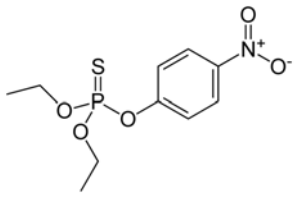
ACUTE EXPOSURE GUIDELINE LEVELS (AEGLs)

INTERIM

PARATHION (CAS Reg. No. 56-38-2)



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.

TABLE OF CONTENTS

PREFACE **2**

LIST OF TABLES **5**

EXECUTIVE SUMMARY **6**

1. INTRODUCTION *9*

2. HUMAN TOXICITY DATA *9*
2.1. Acute Lethality 9
2.2 Nonlethal Toxicity 9
2.3. Developmental/Reproductive Effects 9
2.4. Genotoxicity 9
2.5. Carcinogenicity 10
2.6. Summary 10

3. ANIMAL TOXICITY DATA *10*
3.1. Acute Lethality 10
3.1.1 Rats 10
3.3. Developmental/Reproductive Effects 12
3.4. Genotoxicity 12
3.5. Carcinogenicity 12

4. SPECIAL CONSIDERATIONS *12*
4.1. Metabolism and Disposition 12
4.2. Mechanism of Toxicity 13
4.3. Structure-Activity Relationships 13
4.4. Other Relevant Information 13
4.4.1. Species Variability 13
4.4.2. Susceptible Populations 14
4.4.3. Concurrent Exposure Issues 14

5. DATA ANALYSIS FOR AEGL-1 ..... *14*
5.1. Human Data Relevant to AEGL-1 14
5.2. Animal Data Relevant to AEGL-1 14
5.3. Derivation of AEGL-1 Values 14

6. DATA ANALYSIS FOR AEGL-2 ..... *14*
6.1. Human Data Relevant to AEGL-2 14
6.2. Animal Data Relevant to AEGL-2 15
6.3. Derivation of AEGL-2 Values 15

7. DATA ANALYSIS FOR AEGL-3 ..... *16*
7.1. Human Data Relevant to AEGL-3 16
7.2. Animal Data Relevant to AEGL-3 16
7.3. Derivation of AEGL-3 Values 16

8. SUMMARY OF AEGLs *17*
8.1. AEGL Values and Toxicity Endpoints 17
8.2. Comparisons with Other Standards and Guidelines 17
8.3. Data Adequacy and Research Needs 19

9. REFERENCES *20*

APPENDIX A: Derivation of AEGL Values **23**

APPENDIX B: Time Scaling Calculations **29**

APPENDIX C: Derivation Summary Tables 31

APPENDIX D: Benchmark Dose Derivations 35

APPENDIX E: Category Plot for Parathion 45

LIST OF TABLES

S-1. AEGL Values for parathion (mg/m^3).....7

TABLE 1. Chemical and physical data for parathion. 9
TABLE 2. AEGL-1 values for parathion.....14
TABLE 3. AEGL-2 Values for parathion (mg/m^3) 16
TABLE 4. AEGL-3 values for parathion (mg/m^3) 17
TABLE 5. AEGL Values for Parathion (mg/m^3) 17
TABLE 6. Extant Standards and Guidelines for Parathion (mg/m^3).....18

EXECUTIVE SUMMARY

Parathion (*O,O*-diethyl-*O*-(4-nitrophenyl)phosphorothioate) is an anticholinesterase organophosphate pesticide. The chemical is manufactured under numerous proprietary names and applied in various dilutions.

Information regarding inhalation exposure in humans is limited. Six-month occupational exposures to concentrations up to 0.8 mg/m^3 (estimated average exposure of 0.2–0.3 mg/m^3) resulted in depression of red blood cell and plasma cholinesterase activity that was reversible upon cessation of exposure. Most information on human exposure pertains to dermal contact in agricultural workers.

Animal data regarding nonlethal effects following acute inhalation exposure to parathion are limited to those assessing effects of parathion on respiratory parameters in rats (Pauluhn et al., 1987) and a 4-hour exposure study in dogs and rats (NIOSH, 1974). Pauluhn et al. (1987) reported that a one hour exposure to parathion at 63 mg/m^3 reduced plasma cholinesterase activity but failed to induce physiologically changes in pulmonary resistance or erythrocyte cholinesterase activity. These authors concluded that respiratory function was not as sensitive an indicator of exposure to cholinesterase inhibitors as was plasma cholinesterase depression. Exposure to 134 mg/m^3 for one hour resulted in acute cholinergic symptoms but did not provide details regarding the nature or severity of the response (Pauluhn et al., 1987). In the NIOSH (1974) study, dogs exposed for 4 hours to parathion concentrations up to 8.9 mg/m^3 exhibited a significant but reversible decrease in plasma and red blood cell (RBC) cholinesterase activity but no lethality. Nonlethal effects in rats exposed to parathion (31 to 230 mg/m^3) for 4 hours included decreased plasma and RBC cholinesterase activity, tremors, convulsion, salivation, respiratory difficulty and death at exposures at or above 50 mg/m^3.

Lethality data are limited to studies in rats and 4-hour LC_{50} values of 31.5 mg/m^3, 30 mg/m^3, and 84 mg/m^3, and a 1-hour LC_{50} value of 115 mg/m^3.

There is no evidence for genotoxicity or reproductive/developmental toxicity of parathion. Parathion is currently not classifiable as a human carcinogen.

The anticholinesterase activity of parathion is well described and its metabolism to the active metabolite, paraoxon, is well studied.

Data are insufficient for derivation of AEGL-1 values for parathion.

Information on AEGL-2 severity effects of parathion following inhalation exposure were limited. Human exposure data were unavailable and quantitative data from studies in laboratory species focused on only lethal responses. The exception was exposure-response data for tremors in rats exposed to parathion at various concentrations for 4 hours (NIOSH, 1974). These data were considered discontinuous quantal data and, therefore, appropriate for Benchmark Dose (U.S. EPA, 2007) analysis. The 4-hour $BMCL_{05}$ and 4-hour BMC_{01} values for these data were 32.3 mg/m^3 and 28.9 mg/m^3, respectively. Consistent with AEGL Standing Operating Procedures (2001), the lower value (BMC_{01}) was selected as the POD for AEGL-2 derivation. A total uncertainty factor adjustment of 30 was applied. The interspecies uncertainty factor was

limited to 3 because the mechanism of action of organophosphate anticholinesterases is well understood and their effect on cholinergic systems is consistent across species. Variability in responses is primarily a function of varying cholinesterase activity and types of cholinesterase. 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 parathion, thereby decreasing the availability of the compound to critical targets such as brain cholinesterase. 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 other organophosphate anticholinesterases (NRC, 2003). Data were unavailable with which to empirically derive a time scaling exponent (n) for the equation $C^n \times t = k$. Therefore, temporal scaling from the experimental durations 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).

The AEGL-3 values for parathion were derived using the BMC_{05} of 37.5 mg/m^3 derived from 4-lethality data in rats exposed for 4 hours to concentrations up to 230.5 mg/m^3; the 4-hour BMC_{01} was 41.1 mg/m^3. Uncertainty factor application and justifications, and time scaling are the same as those used in the derivation of the AEGL-2 values.

The AEGL values for parathion are summarized in Table S-1. The close proximity of the AEGL-2 and AEGL-3 values reflect the exposure-response relationship for this compound and other cholinesterase inhibitors. Uncertainty exists regarding the contribution of dermal exposure to the total dose in situations where both exposure routes are likely.

S-1. AEGL Values for 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)	2.8	1.9	1.5	0.96	0.48	BMC_{01} (28.9 mg/m^3) for tremors in rats exposed for 4 hrs; UF= 3 x 10 (NIOSH, 1974); n = 1 or 3
AEGL-3 (Lethality)	3.6	2.5	2.0	1.3	0.63	BMC_{01} (37.5 mg/m^3) for lethality in rats exposed for 4 hrs (NIOSH, 1974); UF = 3 x 10; n = 1 or 3

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

References

Brown, H.V., Bush, A,F. 1950. Parathion inhibition of cholinesterase. Arch. Ind, Hyg. Occup. Med. 1: 633-636.

