2. RELEVANCE TO PUBLIC HEALTH

2.1 BACKGROUND AND ENVIRONMENTAL EXPOSURES TO MALATHION IN THE UNITED STATES

Malathion is an insecticide used for agricultural and non-agricultural purposes and is released to the environment primarily through spraying on agricultural crops and at agricultural sites, spraying for home and garden use, and spraying for public health use in both urban/residential and nonresidential areas; the insecticide is also released to the environment using fogging equipment. Once malathion is introduced into the environment, it may be activated by atmospheric photooxidation, or degraded by hydrolysis, or biodegradation mediated by microorganisms found in most sediment, soils, and water. Malaoxon, the oxon generated from malathion, is more toxic than malathion and is formed by the oxidation of malathion and may also be present as an impurity in the parent compound. Malathion and malaoxon can be transported from the site of application by precipitation, fog, and wind to other areas. Malathion is moderately mobile to very highly mobile in soils, creating the potential for it to move through the soil profile and into groundwater. However, because degradation of malathion occurs rapidly in the environment, the potential for malathion movement into groundwater is generally not significant, and leaching of the chemical into groundwater is usually not observed. Volatilization of malathion from ground surfaces following aerial applications has been observed. Data from limited studies suggest that bioconcentration of malathion does not occur to a significant extent in most aquatic organisms tested, and that it is rapidly metabolized when it is accumulated in such. Malathion is not widely dispersed or persistent in the environment, but is detected frequently in minute quantities in foods. Residue amounts of malathion have been detected in air, water, soil, fish, and agricultural crops consumed as food.

The general population is not likely to be exposed to large amounts of malathion. Some exposure to residues of malathion is possible, however, as many studies show that malathion has been detected in foods and atmosphere samples. Populations living within or very near areas of heavy malathion use would have an increased risk of exposure to relatively larger amounts of malathion through dermal contact with contaminated plants, soils, or nonnatural surfaces such as playground equipment and pavements; by inhalation of the mist formed from the applied insecticide; or by ingestion of water or food-borne residues. Also at increased risk of exposure are persons utilizing malathion for extensive home and garden use, particularly if they consume contaminated, unwashed backyard produce. Those likely to receive the highest levels of exposure are those who are involved in the production, formulation, handling, and application of malathion, as well as farm workers who enter treated fields prior to the

passage of the appropriate restricted entry intervals. Dermal contact appears to be the major route of exposure for workers, while ingestion is also an important route of exposure for the general population not living in areas where malathion is extensively used. Inhalation has not been shown to be a significant route of exposure to malathion.

Because malathion is one of the most frequently detected pesticides in the FDA's Total Diet Studies there is a great potential for exposure of the general population to malathion by consumption of food containing residues of the chemical. In a 10-year study of ready-to-eat foods, malathion was found in 110 foods at an average concentration of 0.0111 ppm. In a study of domestic and imported apples and rice, malathion was found at average concentrations of 0.10–0.11 ppm in apples and at 0.005–0.013 ppm in rice. Detections of malathion in apples were infrequent (<1% of the samples); however, in domestic rice, malathion was detected in 41% of the samples, at a maximum concentration of 2.3 ppm. Additional studies have reported concentrations of malathion of up to 0.40 ppm in various foods. However, based on a risk assessment of malathion conducted by the EPA using, in part, the Dietary Exposure Evaluation Model (DEEM), neither acute nor chronic dietary exposure to malathion (plus malaoxon) is a concern for the majority (95th exposure percentile) of the U.S. population. Individuals who consume unwashed, contaminated backyard produce treated with malathion may be exposed to greater levels of the chemical than others in the general population.

In areas of public health malathion usage, the potential for exposure to the compound has been reported to be greater via the dermal and ingestion routes than through inhalation. Malathion concentrations in indoor, outdoor, and personal air have been measured at two U.S. sites as part of an EPA non-occupational exposure study. The maximum concentrations detected in the indoor, outdoor, and personal air at one site were 20.8, 0.3, and 16.8 ng/m^3, respectively; at the second site, respective maximums were 5.0, 0.8, and 0.5 ng/m^3. At the first site, maximums of 32, 4, and 15% of the population was exposed to malathion in indoor, outdoor, and personal air, respectively. At the second site, however, the respective maximums were only 2, 5, and 4%. In a study of seven homes in New Jersey, from which air and dust samples were collected from two rooms per home, malathion was not detected in any of the samples. Malathion has been detected in the ambient outdoor air at up to 4.6 ng/m^3 and in the ambient air of offices and storage rooms of commercial pest control firms at up to 3.57 µg/m^3 (3,570 ng/m^3).

