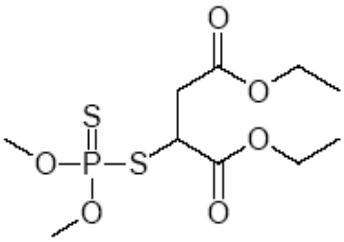
Interim: 09/2009

ACUTE EXPOSURE GUIDELINE LEVELS (AEGLs)

FOR

MALATHION

(CAS Reg. No. 121-75-5)



INTERIM

PREFACE

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

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

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

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

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

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

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SUMMARY

Malathion is a broad-spectrum organophosphorous insecticide used on a wide variety of crops and flowering plants. The chemical is also used in regional pest eradication programs, and to control ectoparasites on cattle and head and body lice on humans (ATSDR 2003, US EPA 2006a). Commercially, malathion is available as an emulsifiable concentrate, dust, wettable powder, ready-to-use liquid, and as a pressurized liquid with the concentration of active ingredient 82-96.8% (US EPA 2006a). Two main impurities found in technical malathion include isomalathion and malaoxon (US EPA 2006a).

Very little information is available concerning human exposure to malathion despite the large quantities of the chemical that are used each year. No deaths have been reported from inhalation exposure to the malathion. Malathion has not been shown to cause cancer in humans. Only limited information was available on laboratory animals following inhalation exposure. Plasma and RBC cholinesterase activity inhibition were measured in rabbits, rats, and mice in the absence of clinical signs.

The best available animal data for derivation of AEGL-1 and AEGL-2 are from a subchronic inhalation study in Sprague-Dawley rats (US EPA 2000). Groups of 15 male and 15 female rats were exposed by inhalation in whole body exposure chambers to malathion (96.4% a.i.) aerosols (in air) at concentrations of 0, 100, 450 or 2010 mg/m^3, 6 hours/day, 5 days/week for 13 weeks. The mass median aerodynamic diameter (MMAD) of the malathion particles was 1.6-1.7 µm. Clinical signs such as urogenital staining, excess salivation and ungroomed fur were seen mostly at 2010 mg/m^3, but also occurred sporadically at 450 and 100 mg/m^3 in both sexes. After 13 weeks, dose-related inhibition of cholinesterase activity was seen in both sexes. Relative to controls, cholinesterase activity inhibition at 100, 450 and 2010 mg/m^3, respectively, was as follows: plasma 2-16%, 7-30% and 18-70%; erythrocytes 9-11%, 22-27% and 43-44%; brain 4-5%, 3-8% and 17-41%. Based on inhibition of erythrocyte and plasma cholinesterase activity exceeding 10% in female rats, and on microscopic lesions of the nasal cavity and larynx, classified as slight to moderate, observed in most animals of both sexes at all three exposure concentrations, the LOAEL was 100 mg/m^3 and a NOAEL was not established.

A concentration of 450 mg/m^3 for 6 hours was chosen as the point of departure for derivation of AEGL-1 values. Because clinical signs at the point of departure were sporadic and cholinesterase activity inhibition was not biologically significant after the 13-week exposure, time scaling was not performed.

A concentration of 2010 mg/m^3 for 6 hours was chosen as the point of departure for derivation of AEGL-2 values. At this concentration clinical signs were reported and, after 13 weeks, microscopic lesions and significant inhibition of brain cholinesterase activity were seen. Values were scaled using the equation $C^n \times t = k$ where n ranges from 0.8 to 3.5 (ten Berge et al. 1986). In the absence of an empirically derived, chemical-specific exponent, scaling was performed using n = 3 for extrapolating to the 30-minute, 1-hour, and 4-hour time points and n = 1 for the 8-hour time point. According to Section 2.7 of the Standing Operating Procedures for Developing Acute Exposure Guideline Levels for Hazardous Chemicals (NRC 2001), 10-minute

values are not to be scaled from an experimental exposure time of ≥4 hours. Therefore the 30-minute value was adopted as the 10-minute AEGL-2 value.

AEGL-3 values for malathion are based on the highest available experimental concentration administered to laboratory animals. No deaths were reported for rats exposed to 5200 mg/m^3 for 4 hours (US EPA 2000) or to mice exposed to 6900 mg/m^3 for 5 hours (Berteau et al. 1976). A concentration of 6900 mg/m^3 for 5 hours was chosen as the point of departure for derivation of AEGL-3. Values were scaled as described for AEGL-2. Although no lethality has been reported in humans or animals from inhalation exposure to malathion, AEGL-3 values are derived to serve as guidance in an emergency situation. It is acknowledged that attaining lethal airborne concentrations of malathion may not be possible.

A total uncertainty factor of 30 was applied to the AEGL-1, -2, and -3 points-of-departure. The total uncertainty factor includes 10 for intraspecies extrapolation to account for the documented variability in sensitivity among different age groups and genders, and the known genetic polymorphisms in A-esterases and 3 for interspecies extrapolation to account for the differences in serum carboxylesterase levels between humans and rats. The uncertainty factor application and rationale are the same as those applied in the derivation of other organophosphate anticholinesterases (NRC 2003).

The calculated values are listed in the table below.

Summary of AEGL Values for Malathion

Classification	10-minute	30-minute	1-hour	4-hour	8-hour	Endpoint (Reference)
AEGL–1 (Nondisabling)	15 mg/m^3	15 mg/m^3	15 mg/m^3	15 mg/m^3	15 mg/m^3	Sporadic clinical signs in rats (US EPA 2000)
AEGL–2 (Disabling)	150 mg/m^3	150 mg/m^3	120 mg/m^3	77 mg/m^3	50 mg/m^3	Clinical signs in rats (US EPA 2000)
AEGL–3* (Lethal)	500 mg/m^3	500 mg/m^3	390 mg/m^3	250 mg/m^3	140 mg/m^3	Highest experimental concentration (Berteau et al. 1976)

* Although no lethality has been reported in humans or animals from inhalation exposure to malathion, AEGL-3 values are derived to serve as guidance in an emergency situation. It is acknowledged that attaining lethal airborne concentrations of malathion may not be possible.

1. INTRODUCTION

Malathion is a broad-spectrum organophosphorous insecticide used on a wide variety of crops and flowering plants. The chemical is also used in regional pest eradication programs, and to control ectoparasites on cattle and head and body lice on humans (ATSDR 2003, US EPA 2006a). Commercially, malathion is available as an emulsifiable concentrate, dust, wettable powder, ready-to-use liquid, and as a pressurized liquid with the concentration of active ingredient 82-96.8% (US EPA 2006a). Two main impurities found in technical malathion include isomalathion and malaoxon (US EPA 2006a).

Selected chemical and physical properties of malathion are listed in Table 1.

TABLE 1: Chemical and Physical Properties of Malathion

Parameter	Value	Reference
Synonyms	1,2-Di(rthoxycarbonyl)ethyl *O,O*-dimethyl phosphorodithioate	ATSDR 2003
Chemical formula	$C_{10}H_{19}O_6PS_2$	ATSDR 2003
Molecular weight	330.36	ATSDR 2003
CAS Reg. No.	121-75-5	
Physical state	Colorless to amber liquid	US EPA 2006a
Solubility in water	145 mg/L at 20°C	ATSDR 2003
Vapor pressure	0.00004 mm Hg	US EPA 2006b
Vapor density (air =1)	No data	
Liquid density (water =1)	1.23 g/cm^3 at 25°C	ATSDR 2003
Melting point	2.9°C	ATSDR 2003
Boiling point	156-157°C	ATSDR 2003
Auto-ignition	No data	
Flammability limits (% in air)	No data	
Lower Explosive Limit	No explosive	ECB 2000
Conversion factors	1 ppm = 13.5 mg/m^3 1 mg/m^3 = 0.07 ppm	$\frac{ppm \times MW}{24.45} = mg/m^3$

2. HUMAN TOXICITY DATA

2.1. Acute Lethality

No reports of human fatalities from inhalation exposure to malathion were found. Case reports from accidental or intentional ingestion of malathion are summarized in ATSDR (2003). Estimated lethal doses in these reports ranged from 350 to 2000 mg/kg and symptoms typical of organophosphate poisoning were described.

