5, 21, 70	6 hours/day, 5 days/week, 13 weeks	No systemic effects. Degeneration of olfactory epithelium at 70 ppm in both sexes; initial body weight decrease in males at 70 ppm. NOAEL for olfactory lesions was 21 ppm	U.S. EPA 2006
Rabbit	0, 30, 100, 300	6 hours/day, 5 days	30 ppm: no signs reported 100 ppm: reduced body weight 300 ppm: death of all 3 rabbits	Nemec et al. 2009

25

1
3.3.   Neurotoxicity
3

Groups of 12 male and 12 female Crl:CD rats inhaled methyl iodide (100% purity), whole-body, for 6 hours (U.S. EPA 2006). Analytically-determined concentrations were 0, 27, 93, and 401 ppm. Neurobehavioral assessment took place pre-exposure, at the predicted time of peak effect on the day of exposure (3 hours post-exposure), and on days 7 and 14 post-exposure. On day 7, there was a slight weight loss, 2-10%, in the groups exposed to 93 and 401 ppm. Neurotoxicity signs were limited to the day of exposure. At 93 ppm on the day of exposure, the following neurotoxicity signs were observed: clonic convulsions in one female (slight repetitive movements of the jaw), decreased body temperature (both sexes), and decreased total motor activity relative to controls (decreases of 75% in males and 81% in females). More animals were affected at the 401 ppm concentration and signs were more severe, e.g., gasping. In addition, one female in the 401 ppm group was found dead on day 6. This animal experienced clonic convulsions, yellow material around the urogenital area, dried red material around the nose, mouth, and eye, shallow respiration, and decreased defecation prior to death. The most common clinical signs in the surviving animals were decreased defecation and dried red material around the nose, mouth, and/or eyes in both sexes. Slightly decreased motor activity in females on the day of exposure was considered equivocal, and 27 ppm was considered a NOAEL for neurotoxicity in both sexes.

3.4.   Developmental/Reproductive Toxicity

An intraperitoneal injection of 100 mg/kg methyl iodide to adult male Sprague-Dawley rats reduced hepatic and epididymal glutathione levels to 2 and 37% of control values, respectively, at 1 hour, but had little effect on testicular glutathione (Gandy et al. 1990). Glutathione may protect against chemical-induced germ cell mutations. Substantial recovery of glutathione took place by 16 hours post-exposure.

A two-generation reproductive toxicity study with rats was reported by U.S. EPA (2006). Tested concentrations were 0, 5, 20, and 50 ppm, and exposure duration was 6 hours/day. Offspring were exposed beginning on post-natal day 28. For the parental generation, both the systemic and portal of entry NOAELs were 20 ppm. The parental LOAELs for portal of entry and systemic effects, both 50 ppm, were based on body weight changes and histopathology including degeneration of the olfactory epithelium. The offspring NOAEL was 5 ppm. The offspring LOAEL of 20 ppm was based on decreases in body weight, body weight gain, and thymus weight. The reproductive NOAEL was 5 ppm; the LOAEL of 20 ppm was based on delayed vaginal patency.

In a developmental toxicity study, female rats (strain unidentified) inhaled 0, 5, 20, or 60 ppm for 6 hours/day on gestation days (GD) 6 through 19 (U.S. EPA 2006). The maternal NOAEL was 20 ppm. The maternal LOAEL was 60 ppm and was based on a decreased body weight gain of 19%. The developmental NOAEL was 60 ppm; a LOAEL was not attained.

In a developmental toxicity study, groups of six timed-pregnant New Zealand rabbits inhaled 0, 10, 26, or 74 ppm methyl iodide during GD 6-28 (U.S. EPA 2006). Due to maternal toxicity, the 74 ppm exposure was reduced to 50 ppm beginning on GD 18. There was a dose-dependent increase in the litter proportions of late fetal deaths and post-implantation loss and/or

1   decreased fetal body weight. Three females were euthanized in extremis between GD 24 and 27.
2   At 25 ppm, there were increased fetal losses (late) and increased post-implantation loss; fetal
3   body weight was non-significantly reduced. At 74/50 ppm, late fetal losses were increased and
4   fetal body weight was reduced. The NOAEL for developmental effects was 10 ppm. No
5   maternal toxicity was observed in the females exposed to 10 ppm. In a second study, groups of
6   24 timed-pregnant rabbits inhaled 0, 2, 10, or 20 ppm on GD 6-28. Effects in the 20 ppm group
7   were similar to those described for the 25 ppm group in the earlier study. There were no evident
8   effects on fetal morphology. The NOAEL for developmental effects was 10 ppm.
9
10   A study was conducted to establish the critical period of exposure during gestation that
11 resulted in fetal loss in the above study with rabbits (Nemec et al. 2009). Groups of 24 pregnant
12 New Zealand white rabbits inhaled 0 or 20 ppm for 6 hours/day during GD 6-28, 6-14, 15-22, 23-
13 24, 25-26, or 27-28 for 6 hours/day. At 20 ppm, increased fetal losses were 21% (GD 6-28), 9%
14 (GD 23-24), and 11% (GD 25-26). The most susceptible window of exposure for eliciting
15 developmental toxicity in rabbits exposed to methyl iodide vapors was GD 23-26.
16
17 **3.5.   Genotoxicity**
18
19   Numerous studies indicate that methyl iodide is genotoxic due to its methylating
20 capabilities (Bolt and Gansewendt 1993). Methyl iodide methylates hemoglobin at the free SH-
21 group of cysteine in experimental animals as well as in humans. Methyl iodide was mutagenic in
22 *Salmonella typhimurium* bacterial strains TA1535 and TA100 (Andrews et al. 1976; McCann et
23 al. 1975). Methyl iodide was a direct-acting mutagen for mouse lymphoma L5178Y/TK+/- cells
24 (Clive et al. 1979) and at the HGPRT locus in Chinese hamster ovary (CHO) cells
25 (concentrations of 0 to 3 µg/mL) (Amacher and Zelljadt 1984). Methyl iodide failed to transform
26 C3H/10T½ CL8 cells (Oshiro et al. 1981).
27
28   Results were conflicting in other studies. In a summary provided by IARC (1986), the
29 authors stated that methyl iodide induced DNA damage and is mutagenic to bacteria (*Salmonella*
30 *typhimurium* TA100 (assayed in desiccators in the absence of S9) but not TA1535, TA1536,
31 TA1537, TA1538, TA98, or TA100 in plate incorporation assays. Methyl iodide gave a positive
32 result in the *Escherichia coli pol A* and WP2 *uvrA* assays in the presence or absence of an
33 exogenous metabolic system. It induced mitotic recombination in yeast and mutations in
34 cultured mammalian cells. It induced transformation in Syrian hamster embryo cells, but not in
35 C3H 10T½ cells. Methyl iodide tested positive in the Syrian hamster embryo micronucleus test
36 *in vitro* (concentrations not provided) (Fritzenschaf et al. 1993).
37
38   In a series of recent unpublished studies submitted to the U.S. EPA (2006), the only
39 evidence of genotoxicity was the induction of structural chromosome aberrations (clastogenesis)
40 in CHO. Methyl iodide was non-mutagenic in *Salmonella typhimurium* strains TA98, TA100,
41 TA1535, and TA1537 and in *Escherichia coli*. It was also negative in an *in vivo* micronucleus
42 assay in mice. Tested concentrations were not provided. The conflict with earlier study results
43 was not addressed.
44
45 **3.6.   Chronic Toxicity/Carcinogenicity**
46
47   Methyl iodide induced local sarcomas in rats injected subcutaneously with a weekly
48 dosage of 10 mg/kg for an unstated period of time (Druckrey et al. 1970). It also produced lung

1   tumors in a cancer-susceptible strain of mice (Strain A) injected intraperitoneally, weekly for 24
2   weeks (Poirier et al. 1975). In the latter study, survival was adversely affected at a dose of 44
3   mg/kg/week. Half this dose, 22 mg/kg/day which equates to 20-25 ppm in a human inhaling
4   methyl iodide for 8 hours (calculated by ACGIH 1992) allowed survival of all 20 treated mice,
5   and a non-significant increase in lung tumors.
6
7   In an inhalation chronic toxicity/carcinogenicity study, groups of 60-70 male and 60-70
8   female Crl:CD (SD)IGS BR rats inhaled 0, 5, 10, 20, or 60 ppm, whole body, for 6 hours/day, 5
9   days/week (U.S. EPA 2006). Animals were examined daily for clinical signs and activity. At 20
10   ppm there was an increased incidence of salivary gland squamous cell metaplasia. At 60 ppm,
11   degeneration of the olfactory epithelium as well as perturbations of the thyroid-pituitary axis,
12   accompanied by thyroid histopathology, were observed. No other histopathological lesions were
13   observed. The NOAEL for effects on the olfactory epithelium was 20 ppm.
14
15   **3.7.   Summary**
16
17   Acute exposures to methyl iodide produce a number of effects in laboratory animals
18   including degeneration of the nasal epithelium and neurotoxicity in rats and fetal toxicity in
19   rabbits. Six-hour exposures to 27 and 93 ppm were a NOAEL and LOAEL for neurotoxicity
20   (U.S. EPA 2006). Exposure to 100 ppm for 6 hours induced reversible lesions in the olfactory
21   epithelium of rats (Reed et al. 1995). Exposures of ≤1 hour to 100 ppm did not result in nasal
22   lesions. The highest non-lethal value for rats in a well-conducted study was a 4-hour exposure to
23   581 ppm (U.S. EPA 2006). Calculated 1-hour and 4-hour LC_{50} values were 1458 (Eastman
24   Kodak Co. 1987) and 691 ppm (U.S. EPA 2006), respectively. Results of genotoxicity studies
25   were conflicting. Methyl iodide was not carcinogenic in a well-conducted chronic study. In
26   developmental studies, rabbits, but not rats, were sensitive to the fetotoxic effects of methyl
27   iodide.
28
29   **4.   SPECIAL CONSIDERATIONS**
30   **4.1.   Metabolism and Disposition**
31   **4.1.1. Clinical and Laboratory Animal Studies**
32
33   Inhaled monohalomethanes such as methyl chloride and methyl bromide are rapidly
34   absorbed by the lungs and metabolized in the liver by conjugation with glutathione (GSH) to
35   form S-methylglutathione (Kornbrust and Bus 1983; U.S. EPA 2007a). Metabolism of methyl
36   iodide following oral or subcutaneous injection follows the same pathway (Barnsley and Young
37   1965; Johnson 1966; Bolt and Gansewendt 1993). Cleavage of the glutamic acid and glycine
38   moieties of GSH yields S-methylcysteine; transamination and decarboxylation yields the
39   mercapturic acid, methylthioacetic acid, which is excreted in the urine. Following subcutaneous
40   injection of rats with methyl iodide, small amounts of S-methylcysteine, methylthioacetylglycine,
41   methylmercapturic acid, and methylthioacetic acid were identified in the urine (Barnsley and
42   Young 1965). The initial conjugation of monohalomethanes with GSH may be either non-
43   enzymatic or enzymatically catalyzed. Although methyl chloride and methyl bromide are
44   conjugated primarily enzymatically, an *in vitro* study with human erythrocyte cytoplasm showed
45   that the major conjugation process of glutathione with methyl iodide is non-enzymatic (Hallier et
46   al. 1990).
47

