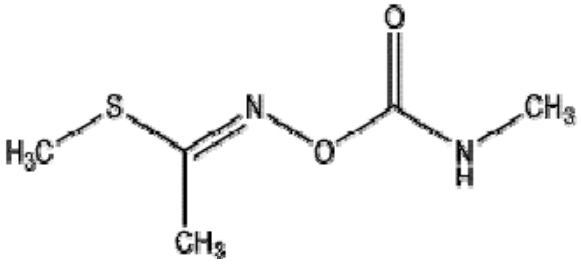
ACUTE EXPOSURE GUIDELINE LEVELS (AEGLs)

FOR

METHOMYL

(CAS Reg. No. 16752-77-5)



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PREFACE

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

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

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

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

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

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

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SUMMARY

Methomyl (CAS No. 16752-77-5) is a crystalline solid *N*-methyl carbamate insecticide with a slightly sulfurous odor. Methomyl is used as an insecticide on field crops such as vegetables, soybeans, and cotton and on some fruits and ornamentals. Technical methomyl is commercially available as a solid, dust or granular formulation, and as a water soluble concentrate. Methomyl is manufactured commercially by the reaction of methyl thiomethyl oxime with methyl isocyanate. An estimated 2.5 to 3.5 million pounds of active ingredient are applied annually in the United States.

Methomyl and other carbamate pesticides are neurotoxic in that they are inhibitors of the enzyme acetylcholinesterase. Inhibition of acetylcholinesterase, responsible for termination of the biological activity of the neurotransmitter acetylcholine at various nerve endings, results in sustained stimulation of electrical activity. Depending on concentrations administered, symptoms following acute exposure of rats to methomyl may include salivation, lacrimation, gasping and tremors or convulsions. Inhibition of acetylcholinesterase activity is reversible. In humans, inhibition of erythrocyte acetylcholinesterase activity is used as a biomarker of methyl carbamate exposure. Based on oral studies, the half-life for methomyl-induced inhibition of erythrocyte acetylcholinesterase activity in humans is 1.6 hours. No inhalation studies involving human subjects were located. Given that methyl carbamate pesticides do not have a port of entry effect, are expected to be rapidly absorbed, and do not require activation, relative acetylcholinesterase activity inhibition levels measured in oral studies with humans and adult and juvenile rodents are applicable for determination of interspecies and intraspecies uncertainty factors. Four inhalation rat studies with methomyl administered in different physical forms provided consistent, concentration-related effects. All exposure durations were for 4 hours.

No studies that adequately reported details of methomyl exposure and effects consistent with the definition of AEGL-1 were located. Therefore, AEGL-1 values are not recommended.

The lethality study of DuPont (1991) in which methomyl was administered to rats via the inhalation route shows that methomyl has a steep concentration-response curve. In the absence of other relevant data, AEGL-2 values for chemicals with a steep concentration-response curve may be derived by dividing the AEGL-3 values by 3 (NRC 2001). For consistency with the aerosol study used to derive AEGL-3 values, the AEGL-2 values were derived by dividing the AEGL-3 values by 3. The AEGL-2 values are supported by the vapor study of DuPont (1966a) in which all six rats exposed to 44 mg/m^3 of methomyl vapor for 4 hours displayed clinical signs of slight salivation and lacrimation, slight to moderate hyperpnea, and mild dyspnea. Application of the same uncertainty factors and time scaling relationship to the 4-hour 44 mg/m^3 value results in AEGL-2 values similar to those derived by dividing the AEGL-3 by 3 (10-minute through 8-hour values of 5.9, 5.9, 4.7, 2.9, and 1.5 mg/m^3).

The exposure of rats for 4 hours to a range of aqueous aerosol concentrations that resulted in lethality at the higher concentrations (DuPont 1991; Panepinto 1991) was chosen as the key study for derivation of AEGL-3 values. The study used an adequate number of rats of both sexes and five test concentrations. Mortality in rats inhaling 137, 181, 182, 232, or 326 mg/m^3 of an aqueous aerosol of methomyl for 4 hours showed mortality of 0/10, 0/10, 1/10, 6/10, and 7/10, respectively. The benchmark concentration program was used to estimate the

threshold for lethality. The benchmark concentration program was run with and without the highest value of 326 mg/m^3. Omitting the highest value resulted in a better fit of the data to the curve. The calculated 4-hour $BMCL_{05}$ was 157.3 mg/m^3, and the BMC_{01} was 166.51 mg/m^3. The $BMCL_{05}$ was considered the threshold for lethality. The 4-hour 157.3 mg/m^3 value was divided by inter- and intraspecies uncertainty factors of 5 and 3.05, respectively, for a total of 15. The methomyl-specific uncertainty factors were derived by U.S. EPA (2007). The methomyl-specific interspecies inhalation uncertainty factor of 5 was based on differences in modeled values for erythrocyte acetylcholinesterase activity inhibition between rats and humans. The intraspecies uncertainty factor was based on comparative brain acetylcholinesterase activity inhibition in post-natal day 11 juvenile rats and adult rats; the U.S. EPA calculated an uncertainty factor of 3.05 to protect sensitive young. The resulting 4-hour 10.48 mg/m^3 value was time-scaled ($C^n \times t = k$) using the default values of 3 and 1 for longer and shorter exposure durations, respectively (NRC 2001).

The calculated values are listed in the table below.

S 1. Summary of AEGL Values for Methomyl

Classification	10-min	30-min	1-h	4-h	8-h	Endpoint (Reference)
AEGL–1 (Nondisabling)	Not recommended	Not recommended	Not recommended	Not recommended	Not recommended	Inadequate data
AEGL–2 (Disabling)	7.0 mg/m^3	7.0 mg/m^3	5.7 mg/m^3	3.3 mg/m^3	1.7 mg/m^3	AEGL-3 values divided by 3 (based on steep concentration-response curve)
AEGL–3 (Lethal)	21 mg/m^3	21 mg/m^3	17 mg/m^3	10 mg/m^3	5.2 mg/m^3	Calculated $BMCL_{05}$ for lethality – rat (DuPont 1991)

Not recommended: absence of AEGL-1 values does not imply that exposure below AEGL-2 levels is without effect.
All values were derived from 4-hour studies.

1. INTRODUCTION

Technical methomyl (CAS No. 16752-77-5) is a crystalline solid *N*-methyl carbamate insecticide with a slight sulfurous odor. Methomyl is a broad-spectrum insecticide used on vegetables, soybeans, cotton and other field crops and on some fruits and ornamentals. The technical material is formulated as a bait/solid, dust, or granular formulation, and as a water soluble concentrate liquid. Formulated products such as Lannate™ contain 90% methomyl (U.S. EPA 1998; O'Neil 2001 et al.; DuPont 2007). Methomyl is available as wettable powder (25%), soluble concentrate (200 g/L), and water soluble powder (deVreede et al. 1988). Dilution instructions are: soluble concentrate, 100-150 mL/100 L water and wettable powder, 80-120 g/100 L water. Products are intended for occupational use only and not for homeowner use. Methomyl is also a degradate of the pesticide thiodicarb (U.S. EPA 1998). Chemical and physical properties are listed in Table 1.

Methomyl is manufactured commercially by the reaction of methyl thiomethyl oxime with methyl isocyanate (HSDB 2009). An estimated 2.5 to 3.5 million pounds of active ingredient of methomyl are applied annually in the United States (U.S. EPA 1998).

1

TABLE 1. Chemical and Physical Properties		
Parameter	**Value**	**Reference**
Synonyms	*N*-[[(Methylamino)carbonyl]oxy] ethanimidothioic acid methyl ester; *N*-[(methylcarbamoly)oxy]thioacetimidic acid methyl ester; S-methyl *N*-[(methylcarbamoyl)oxy]thioacetimidate; methyl O-(methylcarbamyl)thiol acetohydroxamate; Methyl carbamic acid, ester with oxime function of thiolacetohydroxamic acid, S-methyl ester; DuPont 1179; Lannate; Nudrin; DPX-X1179; INX-1179	O'Neil et al. 2001; DuPont 2007
Chemical formula	$C_5H_{10}N_2O_2S$	O'Neil et al. 2001
Molecular weight	162.21	O'Neil et al. 2001
CAS Reg. No.	16752-77-5	O'Neil et al. 2001
Physical state	crystalline solid	O'Neil et al. 2001
Solubility in water	58 g/L	O'Neil et al. 2001
Vapor pressure	5×10^{-5} torr at 25ºC	ACGIH 1992
Vapor density (air =1)	No data	
Liquid density (water =1)	1.2946 at 25ºC	DuPont 2007
Melting point	78-79ºC	O'Neil et al. 2001
Boiling point	136 ºC (autodecomposition)	DuPont 2007
Flammability limits in air	0.096 g/L (lower explosive limit)	DuPont 2007
Conversion factors	1 ppm = 6.63 mg/m^3 1 mg/m^3 = 0.15 ppm	Calculated