2.2. Nonlethal Toxicity

No experimental data on humans were found that could be used in the derivation of AEGL values.

A number of agricultural worker monitoring studies have been conducted in which urinary metabolites were measured as biomarkers of exposure (ATDSR 2003, Bouchard et al. 2003, 2006, Krieger and Dinoff 2000). None of these studies reported health effects, exposure concentrations, or cholinesterase activity measurements. The state of California estimated the inhaled dose of malathion to the general public from aerial spraying to be 0.023-0.078 µg/kg/d for adults and 0.014-0.099 µg/kg/d for infants and children (Marty et al. 1994).

2.4. Developmental/Reproductive Toxicity

Reproductive outcomes were followed in a cohort of pregnant women in the San Francisco Bay area with relation to exposure to malathion from aerial spraying (Thomas et al. 1992). Individual exposure concentrations could not be determined. No association was found between exposure and spontaneous abortion, intrauterine growth retardation, stillbirth, or most congenital anomalies. Gastrointestinal anomalies (mainly pyloric stenoses) were significantly related to exposure during the second trimester with an odds ratio of 2.6 (95% confidence interval not given).

2.5. Genotoxicity

This information has been summarized by ATSDR (2003) and the following is excerpted from that report. The primary references were not reviewed here.

Many *in vivo* and *in vitro* studies in humans and animals have investigated the genotoxic effects of malathion, and evidence suggests that technical-grade malathion has the potential to be a genotoxic agent. Most studies (many with positive results) have used technical or commercial grades of malathion rather than the purified form. This, and the positive genotoxicity results of studies on malaoxon, suggest the possibility that impurities in commercial formulations might be the active genotoxic agents.

[I]n vivo studies of genotoxicity associated with malathion exposure in humans show varying results. Actual exposure levels were not available in any of the studies. In a study of 60 workers in direct contact with malathion who were exposed from 5 to 25 years, significant differences in chromatid aberrations were observed both in groups of individuals exposed for 11–15 years and those exposed for more than 20 years when compared with control groups employed at the plant for similar exposure periods. A study of individuals acutely exposed to malathion showed significant chromatid breaks, total chromatid aberrations, numbers of cells with non-modal chromosomes, and unstable and stable chromosome aberrations in lymphocytes cultured immediately after exposure. One month after exposure, lymphocytes showed only significant levels of stable and unstable chromosome aberrations, and at 6 months postexposure, significant differences were observed only in numbers of cells with nonmodal chromosomes. [S]tud[ies] of

workers who applied malathion as ground treatment during the…med-fly eradication program found no significant differences in the level of micronuclei in lymphocytes between the exposed and unexposed groups. The frequency of variant cells was not associated with malathion exposure.

2.6. Carcinogenicity

From epidemiology studies in agricultural workers, ATSDR (2003) concluded that "[t]he overall evidence from human studies is insufficient to draw any conclusions regarding the association between exposure to malathion and cancer. In general, the magnitude of the excesses is small, exposure assessment is unreliable, and people are seldom exposed to a single pesticide." A carcinogenicity assessment has not been made by US EPA (1992).

2.7. Summary

Very little information is available concerning human exposure to malathion despite the large quantities of the chemical that are used each year. No deaths have been reported from inhalation exposure to malathion. Malathion has not been shown to cause cancer in humans.

3. ANIMAL TOXICITY DATA

Relevant inhalation studies in mammals are described below. A number of studies were identified which used non-mammalian species, including birds and fish, as well as non-inhalation routes of exposure. These studies are not included as they were not considered relevant to derivation of AEGL values.

3.1. Acute Lethality

No lethality studies in experimental animals were found with inhalation exposure. US EPA (2000) listed the 4-hour LC_{50} for male and female rats as >5200 mg/m^3; no other details were given.

3.2. Nonlethal Toxicity

3.2.1 Rabbits

Groups of six male New Zealand white rabbits were exposed whole body to analytically determined aerosol concentrations of 0, 6, 34, 65, or 123 mg/m^3 of technical grade malathion (95%) for 6 hours and plasma and RBC cholinesterase activity were monitored for up to 7 days (Weeks et al. 1977). Aerosols were produced with a Laskin Single Jet (No. 18) Atomizer and mass-size distribution was measured with a cascade impactor. The mass median diameter was 12±2 µm. No deaths or clinical signs were observed in any group. At the high concentration, significantly inhibited cholinesterase activity was found in plasma at 24 and 72 hours (38% and 41% inhibition from control level) and in RBC at 24 hours, 72 hours and 7 days (38%, 49%, and 48% inhibition from control level). However, it is noted that much of the aerosol fraction was not respirable and it is likely that significant exposure occurred both dermally and orally.

3.2.2 Mice

Female NAMRU mice (n = 16) were exposed whole-body to 6900 mg/m^3 of aerosolized malathion (95% technical grade) for 5 hours followed by a 14-day observation period (Berteau et al. 1976, Berteau and Deen 1978). The aerosol, mass median diameter of 1.5-2.0 µm (geometric s.d. 2.0), was generated with a Wells type refluxing atomizer. No deaths occurred and no clinical signs of toxicity were described. Plasma cholinesterase activity inhibition was highly variable with negligible depression after one 5-hour exposure and a maximum of 45% depression from pre-exposure level after a 2 hour exposure; complete recovery was found by post-exposure day 6 (data presented graphically). No further details were given.

3.3. Developmental/Reproductive Toxicity

No reproductive or developmental toxicity data were found on inhalation exposure to malathion.

3.4. Genotoxicity

This information has been summarized by ATSDR (2003) and the following is excerpted from that report. The primary references were not reviewed here.

Many *in vivo* and *in vitro* studies in humans and animals have investigated the genotoxic effects of malathion, and evidence suggests that technical-grade malathion has the potential to be a genotoxic agent. Most studies (many with positive results) have used technical or commercial grades of malathion rather than the purified form [which] suggests the possibility that impurities in commercial formulations might be the active genotoxic agents.

Chromosome abnormalities were observed at a dose of 1.5 mg/kg body weight administered by gavage to mice for 7 days. A dose-response relationship was observed in this study up to the highest dose of 6.0 mg/kg. Feeding male mice with grains treated with a commercial malathion formulation induced chromosomal aberrations in bone marrow cells and chromosomal abnormalities in spermatocytes; maximal responses were seen with the highest dose tested (approximately 7.5 mg/kg/day) in mice that ate grains pre-stored for 24 weeks and were given to the mice for 12 weeks. After 10 days of gavage dosing with 0.2 µg/kg/day, mice spermatocytes had slower rates of meiotic cell division than controls. Another study showed no significant numbers of chromosome aberrations in bone marrow or spermatogonia and no dominant lethal mutations after a single intraperitoneal dose of 300 mg/kg was administered to mice.

In vivo studies in *Drosophila* are more equivocal. [I]ncreased failure of eggs to hatch [was observed] after untreated females were mated with treated males, assumed to be due to dominant lethal mutations. The study also found increased sex-linked recessive lethal mutations. Another study, however, showed no differences in sex-linked recessive lethal mutations, although this test used a *Drosophila* strain selected for increased malathion resistance.