Dermal exposure to malathion is not likely to be a health concern for the general population, with the possible exception of individuals who live in or near areas where malathion is used extensively for public health purposes or for home and garden usage. Dermal exposure is, however, a major source of exposure

for workers who are directly involved in the production, formulation, handling, and application of malathion-containing products, as well as for field workers. Occupational exposure has been reported for workers who are not directly involved with applications of malathion, but work in facilities, such as veterinary clinics, where the products are used. Exposure levels for workers are affected by the type of work activity being conducted at the time of exposure. Dermal exposure levels may also be affected by the type and material constituents of the protective gear utilized, as well as by the carrier solvents in the formulated product.

Children are expected to be exposed to malathion by the same routes that affect adults. Small children are more likely to come into contact with malathion residues that may be present in soil and dust both outside and inside the home, due to increased hand-to-mouth activity and playing habits. Malathion has been detected in foods found in infant and toddler diets at concentrations of up to 0.40 ppm. Only one study was found that detected small amounts of malathion in breast milk; therefore, an adequate determination of the importance of this route of child exposure has not been made.

Populations residing near hazardous waste disposal sites may be subject to higher levels of malathion in environmental media (i.e., air, water, soil) than those experienced by the general population. Malathion has been identified in at least 21 of the 1,623 hazardous waste disposal sites that have been proposed for inclusion on the EPA National Priorities List (NPL). However, the number of sites evaluated for malathion is not known. As more sites are evaluated, the number of sites where malathion has been detected may increase.

See Chapter 6 for more detailed information regarding concentrations of malathion in environmental media.

2.2 SUMMARY OF HEALTH EFFECTS

Malathion is an organophosphate pesticide of relatively low acute toxicity compared to other organophosphates. Signs and symptoms of acute toxicity are typical of those induced by organophosphate insecticides as a group. Almost all of the systemic effects observed following exposure to malathion are due to the action of its active metabolite, malaoxon, on the nervous system, or are secondary to this primary action. Malaoxon inhibits the enzyme acetylcholinesterase at the various sites where the enzyme is present in the nervous system, (i.e., the central nervous system, the sympathetic and parasympathetic divisions of the autonomic nervous system, and the neuromuscular junction). Inhibition

of acetylcholinesterase results in accumulation and continuous action of the neurotransmitter acetylcholine at postsynaptic sites. Information regarding effects of malathion in humans is derived mainly from cases of accidental or intentional ingestion of malathion, studies of the general population exposed during aerial application of the pesticide for pest control, studies of pesticide users exposed to multiple pesticides including malathion, a few controlled exposure studies with volunteers, and cases of dermal exposure to malathion. Oral ingestion of high amounts of malathion resulted in typical signs and symptoms of organophosphate intoxication including reduced plasma and red blood cell (RBC) cholinesterase activity, excessive bronchial secretions, respiratory distress, salivation, pinpoint pupils, bradycardia, abdominal cramps, diarrhea, tremor, fasciculation, and occasionally death.

Epidemiological studies have found weak associations between exposure to malathion and developmental effects and certain types of cancer. Malathion has also been shown to be a contact sensitizer, and results from some studies have suggested that it may cause adverse genetic effects. No chronic effects have been documented in humans following exposure specifically to malathion. Studies in animals support the human data and confirm that the main target of malathion toxicity is the nervous system. Malathion was not a reproductive or developmental toxicant in animals at doses that did not induce maternal toxicity, but transient testicular effects were reported. Malathion induced liver carcinogenicity in female Fischer-344 rats and in male and female B6C3F_1 mice at doses that were considered excessive. Results from a series of studies in animals conducted in the last decade suggest that malathion can modulate (increase or decrease) some immunologic parameters at doses below those that induce neurotoxicity. Although the physiological significance of these effects is yet unclear, it has been suggested that enhancements of the immune response induced by malathion may be responsible for symptoms such as lacrimation, rashes, and irritation of mucous membranes seen occasionally after aerial spraying of the pesticide. The mechanism of action of malathion-induced immunologic alterations is not known. Neurotoxicity is the main effect of malathion in humans and animals, and the mechanism of neurotoxic action has been studied extensively and is well understood. Therefore, the section below will focus only on neurological effects. The reader is referred to Section 3.2, Discussion of Health Effects by Route of Exposure, for information on additional effects that may have been observed sporadically in animal studies and in human case reports, and are of unclear physiological significance.