2
3
4 **2. HUMAN TOXICITY DATA**
5
6 No inhalation studies other than accidental exposures were located. Most of these
7 accidental exposures lacked information on concentrations. A pilot who was spraying methomyl
8 and Bravo (chlorothalonil) accidently crashed and died (Driskell et al. 1991). Gas
9 chromatography/flame ionization analysis of the pilot's blood revealed a methomyl
10 concentration of 570 ng/mL of blood. Blood was not analyzed for Bravo. A farmer who died
11 following several days of application of methomyl in his greenhouse had a blood methomyl
12 concentration of 1.6 mg/L and 89% blood cholinesterase activity inhibition upon admittance to
13 the hospital in an unconscious state (Tsatsakis et al. 2001). Death was attributed to inhalation
14 and dermal exposure as the farmer's hair and clothes were wet with pesticide and no methomyl
15 was found in his stomach. An oral lethal dose for humans has been estimated at 12 to 15 mg/kg
16 (ACGIH 1992).
17
18 In a double-blind human oral dosing study, 19 healthy male volunteers, ages 18-40 years
19 ingested a single oral dose of methomyl formulation (89% a.i.) (McFarlane et al. 1998, reviewed
20 in U.S. EPA 2005). Five subjects comprised each treated group; there were four control
21 subjects. Doses of 0, 0.1, 0.2, or 0.3 mg/kg body weight were ingested in capsule form along
22 with a light breakfast. Clinical symptoms were recorded pre-dose and at set times post-dose.
23 Plasma and erythrocyte cholinesterase activity were assayed pre-dose and at set times post-dose
24 as were clinical chemistry and hematology parameters. One subject in the 0.3 mg/kg group

reported a headache at one hour. The only dose-related clinical sign was an increase in saliva in the 0.3 mg/kg group at 1-hour post dose. Dose-related inhibition of plasma and erythrocyte cholinesterase activity peaked at 45 minutes post dose. At that time, plasma cholinesterase activity in the 0.1, 0.2, and 0.3 mg/kg dose groups were -5.6, -11.5, and -21% of baseline. Respective decreases in erythrocyte cholinesterase activity were -2.5, -20, and -35%. However, erythrocyte acetylcholinesterase activity in the 0.1 and 0.2 mg/kg groups was inhibited by 19% (75 minutes post dose) and 28% (90 minutes post dose), respectively. The Human Studies Review Board (HSRB 2006) reviewed the study and found it met ethical considerations.

3. ANIMAL TOXICITY DATA

Using standard protocols, methomyl has been tested for ocular and dermal irritation in the rabbit and dermal sensitization with the guinea pig (Kaplan and Sherman 1977; U.S. EPA 1998). In studies summarized by U.S. EPA (1998), methomyl induced transient corneal opacity of the rabbit eye following instillation of 10 mg, but failed to induce skin irritation or skin sensitization. A female rabbit treated with 15 mg technical methomyl in the eye died within 20 minutes with typical cholinergic symptoms indicative of neurotoxicity. The oral LD_{50} in male and female rats was 20 mg/kg, and the dermal LD_{50} in rabbits as an aqueous suspension was >5000 mg/kg (Kaplan and Sherman 1977).

3.1. Acute Toxicity

All inhalation studies were conducted with rats (Table 2). Studies were conducted with methomyl vapor (one study), dust/powder (one study), or mist/aerosol (three studies). Methomyl has a low vapor pressure and vapor atmospheres high enough to cause clinical signs are difficult to sustain. In the vapor study, two groups of six male ChR-CD rats inhaled methomyl vapor at nominal concentrations of 36 or 44 mg/m^3 for 4 hours (DuPont 1966a). The vapor was generated by passing dry air through a tube of the test material. Exposures were conducted in a whole-body 16-L chamber. No deaths occurred. Clinical signs during exposure included face-pawing, slight salivation and lacrimation, hyperemia, hyperpnea, and mild dyspnea in all rats in the 44 mg/m^3 group and in one of six rats in the 36 mg/m^3 group. Mild hyperpnea and exophthalmos lasted up to 30 minutes post-exposure. No gross effects attributed to exposure were seen at necropsy. Microscopically, lung and tracheal tissue were similar to those of control rats in other studies conducted by the same laboratory. The atmospheres were characterized as one-tenth of the approximate lethal concentration and almost six times the saturated vapor pressure of 7 x 10^{-4} mm Hg at 35ºC cited in this study.

Fifteen male Wistar rats inhaled 9.9 mg/m^3 methomyl dust/powder for 4 hours in a 0.43 m^3 exposure chamber (Ta'naka et al. 1987). The powder concentration was monitored with a light scattering system. The mass median aerodynamic diameter of the particles was 4.4±2.9 μm. Rats were sacrificed at 0, 1, 2, 4, or 20 hours post-exposure, and erythrocyte and plasma cholinesterase activities were measured by the Ellman method at each time point. Plasma acetylcholinesterase activity was inhibited at 0, 1, 2, and 4 hours by approximately 50% (values read from graph), but had recovered by 20 hours post-exposure. Erythrocyte acetylcholinesterase activity was either not inhibited or only slightly inhibited depending on erythrocyte preparation procedures. Erythrocytes were washed three times with isotonic saline prior to hemolysis. Repeated washing may have removed some of the enzyme from the cell

membrane. Histologic findings in major organs were unremarkable. Clinical signs, if present, were not described.

Groups of five male and five female CrL:CD rats inhaled methomyl mist, nose-only, at concentrations of 137, 181, 182, 232, or 326 mg/m^3 for 4 hours (DuPont 1991; Panepinto 1991). The study adhered to U.S. EPA's Good Laboratory Practice (GLP) standards. Purity of the test material was 97.7%. Atmospheres were generated by suspending the milled solid material at a concentration of 3% in water and maintaining suspensions with a nebulizer. Aerosol atmospheres were measured with a gravimetric method. Mass median aerodynamic diameter of the particles ranged from 1.3 to 3.8 µ. Surviving rats were observed for 14 days post-exposure. There was a moderate weight loss in most rats during the first two days post-exposure. No rats died at the two lower concentrations. In these two groups, clinical signs observed during the first two days post-exposure included diarrhea and stained, ruffled, or wet fur, and discharge from the eyes or nose, the latter in a few males on days 1, 2, or 3. Mortalities were 1/10, 6/10, and 7/10 at the three highest concentrations, with mortality comparable between the sexes. Clinical signs among rats that died included those seen at the lower concentrations and in addition, abnormal gait, tremors, hyperactivity, hyperreactivity, muscle fasciculations, and hunched posture. The calculated 4-hour LC_{50} was 258 mg/m^3.

Groups of six male ChR-CD rats inhaled an aerosol of methomyl, whole-body, for 4 hours (DuPont 1966b). Concentrations were 250, 300, 350, and 560 mg/m^3. The atmospheres were generated by melting 20 grams of the test material followed by aerosolization of the heated compound with a nebulizer in a heated air stream. A second unheated air stream carried the aerosol into a 16-L exposure chamber containing the rats. Aerosol particle size ranged from 1.1-6.8 µ. Gross and histologic examinations were performed on selected rats. No rats died following the 4-hour exposure to 250 mg/m^3. The approximate LC_{50} was 300 mg/m^3. Clinical signs observed in dying rats were ptosis, face-pawing, lacrimation and salivation, moderate to heavy dyspnea, gasping, hyperemia with slight cyanosis, red discharge from the nostrils, and tremor with mild convulsions followed by terminal convulsions. Similar, but milder signs were seen at the non-lethal concentrations. Gross effects at necropsy included slight pulmonary hyperinflation with irregular congestion.

Groups of six male rats (strain not identified) inhaled an aqueous spray mist of methomyl, whole-body in a 16 m^3 chamber for 4 hours (DuPont 1967; Hornberger 1967; summarized in Kaplan and Sherman 1977). The respirable mist of average mass median diameter of 3.2-6.3 µ in the different trials was generated with a nebulizer. Atmospheres were measured gravimetrically. Concentrations were 97, 130, 333, 420, 540, 600, and 950 mg/m^3. Respective mortality was 0/6, 0/6, 1/6, 2/6, 5/6. 5/6, and 6/6. Clinical signs during the first minutes of exposure included rapid tremors, irregular breathing, increased grooming, salivation, and lacrimation. Irregular breathing was observed throughout the exposure. Deaths occurred only during the first 150 minutes of the 4-hour exposure. Surviving rats were maintained for two weeks during which time they displayed normal growth. A second study in the same report indicated that all six rats exposed head-only to 450 mg/m^3 generated as non-respirable droplets >100 µ in size died within 18 minutes. All exposed areas were wet.