1   In a clinical study, eighteen healthy adult volunteers (17 males and 1 female) inhaled
2   methyl iodide labeled with I-132 for 5 minutes (Morgan and Morgan 1967). Subjects inhaled
3   and exhaled through a two-way mouthpiece. Respiratory rate, duration of breath, tidal volume,
4   minute volume and vital capacity were measured or calculated. Absorption was measured as the
5   amount inhaled minus the amount exhaled. Volunteers varied their breathing rates in order to
6   observe the effect of respiratory rate on absorption. Under these conditions, absorption by the
7   lungs ranged from 53% at 19.5 breaths/minute to 92% at 2.3 breaths/minute; the average
8   retention was 72%. There was no excretion of methyl iodide from the lungs at the end of the
9   exposure period. Absorption was correlated with breathing rate to a greater degree than with
10   tidal volume. The concentration of methyl iodide in the inspired air was not provided. The
11   radiation dose to the thyroid averaged 3 mrem; the then current International Commission on
12   Radiological Protection occupational standard was 30 rem/year.
13
14   In a second study, four of the above male subjects inhaled methyl iodide labeled with I-
15   132 in order to address metabolism (Morgan et al. 1967). The subjects inhaled methyl iodide for
16   5 minutes. Iodine uptake by the thyroid was measured externally with a radiation detector over a
17   period of approximately 12 hours. Radioactivity in blood and urine were also sampled. Uptake
18   into the blood was rapid (within minutes). Half-time for buildup of iodine in the thyroid was 200
19   minutes; uptake was 42% of the inhaled dose. About 30% of the radioactive iodine was excreted
20   in the urine in 5 hours. The authors concluded that inhaled methyl iodide is broken down into
21   iodide ion which is subsequently involved in normal iodine metabolism. The amount of iodine
22   in the inhaled air was calculated as equivalent to less than one-quarter of the average daily intake.
23   The radiation dose to the thyroid of the subjects averaged less than 20 mrem/experiment. No
24   further data were provided.
25
26   Thrall et al. (2005; 2009a) described the extent of nasal absorption of methyl iodide in
27   anesthetized rats and rabbits. Nasal absorption in six rats exposed to 1 ppm averaged 63%
28   (range, 51-71%). Nasal absorption in nine rabbits exposed at 2, 10, or 50 ppm averaged 72%
29   (range, 57-92%), regardless of exposure concentration.
30
31   Sprague-Dawley rats inhaled ^{14}C-labeled methyl iodide (U.S. EPA 2006). The only
32   stated concentrations were 25 and 233 ppm. Maximum blood concentrations were achieved
33   within 0-2 hours and were proportional to the air concentrations. The initial half-life was 5.1-7.2
34   hours, and the terminal half-life was 116-136 hours. Recovered radioactivity was primarily as
35   CO_2 (39-61%) and in the urine (27-33%). Feces accounted for <2% of the dose. At 0-1 hour
36   post-treatment, radioactivity was relatively high in the kidney, lung, and nasal turbinates of the
37   rats exposed to 25 ppm, and in the kidney, thyroid, and lung of rats exposed to 233 ppm. The
38   major metabolites were expired CO_2, and N-(methylthioacetyl) glycine and S-methyl glutathione
39   which were excreted in the urine. Minor metabolites were methylthioacetic acid, methyl
40   mercapturic acid, and S-methyl cysteine.
41
42   **4.1.2. Physiologically-Based Pharmacokinetic (PBPK) Modeling**
43
44   Rate constants for the GSH metabolism of methyl iodide were determined in cytosols
45   prepared from the liver and kidneys of rats, human donors, female rabbits and rabbit fetuses;
46   from rabbit olfactory and respiratory epithelium; and from rabbit and rat blood (Poet et al. 2009).
47   Methyl iodide was metabolized in the kidney tissue of adults of all three species, but not in fetal
48   rabbit kidney. Maximal metabolic rates were similar in liver from rat and human donors, but a

1 factor of 4 less in the liver of adult rabbits. A similar pattern was observed in kidney cytosols
2 from the adults of the three species. Metabolism of methyl iodide in nasal tissues of the rabbit
3 was essentially first-order. The metabolism of methyl iodide in human liver cytosol from five
4 donors indicated two populations, one high affinity/low capacity and one with a lower affinity
5 but higher capacity.
6
7   A PBPK model developed by Sweeney et al. (2005; 2009) reduces uncertainties in risk
8 assessment extrapolations for methyl iodide. The model describes (1) nasal tract dosimetry and
9 glutathione depletion in the rat to evaluate nasal toxicity and (2) iodide kinetics in the pregnant
10 rabbit to address developmental toxicity. The model enables calculation of human equivalent
11 concentrations to the animal no-observed levels using chemical-specific parameters to determine
12 the internal dose instead of default assumptions. The proposed mechanism for nasal
13 histopathology involves GSH depletion as a key event leading to damage of the nasal olfactory
14 epithelium. Nasal toxicity may also involve methylation of cell macromolecules, formation of
15 reactive metabolites, or oxidative stress. A sustained decrease in GSH is considered the critical
16 event. Glutathione depletion of 50% or greater from normal levels may be associated with
17 toxicity. Excess serum iodide is implicated as the critical element in the mechanism proposed for
18 fetal losses. Excess iodine has been shown to lead to fetal thyroid hormone disruptions leading
19 to fetal losses. No-observed adverse effect levels for these endpoints were developed for a 1-day,
20 24-hour exposure of bystanders or 8 hour/day exposure of workers. Variability of the PBPK
21 models support application of uncertainty factors of approximately 2 for intra-human
22 pharmacokinetic variability for the nasal effects and acute neurotoxicity. The adult human model
23 indicated that depletion of GSH in the dorsal olfactory epithelium to 50% of control for
24 bystanders would be achieved after 24 hours of exposure to 72 ppm methyl iodide. For workers
25 exposed for 8 hours, 50% GSH depletion would be achieved by the end of the shift at an
26 exposure concentration of 110 ppm.
27
28   Data showing that humans are less sensitive to the effect that causes developmental
29 toxicity in rabbits was incorporated into the PBPK model developed by Sweeney et al. (2009).
30 The result shows that the concentration causing the developmental endpoint in rabbits is higher
31 than that for the nasal endpoint (Mileson et al. 2009). Thus, nasal olfactory degeneration is the
32 primary endpoint for risk assessment of acute exposure to methyl iodide.
33
34 **4.2.   Mechanism of Toxicity**
35
36   In studies performed as part of the registration process for methyl iodide, three effects
37 were identified that warrant consideration for human risk assessment: nasal lesions in the rat,
38 acute neurotoxicity in the rat, and fetal loss in the rabbit. Following a review of recent key
39 studies on metabolism and toxicity, Kirman et al. (2009) evaluated the possible mode(s) of action
40 through which methyl iodide produces toxicity in animals. Key studies were summarized and
41 several possible modes of action were compared to the modified Hill criteria (described in U.S.
42 EPA's 2005 *Guidelines for Carcinogen Risk Assessment*). The available data support the
43 following hypotheses:
44   Nasal lesions in rats: glutathione depletion in the rat nasal epithelium;
45   Transient neurotoxicity in rats: modification of ion currents in nerve cells;
46   Rabbit fetal resorptions: modulation of the thyroid hormones by iodine.

1

2   The olfactory toxicity of methyl iodide is attributed to the sustained depletion of GSH
3 below critical levels due to methyl iodide metabolism (U.S. EPA 2006; Gargas and Kinzell 2007;
4 Kirman et al. 2009). In the nasal cavity of the rat, the olfactory epithelium is the target tissue of
5 methyl iodide. Cytosolic GST catalyzes conjugation with GSH in both the olfactory and
6 respiratory epithelium, but the rate is 4-fold higher in the olfactory epithelium. Conjugation with
7 glutathione, results in S-methyl-glutathione. This pathway is considered a detoxifying
8 mechanism. Cytochrome P-450 metabolism does not appear to play a role in methyl iodide
9 toxicity. Depletion of glutathione leads to olfactory tissue lesions and cell death (Chamberlain et
10 al. 1998a; 1998b). Methyl iodide is also an alkylating agent (Bolt and Gansewendt 1993).

11

12   Male Sprague-Dawley rats inhaled 0, 25, or 100 ppm methyl iodide for 6 hours/day for 2
13 days (Himmelstein et al. 2005; 2009). A time-dependent reduction in GSH levels in blood,
14 kidney, liver, and nasal tissue was observed, with the greatest reduction in nasal and olfactory
15 tissue. In the group exposed to 100 ppm, GSH levels were 24 and 14% of control in olfactory
16 and respiratory epithelia, respectively. Control animals showed normal diurnal fluctuations in
17 tissue levels of GSH. Erythrocyte S-methylcysteine hemoglobin adducts also increased.
18 Evidence of the protection of GSH against toxicity was obtained by pre-treating animals with
19 substances that deplete or replenish GSH.

20

21   The same mechanism of toxicity, mediated via glutathione depletion, was originally
22 considered responsible for neurotoxicity (Bonnefoi et al. 1991; Bonnefoi 1992; Davenport et al.
23 1992). In *in vitro* studies with rat cerebellar granular cells, methyl iodide depleted GSH, likely
24 rendering the tissue susceptible to methylation and/or oxidative stress; in addition DNA repair
25 processes may be inhibited (Chamberlain et al. 1999; Fonnum and Lock 2004). However, based
26 on several factors, Gargas and Kinzell (2007; Kirman et al. 2009) suggest that neurotoxicity
27 observed in rats is most likely the result of a general inhibition of ion currents in the membranes
28 of nerve cells due to high concentrations of the circulating parent chemical. These factors, which
29 include the reversibility of the neurological effects and the speed with which neurological effects
30 occur, suggest that the peak concentration of methyl iodide in the brain is the appropriate internal
31 dose measure.

