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2.1 BACKGROUND AND ENVIRONMENTAL EXPOSURES TO PARATHION IN THE UNITED STATES

Parathion is an organophosphorus insecticide that was primarily used prior to 2006 for agricultural purposes and was released to the environment through spraying on a wide variety of agricultural crops and at agricultural sites. Once parathion is introduced into the environment, it may be degraded by atmospheric photooxidation and catalyzed by ozone or degraded by hydrolysis or biodegradation mediated by microorganisms found in most sediment, soils, and water. Parathion is not likely to migrate through the soil and into groundwater since it has little to no mobility in soils under varying conditions. Volatilization of parathion from water surfaces has been observed; however, volatilization of parathion from soil surfaces is expected to be low. Data from limited studies suggest that bioconcentration of parathion does not occur to a significant extent in most aquatic organisms tested, and that it may be metabolized when it is accumulated.

Significant exposure of the general population to parathion is not likely at present, due to the ban on all uses in the United States. Parathion was formerly used as a widespread insecticide in agriculture. In 1991, parathion was registered as a restricted use insecticide and had been limited to use on nine crops. Due to the toxicity of this chemical, most production of manufacturing use products was cancelled effective as of September 2000 with the remainder cancelled in 2003. The production of end use products was slated to be terminated as of December 31, 2002, with the last legal use of this chemical and its products to be effective on October 31, 2003. The production and registration for the remaining end use products ended in 2006.

When parathion was still used as a registered insecticide, general population exposure may have occurred through ingestion of contaminated food and inhalation. Ingestion of foods contaminated with small residues of parathion was the most likely route of exposure for the general population not living in areas where parathion was extensively used. Populations living within or very near areas of heavy agricultural parathion use would have had an increased risk of exposure to relatively larger amounts of parathion through dermal contact with contaminated plants, soils, or surface waters; by inhalation of the mist formed from the applied insecticide; or by ingestion of food-borne residues. Those likely to have received the highest exposures are those who were involved in the production, formulation, handling, and application of parathion, farm workers who enter treated fields prior to the passage of the appropriate restricted entry intervals, and workers involved in the disposal of parathion or parathion-containing

wastes. Dermal contact appears to have been the major route of exposure for workers. Inhalation of parathion in occupational settings depended on its volatility, the type of formulation used, and the application technique employed.

Children would have been expected to be exposed to parathion by the same routes that affect adults. Small children were more likely to come into contact with parathion residues that may have been present in soil and dust, due to increased hand-to-mouth activity and playing habits. Ingestion of foods contaminated with small residues of parathion was the most likely route of exposure for children. No data were located regarding parathion in breast milk; therefore, an adequate determination of the importance of this route of child exposure has not been made.

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

2.2 SUMMARY OF HEALTH EFFECTS

Parathion is an organophosphate pesticide of relatively high acute toxicity compared to other organophosphates. Signs and symptoms of acute toxicity are typical of those induced by organophosphate insecticides as a group. With the current state of knowledge, the great majority of systemic effects observed following exposure to parathion are due to the action of its active metabolite, paraoxon, on the nervous system, or are secondary to this primary action. Paraoxon inhibits the enzyme, acetylcholinesterase (AChE), at the various sites where the enzyme is present in the nervous system: the central nervous system, the sympathetic and parasympathetic divisions of the autonomic nervous system, and the neuromuscular junction. Inhibition of AChE results in accumulation and continuous action of the neurotransmitter acetylcholine at postsynaptic sites. Information regarding effects of parathion in humans is derived mainly from cases of accidental or intentional ingestion of parathion, studies of workers involved in the manufacture of parathion, studies of agricultural workers, members of the general population, and a few controlled exposure studies with volunteers. Oral ingestion or dermal absorption of high amounts of parathion resulted in typical signs and symptoms of organophosphate intoxication, including reduced plasma and red blood cell cholinesterase activity, excessive bronchial secretions, respiratory distress, salivation, pinpoint pupils, bradycardia, decreased blood pressure, abdominal cramps, diarrhea, tremor, fasciculations, and possibly death.

