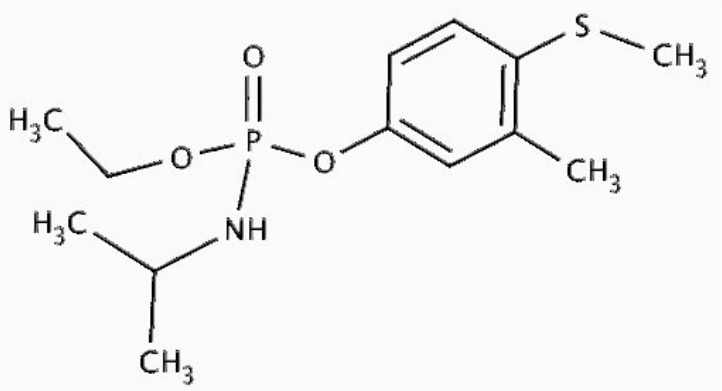
ACUTE EXPOSURE GUIDELINE LEVELS (AEGLs)
FOR
FENAMIPHOS
CAS Reg. No. 22224-92-6



PROPOSED

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PREFACE

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

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

AEGL-1 is the airborne concentration (expressed as parts per million or milligrams per cubic meter [ppm or mg/m3]) 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/m3) 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/m3) 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

Fenamiphos is an organophosphate nematicide and insecticide that is used to control a variety of nematodes, thrips, aphids, beetles, root weevils, and corn borers. It was first registered in 1972 for use on annual field and vegetable crops or on established perennial, deciduous, and tropical fruit crops. In the U.S., the registrant cancelled use and formulation for use of all of its existing fenamiphos registrations in areas with predominantly sand or loamy sand, hydrologic soil group A soils that are excessively drained, and shallow water tables effective May 31, 2005. Registrations were cancelled for use on all other soils in the U.S. effective May 31, 2007. Prior to cancellation, annual domestic use for the United States was approximately 780,000 pounds of active ingredient. The U.S. EPA has tolerances for crops on which fenamiphos is used and for food commodities imported into the U.S.

Fenamiphos is readily absorbed through the skin and numerous studies are available describing the pharmacokinetics and toxicity after topical application. Dermal exposure may increase the total absorbed dose when it occurs with oral or inhalation exposure. However, because the dermal route is not relevant to the inhalation route of exposure, the data on dermal exposure were not analyzed with regard to developing AEGL values for fenamiphos. Relative to occupational dermal and oral exposure, inhalation is a minor exposure route and this is reflected in the paucity of inhalation toxicity data. No quantitative data are available regarding the inhalation toxicity of fenamiphos in humans.

No AEGL-1 values were established because the AEGL-1 values would have been too close to or exceeded AEGL-2 values.

The AEGL-2 values were derived by dividing the AEGL-3 values by three. The lack of experimental data and the steep exposure-response relationship justify estimating AEGL-2 values by a 3-fold reduction of AEGL-3 values (NRC 2001). Male rats experienced 5% mortality after exposure to 75 mg/m^3 for 1 hour; 30% mortality at 87 mg/m^3; and 60% mortality at 103 mg/m^3. All 20 rats died after exposure to 187 mg/m^3 (Kimmerle 1972). In a study by Thyssen (1979a), 20% of the male rats died after exposure to 119 mg/m^3 for 1 hour; 60% died after exposure to 145 mg/m^3; and 90% died after exposure to 148 mg/m^3. Female rats had 70% mortality at 145 mg/m^3 and 90% mortality after exposure to 148 mg/m^3 for 1 hour. In a 4-hour study by Thyssen (1979a), male rats experienced 60% mortality at 100 mg/m^3 and 100% mortality at 155 mg/m^3, and female rats experienced 50% mortality at 100 mg/m^3; 90% mortality at 155 mg/m^3; and 100% mortality at 191 mg/m^3.

The AEGL-3 was derived using the 4-hour $BMCL_{05}$ of 46.6337 mg/m^3 for lethality of fenamiphos in female rats (Thyssen 1979a). This is considered a threshold for lethality for fenamiphos and is the most conservative benchmark value calculated from the test animals used in the study. Lethality data were sufficient for empirical derivation of a time-scaling factor (*n*) for use in the equation $C^n \times t = k$. The value of n was 4.8 and was used to time scale AEGL values. The mechanism of action of organophosphate anticholinesterases is well understood; their activity on cholinergic systems is the same across species. Variability in response is primarily a function of varying cholinesterase activity level and types of cholinesterase. Humans have greater levels of plasma cholinesterase than do other species which allows for greater binding of anticholinesterase compounds such as fenamiphos, thereby decreasing the availability of the compound to brain cholinesterase. 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 justify retention of the intraspecies uncertainty factor of 10. The uncertainty factor application and rationale are the same as those applied in the derivation of AEGLs for other organophosphate anticholinesterases (NRC 2003).

TABLE 1. Summary of AEGL Values for Fenamiphos

Classification	10-minute	30-minute	1-hour	4-hour	8-hour	Endpoint (Reference)
AEGL–1 (Nondisabling)	NR	NR	NR	NR	NR	Not recommended due to exceeding AEGL-2 values
AEGL–2 (Disabling)	1.0 mg/m^3	0.80 mg/m^3	0.70 mg/m^3	0.53 mg/m^3	0.43 mg/m^3	Derived by 3-fold reduction of the AEGL-3 values (NRC 2001; Thyssen 1979a)
AEGL–3 (Lethal)	3.0 mg/m^3	2.4 mg/m^3	2.1 mg/m^3	1.6 mg/m^3	1.3 mg/m^3	Derived based upon a 4-hr $BMCL_{05}$ of 46.6337 mg/m^3 in rats (Thyssen 1979a)

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

References

Kimmerle, G. 1972. Acute inhalation toxicity study with Nemacur active ingredient on rats. Unpublished report. Bayer AG, Wuppertal, Germany.

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.

Thyssen, J. 1979a. SRA 3886 (Nemacur active ingredient) acute inhalational toxicity studies. Report no. 8210. Unpublished study prepared by Bayer AG, Institut fuer Toxikologie, Germany.

1. INTRODUCTION

Fenamiphos is an organophosphate nematicide and insecticide that is used to control a variety of nematodes, thrips, aphids, beetles, root weevils, and corn borers. Fenamiphos is manufactured by reacting 4-methyl-m-creosol with ethylisopropylamido-phosphorochloride or by condensing 4-methylthio-m-cresol with O-ethyl N-isopropyl phosphoramidochloride. It was first registered in 1972 for use in plant control of nematodes on annual field and vegetable crops or on established perennial, deciduous, and tropical fruit crops. In the U.S., the manufacturer agreed to cancel use, and formulation for use, of all of its existing fenamiphos registrations in the U.S. in areas with predominantly sand or loamy sand, hydrologic soil group A soils that are excessively drained, and shallow water tables effective May 31, 2005. Registrations were cancelled for use on all other soils in the U.S. effective May 31, 2007. Prior to cancellation, the annual domestic use for the United States was approximately 780,000 pounds of active ingredient (HSDB 2005). The U.S. EPA has tolerances set for crops on which fenamiphos is used and for food commodities imported into the U.S. (U.S. EPA 2002).

TABLE 2. Chemical and Physical Properties

Parameter	Value	References
Synonyms	Nemacur; Nemacur PR; Phenamiphos; Phosphoramidic acid; ENT 27572; Bay 68138, Bayer 68138, SRA-3886, Ethyl 3-methyl-4-(methylthio)phenyl(1-methylethyl)-phosphoramidate	HSDB 2005 NIOSH 2005 ACGIH 2006
Chemical formula	$C_{13}H_{22}NO_3PS$	HSDB 2005
Molecular weight	303.36	HSDB 2005
CAS Reg. No.	22224-92-6	HSDB 2005
Physical state	Technical fenamiphos- off-white to tan, waxy solid. Colorless crystals; Pure fenamiphos: white crystals	ACGIH 2006 IPCS CEC 2005 IPCS 1994
Solubility in water	329 mg/L at 20ºC 329 mg/L (crystals) 700 mg/L at 20°C	HSBD 2005 O'Neil 2001 IPCS 1994
Vapor pressure	4.7×10^{-5} torr at 20°C 1×10^{-7} mm HG at 25°C	ACGIH 2006 HSDB 2005
Vapor density (air =1)	1.191 at 23ºC	HSDB 2005
Liquid density (water =1)	-	-
Melting point	49.2°C (pure); 40°C (technical)	ACGIH 2006
Boiling point	450°C	U.S. EPA 1987
Flammability limits	-	-
Conversion factors	1.0 ppm = 12.4 mg/m^3 1.0 mg/m^3 = 0.08 ppm	ACGIH 2006

2. HUMAN TOXICITY DATA

2.1. Acute Lethality

No data were located.

2.2. Nonlethal Toxicity

2.2.1. Odor Threshold/Odor Awareness

No data were located.

2.2.2. Case Reports

Incidence reports of poisoning from fenamiphos noted nausea, vomiting, and abdominal pain as effects of exposure (U.S. EPA 2002). The routes of exposure, concentrations, and durations were not specified.

2.2.3. Exposure Studies

Knaak et al. (1986) measured inhalation exposure to fenamiphos in workers at a pesticide application firm. Two mixer/loader workers were monitored for 2 hours during the workday. Two applicator workers were monitored for 2.5 hours during the workday. Two additional workers (mixer/loaders and applicators) were monitored for 4 hours during the workday. Personal air pumps attached to shirt collars were used to measure fenamiphos concentration. The sampling device consisted of a sampling tube connected in series with a fiberglass particulate filter. The samples were analyzed by gas chromatography. Inhalation values were at or below the detectable level of 0.001 mg/hour in all workers.

2.3. Neurotoxicity

No data were located.

2.4. Developmental/Reproductive Toxicity

No data were located.

2.5. Genotoxicity

No data were located.

2.6. Carcinogenicity

Fenamiphos is not classifiable as a human carcinogen (ACGIH 2006). There were no data to evaluate inhalation carcinogenicity under EPA's IRIS program (U.S. EPA 1990).

2.7. Summary

Very few inhalation data are available for humans. In the data that were located, fenamiphos toxicity was similar to that of other cholinesterase inhibitors in terms of effects. The monitoring study revealed that very little fenamiphos is inhaled during mixing, loading, and application.

3. ANIMAL TOXICITY DATA

3.1. Acute Lethality

3.1.1. Rats

Kimmerle (1972) exposed male and female Wistar II rats (20/sex/group) to fenamiphos for 1 hour and observed the animals for 14 days. The exposure was carried out in a dynamic inhalation apparatus in which fenamiphos was mixed with polyethylene glycol and ethanol (1:1) and aerosolized. The concentration of fenamiphos in the chamber was determined by spectrophotometry. The male rats were exposed to 0.029, 0.075, 0.087, 0.103, 0.140, 0.165, or 0.187 mg/L (29, 75, 87, 103, 140, 165, or 187 mg/m^3). The female rats were exposed to 0.029, 0.070, 0.105, 0.117, 0.148, 0.170, 0.185, 0.195, or 0.320 mg/L (29, 70, 105, 117, 148, 170, 185, 195, or 320 mg/m^3). All rats in all the groups except those exposed to 0.029 mg/L (29 mg/m^3) had inhibition of cholinesterase activity within 10-60 minutes of exposure. Mortality occurred at concentrations greater than 0.029 mg/L (29 mg/m^3) in both sexes as shown in Table 3. The calculated LC_{50} for male rats was 0.11 mg/L (110 mg/m^3) and was 0.150 mg/L (150 mg/m^3) for female rats. The calculated $BMCL_{05}$ was 54.181 mg/m^3 for male rats and 112.538 mg/m^3 for female rats. The BMC_{01} was 53.035 mg/m^3 for male rats and 98.4546 mg/m^3 for female rats using the Benchmark Dose Software, version 2.0 (U.S. EPA 2008).

Thyssen (1979a) exposed male and female TNO/W 74 rats (10/sex/group) to fenamiphos (89.8% pure) for 1 or 4 hours and determined the LC_{50}. The rats were exposed nose-only in a dynamic inhalation apparatus. The chamber concentration was analytically determined by spectrophotometry. In the 1-hour exposure study, male and female rats were exposed to 83, 119, 145, 148, or 250 mg/m^3. All rats in all the groups exhibited signs of cholinesterase inhibition including muscle twitching and cramps which lasted for up to 7 hours post exposure. Inactivity and stiff gait were observed in the rats for up to 5 days post exposure. Heavy drowsiness and breathing disorders were observed at the highest concentrations. Mortality occurred at all concentrations in male rats except 83 mg/m^3 and in female rats at the three highest concentrations as shown in Table 3. The 1-hour LC_{50}s for male and female rats were 131 and 130 mg/m^3, respectively. The calculated $BMCL_{05}$ was 86.1218 mg/m^3 for male rats and 113.898 mg/m^3 for female rats. The BMC_{01} was 98.6107 mg/m^3 for male rats and 122.75 mg/m^3 for female rats using the Benchmark Dose Software, version 2.0 (U.S. EPA 2008).

