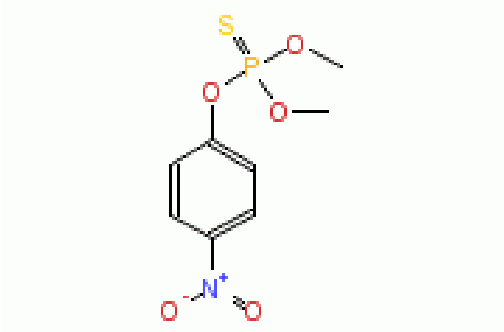
ACUTE EXPOSURE GUIDELINE LEVELS (AEGLs)

INTERIM

METHYL PARATHION (CAS Reg. No. 298-00-0)



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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EXECUTIVE SUMMARY

Methyl parathion is an organophosphorous compound used as a broad spectrum insecticide. The toxicity of methyl parathion is a function of anticholinesterase activity responses that result in effects characteristic of cholinergic-mediated function (e.g., sweating, salivation, diarrhea, miosis, and muscle fasciculations). Annual production (1983 estimates, no recent data are available) was approximately 29 million kg in the U.S. and approximately 10-15 million kg in Europe.

Relative to dermal and oral exposure, inhalation is a relatively minor exposure route and this is reflected in the paucity of inhalation toxicity data. No quantitative data are available regarding the inhalation toxicity of methyl parathion in humans.

Inhalation toxicity data in animals are limited to rats and acute exposure data are limited to lethality assessments. Although several LC_{50} values have been reported, most lack accompanying exposure-response data. One-hour LC_{50} values ranged from 200-287 mg/m^3 and 4-hour LC_{50} values ranged from 34-185 mg/m^3. The only information regarding strictly nonlethal effects are from a study using a multiple exposure (3-week) protocol.

Data to derive AEGL-1 values for methyl parathion were not available and, therefore, AEGL-1 values are not recommended.

Exposure-response data for AEGL-2 severity effects were limited to a multiple exposure protocol study in which rats exposed up to 9.7 mg/m^3 for 6 hours/day, 5 days/week for 3 weeks exhibited decreased brain cholinesterase activity, clinical signs and body weight effects. Although these effects are consistent with AEGL-2 tier severity, they resulted from extended multiple exposures and not a single acute exposure consistent with AEGLs. Organophosphate poisoning exhibits a steep exposure-response curve (NRC, 2003). Data from U.S. EPA (1998) demonstrated an increased lethal response from 20% to 90% with only a 1.5-fold increase in dose for rats exposed to methyl parathion for 4 hours. The tenuous nature of estimating acute effects from a multiple exposure study and the steep exposure-response relationship justify estimating AEGL-2 values by a 3-fold reduction of AEGL-3 values (NRC, 2001).

The point-of-departure (POD) for AEGL-3 derivation was a $BMCL_{05}$ of 66.6 mg/m^3 for lethality in rats exposed for 4 hours (U.S. EPA, 1998). Lethality data were not considered sufficient for empirical derivation of a time-scaling factor (n) for use in the equation $C^n \times t = k$. Therefore, temporal scaling from the experimental duration of the POD to AEGL-specific durations was performed using $n = 3$ when extrapolating to shorter time points and $n = 1$ when extrapolating to longer time points using the $C^n \times t = k$ equation (NRC, 2001). The mechanism of action of organophosphate anticholinesterases is well understood and their activity on cholinergic systems shown to be the same across species. Variability in responses is primarily a function of varying cholinesterase activities and types of cholinesterases. Humans have been shown to have greater levels of plasma cholinesterase than do other species which allows for greater binding of anticholinesterase compounds such as methyl parathion, thereby decreasing the availability of the chemical to critical targets (NRC, 2003). Therefore, the interspecies uncertainty factor is limited to 3. The documented variability in sensitivity among different age groups and genders, and the known genetic polymorphisms in A-esterases justifies retention of

the intraspecies uncertainty factor of 10 (NRC, 2003). The uncertainty factor application and rationale are the same as those applied in the derivation of other organophosphate anticholinesterases (NRC, 2003).

The AEGL values for methyl parathion are summarized in Table S-1. There exists uncertainty regarding the contribution of dermal exposure to the total dose in situations where both exposure routes are likely.

S-1. AEGL Values for methyl parathion (mg/m^3)

Classification	10-min	30-min	1-h	4-h	8-h	Endpoint (Reference)
AEGL-1 (Nondisabling)	NR	NR	NR	NR	NR	Not recommended due to insufficient data
AEGL-2 (Disabling)	2.1	1.5	1.2	0.73	0.37	Derived by 3-fold reduction of the AEGL-3 values (NRC, 2001; U.S. EPA, 1998)
AEGL-3 (Lethality)	6.4	4.4	3.5	2.2	1.1	Derived based upon a 4-hr $BMCL_{05}$ of 66.6 mg/m^3 for lethality in rats (U.S. EPA, 1998); UF = 3 (intersp.) and 10 (intrasp.); n = 1or 3

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

References

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

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

U.S. EPA. 1998. Methyl parathion. MRID Nos. 40364103 and 142803. EPA special docket EPA-HQ-OPP-2007-0151.

1. INTRODUCTION

Methyl parathion is an organophosphorous compound used as a broad spectrum insecticide. Although relatively insoluble in water, it is readily soluble in most organic solvents (HSDB, 2007). Toxic responses are characteristic of cholinesterase inhibition (increased central and peripheral nervous system cholinergic mediating activity such as increased sweating, salivation, diarrhea, miosis, and muscle fasciculations). Annual production (1983 estimates, no recent data are available) was approximately 29 million kg in the U.S. and approximately 10-15 million kg in Europe (ATSDR, 2001). The physico-chemical properties of methyl parathion are summarized in Table 1.

TABLE 1. Chemical and physical data for methyl parathion.

Parameter	Value	Reference
Synonyms	Phosphorothioic acid *O,O*-dimethyl *O*-(4-nitrophenyl) ester ; *O,O*-dimethyl *O*-*p*-nitrophenyl thiophosphate ; dimethyl parathion, metaphos; Wofatox	O'Neil et al., 2001
Chemical formula	$C_8H_{10}NO_5PS$	O'Neil et al., 2001
Molecular weight	263.3	O'Neil et al., 2001
CAS Registry No.	298-00-0	O'Neil et al., 2001
Physical state	crystalline	HSDB, 2007
Solubility in water	55-60 mg/L	HSDB, 2007
Vapor pressure	1.3 mPa @20°C	HSDB, 2007
Boiling point/melting point	289°F/37-38°C	NIOSH, 2005; O'Neil et al., 2001
Conversion factors in air	1 ppm = 10.76 mg/m^3 1 mg/m^3 = 0.0929 ppm	

2. HUMAN TOXICITY DATA

2.1. Acute Lethality

Fazekas (1964) reported on the deaths of four individuals exposed to methyl parathion (Wofatox) as a result of careless spraying. These cases, however, involved dermal exposure as well as inhalation exposure. No exposure concentration data were available.