Assays in bacteria show conflicting results. [S]ome mutagenicity of malathion without metabolic activation in one strain of *Bacillus subtilis* (and greater mutagenicity with activation) and weak DNA damaging potential in several *B. subtilis* strains [were observed]. Studies in various *Salmonella typhimurium* strains dosed with malathion reported no significant differences in gene mutations both with and without activation. Sister chromatid exchanges were observed in human lymphoid cells and lymphocytes, when assays were conducted with [and without] activation. [A] significant increase in micronucleated cells [was found] in isolated human lymphocytes, whereas the genotoxic effects in whole blood cultures (although still significant) were smaller. [T]he frequency of mutations in human lymphocytes [was] significantly greater…in cells dosed with malathion (without activation). [T]wo analogues present in commercial malathion formulations (malaoxon and isomalathion) damaged DNA in a dose dependent manner.

US EPA (2000) has also summarized genetic toxicity data submitted to the agency and published in the open literature as copied in the following paragraph.

Results of three guideline genetic toxicology studies with malathion indicate that the test material did not cause gene mutations in bacteria or unscheduled DNA synthesis (UDS) in cultured rat hepatocytes. Similarly, malathion was neither clastogenic nor aneugenic up to doses that showed clear cytotoxicity for the target tissue *in vivo*. Studies from the open literature indicated that malathion was positive both *in vitro* and *in vivo*. However, there are uncertainties regarding the relevance of these findings to a possible mutagenic mode of action for malathion since positive results from both *in vivo* and *in vitro* studies were seen only at cytotoxic doses and/or the types of induced aberrations were asymmetric and, therefore, not consistent with cell survival. Questions also arise regarding the purity of the test material. Nevertheless, malathion was shown to be weakly reactive with DNA and does contain a structure that suggests electrophilicity. [T]he weight of the evidence neither supports a mutagenic hazard nor a role for mutagenicity in the carcinogenicity associated with malathion. [M]alathion was negative in *Drosophila melanogaster* sex linked recessive lethal assays, mouse dominant lethal assays and spermatogonia and/or spermatocyte cytogenetic assays. An adverse heritable effect has not been suggested for malathion.

3.5. Subchronic and Chronic Toxicity/Carcinogenicity

Hazleton and Holland (1949) conducted a series of inhalation studies with laboratory animals using malathion of 90% purity. No information on atmosphere generation or measurements was given; the atmosphere was referred to as an aerosol, but concentration was given in ppm. In the first study, rabbits, guinea pigs, rats and mice were exposed to 60 ppm, 6 hours/day for 2 days. Clinical signs were limited to sneezing in rabbits and rhinorrhea in guinea pigs. At necropsy, the lungs appeared hyperemic. No effects on RBC, plasma or brain cholinesterase activity were found. In the second experiment, one dog, guinea pigs, rats and mice were exposed to 5 ppm for 8 hours/day, 5 days/week, for 4 weeks. Lacrimation was observed on the dog and guinea pigs. Cholinesterase activity was not inhibited and gross necropsy was unremarkable. Finally, dogs, guinea pigs, and rats were exposed to a 5% dust (stated as equivalent to 5 ppm) 7 hours/day, 5 days/week, for 6 weeks. The respirable particle concentration was given as 0.1 ppm. Interim sacrifice at two week intervals revealed “moderate” cholinesterase activity inhibition in plasma,

RBC, and brain of rats and "mild" inhibition in plasma and RBC of one dog, but not another. After the last exposure all cholinesterase activity values were normal (Hazleton and Holland 1949). No other details were given in the report; the inconsistent reporting of aerosol vs vapor units of concentration makes the reliability of this study questionable.

The following is from the executive summary of a study submitted to US EPA for reregistration of malathion (US EPA 2000). In a subchronic (13-week) inhalation study, groups of 15 male and 15 female Sprague-Dawley rats were exposed by inhalation in whole body exposure chambers to malathion (96.4% a.i.) aerosols (in air) at concentrations of 0, 0.1, 0.45 or 2.01 mg/L, 6 hours/day, 5 days/week for 13 weeks. The mass median aerodynamic diameters (MMAD) of the malathion particles were 1.6 µm at 0.1 mg/L and 1.7 µm at 0.45 and 2.01 mg/L. Assessments included those of clinical signs, body weight, food consumption, ophthalmoscopic examinations, hematology, clinical chemistry (including cholinesterase activity of plasma, erythrocytes and brain), urinalysis and gross and histopathology of Guideline required tissues. Clinical signs such as urogenital staining, excess salivation and ungroomed fur were seen mostly at 2.01 mg/L, but also occurred sporadically at 0.45 and 0.1 mg/L in both sexes. After 13 weeks, dose-related inhibition of cholinesterase activity was seen in both sexes. Relative to controls, cholinesterase activity inhibition at 0.1, 0.45 or 2.01 mg/L, respectively, was as follows: plasma 2%, 7% and 18% (males) and 16%, 30% and 70% (females); erythrocytes 9%, 22% and 43% (males) and 11%, 27% and 44% (females); brain 5%, 3% and 17% (males) and 4%, 8% and 41% (females). Based on inhibition of erythrocyte and plasma cholinesterase activity exceeding 10% in female rats, and on microscopic lesions of the nasal cavity and larynx, classified as slight to moderate, observed in most animals of both sexes at all three exposure concentrations, the LOAEL was 0.1 mg/L and a NOAEL was not established.

No data were found regarding the potential carcinogenicity of malathion following inhalation exposure of laboratory animals.

3.6. Summary

Only limited information was available on inhalation exposure of laboratory animals to malathion. Plasma and RBC cholinesterase activity inhibition were measured in rabbits, rats, and mice in the absence of clinical signs (Table 2.) A reliable lethality study was not found for the inhalation route of exposure.

1

TABLE 2. Summary of inhalation toxicity data in laboratory animals				
Species	Concentration	Duration	Effects	Reference
Rabbit	6, 34, 65 mg/m^3 123 mg/m^3 (MMAD = 12 µm)	6 hr	No effects No deaths; ChEI: 38-41% plasma; 38-49% RBC	Weeks et al. 1977
Rat	100 mg/m^3 450 mg/m^3 2010 mg/m^3 (MMAD = 1.6-1.7 µm)	6 hr/d, 5 d/wk, 13 weeks	ChEI: plasma 2-16%; RBC 9-11%, brain 4-5% ChEI: plasma 7-30%; RBC 22-27%, brain 3-8% Clinical signs; ChEI: plasma 18-70%; RBC 43-44%, brain 17-41%	US EPA 2000
Mice	6900 mg/m^3 (MMAD = 1.5-2.0 µm)	5 hr	ChEI plasma: up to 45%, highly variable	Berteau et al. 1976

2
3
4
5 ## 4. SPECIAL CONSIDERATIONS
6
7 ### 4.1. Metabolism and Disposition
8
9 This information has been recently summarized by ATSDR (2003) and the data given below
10 are taken directly from that review. The primary references were not reviewed here.
11
12 Malathion is rapidly absorbed following oral or dermal exposure but no specific information
13 was found on absorption following inhalation exposure. In female ICR mice the half-time for
14 absorption was 34 minutes following a gavage dose of 1 mg/kg. Following absorption rapid
15 metabolism by some tissues makes measurement of distribution difficult. However, in human
16 case reports, malathion was found in most major tissues and organs, with the highest
17 concentrations in the kidneys, liver, and adipose tissue. Detection of cholinesterase activity
18 inhibition in fetal tissue following maternal dosing implies transfer of malathion or a metabolite
19 across the placenta.
20
21 Malathion concurrently encounters three types of metabolic modifications in animals, one
22 oxidative and another hydrolytic, and the elimination of a methyl group catalyzed by glutathione
23 (GSH) S-transferase (Figure 1). The most important metabolite of the former biotransformation
24 is malaoxon, the ultimate neurotoxic molecule responsible for the acute toxicity. Among the
25 latter reactions, hydrolysis of one of the two carboxylic ester linkages abolishes the potential of
26 acute toxicity and is mainly responsible for the well-known low acute toxicity of malathion to
27 mammals. Pharmacokinetics of malathion is uniquely influenced by the high degree of
28 carboxylester hydrolysis in mammalian tissues.