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Limited data are available regarding health effects in humans exposed to parathion other than neurological effects. Evaluations of participants in the Agricultural Health Study (AHS) have suggested weak associations between exposure to parathion and allergic asthma, hearing loss, cutaneous melanoma, hypothyroidism, and diabetes. The AHS is a prospective cohort study of nearly 90,000 private pesticide applicators (mostly farmers), their spouses, and commercial pesticide applicators in Iowa and North Carolina. Parathion was one of multiple pesticides involved in the evaluations. The AHS is funded by the National Cancer Institute and the National Institute of Environmental Health Sciences in collaboration with the EPA and NIOSH. Results from the AHS also showed no significant association between exposure to parathion and wheezing, non-allergic asthma, neurobehavioral function (memory, motor speed and coordination, sustained attention, verbal learning, and visual scanning and processing), and peripheral nervous system function. However, exposure to parathion was found positively associated with depression in the AHS. Two population-based, case-control studies did not find a significant association between exposure to parathion and Parkinson's disease. A small study of Chinese workers exposed to parathion and methamidophos reported sperm alterations in workers compared to unexposed subjects; however, the small sample size (only 20 workers) renders the results uncertain at best. A study of Latina women living in an agricultural community in California did not find significant associations between several measures of *in utero* exposure to parathion and fetal growth. That study, however, assessed exposure to parathion by measuring urinary *p*-nitrophenol, which could have been produced by exposure to chemicals other than parathion. Studies in animals support the human data and confirm that the main target of parathion toxicity is the nervous system. Exposure levels were not available in the studies mentioned above. Very few studies that evaluated reproductive and developmental effects of parathion in animals were available for review. An intermediate-duration oral study in rats reported that doses of 2.6 mg parathion/kg/day (only dose tested and in the lethal range estimate for human adults) induced testicular tubular atrophy, necrotic spermatogenic cells, and enlargement of the interstitial space of the testes. Oral chronic-duration studies in rats exposed to up to 4.4 mg parathion/kg/day or in mice exposed to up to 27.6 mg parathion/kg/day did not find gross or microscopic alterations in the reproductive organs. Parathion was not embryotoxic or teratogenic in rats and rabbits following repeated oral administration of up to 1 and 0.3 mg parathion/kg/day, respectively, during gestation. An additional study in rats reported that pups exposed during gestation and lactation showed alterations in the electrocardiograms (EKGs) (i.e., decreased rate of atrial depolarization and ventricular repolarization) on postnatal day 25 even with the lowest maternal dose tested, 0.01 mg parathion/kg/day. Since this is not a developmental end point routinely tested in standard developmental studies, it would be helpful to try to replicate these results to determine if they are developmental in nature. A series of studies in which neonatal rats were administered subcutaneous doses of parathion that did not induce significant inhibition

of AChE reported alterations in the development of neurotransmitter systems, neurobehavior, and metabolic dysregulation that were evident at later times up to adulthood.

Parathion increased the incidence of adrenal gland adenomas and carcinomas in Osborne-Mendel rats in a dietary bioassay. Parathion induced immunosuppression in mice in acute oral studies; the lowest dose to do so was 1.5 mg parathion/kg/day. However, none of these studies challenged the mice with an external agent to evaluate whether resistance to infection was compromised. Evidence suggested that cholinergic stimulation played a major role in parathion-induced plaque-forming cell response. Parathion also increased the sensitivity to allergens in mice at the relatively low dose of 0.15 mg parathion/kg/day. The investigators suggested that the effects may involve alterations in the number of helper and cytotoxic T-cells, in levels of T_H1 and T_H2 cytokines, and in gene expression in lymph nodes. Chronic-duration studies in rats and mice did not find gross or microscopic alterations in lymphoreticular organs. In general, little systemic toxicity was reported in the animal studies available for review. Mild liver histopathology was reported in rats in a 90-day gavage study. The chronic-duration oral studies available for review did not find gross or microscopic alterations in the liver, kidneys, heart, or lungs from rats or mice. Neurotoxicity is the main effect of parathion 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 parathion intoxication are typical of organophosphate poisoning. Parathion through its active metabolite, paraoxon, inhibits the enzyme AChE and thus prevents 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, sufficient 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.