NIOSH (National Institute of Occupational Safety and Health) 1974. Inhalation and oral toxicity studies of ethyl parathion administered acutely and subacutely to the rat and dog. Report No. 00134578. Edgewood Arsenal, Toxicology Division, Aberdeen Proving Ground, Maryland.

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.

NRC (National Research Council). 2003. Acute Exposure Guideline Levels for Selected Airborne Contaminants: Nerve agents GA, GB, GD, GF, and VX. Vol. 3. Committee on Toxicology, Board on Toxicology and Environmental Health Hazards, Commission on Life Sciences, National Research Council. National Academy Press, Washington, DC.

Pauluhn, J., Machemer, L., Kimmerle, G. 1987. Effects of inhaled cholinesterase inhibitors on bronchial tonus and on plasma and erythrocyte acetylchlolinesterase activity in rats. Toxicology 46: 177-190.

U.S. EPA (U.S. Environmental Protection Agency). 2007. Benchmark Dose Software. Version 1.4.1. National Center for Environmental Assessment, Office of Research and Development. [Online]. Available: http://www.epa.gov/ncea/bmds.htm

1. INTRODUCTION

Parathion (*O,O*-diethyl-*O*-(4-nitrophenyl)phosphorothioate) is an anticholinesterase organophosphate pesticide. The chemical is manufactured under numerous proprietary names and applied in various dilutions. Technical parathion is generally 98% pure (Gallo and Lawryk, 1991). The physical/chemical properties of parathion are summarized in Table1.

TABLE 1. Chemical and physical data for parathion.

Parameter	Value	Reference
Synonyms	ethyl parathion ; O,O-diethyl O-p-nitrophenyl phosphorothioate ; DNTP ; Bladan® ; Paraphos® ; Alkron® *	ACGIH, 2003
Chemical formula	$C_{10}H_{14}NO_5PS$	ACGIH, 2003
Molecular weight	291.27	O'Neil et al., 2001
CAS Registry No.	56-38-2	O'Neil et al., 2001
Physical state	liquid	O'Neil et al., 2001
Solubility in water	Very slightly soluble	ACGIH, 2003
Vapor pressure	3.78×10^{-5} torr @ 20°C	ACGIH, 2003
Boiling point/Melting point	375°C @ 760 torr/6°C	ACGIH, 2003/O'Neil et al., 2001
Conversion factors in air	1 ppm = 11.9 mg/m^3 1 mg/m^3 = 0.08 ppm	

***** not all registered trade names for parathion preparations have been cited

2. HUMAN TOXICITY DATA

2.1. Acute Lethality

No data are available regarding human mortality following inhalation exposure.

2.2 Nonlethal Toxicity

Brown and Bush (1950) measured plasma and erythrocyte cholinesterase activity in workers at a parathion manufacturing plant. Area sampling of air found parathion concentrations up to 8 mg/10 m^3 (0.8 mg/m^3) with average levels at 2-3 mg/10 m^3 (0.2-0.3 mg/m^3). Over the 6-month monitoring period, plasma cholinesterase activity declined (about 25%) but recovered fully after cessation of parathion manufacturing. The authors noted that changes in red blood cell cholinesterase activity were less conclusive. Although area parathion levels in air were determined, the actual exposure of individuals could not be determined due to the highly variable and intermittent exposures and the fact that personal (breathing zone) data were not collected.

2.3. Developmental/Reproductive Effects

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

2.4. Genotoxicity

No information regarding potential genotoxicity of parathion in humans was available.

2.5. Carcinogenicity

No information regarding the carcinogenic potential of parathion in humans was available.

2.6. Summary

Information regarding inhalation toxicity of parathion in humans was limited to occupational monitoring data (area data) and assessments of decreased plasma cholinesterase activity but no definitive exposure-response data.

3. ANIMAL TOXICITY DATA

3.1. Acute Lethality

3.1.1 Rats

In a study conducted at Edgewood Arsenal (NIOSH, 1974), groups of 35 male rats (Sprague-Dawley cross Wistar) were exposed for 4 hours to parathion (technical grade) at concentrations up to 230.5 mg/m^3 (Table 2). Seventy one rats were used as baseline controls for cholinesterase activity and additional rats used as controls for various parathion exposures (no further details provided). The rats were exposed (whole-body) in a 1000 L dynamic flow chamber. The chamber atmosphere was sampled (frequency of sampling not specified) using fiberglass filter pads. The parathion on the pads was diluted with isopropyl alcohol and analyzed by gas chromatography. A Rochester cascade impactor was used to determine particle size but no data were provided. A 14-day observation period was implied by the fact that blood samples were reportedly collected over this time period. No time-to-death information was provided. A 4-hour LC_{50} of 84 mg/m^3 (78.0-90.4 95% c.i.) was reported.

Table 2. Response frequency of male rats exposed to parathion for4 hrs

Parathion conc. (mg/m^3)	Tremors	Convulsions	Mortality
31.0	0/34	0/34	0/34
35.0	0/34	0/34	0/34
50.0	8/34	3/34	3/34
71.0	19/34	4/34	10/34
97.0	28/34	19/34	25/34
100.6	26/34	21/34	22/34
118.5	29/34	21/34	28/34
230.5	31/34	25/34	34/34

NIOSH, 1974

Kimmerle and Lörke (1968) reported rat 1- and 4-hour LC_{50} values of 0.115 and 0.0315 mg/L, respectively, (equivalent to 115 and 31.5 mg/m^3). The report stated that the values were based upon experiments using 20 male rats "per experiment" and a 14-day observation period. It was noted that the exposure system was designed such that only inhalation exposure was possible and that test article concentrations were determined analytically (no details provided).

In a Good Laboratory Practices guideline study conducted by Cheminova Agro A/S in 1986 (summarized in IUCLID, 2000), groups of 10 rats (males and females) were exposed to parathion (97.1%) for 4 hours. Although several exposure groups were implied by lethality incidences of 2/10 (only females died), 5/10 (only females died), and 10/10, no group-specific exposure concentrations were specified in the IUCLID summary of this industry submission. A 4-hour LC_{50} of 0.03 mg/L (95% c.i. of 0.044-0.021 mg/L equivalent to 30 mg/m^3; 21-44 mg/m^3, c.i.) for rats (gender/strain not reported) was reported. Two female rats exposed to 0.012 mg/L (12 mg/m^3) exhibited tremors following exposure (time not specified) and all surviving female rats exhibited lethargy and hypokinesia at 1 day post exposure. Although not specifically stated , the reference to "surviving" females implied that some lethality may have occurred following exposure to 12 mg/m^3.

Deichmann et al. (1952) stated that a 2-hour exposure to 3-4 mg parathion/m^3 was lethal to rats.

3.1.2 Summary of Lethality Data

In summary, information on the lethality of parathion following inhalation exposure is limited to bioassays in rats. Three studies reported 4-hour LC_{50} values; 31.5 mg/m^3, 30 mg/m^3, and 84 mg/m^3. A 1-hour LC_{50} of 115 mg/m^3 has also been reported.

3.2. Nonlethal Toxicity

3.2.1. Rats

Pauluhn et al. (1987) exposed young (180-200 g) adult male and female Bor:WISW (SPF-Cpb) Wistar rats (5/sex/group) head-nose only for 1 hour to parathion (technical grade). The material was nebulized under dynamic flow conditions into a cylindrical 20 liter chamber. The vehicle was a mixture of 50% ethanol and 50% polyethylene glycol. The MMAD of the generated aerosol was 1-2 µm (σ_g = 1.5-2), thereby optimizing inhalability. Samples of the test atmosphere were collected from the breathing zone of the rats using cotton wool-packed glass tubes and subsequent analysis by gas chromatography. Blood collected from the retroorbital sinus prior to and following exposure was used for plasma and red blood cell cholinesterase assessment. Pulmonary function testing was performed using a Pulmonary Mechanics Analyzer on anesthetized (hexabarbital sodium) rats in a whole-body flow plethysmograph. Tidal volume, respiratory rate, minute volume, lung resistance and lung dynamic compliance were assessed in anesthetized rats following acetylcholine provocation (parathion was expected to accentuate the pulmonary responses to acetylcholine). The investigators found that a one hour exposure to parathion at 63 mg/m^3 reduced plasma cholinesterase activity but there were no physiologically significant effects on lung resistance or erythrocyte cholinesterase activity; respiratory function was not as sensitive an indicator of exposure as was plasma cholinesterase activity. The investigators noted that exposure to 134 mg/m^3 resulted in acute cholinergic symptoms but did not provide details regarding the nature or severity of the response.