TABLE 2. Acute Toxicity of Methomyl in Rats Exposed for 4 Hours			
Concentration (mg/m^3)	**Effect or Mortality**	**LC_{50} (mg/m^3)**	**Reference**
Vapor			
36 44	No mortality, face-pawing, slight salivation and lacrimation hyperemia, hyperpnea, mild dyspnea (1 of 6 animals) No mortality; above clinical signs in 6 of 6 rats	—	DuPont 1966a
Powder			
9.9	Transient plasma acetylcholinesterase activity inhibition (50%); little or no effect on erythrocyte acetylcholinesterase activity[a]	—	Ta'naka et al. 1987
Mist/Liquid Aerosol			
137 181 182 232 326	No mortality; diarrhea, ruffled fur No mortality; diarrhea, ruffled fur Mortality: 1 of 10 rats; stained fur Mortality: 6 of 10 rats; clinical signs including tremors in one female (day 1) Mortality: 7 of 10 rats; tremors, clinical signs including tremors in one male and one female (day 1)	258	DuPont 1991; Panepinto 1991
250 300 350 560	No mortality Mortality: 3 of 6 rats Mortality: 6 of 6 rats Mortality: 6 of 6 rats	300	DuPont 1966b
97 130 333 420 540 600 950	No mortality No mortality Mortality of 1 of 6 rats Mortality of 2 of 6 rats Mortality of 5 of 6 rats Mortality of 5 of 6 rats Mortality of 6 of 6 rats	450	DuPont 1967; Hornberger 1967

[a] The values for erythrocyte cholinesterase activity inhibition are questionable due to repeated washing of the cells.

3.2. Repeat-Exposure Studies

Ten male Wistar rats inhaled 14.8 mg/m^3 methomyl powder for 4 hours/day, 5 days/week for 3 months (Ta'naka et al. 1987). The powder concentration in the chamber was monitored with a light scattering system. The mass median aerodynamic diameter of the particles was 4.4±2.9 μ. Rats were weighed and sacrificed 4 hours after the last exposure, and erythrocyte and plasma cholinesterase activity were measured by the Ellman method. Major organs were weighed and examined microscopically and lungs were analyzed for lipid concentration. No statistically significant differences were found between the control and exposed groups in body or organ weights. At 4 hours post-exposure, mean plasma cholinesterase activity was inhibited by 28% and erythrocyte acetylcholinesterase activity was inhibited by 8%. There were no histopathologic changes in major organs and no accumulation of lipids in the lungs. The authors concluded that the effects of methomyl exposure are not cumulative.

For comparison to the inhalation route, a repeat exposure dermal study and a repeat exposure dietary toxicity study are provided. In a 21-day dermal toxicity study with New Zealand rabbits, the NOAEL was 90 mg/kg/day, the highest dose tested. There were no mortalities and no toxicologically significant inhibition of plasma, erythrocyte, or brain cholinesterase activity. In a 90-day feeding study with CD rats, the NOAEL was 6.25 mg/kg/day (summarized in U.S. EPA 1998), based on lower body weight gain in both sexes and erythroid hyperplasia in male rats at the next higher dose of 12.5 mg/kg/day. There were no mortalities and no inhibition of cholinesterase activity.

3.3. Neurotoxicity

Acute toxicity studies (see Section 3.1) showed that methomyl is neurotoxic. Although no clinical signs were reported in rats inhaling methomyl dust at 9.9 mg/m^3 for 4 hours (Ta'naka et al. 1987), higher concentrations including vapor concentration as low as 36 mg/m^3 and dust aerosols as low as 137 mg/m^3 induced clinical signs consistent with cholinesterase activity inhibition (See Section 4.1 for the mode of action of carbamate insecticides).

In a study of gavage administration of methomyl to male Long-Evans rats, motor activity in the period 15 minutes to 35 minutes post-dosing was a reliable predictor of brain and erythrocyte cholinesterase activity inhibition (McDaniel et al. 2007). Doses were 0.10, 0.25, 0.60, 1.25, or 2.50 mg/kg. Cholinesterase activity inhibition and related decreased motor activity were dose dependent above 0.10 mg/kg. Brain and erythrocyte cholinesterase activity were similarly inhibited at the higher doses. At 2.50 mg/kg, vertical motor activity was 20% of the control value and brain and erythrocyte cholinesterase were 50-60% of the control value.

3.4. Developmental/Reproductive Toxicity

No inhalation studies were conducted that addressed the developmental/reproductive toxicity of methomyl. Reproductive and developmental toxicity studies that used the oral route of administration were reviewed by Kaplan and Sherman (1977) and U.S. EPA (1998). In developmental studies, pregnant CD rats were administered methomyl at concentrations of 0, 4.9, 9.4, or 33.9 mg/kg/day on gestation days 6-19. The maternal LOAEL was 33.9 mg/kg/day based on decreased body weight gain and food consumption; the developmental NOAEL was 33.9 mg/kg/day. In a recent study, pregnant New Zealand rabbits were administered 0, 2, 6, or 16 mg/kg/day by stomach tube on gestation days 7-19. The maternal LOAEL was 16 mg/kg/day based on mortality and clinical signs indicating neurotoxicity. The developmental NOAEL was 16 mg/kg/day, the highest dose tested. In a two-generation reproduction study, the F_0 generation of Sprague-Dawley rats was fed methomyl at dose levels of 0, 3.75, 30, or 60 mg/kg/day. The F_1 offspring were treated at the same dosage. The parental NOAEL and LOAEL were 3.75 and 30 mg/kg/day, respectively; the LOAEL was based on decreased body weight and food consumption and altered hematology parameters. The offspring NOAEL and LOAEL were also 3.75 and 30 mg/kg/day, based on a decrease in mean number of pups and decreased pup body weight at 30 mg/kg/day. The U.S. EPA concluded that the data provided no indication of increased sensitivity of rats or rabbits to *in utero* or postnatal exposure to methomyl. There was no assessment of functional development.

3.5. Genotoxicity

Methomyl has been tested in a range of *in vitro* genotoxicity assays (IPCS 1996; 2001; U.S. EPA 1998; HSDB 2009). Most assays were conducted both with and without metabolic activation. Methomyl did not cause mutagenicity or primary DNA damage in bacterial or mammalian cells. Assay results were negative for point mutations in *Salmonella typhimurium* (TA98, TA100, TA1535, TA1537, and TA1538) and *Escherichia coli* WP2 uvrA. Results were negative for DNA damage in *E. coli; Bacillus subtilis; Saccharomyces cerevisiae*; human lung fibroblasts, lymphocytes, and skin cells; and rat hepatocytes. Methomyl assay results were negative in gene mutation tests with Chinese hamster V79 and ovary cells and in a sister-chromatid exchange assay in human lymphocytes. Methomyl showed cytogenetic potential in human lymphocytes *in vitro* as indicated by an increase in micronuclei and chromosomal aberrations.

3.6. Chronic Toxicity/Carcinogenicity

Methomyl was tested for chronic toxicity and carcinogenicity in two-year dietary studies with male and female beagle dogs, male and female CD rats, and male and female CD-1 mice (Kaplan and Sherman 1977; ACGIH 1992; U.S. EPA 1998). No increased tumor incidence occurred in any study. Dogs fed ≥10 mg/kg/day showed microscopic changes in the kidneys, spleen and liver. The NOAEL for dogs was 5 mg/kg/day. The NOAEL for rats was 5 mg/kg/day based on depressed body weight gain in both sexes at higher doses. No effects were observed in mice at the highest dose, 120 mg/kg/day. The U.S. EPA has classified methomyl in Group E, not likely to be carcinogenic to humans via relevant routes of exposure. The carcinogenicity of methomyl has not been evaluated by the International Agency for Research on Cancer.

3.7. Summary

Acute inhalation lethality studies were conducted with the rat. The 4-hour LC_{50} values for rats ranged from 258 to 510 mg/m^3 for methomyl suspended as a mist or aerosol (DuPont 1966b ; Kaplan and Sherman 1977; DuPont 1991). During exposure rats showed signs indicative of cholinesterase activity inhibition. In another study, clinical signs were either not described or not observed in rats exposed to 9.9 mg/m^3 of dust for 4 hours (Ta'naka et al. 1987). Plasma cholinesterase activity inhibition was greater (50%) following the acute exposure than following exposure to 14.8 mg/m^3 for 4 hours/day, 5 days/week for 3 months (28%). A study with the saturated vapor of methomyl (36 or 44 mg/m^3) did not attain concentrations high enough to elicit mortality, although clinical signs indicative of acetylcholinesterase activity inhibition were evident (DuPont 1966a).

No evidence of teratogenicity was observed in either rats or rabbits treated in the diet with methomyl (rats, up to 60 mg/kg/day) even in the presence of maternal toxicity. A range of genotoxicity assays provided mostly negative results. In 2-year feeding studies with the dog, rat, and mouse at concentrations that approached toxic, there was no evidence of a tumorigenic response.