2.2 Nonlethal Toxicity

No quantitative exposure data are available regarding nonlethal toxicity in humans following acute inhalation exposure to methyl parathion. In a study of individuals exposed at home to illegally sprayed methyl parathion, Rubin et al. (2002) reported several signs and symptoms for the period following spraying: headache (30%), nausea (29%), night waking (28%), diarrhea (26%), restlessness (23%), difficulty breathing (21%), dizziness (21%), abdominal cramps (20%), excessive sweating (13%), incoordination (11%), excessive salivation (95%), and mental confusion (7%).

2.3. Developmental/Reproductive Effects

Data on the developmental/reproductive toxicity of methyl parathion in humans were not available.

2.4. Genotoxicity

Van Bao et al. (1974) reported chromosome aberrations in the lymphocytes of individuals acutely exposed to methyl parathion via inhalation. A significant ($p<0.05$) increase was noted in the frequency of stable chromosomal aberrations in the exposed individuals but the effect was transient. The sample size was small, there was no control group, exposure levels were unknown, and there was a possible concomitant exposure to other substances.

2.5. Carcinogenicity

No information regarding the carcinogenicity of methyl parathion in humans was available.

2.6. Summary

Although there are case reports of human poisonings with methyl parathion, multiple exposure routes are usually involved; dermal and oral being most prevalent. Ware et al. (1973) found that for cotton field workers, the hands were the greatest source of absorbed methyl parathion while the respiratory tract was an "insignificant source". Similar observations have been observed for wine growers (Muttray et al., 2006).

3. ANIMAL TOXICITY DATA

3.1. Acute Lethality

3.1.1. Rats

Thyssen (1979) reported 4-hour LC_{50} values of 185 mg/m^3 for male rats and 170 mg/m^3 for female rats. No further details are available for this study cited in WHO (1993).

Molnar et al. (1980) exposed groups of male CFY rats to methyl parathion for 4 hours. A 4-hr LC_{50} of 34 mg/m^3 (range of 23-51 mg/m^3) was reported. Surviving rats were observed for 2 weeks but no details are available regarding the follow up observations or the experimental protocols.

Two acute inhalation studies in rats were summarized by the U.S. EPA (1998). In one study, Sprague-Dawley rats (5/sex/group) were exposed (nose-only) to methyl parathion technical (80%) for 4 hours at concentrations of 0.108, 0.134, or 0.168 mg/L (equivalent to 108, 134, and 168 mg/m^3). During exposure, all rats exhibited respiratory depression and salivation; post exposure observations included body weight loss, tremors, and unkempt appearance. All surviving rats were normal by 10 days post exposure (14-day follow-up). The investigators calculated a 4–hr LC_{50} of 0.135 mg/L (135 mg/m^3) with a 95% c.i. of 0.125-0.145 mg/L (125-145 mg/m^3). Effects are summarized in Table 2. A $BMCL_{05}$ of 66.6 mg/m^3 and BMC_{01} of 83.6 mg/m^3 were calculated with these data using Benchmark Dose Software (U.S. EPA, 2007) (see Appendix F).

TABLE 2. Effects of methyl parathion on rats following acute inhalation exposure.		
Exposure (mg/m^3)	**Mortality**	**Observations**
108	2/10	2 males dead at 98 min.; surviving animals normal at 5 days post exposure
134	3/10	3 males dead at 120-129 min.; surviving animals normal at 4 days post exposure
168	9/10	5 males, 4 females dead at 43-96 min.; lone survivor exhibited unkempt appearance until post exposure day 9 but normal thereafter

U.S. EPA, 1998

In a second acute inhalation study (U.S. EPA, 1998), Hsd:(SD)BR rats (5/sex/group) were exposed to technical methyl parathion (purity unknown) at a concentration of 0.163 mg/L (163 mg/m^3) for 4 hours or 1.06 mg/L (106 mg/m^3) for 1.5 hours. All rats died prior to scheduled termination of the study although it is unclear if they died during the exposure periods. Clinical observations were consistent with anticholinergic activity (e.g., tremors, salivation, miosis, lacrimation, labored breathing).

A 1-hour LC_{50} of 0.2 mg/L (200 mg/m^3) and a 4-hour LC_{50} of 0.12 mg/L (120 mg/m^3) for male rats were reported by Kimmerle and Lorke (1968). The values were reportedly from experiments using 20 male rats, a 14-day observation period, and an exposure system allowing only inhalation exposure. Although no details were provided, it was stated that the exposure concentrations were analytically determined.

One-hour LC_{50} values of 257 mg/m^3 for male rats and 287 mg/m^3 for female rats were also reported for methyl parathion by EPA (1978). Surviving rats showed no clinical signs at 10-14 days post-exposure.

Molnar and Paksy (1978) reported a 4-hour LC_{50} of 34 mg/m^3 for methyl parathion aerosol (likely the same data as reported in Molnar et al., 1980) . Rats were observed for 14 days; no additional details were available.

3.1.2. Summary of Animal Lethality Data

Information on the lethality of methyl parathion following inhalation exposure is limited to rats. Although several LC_{50} values are reported, only those reported by the U.S. EPA (1998) are accompanied by exposure-response data. The 1-hour LC_{50} ranged from 200-287 mg/m^3 and the 4-hour LC_{50} values ranged from 34-185 mg/m^3. With exception of the 33 mg/m^3 value cited by Molnar and Paksy (1978), the LC_{50} values from different reports are consistent.

3.2. Nonlethal Toxicity

3.2.1. Rats

Data regarding the nonlethal effects of inhaled methyl parathion are limited to the nonlethal responses of rats in the studies discussed in Section 3.1.1 and to a repeat-exposure study in rats showing nonlethal exposures resulting in decreased cholinesterase activity. In studies where group lethality incidences were reported, all exposure groups resulted in some lethality, thereby disallowing a definitive exposure that could be considered nonlethal.