Death generally occurs due to respiratory failure attributed to excessive tracheobronchial and salivary secretions, nicotinic paralysis of the diaphragm and respiratory muscles and depression of central nervous system respiratory centers.

The signs and symptoms described above have been documented in almost all of the cases of accidental or intentional ingestion or dermal exposure to high amounts of parathion. Estimates of lethal doses range from about 2 to 13 mg/kg in adults and from 0.1 to 1.3 mg/kg in children. Studies that measured cholinesterase levels showed significant decreases in both red blood cell AChE and plasma cholinesterase levels. In general, plasma cholinesterase activity can be inhibited by 20–25% without significant physiological consequences. Red blood cell AChE activity can be reduced 20–25% without manifestation of clinical signs. A decrease of 40% is a danger signal for overexposure, and a depression of ≥60% is an indication for removal from the exposure site to prevent overt poisoning. Studies also have shown that the rate of decrease of red blood cell AChE correlates better with the appearance of symptoms than the absolute value reached after exposure. Red blood cell AChE better reflects the AChE content in the central nervous system than plasma cholinesterase. In a study of multiple cases of severe oral intoxication, red blood cell cholinesterase was depressed 78%. In another study of six cases of severe oral poisoning with parathion, red blood cell cholinesterase activity was reduced to <10% of normal in all cases. In workers exposed to high amounts of parathion primarily by dermal contact during the synthesis and handling of various parathion formulations, and who suffered severe symptoms, red blood cell cholinesterase activity reached 11–22% of normal. In two fatal cases of oral poisoning, inhibition of brain AChE was found to be regionally selective. Measurements done within 32 hours of death showed the biggest decreases (65–80%) in the cerebellum, some thalamic nuclei, and the cortex. Moderate decreases of 10–30% were reported in the *substantia nigra* and basal ganglia; no significant changes were seen in the white matter. Studies in volunteers exposed orally to parathion indicate that repeated doses of approximately 0.1 mg parathion/kg may result in reductions of red blood cell AChE activity of <20% and no adverse clinical signs. Application of approximately 100 mg to the hand and forearm of volunteers for 2 hours during 5 consecutive days resulted in maximal inhibition of red blood cell AChE of 14%, and no clinical signs were observed. As detailed in Section 3.2, numerous studies in animals exposed to parathion by any route have shown inhibition of plasma, red blood cell, and brain cholinesterase activities.

A condition that has been reported in humans as a consequence of acute exposure to high amounts of some organophosphate pesticides 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. Single cases due to specific exposure to parathion have been reported. In a report of 68 cases of acute exposure to parathion, 7 developed intermediate syndrome (10.3%).

A serious neurological effect of some organophosphate pesticides is delayed neurotoxicity. Organophosphorus pesticide-induced neuropathy (OPIDN) is a neurodegenerative disorder characterized by a delayed onset of prolonged ataxia and upper motor neuron spasticity. The lesion is a central-peripheral distal axonopathy caused by a Wallerian-type degeneration of the axon, followed by myelin degeneration of the central and peripheral nervous systems. A few cases of parathion-induced delayed neuropathy have been described.

2.3 MINIMAL RISK LEVELS (MRLs)

Estimates of exposure levels posing minimal risk to humans (MRLs) have been made for parathion. An MRL is defined as an estimate of daily human exposure to a substance that is likely to be without an appreciable risk of adverse effects (noncarcinogenic) over a specified duration of exposure. MRLs are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration within a given route of exposure. MRLs are based on noncancerous health effects only and do not consider carcinogenic effects. MRLs can be derived for acute, intermediate, and chronic duration exposures for inhalation and oral routes. Appropriate methodology does not exist to develop MRLs for dermal exposure.