4. SPECIAL CONSIDERATIONS

4.1. Metabolism and Disposition

Inhalation studies with methomyl that addressed metabolism were not located. Oral absorption is near complete (95-98%) and most of the compound is eliminated in 24 hours (ACGIH 1992). The *N*-methyl carbamates do not have a port of entry effect, are expected to be rapidly absorbed, and do not require activation (U.S. EPA 2007). Unlike some organophosphate pesticides that are metabolized by A-esterases which show great inter-individual variation, the biotransformation of the carbamate pesticides does not involve these esterases. Metabolism was outlined following oral dosing of male and female CD rats (Harvey et al. 1973) and male and female Sprague-Dawley rats (Jaglan and Arnold 1984) with radiolabeled methomyl. *Syn*-methomyl, the form of methomyl that is produced and sold, is hydrolyzed at the ester linkage to give rise to an oxime which is metabolized to CO_2. Approximately 34-54% of the label is eliminated in the urine as the oxime or conjugates of the oxime and 20-39% is eliminated as expired CO_2 and acetonitrile (ratio 2:1). The major urinary metabolite was the mercapturic acid derivative of methomyl (IPCS 1996). Acetonitrile is likely formed following partial conversion of the *syn*-isomer to the *anti*-isomer prior to hydrolysis at the ester linkage. Two to three percent of the radiolabel is eliminated in the feces, and less than 10% remains in the carcass.

Metabolism pathways in the monkey were similar to those of the rat, but with differences in the percent of metabolites formed (IPCS 1996). Following administration of an oral dose of 5 mg/kg body weight, expired air contained 32-38% of the dose as CO_2 and 4-7% of the dose as acetonitrile. Eighteen metabolites were characterized in the urine, with no metabolite representing more than 4% of the dose. Most of the metabolites were eliminated in the first 24 hours post-exposure.

In addition to hydrolysis of the carbamate ester linkage, several oxidation and reduction reactions involving cytochrome P450-related monooxygenases can form polar metabolites (Costa 2008). Methyl and *N*-methyl side chains undergo hydroxylation, followed by conjugation with glucuronide or sulfate derivatives.

4.2. Mechanism of Toxicity

Methomyl is an *N*-methyl carbamate insecticide. The mode of action of carbamate pesticides involves cholinesterase inhibition (U.S. EPA 2007; Costa 2008). Carbamic acid esters attach to the serine hydroxyl group of the reactive site of acetylcholinesterase, the enzyme responsible for the destruction and termination of the biological activity of the neurotransmitter acetylcholine. When unbound acetylcholine accumulates at the cholinergic nerve endings, there is continual stimulation of electrical activity. The resulting signs of toxicity resulting from stimulation of the muscarinic receptors of the parasympathetic autonomic nervous system are manifest as increased secretions, bronchoconstriction, miosis, gastrointestinal cramps, diarrhea, urination, and bradycardia. Stimulation of the parasympathetic junctions of the autonomic nervous system as well as the junctions between nerves and muscles cause tachycardia, hypertension, muscle fasciculation, tremors, muscle weakness, and flaccid paralysis. Signs and symptoms resulting from effects on the central nervous system include restlessness, emotional lability, ataxia, lethargy, mental confusion, loss of memory, generalized weakness, convulsion, cyanosis, and coma.

Inhibition of acetylcholinesterase activity is transient and reversible because there is rapid reactivation of the carbamylated enzyme in the presence of water. Maximum inhibition typically occurs between 15 and 45 minutes after exposure. Carbamates also inhibit butylcholinesterase, the primary form found in blood plasma. The toxicological significance of butylcholinesterase activity inhibition is unknown. Acetylcholinesterase is the primary form of cholinesterase found in erythrocytes and is present at neuromuscular and nerve-nerve junctions. A review of studies submitted to U.S. EPA (2007) for pesticide registration shows that clinical signs and behavioral effects are not evident below 10% cholinesterase activity inhibition, but in most studies a 10% brain cholinesterase activity inhibition can be reliably detected. Due to human variability, it is difficult to measure erythrocyte acetylcholinesterase activity inhibition of <20% (U.S. EPA 2000). At greater than 30% erythrocyte or 50% plasma cholinesterase activity inhibition, workers are withdrawn from pesticide application areas (U.S. EPA 2000).

In adult Long-Evans rats dosed orally with 3 mg/kg methomyl, brain and erythrocyte acetylcholinesterase activity were approximately 47 and 33% of control values, respectively, at 0.5 hours; activity in both compartments returned to the level of control values by 4 hours post-dosing (Padilla et al. 2007).

4.3. Structure-Activity Relationships

Organophosphate and carbamate pesticides have a common mode of action (Costa 2008). Compared to organophosphate ester pesticides, the carbamic acid esters are poor substrates for cholinesterase-type enzymes. The carbamic acid esters which attach to the reactive site of acetyl cholinesterase undergo fairly rapid hydrolysis; the carbamylated (inhibited) enzyme is decarbamylated fairly rapidly with the generation of the free, active enzyme.

Information is available on the relative oral toxicity of three *N*-methyl carbamate pesticides (HSRB 2006; U.S. EPA 2007). The endpoints were brain and erythrocyte cholinesterase activity inhibition in the rat and erythrocyte cholinesterase activity inhibition in humans. Raw data consisting of erythrocyte cholinesterase activity inhibition were not provided for all three chemicals, but relative toxicity can be derived from the benchmark doses (BMD_{10} and $BMDL_{10}$) calculated by U.S. EPA (2007) from a range of oral doses (Table 3). For methomyl and oxamyl, rat data on brain and erythrocyte cholinesterase activity are presented by McDaniel et al. (2007). If oxamyl is assigned a relative oral potency factor of 1, then the oral potencies of aldicarb and methomyl are 4 and 0.67, respectively (U.S. EPA 2007).

TABLE 3. Adult Rat and Human BMD_{10} and $BMDL_{10}$ Values for Cholinesterase Activity Inhibition with *N*-Methyl Carbamate Pesticides (Oral Dosing)

Chemical	Rat				Human	
	Brain		Erythrocyte		Erythrocyte	
	Benchmark Dose (mg/kg)	Half-life (h)	Benchmark Dose (mg/kg)	Half-life (h)	Benchmark Dose (mg/kg)	Half-life (h)
Aldicarb	BMD_{10}: 0.052 $BMDL_{10}$: 0.035	1.5	BMD_{10}: 0.031 $BMDL_{10}$: 0.020	1.1	BMD_{10}: 0.016 $BMDL_{10}$: 0.013	1.7
Methomyl	BMD_{10}: 0.486 $BMDL_{10}$: 0.331	1.0	BMD_{10}: 0.204 $BMDL_{10}$: 0.112	0.8	BMD_{10}: 0.040 $BMDL_{10}$: 0.028	1.6
Oxamyl	BMD_{10}: 0.165	0.9	BMD_{10}: 0.278	0.8	BMD_{10}: 0.083	2.4

	$BMDL_{10}$: 0.127		$BMDL_{10}$: 0.158		$BMDL_{10}$: 0.068	

Benchmark dose data for brain cholinesterase activity for aldicarb and oxamyl are the average of male and female rat values.
The $BMDL_{10}$ for 10% brain cholinesterase activity inhibition was used as the point of departure for U.S. EPA (2007) risk assessment.
Source: Table 1.B-9, page 50, U.S. EPA 2007.

4.4. Other Relevant Information

4.4.1. Species Variability

Inhalation studies were conducted only with rats. Subchronic and chronic feeding studies with the rat, mouse, and dog showed little difference in toxicity among the species. The extent of hydrolysis of carbamate ester insecticides varies between species, ranging from 30 to 95%, and is chemical specific (Costa 2008). Baseline erythrocyte acetylcholinesterase activity is higher in humans than in other species (Ellin 1981). The U.S. EPA Office of Pesticide Programs (U.S. EPA 2007) compared the toxicity (endpoint cholinesterase activity inhibition) of three *N*-methyl carbamate pesticides, oxamyl, methomyl, and aldicarb, using oral dosing in humans and in juvenile and adult rats. Most data were available for oxamyl which was used as the index chemical. Benchmark doses were calculated for brain and erythrocyte acetylcholinesterase activity inhibition in juvenile and adult rats and erythrocyte cholinesterase activity inhibition in humans. Based on the comparative erythrocyte acetylcholinesterase activity inhibition for equal oral doses in adult rats and humans, the U.S. EPA calculated a chemical-specific interspecies uncertainty factor of 5 for methomyl. For most of these chemicals, the interspecies uncertainty factor is used for all routes of exposure. The half-lives for regeneration of erythrocyte acetylcholinesterase activity in rats and humans were 0.8 and 1.6 hours, respectively.