In technical malathion, pharmacokinetics of malaoxon is a complex function of malathion level, carboxylesterase titer, concentration of carboxylesterase inhibitors including isomalathion and malaoxon, malathion dose level, and exposure frequency.

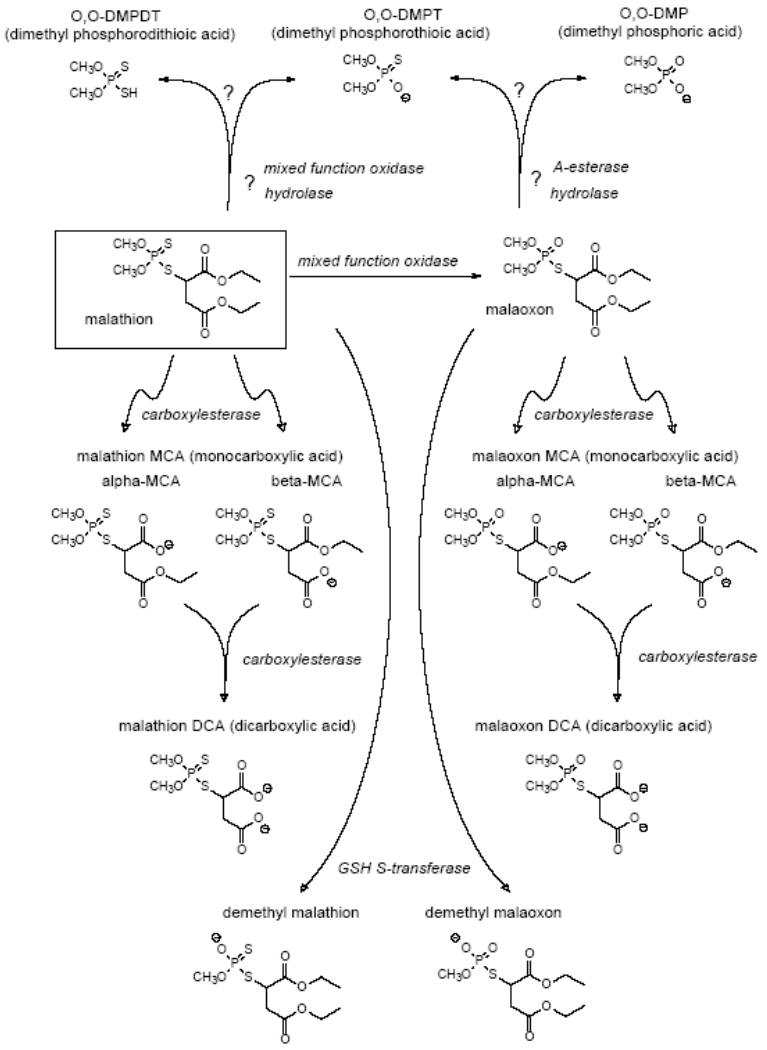

Figure 1. Metabolic pathways for malathion (from ATSDR 2003)

Malathion metabolites were analyzed in the urine of a volunteer who ingested single doses of 7.7 or 15.6 mg of malathion in gelatin capsules. Monocarboxylic acids were more abundant than dicarboxylic acid, and dimethyl phosphorothioic acid was the main alkylphosphate metabolite; more than 95% was recovered in urine. In an earlier study of a subject who ingested a high amount of malathion (200 mL of 50% malathion), analysis of the second 24-hour urine sample also showed monocarboxylic acids as the major metabolites followed by dimethyl phosphorothioic acid. An estimated half-life of 6.2 hours for the fast phase of elimination was reported for a 43-year-old woman who ingested malathion.

In animals, elimination of ingested malathion occurs rapidly mainly via the kidney. For instance, male Holtzman rats eliminated 91.7% of radioactivity of a dose of 25 mg of ^{14}C-ethyl malathion within 24 hours (83.4% in urine, 5.51% in feces, and 2.77% as CO_2); 7.75% remained in the gastrointestinal contents. Urinary excretion at 8 hours was 44.1% of the administered dose.

4.2. Mechanism of Toxicity

This information has been recently summarized by ATSDR (2003) and the data given below are taken directly from that review. The primary references were not reviewed here.

The typical acute neurotoxic action of malathion is cholinergic. It involves the inhibition of neural acetylcholinesterase activity by its active metabolite, malaoxon. The inhibition occurs due to the similarity of malaoxon to the neurotransmitter acetylcholine. Mimicking acetylcholine, malaoxon first binds to the active serine residue of acetylcholinesterase, undergoes a double displacement reaction involving the serine hydroxyl group, and yields dimethyl-phosphorylated acetylcholinesterase. Since the phosphorylated acetylcholineterase is stable within the time frame of poisoning, the inhibition prevents the normally extremely rapid hydrolysis of neurotransmitter acetylcholine, prolonging the impulse transmission. The expression of toxic signs depends on which of the divisions of nervous systems is affected. Thus, commonly observed cholinergic signs of poisoning including salivation, lacrimation, perspiration, and constriction of the pupils are due to the stimulation of muscarinic acetylcholine receptors in the parasympathetic autonomic synapse at exocrine glands and eyes. Other consequences of stimulating muscarinic cholinergic receptors include nausea, vomiting, abdominal cramps, diarrhea, tightness of the chest, incontinence, miosis, and breathing difficulty. The action on nicotinic receptors in the somatic motor endplates at the skeletal muscles leads to muscle fasciculations, generalized muscle weakness, cramping, flaccid or rigid paralysis, and ataxia. Bradycardia or tachycardia with accompanying decrease or increase in blood pressure may occur depending on the relative impact of cholinergic stimulation on the muscarinic parasympathetic neurons or on the nicotinic neurons that innervate the heart. Effects on cholinergic neurons in the central nervous system also yield a variety of effects including mental confusion, insomnia, headache, convulsions, coma, and depression of respiratory centers.

Which effects dominate depends on the sensitivity of the target enzyme at various synapses and the level of the ultimate toxic molecule, malaoxon, which may be produced at or near the nerve from malathion or transported from the site of malathion activation such as the liver, lung, or kidney. Generation and distribution of malaoxon is poorly understood, but undoubtedly depends on the route of exposure to malathion.

4.3. Structure Activity Relationships

Although all organophosphate anticholinergic agents have the same mechanism of action, their potency and physicochemical properties vary. The physicochemical differences 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

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; as noted below, this detoxification potential may vary between humans and rats.

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 activity is in plasma. 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).

From ATSDR (2003):

In humans, hepatic carboxylesterase activities appear similar to those in rat liver. Unlike rats, however, humans lack detectable levels of malathion carboxylesterase activity in the serum; the enzyme is also absent in human erythrocytes. About 30% of blood donors had detectable levels of malathion carboxylesterase activity in serum, activity ranging from 0.1 to 7.2 units/mL; no relation to age, sex, or race was noted. Positive correlations between serum ALT [alanine aminotransferase] and malathion carboxylesterase activities were noted among 46 hospital patients. In addition, activities of the two enzymes in the serum of a patient hospitalized for acetaminophen poisoning were observed to rise and decline in parallel, with the peak being reached on day 4. These data suggest that the low level of malathion carboxylesterase activity found in some human serum is a reflection of liver damage. The lack of malathion carboxylesterase activity in healthy human serum may underlie a significant deviation of pharmacokinetics from the rodent model. [C]linical literature [indicates] that safety of malathion to humans may have been overestimated by acute toxicity data on rats. It has been suggested that rats may not be a proper model and that another species with less extrahepatic carboxylesterase activity may be more appropriate.