32

33   The mechanism of toxicity leading to developmental effects in rabbits is considered
34 excess iodide which leads to fetal thyroid hormone disruptions, resulting in fetal loss (U.S. EPA
35 2006; Gargas and Kinzell 2007; Kirman et al. 2009). The sensitive period during late gestation
36 (GD 23-26) is when the fetal rabbit thyroid is undergoing maturation (Sloter et al. 2009). Two-
37 or four-day exposures of pregnant rabbits to 25 ppm for 6 hours/day during gestation days 23-24
38 or 23-26, respectively, diminished triiodothyronine (T_3) and thyroxine (T_4)in fetal serum and
39 increased TSH. Time-course exposures at 20 ppm methyl iodide revealed highly concentrated
40 levels of iodide in fetal versus maternal serum. Changes in the fetal thyroid included reduced
41 colloid formation, epithelial follicular hypertrophy, and epithelial cytoplasmic vacuolation.
42 Administration of sodium iodide by intravenous infusion during GD 23-26 induced similar
43 effects on fetal thyroid structure and function. Dietary administration of iodine, 250 to 1000 ppm
44 for 2 to 5 days prior to parturition, also induced fetal deaths in pregnant rabbits but not in rats or
45 hamsters (Arrington et al. 1965). These developmental effects in the rabbit fetus are the result of
46 preferential accumulation of iodide in the fetal compartment causing disruption of the fetal
47 hypothalamic-pituitary-thyroid axis at a critical time in the development of the rabbit fetal
48 thyroid. Increased serum iodide is also observed in adult rats following inhalation exposure to

1   methyl iodide (Himmelstein et al. 2009), but methyl iodide exposure did not cause
2   developmental effects in rats (U.S. EPA 2006). See Section 4.4.1 for species differences in
3   transfer of iodide from the dam/mother to the fetus.
4
5   In humans, an acute iodine load can cause a decrease in thyroid hormone production and
6   an increase in TSH. This "Wolff-Chaikoff effect," even with chronic exposure is transient in
7   most individuals, i.e., hypothyroidism and goiter are not common in individuals ingesting large
8   amounts of iodine for asthma (Abraham 2003). Both chronic iodine deficiency and chronic
9   iodine ingestion at therapeutic doses may induce effects on the thyroid in adults as well as in the
10   developing fetus (NSF International 2002; ATSDR 2004). Endemic cretinism is a syndrome
11   associated with iodine deficiency in certain geographic areas of the world.
12
13   During pregnancy and lactation, iodine requirements are higher than normal (Beckers and
14   Reinwein 1991), and sufficient iodine for synthesis of thyroid hormone is important for normal
15   brain development in the developing embryo and fetus (Hetzel and Mano 1989). Chronic
16   ingestion of excessive amounts of iodide during pregnancy, usually as a constituent of
17   medication for the treatment of asthma or Graves' disease (hypothyroidism), may induce iodide
18   goiter in the fetus with or without hypothyroidism. Because there is concern that excess iodine
19   may have an effect on the developing embryo/fetus in humans via its effects on the
20   hypothalamus-pituitary-thyroid-feedback loop, the available data on oral administration of iodine
21   or iodide to individuals with normal thyroid function and on pregnant women taking therapeutic
22   doses of iodine were evaluated. In humans, orally-administered iodine and iodide at similar
23   doses have a similar effect on thyroid function, reflecting similar absorption of iodine and iodide
24   from the gastrointestinal tract (Robinson et al. 1998). In the following studies, volunteers with
25   normal thyroid function as measured by blood T_3, T_4, and TSH were administered either iodine
26   or iodide (iodide is the form taken up by cells; in the thyroid, conversion to reactive iodine and
27   hormone synthesis takes place within cell follicular lumen). Iodine or iodide was administered to
28   healthy adults at doses of 32 mg/day for 7 days (Georgitis et al. 1993), 25 or 70 mg/day for 14
29   days (Robinson et al. 1998), 72 or 360 mg/day for 12-19 days (Vagenakis et al. 1973), 50 or 250
30   mg/day for 13 days (Saberi and Utiger 1975), or 1080 mg iodide/day for 11 weeks (Jubiz et al.
31   1977). In studies in which recovery was addressed, the effects on thyroid function were transient.
32
33   In the Jubiz et al. (1977) study, the thyroid response of four healthy young males and a
34   female subject, ages 27 to 36 years, to potassium iodide was compared to that of 13 hypothyroid
35   patients, ages 40 to 79 years. The hypothyroid patients had been treated with 1080 or 2160 mg
36   potassium iodide/day for 1 month to 8 years. In the healthy subjects, an increase in TSH and
37   decreases in T_4 and T_3 during administration were transient as indicated by a 1 month post-
38   treatment follow-up. None of the healthy subjects developed signs or symptoms of
39   hypothyroidism, and the thyroid gland was not enlarged. Recovery of thyroid function was
40   observed in seven of the 13 patients in whom the iodide was discontinued.
41
42   Congenital goiter is the result of chronic administration of iodine to the pregnant mother.
43   Congenital iodide goiter was observed following maternal oral intakes of 1000 mg/day iodine or
44   iodide throughout pregnancy (Senior and Chernoff 1971), 900-1500 mg/day (Martin and Rento
45   1962), and 2-1650 mg/day (Carswell et al. 1970). Pregnant women with mild Graves' disease
46   ingesting 6-40 mg of iodide or iodide daily beginning at 11-37 weeks of pregnancy delivered
47   normal fetuses (Momotani et al. 1992). In the latter study, fetal serum thyroxine generally
48   reflected maternal thyroxine levels.

1
2 ## 4.3.   Structure-Activity Relationships
3
4   For halogenated methanes, toxicity increases according to atomic weight, in the order
5 methyl chloride, methyl bromide, and methyl iodide (Table 4). All produce similar toxic
6 syndromes in man (Gosselin et al. 1984). The halomethanes are considered respiratory irritants,
7 although inhalation of methyl iodide at up to 100 ppm did not change the breathing rate of rats
8 (DeLorme et al. 2009). The systemic mechanism of toxicity for nasal lesions appears to be the
9 same for all three halomethanes– depletion of cellular glutathione which results in an inability of
10 tissues to suppress lipid peroxidation (Kornbrust and Bus, 1983; see also U.S. EPA 2007a;
11 2007b). The halomethanes also bind to macromolecules (Gansewendt et al. 1990). Following
12 oral exposure of male and female F344 rats to the three compounds, the amount of methyl halide
13 bound to hemoglobin was in the order methyl bromide>methyl iodide> methyl chloride (Xu et al.
14 1990).
15
16

TABLE 4. Comparison of Toxicity Values Among the Monohalomethanes		
Chemical	**Toxicity Value***	**Reference**
Methyl chloride	5000 ppm (6 hours, no deaths)	Chellman et al. 1986
Methyl bromide	1880 ppm (1-hour LC_{50}) 780 ppm (4-hour LC_{50}) 300 ppm (8-hour LC_{50})	Zwart 1988 Kato et al. 1986 Honma et al. 1985
Methyl iodide	1347 ppm (1-hour LC_{50}) 691 ppm (4-hour LC_{50})	Eastman Kodak Co. 1987 U.S. EPA 2006

17 *All data are for the rat.
18
19 ## 4.4.   Other Relevant Information
20 ### 4.4.1. Species Variability
21
22   Results of several studies indicate that there are species differences in the uptake and rate
23 of metabolism of monohalomethanes. In *in vitro* studies, methyl iodide blood:air partition
24 coefficients for rat, rabbit, and human blood were 39, 16, and 18, respectively (Gannon et al.
25 2005; Sweeney et al. 2009). Rodents may metabolize methyl iodide more rapidly than humans.
26 Human GST T1-1 differs from rodent GST by a single amino acid. Substitution of the rodent
27 amino acid arginine for the tryptophan found in the human GST resulted in a 13-fold increase in
28 the specific activity of the enzyme and a 2.7-fold increase in the catalytic efficiency (Shokeer et
29 al. 2005). Furthermore, erythrocyte cytoplasm of rats, mice Rhesus monkeys, cows, pigs, and
30 sheep does not metabolize monohalomethanes whereas the erythrocyte cytoplasm of
31 approximately 60% of humans does (Redford-Ellis and Gowenlock 1971; Peter et al. 1989).
32 Lack of erythrocytic metabolism may explain the rapid equilibrium between the gas phase of the
33 related halomethanes (methyl chloride and methyl bromide) and whole blood of rats observed in
34 pharmacokinetic studies. In addition, both *in vitro* and *in vivo* comparisons of different species
35 indicate that levels of GST enzymes are much lower in human liver and lung than in mice and rat
36 liver and lung (Andersen et al. 1987; Reitz et al. 1989). The data are consistent with the
37 hypothesis that the rate of activation of mono- and dihalomethanes to toxic metabolites by the
38 GST pathway occurs much more slowly in humans than in rodents. Ratios of rat/human and
39 mouse/human GST activity in liver are 3.95 and 7.64, respectively (Griem et al. 2002).
40