4.4.2. Susceptible Populations

Humans are known to vary by gender, age, and genetic make-up in their sensitivity to cholinesterase inhibitors. The erythrocyte acetylcholinesterase activity of adults (153±24 activity units; substrate acetylthiocholine) is greater than that of healthy newborn infants (97±15 activity units) by a factor of 1.6 (Herz et al. 1975). The U.S. EPA (2007) identified infants and juveniles as the population most sensitive to the anticholinesterase effects of *N*-methyl carbamate pesticides. In so doing, they evaluated the relative sensitivity of juvenile and adult rats to *N*-methyl carbamate pesticides including methomyl. Developmental neurotoxicity studies showed that protection of the rat dam against cholinesterase activity inhibition is protective against pup acetylcholinesterase activity inhibition *in utero*. Therefore, intraspecies uncertainty factors were based on relative juvenile and adult rat sensitivity to brain acetylcholinesterase activity inhibition. Based on comparative brain acetylcholinesterase activity inhibition in methomyl-treated post-natal day 11 juvenile rats and adult rats, the U.S. EPA calculated a Food Quality Protection Act (FQPA) uncertainty factor for children of 3.05 . This uncertainty factor corresponds to an AEGL intraspecies uncertainty factor. The estimated half-life for recovery of brain acetylcholinesterase activity in juvenile rats was 0.4 hours (U.S. EPA 2007).

4.4.3. Concentration-Exposure Duration Relationship

No data were available for evaluating the relationship between ambient concentrations of methomyl and exposure duration for a single endpoint. The concentration-time relationship for a

single endpoint for many irritant and systemically acting vapors and gases may be described by $C^n \times t = k$. In the absence of empirical data, the time scaling factors of n = 3 and n = 1 are used to scale to shorter and longer exposure durations respectively (NRC 2001).

4.4.4. Concurrent Exposure Issues

Dermal absorption may occur, but toxicity is low compared to inhalation exposure as indicated by a dermal LD_{50} of >5000 mg/kg in rabbits (Kaplan and Sherman 1977). Concurrent exposure to other N-methyl carbamates in proportion to their potency indicates that they follow a dose-additive model of brain cholinesterase inhibition (Padilla et al. 2006; U.S. EPA 2007).

5. DATA ANALYSIS FOR AEGL-1

5.1. Summary of Human Data Relevant to AEGL-1

No human inhalation studies were located in the available literature. No occupational monitoring data were presented by U.S. EPA (1998).

5.2. Summary of Animal Data Relevant to AEGL-1

Ta'naka et al. (1987) exposed rats to an atmosphere of methomyl powder for 4 hours. Rats inhaling 9.9 mg/m^3 for 4 hours showed plasma cholinesterase activity inhibited by approximately 50%, but erythrocyte acetylcholinesterase activity was reported as either not affected or only slightly inhibited. No clinical signs were described. In the human oral dosing study (McFarlane et al. 1998), plasma cholinesterase activity inhibition was accompanied by a corresponding inhibition in erythrocyte acetylcholinesterase activity. These results raise some questions about the rat inhalation study in which plasma but not erythrocyte activity was significantly inhibited.

5.3. Derivation of AEGL-1

The study of Ta'naka et al. (1987) in which rats inhaled 9.9 mg/m^3 methomyl powder for 4 hours was considered inadequate for derivation of AEGL-1 values. The study did not appear to accurately report erythrocyte acetylcholinesterase activity inhibition. In addition, the presence or absence of clinical signs was not clearly stated. No other studies addressed effects defined by the AEGL-1. Therefore, AEGL-1 values are not recommended.

TABLE 4. AEGL-1 Values for Methomyl

10-min	30-min	1-h	4-h	8-hour
Not recommended	Not recommended	Not recommended	Not recommended	Not recommended

Not recommended: absence of AEGL-1 values does not imply that exposure below AEGL-2 levels is without effect.

6. DATA ANALYSIS FOR AEGL-2

6.1. Summary of Human Data Relevant to AEGL-2

No human inhalation studies were located in the available literature.

6.2. Summary of Animal Data Relevant to AEGL-2

No inhalation studies with methomyl dust that addressed effects consistent with the definition of the AEGL-2 were reported in the available literature. One of six rats exposed to a nominal concentration of 36 mg/m^3 of methomyl vapor showed mild signs of cholinesterase activity inhibition. These signs included face-pawing, slight salivation and slight lacrimation and mild dyspnea (DuPont 1966a). At the higher concentration of 44 mg/m^3, all six rats showed these clinical signs, and the signs were more severe, but recovery within 14 days was complete. Higher vapor atmospheres could not be attained.

The lethality study with an aqueous aerosol of methomyl (DuPont 1991; Panepinto 1991), showed a steep concentration-response relationship. No mortality occurred at 181 mg/m^3, but six of ten rats died at 232 mg/m^3.

6.3. Derivation of AEGL-2

Lethality data show that methomyl has a steep concentration-response curve. In the absence of other relevant data, AEGL-2 values for chemicals with a steep concentration-response curve may be derived by dividing the AEGL-3 values by 3 (NRC 2001). For consistency with the study used to derive AEGL-3 values, the AEGL-2 values were derived by dividing the AEGL-3 values by 3. Values are summarized in Table 5, calculations are in Appendix A, and a category graph of the toxicity data in relation to AEGL values is in Appendix B.

TABLE 5. AEGL-2 Values for Methomyl

10-min	30-min	1-h	4-h	8-h
7.0 mg/m^3	7.0 mg/m^3	5.7 mg/m^3	3.3 mg/m^3	1.7 mg/m^3

The vapor study of DuPont (1966a) supports the values derived by dividing the AEGL-3 by 3. Inhalation exposure of rats to of 44 mg/m^3 over a period of 4 hours induced clinical signs consistent with the definition of the AEGL-2. Dividing the 4-hour 44 mg/m^3 value by 15 (see Section 7.3 for discussion of uncertainty factors) and time-scaling using the default values of 3 and 1 for shorter and longer exposure durations, respectively, results in 10-minute through 8-hour values of 5.9, 5.9, 4.7, 2.9, and 1.5 mg/m^3. These values are comparable with the derived values shown in Table 5. The fact that no rats died at the lowest tested concentration of 137 mg/m^3 in the study by DuPont (1991) also supports the AEGL-2 values.

7. DATA ANALYSIS FOR AEGL-3

7.1. Summary of Human Data Relevant to AEGL-3

No human inhalation studies relevant to development of AEGL-3 values were located in the available literature.

7.2. Summary of Animal Data Relevant to AEGL-3

Three studies with methomyl as a mist or liquid aerosol addressed lethality in the rat. All studies were for 4 hours. Four-hour LC_{50} values were 258 mg/m^3 (DuPont 1991; Panepinto

1991), 300 mg/m^3 (DuPont 1966b), and 450 mg/m^3 (DuPont 1967; Hornberger 1967). Although performed at different times, the three studies by DuPont give consistent values. The 1991 GLP study by DuPont used both sexes of rats and provides good dose-response information. There was little difference in toxicity between the sexes. Tested concentrations were 137, 181, 182, 232, and 326 mg/m^3 and respective mortalities were 0/10, 0/10, 1/10, 6/10, and 7/10 rats.

7.3. Derivation of AEGL-3

The GLP study of DuPont 1991 (Panepinto 1991) was chosen as the basis for AEGL-3 values. In that study, male and female rats inhaled an aerosol of methomyl generated by suspending the solid in water. Benchmark concentrations were calculated (1) using all of the data and (2) deleting the highest value of 326 mg/m^3. Omitting the highest value provided a better mathematical fit of the data to a curve. With omission of the highest value, the calculated 4-hour $BMCL_{05}$ is 157.26 mg/m^3, and the BMC_{01} is 166.51 mg/m^3 (Appendix C). The NAC/AEGL committee generally uses the $BMCL_{05}$ as the estimate at which lethality is not likely to be observed (NRC 2001).

The 157.3 mg/m^3 value was divided by inter- and intraspecies uncertainty factors of 5 and 3.05, respectively, for a total of 15. The U.S. EPA (2007) derived an interspecies uncertainty factor of 5 for methomyl based on differences in modeled red blood cell values for acetylcholinesterase activity inhibition between the rat and humans (See section 4.4.1). Based on comparative brain cholinesterase activity inhibition in post-natal day 11 juvenile rats and adult rats, the U.S. EPA calculated an uncertainty factor of 3.05 to protect sensitive young (See section 4.4.2). The combined uncertainty factor is 15. The data set with application of an uncertainty factor that protects sensitive juveniles provides a reasonable estimate of lethality. The resulting value of 10.49 mg/m^3 (157.3 mg/m^3/15) was time-scaled ($C^n \times t = k$) from the 4-hour data point to 1 hour and to 30 minutes using the default n value of 3 and to the 8-hour exposure duration using the default value of 1 (NRC 2001). Because the key study was 4 hours, the 10-minute value was set equal to the 30-minute value. Values are summarized in Table 6, calculations are in Appendix A, and a category graph of the toxicity data in relation to AEGL values is in Appendix B.

TABLE 6. AEGL-3 Values for Methomyl

10-min	30-min	1-h	4-h	8-h
21 mg/m^3	21 mg/m^3	17 mg/m^3	10 mg/m^3	5.2 mg/m^3

The $BMCL_{05}$ value of 157.3 mg/m^3 is higher than the lowest concentration causing no mortality (137 mg/m^3) in the key study. No deaths occurred at 181 mg/m^3, but this value is virtually identical with the 182 mg/m^3 value that resulted in the death of 1 of 10 rats.