Although methods have been established to derive these levels (Barnes and Dourson 1988; EPA 1990), uncertainties are associated with these techniques. Furthermore, ATSDR acknowledges additional uncertainties inherent in the application of the procedures to derive less than lifetime MRLs. As an example, acute inhalation MRLs may not be protective for health effects that are delayed in development or are acquired following repeated acute insults, such as hypersensitivity reactions, asthma, or chronic bronchitis. As these kinds of health effects data become available and methods to assess levels of significant human exposure improve, these MRLs will be revised.

Inhalation MRLs

An acute-duration inhalation MRL was not derived for parathion. Adequate human data were not available. Hartwell et al. (1964) exposed two volunteers to various formulations of heated parathion dust or liquid technical parathion for periods of 30 minutes and measured red blood cell AChE activity. However, the concentrations of parathion to which the subjects were exposed were not determined. An acute-duration study that identified no-observed-adverse-effect levels (NOAELs) and lowest-observed-adverse-effect levels (LOAELs) for neurological end points including red blood cell AChE activity and clinical signs in rats and dogs was available for review; the exposure period was 4 hours for both species (NIOSH 1974). Red blood cell AChE activity was the most sensitive end point in both species and, since it is a valid neurological end point in the absence of brain AChE data, could be considered for MRL derivation. However, studies of cholinesterase inhibition have shown that it takes approximately 21–28 days for inhibition of cholinesterase activity to reach a steady state and that values obtained in single dose or short-duration studies carry great uncertainty (EPA 2001, 2006). In addition, such studies have shown an apparent lack of dose-response, particularly at the low exposure levels. For example, in the NIOSH (1974) study with parathion, 24 hours after exposure to 0.035, 0.206, 0.235, 0.825, 0.905, 1.21, or 2.17 mg/m^3 parathion aerosol, red blood cell AChE activity in male rats was inhibited 7, 8, 28, 17, 8, 11, and 30%, respectively. Examination of the extent of red blood cell AChE inhibition across time gives a similar picture. For example, in male rats, exposure to 0.235 mg/m^3 parathion aerosol resulted in 0, 23, 14, 0, and 26% inhibition at 4, 24, 48, 168, and 336 hours after exposure ceased, respectively. In dogs, the lowest exposure level tested (0.153 mg/m^3) resulted in levels of red blood cell AChE activity 62.1, 49.3, 44.0, 71.6, and 58.0% of normal at 4 hours, 24 hours, 48 hours, 7 days, and 14 days after exposure, respectively. For these reasons, and also based on data collected on enzyme inhibition for a great number of organophosphate pesticides that suggest that AChE inhibition data obtained in single-dose or short-duration studies carry great uncertainty (EPA 2006), as indicated above, an acute-duration inhalation MRL was not derived for parathion. However, since the lowest acute-duration inhalation LOAEL is 0.153 mg/m^3, the intermediate-duration inhalation MRL of 20 ng/m^3 (see below) is protective of acute effects.

- An MRL of 20 ng/m^3 has been derived for intermediate-duration inhalation exposure (15–364 days) to parathion based on adverse neurological effects in rats.

The only quantitative information regarding long-term exposure of humans to parathion in air is from a study of 13 workers at an industrial plant that manufactured concentrated parathion as well as dusts containing various concentrations of parathion (Brown and Bush 1950). Only one of these workers was

unexposed to parathion. The exact duration of exposure was not known. Parathion was measured in air at different operations. The maximum concentration determined was 0.8 mg/m^3 and the estimated average was about 0.2 or 0.3 mg/m^3. Due to the rotation of personnel, the 12 exposed subjects had only intermittent contact with parathion-contaminated air until July 1949, when production ceased. Therefore, it was impossible to determine exactly what the total exposure had been. Analyses of blood from five subjects who provided successive blood samples over a 6-month period showed a decrease in plasma cholinesterase activity. However, the changes in red blood cell cholinesterase activity were less conclusive. The investigators noted that probably the most significant finding was the fact that measurements of cholinesterase activities conducted 5 months after the plant had stopped manufacturing parathion showed a marked increase in activities in almost all cases. The information presented in this study is inadequate for MRL derivation.