In the 4-hour exposure study, male and female rats were exposed to 57, 62, 100, or 155 mg/m^3. An additional group of female rats was exposed to 191 mg/m^3. All exposed rats exhibited signs of cholinesterase inhibition similar to those observed in rats exposed for only 1 hour. Mortality occurred in both sexes as shown in Table 3. The female rats appeared to be more sensitive than male rats as indicated by mortality at lower concentrations. The 4-hour LC_{50} was 100 mg/m^3 for both sexes. The calculated $BMCL_{05}$ was 59.2137 mg/m^3 for male rats and 46.6337 mg/m^3 for female rats. The BMC_{01} was 81.6062 mg/m^3 for male rats and 49.4464 mg/m^3 for female rats using the Benchmark Dose Software, version 2.0 (U.S. EPA 2008).

The 4-hr LC_{50} for acute inhalation exposure in male and female THO/W74 rats was > 0.1 mg/L (100 mg/m^3). No other data were reported (U.S. EPA 1999).

TABLE 3. Summary of Acute Inhalation Data for Fenamiphos in Laboratory Animals

Species	Concentration (mg/m^3)	Exposure Time	Effect	Reference
Rat male	29 75 87 103 140 165 187 110	1 hr	No effect 5% mortality; (1/20) 30% mortality, (6/20) 60% mortality; (12/20) 65% mortality; (13/20) 95% mortality; (19/20) 100% mortality; (20/20) LC_{50}	Kimmerle 1972
Rat female	29 70 105 117 148 170 185 195 320 150	1 hr	No effect Cholinesterase activity inhibition 5% mortality; (1/20) Cholinesterase activity inhibition 35% mortality; (7/20) 60% mortality; (12/20) 90% mortality; (18/20) 90% mortality; (18/20) 100% mortality; (20/20) LC_{50}	Kimmerle 1972
Rat male	83 119 145 148 250 131	1 hr	Cholinesterase activity inhibition 20% mortality, (2/10) 60% mortality, (6/10) 90% mortality, (9/10) 100% mortality, (10/10) LC_{50}	Thyssen 1979a
Rat female	83 119 145 148 250 130	1 hr	Cholinesterase activity inhibition Cholinesterase activity inhibition 70% mortality, (7/10) 90% mortality, (9/10) 100% mortality, (10/10) LC_{50}	Thyssen 1979a
Rat male	57 62 100 155 100	4 hr	Cholinesterase activity inhibition Cholinesterase activity inhibition 60% mortality, (6/10) 100% mortality, (10/10) LC_{50}	Thyssen 1979a
Rat female	57 62 100 155 191 100	4 hr	Cholinesterase activity inhibition 10% mortality, (1/10) 50% mortality, (5/10) 90% mortality, (9/10) 100% mortality, (10/10) LC_{50}	Thyssen 1979a
Rat	100	4 hr	Less than the LC_{50}	U.S. EPA 1999

3.2. Nonlethal Toxicity

3.2.1. Rats

Repeat Dose

Male and female Wistar rats (10/sex/group) were exposed via inhalation to 0, 0.03, 0.25, or 3.5 µg/L fenamiphos (0, 30, 250, or 350 mg/m^3) for 6 hours/day, 5 days/week, for 21 days (Thyssen 1979b; U.S. EPA 1999). No overt cholinergic symptoms were observed, and there were no changes in physical appearance, behavioral patterns, body weight, hematology, clinical chemistry, urinalysis, gross pathology, or organ weights. Plasma cholinesterase activity was inhibited in males and females, 42-47% and 72-78%, respectively. Erythrocyte cholinesterase activity was inhibited in female rats 15-19%. Brain cholinesterase activity in the treated rats was comparable to that of control rats. The LOAEL was 350 mg/m^3, and the NOAEL was 250

mg/m^3. No details were reported on atmosphere generation and analysis.

3.3. Developmental/Reproductive Toxicity

No inhalation developmental/reproductive studies were located.

Groups of rabbits were given fenamiphos by oral gavage at doses of 0, 0.1, 0.3, or 1.0 mg/kg on days 6-18 of pregnancy. A hint of maternal toxicity was shown by a trend toward decreases in body weight gain at the highest two doses. The chemical was not fetotoxic or embryotoxic at any dose; no statistically significant differences were seen in the mean numbers of corpora lutea or implants, in implantation efficiency, litter size or sex ratio, or in the number or percent of live or resorbed fetuses. The authors concluded that the finding of a fused "chain" of sternebrae in five fetuses at the highest dose may have been a treatment-related anomaly, but noted that the anomaly appeared at a maternally-toxic dose (Hazleton Raltech Inc. 1982).

Chinchilla rabbits (16/group) were given fenamiphos technical by oral gavage at doses of 0, 0.1, 0.5, or 2.5 mg/kg on days 6-18 of pregnancy. While no maternal toxicity was seen at the lower two doses, maternal toxicity at the highest dose was shown by numerous cholinergic effects and four treatment-induced deaths, decreased body weight gain, and decreased food consumption. No effects were seen on the mean number of corpora lutea, number of live or dead fetuses, litter size, sex ratio, or number of live or resorbed fetuses. At the highest dose only, there was a slight reduction in mean live pup weight as well as an increase in preimplantation loss. The only visceral anomaly seen was one malformation in the high dose group (Becker 1986; U.S. EPA 1999).

Long Evans rats (25/dose) were given fenamiphos by oral gavage at doses of 0, 0.3, 1.0, or 3.0 mg/kg on days 6-15 of pregnancy. There were no treatment-related effects on the numbers of live fetuses or abnormal fetuses at any dose level, and there was no increase in the incidence of fetuses with gross visceral or skeletal anomalies. At the highest dose, evidence of toxicity to the pregnant dams was seen and cholinergic signs were seen within 30 minutes after treatment. Two dams in that group died, although the cause of death was not determined (Schlueter 1981).

Sprague-Dawley (Crl:CDBR) rats were given fenamiphos by oral gavage at doses of 0, 0.25, 0.85, or 3.0 mg/kg on days 6-15 of pregnancy. Five females per group were killed on day 16 of pregnancy, and the rest at day 20 of pregnancy, for examination of uterine contents. At the highest dose, all pregnant dams exhibited tremors, and 6 died during the treatment period. At that dose level, body weight and food consumption were also reduced, and plasma and RBC (but not brain) cholinesterase activity were significantly inhibited at 16 days of pregnancy. At 20 days of pregnancy (5 days after the treatment regimen ended), there was no significant inhibition of plasma cholinesterase activity, and there was less inhibition of RBC cholinesterase activity than was seen one day after the treatment regimen ended. No treatment-related maternal effects were seen at the lower doses, and no embryotoxicity or teratogenicity was observed at any dose level. There was no effect on fetal brain cholinesterase activity; brain cholinesterase activity was the only cholinesterase tested in fetuses (Astroff and Young 1998).

In a 3-generation reproduction study, fenamiphos was fed to rats at concentrations of 0, 3, 10 or 30 ppm (equivalent to about 0, 0.15, 1.0, or 1.5 mg/kg/day as estimated by the EPA). At the highest dose there was a reduction of body weight gain in the F2b generation males only. There were no significant effects on fertility, litter size or pup weight, and no malformed pups

were seen at any treatment level. Histopathological examination revealed no treatment-related effects in the F3b generation (Löser 1972).

In a 2-generation reproduction study, fenamiphos was fed to Sprague-Dawley rats at concentrations of 0, 2.5, 10 or 40 ppm (0, 0.2, 0.73, or 3.2 mg/kg/day in females or 0, 0.17, 0.64, or 2.8 mg/kg/day in males). There were no treatment-related endocrine or reproductive effects or clinical signs seen in either adults or pups. However, at the highest dose, F_1 pups showed decreased body weight gain during lactation, and F_0 and F_1 females had reduced body weight during lactation. Also at the highest dose, body weight of adult rats was significantly reduced at the end of the experiment, and absolute and relative ovary weights were significantly decreased. Plasma cholinesterase activity was significantly inhibited at all concentrations in adult females but only at 10 and 40 ppm in adult males. RBC cholinesterase activity was significantly inhibited at 10 ppm (but not at 40 ppm) in adults of both sexes as well as in 4-day-old pups. Brain cholinesterase activity was significantly inhibited at 40 ppm in adults of both sexes but not in pups, in which this activity was measured at 4 and 21 days of age (Eigenberg 1991).

3.4. Genotoxicity

Fenamiphos was not mutagenic in the dominant lethal test with NMRI mice (Herbold and Lorke 1980).

Fenamiphos did not cause an increase in sister chromatid exchange in Chinese hamster V-79 cells without S9 activation (Chen et al. 1982a) or with S9 activation (Chen et al. 1982b).

Fenamiphos was negative in the Ames test both with and without metabolic activation using the following *Salmonella typhimurium* strains: TA1535, TA1537, TA1538, TA98, and TA100 (Herbold 1985).

Results are considered equivocal in chromosomal aberration induction because aberrations were induced only in the cytotoxic range (based on a significant reduction in the mitotic index) in human lymphocytes with and without metabolic activation. Hemolysis also occurred in the cells that yielded the positive result with metabolic activation (Herbold 1987).

3.5. Chronic Toxicity/Carcinogenicity

No inhalation data were located.

3.6. Summary

Fenamiphos exposure caused decreased plasma and erythrocyte cholinesterase activity similar to other organophosphate pesticides. Information on the lethality of fenamiphos following inhalation exposure was limited to rats. Signs of cholinesterase activity inhibition were observed in male and female rats. Fenamiphos has a steep exposure-response curve. Male rats experienced 5% mortality after exposure to 75 mg/m^3 for 1 hour; 30% mortality at 87 mg/m^3; and 60% mortality at 103 mg/m^3. All 20 rats died after exposure to 187 mg/m^3 (Kimmerle 1972). In a study by Thyssen (1979a), 20% of the male rats died after exposure to 119 mg/m^3 for 1 hour; 60% died after exposure to 145 mg/m^3; and 90% died after exposure to 148 mg/m^3. Female rats had 70% mortality at 145 mg/m^3 and 90% mortality after exposure to 148 mg/m^3 for 1 hour. In a 4-hour study by Thyssen (1979a), male rats experienced 60%

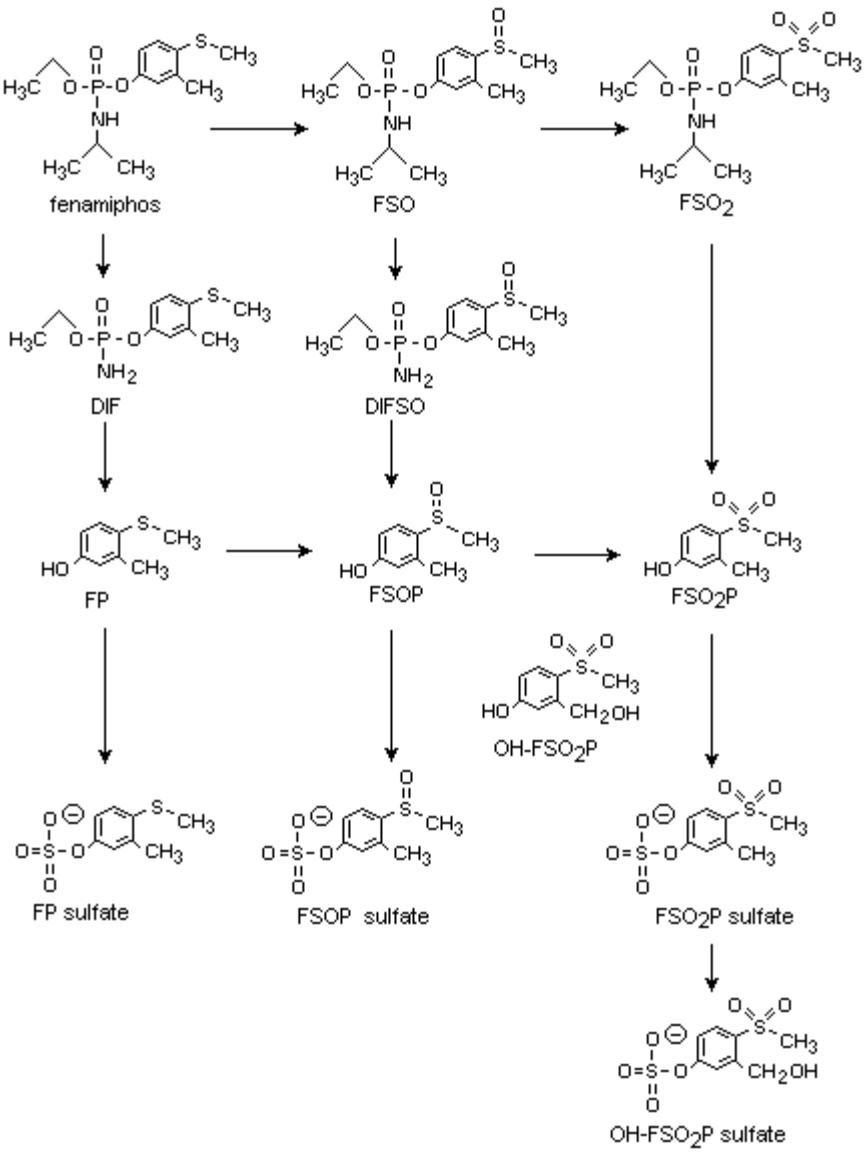
mortality at 100 mg/m^3 and 100% mortality at 155 mg/m^3, and female rats experienced 50% mortality at 100 mg/m^3; 90% mortality at 155 mg/m^3; and 100% mortality at 191 mg/m^3. The 1-hour LC_{50} ranged from 100 to 155 mg/m^3, and the 4-hour LC_{50} values were 100 mg/m^3 or greater.