8. SUMMARY OF AEGLs

8.1. AEGL Values and Toxicity Endpoints

AEGL values are summarized in Table 7. Derivations are summarized in Appendix D.

TABLE 7. Summary of AEGL Values for Methomyl					
Classification	Exposure Duration				
	10-min	30-min	1-h	4-h	8-h
AEGL-1 (Nondisabling)	Not recommended	Not recommended	Not recommended	Not recommended	Not recommended
AEGL-2 (Disabling)	7.0 mg/m^3	7.0 mg/m^3	5.7 mg/m^3	3.3 mg/m^3	1.7 mg/m^3
AEGL-3 (Lethal)	21 mg/m^3	21 mg/m^3	17 mg/m^3	10 mg/m^3	5.2 mg/m^3

Not recommended: absence of AEGL-1 values does not imply that exposure below AEGL-2 levels is without effect.

8.2. Comparison with Other Standards and Guidelines

Standards and guidelines for methomyl are listed in Table 8. The American Conference of Government Industrial Hygienists (ACGIH 1992) Threshold Limit Value-Time Weighted Average (TLV-TWA) is 2.5 mg/m^3. Although far less than the no-adverse-effect-level identified in animal studies, this value incorporates a margin of safety in view of doses associated with human poisoning. This 8-hour value is for healthy adults, whereas the lower AEGL-2 value of 1.7 mg/m^3 is protective of infants and children. The ACGIH has derived a Biological Exposure Index (BEI) for workers based on erythrocyte cholinesterase activity of acetylcholinesterase inhibiting chemicals (ACGIH 2008). The value is ≤70% of an individual's baseline red blood cell acetylcholinesterase activity.

TABLE 8. Standards and Guidelines for Methomyl					
Guideline	Exposure Duration				
	10 min	30 min	1 h	4 h	8 h
AEGL-1	Not recommended	Not recommended	Not recommended	Not recommended	Not recommended
AEGL-2	7.0 mg/m^3	7.0 mg/m^3	5.7 mg/m^3	3.3 mg/m^3	1.7 mg/m^3
AEGL-3	21 mg/m^3	21 mg/m^3	17 mg/m^3	10 mg/m^3	5.2 mg/m^3
ERPG-1 (AIHA)[a]			—		
ERPG-2 (AIHA)			—		
ERPG-3 (AIHA)			—		
IDLH (NIOSH)[b]		—			
REL-TWA (NIOSH)[c]					2.5 mg/m^3
OSHA PEL (NIOSH)[d]					—
TLV-TWA (ACGIH)[e]					2.5 mg/m^3
MAK (Germany)[f]					—
MAC (The Netherlands)[g]					2.5 mg/m^3

Not recommended: absence of AEGL-1 values does not imply that exposure below AEGL-2 levels is without effect.

[a]ERPG (Emergency Response Planning Guidelines, American Industrial Hygiene Association
The ERPG-1 is the maximum airborne concentration below which it is believed nearly all individuals could be exposed for up to one hour without experiencing other than mild, transient adverse health effects or without perceiving a clearly defined objectionable odor.
The ERPG-2 is the maximum airborne concentration below which it is believed nearly all individuals could be exposed for up to one hour without experiencing or developing irreversible or other serious health effects or

symptoms that could impair an individual's ability to take protective action.
The ERPG-3 is the maximum airborne concentration below which it is believed nearly all individuals could be exposed for up to one hour without experiencing or developing life-threatening health effects.

[b]**IDLH (Immediately Dangerous to Life and Health, National Institute of Occupational Safety and Health)** represents the maximum concentration from which one could escape within 30 minutes without any escape-impairing symptoms, or any irreversible health effects.

[c]**NIOSH REL-TWA (National Institute of Occupational Safety and Health, Recommended Exposure Limits - Time Weighted Average)** (NIOSH 2008) is defined analogous to the ACGIH-TLV-TWA.

[d]**OSHA PEL-TWA (Occupational Safety and Health Administration, Permissible Exposure Limits - Time Weighted Average)** is defined analogous to the ACGIH-TLV-TWA, but is for exposures of no more than 10 hours/day, 40 hours/week.

[e]**ACGIH TLV-TWA (American Conference of Governmental Industrial Hygienists, Threshold Limit Value - Time Weighted Average)** (ACGIH 1992) is the time-weighted average concentration for a normal 8-hour workday and a 40-hour workweek, to which nearly all workers may be repeatedly exposed, day after day, without adverse effect.

[f]**MAK (Maximale Arbeitsplatzkonzentration [Maximum Workplace Concentration])** (Deutsche Forschungsgemeinschaft [German Research Association]) is defined analogous to the ACGIH-TLV-TWA.

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

8.3. Data Adequacy and Research Needs

Methomyl has a low vapor pressure and no suitable studies involving inhalation exposure of humans were located in the available literature. An oral dosing study with human volunteers addressed effects consistent with cholinesterase activity inhibition. Five inhalation studies with rats as the test species were sufficient for derivation of two AEGL levels for five timepoints. Studies involving comparisons of cholinesterase activity inhibition between juvenile and adult rats and between rats and humans addressed chemical-specific uncertainty factors. Metabolism pathways and mode of action are well understood.

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APPENDIX A: Derivation of Methomyl AEGLs

Derivation of AEGL-1 Values

No human inhalation studies or adequately reported animal studies were located that reported effects consistent with the definition of the AEGL-1. Therefore, AEGL-1 values are not recommended.

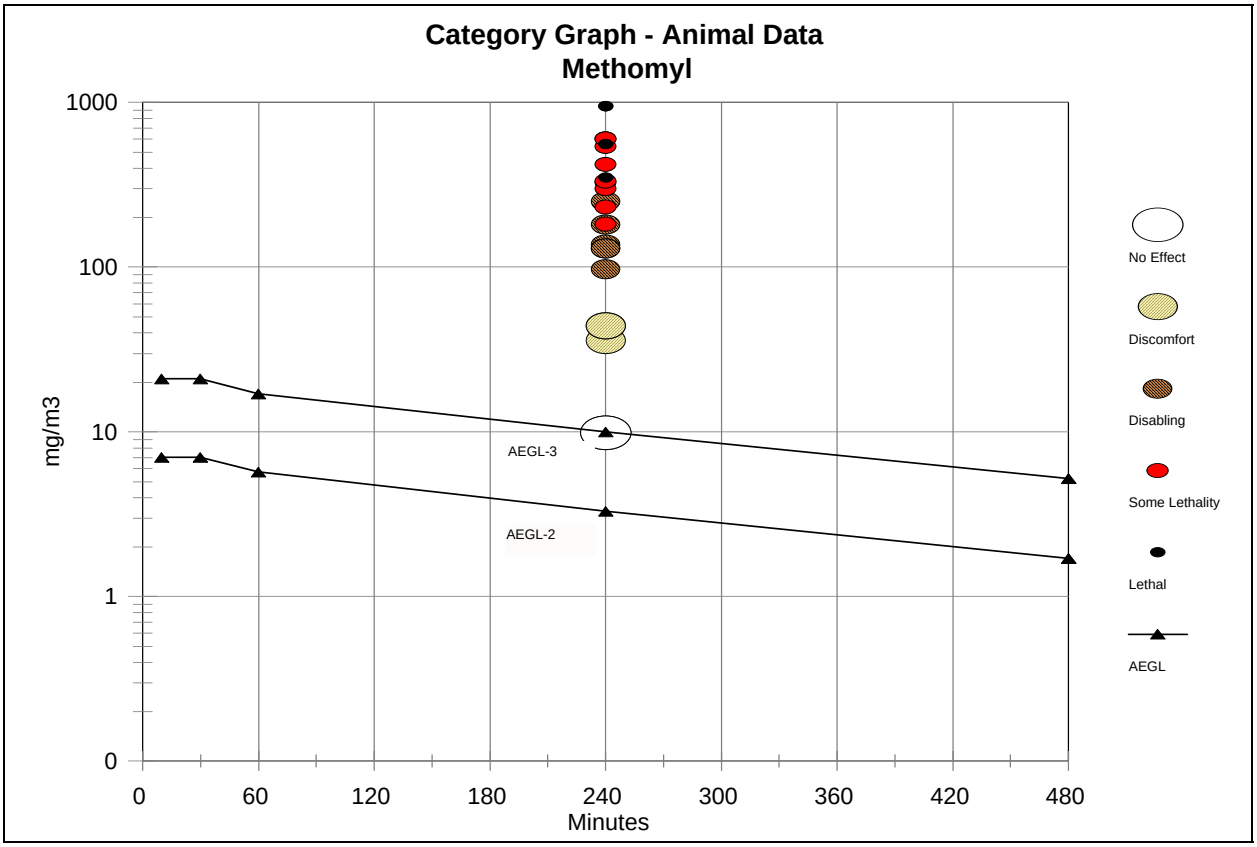
Derivation of AEGL-2 Values

Key Study:	DuPont. 1991. Acute Inhalation Toxicity Study with DPX-X1179-427 in Rats. Haskell Laboratory Report No. 678-91. Haskell Laboratory for Toxicology and Industrial Medicine, Newark, DE. (same as Panepinto 1991).
Toxicity endpoint:	AEGL-3 values divided by 3. The steep concentration-response line curve by the DuPont 1991 data justifies deriving AEGL-2 values by dividing the AEGL-3 values by 3 (NRC 2001).
Time scaling	See AEGL-3 derivation, next page
Uncertainty factors:	Total uncertainty factor: 15 (See AEGL-3 derivation, next page).
Calculations:	AEGL-3 values divided by 3
10-min AEGL-2:	$C = 21\ mg/m^3/3 = 7.0\ mg/m^3$
30-min AEGL-2:	$C = 21\ mg/m^3/3 = 7.0\ mg/m^3$
1-h AEGL-2:	$C = 17\ mg/m^3/3 = 5.7\ mg/m^3$
4-h AEGL-2:	$C = 10\ mg/m^3/3 = 3.3\ mg/m^3$
8-h AEGL-2:	$C = 5.2\ mg/m^3/3 = 1.7\ mg/m^3$