Although only one intermediate-duration study provided information regarding effects of parathion in animals, the study was considered adequate for derivation of an intermediate-duration MRL (NIOSH 1974). The study monitored clinical signs and plasma cholinesterase and red blood cell AChE activities in male Sprague-Dawley rats and in male beagle dogs exposed whole-body to aerosolized technical parathion.

Groups of male rats (20/group) were exposed to 0, 0.01, 0.1, or 0.74 mg parathion/m^3 7 hours/day, 5 days/week for 6 weeks. Blood samples obtained from 71 rats were assayed for red blood cell and plasma cholinesterase and served as baseline controls. Ten rats per exposure group and control group were sacrificed at various times during the exposure period and during a 6-week post-exposure period to collect blood samples. The rats were observed for clinical signs and were weighed before blood sampling and sacrifice. No clinical signs were seen in rats exposed to 0.01 or 0.1 mg parathion/m^3. Some rats in the high-concentration group showed signs of parathion toxicity, including tremors and ataxia. Blood collected from the high-dose group after the last exposure showed no significant alteration in hematocrit. Body weight was not significantly altered by exposure to parathion. In the low-exposure group, red blood cell AChE activity was maximally decreased by approximately 30% on exposure weeks 4 and 5; no data were available for week 3. On exposure week 6, red blood cell AChE activity in the low-exposure group had recovered to 97.3% of control levels. In the mid-exposure group, the maximum decrease in red blood cell AChE was 43% and occurred on week 1. During the rest of the exposure period, red blood cell cholinesterase activity was 60–70% of pretest levels, suggesting that a steady state had been achieved. Red blood cell AChE activity during the first and second week of the post-exposure period was 82 and 84.4% of controls, indicating that recovery was in progress. In the high-exposure group, red blood cell

AChE activity achieved its maximal depression on week 5 of exposure, reaching 15% of controls. In general, enzyme activities recovered during the 6-week post-dosing period. Changes in plasma cholinesterase activity paralleled red blood cell changes, but recovered faster and significantly exceeded controls starting the first week post-exposure. Since the exposure level of 0.1 mg parathion/m^3 induced a level of depression of red blood cell AChE activity that appeared to achieve steady state at approximately 60–70% of controls during exposure, this exposure concentration constitutes a less serious LOAEL for neurological effects in rats; the exposure concentration of 0.01 mg parathion/m^3 is a NOAEL.

Male beagle dogs (6/group) were exposed to parathion aerosol at concentrations of 0, 0.001, 0.01, or 0.2 mg/m^3 7 hours/day, 5 days/week for 6 weeks and were held for an additional 6-week post-exposure period. Blood samples obtained from the dogs at various times during the exposure and post-exposure periods were assayed for red blood cell AChE and plasma cholinesterase. Blood samples were taken pre-exposure so that each dog served as its own control. No clinical signs were observed in the dogs. Exposure to parathion did not affect body weight gain in the dogs. No significant effects on red blood cell AChE activity were observed at the low-exposure level. Exposure to 0.01 mg parathion/m^3 reduced red blood cell AChE activity by 21% by the end of the second week of exposure, but levels recovered to 86% of pre-exposure values by the third week of exposure and to 100% of pretest levels during the remaining of the exposure period. In the high-exposure group, red blood cell AChE activity was reduced between 26 and 46% during the first 5 weeks of exposure and inhibition reached a maximum of 41% of pre-exposure levels on week 6 of exposure. Slow recovery was evident during the post-exposure period, with complete recovery at 6 weeks in dogs exposed to 0.20 mg/m^3. Plasma cholinesterase activity was inhibited to a greater extent during the exposure period, but seemed to recover faster during the post-exposure period. Based on the fact that red blood cell AChE activity was depressed over 20% (21%) only on week 2 of exposure in the 0.01 mg/m^3 group, this exposure level is considered a NOAEL for neurological effects in dogs in an intermediate-duration study; the LOAEL was 0.2 mg/parathion/m^3.