4. SPECIAL CONSIDERATIONS

4.1. Metabolism and Disposition

Fenamiphos is absorbed from the gastrointestinal tract, by inhalation, or through intact skin. It is oxidized to form sulfoxide and sulfone analogs (HSDB 2005). In an *in vitro* study using rat liver preparations, fenamiphos was metabolized to its sulfoxide, an N-alkylated product, and an unidentified product (ACGIH 2006). No information was located regarding absorption in humans or animals after inhalation exposure to fenamiphos. Oral studies have shown that distribution following oral absorption is rapid and excretion occurs within 8 hours of the administered dose. A single oral exposure to 6 mg/kg fenamiphos in rats yielded a half-life in brain of 100 hours and a half-life in plasma of 212 hours (HSDB 2005; ACGIH 2006). Fenamiphos given to rats at 0.3 or 3 mg/kg both orally and by i.p. injection, was completely and rapidly absorbed and eliminated, with 99% of the dose gone by 48 hours after treatment. Residues found in the bodies represented only 0.045-0.23% of the amount of fenamiphos administered. The great majority (96-98%) was eliminated in the urine, with the rest being eliminated in feces. Treatment with fenamiphos for 14 days prior to treatment with [^{14}C]fenamiphos did not change the absorption, distribution, or elimination patterns (ACGIH 2006). The proposed metabolic pathway of fenamiphos is shown in Figure 1 (IPCS 1997).

Figure 1. Proposed metabolic pathway of fenamiphos



4.2. Mechanism of Toxicity

Fenamiphos directly inhibits cholinesterases. The sulfoxide and sulfone metabolites of fenamiphos are more potent inhibitors than fenamiphos itself (ACGIH 2006). Inhibition of cholinesterase results in the accumulation of acetylcholine in the synaptic cleft which continues to stimulate the nicotinic and muscarinic receptors leading to increased secretions, bronchoconstriction, gastrointestinal cramps, muscle fasciculation, tremors, weakness, mental confusion, miosis, coma, and death. There is evidence that overstimulation of the receptors by acetylcholine causes desensitization and down-regulation of receptor numbers that causes persistent muscle weakness (Ecobichon 2001).

4.3. Structure Activity Relationships

Although all organophosphate cholinesterase inhibitors have the same mechanism of

action, their potency and physicochemical properties vary. The physicochemical differences 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

Variability in types of esterases and their respective activity is important in determining interspecies variability in organophosphate poisoning. This affects 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).

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 adults), gender differences (females tend to have approximately 10% lower plasma and red blood cell cholinesterase activity), and genetic 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 fenamiphos. Additionally, polymorphic variability in A-esterases such as paraoxonase/ arylesterase, may contribute to individual variability in organophosphate ester detoxification processes (NRC 2003).

4.4.3. Concentration-Exposure Duration Relationship

The concentration-time relationship for a single endpoint for many irritant and systemically acting vapors and gases may be described by $C^n \times t = k$ (ten Berge et al. 1986). Exposure-response data for time-scaling were available for two time points, 1 and 4 hours. The estimation ratio between regression coefficients of ln (concentration) and ln (minutes) was 4.8 (Appendix B).

4.4.4. Concurrent Exposure Issues

Both concurrent exposure to other organophosphates and simultaneous exposure via other

exposure routes are of concern. Fenamiphos may enter the body and be bioavailable by dermal, oral, and inhalation pathways. Animal studies show that fenamiphos is readily absorbed through the skin and gastrointestinal tract, as evidenced by its high acute toxicity via these routes of exposure (ACGIH 2006).

5. DATA ANALYSIS FOR AEGL-1

5.1. Summary of Human Data Relevant to AEGL-1

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

5.2. Summary of Animal Data Relevant to AEGL-1

Kimmerle (1972) exposed male and female Wistar II rats to 29 mg/m^3 fenamiphos for 1 hour. The rats did not exhibit any signs of cholinesterase activity inhibition, and no mortality occurred in these rats.

5.3. Derivation of AEGL-1

No AEGL-1 values were established because the AEGL-1 values were too close to, or exceeded AEGL-2 values. If a point of departure of 29 mg/m^3 (no effect level) was used to derive AEGL-1 values, values of 1.4, 1.1, 0.97, 0.72, and 0.63 mg/m^3 for the 10-minute, 30-minute, 1-hour, 4-hour, and 8-hour time points, respectively, would exceed the AEGL-2 values (Appendix A).

TABLE 4. AEGL-1 Values for Fenamiphos

10-minute	30-minute	1-hour	4-hour	8-hour
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. Summary of Human Data Relevant to AEGL-2

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

6.2. Summary of Animal Data Relevant to AEGL-2

No animal data relevant to derivation of AEGL-2 were located.

6.3. Derivation of AEGL-2

The AEGL-2 values were derived by dividing the AEGL-3 values by three. The lack of experimental data and the steep exposure-response relationship justify estimating AEGL-2 values by a 3-fold reduction of AEGL-3 values (NRC 2001). Male rats experienced 5% mortality after exposure to 75 mg/m^3 for 1 hour; 30% mortality at 87 mg/m^3; and 60% mortality at 103 mg/m^3. All 20 rats died after exposure to 187 mg/m^3 (Kimmerle 1972). In a study by Thyssen (1979a), 20% of the male rats died after exposure to 119 mg/m^3 for 1 hour; 60% died after exposure to 145 mg/m^3; and 90% died after exposure to 148 mg/m^3. Female rats had 70% mortality at 145 mg/m^3 and 90% mortality after exposure to 148 mg/m^3 for 1 hour. In a 4-hour study by Thyssen (1979a), male rats experienced 60% mortality at 100 mg/m^3 and 100%

mortality at 155 mg/m^3, and female rats experienced 50% mortality at 100 mg/m^3; 90% mortality at 155 mg/m^3; and 100% mortality at 191 mg/m^3. The resulting AEGL-2 values compared to the values derived from the no effect level demonstrate the conservative nature of using the 3-fold reduction approach to derive AEGL-2 values. AEGL-2 values are shown in Table 5.

TABLE 5. AEGL-2 Values for Fenamiphos

10-minute	30-minute	1-hour	4-hour	8-hour
1.0 mg/m^3	0.80 mg/m^3	0.70 mg/m^3	0.53 mg/m^3	0.43 mg/m^3

7. DATA ANALYSIS FOR AEGL-3

7.1. Summary of Human Data Relevant to AEGL-3

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

7.2. Summary of Animal Data Relevant to AEGL-3

Kimmerle (1972) calculated a 1-hour LC_{50} of 100 mg/m^3 for male rats and 150 mg/m^3 for female rats. Using the exposure-response data from this study, a $BMCL_{05}$ of 54.181 mg/m^3 (male) and 112.538 mg/m^3 (female) and BMC_{01} of 53.035 mg/m^3 (male) and 98.4546 mg/m^3 (female) were calculated using Benchmark Dose Software, version 2.0 (U.S. EPA 2008). Thyssen (1979a) calculated a 1-hour LC_{50} of 131 mg/m^3 for male rats and 131 mg/m^3 for female rats. The calculated $BMCL_{05}$ was 86.1218 mg/m^3 for male rats and 113.898 mg/m^3 for female rats. The BMC_{01} was calculated to be 98.6107 mg/m^3 for male rats and 122.75 mg/m^3 for female rats. The 4-hour LC_{50} was 100 mg/m^3 for both sexes. The calculated $BMCL_{05}$ was 59.2137 mg/m^3 for male rats and 46.6337 mg/m^3 for female rats. The BMC_{01} was 81.6062 mg/m^3 for male rats and 49.4464 mg/m^3 for female rats (see Appendix E).

7.3. Derivation of AEGL-3

Due to the availability of group-specific response data, the Thyssen (1979a) report was selected as the key study, and the female rat 4-hour $BMCL_{05}$ of 46.6337 mg/m^3 was selected as the point of departure for AEGL-3 derivation. This is considered a threshold for lethality and is the most conservative benchmark value calculated from the test animal used in the study. Lethality data were sufficient for empirical derivation of a time-scaling factor (n) for use in the equation $C^n \times t = k$. The value of n was 4.8 and was used to time scale AEGL values. As described in Sections 4.2 and 4.4, the mechanism of action of organophosphate anti-cholinesterases is well understood; their activity on cholinergic systems has been shown to be the same across species. Variability in responses is primarily a function of varying cholinesterase levels and types of cholinesterase. Humans have greater levels of plasma cholinesterase than do other species which allows for greater binding of anticholinesterase compounds such as fenamiphos, thereby decreasing the availability of the compound to critical targets such as brain cholinesterase. 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 justify 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). The AEGL-3 values for fenamiphos are shown in Table 6, and the derivation is presented in Appendix A.

TABLE 6. AEGL-3 Values for Fenamiphos				
10-minute	30-minute	1-hour	4-hour	8-hour
3.0 mg/m^3	2.4 mg/m^3	2.1 mg/m^3	1.6 mg/m^3	1.3 mg/m^3

8. SUMMARY OF AEGLS

8.1. AEGL Values and Toxicity Endpoints

Very limited data are available regarding the inhalation toxicity of fenamiphos. Data were available with which to derive AEGL-1 values, however, those values would have exceeded AEGL-2 values. Therefore, AEGL-1 values are not recommended. Exposure-response data for AEGL-2 tier severity effects were not available for single acute exposures. However, the exposure-response curve for fenamiphos, 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 based upon the estimated lethality threshold ($BMCL_{05}$ of 46.6337 mg/m^3) in female rats exposed for 4 hours. AEGL values are summarized in Table 7.

TABLE 7. Summary of AEGL Values					
Classification	Exposure Duration				
	10-minute	30-minute	1-hour	4-hour	8-hour
AEGL-1 (Nondisabling)	NR	NR	NR	NR	NR
AEGL-2 (Disabling)	1.0 mg/m^3	0.80 mg/m^3	0.70 mg/m^3	0.53 mg/m^3	0.43 mg/m^3
AEGL-3 (Lethal)	3.0 mg/m^3	2.4 mg/m^3	2.1 mg/m^3	1.6 mg/m^3	1.3 mg/m^3

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

8.2. Comparison with Other Standards and Guidelines

AEGL values for fenamiphos are compared to other guidelines and standards for this compound (Table 8). The AEGL values for fenamiphos are slightly lower than the other guidelines and standards. The majority of the guidelines and standards were based on repeated dose inhalation, oral toxicity, and dermal toxicity data in animals rather than acute inhalation data.

TABLE 8. Extant Standards and Guidelines for Fenamiphos

Guideline	Exposure Duration				
	10 minute	**30 minute**	**1 hour**	**4 hour**	**8 hour**
AEGL-1	NR	NR	NR	NR	NR
AEGL-2	1.0 mg/m^3	0.80 mg/m^3	0.70 mg/m^3	0.53 mg/m^3	0.43 mg/m^3
AEGL-3	3.0 mg/m^3	2.4 mg/m^3	2.1 mg/m^3	1.6 mg/m^3	1.3 mg/m^3
REL-TWA (NIOSH)[a]					0.1 mg/m^3 (skin)
TLV-TWA (ACGIH)[b]					0.05 mg/m^3 (IFV, skin)
MAC-Peak Category (The Netherlands)[c]					0.1 mg/m^3

NR: Not Recommended. Absence of AEGL-1 values does not imply that concentrations below the AEGL-2 are without effect.
IFV= inhalable fraction and vapor

[a] 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.

[b] ACGIH TLV-TWA (American Conference of Governmental Industrial Hygienists, Threshold Limit Value - Time Weighted Average) (ACGIH 2008) 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

[c] 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

Although toxicity data for fenamiphos are available for oral and dermal exposure routes, acute inhalation data are limited. Limited quantitative data are available regarding human inhalation exposures and very few detailed data regarding health effects from fenamiphos exposure are documented. Animal inhalation studies were found for only one species and most of the studies lacked data on effects other than death. The most useful data to allow for a more robust analysis relative to AEGL development would be dose-response data identifying AEGL-2 severity effects.

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APPENDIX A: Derivation of AEGL Values

Derivation of AEGL-1

No AEGL-1 values were established because the AEGL-1 values would have been too close to or exceeded AEGL-2 values.

The calculations for deriving AEGL values from the no effect level are presented below for comparison with AEGL-2 values.