Thyssen (1979) conducted a multiple exposure study in which groups of 10 male and 10 female rats (strain not specified in available report) were exposed to methyl parathion aerosol at concentrations of 0, 0.9, 2.6, or 9.7 mg/m^3 for 6 hours/day, 5 days/week for 3 weeks. No deaths occurred. Both brain and plasma cholinesterase were significantly decreased in rats of the high-dose group. The high-dose rats also exhibited clinical signs of toxicity consistent with anticholinesterase activity and decreased body weight gain. A slight decrease in plasma cholinesterase activity (data not provided in summary report) was detected in rats of the 2.6 mg/m^3 group. Histological findings were unremarkable among the treatment and control groups (Thyssen and Mohr, 1982).

3.3. Developmental/Reproductive Effects

No information is available regarding developmental/reproductive effects of methyl parathion following inhalation exposure.

3.4. Genotoxicity

ATSDR (2001) reviewed numerous genotoxicity assays in which methyl parathion was tested using prokaryotic and eukaryotic systems. Overall, the results were equivocal. Results of testing with various *Salmonella typhimurium* strains (both with and without metabolic activation) were also contradictory.

Similarly, a review of assays assessing chromosomal effects indicates these studies have also been contradictory.

Overall, the available data are inconclusive regarding the potential genotoxic risk resulting from methyl parathion exposure.

3.5. Carcinogenicity

No studies were available that evaluated the carcinogenic potential of methyl parathion following inhalation exposure. Results of a 2-year cancer bioassay (dosed-feed) by the National Toxicology Program (NTP, 1978) were negative in male and female rats and mice.

4. SPECIAL CONSIDERATIONS

4.1. Metabolism and Disposition

No information was located regarding absorption in humans or animals after inhalation exposure to methyl parathion. However, it may be assumed that pulmonary absorption occurs as evidenced by systemic effects following acute inhalation exposure. Methyl parathion is rapidly and extensively metabolized in the liver. The resulting polar metabolites are rapidly excreted in the urine. Oxidative desulfuration by microsomal oxidases transforms methyl parathion into the neurotoxic, active metabolite, methyl paraoxon. Detoxification reactions occur via oxidation, hydrolysis, dearylation, and dealkylation. A major detoxification pathway being the enzymatic hydrolysis of methyl paraoxon to dimethyl phosphate and 4-nitrophenol both eliminated primarily in the urine in humans, rats, and mice. The metabolic pathway of methyl parathion is shown in Figure 1.

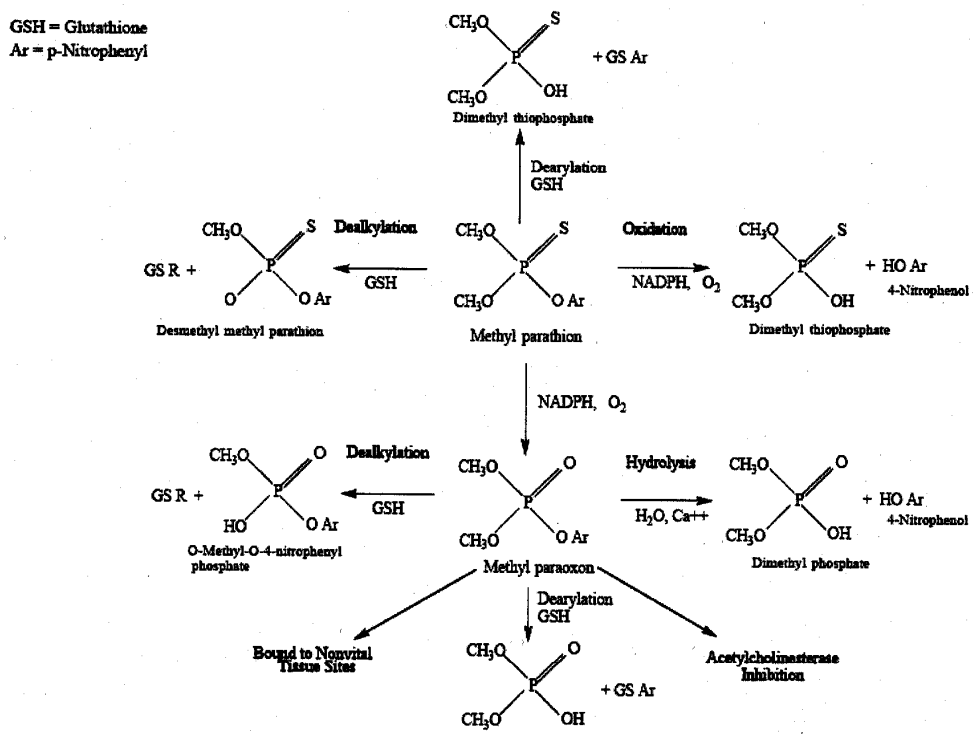

FIGURE 1. Metabolic pathway of methyl parathion (Adapted from Benke and Murphy, 1974)

4.2. Mechanism of Toxicity

Methyl parathion inhibits acetyl cholinesterase activity resulting in an excess of acetylcholine at neuronal synapses and myoneural junctions. Like other organophosphates, methyl parathion phosphorylates cholinesterase by reacting at the esteratic subsite of the enzyme which in turn prevents the enzyme from deactivating acetylcholine (Taylor, 1985). The overall result is an enhancement of cholinergic-mediated function (e.g., miosis, salivation, sweating, muscle fasciculations and tremors). The health effects and mechanism of action of methyl parathion have been reviewed by Garcia et al. 2003).

4.3. Structure-Activity Relationships

Although all anticholinergic organophosphates have the same mechanism of action, their potencies and physicochemical properties vary. The physicochemical differences will also affect environmental persistence and metabolic fate. Development of AEGL values by structure-activity analysis would be tenuous and uncertain without rigorous relative potency data.

4.4. Other Relevant Information

4.4.1. Species Variability

Chemical-specific data are insufficient for assessing species variability in the toxic response to inhaled methyl partathion.. Variability in types of esterases and their respective activities is important regarding interspecies variability in organophosphate poisoning. This will affect susceptibility to organophosphates due to differences in detoxification potential (NRC, 2003). Baseline red blood cell acetylcholinesterase activity is slightly higher in humans (12.6 μmol/mL/min) than in monkeys (7.1 μmol/mL/min) and much higher compared to other species (4.7 μmol/mL/min for pigs; 4.0 μmol/mL/min for goats; 2.9 μmol/mL/min for sheep; 2.4 μmol/mL/min for mice; 2.0 μmol/mL/min for dogs; 2.7 μmol/mL/min for guinea pigs; 1.7 μmol/mL/min for both rats and rabbits; and 1.5 μmol/mL/min for cats) (Ellin, 1981). Similarly, humans tend to have greater plasma cholinesterase activity levels than other species (Wills, 1972). In humans, approximately 50% of the total blood cholinesterase consists of plasma cholinesterase. Plasma cholinesterase activity constitutes approximately 40% of the total blood cholinesterase in dogs, 30% in rats, 20% in monkeys, and only 10% in sheep, horses, and cows. Both of these findings suggest that humans will have greater potential for buffering the activity of organophosphate anticholinesterases by preventing interaction with red blood cell and brain cholinesterase as well as cholinesterase at neuromuscular junctions (NRC, 2003). Carboxylesterases known to occur in human erythrocytes, liver, lung, skin, and nasal tissue may also contribute to detoxification of organophosphates but the quantitative aspect of this has not been fully characterized (NRC, 2003).