Neurological Effects. Clinical signs and symptoms of malathion intoxication are typical of organophosphate poisoning. Malathion and its metabolite, malaoxon, inhibit the enzyme acetylcholinesterase and thus, prevent the hydrolysis of the neurotransmitter acetylcholine in the central and peripheral nervous systems. Continuous presence of acetylcholine at parasympathetic autonomic

muscarinic receptors results in ocular effects (miosis, blurred vision), gastrointestinal effects (nausea, vomiting, abdominal cramps, diarrhea), respiratory effects (excessive bronchial secretions, chest tightness, bronchoconstriction), cardiovascular effects (bradycardia, decreased blood pressure), effects on exocrine glands (increased salivation, lacrimation), and effects on the bladder (incontinence). At the level of parasympathetic and sympathetic autonomic nicotinic receptors, acetylcholine will induce tachycardia and increase blood pressure. At the neuromuscular junction, excess acetylcholine will induce muscle fasciculations, cramps, diminished tendon reflexes, muscle weakness in peripheral and respiratory muscles, ataxia, and paralysis. Finally, overstimulation of brain cholinergic receptors will lead to drowsiness, lethargy, fatigue, headache, generalized weakness, dyspnea, convulsions, and cyanosis.

The signs and symptoms described above have been documented in almost all of the cases of accidental or intentional ingestion of high amounts of malathion and in cases of dermal intoxication. Lethal doses can be estimated from case reports to have been between 350 and 2,000 mg/kg. These dose levels usually inhibited plasma and RBC cholinesterase activities to levels ranging from undetectable to 10–30% of normal. Studies of workers exposed to a combination of pesticides, including malathion, have shown decreases between 10 and 50% in both plasma and RBC cholinesterase activities. In general, plasma cholinesterase activity can be inhibited by 20–25% without significant physiological consequences. Studies also have shown that the rate of decrease of RBC cholinesterase correlates better with appearance of symptoms than the absolute value reached after exposure. It was found that plasma cholinesterase activity in workers who exhibited cholinergic symptoms and signs was 17% lower than in workers without symptoms and signs. Similar findings were reported in another study (Ernest et al. 1995). No cholinergic signs were seen in a study in which the activities of RBC and plasma cholinesterase varied less than 10% between pre- and postexposure. A study in volunteers exposed to 85 mg/m^3 of a malathion aerosol for 2 hours/day over a 42-day period observed no clinical signs and no significant inhibition of plasma or RBC cholinesterase activity over the study period. In an additional study of volunteers orally administered 0.34 mg malathion/kg/day for 56 days, there was a maximum depression of 25% in plasma cholinesterase approximately 3 weeks after cessation of treatment. A similar depression in RBC cholinesterase was observed, but occurred later. Administration of 0.11 mg malathion/kg/day for 32 days or 0.23 mg/kg/day for 47 days did not produce any significant depression of plasma or RBC cholinesterase activity. No clinical signs were seen in the volunteers. As detailed in Section 3.2, numerous studies in animals exposed to malathion by any route have shown inhibition of plasma, RBC, and brain cholinesterase activities.

There is also some evidence that exposure to malathion may result in alterations in some neurophysiological parameters. For example, electromyography testing demonstrated neuromuscular blockade in some cases of intoxication, but not in a case in which neither motor nor sensory peripheral nerve conduction velocities were significantly altered. Slightly reduced motor nerve conduction velocity was reported in a case in which the tests were conducted 10 days following the poisoning episode. Acute sensorimotor distal axonal polyneuropathy has been described. The alterations consisted of mild reductions of most compound muscle and sensory nerve action potentials amplitudes, slightly prolonged sensory distal latencies, and mildly slowed nerve conduction velocities. This was accompanied by morphological evidence of denervation and reinnervation of the gastrocnemius muscle and degenerating axons from the sural nerve. In these cases, isopropylmalathion was found in relatively large quantities in the formulation ingested. Some studies of exposure to multiple organophosphates also have reported signs of peripheral neuropathies, whereas others have reported negative findings.

