2. RELEVANCE TO PUBLIC HEALTH

2.1 BACKGROUND AND ENVIRONMENTAL EXPOSURES TO METHYL PARATHION IN THE UNITED STATES

Methyl parathion is a broad-spectrum agricultural insecticide that is released to the environment primarily through spraying of the insecticide on a variety of agricultural products. Once methyl parathion is introduced to the environment, it is degraded by hydrolysis, photolysis, or by biodegradation from microorganisms found in most sediment, soils, and water. Methyl parathion is primarily confined to the application area, but some can be transported by rain, fog, and wind to other areas. Methyl parathion adsorbs to the soil and is relatively immobile. As a result, leaching into groundwater is not usually observed. Volatilization has been observed to occur from plants and soil post-application, with volatilization from plants being the faster of the two. Limited studies show that bioconcentration of methyl parathion does not occur to a significant extent; that which is accumulated in plants and animals is rapidly metabolized. Methyl parathion is not widely dispersed or persistent in the environment. Residue amounts of methyl parathion have been detected in air, water, fish, soil, and agricultural crops consumed as foods.

Methyl parathion is approved by the EPA only for use on agricultural crops. As a result, the general population is not likely to be exposed to large amounts of methyl parathion. Some exposure to residues of methyl parathion is possible, however, as many studies show that methyl parathion has been detected in foods and atmosphere samples. Populations living within or very near areas of heavy methyl parathion use would have an increased risk of exposure to large amounts of methyl parathion through dermal contact with contaminated plants, by inhalation of the mist formed from the applied insecticide, or by ingestion of water or food-borne residues. Those likely to receive the highest levels of exposure are those who are involved in the production, formulation, handling, and application of methyl parathion. Dermal contact appears to be the major route of exposure, while inhalation may also be an important route of exposure for those working in these operations.

The greatest potential for exposure of the general population to methyl parathion is by consumption of food containing residues from spray applications of the insecticide. In a 10-year study, methyl parathion was found at an average concentration of 0.0035 ppm in a few examples of ready-to-eat foods. Concentrations in the range of 0.05–2.0 ppm were reported in 0.5% of the samples of domestic and

imported foods and animal feeds in a 5-year analysis. Additional studies have reported concentrations of methyl parathion of 0.016–3.8 ppm in a small percentage of samples of various foods.

Residues in many foods should decrease because EPA has canceled many of the food crop uses of methyl parathion, including fruits and vegetables commonly eaten by children, some other vegetable uses, some feed uses, and all nonfood uses such as ornamental plants and nursery stock uses. Tolerances for methyl parathion on these foods and feed also have been canceled. This action was taken because of a concern for risks to children and workers. Some food and feed uses and tolerances are to be maintained.

In areas of agricultural methyl parathion usage, both outdoor and indoor air levels of methyl parathion of approximately 12 ng/m^3 have been measured, and household dust was found to contain 21 ppb of methyl parathion. Outdoor and indoor air concentrations of methyl parathion as high as 0.71 and 9.4 µg/m^3, respectively, have been measured at the homes of individuals employed as pesticide formulators.

Dermal exposure to methyl parathion is not likely to be a health concern to the general population, with the possible exception of individuals in the immediate vicinity of a field during application of the pesticide. Dermal exposure, however, is a major source of exposure for workers directly involved in the manufacture, application, and cleanup of the chemical, and for field workers. Laundry workers cleaning the clothing of such workers may also be exposed.

Children are expected to be exposed to methyl parathion by the same routes that affect adults. Small children are more likely to come into contact with methyl parathion 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. Methyl parathion has been detected in a few samples of breast milk, indicating potential for exposure of nursing infants. However, available data are not adequate for determination of the importance of this route of child exposure.

Populations residing near hazardous waste disposal sites may be subject to higher levels of methyl parathion in environmental media (i.e., air, groundwater, soil) than those experienced by the general population. Methyl parathion has been identified in at least 16 of the 1,585 hazardous waste sites that have been proposed for inclusion on the EPA National Priorities List (NPL). However, the number of sites evaluated for methyl parathion is not known. As more sites are evaluated, the number of sites where methyl parathion has been detected may increase.