The mechanism of action of organophosphates is well characterized (NRC, 2003) and is similar across species. Species variability in toxic response is more a function of variability in detoxification potential.

4.4.2. Susceptible Populations

Individual variability in plasma cholinesterase activity is well documented (NRC, 2003). This variability includes age-related differences (neonates are more susceptible than are adults), gender differences (females tend to have approximately 10% lower plasma and red blood cell cholinesterase activity), and genetically determined variations in plasma cholinesterase activity. This genetically determined variability, sometimes resulting in greatly reduced (64% of normal) activity of plasma cholinesterase may impart deficiencies in ability to detoxify organophosphates such as parathion. Additionally, polymorphic variability in A-esterases (i.e., paraoxonase/arylesterase) may also contribute to individual variability in organophosphate ester detoxification processes (NRC, 2003).

4.5. Concurrent Exposure Issues

Both concurrent exposure to other organophosphates and simultaneous exposure via other exposure routes would be of concern. Methyl parathion may enter the body and be bioavailable by dermal, oral and inhalation pathways. In a study of winegrowers exposed to methyl parathion, Muttray et al. (2006) found that dermal exposure considerably exceeded inhalation exposure. This finding was based upon monitoring of 23 healthy winegrowers during a 50-minute period of spraying. Exposure data were obtained from personal air samplers for inhalation exposure and from filter papers affixed to the workers.

5. DATA ANALYSIS FOR AEGL-1

5.1. Human Data Relevant to AEGL-1

No human data relevant to derivation of AEGL-1 values were available.

5.2. Animal Data Relevant to AEGL-1

There are no animal data with which to assess AEGL-1 severity effects following acute inhalation exposure to methyl parathion.

5.3. Derivation of AEGL-1 Values

Data are insufficient for derivation of AEGL-1 values for methyl parathion. Changes in plasma cholinesterase activity, although a marker of exposure, are not suitable indicators or predictors of health effects (U.S. EPA, 2000; NRC, 2003). The data reported in Thyssen (1979) and Thyssen and Mohr (1982) relate to multiple exposures over 3 weeks, and to assume a specific effect after just one exposure is not tenable. Therefore, AEGL-1 values are not recommended (Table 3; Appendix A).

TABLE 3. AEGL-1 values for methyl parathion

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

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

6. DATA ANALYSIS FOR AEGL-2

6.1. Human Data Relevant to AEGL-2

No human data relevant to derivation of AEGL-2 values were available.

6.2. Animal Data Relevant to AEGL-2

The only data identifying nonlethal effects in animals following inhalation exposure to methyl parathion is that of Thyssen (1979) and Thyssen and Mohr (1982) who reported that multiple exposure (6 hrs/day, 5 days/week for 3 weeks) of rats to 0.9, 2.6, or 9.7 mg/m^3 resulted in no lethalities. Both brain and plasma cholinesterase activity were significantly inhibited in rats of the high-dose group. These rats also exhibited clinical signs of toxicity consistent with anticholinesterase activity and decreased body weight gain. A slight decrease in plasma cholinesterase activity (data not provided in summary report) was detected in rats of the 2.6 mg/m^3 group. Histological findings were unremarkable among the treatment and control groups. It is uncertain if any of these effects would have resulted from a single 6-hour exposure.

6.3. Derivation of AEGL-2 Values

Although the effects reported by Thyssen (1979) and Thyssen and Mohr (1982) for rats following multiple exposures to methyl parathion (9.7 mg/m^3 ; decreased brain cholinesterase,

clinical signs and body weight effects) are consistent with AEGL-2 severity effects, it is not certain that such effects would have occurred following a single exposure. The resulting AEGL-2 values would likely be overly conservative.

Organophosphate poisoning exhibits a steep exposure-response curve (NRC, 2003) and data from U.S. EPA (1998) (see Table 2, Section 3.1.1) demonstrate an increased lethal response from 20% to 90% with a 1.5-fold increase in dose for rats exposed to methyl parathion for 4 hours. The steep exposure-response relationship (lethality rate in rats increased from 20% to 90% with a 1.5-fold increase in exposure concentration [U.S. EPA, 1998]) justifies estimating AEGL-2 values by a 3-fold reduction of AEGL-3 values (NRC, 2001). The resulting AEGL-2 values are shown in Table 4.

Although not applicable for AEGL-2 derivation, AEGL-2 values derived using the 9.7 mg/m^3 multiple exposure valued from Thyssen (1979) as a POD, would be about 2-fold lower than those estimated by a 3-fold reduction of the AEGL-3 values. Due to the assumption that only one exposure of a multiple exposure regimen (5 days/week for 3 weeks) would produce the effects observed following the full multiple exposure regimen, this is expected.

TABLE 4. AEGL-2 Values for methyl parathion (mg/m^3)

Classification	10-min	30-min	1-h	4-h	8-h
AEGL-2	2.1	1.5	1.2	0.73	0.37

7. DATA ANALYSIS FOR AEGL-3

7.1. Human Data Relevant to AEGL-3

No human data relevant to derivation of AEGL-3 values were available.

7.2. Animal Data Relevant to AEGL-3

Although several LC_{50} values are reported, only those reported by the U.S. EPA (1998) are accompanied by exposure-response data. The investigators calculated a 4–hr LC_{50} of 0.135 mg/L (135 mg/m^3) from these data. Using the exposure-response data from this study, a $BMCL_{05}$ of 66.6 mg/m^3 and BMC_{01} of 83.6 mg/m^3 were calculated using Benchmark Dose Software (U.S. EPA, 2007) (see Appendix F).

One-hour LC_{50} values from other reports ranged from 200-287 mg/m^3 and the 4-hour LC_{50} values ranged from 34-135 mg/m^3.