1   When inhaling the same concentration, uptake for the related chemical, methyl chloride,
2   was greater in the rat and dog than in humans, regardless of human metabolic rate (Landry et al.
3   1983; Nolan et al. 1985). Blood concentrations at steady state during a 3-hour exposure to 50
4   ppm for the rat and dog were 194 and 160 ng/g, respectively; whereas, blood concentrations in
5   rapid and slow human metabolizers were 100 and 35 ng/g, respectively.
6
7   The relative rate of thyroid hormone metabolism in humans and rats is significantly
8   different (Robinson et al. 1998; Capen 2008). In humans thyroxine is bound to a greater degree
9   to plasma proteins than in rats. The half-life of thyroxine in humans varies between 5 and 9
10   days; whereas, it is 12-24 hours in the rat. Poet et al. (2005) compared the metabolism of methyl
11   iodide in the kidney and liver cytosols of the rat, rabbit, and humans. Methyl iodide was well
12   metabolized in most of the tissue cytosol samples, but not in blood or fetal rabbit kidney. The
13   maximum rates of reaction (V_{max}) were similar in liver and kidney cytosols from rats and humans
14   donors, but were lower in rabbit tissues. In an *in vitro* study, thyroid tissue from fetal rabbits
15   failed to exhibit autoregulation of iodide uptake compared to maternal thyroid tissue (Price and
16   Sherwin 1986). Fetal iodide transport into thyroid cells was 10 times higher than maternal
17   transport.
18
19   The placentas of certain species possess an active transport mechanism for transporting
20   iodide from mother to fetus. Logothetopoulos and Scott (1956) observed active transport of
21   iodide across the placentas of guinea pigs, rabbits, and to a lesser extent, the rat. Using
22   radiotracer techniques, measurement of fetal to maternal blood iodide ratios ranged up to 4- to 5-
23   fold for guinea pigs and up to six-fold in rabbits. Crone and Waago (1961) found a similar two-
24   to six-fold difference in fetal and maternal blood iodide measurements of rabbits. Following
25   injection of Na[131]-radiolabeled sodium iodide to pregnant rabbits, Thrall et al. (2009b) found a
26   three-fold greater blood radioiodide level in fetuses compared with dams. Levels of radioiodide
27   were higher in fetal than maternal tissues, and in contrast to maternal animals, showed no
28   evidence of clearance over a 24-hour sampling period. In contrast, human fetal to maternal blood
29   iodide ratios, measured following term (37-41 weeks) and preterm (29-36 weeks) deliveries were
30   approximately 1:1 (Rayburn et al. 2008). The authors concluded that the human fetus, unlike the
31   rabbit and other species, does not highly concentrate iodide relative to the maternal plasma iodide
32   level during late gestation.
33
34   The related chemical, methyl bromide, was specifically toxic to the olfactory epithelium
35   of the rat, whereas, the other nasal epithelia were unaffected (Hurtt et al. 1988). Histochemical
36   techniques revealed degeneration of the sensory and sustentacular cells but not the basal cells
37   from which the former cells are regenerated. This was a reversible effect as the basal cells were
38   not affected. The olfactory region (dorsal meatus) of rats is highly exposed to chemicals due to
39   air flow characteristics in the nasal turbinates. In rodents, an inhaled vapor traverses a few
40   millimeters of resistant respiratory epithelium before reaching sensitive olfactory tissue; whereas,
41   in humans an inhaled vapor has to traverse several centimeters and a much larger surface area of
42   respiratory epithelium to reach the olfactory tissue. A mathematical model based on a
43   combination of computational fluid dynamics and physiologically-based pharmacokinetics
44   showed that the dorsal meatus region of the rat nose receives 12 to 20% of the inhaled air (Bush
45   et al. 1998; Frederick et al. 1998). A comparison with airflow patterns in the human nose shows
46   that the olfactory epithelium in the dorsal meatus region of the nasal cavity of the rat is exposed
47   to two- to three-fold greater concentrations of chemicals. Therefore, compared with the rat, it is
48   likely that higher concentrations of methyl bromide would be required to induce this lesion in

1   humans. In addition, rat nasal tissue is higher in nonprotein sulfhydral content (primarily
2   glutathione) than human tissue.
3
4   **4.4.2. Susceptible Populations**
5
6   Inter-individual variation in the rate of metabolism of methyl halides has been observed
7   in humans. Three distinct populations with differences in the rate of metabolism of the related
8   chemical, methyl chloride, have been identified (Nolan et al. 1985; Warholm et al. 1994; ATSDR
9   1998; Lof et al. 2000; WHO 2000). The differences in metabolism rate are attributed to the
10 genetic polymorphism of glutathione transferase theta 1 (GSTT-1). Depending on the presence
11 or absence of GST and the number of alleles, humans may be fast, slow, or non-metabolizers.
12 Fast metabolism may lead to the formation of toxic metabolites that can exert their action before
13 they can be eliminated. Slow metabolizers would be expected to be less susceptible to the toxic
14 effects of the metabolites. Because the elimination of methyl chloride is rapid in both
15 populations, the difference is of questionable toxicological significant. Exposure of humans to
16 50 ppm methyl chloride did not affect the blood GST levels of either population. Although
17 humans differ in their capacity to metabolize the related chemical, methyl chloride, the
18 difference, toxicologically, is considered to be less than three-fold (Nolan et al. 1985). The
19 metabolism of methyl iodide in human liver cytosols prepared from 5 human donors indicated a
20 single outlier, with much less metabolism than the other human liver samples (Poet et al. 2005).
21 Because methyl iodide is thought to be non-enzymatically conjugated, the significance of the
22 variation in human genotype is unknown.
23
24   Although individuals who are lacking the GSTT-1 enzyme would have lower
25 susceptibility to the potential nasal toxicity of methyl iodide, these individuals could be at greater
26 risk for acute neurotoxicity because reduced metabolism of methyl iodide results in higher
27 concentrations reaching the brain (Sweeney et al. 2009). Based on the *in vitro* studies of
28 Chamberlain et al. (1998a) in which rat nasal or liver homogenates were co-incubated with GSH,
29 GSH inhibitors, and methyl iodide, Sweeney et al. (2009) estimated that GSH conjugation with
30 methyl iodide in a GSTT-1 null person would be a factor of 1.4 lower than derived for a person
31 with full GST activity.
32
33   Maternal ingestion of iodide has been implicated in the causation of congenital goiter in
34 the newborn (Carswell et al. 1970). Chronic ingestion of excessive amounts of iodine, ten times
35 or more the normal daily requirement, may cause iodide goiter, with or without hypothyroidism
36 in both the mother and fetus (Senior and Chernoff 1971). Following an acute exposure, iodine
37 inhibition of thyroid hormone synthesis is transient in normal subjects and is not likely to result
38 in alterations in thyroid function in subjects having adequate preformed stores of T_4 and T_3
39 (Saberi and Utiger 1975). Individuals with thyroid diseases may be more susceptible to the
40 increased iodine load from methyl iodide than individuals with normal thyroid function (ATSDR
41 2004).
42
43 **4.4.3. Concentration-Exposure Duration Relationship**
44
45   The concentration-time relationship for many irritant and systemically acting vapors and
46 gases may be described by $C^n \times t = k$. A computer program developed by ten Berge (2006) and
47 based on probit analysis integrates all concentration and time information for a range of lethality
48 data. Concentration, exposure duration, and response, including the number of animals

1   responding, are considered simultaneously in a linear regression equation, with the Maximum
2   Likelihood statistical method used to find the closest estimates of the regression coefficients for
3   each parameter. The probit-analysis dose-response program of ten Berge was applied to the
4   Eastman Kodak Co. (1987), Reed et al. (1995), and U.S. EPA (2006) lethality data (see Table 2)
5   to estimate the threshold for lethality at each AEGL exposure duration (with confidence limits of
6   95%). The calculated value of n in $C^n \times t = k$ is 2.
7
8   **4.4.4. Concurrent Exposure Issues**
9
10   No information relevant to concurrent exposure issues was located.
11
12 **5.   DATA ANALYSIS FOR AEGL-1**
13 **5.1.   Summary of Human Data Relevant to AEGL-1**
14
15   No clinical studies were available for derivation of AEGL-1 values.
16
17 **5.2.   Summary of Animal Data Relevant to AEGL-1**
18
19   A 1-hour exposure to 100 ppm was a no-effect concentration for lesions of the nasal
20 passage in rats, and a 2-hour exposure to 100 ppm resulted in minimal lesions to the olfactory
21 epithelium (Reed et al. 1995). Results of studies with longer exposure durations showed that the
22 nasal lesions are reversible. A 6-hour exposure to 27 ppm was a NOAEL for clinical signs that
23 addressed neurotoxicity (U.S. EPA 2006). In a repeat-exposure (4-week) study, 25 ppm was a
24 no-effect level for irritation, neurotoxic signs, and gross pathologic changes in rats (Monsanto
25 Company 1983). In a 13-week study described in U.S. EPA (2006), 21 ppm was a NOAEL for
26 nasal degeneration in rats.
27
28 **5.3.   Derivation of AEGL-1**
29
30   Based on the acute studies of Reed et al. (1995) and U.S. EPA (2006) with support from
31 the repeat-exposure studies of Monsanto Company (1983) and U.S. EPA (2006), a weight-of-
32 evidence approach shows that exposures up to 27 ppm for 6 hours and to 100 ppm for 30 or 60
33 minutes are NOAELs for both nasal lesions and neurotoxicity. The 6-hour 27 ppm concentration
34 was used as the point of departure for the AEGL-1. Based on a higher blood:air partition
35 coefficient for rats than humans (Sweeney et al. 2009), uptake is greater in rats than humans. In
36 addition, higher inhalation rate and cardiac output in rodents indicate faster uptake. Thus, an
37 interspecies uncertainty factor of 1 was applied. Metabolism via glutathione conjugation is not
38 expected to vary greatly among humans (Nolan et al. 1985). In addition, conjugation of methyl
39 iodide with glutathione, the primary route of metabolism, may be non-enzymatic, further
40 minimizing individual differences. Therefore, an intraspecies uncertainty factor of 3 was
41 applied.
42
43   Neurotoxicity and nasal lesions are systemic effects; therefore, the values were time
44 scaled. The 6-hour NOAEL for nasal lesions and neurotoxicity of 9 ppm (27 ppm/3) was time
45 scaled using $C^n \times t = k$. Because glutathione depletion resulting in nasal lesions and
46 neurotoxicity is on a continuum with lethality, time scaling was based on the rat lethality data
47 sets of Eastman Kodak Co. (1987), Reed et al. (1995), and U.S. EPA (2006). The time scaling
48 value was 2 ($C^2 \times t = k$). The 6-hour value was time scaled to 10 minutes because one of the key

1   studies (Reed et al. 1995) utilized a 0.5-hour exposure. Because the 8-hour time-scaled value of
2   less than 10 ppm appears unrealistic in light of no-effect concentrations of 10 ppm and 20 ppm in
3   subchronic and chronic studies reported by Blank et al. (1984) and U.S. EPA (2006),
4   respectively, the 8-hour value was set equal to the 4-hour value of 11 ppm. Values are listed in
5   Table 5, and calculations are in Appendix A. A category graph of the AEGL values in relation to
6   the toxicity data is in Appendix B.

7

8

TABLE 5. AEGL-1 Values for Methyl Iodide				
10-min	**30-min**	**1-h**	**4-h**	**8-hour**
54 ppm (310 mg/m^3)	31 ppm (180 mg/m^3)	22 ppm (130 mg/m^3)	11 ppm (64 mg/m^3)	11 ppm (64 mg/m^3)

9

10

11   **6.   DATA ANALYSIS FOR AEGL-2**
12   **6.1.   Summary of Human Data Relevant to AEGL-2**

13

14   No clinical studies were available for development of AEGL-2 values.

15

16   **6.2.   Summary of Animal Data Relevant to AEGL-2**

17

18   Reed et al. (1995) addressed the effect of methyl iodide on the nasal olfactory epithelium
19   of Wistar-derived rats. A concentration of 100 ppm was tested over exposure durations of 0.5 to
20   6 hours. At the highest concentration-exposure duration, 100 ppm for 6 hours, lesions of the
21   olfactory epithelium were marked, but almost complete regeneration took place over a
22   subsequent two-week post-exposure period.