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 lower plasma and red blood cell cholinesterase activity) and genetically determined variations in plasma cholinesterase activity. This genetic variability (sometimes resulting in greatly reduced activity of plasma cholinesterase) may impart deficiencies in ability to detoxify organophosphates such as methyl parathion. Additionally, polymorphic variability in A-esterases (i.e., paraoxonase/arylesterase) may also contribute to individual variability in organophosphate ester detoxification processes (NRC 2003).

Variation in carboxylesterase levels in human liver was assessed by Hosokawa et al. (1995). Liver samples were obtained from 10 male and 2 female cadavers in Japan; causes of death were varied, five were from heart disease and two from liver disease. Microsomal carboxylesterase activity to malathion varied by 9.8x between the individuals. The specific isozyme was immunoreactive with anti-rat RH1 antibody (Hosokawa et al. 1995).

Age-related differences in susceptibility to malathion (99.3% purity) were shown by Mendoza (1976) who determined LD_{50} values for 1-, 6-, 12-, and 17-day-old Wistar rat pups. Following a single oral dose, LD_{50} values were 209, 707, 1085, and 1806 mg/kg, respectively. Thus, the 1-day-old pups were nine times more sensitive than the 17-day-old pups. *In vitro*, esterase activity from liver, kidney, and brain generally increased during the first 7 days after birth and remained constant thereafter (Mendoza 1976).

In a comparative cholinesterase activity study, malathion (96.0% a.i.) was administered to groups of Crl:CD® (SD) IGS BR rats by gavage to determine the effect of malathion on blood and brain cholinesterase activities in adult male and female rats, pregnant dams, fetuses, and juvenile rats following both single and repeated exposures (US EPA 2006b). A single dose of 450 mg malathion/kg resulted in tremors in 5 of 16 PND 11 pups at 1-2 hours posttreatment, as well as moribundity in one pup; no clinical observations were noted in young adults at this dose. Repeated doses of malathion resulted in post-dose salivation at 150 mg/kg/day in dams during gestation and/or lactation, but did not adversely affect survival, clinical observations, body weight, body weight gain, brain weight, or gross pathology in adult male and female rats, juveniles, or fetuses. In pups, inhibition of RBC cholinesterase activity was noted at 5 mg/kg in males and 50 mg/kg in females following single dose exposures, and at 5 mg/kg/day in both sexes after repeated exposures. Following a single dose to young adults, effects were observed at 450 mg/kg, while after 11 or 14 doses, effects were observed at 50 mg/kg/day in young adults and pregnant dams. Based on these results US EPA (2006b) concluded that juvenile rats were more susceptible to cholinesterase activity inhibition than adults following direct dosing with malathion.

4.4.3. Concurrent Exposure Issues

Both concurrent exposure to other organophosphates and simultaneous exposure via other exposure routes are of concern. Malathion is readily absorbed through the skin and significant toxicity can occur from dermal exposure although the contribution of dermal absorption to a received dose may be difficult to quantify. This route of exposure has been extensively studied and is reviewed by ATSDR (2003) so these studies are not included here. Although the dermal

route is not applicable to AEGL development, it should be recognized that if the skin is exposed, dermal absorption will contribute to the toxicity of malathion.

5. DATA ANALYSIS FOR AEGL-1

5.1. Summary of Human Data Relevant to AEGL-1

No human data relevant to AEGL-1 derivation were found.

5.2. Summary of Animal Data Relevant to AEGL-1

The best available animal data for derivation of AEGL-1 are from the subchronic inhalation study in male and female Sprague-Dawley rats exposed for 6 hours/day (US EPA 2000). The mass median aerodynamic diameters (MMAD) of the malathion particles were 1.6 µm at 100 mg/m^3 and 1.7 µm at 450 and 2010 mg/m^3. Clinical signs such as urogenital staining, excess salivation and ungroomed fur were seen mostly at 2010 mg/m^3, but also occurred sporadically at 450 and 100 mg/m^3 in both sexes. After 13 weeks, dose-related inhibition of cholinesterase activity was measured and slight to moderate lesions of the nasal cavity and larynx were seen in both sexes.

Use of acute exposure data from animal studies is not recommended for derivation of AEGL-1 values. In the rabbit study (Weeks et al. 1977), a respirable particle size was not produced and it is likely that significant oral and dermal exposure occurred concurrently. Results in the mouse for cholinesterase activity inhibition were highly variable with limited study details (Berteau et al. 1976, Berteau and Deen 1978).

5.3. Derivation of AEGL-1 values

A concentration of 450 mg/m^3 for 6 hours was chosen as the point of departure for derivation of AEGL-1 values. A total uncertainty factor of 30 was applied which includes 10 for intraspecies extrapolation to account for the documented variability in sensitivity among different age groups and genders, and the known genetic polymorphisms in A-esterases and 3 for interspecies extrapolation to account for the differences in serum carboxylesterase activity levels between humans and rats. The uncertainty factor application and rationale are similar to those applied in the derivation of other organophosphate anticholinesterases (NRC 2003). Because clinical signs at the point of departure were sporadic and cholinesterase activity inhibition was not biologically significant after the 13-week exposure, time scaling was not performed. AEGL-1 values are shown in Table 3.

TABLE 3: AEGL-1 Values for Malathion

10-minute	30-minute	1-hour	4-hour	8-hour
15 mg/m^3	15 mg/m^3	15 mg/m^3	15 mg/m^3	15 mg/m^3

6. DATA ANALYSIS FOR AEGL-2

6.1. Summary of Human Data Relevant to AEGL-2

No human data relevant to AEGL-2 derivation were found.

6.2. Summary of Animal Data Relevant to AEGL-2

Animal data relevant to derivation of AEGL-2 values were the same as those used for derivation of the AEGL-1 values. Rats were exposed to malathion by whole-body inhalation for 6 hours/day, 5 days/week, for 13 weeks (US EPA 2000). Clinical signs such as urogenital staining, excess salivation and ungroomed fur were seen mostly at 2010 mg/m^3, but also occurred sporadically at 450 and 100 mg/m^3 in both sexes. After 13 weeks, dose-related inhibition of cholinesterase activity was measured and slight to moderate lesions of the nasal cavity and larynx were seen in both sexes.

6.3. Derivation of AEGL-2 values

A concentration of 2010 mg/m^3 for 6 hours was chosen as the point of departure for derivation of AEGL-2 values. At this concentration clinical signs were reported and, after 13 weeks, microscopic lesions and significant inhibition of brain cholinesterase activity were seen. A total uncertainty factor of 30 was applied which includes 10 for intraspecies extrapolation to account for the documented variability in sensitivity among different age groups and genders, and the known genetic polymorphisms in A-esterases and 3 for interspecies extrapolation to account for the differences in serum carboxylesterase levels between humans and rats. The uncertainty factor application and rationale are similar those applied in the derivation of other organophosphate anticholinesterases (NRC 2003). Values were scaled using the equation $C^n \times t = k$ where n ranges from 0.8 to 3.5 (ten Berge et al. 1986). In the absence of an empirically derived, chemical-specific exponent, scaling was performed using n = 3 for extrapolating to the 30-minute, 1-hour, and 4-hour time points and n = 1 for the 8-hour time point. According to Section 2.7 of the Standing Operating Procedures for Developing Acute Exposure Guideline Levels for Hazardous Chemicals (NRC 2001), 10-minute values are not to be scaled from an experimental exposure time of ≥4 hours. Therefore the 30-minute value was adopted as the 10-minute AEGL-2 value.

AEGL-2 values are shown in Table 4.