7.3. Derivation of AEGL-3 Values

Due to the availability of group-specific response data, the U.S. EPA (1998) report was selected as the key study and the $BMCL_{05}$ of 66.6 mg/m^3 was selected as the point-of-departure (POD) for AEGL-3 derivation. Lethality data were not considered sufficient for empirical derivation of a time-scaling factor (n) for use in the equation $C^n \times t = k$. Therefore, temporal scaling from the experimental duration of the respective POD to AEGL-specific durations was performed using $n = 3$ when extrapolating to shorter time points and $n = 1$ when extrapolating to longer time points using the $C^n \times t = k$ equation (NRC, 2001). Due to uncertainties in

extrapolating from the 4-hour POD, the 30-minute AEGL-3 value was adopted as the 10-minute AEGL-3 value (NRC, 2001). As previously described, the mechanism of action of organophosphate anticholinesterases is well understood and the activity on cholinergic systems shown to be the same across species. Variability in responses is primarily a function of varying cholinesterase activities and types of cholinesterase (see Section 4.4.1). Humans have been shown to have greater levels of plasma cholinesterase than do other species which allows for greater binding of anticholinesterase compounds such as methyl parathion, thereby decreasing the availability of the compound to critical targets such as brain cholinesterase. Therefore, the interspecies uncertainty is limited to 3. The documented variability in sensitivity among different age groups and genders, and the known genetic polymorphisms in A-esterases justifies retention of the intraspecies uncertainty factor of 10. The uncertainty factor application and rationale are the same as those applied in the derivation of AEGL values for other organophosphate cholinesterase inhibitors (NRC, 2003).

The AEGL-3 values for methyl parathion are shown in Table 5 and their derivation is presented in Appendix A.

TABLE 5. AEGL-3 values for methyl parathion (mg/m^3)

Classification	10-min	30-min	1-h	4-h	8-h
AEGL-3	6.4	4.4	3.5	2.2	1.1

8. SUMMARY OF AEGLs

8.1. AEGL Values and Toxicity Endpoints

Only limited animal data are available regarding the inhalation toxicity of methyl parathion. Human exposure to methyl parathion usually involves multiple exposure routes with dermal exposure generally being the most prominent pathway and that most relevant to human health concerns. Data were not available with which to derive scientifically defensible AEGL-1 values. Inhibition of plasma cholinesterase activity, although, a biological marker of exposure has no significant health effect correlates. Exposure-response data for AEGL-2 severity effects were not available for single acute exposures. However, the exposure-response curve for methyl parathion, like most organophosphate anticholinesterases is steep, thereby allowing for estimation of the AEGL-2 values by a three-fold reduction of the AEGL-3 values (NRC, 2001; 2003). The AEGL-3 values were a based upon the estimated lethality threshold ($BMCL_{05}$ of 66.6 mg/m^3) in male and female rats exposed nose-only for 4 hours. AEGL values are summarized in Table 6.

TABLE 6. AEGL values for methyl parathion (mg/m^3)

Classification	10-min	30-min	1-h	4-h	8-h
AEGL-1 (Nondisabling)	NR	NR	NR	NR	NR
AEGL-2 (Disabling)	2.1	1.5	1.2	0.73	0.37
AEGL-3 (Lethality)	6.4	4.4	3.5	2.2	1.1

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

8.2. Comparisons with Other Standards and Guidelines

AEGL values for methyl parathion are compared to other guidelines and standards for this compound (Table 7).

TABLE 7. Extant Standards and Guidelines for Methyl Parathion

Guideline	Exposure Duration				
	10 min	30 min	1 h	4 h	8 h
AEGL-1	NR	NR	NR	NR	NR
AEGL-2	2.1	1.5	1.2	0.73	0.37
AEGL-3	6.4	4.4	3.5	2.2	1.1
ERPG-1 (AIHA)[a]					
ERPG-2 (AIHA)					
ERPG-3 (AIHA)					
EEGL (NRC)[b]					
PEL-TWA (OSHA)[c]					
PEL-STEL (OSHA)[d]					
IDLH (NIOSH)[e]					
REL-TWA (NIOSH)[f]					0.2 mg/m^3
REL-STEL (NIOSH)[g]					
TLV-TWA (ACGIH)[h]					0.2 mg/m^3
TLV-STEL (ACGIH)[i]					
MAK (Germany)[j]					
MAK Spitzenbegrenzung (Germany)[k]					
Einsaztoleranzwert (Germany)[l]					
MAC-Peak Category (The Netherlands)[m]					0.2 mg/m^3

[a] ERPG (Emergency Response Planning Guidelines, American Industrial Hygiene Association) (AIHA, 2007)
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] EEGL (Emergency Exposure Guidance Levels, National Research Council) (NRC, 1985) is the concentration of contaminants that can cause discomfort or other evidence of irritation or intoxication in or around the workplace, but avoids death, other severe acute effects and long-term or chronic injury.

[c] OSHA PEL-TWA (Occupational Health and Safety Administration, Permissible Exposure Limits - Time Weighted Average) (OSHA, 2007) is defined analogous to the ACGIH-TLV-TWA, but is for exposures of no more than 10 hours/day, 40 hours/week.

[d] OSHA PEL-STEL (Permissible Exposure Limits - Short Term Exposure Limit) (OSHA, 2007) is defined analogous to the ACGIH-TLV-STEL.

[e] IDLH (Immediately Dangerous to Life and Health, National Institute of Occupational Safety and Health) (NIOSH, 2005) represents the maximum concentration from which one could escape within 30 minutes without any escape-impairing symptoms, or any irreversible health effects.

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

[g] NIOSH REL-STEL (Recommended Exposure Limits - Short Term Exposure Limit) (NIOSH, 2005) is defined analogous to the ACGIH-TLV-STEL.

[h] ACGIH TLV-TWA (American Conference of Governmental Industrial Hygienists, Threshold Limit Value - Time Weighted Average) (ACGIH, 2007) is the time-weighted average concentration for a normal 8-hour workday and a 40-hour work week, to which nearly all workers may be repeatedly exposed, day after day, without adverse effect

[i] ACGIH TLV-STEL (Threshold Limit Value - Short Term Exposure Limit) (ACGIH, 2007) is defined as a 15-minute TWA exposure which should not be exceeded at any time during the workday even if the 8-hour TWA is within the TLV-TWA. Exposures above the TLV-TWA up to the STEL should not be longer than 15 minutes and should not occur more than 4 times per day. There should be at least 60 minutes between successive exposures in this range.

[j] MAK (Maximale Arbeitsplatzkonzentration [Maximum Workplace Concentration], Deutsche Forschungs-gemeinschaft [German Research Association], Germany) (DFG, 2007) is defined analogous to the ACGIH-TLV-TWA.

[k] MAK Spitzenbegrenzung (Kategorie II,2) [Peak Limit Category II,2] (DFG, 2007) constitutes the maximum average concentration to which workers can be exposed for a period up to 30 minutes, with no more than 2 exposure periods per work shift; total exposure may not exceed 8-hour MAK. Cat. III indicates possible significant contribution to cancer risk.