Derivation of AEGL-3 Values

Key Study:	DuPont. 1991. Acute Inhalation Toxicity Study with DPX-X1179-427 in Rats. Haskell Laboratory Report No. 678-91. Haskell Laboratory for Toxicology and Industrial Medicine, Newark, DE (same as Panepinto 1991).
Toxicity endpoint:	Threshold for lethality in rats at the $BMCL_{05}$ of 157.264 mg/m^3 calculated from the rat lethality data of DuPont (1991) (with omission of the highest value).
Time scaling	$C^n \times t = k$ where n = 3 and 1 for shorter and longer exposure durations, respectively
Uncertainty factors:	Total uncertainty factor: 15 Interspecies: 5 – Based on differences in modeled values for red blood cell cholinesterase activity inhibition between rats and humans following oral ingestion of methomyl (U.S. EPA 2007). Intraspecies: 3.05 – Based on comparative brain acetylcholinesterase activity inhibition in post-natal day 11 juvenile rats and adult rats exposed to methomyl (U.S. EPA 2007).
Modifying factor:	None applied
Calculations:	$(157.264\ mg/m^3/15)^3 \times 240$ minutes = $(27.66 \times 10^4)\ mg/m^3 \cdot min$ $(157.264\ mg/m^3/15)^1 \times 240$ minutes = 2516.22 $mg/m^3 \cdot min$
10-min AEGL-3:	C = 21 mg/m^3 (set equal to the 30-minute value because of the long study duration)
30-min AEGL-3:	$C = \sqrt[3]{(27.66 \times 10^4\ mg/m^3 \cdot min)} = 21\ mg/m^3$
1-h AEGL-3:	$C = \sqrt[3]{(27.66 \times 10^4\ mg/m^3 \cdot min)} = 17\ mg/m^3$
4-h AEGL-3:	$C = 157.264\ mg/m^3/15 = 10\ mg/m^3$
8-h AEGL-3:	$C = 2516.22\ mg/m^3 \cdot min/480\ min = 5.2\ mg/m^3$

APPENDIX B: Category Graph of AEGL Values and Toxicity Data



Data:

For Category: 0 = No effect, 1 = Discomfort, 2 = Disabling, SL = Some Lethality, 3 = Lethal				
Source	**Species**	**mg/m^3**	**Minutes**	**Category**
NAC/AEGL-1		NR	10	AEGL
NAC/AEGL-1		NR	30	AEGL
NAC/AEGL-1		NR	60	AEGL
NAC/AEGL-1		NR	240	AEGL
NAC/AEGL-1		NR	480	AEGL
NAC/AEGL-2		7.0	10	AEGL
NAC/AEGL-2		7.0	30	AEGL
NAC/AEGL-2		5.7	60	AEGL
NAC/AEGL-2		3.3	240	AEGL
NAC/AEGL-2		1.7	480	AEGL
NAC/AEGL-3		21	10	AEGL
NAC/AEGL-3		21	30	AEGL
NAC/AEGL-3		17	60	AEGL
NAC/AEGL-3		10	240	AEGL
NAC/AEGL-3		5.2	480	AEGL

Ta'naka et al. 1987	rat	9.9	240	0 (clinical signs either absent or not described)
DuPont 1966a	rat	36	240	1 (slight lacrimation, salivation, mild dyspnea in 1 of 6 rats)
	rat	44	240	1 (slight lacrimation, salivation, mild dyspnea in 6 of 6 rats)
DuPont 1966b	rat	250	240	2 (lacrimation, salivation, mild to moderate dyspnea, tremor, convulsions)
	rat	300	240	SL (death of 3 of 6 rats)
	rat	350	240	3 (death of 6 of 6 rats)
	rat	560	240	3 (death of 6 of 6 rats)
DuPont 1967; Hornberger 1967	rat	97	240	2 (tremors, lacrimation, salivation)
	rat	130	240	2 (tremors, lacrimation, salivation)
	rat	333	240	SL (death of 1 of 6 rats)
	rat	420	240	SL (death of 2 of 6 rats)
	rat	540	240	SL (death of 5 of 6 rats)
	rat	600	240	SL (death of 5 of 6 rats)
	rat	950	240	3 (death of 6 of 6 rats)
DuPont 1991	rat	137	240	2 (diarrhea, ruffled fur)
	rat	181	240	2 (diarrhea, ruffled fur)
	rat	182	240	SL (death of 1 of 10 rats))
	rat	232	240	SL (death of 6 of 10 rats)
	rat	326	240	SL (death of 7 of 10 rats)

Atmospheres of methomyl include powder (Ta'naka et al. 1987), vapor (DuPont 1966a), and mist or liquid aerosol (DuPont 1966b; 1967; 1991).
NR = not recommended. Absence of AEGL-1 values does not imply that exposure below AEGL-2 levels is without effect.

APPENDIX C: Benchmark Concentration Calculations

Calculation of $BMCL_{05}$
Rat lethality data (DuPont 1991; Panepinto 1991)

```
==============================================================
        Probit Model. (Version: 2.8;  Date: 02/20/2007)
        Input Data File: C:\BMDS\UNSAVED1.(d)
        Gnuplot Plotting File:  C:\BMDS\UNSAVED1.plt
                                          Thu Apr 23 09:12:05 2009
==============================================================

BMDS MODEL RUN
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

  The form of the probability function is:
  P[response] = Background + (1-Background)  CumNorm(Intercept+Slope*Log(Dose)),
  where CumNorm(.) is the cumulative normal distribution function

  Dependent variable = COLUMN3
  Independent variable = COLUMN1
  Slope parameter is not restricted

  Total number of observations = 5
  Total number of records with missing values = 0
  Maximum number of iterations = 250
  Relative Function Convergence has been set to: 1e-008
  Parameter Convergence has been set to: 1e-008

  User has chosen the log transformed model

   Default Initial (and Specified) Parameter Values
              Background     =         0
              intercept      =    -19.7475
                 slope       =     3.59092

    Asymptotic Correlation Matrix of Parameter Estimates
         The model parameter(s)  -background have been estimated at a boundary point, or
         have been specified by the user,   and do not appear in the correlation matrix )

                    intercept       slope
intercept               1              -1
  slope                -1               1

                        Parameter Estimates

                                                95.0% Wald Confidence Interval
     Variable       Estimate       Std. Err.    Lower Conf. Limit   Upper Conf. Limit
   background            0            NA
```

intercept	-42.1724	13.4943	-68.6207	-15.7242
slope	7.78999	2.52426	2.84253	12.7374

NA - Indicates that this parameter has hit a bound implied by some inequality constraint and thus has no standard error.