TABLE 4: AEGL-2 Values for Malathion

10-minute	30-minute	1-hour	4-hour	8-hour
150 mg/m^3	150 mg/m^3	120 mg/m^3	77 mg/m^3	50 mg/m^3

7. DATA ANALYSIS FOR AEGL-3

7.1. Summary of Human Data Relevant to AEGL-3

Human exposure data relevant to derivation of AEGL-3 values were not available. No reports of human lethality from inhalation exposure to malathion were found in the literature.

7.2. Summary of Animal Data Relevant to AEGL-3

No data on animal lethality following inhalation exposure were found. No deaths were reported for rats exposed to 5200 mg/m^3 for 4 hours (US EPA 2000) or to mice exposed to 6900 mg/m^3 for 5 hours (Berteau et al. 1976). These are the highest available experimental concentrations in laboratory animals.

7.3. Derivation of AEGL-3 values

AEGL-3 values for malathion are based on the highest available experimental concentration administered to laboratory animals. A concentration of 6900 mg/m^3 for 5 hours was chosen as the point of departure for derivation of AEGL-3. A total uncertainty factor of 30 was applied which includes 10 for intraspecies extrapolation to account for the documented variability in sensitivity among different age groups and genders, and the known genetic polymorphisms in A-esterases and 3 for interspecies extrapolation to account for the differences in serum carboxylesterase levels between humans and rats. The uncertainty factor application and rationale are the same as those applied in the derivation of other organophosphate anticholinesterases (NRC 2003). Values were scaled using the equation $C^n \times t = k$ where n ranges from 0.8 to 3.5 (ten Berge et al. 1986). In the absence of an empirically derived, chemical-specific exponent, scaling was performed using n = 3 for extrapolating to the 30-minute, 1-hour, and 4-hour time points and n = 1 for the 8-hour time point. According to Section 2.7 of the Standing Operating Procedures for Developing Acute Exposure Guideline Levels for Hazardous Chemicals (NRC 2001), 10-minute values are not to be scaled from an experimental exposure time of ≥4 hours. Therefore the 30-minute value was adopted as the 10-minute AEGL-3 value. Although no lethality has been reported in humans or animals from inhalation exposure to malathion, AEGL-3 values are derived to serve as guidance in an emergency situation. It is acknowledged that attaining lethal airborne concentrations of malathion may not be possible.

AEGL-3 values are shown in Table 5.

TABLE 5: AEGL-3 Values for Malathion

10-minute	30-minute	1-hour	4-hour	8-hour
500 mg/m^3	500 mg/m^3	390 mg/m^3	250 mg/m^3	140 mg/m^3

8. SUMMARY OF AEGLS

8.1. AEGL Values and Toxicity Endpoints

The derived AEGL values for various levels of effect and durations of exposure are summarized in Table 6. AEGL-1 and AEGL-2 values were based on a repeated exposure study in rats. AEGL-3 values were based on the highest available experimental concentration administered to laboratory animals.

TABLE 6: Summary of AEGL Values

Classification	Exposure Duration				
	10-minute	**30-minute**	**1-hour**	**4-hour**	**8-hour**
AEGL-1 (Nondisabling)	15 mg/m^3	15 mg/m^3	15 mg/m^3	15 mg/m^3	15 mg/m^3
AEGL-2 (Disabling)	150 mg/m^3	150 mg/m^3	120 mg/m^3	77 mg/m^3	50 mg/m^3
AEGL-3* (Lethal)	500 mg/m^3	500 mg/m^3	390 mg/m^3	250 mg/m^3	140 mg/m^3

* Although no lethality has been reported in humans or animals from inhalation exposure to malathion, AEGL-3 values are derived to serve as guidance in an emergency situation. It is acknowledged that attaining lethal airborne concentrations of malation may not be possible.

8.2. Comparison with Other Standards and Guidelines

Standards and guidance levels for workplace and community exposures are listed in Table 7. The time-weighted average exposure concentrations for workers range from 1 to 15 mg/m^3 (ACGIH 2008, NIOSH 1996, 2005, OSHA 1999) all with skin designations. A NIOSH IDLH has been established at 250 mg/m^3 based extrapolation from oral dosing. The occupational exposure limit from The Netherlands is 10 mg/m^3 and from Germany is 15 mg/m^3. Sweden has not set an occupational exposure limit for malathion.

TABLE 7: Extant Standards and Guidelines for Malathion

Guideline	Exposure Duration				
	10 minute	**30 minute**	**1 hour**	**4 hour**	**8 hour**
AEGL-1	15 mg/m^3	15 mg/m^3	15 mg/m^3	15 mg/m^3	15 mg/m^3
AEGL-2	150 mg/m^3	150 mg/m^3	120 mg/m^3	77 mg/m^3	50 mg/m^3
AEGL-3	500 mg/m^3	500 mg/m^3	390 mg/m^3	250 mg/m^3	140 mg/m^3
SMACs[a]					
REL-TWA (NIOSH)[b]					10 mg/m^3 (skin)
REL-STEL (NIOSH)[c]					
IDLH (NIOSH)[d]		250 mg/m^3			
TLV-TWA (ACGIH)[e]					1.0 mg/m^3 (skin)
TLV-STEL (ACGIH)[f]					
PEL-TWA (OSHA)[g]					15 mg/m^3 (skin)
MAK (Germany)[h]					15 mg/m^3 (peak limitation; pregnancy risk)
MAC (The Netherlands)[i]					10 mg/m^3
OEL-TWA (Sweden)[j]					
OEL-STEL (Sweden)[k]					

[a] **SMACs (Spacecraft Maximum Allowable Concentrations)** (NRC 1997) provide guidance on chemical exposures during normal operations of spacecraft as well as emergency situations. The one-hour SMAC is a concentration of airborne substance that will not compromise the performance of specific tasks by astronauts during emergency conditions or cause serious or permanent toxic effects. Such exposure may cause reversible effects such as skin or eye irritation, but they are not expected to impair judgment or interfere with proper responses to emergencies.

[b] **NIOSH REL-TWA (National Institute of Occupational Safety and Health, Recommended Exposure Limits - Time Weighted Average)** (NIOSH 1996, 2005) is defined analogous to the ACGIH-TLV-TWA.

[c] **NIOSH REL-STEL (Recommended Exposure Limits - Short Term Exposure Limit)** (NIOSH 1996, 2005) is defined analogous to the ACGIH TLV-STEL.

[d] **IDLH (Immediately Dangerous to Life and Health, National Institute of Occupational Safety and Health)** (NIOSH 1996, 2005) represents the maximum concentration from which one could escape within 30 minutes without any escape-impairing symptoms, or any irreversible health effects.

[e] **ACGIH TLV-TWA (American Conference of Governmental Industrial Hygienists, Threshold Limit Value - Time Weighted Average)** (ACGIH 2003, 2008) is the time-weighted average concentration for a normal 8-hour workday and a 40-hour workweek, to which nearly all workers may be repeatedly exposed, day after day, without adverse effect. SEN:sensitizer

[f]**ACGIH TLV-STEL (Threshold Limit Value - Short Term Exposure Limit)** (ACGIH 2003, 2008) 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.

[g]**OSHA PEL-TWA (Occupational Safety and Health Administration, Permissible Exposure Limits - Time Weighted Average)** (OSHA 1999) is defined analogous to the ACGIH-TLV-TWA, but is for exposures of no more than 10 hours/day, 40 hours/week.

[h]**MAK (Maximale Arbeitsplatzkonzentration [Maximum Workplace Concentration]) DFG** (Deutsche Forschungsgemeinschaft [German Research Association] 2007) is defined analogous to the ACGIH-TLV-TWA. The concentration is measured as the inhalable fraction of the aerosol. Excursions above the average are to be limited to four per shift at no greater than one hour intervals.

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

[j]**OEL-TWA (Occupational Exposure Limits - Time-weighted-average)** (Swedish National Board of Occupational Safety and Health 2005) is an occupational exposure limit value for exposure during one working day.