Another condition that has been reported in humans as a consequence of acute exposure to high amounts of malathion is the intermediate syndrome. The intermediate syndrome is termed as such because it occurs in the time interval (24–96 hours) between the end of the acute cholinergic crisis and the usual onset of delayed neuropathy, and it is thought to be due to persistent cholinesterase inhibition leading to combined pre- and post-synaptic impairment of neuromuscular transmission. Clinically, it was characterized by weakness in the territory of several motor cranial nerves, weakness of neck flexors and proximal limb muscles, and respiratory paralysis.

A serious neurological effect of some organophosphate pesticides is delayed neurotoxicity. Organophosphorus-induced delayed polyneuropathy (OPIDP) is caused by inhibition of an enzyme known as neuropathy target esterase (NTE), which is widely distributed throughout both the central and peripheral nervous systems. The animal of choice for testing for OPIDP is the adult hen. OPIDP has been defined as a central-peripheral, distal, sensory-motor axonopathy and involves extensive morphological damage to the central and peripheral nervous system. Thus far, there is no evidence that malathion induces delayed neurotoxicity in humans or in animals. Neither malathion nor malaoxon inhibited NTE in a human neuroblastoma cell line. Furthermore, malathion did not induce OPIDP in the adult hen at oral doses of up to 300 mg/kg. These dose levels inhibited both NTE and brain acetylcholinesterase, but inhibited the latter to a greater extent, which is opposite to what is normally seen with OPIDP inducers.

2.3 MINIMAL RISK LEVELS (MRLs)

Inhalation MRLs

- An MRL of 0.2 mg/m^3 has been derived for acute-duration inhalation exposure (14 days or less) to malathion.

An acute-duration inhalation MRL of 0.2 mg/m^3 was derived for malathion based on a no-observed-adverse-effect-level (NOAEL) of 65 mg/m^3 for inhibition of RBC cholinesterase activity in rabbits exposed to a malathion aerosol (Weeks et al. 1977). Groups of male New Zealand rabbits (6/exposure level) were exposed for 6 hours to 0 (chamber air), 6, 34, 65, or 123 mg malathion/m^3 as an aerosol generated from a technical malathion formulation (95% pure). Blood was collected at 10 minutes, 24 hours, 72 hours, and 7 days postexposure for determination of cholinesterases activities. Tissues were also removed for histopathological examination. There were no signs of toxicity throughout the study. Exposure to the highest concentration of malathion inhibited plasma cholinesterase by 37% 24 hours postexposure and by 41% 72 hours postexposure. RBC cholinesterase was inhibited by 38, 48, and 48% by the high exposure concentration 24 hours, 72 hours, and 7 days postexposure, respectively. Exposure to malathion caused no histopathological alterations in the organs examined. One human study provided quantitative exposure information. In that study, 16 volunteers were exposed to malathion aerosols 2 hours/day for 42 days (Golz 1959). The malathion aerosol concentrations were 0 (controls), 5.3, 21, and 85 mg/m^3. There were no signs of toxicity during the study with the exception of complaints of nasal and eye irritation within 5–10 minutes of exposure to 85 mg/m^3 of malathion aerosol; no effects were reported at 21 mg/m^3. Analyses of blood samples taken weekly showed no significant effect on plasma or RBC cholinesterase activity over the study period. The MRL was derived by dividing the NOAEL of 65 mg/m^3 by an uncertainty factor of 100 (10 for extrapolation from animal to human and 10 to account for sensitive human subpopulations) (1959). A conversion factor was used to adjust from intermittent exposure to continuous exposure (6/24hours).

- An MRL of 0.02 mg/m^3 has been derived for intermediate-duration inhalation exposure (15–364 days) to malathion.