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-9.98095	5			
Fitted model	-10.6556	2	1.34926	3	0.7175
Reduced model	-20.2482	1	20.5345	4	0.0003916
AIC:	25.3112				

Goodness of Fit

Dose	Est._Prob.	Expected	Scaled Observed	Size	Residual
0.0000	0.0000	0.000	0	10	0.000
137.0000	0.0001	0.001	0	10	-0.025
181.0000	0.0468	0.468	0	10	-0.701
182.0000	0.0512	0.512	1	10	0.700
232.0000	0.6016	6.016	6	10	-0.011

Chi^2 = 0.98 d.f. = 3 P-value = 0.8055

Benchmark Dose Computation

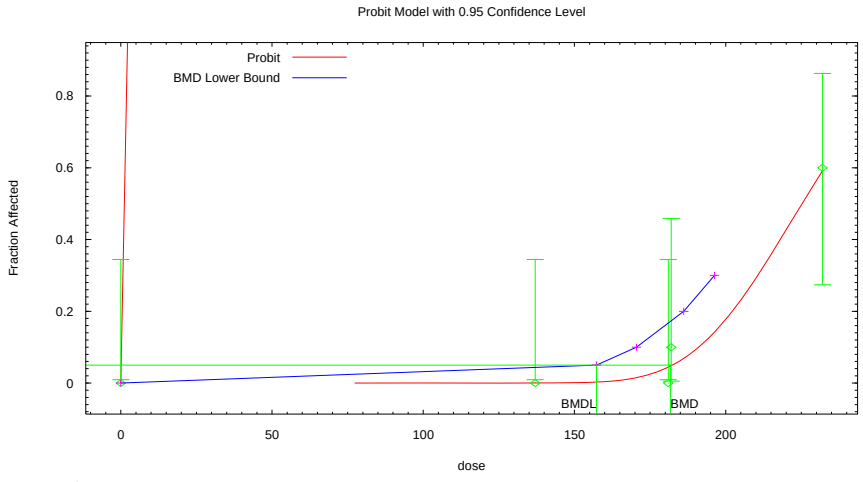
Specified effect = 0.05

Risk Type = Extra risk

Confidence level = 0.95

BMC_{05} = 181.73

$BMCL_{05}$ = 157.264



Calculation of $BMCL_{01}$
Rat lethality data (DuPont 1991; Panepinto 1991)

```
==============================================================
        Probit Model. (Version: 2.8;  Date: 02/20/2007)
        Input Data File: C:\BMDS\UNSAVED1.(d)
        Gnuplot Plotting File:  C:\BMDS\UNSAVED1.plt
                                                Thu Apr 23 09:21:15 2009
==============================================================

BMDS MODEL RUN
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

  The form of the probability function is:
       P[response] = Background  + (1-Background) *
      CumNorm(Intercept+Slope*Log(Dose)), where CumNorm(.) is the cumulative normal
      distribution function

  Dependent variable = COLUMN3
  Independent variable = COLUMN1
  Slope parameter is not restricted

  Total number of observations = 5
  Total number of records with missing values = 0
  Maximum number of iterations = 250
  Relative Function Convergence has been set to: 1e-008
  Parameter Convergence has been set to: 1e-008

  User has chosen the log transformed model

            Default Initial (and Specified) Parameter Values
              Background     =         0
              Intercept      =    -19.7475
                 Slope       =    3.59092

Asymptotic Correlation Matrix of Parameter Estimates
The model parameter(s)  -background   have been estimated at a boundary point, or have been
specified by the user,  and do not appear in the correlation matrix )

                  intercept      slope
 intercept            1           -1
    slope            -1            1

                      Parameter Estimates
                                  95.0% Wald Confidence Interval
     Variable      Estimate      Std. Err.    Lower Conf. Limit   Upper Conf. Limit
   background          0            NA
    intercept     -42.1724       13.4943         -68.6207          -15.7242
```

slope	7.78999	2.52426	2.84253	12.7374

NA - Indicates that this parameter has hit a bound implied by some inequality constraint and thus has no standard error.

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-9.98095	5			
Fitted model	-10.6556	2	1.34926	3	0.7175
Reduced model	-20.2482	1	20.5345	4	0.0003916
AIC:	25.3112				

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Scaled Size	Residual
0.0000	0.0000	0.000	0	10	0.000
137.0000	0.0001	0.001	0	10	-0.025
181.0000	0.0468	0.468	0	10	-0.701
182.0000	0.0512	0.512	1	10	0.700
232.0000	0.6016	6.016	6	10	-0.011

Chi^2 = 0.98 d.f. = 3 P-value = 0.8055

Benchmark Dose Computation

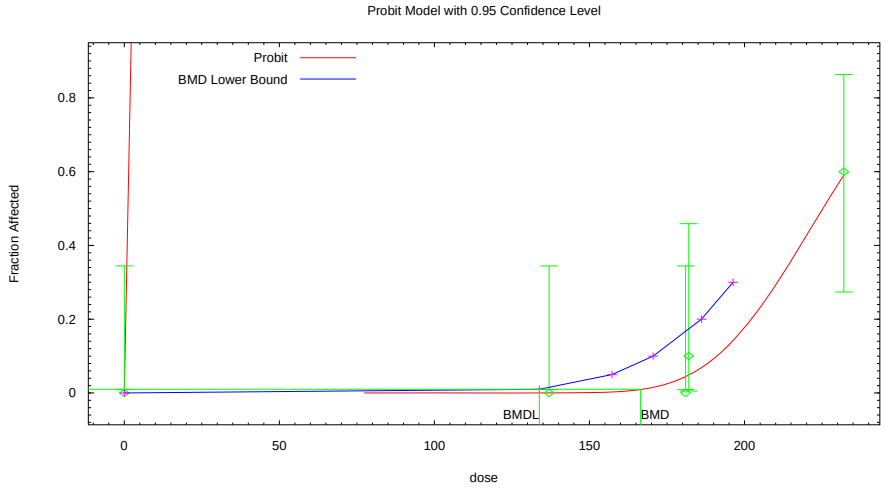
Specified effect = 0.01

Risk Type = Extra risk

Confidence level = 0.95

BMC_{01} = 166.508

$BMCL_{01}$ = 133.852



APPENDIX D: Derivation Summary for Methomyl AEGLs

Acute Exposure Guideline Levels for Methomyl

(CAS Reg. No. 16752-77-5)

AEGL-1 VALUES				
10-min	**30-min**	**1-h**	**4-h**	**8-hour**
Not recommended	Not recommended	Not recommended	Not recommended	Not recommended

Key Reference: Insufficient data
Test Species/Strain/Sex/Number:
Exposure Route/Concentration/Duration:
Effects:
Endpoint/Concentration/Rationale:
Uncertainty Factors/Rationale: **Total uncertainty factor:** **Interspecies**: **Intraspecies**:
Modifying Factor:
Animal to Human Dosimetric Adjustment:
Time Scaling:
Data Adequacy:

Not recommended: absence of AEGL-1 values does not imply that exposure below AEGL-2 levels is without effect.

1

AEGL-2 VALUES				
10-min	**30-min**	**1-h**	**4-h**	**8-h**
7.0 mg/m^3	7.0 mg/m^3	5.7 mg/m^3	3.3 mg/m^3	1.7 mg/m^3
Key Reference: DuPont. 1991. Acute Inhalation Toxicity Study with DPX-X1179-427 in Rats. Haskell Laboratory Report No. 678-91. Haskell Laboratory for Toxicology and Industrial Medicine, Newark, DE.				
Test Species/Strain/Number: Rat/CrL-CD/6 males per group				
Exposure Route/Concentration/Duration: Inhalation/137, 181, 182, 232, and 326 mg/m^3/4 hours				
Effects: acetylcholinesterase activity inhibition estimated at 1/3 of the AEGL-3 values.				
Endpoint/Concentration/Rationale: One-third of the AEGL-3 values based on the steep concentration-response curve in the key AEGL-3 study (NRC 2001).				
Uncertainty Factors/Rationale: **Total uncertainty factor**: 15 (See AEGL-3 summary) **Interspecies:** **Intraspecies:**:				
Modifying Factor: None applied				
Animal to Human Dosimetric Adjustment: Not applicable				
Time Scaling: See AEGL-3 summary				
Data Adequacy: Four studies performed in the same laboratory at different times provided consistent, concentration-related results, regardless of the physical state of the test material. The values are supported by the 4-hour vapor study of DuPont 1966a in which rats inhaling 44 mg/m^3 for 4 hours exhibited clinical signs consistent with the definition of the AEGL-2.				

2
3
4

1

AEGL-3 VALUES				
10-min	**30-min**	**1-h**	**4-h**	**8-h**
21 mg/m^3	21 mg/m^3	17 mg/m^3	10 mg/m^3	5.2 mg/m^3

Key References: DuPont. 1991. Acute Inhalation Toxicity Study with DPX-X1179-427 in Rats. Haskell Laboratory Report No. 678-91. Haskell Laboratory for Toxicology and Industrial Medicine, Newark, DE.

Test Species/Strain/Number: Rat/Crl-CD/groups of 5 male and 5 female

Exposure Route/Concentration/Duration: Inhalation/137, 181, 182, 232, or 326 mg/m^3 liquid aerosol/ 4 hours

Effect: Concentration-related clinical signs and mortality

Endpoint/Concentration/Rationale: Threshold for lethality, $BMCL_{05}$ calculated using the benchmark dose computer program (highest data point omitted for better curve fitting).

Uncertainty Factors/Rationale:

Total uncertainty factor: 15

Interspecies: 5, Based on differences in modeled values for red blood cell cholinesterase activity inhibition between rats and humans following oral ingestion of methomyl (U.S. EPA 2007).

Intraspecies: 3.05, Based on comparative brain acetylcholinesterase activity inhibition in post-natal day 11 juvenile rats and adult rats exposed to methomyl (U.S. EPA 2007).

Modifying Factor: None applied

Animal to Human Dosimetric Adjustment: Not applicable

Time Scaling: $C^n \times t = k$ where n = 3 and 1 for shorter and longer exposure durations, respectively (NRC 2001)

Data Adequacy: Four studies performed in the same laboratory but at different times provided consistent, concentration-related results, regardless of the physical state of the test material.

2