23

24   **6.3.   Derivation of AEGL-2**

25

26   The 100 ppm, 6-hour exposure of rats in the study of Reed et al. (1995) was used as the
27   point of departure for the AEGL-2. The endpoint of reversible lesions of the nasal olfactory
28   epithelium, a NOAEL for irreversible lesions, meets the definition of an AEGL-2. Based on a
29   higher blood:air partition coefficient for rats than humans (Sweeney et al. 2009), uptake is greater
30   in rats than humans. In addition, higher inhalation rate and cardiac output in rodents indicate
31   faster uptake. Thus, an interspecies uncertainty factor of 1 was applied. Metabolism via
32   glutathione conjugation is not expected to vary greatly among humans (Nolan et al. 1985). In
33   addition, the conjugation of methyl iodide with glutathione, the primary route of metabolism,
34   may be non-enzymatic, further minimizing individual differences. Therefore, an intraspecies
35   uncertainty factor of 3 was applied. Values were time-scaled using C^2 x t = k. Calculations are
36   in Appendix A and values are summarized in Table 6. A category graph of the AEGL values in
37   relation to the toxicity data is in Appendix B.

38

TABLE 6. AEGL-2 Values for Methyl Iodide				
10-min	**30-min**	**1-h**	**4-h**	**8-h**
200 ppm (1200 mg/m^3)	120 ppm (700 mg/m^3)	82 ppm (480 mg/m^3)	41 ppm (240 mg/m^3)	29 ppm (170 mg/m^3)

39

1   Support for the AEGL-2 values consists of data from acute and subchronic studies. The
2 8-hour AEGL-2 value of 29 ppm is close to the 6-hour NOAEL for neurotoxicity of 27 ppm in an
3 acute 6-hour study with the rat and only slightly higher than the 6 hour/day 13-week NOAEL for
4 olfactory lesions of 21 ppm in rats (U.S. EPA 2006).
5
6   There is concern that inhalation of methyl iodide may have an effect on the developing
7 fetus. Iodine released from methyl iodide may decrease thyroid hormones and increase TSH via
8 the hypothalamus-pituitary-thyroid negative feedback loop. The developing fetuses of rabbits
9 were susceptible to methyl iodide toxicity (Nemec et al. 2005; 2009; U.S. EPA 2006). Although
10 it is unlikely that iodide would concentrate in the human fetus as it does in the rabbit fetus
11 (Rayburn et al. 2008), the intake of iodine at the 8-hour AEGL-2 was calculated. The intake of
12 iodine from methyl iodide by a pregnant woman at the 8-hour AEGL-2 is 170 mg/m^3. The
13 breathing rate of an adult human is 20 m^3/day. Methyl iodide is 89% iodide. Assuming
14 complete uptake of methyl iodide from the respiratory tract, the resulting uptake of iodine for the
15 pregnant female is:
16
17   170 mg/m^3 x 20 m^3/24 hours x 8 hours x 0.89 = 1009 mg.
18
19   Assuming 100% absorption from the gastrointestinal tract of both iodine and iodide
20 (Robinson et al. 1998; ATSDR 2004), this value is close to the 1080 mg/day that produced only
21 transient changes in hormone status in healthy adults following ingestion for 11 weeks (Jubiz et
22 al. 1977). Thus, iodine inhibition of thyroid hormone synthesis is transient in normal subjects
23 and is not likely to result in alterations in thyroid function in subjects with adequate preformed
24 stores of T_4 and T_3 (Saberi and Utiger 1975). Chronic administration of similar or slightly higher
25 doses, 900-1650 mg/day, to pregnant women may induce congenital goiter of the newborn
26 (Martin and Rento 1962; Carswell et al. 1970; Senior and Chernoff 1971). Two newborns
27 diagnosed with goitrous cretinism secondary to transplacental transfer of maternal iodide, 900 or
28 1500 mg/day orally, improved spontaneously in the months following birth, and later studies
29 showed normal thyroid indices (Martin and Rento 1962).
30
31   The above studies involve oral administration of iodine or iodide. The absorption of
32 iodide via the inhalation and oral route can be compared. Approximately 72% of inhaled methyl
33 iodide (I-132 at tracer concentrations) is absorbed in healthy adults (Morgan and Morgan 1967).
34 The half-life in the respiratory tract is approximately 5 seconds, suggesting extremely rapid
35 absorption at the alveolar-blood interface. Water soluble iodide salts such as potassium or
36 sodium iodide are approximately 100% absorbed after oral ingestion (ATSDR 2004). The fate of
37 iodine following inhalation of radiolabeled methyl iodide in tracer amounts was similar to that of
38 iodine following ingestion of sodium iodide. This was confirmed by thyroid uptake and urinary
39 excretion rates (Morgan et al. 1967). Thus, the effect of total dose to the primary target tissue,
40 the thyroid, would not likely vary with exposure route.
41
42   In summary, the rabbit is unique in that the rabbit fetus does not regulate the uptake of
43 iodine and is not a good model for human iodine-induced fetotoxicity (See Section 4.4.1).
44 Rabbit fetal blood contains up to 6 times the iodine of maternal blood (Crone and Waago 1961).
45 The high iodine uptake in the rabbit fetus results in thyroid dysfunction and early death. In
46 humans, iodine uptake by the fetus is regulated, and the maternal to fetal ratio of blood iodine is
47 1:1 (Rayburn et al. 2008).
48

1   **7.   DATA ANALYSIS FOR AEGL-3**
2   **7.1.   Summary of Human Data Relevant to AEGL-3**
3
4   No clinical studies were available for development of AEGL-3 values.
5
6   **7.2.   Summary of Animal Data Relevant to AEGL-3**
7
8   Several studies addressed the threshold for lethality. A recent, well-conducted study
9   reported by U.S. EPA (2006) showed mortality values for male and female rats of 0, 80, 80, and
10 100% following 4-hour exposures to 581, 710, 797, and 1198 ppm, respectively; the calculated
11 4-hour LC_{50} was 691 ppm, and the calculated benchmark concentration (4-hour $BMCL_{05}$) was
12 489 ppm (Appendix B). The calculated 1-hour LC_{50} was1347 ppm in a similar study with rats,
13 and the calculated 1-hour $BMCL_{05}$ was 612 ppm (Eastman Kodak Co. 1987). One of 24 rats died
14 following a 6-hour exposure to 401 ppm (U.S. EPA 2006). The 57-minute LC_{50} in mice was 860
15 ppm (Buckell 1950). No mortality was observed in rats inhaling 100 ppm for 0.5 to 6 hours
16 (Reed et al. 1995).
17
18 **7.3.   Derivation of AEGL-3**
19
20   The lethality and toxicity data sets for the rat (Eastman Kodak Co. 1987, Reed et al. 1995,
21 and U.S. EPA 2006) were combined to estimate the threshold for lethality at each AEGL-3
22 exposure duration using the probit-analysis based dose-response program of ten Berge (2006).
23 The thresholds for lethality at each exposure duration were set at the lower limit of the 5%
24 response for lethality (the lower limit of the 95% confidence limit). These values are similar to
25 the benchmark dose $BMCL_{05}$. The data indicated a time-scaling value of 2 (C^2 x t = k). Values
26 for the 10-minute through 8-hour exposure duration were: 670, 400, 290, 150, and 98 ppm,
27 respectively. Based on a higher blood:air partition coefficient for rats than humans (Sweeney et
28 al. 2009), uptake is greater in rats than humans. In addition, higher inhalation rate and cardiac
29 output in rodents indicate faster uptake. Thus, an interspecies uncertainty factor of 1 was
30 applied. Although humans vary in the rate at which they metabolize halomethanes, the
31 difference is not expected to be greater than three-fold (Nolan et al. 1985). Furthermore, the
32 conjugation of methyl iodide with glutathione may be non-enzymatic, further minimizing
33 differences in metabolism rates. Persons lacking the GSTT-1 enzyme would be more sensitive to
34 the neurotoxic effects of the circulating unconjugated methyl iodide by a factor of 1.4 compared
35 to persons with full GSTT-1 activity (Sweeney et al. 2009). Therefore, the default intraspecies
36 uncertainty factor of 10 was reduced to 3. Calculations are in Appendix A and AEGL-3 values
37 are summarized in Table 7. A category graph of the AEGL values in relation to the toxicity data
38 is in Appendix B.
39

TABLE 7. AEGL-3 Values for Methyl Iodide				
10-min	**30-min**	**1-h**	**4-h**	**8-h**
670 ppm (3900 mg/m^3)	400 ppm (2300 mg/m^3)	290 ppm (1700 mg/m^3)	150 ppm (870 mg/m^3)	98 ppm (570 mg/m^3)

40
41

1   **8.   SUMMARY OF AEGLs**
2   **8.1.   AEGL Values and Toxicity Endpoints**
3
4   AEGL values are summarized in Table 8. Derivations are summarized in Appendix C.
5

TABLE 8. Summary of AEGL Values					
	Exposure Duration				
Classification	**10-min**	**30-min**	**1-h**	**4-h**	**8-h**
AEGL-1 (Nondisabling)	54 ppm (310 mg/m^3)	31 ppm (180 mg/m^3)	22 ppm (130 mg/m^3)	11 ppm (64 mg/m^3)	11 ppm (64 mg/m^3)
AEGL-2 (Disabling)	200 ppm (1200 mg/m^3)	120 ppm (700 mg/m^3)	82 ppm (480 mg/m^3)	41 ppm (240 mg/m^3)	29 ppm (170 mg/m^3)
AEGL-3 (Lethal)	670 ppm (3900 mg/m^3)	400 ppm (2300 mg/m^3)	290 ppm (1700 mg/m^3)	150 ppm (870 mg/m^3)	98 ppm (570 mg/m^3)

6
7
8   **8.2.   Comparison with Other Standards and Guidelines**
9
10   Standards and guidelines for methyl iodide are summarized in Table 9. The Emergency
11 Response Planning Guideline (ERPG) values are for 1 hour and are based primarily on
12 unpublished studies (AIHA 2004). The ERPG-1 of 25 ppm was based on eye irritation noted in
13 some rats exposed to 72 ppm, 6 hr/day, after 17 exposures but not in rats exposed to 24 ppm, 6
14 hours/day for 20 exposures. The ERPG-2 of 50 ppm was based on a weight-of-evidence
15 approach with repeat exposures of rats to concentrations ranging from 72 to 85 ppm. The ERPG-
16 3 of 125 ppm was based on no deaths of rats exposed to 150 ppm, 6 hr/day, for 3 days and
17 following a 1-hour exposure of rats to 960 ppm or of mice to 860 ppm for 20 minutes. The
18 NIOSH Immediately Dangerous to Life or Health (IDLH) value of 100 ppm is based on the
19 lethality studies of Bakhishev (1975), Buckell (1950), and Monsanto Company (1982a; 1982b;
20 1983).
21
22   The ACGIH TLV is 2 ppm and carries skin and suspected human carcinogen notations.
23 The Occupational Safety and Health Administration 8-hr permissible exposure limit (PEL) is 2
24 ppm (skin) (NIOSH 2005) as is The Netherlands MAC. The Swedish LLV is 1 ppm with a 15-
25 minute short-term limit of 5 ppm. It also bears skin and carcinogen notations. The German
26 MAK places methyl iodide in carcinogen category 2, human or animal carcinogen.
27
28