Key Study:	Kimmerle, G. 1972. Acute inhalation toxicity study with Nemacur active ingredient on rats. Unpublished report. Bayer AG, Wuppertal, Germany.
Toxicity endpoint:	Male and female rats exposed to 29 mg/m^3 for 1 hour did not exhibit any effects of toxicity.
Time scaling:	$C^n \times t = k$, where n = 4.8
Uncertainty factors:	Total uncertainty factor adjustment is 30. Interspecies: 3: Variability 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 fenamiphos 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 justify retention of the intraspecies uncertainty factor of 10.
Modifying factor:	None
Calculation:	$29\ mg/m^3 / 30 = 0.96667\ mg/m^3$ $C^{4.8} \times t = k$ $(0.96667\ mg/m^3)^{4.8} \times 60\ min = 50.998\ mg/m^{3(4.8)} \cdot min$
10-minute AEGL-1	$C^{4.8} \times 10\ min = 50.998\ mg/m^{3(4.8)} \cdot min$ $C = 1.4\ mg/m^3$
30-minute AEGL-1	$C^{4.8} \times 30\ min = 50.998\ mg/m^{3(4.8)} \cdot min$ $C = 1.1\ mg/m^3$
1-hour AEGL-1	$C^{4.8} \times 60\ min = 50.998\ mg/m^{3(4.8)} \cdot min$ $C = 0.97\ mg/m^3$
4-hour AEGL-1	$C^{4.8} \times 240\ min = 50.998\ mg/m^{3(4.8)} \cdot min$ $C = 0.72\ mg/m^3$
8-hour AEGL-1	$C^{4.8} \times 480\ min = 50.998\ mg/m^{3(4.8)} \cdot min$ $C = 0.63\ mg/m^3$

Derivation of AEGL-2

The AEGL-2 values were derived by dividing the AEGL-3 values by three. The lack of experimental data and the steep exposure-response relationship justify estimating AEGL-2 values by a 3-fold reduction of AEGL-3 values (NRC 2001). Male rats experienced 5% mortality after exposure to 75 mg/m^3 for 1 hour; 30% mortality at 87 mg/m^3; and 60% mortality at103 mg/m^3. All 20 rats died after exposure to 187 mg/m^3 (Kimmerle 1972). In a study by Thyssen (1979a), 20% of the male rats died after exposure to 119 mg/m^3 for 1 hour; 60% died after exposure to 145 mg/m^3; and 90% died after exposure to 148 mg/m^3. Female rats had 70% mortality at 145 mg/m^3 and 90% mortality after exposure to 148 mg/m^3 for 1 hour. In a 4-hour study by Thyssen (1979a), male rats experienced 60% mortality at 100 mg/m^3 and 100% mortality at 155 mg/m^3, and female rats experienced 50% mortality at 100 mg/m^3; 90% mortality at 155 mg/m^3; and 100% mortality at 191 mg/m^3.

Calculations:

10-minute AEGL-2	3.0 $mg/m^3/3 = 1.0$ mg/m^3
30-minute AEGL-2	2.4 $mg/m^3/3 = 0.80$ mg/m^3
1-hour AEGL-2	2.1 $mg/m^3/3 = 0.70$ mg/m^3
4-hour AEGL-2	1.6 $mg/m^3/3 = 0.53$ mg/m^3
8-hour AEGL-2	1.3 $mg/m^3/3 = 0.43$ mg/m^3

Derivation of AEGL-3

Key Studies:	Thyssen, J. 1979a. SRA 3886 (Nemacur active ingredient) acute inhalational toxicity studies. Report no. 8210. Unpublished study prepared by Bayer AG, Institut fuer Toxikologie, Germany.
Toxicity endpoint:	4-hr $BMCL_{05}$ of 46.6337 mg/m^3 used as an estimate of lethality threshold in female rats.
Time scaling:	$C^n \times t = k$, where n = 4.8
Uncertainty factors:	Total uncertainty factor adjustment is 30. Interspecies: 3: Variability 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 fenamiphos 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 justify retention of the intraspecies uncertainty factor of 10.
Modifying factor:	None
Calculation:	$46.6337\ mg/m^3 / 30 = 1.5545\ mg/m^3$ $C^{4.8} \times t = k$ $(1.5545\ mg/m^3)^{4.8} \times 240\ min = 1994.558\ mg/m^{3(4.8)} \cdot min$
10-minute AEGL-3	$C^{4.8} \times 10\ min = 1994.558\ mg/m^{3(4.8)} \cdot min$ $C = 3.0\ mg/m^3$
30-minute AEGL-3	$C^{4.8} \times 30\ min = 1994.558\ mg/m^{3(4.8)} \cdot min$ $C = 2.4\ mg/m^3$
1-hour AEGL-3	$C^{4.8} \times 60\ min = 1994.558\ mg/m^{3(4.8)} \cdot min$ $C = 2.1\ mg/m^3$
4-hour AEGL-3	$C^{4.8} \times 240\ min = 1994.558\ mg/m^{3(4.8)} \cdot min$ $C = 1.6\ mg/m^3$
8-hour AEGL-3	$C^{4.8} \times 480\ min = 1994.558\ mg/m^{3(4.8)} \cdot min$ $C = 1.3\ mg/m^3$

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. 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.

Filename: Fenamiphos Rat for Log Probit Model
Date: 29 June 2009 Time: 13:55:58

Used Probit Equation Y = B0 + B1*X1 + B2*X2
X1 = conc ppm, ln-transformed
X2 = minutes, ln-transformed

ChiSquare = 85.89
Degrees of freedom = 32
Probability Model = 8.05E-07

Ln(Likelihood) = -70.87

B 0 = -6.0550E+00 Student t = -3.2592
B 1 = 3.4435E+00 Student t = 7.7738
B 2 = 7.2006E-01 Student t = 2.6363

variance B 0 0 = 3.4514E+00
covariance B 0 1 = -6.7025E-01
covariance B 0 2 = -4.3645E-01
variance B 1 1 = 1.9621E-01
covariance B 1 2 = 4.9704E-02

variance B 2 2 = 7.4601E-02

Estimation ratio between regression coefficients of ln(conc) and ln(minutes)
Point estimate = 4.782
Lower limit (95% CL) = 1.415
Upper limit (95% CL) = 8.150

APPENDIX C: Derivation Summary for Fenamiphos AEGLs

ACUTE EXPOSURE GUIDELINE LEVELS FOR
FENAMIPHOS (CAS Reg. No. 22224-92-6)
DERIVATION SUMMARY

AEGL-1 VALUES				
10-minute	**30-minute**	**1-hour**	**4-hour**	**8-hour**
NR	**NR**	**NR**	**NR**	**NR**
Key Reference: NA				
Test Species/Strain/Number: NA				
Exposure Route/Concentrations/Duration: NA				
Effects: NA				
Endpoint/Concentration/Rationale: NA				
Uncertainty Factors/Rationale: NA				
Modifying Factor: NA				
Animal to Human Dosimetric Adjustment: NA				
Time Scaling: NA				
Data Adequacy: No AEGL-1 values were established because the AEGL-1 values would have been too close to or exceeded AEGL-2 values. Absence of AEGL-1 values does not imply that concentrations below the AEGL-2 are without effect.				

1

AEGL-2 VALUES				
10-minute	**30-minute**	**1-hour**	**4-hour**	**8-hour**
1.0 mg/m^3	**0.80 mg/m^3**	**0.70 mg/m^3**	**0.53 mg/m^3**	**0.43 mg/m^3**
Key Reference: Thyssen, J. 1979a. SRA 3886 (Nemacur active ingredient) acute inhalational toxicity studies. Report no. 8210. Unpublished study prepared by Bayer AG, Institut fuer Toxikologie, Germany.				
Test Species/Strain/Number: NA				
Exposure Route/Concentrations/Durations: One-third the AEGL-3 values. Supported by steep concentration-response curve. Male rats experienced 5% mortality after exposure to 75 mg/m^3 for 1 hour; 30% mortality at 87 mg/m^3; and 60% mortality at 103 mg/m^3. All 20 rats died after exposure to 187 mg/m^3 (Kimmerle 1972). In a study by Thyssen (1979a), 20% of the male rats died after exposure to 119 mg/m^3 for 1 hour; 60% died after exposure to 145 mg/m^3; and 90% died after exposure to 148 mg/m^3. Female rats had 70% mortality at 145 mg/m^3 and 90% mortality after exposure to 148 mg/m^3 for 1 hour. In a 4-hour study by Thyssen (1979a), male rats experienced 60% mortality at 100 mg/m^3 and 100% mortality at 155 mg/m^3, and female rats experienced 50% mortality at 100 mg/m^3; 90% mortality at 155 mg/m^3; and 100% mortality at 191 mg/m^3.				
Effects: NA				
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 were not available on AEGL-2 tier effects.				

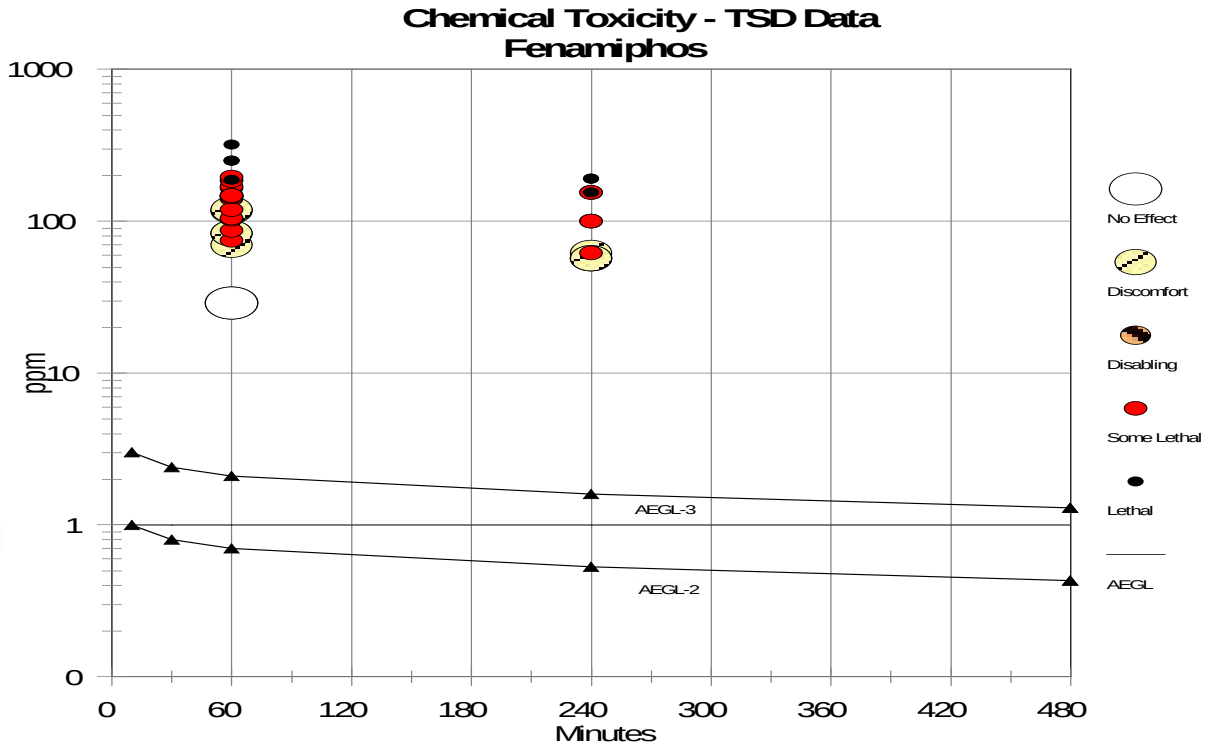
2

1
2

AEGL-3 VALUES				
10-minute	**30-minute**	**1-hour**	**4-hour**	**8-hour**
3.0 mg/m^3	**2.4 mg/m^3**	**2.1 mg/m^3**	**1.6 mg/m^3**	**1.3 mg/m^3**
Key Reference: Thyssen, J. 1979a. SRA 3886 (Nemacur active ingredient) acute inhalational toxicity studies. Report no. 8210. Unpublished study prepared by Bayer AG, Institut fuer Toxikologie, Germany.				
Test Species/Strain/Number: Female Rat/TNO/W74 / 10/group				
Exposure Route/Concentrations/Duration: Inhalation/ 57, 62, 100, 155, 191 mg/m^3/240 min				
Effects: 57 mg/m^3 Cholinesterase activity inhibition 62 mg/m^3 10% mortality; (1/10) 100 mg/m^3 50% mortality, (5/10) 155 mg/m^3 90% mortality; (9/10) 191 mg/m^3 100% mortality; (10/10)				
Endpoint/Concentration/Rationale: Estimated threshold of lethality, $BMCL_{05}$ of 46.6337 mg/m^3				
Uncertainty Factors/Rationale: Total uncertainty factor adjustment is 30 Interspecies: 3: Variability 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 antichlolinesterase agents such as fenamiphos 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 justify retention of the intraspecies uncertainty factor of 10.				
Modifying Factor: none applied				
Animal to Human Dosimetric Adjustment: NA				
Time Scaling: $C^n \times t = k$, where n = 4.8				
Data Adequacy: Data are limited to one species but consistent and adequate for AEGL-3 derivation.				