In a NIOSH-sponsored study (NIOSH, 1974), 4-hour-hour exposure of rats to parathion at concentrations of 31.0 or 35.0 mg/m^3 was not lethal and did not cause tremors or convulsions (see Table 2). Exposure to these concentrations, while not causing tremors or convulsions, resulted in evidence of nasal irritation within 1 hour, and diarrhea, incontinence and lethargy at 3-4 hours into exposure. Exposure to parathion at concentrations of 50 mg/m^3 or greater induced

salivation, respiratory difficulty, tremors, convulsions, and death. The effects were exposure concentration-related. An ED_{50} of 73.67 mg/m^3 (67.15-80.83 mg/m^3 c.i.) for tremors and an ED_{50} of 110.6 mg/m^3 (96.0-127.4 mg/m^3, c.i.) for convulsions were reported.

3.2.2. Dogs

Plasma and RBC cholinesterase activity were assessed in groups of 4 adult male beagle dogs were exposed to parathion at concentrations of 0.0153, 0.145, 3.42, 8.93, or 37.13 mg/m^3 for 4 hours (NIOSH, 1974). Compared to pre-exposure baseline values, both RBC and plasma cholinesterase activity were notably decreased with maximum reductions varying between 24 hours and 7 days. The decreases in cholinesterase activity exhibited considerable variability among and within the exposure groups. It was reported that a ChE_{50} (statistically-derived concentration that would consistently induce a 50% decrease in cholinesterase activity) could not be determined due to extreme level of depression and the lack of additional dogs for testing at lower exposures. Both plasma and RBC cholinesterase activity exhibited recovery.

3.3. Developmental/Reproductive Effects

No information is available in the open literature regarding potential developmental and reproductive toxicity of parathion following inhalation exposure.

3.4. Genotoxicity

IARC (1983) reviewed the literature and found no genotoxic effects in several species of microorganism: *Escherichia coli, Salmonella typhimurium, Serratia marcascens, Sacccharmoyces cerevisiae,* and *Schizosaccharomyces pombe* with or without metabolic activation. Sex-linked recessive mutations were not detected in *Drosophila melanogaster*, and there was no evidence for induction of unscheduled DNA synthesis in human fibroblasts.

3.5. Carcinogenicity

No inhalation exposure studies were available that evaluated the carcinogenic potential of parathion following inhalation exposure. Parathion is currently not classifiable as a human carcinogen (ACGIH, 2003). IARC (1983) found that there is inadequate evidence to evaluate the carcinogenicity of parathion to experimental animals and that no data on humans were available. The available data were insufficient to evaluate the carcinogenicity of parathion to humans.

4. SPECIAL CONSIDERATIONS

4.1. Metabolism and Disposition

Respiratory tract absorption of parathion is rapid and complete, although exposure is limited due to the low vapor pressure (Gallo and Lawryk, 1991; see Table 1). Based upon default respiratory parameters and the vapor pressure at 25°C, Gallo and Lawryk (1991) estimated a total dose of 0.14 mg/kg/day for a human adult at rest. Parathion is rapidly and extensively metabolized in the liver. The compound is converted (via desulfuration) to the more toxic paraoxon metabolite by microsomal enzymes. Detoxication occurs via dearylation,

aliesterase phosphorylation and A-esterase-mediated hydrolysis (Chambers et al., 1994) with diethylphopshate, 3,5,6-trichloropyridinol, and paranitrophenol being major metabolites.

4.2. Mechanism of Toxicity

Initial studies on the lethality and mode of action in multiple species showed parathion was a potent inhibitor of cholinesterase (DuBois et al., 1949). Like other organophosphates, parathion inhibits acetylcholinesterase resulting in an excess of acetylcholine resulting at neuronal synapses and myoneural junctions. Metabolism to paraoxon is necessary for this activity. The oxon phosphorylates cholinesterase by phosphorylating the serine hydroxyl group of the esteratic subsite of the enzyme which in turn prevents the enzyme from deactivating acetylcholine (Taylor, 1985; Vale, 1998). The overall result is an enhancement of cholinergic-mediated function (e.g., miosis, salivation, sweating, muscle fasciculations and tremors). Detoxication of paraoxon may occur via hydrolysis by A-esterases found in various tissues and by aliesterases (carboxylesterases) (Pond et al., 1995).

4.3. Structure-Activity Relationships

Although all organophosphate anticholinergic agents 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

Quantitative data are not available to assess species variability in the toxic response to inhaled parathion *per se*. 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).

4.4.3. Concurrent Exposure Issues

Concurrent exposure to other organophosphates or carbamates may be critical in determining potential hazard. Simultaneous direct skin contact with parathion may increase the total absorbed dose and increase the potential hazard.

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

No animal data were located in the open literature to assess AEGL-1 severity responses following acute inhalation exposure to parathion.

5.3. Derivation of AEGL-1 Values

Data are insufficient for derivation of AEGL-1 values for parathion (Table 2).

TABLE 2. AEGL-1 values for 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

Quantitative data regarding AEGL-2 severity adverse health effects in humans who inhaled parathion were not available. The report by Brown and Bush (1950), although

indicating depression of plasma cholinesterase activity in workers exposed to parathion (up to 0.8 mg/m^3), lacks definitive exposure terms.

6.2. Animal Data Relevant to AEGL-2

Data with which to develop AEGL-2 values for airborne parathion are limited. Most lethality bioassays reported lethal response data, but they neither provided information on sublethal effects nor did these reports identify any exposures that were without lethal responses. The respiratory function assay conducted by Pauluhn et al (1987) reported that 1-hour exposures of rats to 63 mg parathion/m^3 decreased plasma cholinesterase activity with no observable effects on lung resistance and no effect on erythrocyte cholinesterase activity. Similar exposure to 134 mg/m^3 induced signs of acute cholinergic stimulation although the nature and severity of these effects were not described.

Unlike the aforementioned publications, the NIOSH (1974) report described inhibition of plasma and RBC cholinesterase activity in dogs exposed to parathion for 4 hours. Although substantially decreased, the changes in these enzyme activity levels were highly variable and not correlated with AEGL-2 severity effects. This reports also provided quantitative exposure-response data for tremors and convulsions in rats exposed to parathion for 4 hours at concentrations ranging from 31 to 230.5 mg/m^3.

6.3. Derivation of AEGL-2 Values

The exposure-response data for parathion-induced tremors in rats exposed for 4 hours (NIOSH, 1974) were considered discontinuous quantal data and appropriate for analysis using the Benchmark Dose software (U.S. EPA, 2007). The 4-hour $BMCL_{05}$ and 4-hour BMC_{01} values for these data were 32.3 mg/m^3 and 28.9 mg/m^3, respectively. Consistent with AEGL Standing Operating Procedures (NRC, 2001), the lower value (BMC_{01}) was selected as the POD for AEGL-2 derivation (Appendix A). The validity of the AEGL-2 values is supported by the data of Pauluhn et al. (1987) showing that a 1-hour exposure of rats to 134 mg parathion/m^3 produced signs of acute cholinergic toxicity (i. e.; applying the total uncertainty factor of 30 to this exposure results in a 1-hour exposure concentration which is notably greater (4.5 vs 1.5 mg/m^3) than the 1-hour AEGL-2). Additionally, Brown and Bush (1950) reported that up to 0.8 mg/m^3 (specific duration not stated but assumed to be for more than several hours in an occupational setting) resulted in decreased red blood cell and plasma cholinesterase activity levels but no effects consistent with AEGL-2 tier severity.