Since only means without deviation parameters were reported for red blood cell AChE values, dose-responses using the benchmark dose approach could not be constructed to estimate points of departure from the rat and dog data. Therefore, a NOAEL/LOAEL approach was be used and the NOAEL of 0.01 mg parathion/m^3 for red blood cell AChE in rats was the point of departure for MRL derivation. Although the NOAEL was the same in both species, the data from the rat study was preferred over that from the dog study because a lower LOAEL was established in the rat study, there were 20 rats per group compared to 6 dogs per group, and more extensive data regarding cholinesterase inhibition have been collected in rats than in dogs. In addition, the data from dogs support the findings in rats.

Although NIOSH (1974) stated that particle size was determined by the use of a Rochester cascade impactor, no data regarding droplet size were located in the report available for review. In the absence of droplet size data, a dosimetric adjustment could not be performed to estimate a human equivalent concentration. Therefore, the MRL was derived by applying an uncertainty factor of 100 (10 for animal to human extrapolation and 10 for human variability) to the duration-adjusted NOAEL (0.01 mg/m^3 x 7 hours/24 hours x 5 days/7 days x 1/100). This yielded an intermediate-duration inhalation MRL of 20 ng/m^3 for parathion.

A chronic-duration inhalation MRL was not derived for parathion. No chronic-duration inhalation studies in humans or animals exposed to parathion were located. It is possible that in the study of workers exposed to parathion conducted by Brown and Bush (1950) summarized above, some workers could have been exposed for over a year.

Oral MRLs

An acute-duration oral MRL was not derived for parathion for the reasons discussed below. Data regarding inhibition of red blood cell AChE activity in short-term studies, including a 5-day exposure study in volunteers (Morgan et al. 1977), were not considered for MRL derivation for the reasons previously discussed regarding an acute-duration inhalation MRL for parathion. The decision is based on the fact that studies of cholinesterase inhibition have shown that it takes approximately 21–28 days for inhibition of cholinesterase activity to reach a steady state, and that values obtained in single-dose or short-duration studies carry great uncertainty. In addition to data on blood cholinesterase activity, intermediate-duration oral studies in animals provided information on systemic effects (mostly body weight), developmental effects, and effects on the immune system. Acute oral developmental studies in rats and rabbits reported NOAEL values of 1 and 0.3 mg parathion/kg/day, respectively, the highest doses tested (Renhof 1984, 1985). A study in mice identified a relatively low LOAEL of 0.15 mg parathion/kg/day for increased sensitivity to allergens (Fukuyama et al. 2011); that dose was the lowest dose tested. Another study from the same group of investigators found that mice dosed with 1.5 mg parathion/kg/day for 5 days exhibited decreased IgM antibody plaque-forming cells in response to sheep red blood cell (SRBC) antigen; the NOAEL was 0.15 mg parathion/kg/day (Fukuyama et al. 2012). Other studies had reported similar effects, but had tested higher doses (Casale et al. 1983, 1984; Kim et al. 2005; Wiltrout et al. 1978). The plaque-forming cell assay is a widely used test of immuno-competence, specifically humoral-mediated immunity, and has been shown to be a sensitive target of toxicity. This

end point has been used to derive MRLs for various chemicals (Abadin et al. 2007) and could have been considered for derivation of an acute-oral MRL for parathion. However, as explained below, an intermediate-duration oral study in humans (Rider et al. 1969) identified a LOAEL of 0.11 mg parathion/kg/day and a NOAEL of 0.09 mg parathion/kg/day for red blood cell AChE inhibition. The NOAEL of 0.09 mg parathion/kg/day is lower than the LOAEL for increased sensitivity to allergens (0.15 mg/kg/day) and decreased humoral-mediated immunity (1.5 mg/kg/day) identified in the Fukuyama et al. (2011, 2012) studies. Because human data are preferred over animal data, and because an intermediate-duration oral MRL based on the human NOAEL would be protective of the immunological effects reported in the acute-duration studies in mice, the immunological data were not used for derivation of an acute-duration oral MRL for parathion.