[k]**OEL-STEL (Occupational Exposure Limits - Short-term exposure limit)** (Swedish National Board of Occupational Safety and Health 2000) is an occupational exposure limit value for exposure during a reference period of fifteen minutes.

8.3. Data Adequacy and Research Needs

Limited human and animal data were available despite the widespread use of the chemical. Because of lack of data, a clear concentration-response was difficult to assess for non-lethal concentrations and no lethality was reported from inhalation exposure.

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APPENDIX A: Derivation of AEGL Values

Derivation of AEGL-1

Key Study:	US EPA 2000
Toxicity endpoint:	Sporadic clinical signs in rats exposed to 450 mg/m^3 for 6 hours/day, 5 days/week, for 13 weeks
Time scaling:	none; because clinical signs at the point of departure were sporadic and cholinesterase activity inhibition was not biologically significant after the 13-week exposure, time scaling was not performed
Uncertainty factors:	30 (10 for intraspecies variability and 3 for interspecies variability)
Modifying factor:	None
Calculations:	(C/UFs) (450 mg/m^3/30) = 15 mg/m^3 for all time points

Derivation of AEGL-2

Key Study:	US EPA 2000
Toxicity endpoint:	Clinical signs and microscopic lesions and significant inhibition of brain cholinesterase activity in rats exposed to 2010 mg/m^3 for 6 hours/day, 5 days/week, for 13 weeks.
Time scaling:	$C^n \times t = k$ (ten Berge et al. 1986) n = 3 for extrapolating to the 30-min, 1-hr, and 4-hr time points; n = 1 for extrapolating to the 8-hr time point
Uncertainty factors:	30 (10 for intraspecies variability and 3 for interspecies variability)
Modifying factor:	None
Calculations:	*30-min, 1-hr, and 4-hr time points* $(C/UFs)^3 \times t = k$ $(2010\ mg/m^3/30)^3 \times 6\ hr = 1804578\ (mg/m^3)^3 \cdot hr$ *8-hr time point* $(C/UFs)^1 \times t = k$ $(2010\ mg/m^3/30)^1 \times 6\ hr = 402\ (mg/m^3)^1 \cdot hr$
10-minute AEGL-2:	= 150 mg/m^3; According to Section 2.7 of the Standing Operating Procedures for Developing Acute Exposure Guideline Levels for Hazardous Chemicals (NRC 2001), 10-minute values are not to be scaled from an experimental exposure time of 4 hours. Therefore the 30 - minute value was adopted as the 10-minute AEGL-2 value.
30-minute AEGL-2:	$[1804578\ (mg/m^3)^3 \cdot hr]/0.5\ hr = 150\ mg/m^3$
1-hour AEGL-2:	$[1804578\ (mg/m^3)^3 \cdot hr]/1\ hr = 120\ mg/m^3$
4-hour AEGL-2:	$[1804578\ (mg/m^3)^3 \cdot hr]/4\ hr = 77\ mg/m^3$
8-hour AEGL-2:	$402\ (mg/m^3)^1 \cdot hr/8\ hr = 50\ mg/m^3$

Derivation of AEGL-3

Key Study:	Berteau et al. 1976
Toxicity endpoint:	Highest available experimental concentration administered to laboratory animals is 6900 mg/m^3 for 5 hours to mice.
Time scaling	$C^n \times t = k$ (ten Berge et al. 1986) n = 3 for extrapolating to the 30-min, 1-hr, and 4-hr time points; n = 1 for extrapolating to the 8-hr time point
Uncertainty factors:	30 (10 for intraspecies variability and 3 for interspecies variability)
Modifying factor:	None
Calculations:	*30-min, 1-hr, and 4-hr time points* $(C/UFs)^3 \times t = k$ $(6900\ mg/m^3/30)^3 \times 5\ hr = 60835000\ (mg/m^3)^3 \cdot hr$ *8-hr time point* $(C/UFs)^1 \times t = k$ $(6900\ mg/m^3/30)^1 \times 5\ hr = 1150\ (mg/m^3)^1 \cdot hr$
10-minute AEGL-3:	= 500 mg/m^3; According to Section 2.7 of the Standing Operating Procedures for Developing Acute Exposure Guideline Levels for Hazardous Chemicals (NRC 2001), 10-minute values are not to be scaled from an experimental exposure time of≥4 hours. Therefore the 30 - minute value was adopted as the 10-minute AEGL-3 value.
30-minute AEGL-3:	$[60835000\ (mg/m^3)^3 \cdot hr]/0.5\ hr = 500\ mg/m^3$
1-hour AEGL-3:	$[60835000\ (mg/m^3)^3 \cdot hr]/1\ hr = 390\ mg/m^3$
4-hour AEGL-3:	$[60835000\ (mg/m^3)^3 \cdot hr]/4\ hr = 250\ mg/m^3$
8-hour AEGL-3:	$1150\ (mg/m^3)^1 \cdot hr/8\ hr = 140\ mg/m^3$

APPENDIX B: Derivation Summary for Malathion AEGLs

ACUTE EXPOSURE GUIDELINE LEVELS FOR MALATHION (CAS Reg. No. 121-75-5) DERIVATION SUMMARY

AEGL-1 VALUES				
10-minute	**30-minute**	**1-hour**	**4-hour**	**8-hour**
15 mg/m^3	**15 mg/m^3**	**15 mg/m^3**	**15 mg/m^3**	**15 mg/m^3**

Key Reference: US EPA (US Environmental Protection Agency). 2000. Malathion: Toxicology Chapter for the RED. US EPA, Office of Pesticide Programs. Special docket EPA-HQ-OPP-2007-0151.

Test Species/Strain/Number: Rat/ Sprague-Dawley/ 15 per sex per group

Exposure Route/Concentrations/Durations: Inhalation/ 100-2010 mg/m^3 / 6 hours/day, 5 d/wk, 13 wk

Effects:

100 and 450 mg/m^3: sporadic clinical signs; no biologically significant inhibition of plasma, RBC, or brain cholinesterase activity after 13 weeks

2010 mg/m^3: clinical signs; microscopic lesions and significant inhibition of brain cholinesterase activity

Endpoint/Concentration/Rationale: The single exposure to rats of 450 mg/m^3 for 6 hours resulting in sporadic clinical signs and no biologically significant inhibition of cholinesterase activity.

Uncertainty Factors/Rationale:

Total uncertainty factor: 30

Interspecies: 3, to account for differences in carboxylesterase levels between humans and rats.

Intraspecies: 10, to account for the documented variability in sensitivity among different age groups and genders, and the known genetic polymorphisms in A-esterases. The uncertainty factor application and rationale are the same as those applied in the derivation of other organophosphate anticholinesterases (NRC 2003).

Modifying Factor: None

Animal to Human Dosimetric Adjustment: Not applicable

Time Scaling: none; because clinical signs at the point of departure were sporadic and cholinesterase activity inhibition was not biologically significant after the 13-week exposure, time scaling was not performed.

Data Adequacy: Study details were limited.