[l] Einsatztoleranzwert [Action Tolerance Levels] (Vereinigung zur Förderung des deutschen Brandschutzes e.V. [Federation for the Advancement of German Fire Prevention]) constitutes a concentration to which unprotected firemen and the general population can be exposed to for up to 4 hours without any health risks.

[m] MAC (Maximaal Aanvaaarde Concentratie [Maximal Accepted Concentration - Peak Category]) (SDU Uitgevers [under the auspices of the Ministry of Social Affairs and Employment], The Hague, The Netherlands 2007) is defined analogous to the ACGIH-Ceiling.

8.3. Data Adequacy and Research Needs

Although toxicity data for methyl parathion are available for oral and dermal exposure routes, inhalation data are very limited. No quantitative data are available regarding human exposures. Animal data are limited to one species (rat) and primarily lethality data. The most

useful data to allow for a more robust analysis relative to AEGL development would be dose-response data identifying the AEGL-2 severity effects. Also, there exists uncertainty regarding the contribution of dermal exposure to the total dose in situations where both exposure routes are likely.

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APPENDIX A: Derivation of AEGL Values

Derivation of AEGL-1 Values for Methyl Parathion

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

APPENDIX B: Derivation of AEGL-2 Values for Methyl Parathion

Data were insufficient for empirical derivation of AEGL-2 values for methyl parathion. Due to the steep exposure-response relationship demonstrated by lethality data for this chemical, the AEGL-2 values have been estimated as a 3-fold reduction of the AEGL-3 values (NRC, 2001).

10-minute AEGL-2	6.4/3 = 2.1
30-minute AEGL-2	4.4/3 = 1.5
1-hr AEGL-2	3.5/3 = 1.2
4-hr AEGL-2	2.2/3 = 0.73
8-hr AEGL-2	1.1/3 = 0.37

Derivation of AEGL-3 Values for Methyl Parathion

Key study: U.S. EPA. 1998. Methyl parathion. MRID Nos. 40364103 and 142803. EPA special docket EPA-HQ-OPP-2007-0151.

Critical effect: 4-hour $BMCL_{05}$ of 66.6 mg/m^3 used as estimate of the lethality threshold in rats.

Time scaling: $C^n \times t = k$, where n = 1 or 3
The exposure concentration-exposure duration relationship for many irritant and systemically acting vapors and gases may be described by $C^n \times t = k$, where the exponent, *n*, ranges from 0.8 to 3.5 (ten Berge et al., 1986). In the absence of an empirically derived exponent (*n*), temporal scaling from the experimental duration of the POD to AEGL-specific durations was performed using *n* = 3 when extrapolating to shorter time points and *n* = 1 when extrapolating to longer time points using the $C^n \times t = k$ equation (NRC, 2001).

Uncertainty factors: Total uncertainty factor adjustment is 30.
Interspecies: 3; variability in the toxic responses is primarily a function of varying cholinesterase activity levels and types of cholinesterase present; humans have greater levels of plasma cholinesterase with which to bind anticholinesterases such as methyl parathion than do other species. This decreases the dose to critical targets. Therefore, the interspecies uncertainty factor is limited to 3.
Intraspecies: 10; the documented variability in sensitivity among different age groups and genders, and the known genetic polymorphisms in A-esterases justifies retention of the intraspecies uncertainty factor of 10.

Modifying Factor: none applied

Calculation: $(66.6\ mg/m^3)^1 \times 4\ hrs = 266.4 mg/m^3 \cdot hrs$
$(66.6\ mg/m^3)^3 \times 4\ hrs = 1{,}181{,}633\ mg/m^3 \cdot hrs$

10-minute AEGL-3

$C^3 \times 0.167\ hrs = 1{,}181{,}633\ mg/m^3 \cdot hrs$
$C = 192\ mg/m^3$
$C = 192\ mg/m^3 / 30 = 6.4\ mg/m^3$

30-minute AEGL-3

$C^3 \times 0.5\ hrs = 1{,}181{,}633\ mg/m^3 \cdot hrs$
$C = 133.2\ mg/m^3$
$C = 133.2\ mg/m^3 / 30 = 4.4\ mg/m^3$

1-hour AEGL-3

$C^3 \times 1\ hr = 1{,}181{,}633\ mg/m^3 \cdot hrs$

$C = 105.7\ mg/m^3$

$C = 105.7\ mg/m^3 / 30 = 3.5\ mg/m^3$

4-hour AEGL-3

$C \times 4\ hrs = 266.4\ mg/m^3 \cdot hrs$

$C = 66.6\ mg/m^3$

$C = 66.6\ mg/m^3 / 30 = 2.2\ mg/m^3$

8-hour AEGL-3

$C \times 8\ hrs = 266.4\ mg/m^3 \cdot hrs$

$C = 33.3\ mg/m^3$

$C = 33.3\ mg/m^3 / 30 = 1.1\ mg/m^3$

APPENDIX C: Time Scaling Calculations

The relationship between dose and time for any given chemical is a function of the physical and chemical properties of the substance and the unique toxicological and pharmacological properties of the individual substance. Historically, the relationship according to Haber (1924), commonly called Haber's Law or Haber's Rule (i.e., $C \times t = k$, where C = exposure concentration, t = exposure duration, and k = a constant) has been used to relate exposure concentration and duration to effect (Rinehart and Hatch, 1964). This concept states that exposure concentration and exposure duration may be reciprocally adjusted to maintain a cumulative exposure constant (k) and that this cumulative exposure constant will always reflect a specific quantitative and qualitative response. This inverse relationship of concentration and time may be valid when the toxic response to a chemical is equally dependent upon the concentration and the exposure duration. However, an assessment by ten Berge et al. (1986) of LC_{50} data for certain chemicals revealed chemical-specific relationships between exposure concentration and exposure duration that were often exponential. This relationship can be expressed by the equation $C^n \times t = k$, where n represents a chemical specific, and even a toxic endpoint specific, exponent. The relationship described by this equation is basically in the form of a linear regression analysis of the log-log transformation of a plot of C vs t. ten Berge et al. (1986) examined the airborne concentration (C) and short-term exposure duration (t) relationship relative to death for approximately 20 chemicals and found that the empirically derived value of n ranged from 0.8 to 3.5 among this group of chemicals. Hence, the value of the exponent (n) in the equation $C^n \times t = k$ quantitatively defines the relationship between exposure concentration and exposure duration for a given chemical and for a specific health effect endpoint. Haber's Rule is the special case where $n = 1$. As the value of n increases, the plot of concentration vs time yields a progressive decrease in the slope of the curve.