As described in Sections 4.2 and 4.4.1 the mechanism of action of organophosphate anticholinesterases is well understood and their effect on cholinergic systems shown to be the same across species. Variability in responses is primarily a function of varying cholinesterase activity and types of cholinesterase. 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 parathion, thereby decreasing the availability of the compound to critical targets such as brain cholinesterase. Therefore, the interspecies uncertainty was 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. These uncertainty factors and their rationale are the same as those applied in the

derivation of other organophosphate anticholinesterases (NRC, 2003). The total uncertainty factor application is 30.

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

Classification	10-min	30-min	1-h	4-h	8-h
AEGL-2	2.8	1.9	1.5	0.96	0.48

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

Animal data relevant to derivation of AEGL-3 values for parathion include 1-hour and 4-hour rat LC_{50} values of 115 and 31.5 mg/m^3, respectively reported by Kimmerle and Lörke (1968) and a 4-hour rat LC_{50} value of 30 mg/m^3 for a GLP guideline study by Cheminova Agro A/S (reported in IUCLID, 2000). Response data for specific exposure groups were not available for these studies, which precluded calculation of a lethality threshold value. A study conducted at Aberdeen Proving Ground (NIOSH, 1974) provided exposure-response data on rats exposed to various concentrations of parathion for 4 hours. The responses among the test groups (34 rats/group) ranged from no lethality to 100 % lethality. Also provided in this report was a 4-hour LC_{50} of 84.0 mg/m^3.

7.3. Derivation of AEGL-3 Values

The rat lethality data from the NIOSH (1974) report were selected for AEGL-3 derivation. Parathion concentrations for the test groups ranged from 31 to 230.5 mg/m^3 which included effects ranging from minimal effects to100% lethality. Benchmark Dose analysis (U.S. EPA, 2007) of these data provided a 4-hour $BMCL_{05}$ of 37.5 mg/m^3 and a 4-hour BMC_{01} of 41.1 mg/m^3 (Appendix D). The 4-hour $BMCL_{05}$ (37.5 mg/m^3) was used as an estimate of the lethality threshold and the POD for AEGL-3 derivation.

Uncertainty factor application is the same as for AEGL-2 derivation (Section 6.3) and is justified by the fact that all of the effects of parathion from cholinesterase inhibition to tremors, convulsions and death are a continuum of the same mode of action (NRC, 2003).

The AEGL-3 values for parathion are shown in Table 4 and their derivation is presented in Appendix A.

TABLE 4. AEGL-3 values for parathion (mg/m^3)					
Classification	**10-min**	**30-min**	**1-h**	**4-h**	**8-h**
AEGL-3	3.6	2.5	2.0	1.3	0.63

8. SUMMARY OF AEGLs

8.1. AEGL Values and Toxicity Endpoints

Data were unavailable with which to develop AEGL-1 values. Exposure-response data for AEGL-2 severity effects included qualitative descriptions of effects consistent with cholinesterase inhibition but were usually associated with exposures that ultimately resulted in death. A single 4-hour exposure study provided quantitative data allowing for analysis and estimation of a threshold for parathion-induced tremors in rats. The induction of tremors was considered a component in the continuum of parathion-induced toxicity. These tremor response data were considered discontinuous quantal type data appropriate for Benchmark Dose analysis (the 4-hr BMC_{01} for tremors) and were used as the basis for the POD for AEGL-2 derivation. The AEGL-3 values were based upon an estimated lethality ($BMCL_{05}$) threshold in rats following a single 4-hour exposure to parathion.

TABLE 5. AEGL Values for 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)	2.8	1.9	1.5	0.96	0.48
AEGL-3 (Lethality)	3.6	2.5	2.0	1.3	0.63

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

A comparison of the AEGL values for parathion to other guidelines and standards for this compound is summarized in Table 6.

TABLE 6. Extant Standards and Guidelines for Parathion (mg/m^3)

Guideline	Exposure Duration				
	10 min	30 min	1 h	4 h	8 h
AEGL-1	NR	NR	NR	NR	NR
AEGL-2	2.8	1.9	1.5	0.96	0.48
AEGL-3	3.6	2.5	2.0	1.3	0.63
ERPG-1 (AIHA)[a]					
ERPG-2 (AIHA)					
ERPG-3 (AIHA)					
EEGL (NRC)[b]					
PEL-TWA (OSHA)[c]					0.1
PEL-STEL (OSHA)[d]					
IDLH (NIOSH)[e]		10			
REL-TWA (NIOSH)[f]					0.05
REL-STEL (NIOSH)[g]					
TLV-TWA (ACGIH)[h]					0.05
TLV-STEL (ACGIH)[i]					
MAK (Germany)[j]					
MAK Spitzenbegrenzung (Germany)[k]					0.1
Einsaztoleranzwert (Germany)[l]					
MAC-Peak Category (The Netherlands)[m]					0.1

[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 2000) is defined analogous to the ACGIH-Ceiling.

8.3. Data Adequacy and Research Needs

Although toxicity data were sufficient for developing AEGL-2 and AEGL-3 values, definitive exposure-response data for nonlethal effects of inhalation exposure to parathion are limited and not available for AEGL-1 tier effects. Comparison of the AEGL-2 values to limited occupational exposure data suggests the AEGL-2 values are appropriate. The close proximity of the AEGL-2 and AEGL-3 values reflect the exposure-response relationship for this compound and other cholinesterase inhibitors. There exists uncertainty regarding the contribution of dermal exposure to the total dose in situations where both exposure routes are likely.

9. REFERENCES

AIHA (American Industrial Hygiene Association). 2006. The AIHA 2007 Emergency Response Planning Guidelines and Workplace Environmental Exposure Level Handbook. Amer. Ind. Hyg. Assoc., Fairfax, Virginia.

ACGIH (American Conference of Governmental Industrial Hygienists). 2003. Parathion. Documentation of the Threshold Limit Values and Biological Exposure Indices. Suppl. to the 7th edition. ACGIH, Cincinnati, OH.

ACGIH (American Conference of Governmental Industrial Hygienists). 2007. Threshold Limit Values and Biological Exposure Indices. American Conference of Governmental Industrial Hygienists, Inc. Cincinnati, OH.

Brown, H.V., Bush, A,F. 1950. Parathion inhibition of cholinesterase. Arch. Ind, Hyg. Occup. Med. 1: 633-636.

Chambers, J.E., Ma, T., Boone, J.S., Chambers, H.W. 1994. Role of detoxication pathways in acute toxicity levels of phosphorothionate insecticdes in the rat. Life Sciences 54: 1357-1364.

Deichmann, W.B., Pugliese, W., Cassidy,J. 1952. Effects of dimethyl and diethyl paranitrophenyl thiophosphate on experimental animals. Arch. Ind. Hyg. Occup. Med. 5: 44-51. (cited in ACGIH, 2003).

DFG(Deutsche Forschungsgemeinschat). 2007. List of MAK and BAT Values. Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim.

DuBois, K.P., Doull, J., Salerno, P.R., Coon, J. M. 1949. Studies on the toxicity and mechanism of action of p-nitrophenyl diethyl thionophosphate (Parathion). J. Pharmacol. Exp. Ther. 95: 79-91.

Ellin, R. I. 1981. Anomalies in theories and therapy of intoxication by potent organophosphorous anticholinesterase compounds. U.S. Army Medical Research and Development Command, Biomedical Laboratory, Report No. USABML-SP-81-003. Aberdeen Proving Ground, MD. DTIC, AD A1010364.

Gallo, M.A., Lawryk, N.J. 1991. Organic phosphorus pesticides. In: Hayes, W.J., Laws, E.R., Jr. Eds. Handbook of Pesticide Toxicology, vol. 2, Academic Press, Inc. New York, New York.