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AEGL-2 VALUES				
10-minute	**30-minute**	**1-hour**	**4-hour**	**8-hour**
150 mg/m^3	**150 mg/m^3**	**120 mg/m^3**	**77 mg/m^3**	**50 mg/m^3**
Key Reference: US EPA (US Environmental Protection Agency). 2000. Malathion: Toxicology Chapter for the RED. US EPA, Office of Pesticide Programs. Special docket EPA-HQ-OPP-2007-0151.				
Test Species/Strain/Number: Rat/ Sprague-Dawley/ 15 per sex per group				
Exposure Route/Concentrations/Durations: Inhalation/ 100-2010 mg/m^3 / 6 hours/day, 5 d/wk, 13 wk				
Effects: 100 and 450 mg/m^3: sporadic clinical signs; no biologically significant inhibition of plasma, RBC, or brain cholinesterase activity after 13 weeks 2010 mg/m^3: clinical signs; microscopic lesions and significant inhibition of brain cholinesterase activity				
Endpoint/Concentration/Rationale: Clinical signs and microscopic lesions and significant inhibition of brain cholinesterase activity in rats exposed to 2010 mg/m^3 for 6 hours/day, 5 days/week, for 13 weeks.				
Uncertainty Factors/Rationale: Total uncertainty factor: 30 Interspecies: 3, to account for differences in carboxylesterase levels between humans and rats. Intraspecies: 10, to account for the documented variability in sensitivity among different age groups and genders, and the known genetic polymorphisms in A-esterases. The uncertainty factor application and rationale are the same as those applied in the derivation of other organophosphate anticholinesterases (NRC 2003).				
Modifying Factor: None				
Animal to Human Dosimetric Adjustment: Not applicable				
Time Scaling: $C^n \times t = k$ where n ranges from 0.8 to 3.5 (ten Berge et al. 1986). In the absence of an empirically derived, chemical-specific exponent, scaling was performed using n = 3 for extrapolating to the 30-minute, 1-hour, and 4-hour time points and n = 1 for the 8-hour time point. According to Section 2.7 of the Standing Operating Procedures for Developing Acute Exposure Guideline Levels for Hazardous Chemicals (NRC 2001), 10-minute values are not to be scaled from an experimental exposure time of ≥4 hours. Therefore the 30-minute value was adopted as the 10-minute AEGL-2 value.				
Data Adequacy: Limited data were available.				

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AEGL-3 VALUES				
10-minute	**30-minute**	**1-hour**	**4-hour**	**8-hour**
500 mg/m^3	**500 mg/m^3**	**390 mg/m^3**	**250 mg/m^3**	**140 mg/m^3**
Key Reference: Berteau, P.E., W.A. Deen, and R.L. Dimmick. 1976. Studies of effects of particle size on the toxicity of insecticide aerosols. Naval Biosciences Lab., Oakland CA. NTIS ADA037015. 75pp.				
Test Species/Strain/Number: Mouse / NAMRU / 16 females				
Exposure Route/Concentrations/Durations: Inhalation / 6900 mg/m^3 / 5 hours				
Effects: no deaths; no clinical signs were described; plasma cholinesterase activity inhibition was highly variable				
Endpoint/Concentration/Rationale: The highest available experimental concentration is 6900 mg/m^3. Although no lethality has been reported in humans or animals from inhalation exposure to malathion, AEGL-3 values are derived to serve as guidance in an emergency situation. It is acknowledged that attaining lethal airborne concentrations of malathion may not be possible.				
Uncertainty Factors/Rationale: Total uncertainty factor: 30 Interspecies: 3, to account for differences in carboxylesterase levels between humans and rats. Intraspecies: 10, to account for the documented variability in sensitivity among different age groups and genders, and the known genetic polymorphisms in A-esterases. The uncertainty factor application and rationale are the same as those applied in the derivation of other organophosphate anticholinesterases (NRC 2003).				
Modifying Factor: None				
Animal to Human Dosimetric Adjustment: Not applicable				
Time Scaling: Time Scaling: $C^n \times t = k$ where n ranges from 0.8 to 3.5 (ten Berge et al. 1986). In the absence of an empirically derived, chemical-specific exponent, scaling was performed using n = 3 for extrapolating to the 30-minute, 1-hour, and 4-hour time points and n = 1 for the 8-hour time point. According to Section 2.7 of the Standing Operating Procedures for Developing Acute Exposure Guideline Levels for Hazardous Chemicals (NRC 2001), 10-minute values are not to be scaled from an experimental exposure time of ≥4 hours. Therefore the 30-minute value was adopted as the 10-minute AEGL-3 value.				
Data Adequacy: No lethality data were found.				

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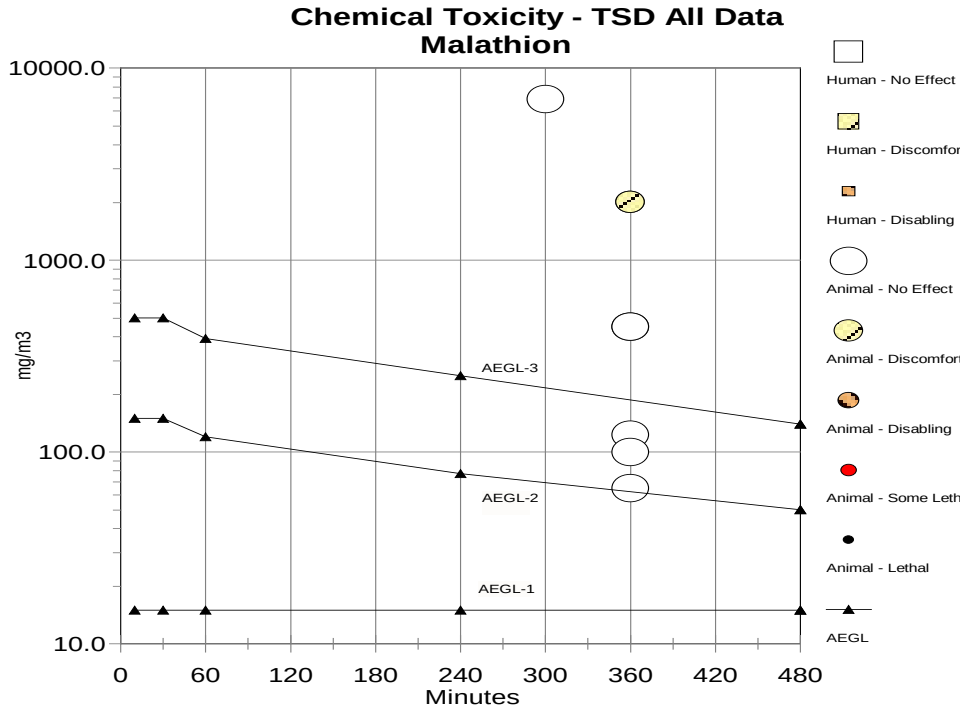
APPENDIX C: Time-scaling Category Plot for Malathion



Malathion							
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				15	10	AEGL	
NAC/AEGL-1				15	30	AEGL	
NAC/AEGL-1				15	60	AEGL	
NAC/AEGL-1				15	240	AEGL	
NAC/AEGL-1				15	480	AEGL	
NAC/AEGL-2				150	10	AEGL	
NAC/AEGL-2				150	30	AEGL	
NAC/AEGL-2				120	60	AEGL	
NAC/AEGL-2				77	240	AEGL	
NAC/AEGL-2				50	480	AEGL	
NAC/AEGL-3				500	10	AEGL	
NAC/AEGL-3				500	30	AEGL	

NAC/AEGL-3				390	60	AEGL	
NAC/AEGL-3				250	240	AEGL	
NAC/AEGL-3				140	480	AEGL	
Weeks et al. 1977	rabbit	M		65	360	0	MMAD = 12 µm
Weeks et al. 1977	rabbit	M		123	360	0	MMAD = 12 µm
Berteau et al. 1976	mouse	F		6900	300	0	MMAD = 1.5-2.0 µm; highly variable ChEI
US EPA 2000	rat	m/f	5 d/wk, 13 wk	100	360	0	MMAD = 1.6 µm; sporadic clinical signs
US EPA 2000	rat	m/f	5 d/wk, 13 wk	450	360	0	MMAD = 1.7 µm; sporadic clinical signs
US EPA 2000	rat	m/f	5 d/wk, 13 wk	2010	360	1	MMAD = 1.7 µm; clinical signs

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