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

2.2 SUMMARY OF HEALTH EFFECTS

Methyl parathion is a highly toxic pesticide, and humans are susceptible to its acute toxic effects by various routes of exposure. Signs and symptoms of acute toxicity are typical of those induced by organophosphate insecticides as a group. Almost all systemic effects of methyl parathion are related to the action of this compound on the nervous system or are secondary to this primary action. Methyl parathion and its active metabolite, methyl paraoxon, exert their profound toxic effect by inhibiting the activity of acetylcholinesterase in the nervous system and at the motor end-plate. Hydrolysis of acetylcholine is inhibited and the neurotransmitter accumulates at its site of action, producing over-stimulation of cholinergic end organs. Information regarding effects in humans is limited to a few case reports of people acutely exposed to high levels of methyl parathion either by intentional ingestion or by multiple-route exposure from direct contact with spray material either in field applications or through illegal indoor spraying. Manifestations of acute poisoning are similar in humans and animals and include reduced cholinesterase levels in brain, erythrocytes, and plasma, clinical signs of neurological effects such as tremors and convulsions, and cardiac arrhythmia. Except for neuropsychiatric disorders reported in humans after chronic occupational exposure to organophosphates including methyl parathion, no chronic effects have been documented in humans. Effects in animals chronically exposed to methyl parathion include hematological and ocular changes. Available data regarding the genotoxicity of methyl parathion is inconclusive. Based on the lack of a carcinogenic effect in animals and the lack of evidence to indicate a strong genotoxic effect, methyl parathion does not appear to present a substantial carcinogenic risk to humans.

Neurological Effects. Clinical symptoms and signs of methyl parathion intoxication are typical of organophosphate poisoning. In mild or moderate cases, patients are alert and oriented; in severe cases, they can be confused and ataxic, with slurred speech. Headache, dizziness, and incoordination are common. Respiratory symptoms consist of chest tightness, a productive cough, and wheezing. Gastrointestinal symptoms are nausea, vomiting, diarrhea, and abdominal cramps. Findings considered characteristic of organophosphate intoxication are muscle fasciculations and miosis, although the latter sign is not always present. Severely intoxicated patients have extreme salivation, involuntary urination and defecation, sweating, lacrimation, bradycardia, and hypotension. Unconsciousness, respiratory arrest (due to depression of the respiratory center and paralysis of respiratory muscles), and death can result, the

latter from a combination of respiratory and cardiovascular failure. Marked depressions in erythrocyte and/or plasma cholinesterase levels are typically observed in individuals exhibiting clinical signs of organophosphate poisoning. Available data suggest that a rapid decline in cholinesterase levels may be more important than the degree of decline. Neurological signs and depressed cholinesterase levels have been observed in animals either acutely exposed to atmospheres containing 264 mg/m^3 of methyl parathion or administered single oral doses in the range of 4–8 mg/kg. Rats given single oral doses as low as 1.5 mg/kg exhibited significantly depressed plasma, erythrocyte, and brain cholinesterase within 30 minutes of dosing.

More subtle psychological symptoms have been reported after acute mild organophosphate intoxication. Psychological changes associated with dermal application of a potent organophosphate anticholinesterase (an unspecified military chemical) occurred in male volunteers who had no other clinical signs or symptoms of toxicity except nausea and vomiting. Psychological changes tended to occur when cholinesterase levels were depressed to 10–40% of controls. Changes were a state of altered awareness characterized by slowed intellectual and motor processes and difficulty in sustaining attention. Subjects felt slowed down, agitated, and confused. These changes may be a concern with exposure to other organophosphate insecticides, including methyl parathion.

Another condition that has been reported as a consequence of very high acute exposures to organophosphate insecticides is the intermediate syndrome. The onset occurs approximately 1–4 days after the acute cholinergic crisis has resolved. Clinical observations include acute respiratory insufficiency and muscular weakness, primarily of the neck flexors, proximal limb, and respiratory muscles, and motor cranial nerve palsies. Death may ensue from respiratory insufficiency. The syndrome is thought to result from prolonged acetylcholinesterase inhibition at the neuromuscular junction. The intermediate syndrome has been observed primarily in cases of exposure to fenthion, dimethoate, monocrotophos, and methamidophos, but also in one case of parathion ingestion, and in a few cases of ingestion and one of inhalation of a mixture of parathion and methyl parathion.