Haber, F.R. 1924. Zur geschichte des gaskrieges [On the history of the gas war]. In: Fuenf Vortraege aus den Jahren 1920-23 [Five lectures from the years 1920-1923]. Berlin, Germany: Verlag von Julius Springer; pp. 76-92.

IARC (International Agency for Research on Cancer). 1983. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans, Vol. 30, Miscellaneous Pesticides. (cited in ACGIH, 2003)

IUCLID (International Uniform Chemical Information Database). 2000. Parathion, CAS No. 56-38-2. European Commission, European Chemicals Bureau.

Kimmerle, G. and D. Lorke. 1968. Toxicology of insecticidal organophosphates. Pflanzenschutz-Nacher 21:111-142.

NIOSH (National Institute of Occupational Safety and Health) 1974. Inhalation and oral toxicity studies of ethyl parathion administered acutely and subacutely to the rat and dog. Report No. 00134578. Edgewood Arsenal, Toxicology Division, Aberdeen Proving Ground, Maryland.

NIOSH (National Institute for Occupational Safety and Health). 2005. NIOSH Pocket Guide to Chemical Hazards**.** Parathion. CDC/NIOSH. Retrieved at http://www.cdc.gov/niosh/npg/npgd0427.html

NRC (National Research Council), 1985. Emergency and continuous exposure guidance levels f or selected airborne contaminants. Committee on Toxicology, Board on Toxicology and Environmental Health, Commission on Life Sciences. National Academy Press, Wash., D.C., Vol. 5.

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.

NRC (National Research Council). 2003. Acute Exposure Guideline Levels for Selected Airborne Contaminants: Nerve agents GA, GB, GD, GF, and VX. Vol. 3. Committee on Toxicology, Board on Toxicology and Environmental Health Hazards, Commission on Life Sciences, National Research Council. National Academy Press, Washington, DC

O'Neil, M.J., Smith, A., Heckelman, P.E., et al. 2001. The Merck Index. 13th ed. Merck & Co., Inc. Whitehouse Station, NJ. P. 1088.

OSHA (Occupational Safety and Health Administration). 2007. Table Z-1 Limits for Air Contaminants. 1910.1000 TABLE Z-1. Retrieved online at http://www.osha.gov

Pauluhn, J., Machemer, L., Kimmerle, G. 1987. Effects of inhaled cholinesterase inhibitors on bronchial tonus and on plasma and erythrocyte acetylchlolinesterase activity in rats. Toxicology 46: 177-190.

Pond, A.L., Chambers, H.W., Chambers, J.E. 1995. Organophosphate detoxication potential of various rat tissues via A-esterase and aliesterase activities. Toxicology Letters 78: 245-252.

Rinehart, W. E., Hatch, T. 1964. Concentration-time product (CT) as an expression of dose in sublethal exposures to phosgene. Ind. Hyg. J. 25: 545-553.

Taylor, P. 1985. Anticholinesterase agents. In: Gilman, A.G., Goodman, L.S., Rall, T.W., Murad, F., eds. The Pharmacological Basis of Therapeutics. MacMillan Publ. Co., New York., pp. 110-129.

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.

Vale, J.A. 1998. Toxicokinetics and toxicodynamic aspects of organophosphorous (OP) insecticide poisoning. Toxicology Letters 102-103: 649-652.

Van Bao T., I. Szabo, P. Ruzicska, and A. Czeizel. 1974. Chromosome aberrations in patients suffering acute organic phosphate insecticide intoxication. Humangenetik 24:33-57. As cited in Cal/EPA 1999.

Wills, J.H. 1972. The measurement and significance of changes in the cholinesterase activities of erythrocytes and plasma in man and animals. CRC. Crit. Rev. Toxicol. 1:153-202.

APPENDIX A: Derivation of AEGL Values

Derivation of AEGL-1 Values for Parathion

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

Derivation of AEGL-2 Values for Parathion

Key study: NIOSH (National Institute of Occupational Safety and Health) 1974. Inhalation and oral toxicity studies of ethyl parathion administered acutely and subacutely to the rat and dog. Report No. 00134578. Edgewood Arsenal, Toxicology Division, Aberdeen Proving Ground, Maryland.

Critical effect: POD is an estimate (BMC_{01} = 28.9 mg/m^3) of the threshold for muscle tremors based upon exposure-response data for rats exposed to parathion for 4 hours.

Time scaling: The concentration-exposure time relationship for many irritant and systemically acting vapors and gases may be described by $C^n \times t = k$, where the exponent n ranges from 0.8 to 3.5 (ten Berge et al. 1986). Data are unavailable with which to evaluate the exposure time-exposure concentration relationship and empirical derivation of the exponent, *n*, for the relationship $C^n \times t = k$ is not possible. Therefore, temporal scaling was performed using n = 3, when extrapolating to the shorter AEGL-specific time points and an n = 1 for extrapolating to the 8-hour AEGL duration (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 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: (28.9 mg/m^3) x 4 hrs = 115.6 mg-hrs/m^3
(28.9 mg/m^3)^3 x 4 hrs = 96,550.3 mg^3-hrs/m^3

10-minute AEGL-2

$C^3 \times 0.167 \text{ hrs} = 96{,}550.3 \text{ mg/m}^3 \cdot \text{hrs}$

$C = 83.3 \text{ mg/m}^3$

$C = 83.3 \text{ mg/m}^3 / 30 = 2.8 \text{ mg/m}^3$

30-minute AEGL-2

$C^3 \times 0.5 \text{ hrs} = 96{,}550.3 \text{ mg/m}^3 \cdot \text{hrs}$

$C = 57.8 \text{ mg/m}^3$

$C = 57.8 \text{ mg/m}^3 / 30 = 1.9 \text{ mg/m}^3$

1-hour AEGL-2

$C^3 \times 1 \text{ hr} = 96{,}550.3 \text{ mg/m}^3 \cdot \text{hrs}$

$C = 45.9 \text{ mg/m}^3$

$C = 45.9 \text{ mg/m}^3 / 30 = 1.5 \text{ mg/m}^3$

4-hour AEGL-2

$C^1 \times 4 \text{ hrs} = 115.6 \text{ mg/m}^3 \cdot \text{hrs}$

$C = 28.9 \text{ mg/m}^3$

$C = 28.9 \text{ mg/m}^3 / 30 = 0.96 \text{ mg/m}^3$

8-hour AEGL-2

$C^1 \times 8 \text{ hrs} = 115.6 \text{ mg/m}^3 \cdot \text{hrs}$

$C = 14.5 \text{ mg/m}^3$

$C = 14.5 \text{ mg/m}^3 / 30 = 0.48 \text{ mg/m}^3$

Derivation of AEGL-3 Values for Parathion

Key study: NIOSH (National Institute of Occupational Safety and Health) 1974. Inhalation and oral toxicity studies of ethyl parathion administered acutely and subacutely to the rat and dog. Report No. 00134578. Edgewood Arsenal, Toxicology Division, Aberdeen Proving Ground, Maryland.

Critical effect: lethality; POD is an estimate ($BMCL_{05}$ = 37.5 mg/m^3) of the lethality threshold based upon lethal response of rats following a 4-hour exposure to parathion.