The available data do not allow for empirical derivation of a temporal scaling factor (n) for methyl parathion. The exposure concentration-exposure duration relationship for many irritant and systemically acting vapors and gases may be described by $C^n \times t = k$, where the exponent, n, ranges from 0.8 to 3.5 (ten Berge et al., 1986). In the absence of an empirically derived exponent (n), temporal scaling from the experimental durations of the respective PODs to AEGL-specific durations was performed using $n = 3$ when extrapolating to shorter time points and $n = 1$ when extrapolating to longer time points using the $C^n \times t = k$ equation.

APPENDIX D: Derivation Summary Tables

ACUTE EXPOSURE GUIDELINE LEVELS FOR METHYL PARATHION DERIVATION SUMMARY

AEGL-1 VALUES FOR METHYL PARATHION (ppm)				
10 min	**30 min**	**1 h**	**4 h**	**8 h**
NR	NR	NR	NR	NR
Reference: NA				
Test Species/Strain/Number: NA				
Exposure Route/Concentrations/Durations : NA				
Effects: NA				
Endpoint/Concentration/Rationale:				
Uncertainty Factors/Rationale : NA				
Modifying Factor: NA				
Animal to Human Dosimetric Adjustment: NA				
Time Scaling: NA				
Data Adequacy: Data are insufficient for derivation of AEGL-1 values for methyl parathion. Therefore, AEGL-1 values are not recommended. Absence of AEGL-1 values does not imply that concentrations below the AEGL-2 are without effect.				

1

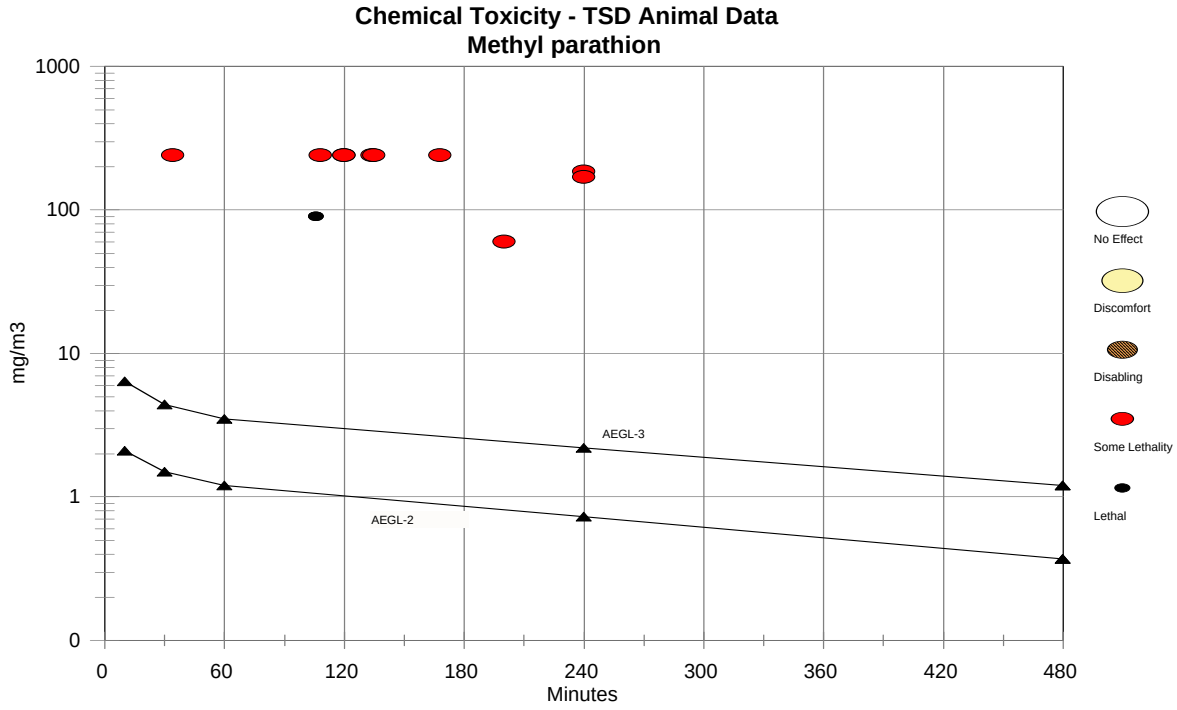
AEGL-2 VALUES FOR METHYL PARATHION (mg/m^3)				
10 min	**30 min**	**1 h**	**4 h**	**8 h**
2.1	**1.5**	**1.2**	**0.73**	**0.37**
Reference: NA				
Test Species/Strain/Sex/Number: NA				
Exposure Route/Concentrations/Durations: One-third the AEGL-3 values. Supported by steep concentration-response curve. (20% mortality in rats exposed to 108 mg/m^3 and 90% mortality at 168 mg/m^3 for 4 hrs).				
Effects:				
Endpoint/Concentration/Rationale: : One-third the AEGL-3 values.				
Uncertainty Factors/Rationale: NA				
Modifying Factor: NA				
Animal to Human Dosimetric Adjustment: NA				
Time Scaling: NA				
Data Adequacy: Data available on AEGL-2 severity effects only from a multiple exposure protocol study.				

2

1

AEGL-3 VALUES FOR METHYL PARATHION (mg/m^3)				
10 min	**30 min**	**1 h**	**4 h**	**8 h**
6.4	**4.4**	**3.5**	**2.2**	**1.1**
Reference: U.S. EPA. 1998. Methyl parathion. MRID Nos. 40364103 and 142803. EPA special docket EPA-HQ-OPP-2007-0151.				
Test Species/Strain/Sex/Number: Sprague-Dawley rats (5/sex/group)				
Exposure Route/Concentrations/Durations: inhalation (nose-only); methyl parathion technical (80%); 0.108, 0.134, or 0.168 mg/L (equivalent to 108, 134, and 168 mg/m^3) for 4 hrs				
Effects: 108 mg/m^3 20% (2/10) lethality 134 mg/m^3 30% (3/10) lethality 168 mg/m^3 90% (9/10) lethality				
Endpoint/Concentration/Rationale: $BMCL_{05}$ of 66.6 mg/m^3				
Uncertainty Factors/Rationale: 30 Total uncertainty factor adjustment is Interspecies: 3; variability in the toxic responses is primarily a function of varying cholinesterase activity levels and types of cholinesterase present; humans have greater levels of plasma cholinesterase with which to bind chlolinesterase inhibiting agents such as methyl parathion than do other species. Intraspecies: 10; the documented variability in sensitivity among different age groups and genders, and the known genetic polymorphisms in A-esterases justifies retention of the intraspecies uncertainty factor of 10.				
Modifying Factor: none applied				
Animal to Human Dosimetric Adjustment: Not applicable				
Time Scaling: $C^n \times t = k$, where n = 1 or 3 (NRC, 2001)				
Data Adequacy: Data are limited to one species but consistent and adequate for AEGL-3 derivation.				