Mental disturbances have been reported after organophosphate exposure. Neuropsychiatric symptoms occurred in two aerial applicators, one of whom used methyl parathion as well as other insecticides. One of these pilots had high levels of exposure to a mixture containing methyl parathion, toxaphene, and Dipterex® when his clothing became saturated when the tank of his aircraft accidentally overflowed. Several months after the accident, the subject complained of anxiety, dizziness, emotional lability, and frequent and severe disagreements with family members and associates. Similar observations had been

made among a group of 16 men who had worked with a variety of organophosphates over a number of years. Exposure was likely by both dermal and inhalation routes. During exposure, the men had periodic episodes of acute organophosphate toxicity: nausea, vomiting, excessive perspiration, muscle weakness, confusion, etc. When these men consulted psychiatrists or were admitted to mental hospitals, they had depressive or schizophrenic manifestations or major impairment of memory and concentration. These findings were attributed to the action of organophosphates on acetylcholinesterase in the central nervous system. Follow-up of the cases showed that these effects persisted for 6 months after exposure had ceased, but had disappeared by 12 months after exposure.

In animals, longer duration feeding studies have reported plasma, erythrocyte, and brain cholinesterase inhibition in dogs at 3.0 mg/kg/day for 13 weeks and in rats at 2.5 mg/kg/day for 2 years. Cholinergic signs were seen in the rats during the first few months. Electrophysiological effects were detected in the central nervous systems of male rats exposed to methyl parathion through gavage administration of 0.22 mg/kg/day to the dams on days 5–15 of gestation and days 2–28 of lactation, followed by direct administration of the same dose to the male pups for 8 weeks.

A serious neurological effect of some organophosphates and triarylphosphates, such as tri-*ortho*-cresyl-phosphate, is delayed neurotoxicity. Delayed neurotoxicity has been associated with inhibition of a neurotoxic esterase in nerve tissue. Axons in the spinal cord and peripheral nerves are targets for compound-induced damage. A classic screening test for such an effect is to administer the suspect chemical to atropinized chickens and to observe the animals for signs of leg weakness or paralysis. Methyl parathion does not appear to be a delayed neurotoxin, although studies in rats suggested that chronic oral exposure to 2.5 mg/kg/day methyl parathion may result in distal axonopathy, and intermediate oral exposure to 0.22 mg/kg/day may result in decreased nerve conduction velocity and increased refractory period.

Hematological Effects. No information was found regarding hematological effects in humans following exposure to methyl parathion. Repeated oral exposure to methyl parathion resulted in decreased mean corpuscular volume in one study and decreased hematocrit and erythrocyte count in another study in rats. Chronic ingestion of methyl parathion induced reduction of mean hemoglobin, hematocrit, and erythrocyte counts in rats.

Cardiovascular Effects. A number of cardiovascular lesions, such as acute myocardial degeneration and vascular degeneration, congestion, and hemorrhage, have been observed in individuals exposed to

fatal doses of methyl parathion. These effects may be secondary to neurological effects of methyl parathion on the central and peripheral nervous system and on heart contractility and vascular smooth muscle. Acute oral doses of methyl parathion, administered to rats in single doses $9.5 mg/kg, resulted in severe cardiac arrhythmias. Similar results were observed following dermal application of doses $34 mg/kg.

Developmental Effects. Adverse effects of methyl parathion on human fetal development have not been reported. Based on studies in animals, such effects appear to be possible if pregnant women were exposed during the first trimester to high concentrations of methyl parathion that resulted in significant depression of cholinesterase levels, particularly if concomitant signs and symptoms of organophosphate intoxication occur. Such an exposure scenario may occur with occupational exposure, exposure in homes or offices illegally sprayed with methyl parathion, or accidental exposure to methyl parathion, but is less likely as a result of low-level exposure.