An intermediate-duration inhalation MRL of 0.02 mg/m^3 was derived for malathion based on a lowest-observed-adverse-effect-level (LOAEL) of 100 mg/m^3 for upper respiratory tract effects in rats in a 13-week study (Beattie 1994). Groups of male and female Sprague-Dawley rats (15/sex/exposure level) were exposed whole body to malathion (96.4% pure) aerosols at concentrations of 0 (air control), 100, 450, or 2,010 mg/m^3 6 hours/day, 5 days/week, for 13 weeks. Rats were monitored for clinical signs and

body weight changes. At termination, gross necropsies were conducted and tissues were processed for microscopical evaluation. Cholinesterase activity was determined in plasma, RBCs, and brain. There were no malathion-related effects on survival, body weight, or food intake. Adverse clinical signs consisting of urogenital staining, excessive salivation, and ungroomed fur were seen mostly in the high-exposure group, but also occurred sporadically in the other exposed groups. Histopathological treatment-related alterations were restricted to the respiratory epithelium. Exposure-concentration-related lesions in the nasal cavity and the larynx of both sexes were seen. The lesions in the nasal cavity consisted of slight to moderate degeneration and/or hyperplasia of the olfactory epithelium. The lesions in the larynx consisted of epithelial hyperplasia with squamous keratization seen in some rats. The effects on cholinesterase activities were concentration-related and effects on females seemed more pronounced than in males. Plasma cholinesterase activity was decreased 30 and 70% in the mid-exposure level and high-exposure level females, respectively. RBC cholinesterase activity was decreased 22 and 27% in mid-exposure level males and females, respectively, and 43 and 44% in high-exposure level males and females, respectively. Brain cholinesterase activity was decreased 41% in high-exposure level females. In the study by Golz (1959) mentioned above, the subjects were exposed to malathion 2 hours /day for 42 days, but given that malathion is rapidly eliminated from the body (see Section 3.4, Toxicokinetics), this exposure regime better reflects repeated single exposures than an intermediate-duration exposure study. The MRL was derived by dividing the LOAEL of 100 mg/m^3 by an uncertainty factor of 1,000 (10 for animal to human extrapolation, 10 for using a LOAEL, and 10 to account for sensitive subpopulations).

No chronic-duration inhalation MRL was derived for malathion because of lack of adequate data. Information on effects in humans is derived mostly from studies of workers in which both the inhalation and dermal routes of exposure play significant roles. No adequate data were available from these studies to construct dose-response relationships. No chronic inhalation studies in animals were located.

Oral MRLs

No acute oral MRL was derived for malathion. Acute oral data in humans come almost exclusively from case reports of accidental or intentional ingestion of high amounts of malathion formulations and do not provide information for establishing dose-response relationships (Choi et al. 1998; Crowley and Johns 1966; Dive et al. 1994; Faragó 1967; Jušić and Milić 1978; Lee and Tai 2001; Monje Argiles et al. 1990; Morgade and Barquet 1982; Namba et al. 1970; Peedicayil et al. 1991; Stålberg et al. 1978; Tuthill 1958; Zivot et al. 1993). Almost all cases presented the typical signs and symptoms of cholinergic stimulation. Acute oral studies in animals provided information on systemic (Krause 1977; Krause et al. 1976; Lox

1983; Ojha et al. 1992; Piramanayagam et al. 1996; Simionescu et al. 1977), immunological (Casale et al. 1983; Rodgers and Xiong 1996, 1997b, 1997d; Rodgers et al. 1986), neurological (Casale et al. 1983; Ehrich et al. 1993; Mathews and Devi 1994; Vijayakumar and Selvarajan 1990; Weeks et al. 1977), reproductive (Krause et al. 1976; Lochry 1989; Ojha et al. 1992; Prabhakaran et al. 1993; Siglin 1985), and developmental effects (Khera et al. 1978; Lochry 1989; Machin and McBride 1989a, 1989b; Mathews and Devi 1994). Although there appears to be an extensive database from animal studies, the quality of many studies precludes their use for risk assessment. Some of the limitations include poor reporting of the results and/or only one dose level tested. Well-conducted studies by Rodgers and colleagues identified the lowest effects levels for immunological alterations in mice (degranulation of mast cells) administered 0.1 mg malathion/kg/day for 14 days (Rodgers and Xiong 1997d). An additional study from this series found increased serum histamine levels in rats and mice after a single dose of 10 mg/kg (Rodgers and Xiong 1997b); the NOAEL was 1 mg/kg. The physiological significance of these immunological effects is unknown and should be addressed in further studies in which the animals are challenged with pathogens. Therefore, it seems inappropriate at this time to base an acute oral MRL on subtle immunological alterations of unknown physiological significance. A relatively low LOAEL of 4.4 mg/kg (the only dose level tested) was identified for decreased hematocrit and platelet counts in rats administered malathion once by gavage in water. No other acute gavage or feeding study reported a similar effect at any dose level. Therefore, it would also be inappropriate to base an acute oral MRL on a free standing LOAEL of unknown toxicological significance.