TABLE 9. Standards and Guidelines for Methyl Iodide					
	Exposure Duration				
Guideline	10 min	30 min	1 h	4 h	8 h
AEGL-1	54 ppm	31 ppm	22 ppm	11 ppm	11 ppm
AEGL-2	200 ppm	120 ppm	82 ppm	41 ppm	29 ppm
AEGL-3	670 ppm	400 ppm	290 ppm	150 ppm	98 ppm
ERPG-1 (AIHA)[a]			25 ppm		
ERPG-2 (AIHA)			50 ppm		
ERPG-3 (AIHA)			125 ppm		
PEL-TWA (NIOSH)[b]					5 ppm (skin)*
IDLH (NIOSH)[c]		100 ppm			
REL-TWA (NIOSH)[d]					2 ppm (skin)
TLV-TWA (ACGIH)[e]					2 ppm (skin)
MAK (Germany)[f]	No values; skin notation; carcinogen category 2 (human or animal carcinogen)				
LLV (Sweden)[g]					1 ppm (skin, carcinogen); 5 ppm (15 min)
MAC (The Netherlands)[h]					2 ppm (skin)

1   * The skin notation indicates the potential for dermal absorption.
2
3   **[a]ERPG (Emergency Response Planning Guidelines, American Industrial Hygiene Association** (AIHA 2004)
4   The ERPG-1 is the maximum airborne concentration below which it is believed nearly all individuals could be
5   exposed for up to one hour without experiencing other than mild, transient adverse health effects or without
6   perceiving a clearly defined objectionable odor.
7   The ERPG-2 is the maximum airborne concentration below which it is believed nearly all individuals could be
8   exposed for up to one hour without experiencing or developing irreversible or other serious health effects or
9   symptoms that could impair an individual's ability to take protective action.
10 The ERPG-3 is the maximum airborne concentration below which it is believed nearly all individuals could be
11 exposed for up to one hour without experiencing or developing life-threatening health effects.
12
13 **[b]OSHA PEL-TWA (Occupational Safety and Health Administration, Permissible Exposure Limits - Time**
14 **Weighted Average)** (NIOSH 2005) is defined analogous to the ACGIH-TLV-TWA, but is for exposures of no more
15 than 10 hours/day, 40 hours/week.
16
17 **[c]IDLH (Immediately Dangerous to Life and Health, National Institute of Occupational Safety and Health)**
18 (NIOSH 2005) represents the maximum concentration from which one could escape within 30 minutes without any
19 escape-impairing symptoms, or any irreversible health effects.
20
21 **[d]NIOSH REL-TWA (National Institute of Occupational Safety and Health, Recommended Exposure Limits -**
22 **Time Weighted Average)** (NIOSH 2005) is defined analogous to the ACGIH-TLV-TWA.
23
24 **[e]ACGIH TLV-TWA (American Conference of Governmental Industrial Hygienists, Threshold Limit Value -**
25 **Time Weighted Average)** (ACGIH 1992) is the time-weighted average concentration for a normal 8-hour workday
26 and a 40-hour workweek, to which nearly all workers may be repeatedly exposed, day after day, without adverse
27 effect.
28
29 **[f]MAK (Maximale Arbeitsplatzkonzentration [Maximum Workplace Concentration])** (Deutsche
30 Forschungsgemeinschaft [German Research Association] 2007) is defined analogous to the ACGIH-TLV-TWA.
31
32 **[g]LLV (level Limit Value)** Occupational Exposure Limit Values and Measures against Air Contaminants. 2000.
33 Swedish National Board of Occupational Safety and Health.

1
2 [h]**MAC (Maximaal Aanvaarde Concentratie [Maximal Accepted Concentration])** (SDU Uitgevers [under the
3 auspices of the Ministry of Social Affairs and Employment], The Hague, The Netherlands 2000) is defined similar to
4 the ACGIH TLV.
5
6 **8.3.   Data Adequacy and Research Needs**
7
8   Although no quantitative human data were located, studies with animal models were
9 adequate for derivation of AEGL values for methyl iodide. The relative toxicities of the
10 halomethanes are: methyl iodide > methyl bromide > methyl chloride (see Section 4.3. Structure-
11 Activity Relationships). The derived AEGL values for the three chemicals reflect the relative
12 toxicities. The Interim AEGL values for methyl bromide and methyl chloride along with the
13 draft values for methyl iodide are summarized in Table 10.
14

TABLE 10. AEGL Values for Halomethanes					
	Exposure Duration				
Classification	10-min	30-min	1-h	4-h	8-h
Methyl Iodide					
AEGL-1	54 ppm	31 ppm	22 ppm	11 ppm	11 ppm
AEGL-2	200 ppm	120 ppm	82 ppm	41 ppm	29 ppm
AEGL-3	670 ppm	400 ppm	290 ppm	150 ppm	98 ppm
Methyl Bromide					
AEGL-1	NR	NR	NR	NR	NR
AEGL-2	940 ppm	380 ppm	210 ppm	67 ppm	67 ppm
AEGL-3	3300 ppm	1300 ppm	740 ppm	230 ppm	130 ppm
Methyl Chloride					
AEGL-1	NR	NR	NR	NR	NR
AEGL-2	1100 ppm	1100 ppm	910 ppm	570 ppm	380 ppm
AEGL-3	3800 ppm	3800 ppm	3000 ppm	1900 ppm	1300 ppm

15 NR = Not Recommended; values are not recommended because there are no odor or warning properties and toxic
16 effects may occur below the odor threshold.
17

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APPENDIX A: Derivation of Methyl Iodide AEGLs

Derivation of AEGL-1 Values

Key Studies: (1) Reed et al. 1995. Olfactory toxicity of methyl iodide in the rat. Arch. Toxicol. 70:51-56; (2) U.S. EPA. 2006. Human Health Risk Assessment: Iodomethane. Washington, DC: Health Effects Division, Office of Pesticide Programs.

Toxicity endpoint: Weight of Evidence: NOAEL for clinical signs and neurotoxicity in rats (27 ppm for 6 hours (U.S. EPA 2006). Supported by acute no-effect study (100 ppm for 1 hour) and repeat-exposure and subchronic studies).

Time scaling: $C^n \times t = k$ where $n = 2.0$ based on the rat toxicity/lethality data sets of Eastman Kodak Co. (1987), Reed et al. (1995), and U.S. EPA (2006).

Uncertainty factors: Total uncertainty factor: 3
                        Interspecies: 1 – Chemical uptake is higher in rodents than humans based on a higher blood:air partition coefficient. In addition, the respiratory rate and cardiac output of rodents is higher than in humans.
                        Intraspecies: 3 – Humans do not differ greatly in their ability to metabolize monohalomethanes (Nolan et al. 1985).

Modifying factor: None applied

Calculations: $C^2 \times t = k$
                        $(27 \text{ ppm}/3)^2 \times 360 \text{ minutes } 29160 \text{ ppm}^2 \bullet \text{minutes}$

10-minute AEGL-1: $C = (29160 \text{ ppm}^2 \bullet \text{minutes}/10)^{1/2}$
                        $C = 54 \text{ ppm}$

30-minute AEGL-1: $C = (29160 \text{ ppm}^2 \bullet \text{minutes}/10)^{1/2}$
                        $C = 31 \text{ ppm}$

1-hour AEGL-1: $C = (29160 \text{ ppm}^2 \bullet \text{minutes}/10)^{1/2}$
                        $C = 22 \text{ ppm}$

4-hour AEGL-1: $C = (29160 \text{ ppm}^2 \bullet \text{minutes}/10)^{1/2}$
                        $C = 11 \text{ ppm}$

8-hour AEGL-1:   Because the time-scaled value of 7.8 ppm appears low in comparison with subchronic and chronic NOAELs for effects on the olfactory epithelium of 20 ppm (U.S. EPA 2006), the 8-hour value was set equal to the 4-hour value.
                        $C = 11 \text{ ppm}$

1
2   **Derivation of AEGL-2 Values**
3
4   Key Study: Reed, C.J., B.A. Gaskell, K.K. Banger, and E.A. Lock. 1995. Olfactory
5   toxicity of methyl iodide in the rat. Arch. Toxicol. 70:51-56.
6
7   Toxicity endpoint: Reversible lesions of the olfactory epithelium following a 6-hour exposure of
8   rats to 100 ppm
9
10   Time scaling $C^n \times t = k$ where $n = 2$ based on the rat lethality data sets of Eastman Kodak
11   Co. (1987) and U.S. EPA (2006).
12
13   Uncertainty factors: Total uncertainty factor: 3
14   Interspecies: 1 – Chemical uptake is higher in rodents than humans based on
15   a higher blood:air partition coefficient. In addition, rodents have a higher
16   respiratory rate and cardiac output than humans.
17   Intraspecies: 3 – Humans do not differ greatly in their ability to metabolize
18   monohalomethanes (Nolan et al. 1985).
19
20   Calculations: $C^2 \times t = k$
21                              $(100 \text{ ppm}/3)^2 \times 360 \text{ minutes} = 400{,}000 \text{ ppm}^2\text{-minutes}$
22
23   10-minute AEGL-2: $C = 400{,}000 \text{ ppm}^2\text{-minutes}/10)^{1/2}$
24                              $C = 200 \text{ ppm}$
25
26   30-minute AEGL-2: $C = (400{,}000 \text{ ppm}^2\text{-minutes}/30)^{1/2}$
27                              $C = 120 \text{ ppm}$
28
29   1-hour AEGL-2: $C = (400{,}000 \text{ ppm}^2\text{-minutes}/60)^{1/2}$
30                              $C = 82 \text{ ppm}$
31
32   4-hour AEGL-2: $C = (400{,}000 \text{ ppm}^2\text{-minutes}/240)^{1/2}$
33                              $C = 41 \text{ ppm}$
34
35   8-hour AEGL-2: $C = (400{,}000 \text{ ppm}^2\text{-minutes}/480)^{1/2}$
36                              $C = 29 \text{ ppm}$
37
38