Time scaling: The concentration-exposure time relationship for many irritant and systemically acting vapors and gases may be described by $C^n \times t = k$, where the exponent n ranges from 0.8 to 3.5 (ten Berge et al. 1986). Data are unavailable with which to evaluate the exposure time-exposure concentration relationship and empirical derivation of the exponent, *n*, for the relationship $C^n \times t = k$ is not possible. Therefore, temporal scaling was performed using n = 3, when extrapolating to the shorter AEGL-specific time points and an n = 1 for extrapolating to the 8-hour AEGL duration (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 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: (37.5 mg/m^3) x 4 hrs = 150 mg-hrs/m^3
(37.5 mg/m^3)^3 x 4 hrs = 210,937.5 mg^3-hrs/m^3

10-minute AEGL-3

$C^3 \times 0.167 \text{ hrs} = 210{,}937.5 \text{ mg/m}^3 \cdot \text{hrs}$

$C = 108.1 \text{ mg/m}^3$

$C = 108.1 \text{ mg/m}^3 / 30 = 3.6 \text{ mg/m}^3$

30-minute AEGL-3

$C^3 \times 0.5 \text{ hrs} = 210{,}937.5 \text{ mg/m}^3 \cdot \text{hrs}$

$C = 75.0 \text{ mg/m}^3$

$C = 75.0 \text{ mg/m}^3 / 30 = 2.5 \text{ mg/m}^3$

1-hour AEGL-3

$C^3 \times 1 \text{ hr} = 210{,}937.5 \text{ mg/m}^3 \cdot \text{hrs}$

$C = 59.5 \text{ mg/m}^3$

$C = 59.5 \text{ mg/m}^3 / 30 = 2.0 \text{ mg/m}^3$

4-hour AEGL-3

$C^1 \times 4 \text{ hrs} = 150 \text{ mg/m}^3 \cdot \text{hrs}$

$C = 37.5 \text{ mg/m}^3$

$C = 37.5 \text{ mg/m}^3 / 30 = 1.3 \text{ mg/m}^3$

8-hour AEGL-3

$C^1 \times 8 \text{ hrs} = 150 \text{ mg/m}^3 \cdot \text{hrs}$

$C = 18.8 \text{ mg/m}^3$

$C = 18.8 \text{ mg/m}^3 / 30 = 0.63 \text{ mg/m}^3$

APPENDIX B: 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 parathion. The concentration-exposure time relationship for many irritant and systemically acting vapors and gases may be described by $C^n \times t = k$, where the exponent n ranges from 0.8 to 3.5 (ten Berge et al. 1986). Data are unavailable with which to evaluate the exposure time-exposure concentration relationship and empirical derivation of the exponent, n, for the relationship $C^n \times t = k$ is not possible. Therefore, temporal scaling was performed using n = 3, when extrapolating to the shorter AEGL-specific time points and an n of 1 for extrapolating to the 8-hour AEGL duration (NRC 2001).

APPENDIX C: Derivation Summary Tables

ACUTE EXPOSURE GUIDELINE LEVELS FOR PARATHION DERIVATION SUMMARY

AEGL-1 VALUES FOR PARATHION (ppm)				
10 min	**30 min**	**1 h**	**4 h**	**8 h**
NR	NR	NR	NR	NR
Reference: not applicable				
Test Species/Strain/Number: not applicable				
Exposure Route/Concentrations/Durations : not applicable				
Effects: not applicable				
Endpoint/Concentration/Rationale:				
Uncertainty Factors/Rationale: not applicable				
Modifying Factor: not applicable				
Animal to Human Dosimetric Adjustment: not applicable				
Time Scaling: not applicable				
Data Adequacy: Data are insufficient for derivation of AEGL-1 values for 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 PARATHION (mg/m^3)				
10 min	**30 min**	**1 h**	**4 h**	**8 h**
2.8	**1.9**	**1.5**	**0.96**	**0.48**

Reference: NIOSH (National Institute of Occupational Safety and Health) 1974. Inhalation and oral toxicity studies of ethyl parathion administered acutely and subacutely to the rat and dog. Report No. 00134578. Edgewood Arsenal, Toxicology Division, Aberdeen Proving Ground, Maryland.

Test Species/Strain/Sex/Number: male Sprague-Dawley x Wistar rats/34 per group

Exposure Route/Concentrations/Durations: inhalation, 4 hrs, 0, 31.0, 35.0, 50.0, 71.0, 97.0, 100.6, 118.5, 230.5 mg/m^3; analytically measured using gas chromatography

Effects: tremors were considered the critical effect for AEGL-2 derivation.

Conc. (mg/m^3)	**Tremors**	Convulsions	Mortality
31.0	**0/34**	0/34	0/34
35.0	**0/34**	0/34	0/34
50.0	**8/34**	3/34	3/34
71.0	**19/34**	4/34	10/34
97.0	**28/34**	19/34	25/34
100.6	**26/34**	21/34	22/34
118.5	**29/34**	21/34	28/34
230.5	**31/34**	25/34	34/34

Endpoint/Concentration/Rationale: The 4-hr BMC_{01} of 28.9 mg/m^3 was used as the POD; the 4-hr $BMCL_{05}$ was 32.3 mg/m^3

Uncertainty Factors/Rationale: 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 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

Animal to Human Dosimetric Adjustment: not applicable

Time Scaling: $C^n \times t = k$, where n = 1 or 3 (NRC, 2001)

Data Adequacy: the critical effect is appropriate for AEGL-2 derivation and is consistent with the continuum of effects for a cholinesterase inhibitor such as parathion. The exposure-response data come from a well-described study using an adequate number of animals per exposure group.

2

1

AEGL-3 VALUES FOR PARATHION (mg/m^3)				
10 min	**30 min**	**1 h**	**4 h**	**8 h**
3.6	**2.5**	**2.0**	**1.3**	**0.63**

Reference: NIOSH (National Institute of Occupational Safety and Health) 1974. Inhalation and oral toxicity studies of ethyl parathion administered acutely and subacutely to the rat and dog. Report No. 00134578. Edgewood Arsenal, Toxicology Division, Aberdeen Proving Ground, Maryland.

Test Species/Strain/Sex/Number: male Sprague-Dawley x Wistar rats/34 per group

Exposure Route/Concentrations/Durations: : inhalation, 4 hrs, 0, 31.0, 35.0, 50.0, 71.0, 97.0, 100.6, 118.5, 230.5 mg/m^3; analytically measured using gas chromatography

Effects:

Conc. (mg/m^3)	Tremors	Convulsions	**Mortality**
31.0	0/34	0/34	**0/34**
35.0	0/34	0/34	**0/34**
50.0	8/34	3/34	**3/34**
71.0	19/34	4/34	**10/34**
97.0	28/34	19/34	**25/34**
100.6	26/34	21/34	**22/34**
118.5	29/34	21/34	**28/34**
230.5	31/34	25/34	**34/34**

Endpoint/Concentration/Rationale: The 4-hr $BMCL_{05}$ of 37.5 mg/m^3 was used as an estimate of the lethality threshold; the BMC_{01} was 41.1 mg/m^3

Uncertainty Factors/Rationale:
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 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

Animal to Human Dosimetric Adjustment: not applicable

Time Scaling: $C^n \times t = k$, where n = 1 or 3 (NRC, 2001)

Data Adequacy: Although limited to one species (rat), lethality data on parathion are adequate for derivation of AEGL-3 values. Information regarding the mode of action of parathion is sufficient to justify the uncertainty factors and the use of the rat data. Additionally, the exposure-response data come from a well-described study using an adequate number of animals per exposure group.