- An MRL of 0.009 mg/kg/day has been derived for intermediate-duration oral exposure (15–364 days) to parathion based on neurological effects in humans.

Two intermediate-duration oral studies in volunteers provide information on red blood cell AChE activity in humans during exposure to parathion. The first study identified a NOAEL of 0.1 mg parathion/kg/day (the highest dose tested) for red blood cell AChE activity in female volunteers administered the pesticide orally for 6 weeks; no further information regarding red blood cell AChE was provided (Edson 1964). The second human study identified a NOAEL of approximately 0.09 mg parathion/kg/day for red blood cell AChE activity in male volunteers administered the pesticide in a capsule for 30 days (Rider et al. 1969). The intermediate-duration oral studies in animals provided information on body weight, neurological effects, immunological effects, and reproductive and developmental effects. The lowest LOAEL for neurological effects was 0.047 mg parathion/kg/day for a 25% inhibition of red blood cell AChE in dogs in a 24-week dietary study; the NOAEL was 0.021 mg/kg/day (Frawley and Fuyat 1957). In another study in dogs, doses of 0.5 mg parathion/kg/day in a capsule reduced red blood cell AChE activity 25–58% during a 6-week treatment period followed by a 6-week recovery period; the NOAEL was 0.1 mg/kg/day (NIOSH 1974). Two studies in rats dosed for several weeks identified LOAELs of 0.1 mg parathion/kg/day for red blood cell AChE; the NOAELs were 0.024 and 0.05 mg parathion/kg/day (Ivens et al. 1998; NIOSH 1974). An intermediate-duration oral study in monkeys identified a LOAEL of 0.1 mg parathion/kg/day (the only dose tested) for altered auditory detection behavior; no measurements of enzyme activities were conducted in this study (Reishchl et al. 1975). Increased sensitivity to allergens was reported in a study in mice exposed to ≥0.15 mg parathion/kg/day for 56 weeks (Nishino et al. 2013). Data on reproductive effects are limited to a study in male rats in which daily gavage administration of 2.6 mg parathion/kg/day (only dose tested) for 90 days caused tubular atrophy in the testes, necrosed spermatogenic cells, and enlargement of the interstitial space of the testes (Dikshith et al. 1978). The only

developmental study available for review reported a considerably lower LOAEL of 0.01 mg parathion/kg/day (the lowest dose tested) for altered EKGs in 24-day-old pups from rats dosed from day 2 of gestation through day 15 of lactation (Deskin et al. 1979). Since this is not a developmental end point routinely tested in guideline developmental studies, it would be helpful to try to replicate these results before it could be considered for MRL derivation.

The available intermediate-duration oral studies suggest that in humans, rats, and dogs, significant inhibition (>20%) of red blood cell AChE activity occurs with repeated doses ≥0.1 mg parathion/kg/day. In the Frawley and Fuyat (1957) study, red blood cell AChE activity was depressed approximately 25% in dogs dosed 0.047 mg parathion/kg/day for 12 weeks, but appeared to increase to near 90% of pretest values on week 16 of exposure. Another study in dogs showed that a constant inhibition of the enzyme of >20% could be achieved only with repeated doses of 0.5 mg parathion/kg/day (NIOSH 1974). Since utilizing human data will reduce the uncertainty over using animal data, the study of Rider et al. (1969) in volunteers was selected for derivation of an intermediate-duration oral MRL for parathion.