3
4

APPENDIX D: Category Plot for Fenamiphos



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For Category 0 = No effect, 1 = Discomfort, 2 = Disabling, SL = Some Lethality, 3 = Lethal							
Source	Species	Sex	# Exposures	Mg/m^3	Minutes	Category	Comments
NAC/AEGL-1				NR	10	AEGL	
NAC/AEGL-1				NR	30	AEGL	
NAC/AEGL-1				NR	60	AEGL	
NAC/AEGL-1				NR	240	AEGL	
NAC/AEGL-1				NR	480	AEGL	
NAC/AEGL-2				1.0	10	AEGL	
NAC/AEGL-2				0.80	30	AEGL	
NAC/AEGL-2				0.70	60	AEGL	
NAC/AEGL-2				0.53	240	AEGL	
NAC/AEGL-2				0.43	480	AEGL	
NAC/AEGL-3				3.0	10	AEGL	
NAC/AEGL-3				2.4	30	AEGL	
NAC/AEGL-3				2.1	60	AEGL	
NAC/AEGL-3				1.6	240	AEGL	
NAC/AEGL-3				1.3	480	AEGL	
Kimmerle 1972	rat	m	1	29	60	0	No effect
Kimmerle 1972	rat	m	1	75	60	SL	5% mortality
Kimmerle 1972	rat	m	1	87	60	SL	30% mortality
Kimmerle 1972	rat	m	1	103	60	SL	60% mortality
Kimmerle 1972	rat	m	1	140	60	SL	65% mortality
Kimmerle 1972	rat	m	1	165	60	SL	95% mortality
Kimmerle 1972	rat	m	1	187	60	3	100% mortality
Kimmerle 1972	rat	f	1	29	60.0	0	No effect
Kimmerle 1972	rat	f	1	70	60.0	1	Cholinesterase activity inhibition
Kimmerle 1972	rat	f	1	105	60	SL	5% mortality
Kimmerle 1972	rat	f	1	117	60	1	Cholinesterase activity inhibition
Kimmerle 1972	rat	f	1	148	60	SL	35% mortality
Kimmerle 1972	rat	f	1	170	60	SL	60% mortality
Kimmerle 1972	rat	f	1	185	60	SL	90% mortality
Kimmerle 1972	rat	f	1	195	60	SL	90% mortality
Kimmerle 1972	rat	f	1	320	60	3	100% mortality
Thyssen 1979 a	rat	m	1	83	60	1	Cholinesterase activity inhibition
Thyssen 1979 a	rat	m	1	119	60	SL	20% mortality
Thyssen 1979 a	rat	m	1	145	60	SL	60% mortality
Thyssen 1979 a	rat	m	1	148	60	SL	90% mortality
Thyssen 1979 a	rat	m	1	250	60	3	100% mortality
Thyssen 1979 a	rat	f	1	83	60	1	Cholinesterase activity inhibition
Thyssen 1979 a	rat	f	1	119	60	1	Cholinesterase activity

							inhibition
Thyssen 1979 a	rat	f	1	145	60	SL	70% mortality
Thyssen 1979 a	rat	f	1	148	60	SL	90% mortality
Thyssen 1979 a	rat	f	1	250	60	3	100% mortality
Thyssen 1979 a	rat	m	1	57	240	1	Cholinesterase activity inhibition
Thyssen 1979 a	rat	m	1	62	240	1	Cholinesterase activity inhibition
Thyssen 1979 a	rat	m	1	100	240	SL	60% mortality
Thyssen 1979 a	rat	m	1	155	240	3	100% mortality
Thyssen 1979 a	rat	f	1	57	240	1	Cholinesterase activity inhibition
Thyssen 1979 a	rat	f	1	62	240	SL	10% mortality
Thyssen 1979 a	rat	f	1	100	240	SL	50% mortality
Thyssen 1979 a	rat	f	1	155	240	SL	90% mortality
Thyssen 1979 a	rat	f	1	191	240	3	100% mortality

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

APPENDIX E: Benchmark Exposure Calculations

Kimmerle 1972, Male rat BMC_{01} & $BMCL_{05}$

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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 = Incidence
Independent variable = DOSE
Slope parameter is restricted as slope >= 1
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 = -9.96579
slope = 2.17922

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	-15.5684	2.36683	-20.2073	-10.9295
slope	3.33473	0.502325	2.35019	4.31926

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	-46.5671	8			
Fitted model	-50.4366	2	7.73902	6	0.2579
Reduced model	-109.889	1	126.644	7	<.0001
AIC:	104.873				

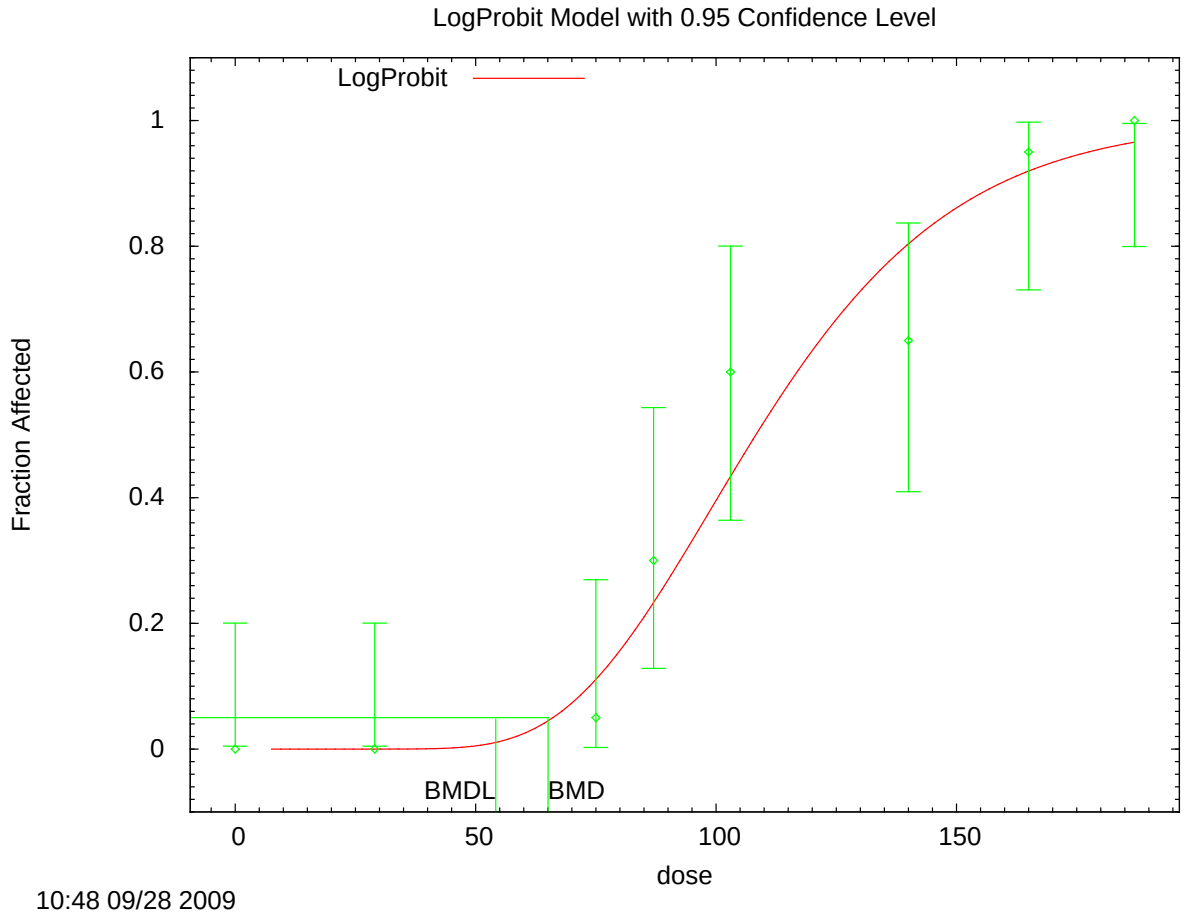
Goodness of Fit

Dose	Est._Prob.	Expected	Scaled Observed	Size	Residual
0.0000	0.0000	0.000	0.000	20	0.000
29.0000	0.0000	0.000	0.000	20	-0.012
75.0000	0.1209	2.417	1.000	20	-0.972
87.0000	0.2496	4.992	6.000	20	0.521
103.0000	0.4551	9.102	12.000	20	1.301
140.0000	0.8188	16.375	13.000	20	-1.959
165.0000	0.9277	18.553	19.000	20	0.386
187.0000	0.9697	19.393	20.000	20	0.791

Chi^2 = 7.52 d.f. = 6 P-value = 0.2752
~~~~~~~~~~

Benchmark Dose Computation

Specified effect =	0.05	0.01
Risk Type =	Extra risk	Extra risk
Confidence level =	0.95	0.95
BMC =	65.0603	**53.035**
BMCL =	**54.181**	41.6366



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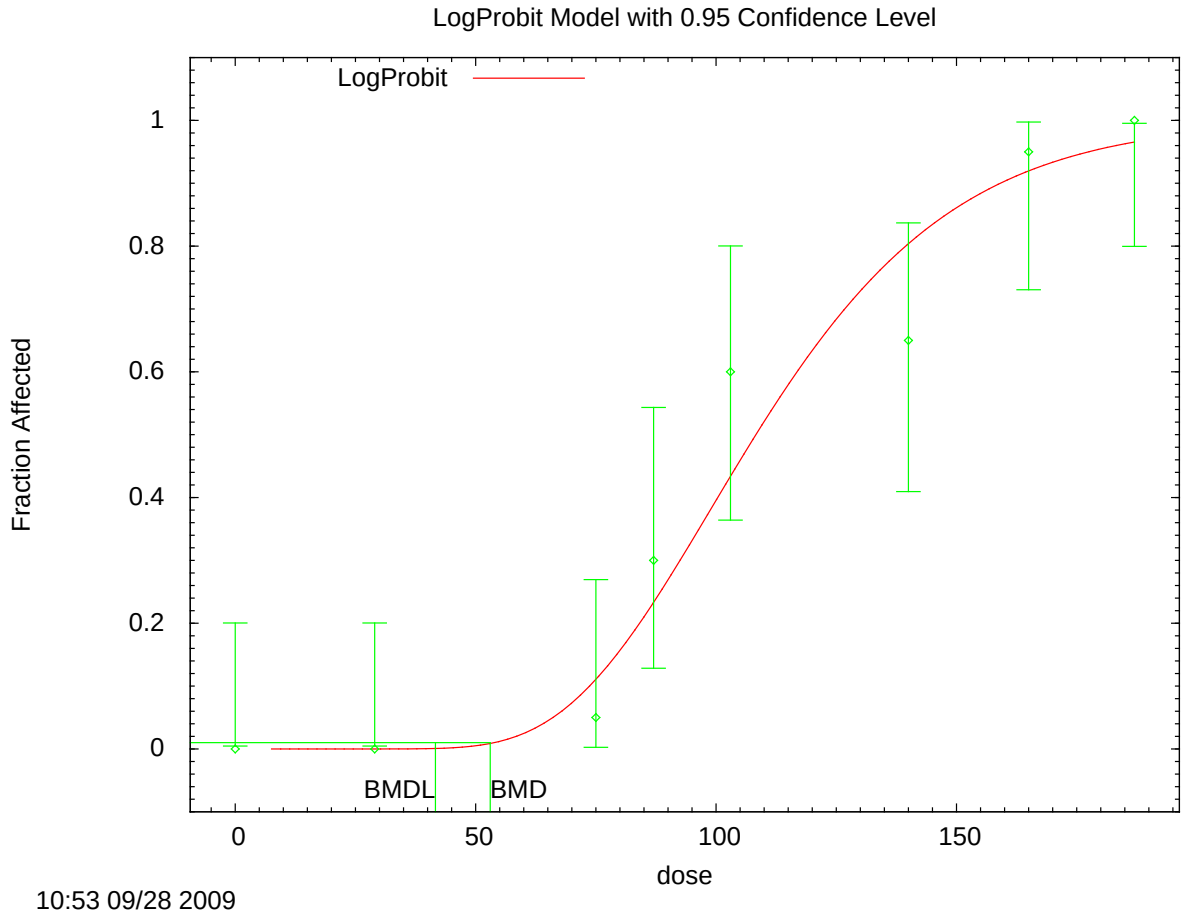
$BMCL_{05}$ graph



BMC$_{01}$ graph

Kimmerle 1972, Female rat BMC$_{01}$ & BMCL$_{05}$

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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 = Incidence
Independent variable = DOSE
Slope parameter is restricted as slope >= 1
Total number of observations = 10
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 = -9.31195
slope = 1.86448

Asymptotic Correlation Matrix of Parameter Estimates
~~~~~~~~~~

	background	intercept	slope
background	1	-0.14	0.14
intercept	-0.14	1	-1
slope	0.14	-1	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
background	0.0198728	0.0144703	-0.00848849	0.048234
intercept	-36.2316	7.26212	-50.465	-21.9981
slope	7.13557	1.41567	4.36092	9.91023

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-47.3531	10			
Fitted model	-50.0328	3	5.35949	7	0.6162
Reduced model	-133.292	1	171.877	9	<.0001
AIC:	106.066				