APPENDIX E: Category Plot for Methyl Parathion



Insufficient data for derivation of AEGL-1 values for methyl parathion.

1

Methyl parathion

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

Source	Species	Sex	# Exp.	mg/m3	Min.	Category	Comments
NAC/AEGL-1					10	AEGL	
NAC/AEGL-1					30	AEGL	
NAC/AEGL-1					60	AEGL	
NAC/AEGL-1					240	AEGL	
NAC/AEGL-1					480	AEGL	
NAC/AEGL-2				2.1	10	AEGL	
NAC/AEGL-2				1.5	30	AEGL	
NAC/AEGL-2				1.2	60	AEGL	
NAC/AEGL-2				0.73	240	AEGL	
NAC/AEGL-2				0.37	480	AEGL	
NAC/AEGL-3				6.4	10	AEGL	
NAC/AEGL-3				4.4	30	AEGL	
NAC/AEGL-3				3.5	60	AEGL	
NAC/AEGL-3				2.2	240	AEGL	
NAC/AEGL-3				1.1	480	AEGL	
	rat	m	1	185	240	PL	LC50 (Thyssen, 1979)
	rat	f	1	170	240	PL	LC50 (Thyssen, 1979)
	rat		1	240	34	PL	LC50 (Molnar et al., 1980)
	rat	b	1	240	108	PL	20% lethality (2/10) (U.S. EPA, 1998)
	rat	b	1	240	134	PL	30% (3/10) lethality (U.S. EPA, 1998)
	rat	b	1	240	168	PL	90% (9/10) lethality (U.S. EPA., 1998)
	rat	b	1	240	135	PL	LC50 (U.S. EPA, 1998)
	rat	b	1	90	106	3	100% lethality (U.S. EPA, 1998)
	rat	m	1	60	200	PL	LC50 (U.S. EPA, 1978) cited in ATSDR, 2001
	rat	m	1	240	120	PL	LC50 (U.S. EPA, 1978) cited in ATSDR, 2001

2

APPENDIX F: Benchmark Dose Derivations

U.S. EPA. 1998, rats; 4-hr, nose-only $BMCL_{05}$

==========

Probit Model. (Version: 2.8; Date: 02/20/2007)
Input Data File: C:\BMDS\UNSAVED1.(d)
Gnuplot Plotting File: C:\BMDS\UNSAVED1.plt

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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 = 4
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 = -23.7062
slope = 4.83096

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

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
background	0	NA		
intercept	-23.1845	7.5943	-38.0691	-8.29999
slope	4.71203	1.549	1.67604	7.74801

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	-14.3635	4			
Fitted model	-15.2604	2	1.79384	2	0.4078
Reduced model	-25.8979	1	23.0687	3	<.0001
AIC:	34.5208				

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Scaled Size	Residual
0.0000	0.0000	0.000	0	10	0.000
108.0000	0.1309	1.309	2	10	0.648
134.0000	0.4579	4.579	3	10	-1.002
168.0000	0.8314	8.314	9	10	0.579

Chi^2 = 1.76 d.f. = 2 P-value = 0.4148

Benchmark Dose Computation

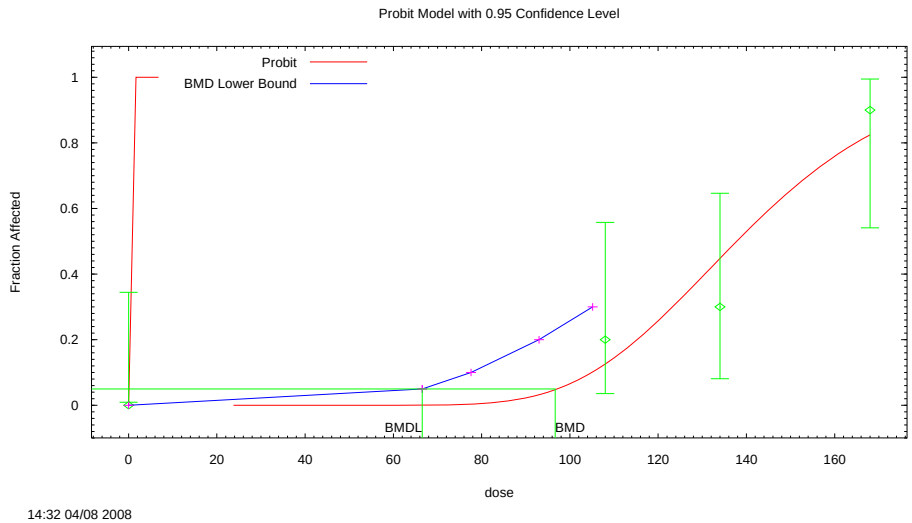
Specified effect = 0.05

Risk Type = Extra risk

Confidence level = 0.95

BMC = 96.6614

BMCL = 66.5521



14:32 04/08 2008

U.S. EPA, 1998. rats; 4-hr nose-only BMC_{01}

```
 ================================================================================
                          Probit Model. (Version: 2.8;  Date: 02/20/2007)
                        Input Data File: C:\BMDS\METHYLPARA05.(d)
                      Gnuplot Plotting File:  C:\BMDS\METHYLPARA05.plt
                                                                          Tue
Apr 08 14:44:12 2008
 ================================================================================

 BMDS MODEL RUN
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 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 = 4
   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    =   -23.7062
                    slope =      4.83096

          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       -23.1845        7.5943          -38.0691          -8.29999
         slope        4.71203         1.549           1.67604           7.74801

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	-14.3635	4			
Fitted model	-15.2604	2	1.79384	2	0.4078
Reduced model	-25.8979	1	23.0687	3	<.0001
AIC:	34.5208				

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Scaled Size	Residual
0.0000	0.0000	0.000	0	10	0.000
108.0000	0.1309	1.309	2	10	0.648
134.0000	0.4579	4.579	3	10	-1.002
168.0000	0.8314	8.314	9	10	0.579

Chi^2 = 1.76 d.f. = 2 P-value = 0.4148

Benchmark Dose Computation

Specified effect = 0.01
Risk Type = Extra risk
Confidence level = 0.95
BMC = 83.6454
BMCL = 49.6493