In the Rider et al. (1969) study, five male volunteers were administered 3, 4.5, 6, or 7.5 mg parathion/day in a capsule (0.04, 0.06, 0.09, and 0.11 mg/kg/day assuming 70 kg body weight) for approximately 30 days; two additional subjects served as controls. Although not explicitly stated in the paper, it appeared that all of the subjects were exposed to all of the doses. In a pretest period of 30 days, blood was collected to establish baseline levels of plasma cholinesterase and red blood cell AChE. The subjects were also monitored during a post-test period of about 30 days. At the beginning of the pretest period, routine blood counts, urinalysis, and prothrombin time were performed, and these were repeated at the end of each test period. Doses of 0.04 or 0.06 mg parathion/kg/day did not affect the levels of either enzyme. Administration of 0.09 mg parathion/kg/day caused a slight depression of plasma cholinesterase (data not provided). Doses of 0.11 mg parathion/kg/day induced a 27% decrease in the plasma enzyme in one subject on day 4. On day 9, two subjects showed 36 and 32% inhibition of the plasma enzyme. On day 16, the levels of plasma cholinesterase in these two subjects were 50 and 52% of pretest levels, and parathion dosing was discontinued. In the other three subjects, plasma cholinesterase levels were 97, 82, and 69% of pretest levels. On day 16, the mean levels of plasma cholinesterase in the five exposed subjects was reduced by 28% from the control value. In two subjects who received parathion during 35 days, the lowest plasma cholinesterase levels were 86 and 78% of their pretest values. Red blood cell AChE activity in the three subjects who discontinued the parathion dosing achieved maximal inhibition levels of 63, 78, and 86% of pretest levels. In the two subjects who completed the test period, there was no significant effect on red blood cell AChE activity. By the end of the post-test period, both enzymes

had returned to pretest levels. No information was provided regarding blood counts, urinalysis, or prothrombin test results. Based on a >20% inhibition of red blood cell AChE activity in two out of five subjects for 16 days, the dose of 0.11 mg parathion/kg/day is a LOAEL for neurological effects; the next lower dose, 0.09 mg parathion/kg/day, is a NOAEL. Benchmark dose analysis could not be performed because the data were not presented as means plus or minus a measure of dispersion such as standard deviation or standard error of the mean. The intermediate-duration oral MRL for parathion was derived by dividing the NOAEL of 0.09 mg parathion/kg/day by an uncertainty factor of 10 (to account for human variability); this yielded an MRL of 0.009 mg parathion/kg/day (9 µg/kg/day).

A comparison of the intermediate-duration inhalation (20 ng/m^3) and oral (9,000 ng/kg/day) MRLs for parathion suggests that there may be a relatively large difference (perhaps as large as 3 orders of magnitude) in the exposure dose between these two route-specific MRLs. This could be due, in part, to differences in study design, as well as species- and route-specific differences in parathion toxicokinetics and toxicodynamics. For example, dose spacing in the rat inhalation study resulted in a 10-fold difference between the NOAEL and the LOAEL, compared to a 0.12-fold difference in the human oral study—a difference equivalent to almost 2 orders of magnitude. The lack of absorption data in humans and rats for the inhalation and oral routes of exposure and limited species-specific toxicodynamics data preclude making a direct comparison of MRL values. Although our understanding of the differences in rat and human toxicokinetics to parathion is as yet incomplete, the currently available information indicates that both of these MRLs should be adequately protective of human health.

A chronic-duration oral MRL was not derived for parathion. No chronic-duration oral studies with parathion in humans were located, and the available animal studies were inadequate for MRL derivation. In an early dietary study in rats, administration of up to approximately 1.7 mg parathion/kg/day for 365 days did not induce adverse clinical signs (Barnes and Denz 1951). Histological examination of the major organs and tissues from 14 out of 70 rats did not show treatment-related alterations. In another chronic-duration study, exposure of rats to up to 4.4 mg parathion/kg/day or of mice to up to approximately 27.6 mg parathion/kg/day did not result in gross or microscopic alterations in the brain (NCI 1979). In the NCI (1979) study, the investigators noted that during the first half of the second year, clinical signs among dosed rats appeared at a low or moderate incidence, and during the second half of the year, they increased. However, no quantitative data were presented. In addition, the investigators mentioned that by week 60 of the study, all high-dose male mice (approximately 27.6 mg parathion/kg/day) showed signs of hyperexcitability, but no data were shown. Furthermore, none of these studies monitored AChE activity.