- An MRL of 0.02 mg/kg/day has been derived for intermediate-duration oral exposure (15–364 days) to malathion.

An intermediate-duration oral MRL of 0.02 mg/kg/day was derived for malathion based on inhibition of plasma and RBC cholinesterase activity in humans (Moeller and Rider 1962). The study was conducted in three phases. In the first phase, five male volunteers were administered daily capsules containing malathion (purity not reported) in corn oil that provided an approximate dose of 0.11 mg malathion/kg/day for 32 days. In the second phase, which started 3 weeks after the first phase had terminated, five male volunteers received daily capsules with malathion providing about 0.23 mg malathion/kg/day for 47 days. In the third phase, five new subjects received approximately 0.34 mg malathion/kg/day for 56 days. Plasma and RBC cholinesterase was determined twice weekly before, during, and after administration of malathion. Routine blood counts and urinalyses were conducted at the end of each study period. Administration of 0.11 mg malathion/kg/day for 32 days or 0.23 mg/kg/day for 47 days did not produce any significant depression of plasma or RBC cholinesterase activity, nor did it alter blood counts or urinalyses, or induce clinical signs. In phase three, 0.34 mg malathion/kg/day for

56 days caused a maximum depression of 25% in plasma cholinesterase approximately 3 weeks after cessation of treatment. A similar depression in RBC cholinesterase was observed, but occurred later. No clinical signs were seen in the volunteers. The MRL was derived by dividing the NOAEL of 0.23 mg/kg/day by an uncertainty factor of 10 (to account for sensitive subpopulations).

- An MRL of 0.02 mg/kg/day has been derived for chronic-duration oral exposure (365 days or more) to malathion.

A chronic-duration oral MRL of 0.02 mg/g/day was derived for malathion based on inhibition of plasma and RBC cholinesterase activity in rats fed malathion in the diet for 2 years (Daly 1996a). Groups of male and female Fischer-344 rats (90/sex/dose level) were administered malathion (97.1%) in the diet at levels of 0, 50, 500, 6,000, or 12,000 ppm for 2 years. This diet provided approximately 0, 2, 29, 359, or 739 mg malathion/kg/day to males and 0, 3, 35, 415, or 868 mg/kg/day to females. Ten rats/sex/group were sacrificed at 3 and 6 months primarily for ocular tissue evaluation. Additional sacrifices were conducted at 12 months for more complete assessments. Administration of malathion significantly increased mortality in males at 6,000 ppm and in both sexes at 12,000 ppm. Body weight gain was reduced both in males and females at the two highest exposure levels, but food intake was not decreased. Hemoglobin, hematocrit, mean corpuscular volume (MCV), and mean cell hemoglobin were in both sexes at the two highest dietary levels of malathion. Absolute and relative liver and kidney weights were increased in males and females from the 6,000 and 12,000 ppm groups. Relative absolute thyroid and parathyroid weights were increased in males at 6,000 ppm at 12 months and in females at 6,000 and 12,000 ppm at termination. At 24 months, at the 500 ppm malathion dietary level (29 mg/kg/day for males, 35 mg/kg/day for females), plasma cholinesterase activity was reduced 29 and 18% in males and females, respectively, RBC cholinesterase was reduced 17 and 27%, respectively, and brain cholinesterase was reduced 3 and 1%, respectively. At the 6,000 ppm level, plasma cholinesterase in males and females was reduced 64 and 61%, respectively, and brain cholinesterase was reduced 21 and 18%, respectively. No significant reduction in enzyme activities was observed at the lowest dietary level of malathion, 2 mg/kg/day for males and 3 mg/kg/day for females. The MRL was derived by dividing the NOAEL of 2 mg/kg/day by an uncertainty factor of 100 (10 for extrapolation from animal to human and 10 to account for sensitive subpopulations).