2

APPENDIX D: Benchmark Dose Derivations

NIOSH, 1974. rats; tremors, 4-hr BMC_{01}

```
==========================================================================
        Probit Model. (Version: 2.8;  Date: 02/20/2007)
        Input Data File: C:\BMDS\UNSAVED1.(d)
        Gnuplot Plotting File:  C:\BMDS\UNSAVED1.plt
                                                  Wed Jul 30 10:04:23 2008
==========================================================================

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 = 8
  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      =   -11.1325
                slope        =     2.59829

       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      -10.9508      1.19572         -13.2944            -8.60728
     slope         2.56317      0.275432          2.02334            3.10301

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	-90.4731	8			
Fitted model	-93.6071	2	6.26813	6	0.3938
Reduced model	-183.535	1	186.123	7	<.0001

AIC: 191.214

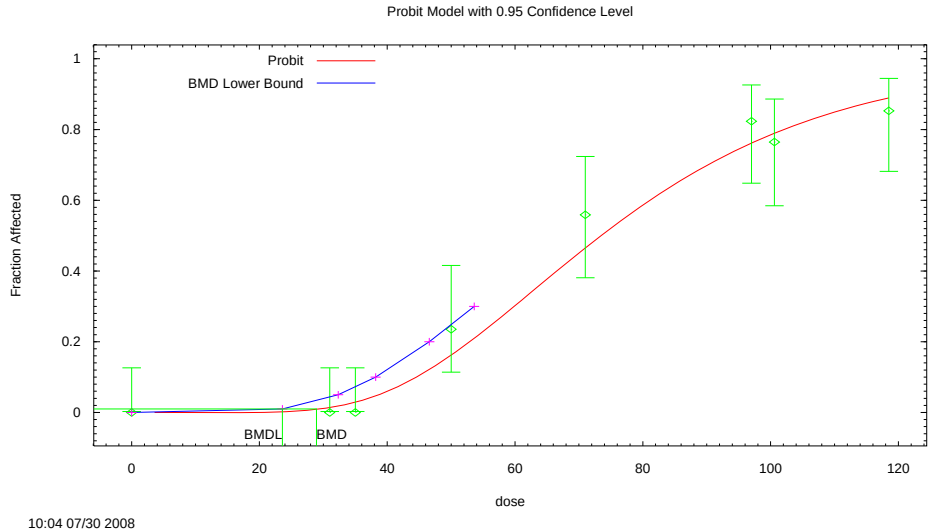
Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Scaled Size	Residual
0.0000	0.0000	0.000	0	34	0.000
31.0000	0.0158	0.538	0	34	-0.739
35.0000	0.0330	1.123	0	34	-1.078
50.0000	0.1778	6.046	8	34	0.876
71.0000	0.4901	16.663	19	34	0.802
97.0000	0.7808	26.548	28	34	0.602
100.6000	0.8074	27.452	26	34	-0.631
118.5000	0.9011	30.639	29	34	-0.942

Chi^2 = 4.77 d.f. = 6 P-value = 0.5741

Benchmark Dose Computation

Specified effect	=	0.01
Risk Type	=	Extra risk
Confidence level	=	0.95
BMC	=	28.9268
BMCL	=	23.5817



NIOSH 1974 rat tremors 4-hr parathion $BMCL_{05}$

```
==========================================================================
        Probit Model. (Version: 2.8;  Date: 02/20/2007)
        Input Data File: C:\BMDS\PARARTHION_TREMORS_BMC01.(d)
        Gnuplot Plotting File:  C:\BMDS\PARARTHION_TREMORS_BMC01.plt
                                                  Wed Jul 30 10:13:32 2008
==========================================================================

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 = 8
  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     =    -11.1325
                   slope     =     2.59829

       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       -10.9508       1.19572          -13.2944           -8.60728
       slope        2.56317      0.275432           2.02334            3.10301

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	-90.4731	8			
Fitted model	-93.6071	2	6.26813	6	0.3938
Reduced model	-183.535	1	186.123	7	<.0001

AIC: 191.214

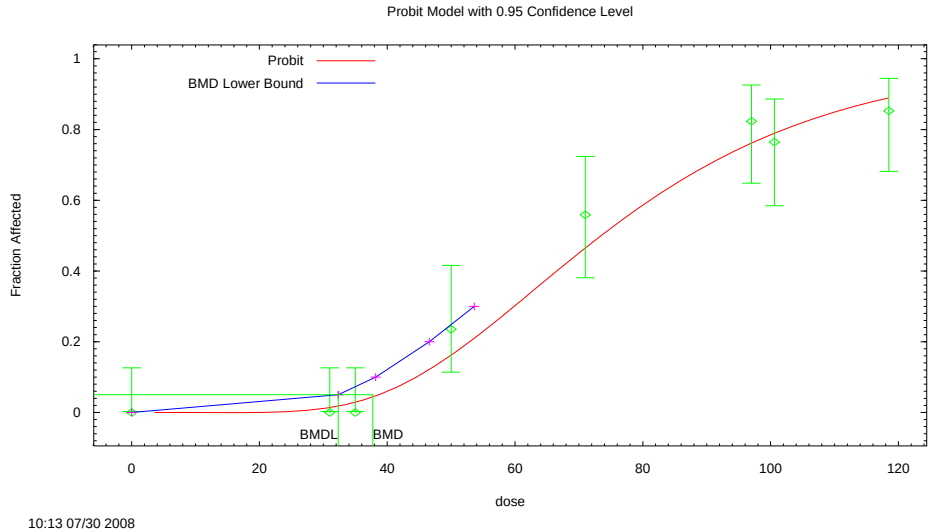
Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Scaled Size	Residual
0.0000	0.0000	0.000	0	34	0.000
31.0000	0.0158	0.538	0	34	-0.739
35.0000	0.0330	1.123	0	34	-1.078
50.0000	0.1778	6.046	8	34	0.876
71.0000	0.4901	16.663	19	34	0.802
97.0000	0.7808	26.548	28	34	0.602
100.6000	0.8074	27.452	26	34	-0.631
118.5000	0.9011	30.639	29	34	-0.942

Chi^2 = 4.77 d.f. = 6 P-value = 0.5741

Benchmark Dose Computation

Specified effect	=	0.05
Risk Type	=	Extra risk
Confidence level	=	0.95
BMC	=	37.7373
BMCL	=	32.3202



10:13 07/30 2008

NIOSH (1974) Rat lethality; 4-hr exposure PARATHION. BMC_{01}

==========

Probit Model. (Version: 2.8; Date: 02/20/2007)
Input Data File: C:\BMDS\UNSAVED1.(d)
Gnuplot Plotting File: C:\BMDS\UNSAVED1.plt
Wed Jul 30 08:08:10 2008

==========

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 = 9
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 = -10.3371
slope = 2.33037

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	-12.8114	1.55762	-15.8643	-9.75853
slope	2.89149	0.348793	2.20787	3.57511

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	-88.3117	9			
Fitted model	-89.4549	2	2.28634	7	0.9423
Reduced model	-205.778		234.933	8	<.0001

AIC: 182.91

Goodness of Fit

Dose	Est._Prob.	Expected	Scaled Observed	Size	Residual
0.0000	0.0000	0.000	0	34	0.000
31.0000	0.0020	0.067	0	34	-0.259
35.0000	0.0057	0.193	0	34	-0.441
50.0000	0.0668	2.272	3	34	0.500
71.0000	0.3135	10.660	10	34	-0.244
97.0000	0.6614	22.488	25	34	0.910
100.6000	0.6991	23.768	22	34	-0.661
118.5000	0.8402	28.566	28	34	-0.265
230.5000	0.9982	33.940	34	34	0.245

Chi^2 = 1.97 d.f. = 7 P-value = 0.9617

Benchmark Dose Computation

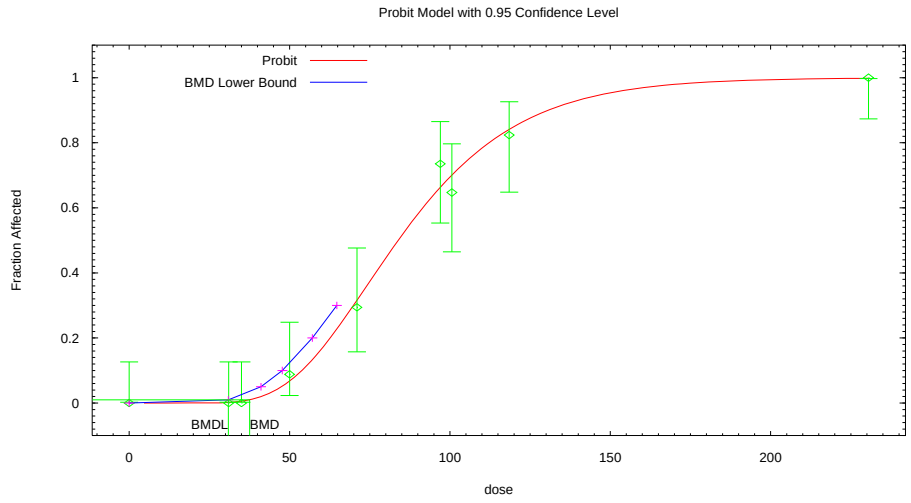
Specified effect = 0.01

Risk Type = Extra risk

Confidence level = 0.95

BMC = 37.5688

BMCL = 30.9377



NIOSH (1974) rat lethality 4-hr parathion $BMCL_{05}$

==========

Probit Model. (Version: 2.8; Date: 02/20/2007)
Input Data File: C:\BMDS\PARATHION_BMC01.(d)
Gnuplot Plotting File: C:\BMDS\PARATHION_BMC01.plt
Wed Jul 30 08:48:47 2008