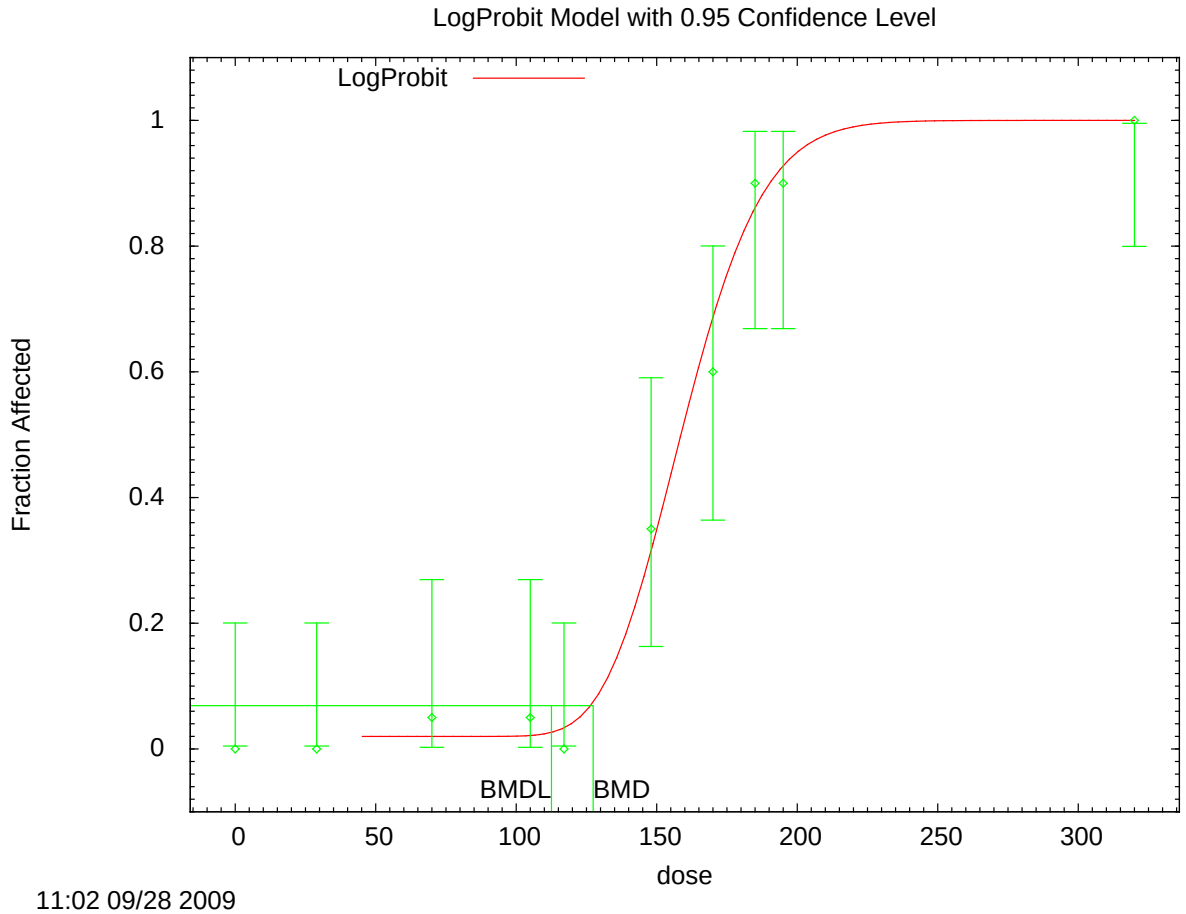
Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Scaled Size	Residual
0.0000	0.0199	0.397	0.000	20	-0.637
29.0000	0.0199	0.397	0.000	20	-0.637
70.0000	0.0199	0.397	1.000	20	0.965
105.0000	0.0211	0.422	1.000	20	0.899
117.0000	0.0318	0.637	0.000	20	-0.811
148.0000	0.2974	5.948	7.000	20	0.515
170.0000	0.6678	13.356	12.000	20	-0.644
185.0000	0.8489	16.978	18.000	20	0.638
195.0000	0.9200	18.400	18.000	20	-0.330
320.0000	1.0000	20.000	20.000	20	0.003

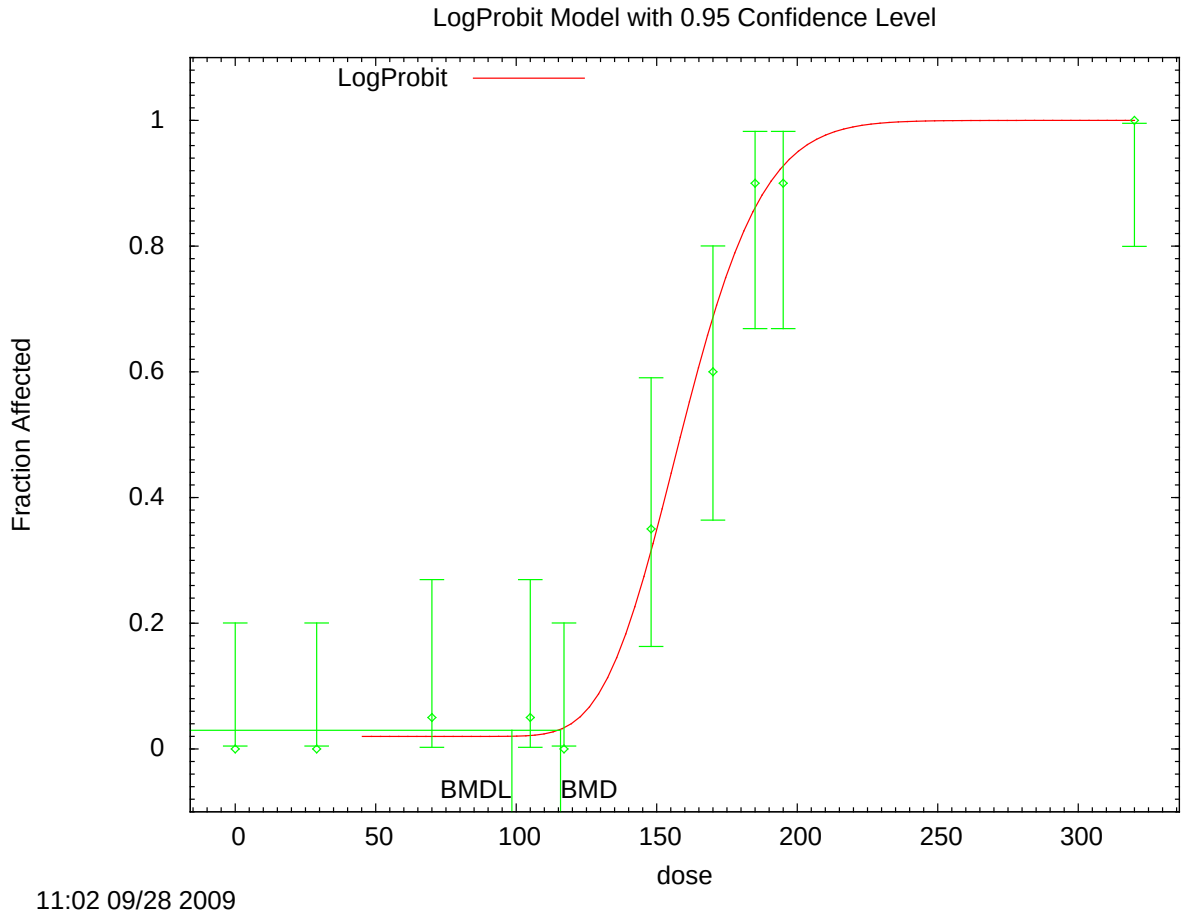
Chi^2 = 4.40 d.f. = 7 P-value = 0.7321

Benchmark Dose Computation

Specified effect =	0.05	0.01
Risk Type =	Extra risk	Extra risk
Confidence level =	0.95	0.95
BMC =	127.368	**115.766**
BMCL =	**112.538**	98.4546



BMCL$_{05}$ graph



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BMC_{01} graph

Thyssen 1979a, Male rat BMC_{01} & $BMCL_{05}$ (1-hr exposure)

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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 = Incidence
Independent variable = DOSE
Slope parameter is restricted as slope >= 1
Total number of observations = 6
Total number of records with missing values = 1
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 = -21.4189
slope = 4.41679

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	-37.4632	12.8407	-62.6304	-12.2959
slope	7.65312	2.60905	2.53947	12.7668

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	-14.985	5			
Fitted model	-15.8938	2	1.81769	3	0.6111
Reduced model	-32.0518	1	34.1336	4	<.0001
AIC:	35.7876				

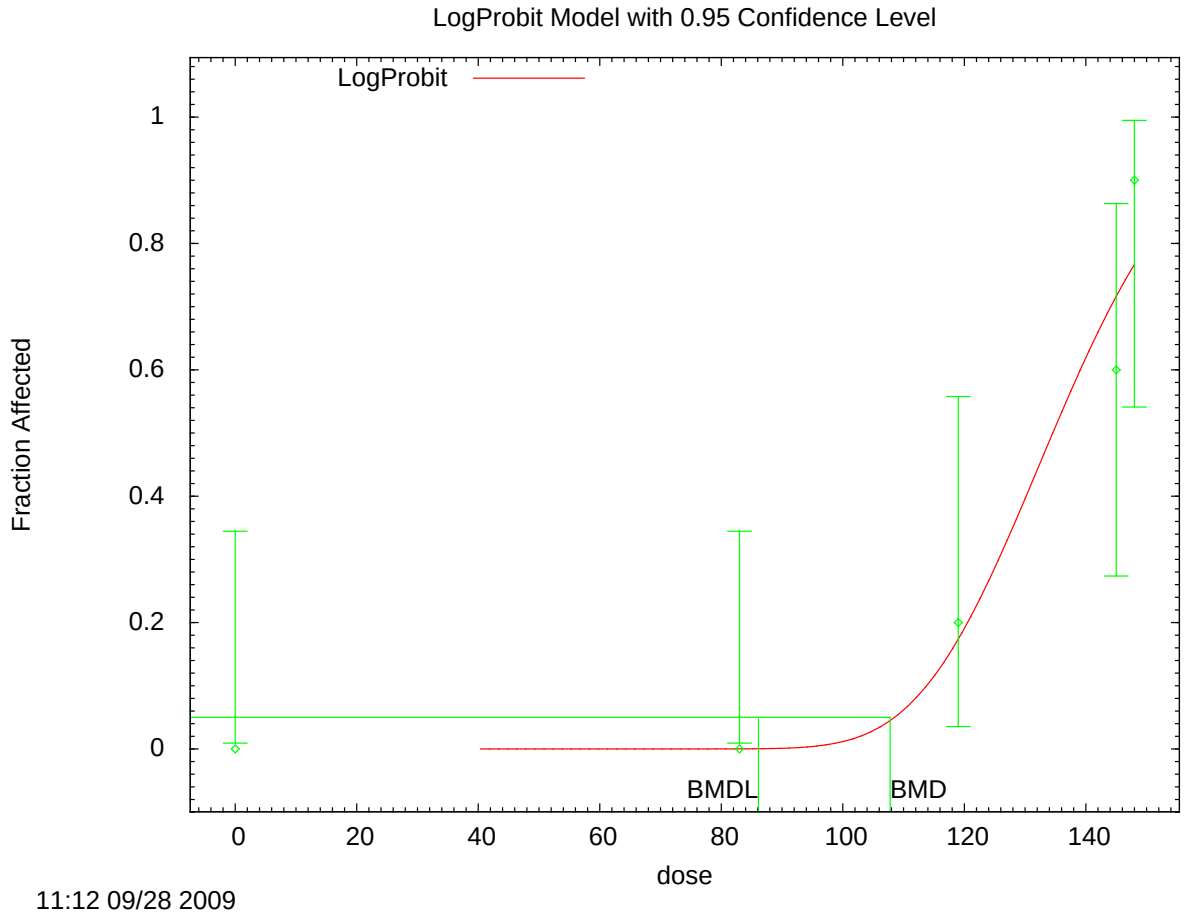
Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Scaled Size	Residual
0.0000	0.0000	0.000	0.000	10	0.000
83.0000	0.0001	0.001	0.000	10	-0.037
119.0000	0.1873	1.873	2.000	10	0.103
145.0000	0.7338	7.338	6.000	10	-0.957
148.0000	0.7826	7.826	9.000	10	0.900

Chi^2 = 1.74 d.f. = 3 P-value = 0.6284

Benchmark Dose Computation

Specified effect =	0.05	0.01
Risk Type =	Extra risk	Extra risk
Confidence level =	0.95	0.95
BMC =	107.795	**98.6107**
BMCL =	**86.1218**	72.8367



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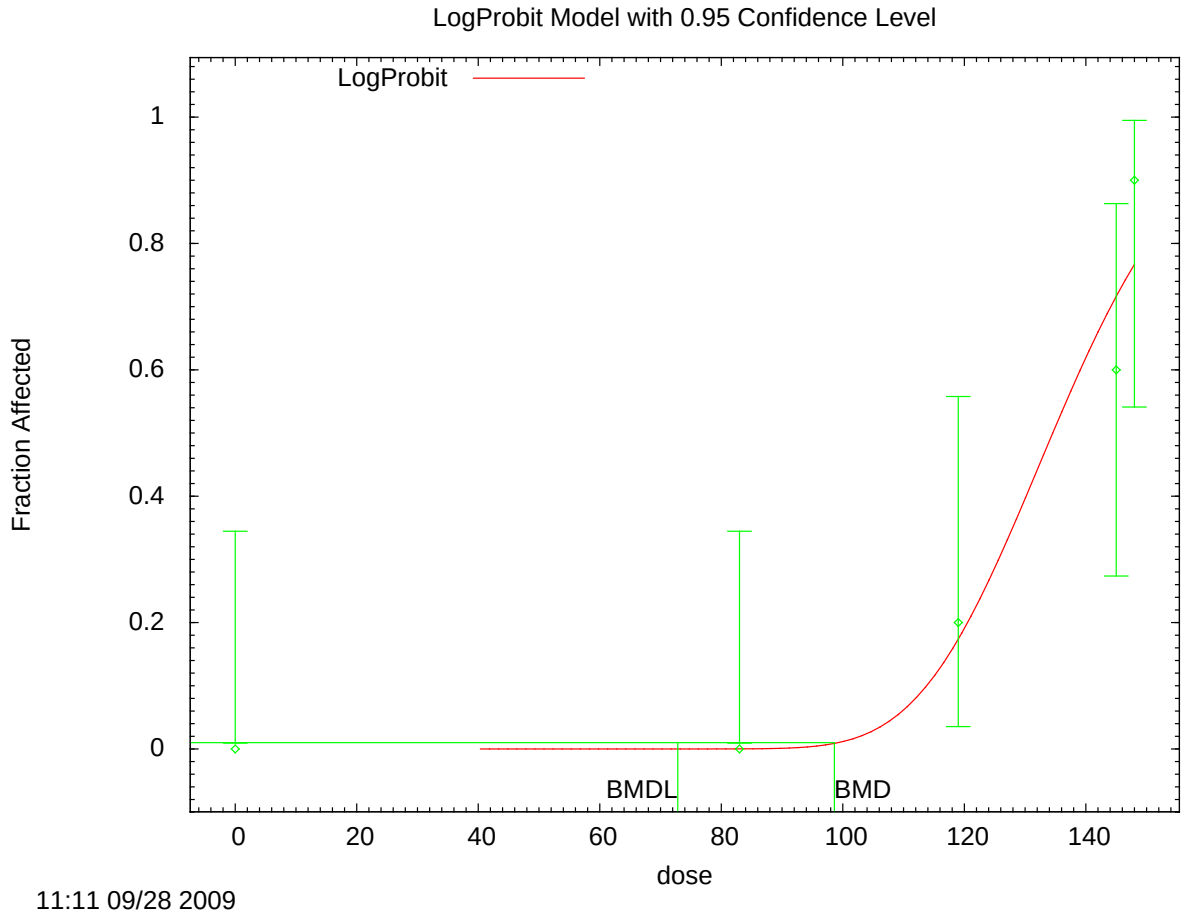
Male $BMCL_{05}$ graph