1
2   **Derivation of AEGL-3 Values**
3
4   Key Studies: (1) Eastman Kodak Co. 1987. Initial Submission: Acute Inhalation Toxicity
5   of Methyl Iodide in the Rat with Cover Letter Dated 08/26/92. National
6   Technical Information Service, Springfield, VA; (2) Reed, C.J., B.A.
7   Gaskell, K.K. Banger, and E.A. Lock. 1995. Olfactory toxicity of methyl
8   iodide in the rat. Arch. Toxicol. 70:51-56; (3) U.S. EPA (U.S.
9   Environmental Protection Agency). 2006. Human Health Risk Assessment:
10   Iodomethane. Washington, DC: Health Effects Division, Office of Pesticide
11   Programs.
12
13   Toxicity endpoint: Threshold for lethality in rats at the lower limit of the 95% confidence limit,
14   calculated using probit-analysis dose-response program of ten Berge (2006).
15
16   Time scaling $C^n \times t = k$ where $n = 2.0$ based on the rat toxicity/lethality data sets of Eastman
17   Kodak Co. (1987), Reed et al. (1995), and U.S. EPA (2006).
18
19   Uncertainty factors: Total uncertainty factor: 3
20   Interspecies: 1 – Chemical uptake is higher in rats than humans based on a
21   higher blood:air partition coefficient (Sweeney et al. 2009); in addition, the
22   respiratory rate and cardiac output is higher in rats than humans resulting in
23   faster uptake.
24   Intraspecies: 3 – Humans do not differ greatly in their ability to metabolize
25   monohalomethanes (Nolan et al. 1985).
26
27   Modifying factor: None applied
28
29   Data for calculations:

Exposure Duration (minutes)	Concentration (ppm)	Mortality (percent)	Reference
60	1190 1554 1973	20 60 90	Eastman Kodak Co. (1987)
30, 60, 120, 180, 240, 360	100	0 at all time points	Reed et al. (1995)
240	581 710 797 1198	0 80 80 100	U.S. EPA (2006)
360	27 93 401	0 0 4	U.S. EPA (2006)

30
31   Program output (with intraspecies uncertainty factor of 3 applied):

Exposure Duration	AEGL-3 Value
10 minutes	670 ppm
30 minutes	400 ppm
60 minutes	290 ppm
4 hours	150 ppm
8 hours	98 ppm

32   $n = 2.0$

1 **Calculations: Methyl Iodide – Log Probit Model (ten Berge 2006)**
2
3 Filename: methyl iodide for Log Probit Model
4 Date: 20 June 2008   Time: 11:51:12
5 Data of Eastman Kodak Co. (1987), Reed et al. (1995), and U.S. EPA (2006)
6 Lower limit of the 5% response
7
8 | Seq.Nr | conc ppm | min | exposed | responded |
   |--------|----------|-----|---------|-----------|
9 | 1 | 1190 | 60 | 10 | 2 |
10 | 2 | 1554 | 60 | 10 | 6 |
11 | 3 | 1973 | 60 | 10 | 9 |
12 | 4 | 581 | 240 | 10 | 0 |
13 | 5 | 710 | 240 | 10 | 8 |
14 | 6 | 797 | 240 | 10 | 8 |
15 | 7 | 1198 | 240 | 10 | 10 |
16 | 8 | 27 | 360 | 24 | 0 |
17 | 9 | 93 | 360 | 24 | 0 |
18 | 10 | 401 | 360 | 24 | 1 |
19 | 11 | 100 | 30 | 3 | 0 |
20 | 12 | 100 | 60 | 3 | 0 |
21 | 13 | 100 | 120 | 3 | 0 |
22 | 14 | 100 | 180 | 3 | 0 |
23 | 15 | 100 | 240 | 3 | 0 |
24 | 16 | 100 | 360 | 3 | 0 |
25
26 Observations 1 through 16 considered!
27
28 | Seq.nr | conc ppm | min | exposed | responded |
   |--------|----------|-----|---------|-----------|
29 | | | | | |
30 | 1 | 1190 | 60 | 10 | 2 |
31 | 2 | 1554 | 60 | 10 | 6 |
32 | 3 | 1973 | 60 | 10 | 9 |
33 | 4 | 581 | 240 | 10 | 0 |
34 | 5 | 710 | 240 | 10 | 8 |
35 | 6 | 797 | 240 | 10 | 8 |
36 | 7 | 1198 | 240 | 10 | 10 |
37 | 8 | 27 | 360 | 24 | 0 |
38 | 9 | 93 | 360 | 24 | 0 |
39 | 10 | 401 | 360 | 24 | 1 |
40 | 11 | 100 | 30 | 3 | 0 |
41 | 12 | 100 | 60 | 3 | 0 |
42 | 13 | 100 | 120 | 3 | 0 |
43 | 14 | 100 | 180 | 3 | 0 |
44 | 15 | 100 | 240 | 3 | 0 |
45 | 16 | 100 | 360 | 3 | 0 |
46
47 Used Probit Equation $Y = B0 + B1*X1 + B2*X2$
48 $X1$ = conc ppm, ln-transformed
49 $X2$ = min, ln-transformed
50
51 ChiSquare   =   5.32
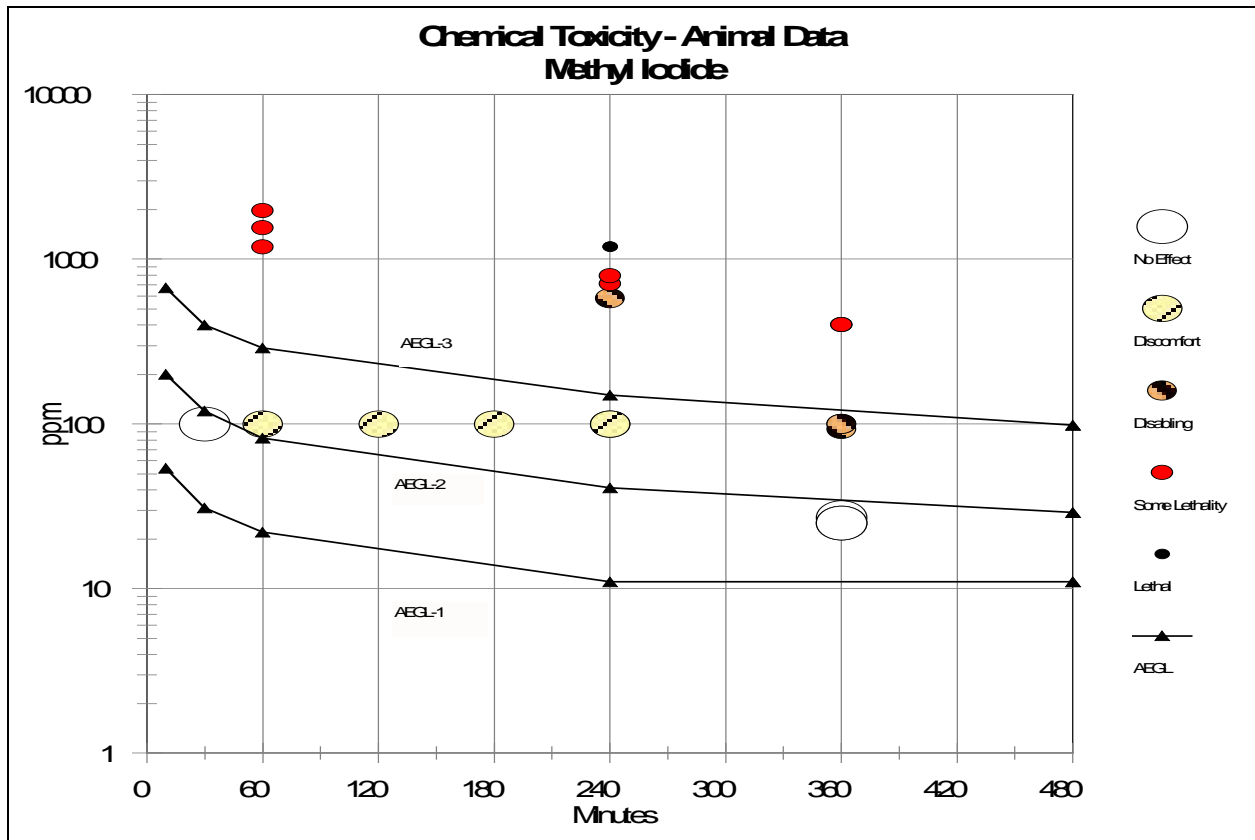52 Degrees of freedom =   13

1   Probability Model =   9.68E-01
2
3   Ln(Likelihood)   = -10.45
4
5   B 0 = -4.8449E+01   Student t = -4.8126
6   B 1 = 5.5950E+00   Student t =   5.5485
7   B 2 = 3.0903E+00   Student t =   4.5552
8
9   variance B 0 0 = 1.0135E+02
10   covariance B 0 1 = -1.0077E+01
11   covariance B 0 2 = -6.6311E+00
12   variance B 1 1 = 1.0168E+00
13   covariance B 1 2 = 6.3995E-01
14   variance B 2 2 = 4.6026E-01
15
16   Estimation of conc ppm at response of 5 %
17   min   = 10
18   Point estimate   conc ppm = 2.943E+03 for response of 5 %
19   **Lower limit (95% CL) conc ppm = 2.002E+03 for response of 5 %**
20   Upper limit (95% CL) conc ppm = 3.778E+03 for response of 5 %
21
22   Estimation of conc ppm at response of 5 %
23   min   = 30
24   Point estimate   conc ppm = 1.604E+03 for response of 5 %
25   **Lower limit (95% CL) conc ppm = 1.213E+03 for response of 5 %**
26   Upper limit (95% CL) conc ppm = 1.899E+03 for response of 5 %
27
28   Estimation of conc ppm at response of 5 %
29   min   = 60
30   Point estimate   conc ppm = 1.094E+03 for response of 5 %
31   **Lower limit (95% CL) conc ppm = 8.777E+02 for response of 5 %**
32   Upper limit (95% CL) conc ppm = 1.239E+03 for response of 5 %
33
34   Estimation of conc ppm at response of 5 %
35   min   = 240
36   Point estimate   conc ppm = 5.086E+02 for response of 5 %
37   **Lower limit (95% CL) conc ppm = 4.365E+02 for response of 5 %**
38   Upper limit (95% CL) conc ppm = 5.552E+02 for response of 5 %
39
40   Estimation of conc ppm at response of 5 %
41   min   = 480
42   Point estimate   conc ppm = 3.468E+02 for response of 5 %
43   **Lower limit (95% CL) conc ppm = 2.938E+02 for response of 5 %**
44   Upper limit (95% CL) conc ppm = 3.895E+02 for response of 5 %
45
46   AEGL concentrations at 5% lethality response (The point estimate is similar to the BMC_{05}. The
47   $BMCL_{05}$ would be similar to the lower limit)
48
49