The following studies in animals suggest that adverse effects on human fetal development could occur. Methyl parathion has been shown to transfer across the placenta of rats after oral exposure of pregnant females. Fetotoxicity and offspring with altered brain enzymes and impaired behavior have been reported in rats after oral or parenteral maternal administration of methyl parathion at doses that inhibited acetylcholinesterase activity and, in some studies, produced cholinergic signs in the dams. Pregnant female mice exposed to 60 mg/kg methyl parathion by the intraperitoneal route had a significant increase in fetuses with cleft palate compared to control litters. There was also a dose-related increase in fetal deaths. These observations suggest that developmental effects may occur in a susceptible population exposed to low doses of methyl parathion during pregnancy.

In addition, oral administration of methyl parathion at relatively low doses to male rats through the dams during gestation and lactation and then directly to the offspring until 12 weeks of age resulted in electro-physiological changes in the brain and peripheral nervous system, as described under neurological effects. These effects were seen at dose levels that did not cause cholinergic signs; cholinesterase activity was not monitored. Such effects were not seen in the same study when the period of administration was confined to gestation and lactation.

Ocular Effects. Pinpoint pupils (miosis) have been observed in individuals following acute exposure to methyl parathion. Electroretinographic changes have been reported in mice following intraperitoneal injection of 1.5 mg of methyl parathion. These changes were a direct effect of methyl parathion on

repolarization of retinal photoreceptors. Other data from animal studies indicate that oral exposure to methyl parathion may induce retinal degeneration and bilateral retinal atrophy. The relevance of the ocular effects noted in animals to humans is unknown.

2.3 MINIMAL RISK LEVELS

Inhalation MRLs

Although a number of studies have reported the effects of inhalation exposure to methyl parathion in humans, no inhalation MRLs were derived based on human data because of the lack of adequate quantitative exposure information. Animal data were also insufficient to support the derivation of an acute-, intermediate-, or chronic-duration inhalation MRL.

Oral MRLs

No acute oral MRL was derived for methyl parathion because data regarding the most sensitive effect that was observed after acute oral exposure are conflicting. Increased pup mortality and altered behavior occurred in offspring of rats exposed to 1 mg/kg/day methyl parathion during, but no effects on pup survival or on sensitive electrophysiological indices of neurotoxicity were seen at virtually the same dose, 0.88 mg/kg/day, in a similar developmental toxicity study.

- An MRL of 0.0007 mg/kg/day has been derived for intermediate-duration oral exposure (15–364 days) to methyl parathion.

An intermediate-duration oral MRL of 0.0007 mg/kg/day was derived for methyl parathion based on the observation of electrophysiological effects in the central and peripheral nervous systems of male rats exposed to methyl parathion through gavage administration of 0.22 mg/kg/day to the dams on days 5–15 of gestation and days 2–28 of lactation, followed by direct administration of the same dose to the male pups for 8 weeks. More marked effects occurred at the two higher doses, 0.44 and 0.88 mg/kg/day. The effects were dose-related, and were statistically significant at all three dose levels. The MRL was derived by dividing the LOAEL from this study (0.22 mg/kg/day) by an uncertainty factor of 300 (3 for a minimal LOAEL, 10 for extrapolation from animals to humans, and 10 for human variability).

- An MRL of 0.0003 mg/kg/day has been derived for chronic-duration oral exposure (365 days or more) to methyl parathion.

2. RELEVANCE TO PUBLIC HEALTH

A chronic-duration oral MRL of 0.0003 mg/kg/day was derived for methyl parathion based on the observation of reduced mean hematocrit and erythrocyte counts in rats fed methyl parathion in the diet for 2 years. Significantly decreased mean hematocrit and erythrocyte counts were observed at 24 months in males that consumed 0.25 and 2.5 mg/kg/day for 24 months; no effect on these end points in males was observed at 0.025 mg/kg/day. Significantly decreased mean hemoglobin, hematocrit, and erythrocyte counts were seen at 6–24 months in females that ingested 2.5 mg/kg/day, with no effect at 0.025–0.25 mg/kg/day. In the same study, significantly decreased plasma, erythrocyte, and brain cholinesterase activities, and abnormal gait, tremor, and peripheral neuropathy, were observed in the rats that consumed 2.5 mg/kg/day methyl parathion, but not in rats consuming the lower doses. The MRL was derived by dividing the NOAEL of 0.025 mg/kg/day for hematological effects in this study by an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).