==========

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 = 9
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 = -10.3371
slope = 2.33037

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	-12.8114	1.55762	-15.8643	-9.75853
slope	2.89149	0.348793	2.20787	3.57511

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	-88.3117	9			
Fitted model	-89.4549	2	2.28634	7	0.9423
Reduced model	-205.778	1	234.933	8	<.0001
AIC:	182.91				

Goodness of Fit

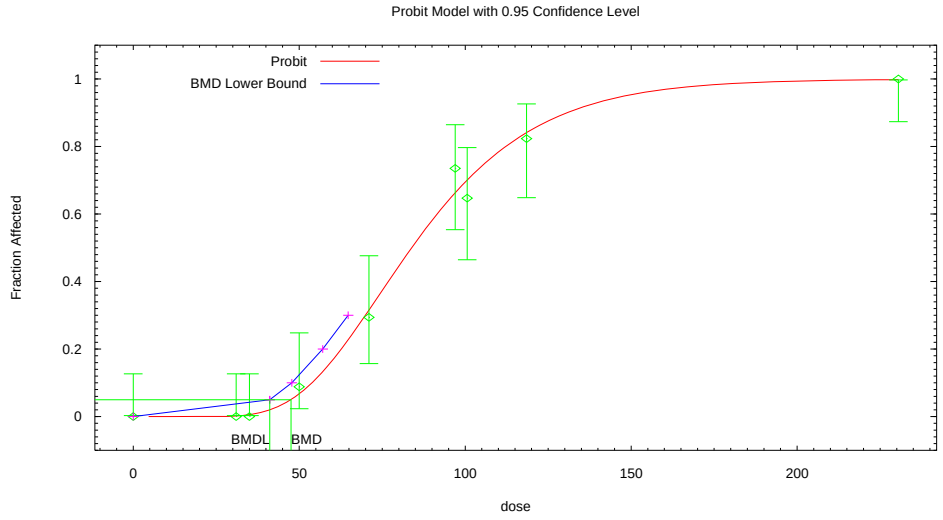
Dose	Est._Prob.	Expected	Scaled Observed	Size	Residual
0.0000	0.0000	0.000	0	34	0.000
31.0000	0.0020	0.067	0	34	-0.259
35.0000	0.0057	0.193	0	34	-0.441
50.0000	0.0668	2.272	3	34	0.500
71.0000	0.3135	10.660	10	34	-0.244
97.0000	0.6614	22.488	25	34	0.910
100.6000	0.6991	23.768	22	34	-0.661
118.5000	0.8402	28.566	28	34	-0.265
230.5000	0.9982	33.940	34	34	0.245

Chi^2 = 1.97 d.f. = 7 P-value = 0.9617

Benchmark Dose Computation

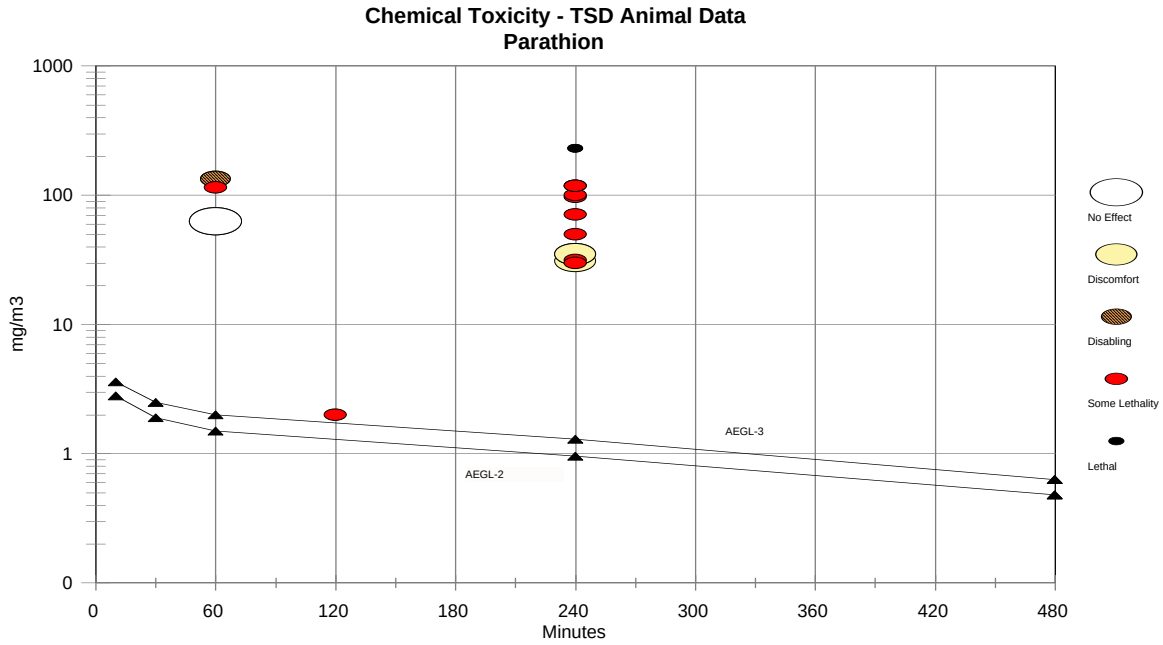
Specified effect	=	0.05
Risk Type	=	Extra risk
Confidence level	=	0.95
BMC	=	47.5539
BMCL	=	41.1009

1


Probit Model with 0.95 Confidence Level
Probit
BMD Lower Bound
Fraction Affected
1
0.8
0.6
0.4
0.2
0
BMDL
BMD
0
50
100
150
200
dose
08:48 07/30 2008

2
3

APPENDIX E: Category Plot for Parathion



NOTE: Data are insufficient for derivation of AEGL-1 values. Where inhalation exposure occurs there is potential for dermal exposure.

1

Parathion

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

Source	Sp.	Sex	# Expos.	mg/m^3	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				2.8	10	AEGL	
NAC/AEGL-2				1.9	30	AEGL	
NAC/AEGL-2				1.5	60	AEGL	
NAC/AEGL-2				0.96	240	AEGL	
NAC/AEGL-2				0.48	480	AEGL	
NAC/AEGL-3				3.6	10	AEGL	
NAC/AEGL-3				2.5	30	AEGL	
NAC/AEGL-3				2.0	60	AEGL	
NAC/AEGL-3				1.3	240	AEGL	
NAC/AEGL-3				0.63	480	AEGL	
	rat	M	1	115	60	PL	1-hr LC50 (Kimmerle and Lorke, 1968)
	rat	M	1	31.5	240	PL	4-hr LC50 (Kimmerle and Lorke, 1968)
	rat	B	1	30	240	PL	4-hr LC50 (IUCLID, 2000: Cheminova Agro)
	rat	-	1	2	120	PL	lethal; no details (Deichmann et al., 1952)
	rat	M	1	63	60	0	no significant effect (Pauluhn et al.,1987)
	rat	M	1	134	60	2	non-specified cholinergic effects (Pauluhn et al., 1987)
	rat	M	1	31.0	240	1	0/34; mild effects (NIOSH, 1974)
	rat	M	1	35.0	240	1	0/34; mild effects (NIOSH, 1974)
	rat	M	1	50.0	240	PL	3/34 deaths (NIOSH, 1974)
	rat	M	1	71.0	240	PL	10/34 (NIOSH, 1974)
	rat	M	1	97.0	240	PL	25/34 (NIOSH, 1974)
	rat	M	1	100.6	240	PL	22/34 (NIOSH, 1974)
	rat	M	1	118.5	240	PL	28/34 (NIOSH, 1974)
	rat	M	1	230.5	240	3	34/34 (NIOSH, 1974)

2
3