1
2   **1% response**
3
4   Estimation of conc ppm at response of 1 %
5   min   = 10
6   Point estimate   conc ppm = 2.605E+03 for response of 1 %
7   Lower limit (95% CL) conc ppm = 1.688E+03 for response of 1 %
8   Upper limit (95% CL) conc ppm = 3.393E+03 for response of 1 %
9
10 Estimation of conc ppm at response of 1 %
11 min   = 30
12 Point estimate   conc ppm = 1.420E+03 for response of 1 %
13 Lower limit (95% CL) conc ppm = 1.017E+03 for response of 1 %
14 Upper limit (95% CL) conc ppm = 1.714E+03 for response of 1 %
15
16 Estimation of conc ppm at response of 1 %
17 min   = 60
18 Point estimate   conc ppm = 9.684E+02 for response of 1 %
19 Lower limit (95% CL) conc ppm = 7.331E+02 for response of 1 %
20 Upper limit (95% CL) conc ppm = 1.123E+03 for response of 1 %
21
22 Estimation of conc ppm at response of 1 %
23 min   = 240
24 Point estimate   conc ppm = 4.503E+02 for response of 1 %
25 Lower limit (95% CL) conc ppm = 3.646E+02 for response of 1 %
26 Upper limit (95% CL) conc ppm = 5.032E+02 for response of 1 %
27
28 Estimation of conc ppm at response of 1 %
29 min   = 480
30 Point estimate   conc ppm = 3.071E+02 for response of 1 %
31 Lower limit (95% CL) conc ppm = 2.480E+02 for response of 1 %
32 Upper limit (95% CL) conc ppm = 3.492E+02 for response of 1 %
33
34
35
36

1 **APPENDIX B: Category Graph of AEGL Values and Toxicity Data**
2

Chemical Toxicity - Animal Data
Methyl Iodide

ppm (y-axis: 1, 10, 100, 1000, 10000)

AEGL-3
AEGL-2
AEGL-1

Minutes (x-axis: 0, 60, 120, 180, 240, 300, 360, 420, 480)

Legend:
No Effect
Discomfort
Disabling
Some Lethality
Lethal
AEGL

3
4
5 **Data:**

Category: 0 = No effect, 1 = Discomfort, 2 = Disabling, SL = Some Lethality, 3 = Lethal					
Source	**Species**	**ppm**	**Minutes**	**Category**	**Comments**
NAC/AEGL-1		54	10	AEGL	
NAC/AEGL-1		31	30	AEGL	
NAC/AEGL-1		22	60	AEGL	
NAC/AEGL-1		11	240	AEGL	
NAC/AEGL-1		11	480	AEGL	
NAC/AEGL-2		200	10	AEGL	
NAC/AEGL-2		120	30	AEGL	
NAC/AEGL-2		82	60	AEGL	
NAC/AEGL-2		41	240	AEGL	
NAC/AEGL-2		29	480	AEGL	
NAC/AEGL-3		670	10	AEGL	
NAC/AEGL-3		400	30	AEGL	
NAC/AEGL-3		290	60	AEGL	
NAC/AEGL-3		150	240	AEGL	
NAC/AEGL-3		98	480	AEGL	

Eastman Kodak Co. 1987	rat	1190	60	SL	20% mortality
	rat	1554	60	SL	60% mortality
	rat	1973	60	SL	90% mortality
U.S. EPA 2006	rat	581	240	2	No mortality
	rat	710	240	SL	80% mortality
	rat	797	240	SL	80% mortality
	rat	1198	240	3	100% mortality
U.S. EPA 2006	rat	27	360	0	NOAEL for neurotoxicity
	rat	93	360	2	Clonic convulsions
	rat	401	360	SL	Neurotoxicity, gasping, 4% mortality
Reed et al. 1995	rat	100	30	0	No lesions, nasal passages
	rat	100	60	1	No lesions, nasal passages
	rat	100	120	1	Minimal lesions, nasal passages
	rat	100	180	1	Slight lesions, nasal passages
	rat	100	240	1	Moderate lesions, nasal passages
	rat	100	360	2	Marked lesions, nasal passages; regeneration after 2 weeks
Delorme et al. 2005	rat	25	360	0	No effect, respiratory parameters

1
2

1   # APPENDIX C: Derivation Summary for Methyl Iodide AEGLs

2

3   ## ACUTE EXPOSURE GUIDELINE LEVELS FOR METHYL IODIDE
4   ## (CAS Reg. No. 79-38-9)

5

AEGL-1 VALUES				
10-min	**30-min**	**1-h**	**4-h**	**8-hour**
54 ppm	**31 ppm**	**22 ppm**	**11 ppm**	**11 ppm**

Key References: (1) U.S. EPA. 2006. Human Health Risk Assessment: Iodomethane. Washington, DC: Health Effects Division, Office of Pesticide Programs.   (2) Reed, C.J., B.A. Gaskell, K.K. Banger, and E.A. Lock. 1995. Olfactory toxicity of methyl iodide in the rat. Arch. Toxicol. 70:51-56.
Test Species/Strain/Number: (1) Rat/CRL/5 males and 5 females per group; (2) Rat/Wistar/3 males per group
Exposure Route/Concentration/Duration: (1) Inhalation/27, 93, or 401 ppm for 6 hours; (2) Inhalation/100 ppm for 0.5, 1, 2, 3, 4, or 6 hours

Effects:
   (1) 27 ppm for 6 hours was a NOAEL for neurotoxic signs
   (2) No observable change, respiratory epithelium following 1 hour exposure to 100 ppm

Endpoint/Concentration/Rationale: NOAEL for clinical signs: 27 ppm for 6 hours and 100 ppm for 1 hour   The point of departure was the 6-hour exposure to 27 ppm.

Uncertainty Factors/Rationale:
   Total uncertainty factor: 3
     Interspecies: 1, considered sufficient as chemical uptake is greater in rodents than humans
     Intraspecies: 3, considered sufficient to account for metabolism-mediated variability

Modifying Factor: None applied
Animal to Human Dosimetric Adjustment: Not applicable
Time Scaling: $C^n \times t = k$, where $n = 2$ based on toxicity studies with the rat (Eastman Kodak Co. 1987, Reed et al. 1995, U.S. EPA 2006) and calculated using the ten Berge (2006) probit analysis dose-response program. The 8-hour value was set equal to the 4-hour value because the time-scaled 8-hour value of 7.8 ppm appears inconsistent with the 20 ppm NOAELs reported in subchronic and chronic studies (U.S. EPA 2006).
Data Adequacy: There are no clinical data with clearly stated exposure concentrations. The animal data were adequate for derivation of three levels of AEGLs.

6
7

AEGL-2 VALUES				
10-minute	**30-minute**	**1-hour**	**4-h**	**8-h**
200 ppm	**120 ppm**	**82 ppm**	**41 ppm**	**29 ppm**

Key Reference: Reed, C.J., B.A. Gaskell, K.K. Banger, and E.A. Lock. 1995. Olfactory toxicity of methyl iodide in the rat. Arch. Toxicol. 70:51-56.
Test Species/Strain/Number: Rat/Wistar/three males per group,
Exposure Route/Concentration/Duration: Inhalation/100 ppm for 0.5, 1, 2, 3, 4, or 6 hours

Effects:
    0.5 hours: no observable change, nasal passages
    1 hour: no observable change, nasal passages
    2 hours: minimal lesions, olfactory epithelium
    3 hour: slight lesions, olfactory epithelium
    4 hours: moderate lesions, olfactory epithelium
    6 hours: marked lesions, olfactory epithelium; regeneration after 2 weeks

Endpoint/Concentration/Rationale: 6 hour exposure to 100 ppm resulted in reversible lesions in the olfactory epithelium.

Uncertainty Factors/Rationale:
    Total uncertainty factor: 3
      Interspecies: 1, considered sufficient as chemical uptake is greater in rodents than humans
      Intraspecies: 3, considered sufficient to account for metabolism-mediated variability

Modifying Factor: None applied
Animal to Human Dosimetric Adjustment: Not applicable
Time Scaling: C^n x t = k, where n = 2 based on toxicity studies with the rat (Eastman Kodak Co. 1987, Reed et al. 1995, U.S. EPA 2006) and calculated using the ten Berge (2006) probit analysis dose-response program.
Data Adequacy: There are no clinical studies with clearly stated exposure concentrations. Several studies showed that the olfactory epithelium was a target organ for methyl iodide. The data base of acute, repeat-exposure, genotoxicity, developmental, subchronic, and chronic animal studies was sufficient for derivation of AEGL values.

1
2
3

AEGL-3 VALUES				
10-min	**30-min**	**1-h**	**4-h**	**8-h**
670 ppm	**400 ppm**	**290 ppm**	**150 ppm**	**98 ppm**

Key References: (1) Eastman Kodak Co. 1987. Initial Submission: Acute Inhalation Toxicity of Methyl Iodide in the Rat with Cover Letter Dated 08/26/92. Available from National Technical Information Service, Springfield, VA. (2) Reed, C.J., B.A. Gaskell, K.K. Banger, and E.A. Lock. 1995. Olfactory toxicity of methyl iodide in the rat. Arch. Toxicol. 70:51-56. (3) U.S. EPA (U.S. Environmental Protection Agency). 2006. Human Health Risk Assessment: Iodomethane. Washington, DC: Health Effects Division, Office of Pesticide Programs.
Test Species/Strain/Number: (1) Rat/Crl:CD/10 per group; (2) Rat (male)/Wistar/3per group; (3) Rat/Sprague-Dawley/10 per group
Exposure Route/Concentration/Duration: (1) Inhalation/1190, 1554, or 1973 ppm for 1 hour; (2) Inhalation/100 ppm for 0.5-6 hours ; (3) Inhalation/581, 710, 797, or 1198 ppm for 4 hours; 27, 93, 401 ppm for 6 hours
Effects: (1) Respectively mortalities of 20, 60, and 90%; (2) No mortality (3) Respective mortalities of 0, 80, 80, and 100% (4 hours); 0, 0, 4% (6 hours)
Endpoint/Concentration/Rationale: Lower limit of the 95% confidence limit, calculated at each AEGL exposure duration using the probit-analysis dose-response program of ten Berge (2006).

Uncertainty Factors/Rationale:
  Total uncertainty factor: 3
    Interspecies: 1, considered sufficient as chemical uptake is greater in rodents than humans.
    Intraspecies: 3, considered sufficient to account for metabolism-mediated variability.

Modifying Factor: None applied
Animal to Human Dosimetric Adjustment: Not applicable
Time Scaling: Calculated using the ten Berge program (n in C^n x t = 2)
Data Adequacy: Several well-conducted toxicity/lethality studies with rats were available. The data base of acute, repeat-exposure, genotoxicity, developmental, subchronic, and chronic animal studies was sufficient for derivation of AEGL values.

1