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Male BMC_{01} graph

Thyssen 1979a, Female rat BMC_{01} & $BMCL_{05}$ (1-hr exposure)

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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 = Incidence
Independent variable = DOSE
Slope parameter is restricted as slope >= 1
Total number of observations = 6
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 = -17.1708
slope = 3.48147

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

	intercept
intercept	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
background	0	NA		
intercept	-88.909	0.320323	-89.5369	-88.2812
slope	18	NA		

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

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-9.35947	6			
Fitted model	-9.54616	1	0.373373	5	0.996
Reduced model	-41.0539	1	63.3889	5	<.0001
AIC:	21.0923				

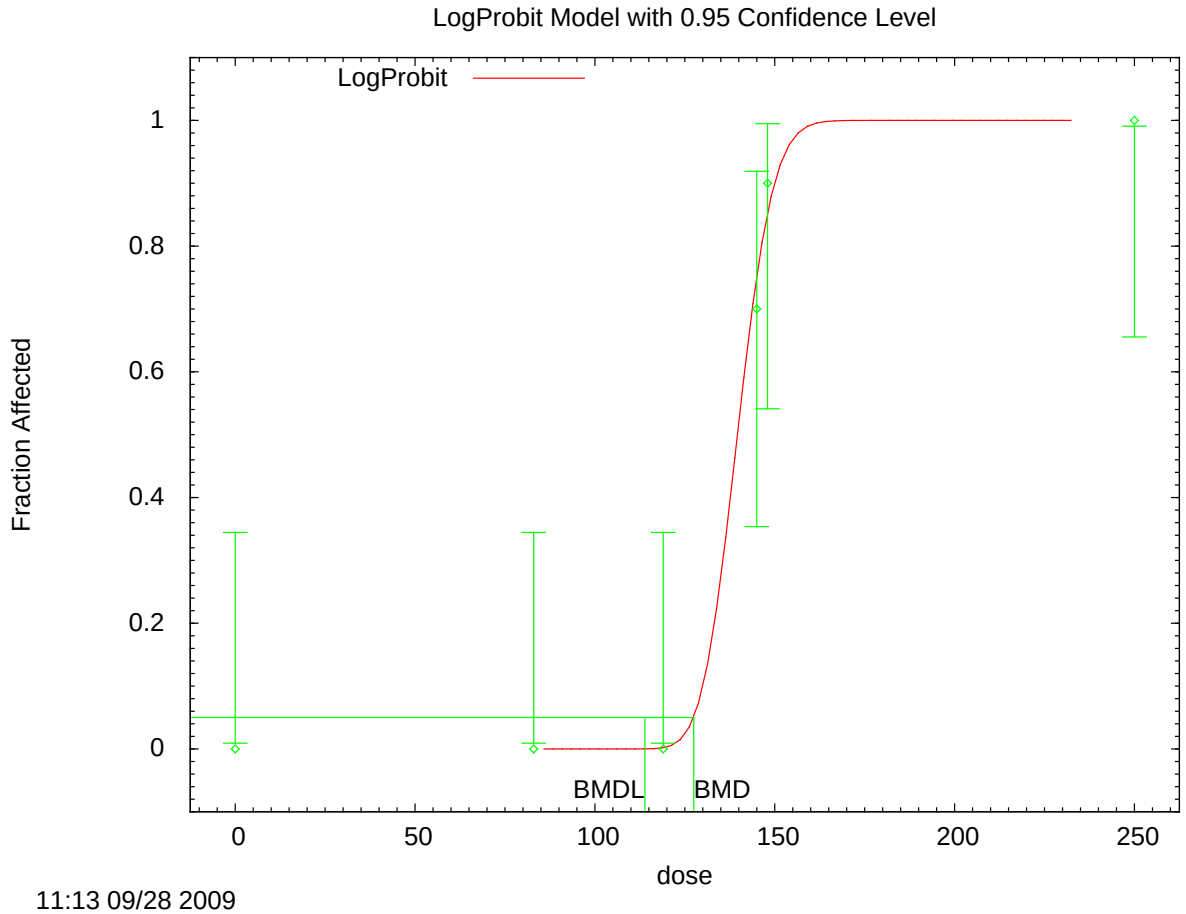
Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Scaled Size	Residual
0.0000	0.0000	0.000	0.000	10	0.000
83.0000	0.0000	0.000	0.000	10	-0.000
119.0000	0.0020	0.020	0.000	10	-0.140
145.0000	0.7493	7.493	7.000	10	-0.359
148.0000	0.8510	8.510	9.000	10	0.435
250.0000	1.0000	10.000	10.000	10	0.000

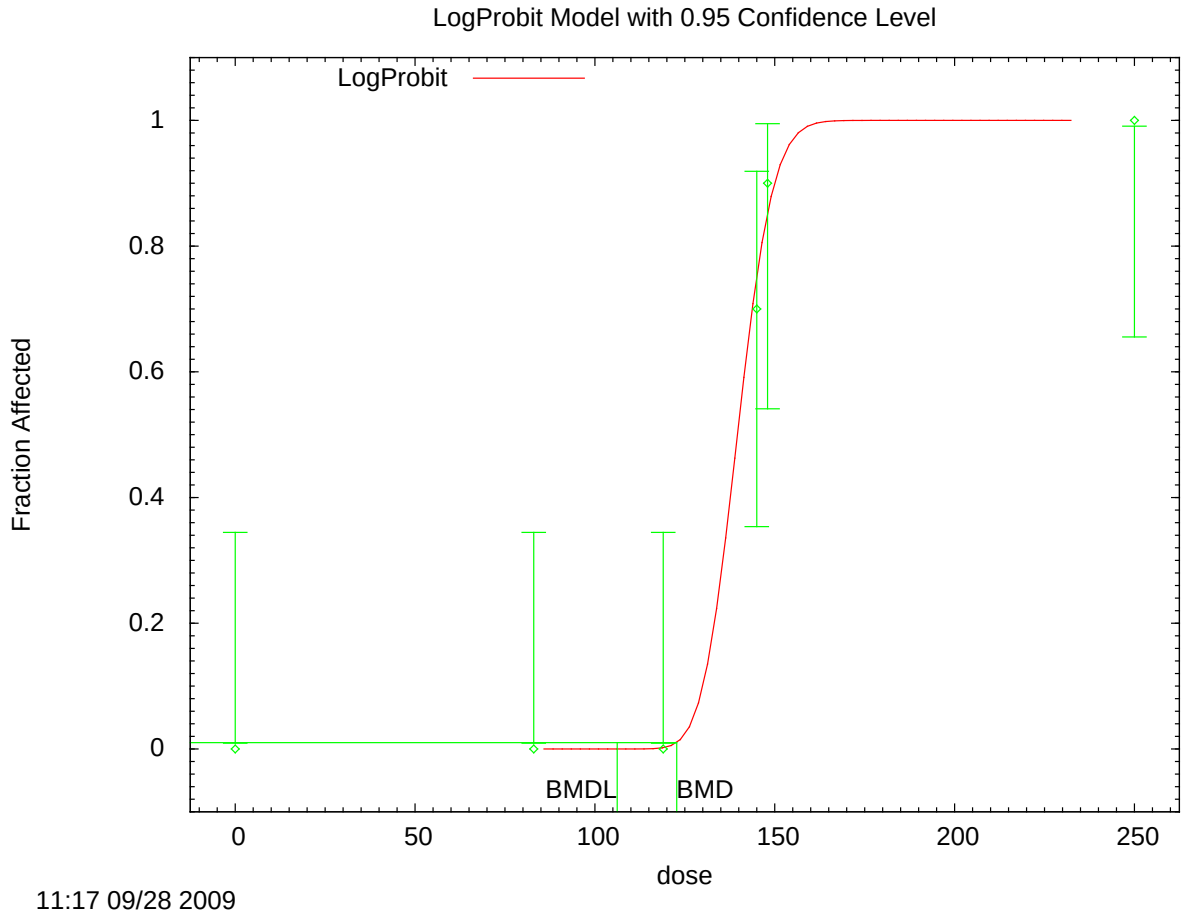
Chi^2 = 0.34 d.f. = 5 P-value = 0.9969

Benchmark Dose Computation

Specified effect =	0.05	0.01
Risk Type =	Extra risk	Extra risk
Confidence level =	0.95	0.95
BMC =	127.487	**122.75**
BMCL =	**113.898**	106.19



Female $BMCL_{05}$ graph



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Female BMC_{01} graph

Thyssen 1979a, Male BMC_{01} & $BMCL_{05}$ (4-hr exposure)

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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 = Incidence
Independent variable = DOSE
Slope parameter is restricted as slope >= 1
Total number of observations = 5
Total number of records with missing values = 0
Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

User has chosen the log transformed model

Default Initial (and Specified) Parameter Values
background = 0
intercept = -16.1037
slope = 3.53434

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	-58.192	6825.98	-13436.9	13320.5
slope	12.6913	1482.24	-2892.45	2917.84

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	-6.73012	5			
Fitted model	-6.73012	2	1.21757e-007	3	1
Reduced model	-31.3435	1	49.2267	4	<.0001
AIC:	17.4602				

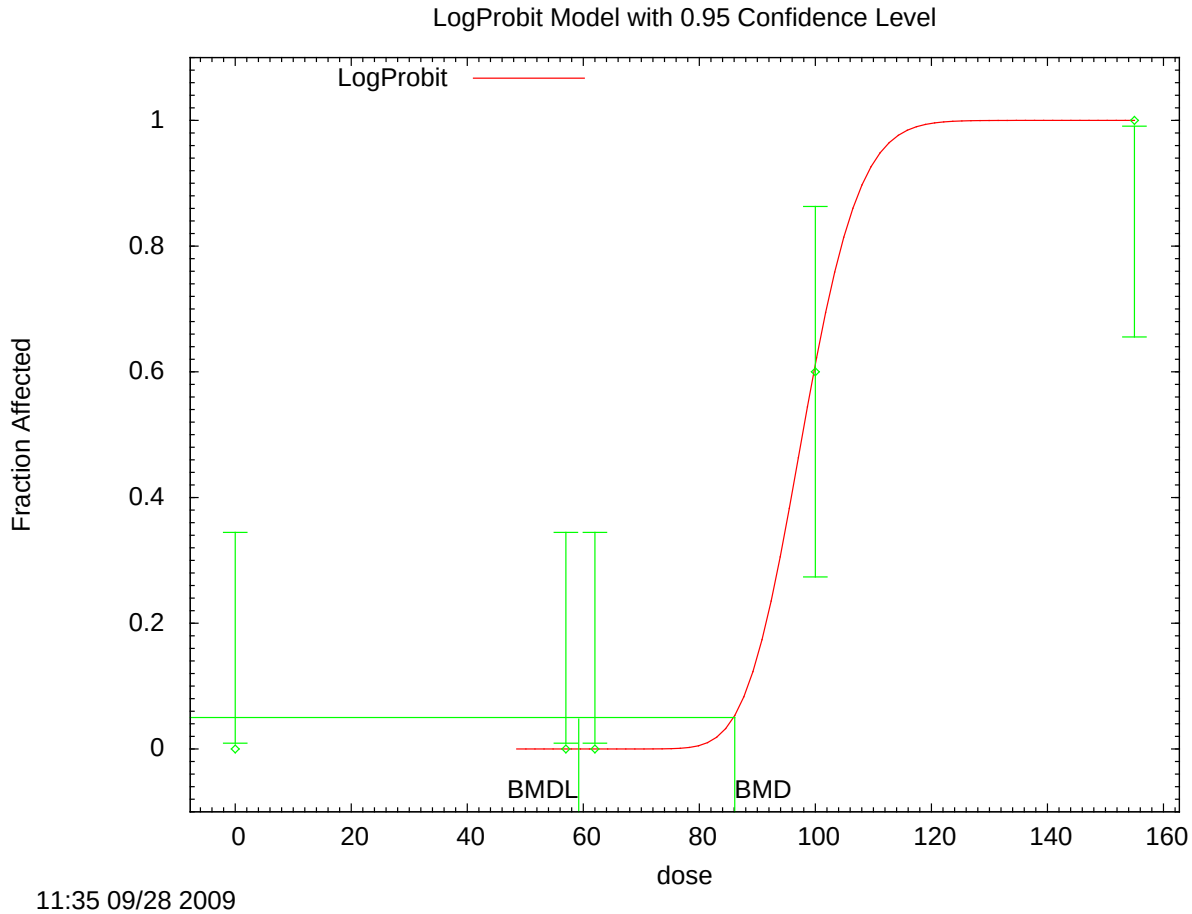
Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Scaled Size	Residual
0.0000	0.0000	0.000	0.000	10	0.000
57.0000	0.0000	0.000	0.000	10	-0.000
62.0000	0.0000	0.000	0.000	10	-0.000
100.0000	0.6000	6.000	6.000	10	0.000
155.0000	1.0000	10.000	10.000	10	0.000

Chi^2 = 0.00 d.f. = 3 P-value = 1.0000

Benchmark Dose Computation

Specified effect =	0.05	0.01
Risk Type =	Extra risk	Extra risk
Confidence level =	0.95	0.95
BMC =	86.108	**81.6062**
BMCL =	**59.2137**	49.4938



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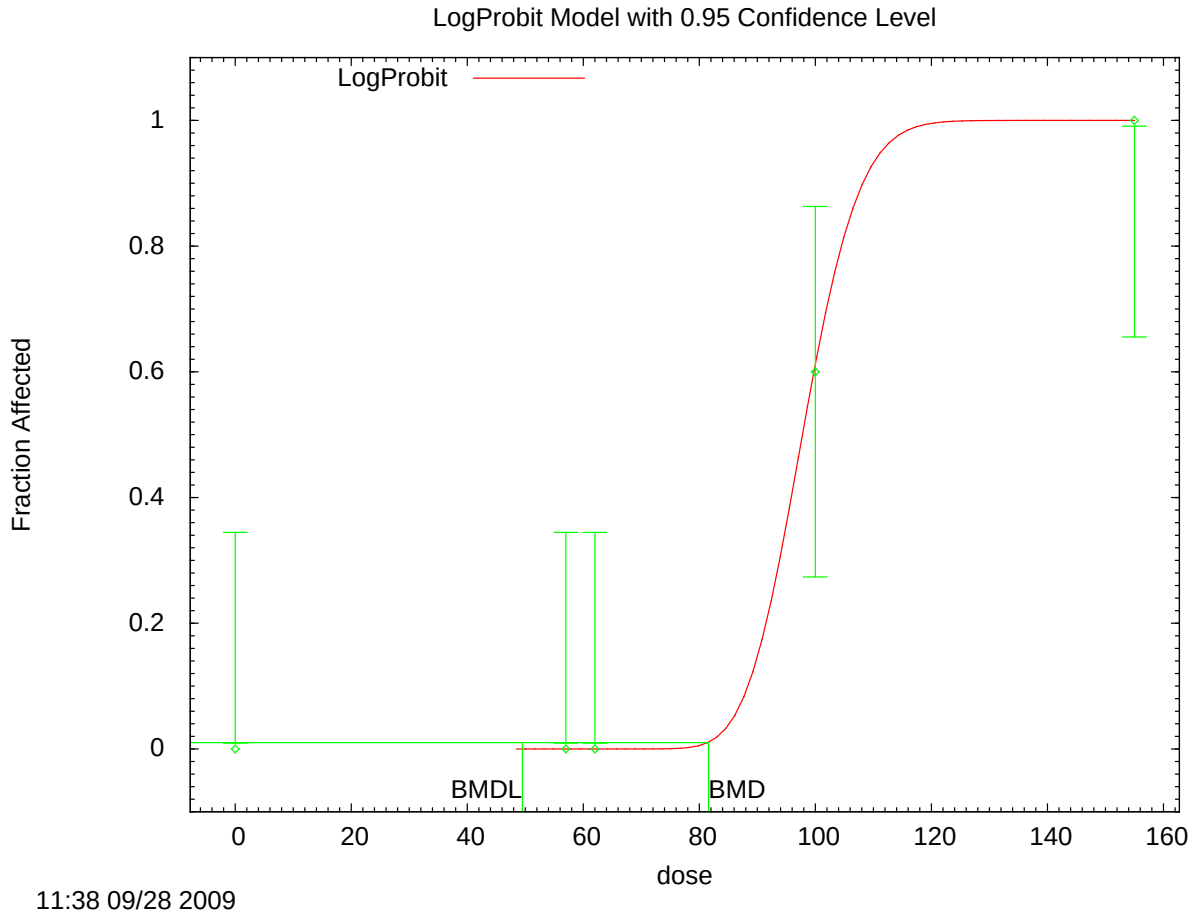
Male $BMCL_{05}$ graph



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Male BMC_{01} graph

Thyssen 1979a, Female BMC_{01} & $BMCL_{05}$ (4-hr exposure)

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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 = Incidence
Independent variable = DOSE
Slope parameter is restricted as slope >= 1
Total number of observations = 6
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 = -12.8595
slope = 2.78692

Asymptotic Correlation Matrix of Parameter Estimates
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(*** 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	-15.2331	3.24344	-21.5901	-8.87605
slope	3.30866	0.704182	1.92849	4.68883

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	-13.4331	6			
Fitted model	-14.1051	2	1.34385	4	0.8539
Reduced model	-40.7516	1	54.6369	5	<.0001
AIC:	32.2101				

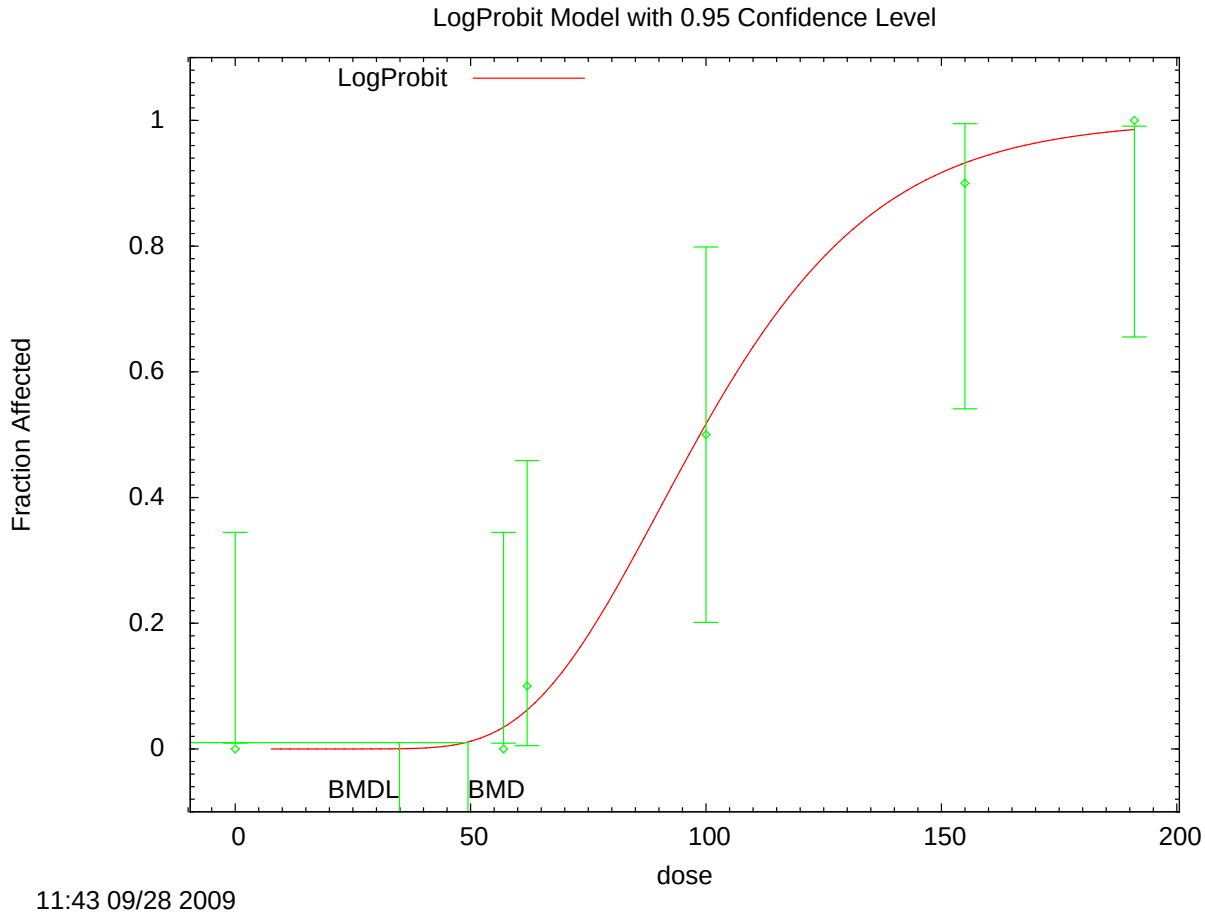
Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Scaled Size	Residual
0.0000	0.0000	0.000	0.000	10	0.000
57.0000	0.0317	0.317	0.000	10	-0.572
62.0000	0.0573	0.573	1.000	10	0.581
100.0000	0.5015	5.015	5.000	10	-0.010
155.0000	0.9270	9.270	9.000	10	-0.328
191.0000	0.9840	9.840	10.000	10	0.403

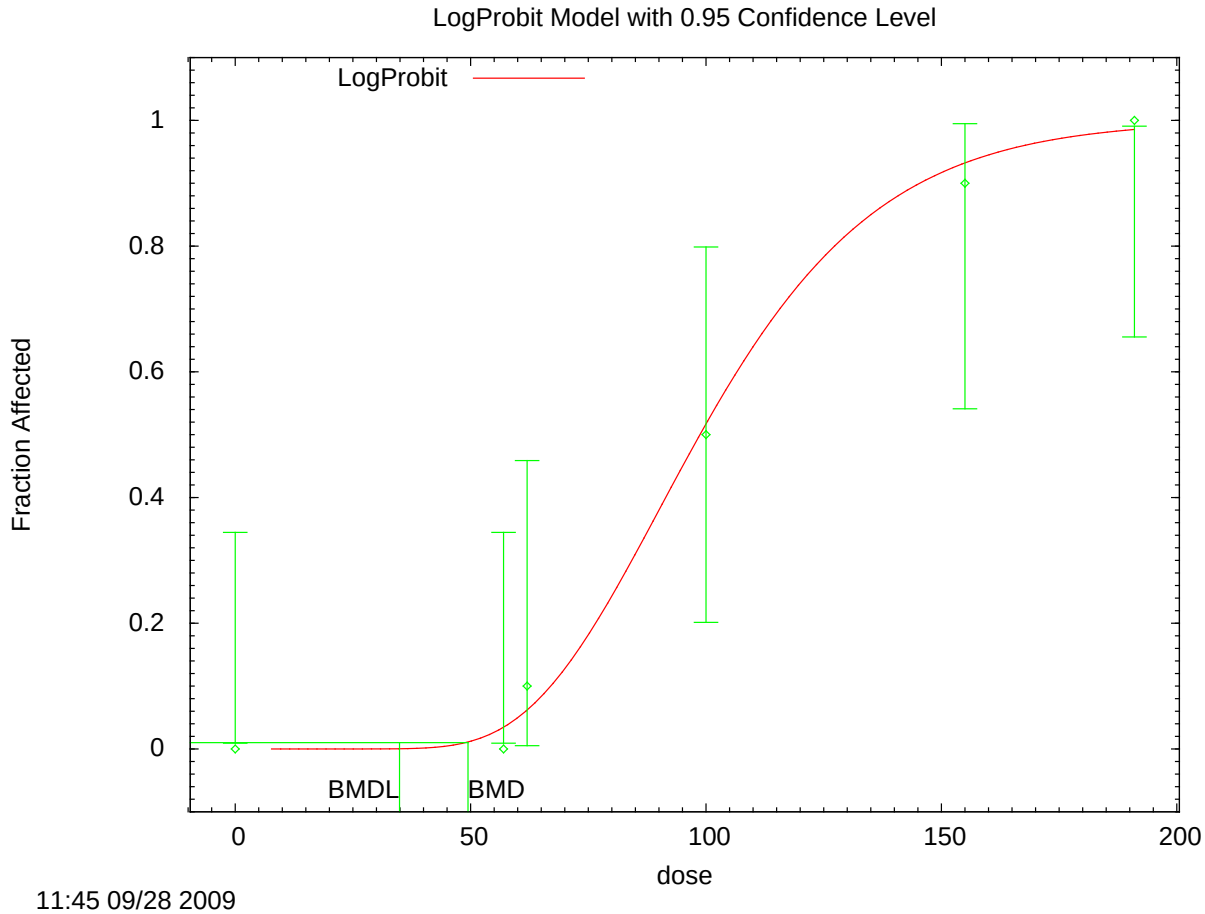
Chi^2 = 0.94 d.f. = 4 P-value = 0.9194

Benchmark Dose Computation

Specified effect =	0.05	0.01
Risk Type =	Extra risk	Extra Risk
Confidence level =	0.95	0.95
BMC =	60.7558	**49.4464**
BMCL =	**46.6337**	34.904



Female $BMCL_{05}$ graph



Female BMC_{01} graph