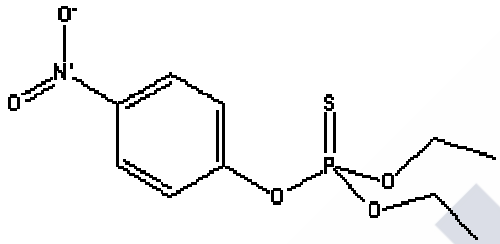
PARATHION

CAS number: 56-38-2

Synonyms: Bladan®; O,O-Diethyl O-p-nitrophenyl phosphorothioate; DNTP; Ethyl parathion: Paraphos®; Alkron®; Alleron®; Aphamite®; Etilon®; Folidol®; Fosferno®; Niram®; Parapos®; Rhodiatos®

Molecular formula: $C_{10}H_{14}NO_5PS$

Structural formula:



TLV–TWA, 0.05 mg/m^3, Inhalable aerosol and vapor

Skin

A4 — Not Classifiable as a Human Carcinogen

Summary

Parathion is a broad-spectrum organophosphate pesticide and miticide. The first biologic response to parathion involves decreased activity of cholinesterase enzymes. In animal studies with varying endpoints, adverse effects were seen with oral doses ranging from 0.5 to 6 g/kg. In humans, levels of 0.1 mg/kg or below were not associated with decreases in red blood cell (RBC) cholinesterase activity. Workplace exposures of 0.2 to 0.8 mg/m^3 were associated with decreases in RBC cholinesterase activity. This suggests that a dose of 0.05 mg/kg, considered equivalent to an inhalation exposure of 0.35 mg/m^3, would not produce this effect and would protect against this and all other adverse biologic effects. Thus, a TLV–TWA of 0.05 mg/m^3 (inhalable aerosol and vapor) is recommended for occupational exposure to parathion. This exposure limit is intended to prevent the occurrence of cholinergic symptoms and other adverse biologic effects in workers. It is derived from a no-observed-adverse-effect level (NOAEL) obtained in humans and corresponds to a dose that is not expected to result in any reductions in RBC acetylcholinesterase activity in a group of workers. This approach is consistent with the use of the Biological Exposure Index, which is used to ensure that significant RBC acetylcholinesterase inhibition does not occur in a single user. A Skin notation is assigned since dermal exposures in humans have been associated with clinical signs of response up to and including death. Lifetime feeding studies in rats did not produce a clear increase in tumors; hence, parathion is given an A4, Not Classifiable as a Human Carcinogen, designation. Sufficient data were not available to recommend a TLV–STEL or a sensitization (SEN) notation. To aid in monitoring occupational exposure to parathion, see the *BEI® Documentation* on Acetylcholinesterase Inhibiting Pesticides.

Chemical and Physical Properties

Parathion is a pale yellow liquid with a faint odor of garlic at temperatures above 6°C.[1] Parathion hydrolyzes slowly at pH 7 or below but is otherwise stable at normal temperatures. At temperatures above 120°C, parathion decomposes and may develop enough pressure to cause containers to explode. Thermal decomposition may release toxic gases such as diethyl sulfide, sulfur dioxide, carbon monoxide, carbon dioxide, phosphorus pentoxide, and nitrogen oxides.[2] Chemical and physical properties include:[2,3]

- Molecular weight: 291.27
- Specific gravity: 1.26 at 25°C
- Melting point: 6°C
- Boiling point: 375°C at 760 torr
- Vapor pressure: 3.78×10^{-5} torr at 20°C
- Solubility: very slightly soluble in water (20 ppm); completely soluble in esters, alcohols, ketones, ethers, aromatic hydrocarbons, or animal and vegetable oils; insoluble in petroleum ether, kerosene, or spray oils
- Reactivity: stable in acids; hydrolyzes readily in alkaline solutions

Decomposition products: slowly decomposes in air to paraoxon

Conversion factors at 25°C and 760 torr:
1 mg/m^3 = 0.08 ppm; 1 ppm = 11.91 mg/m^3

Major Sources of Occupational Exposure

Parathion is a broad-spectrum pesticide and miticide with a wide range of applications on many crops against numerous insect species.[4,5] Reports of crop-worker exposures were widespread in the United States prior to voluntary cancellation of its use on over 80 crops in 1991.[2] In January 1992, the U.S. Environmental Protection Agency (EPA) canceled all uses of parathion on fruit, nut, and vegetable crops. The only uses continued are those on alfalfa, barley, corn, cotton, sorghum, soybeans, sunflowers, and wheat. In order to reduce exposures to agricultural workers, parathion may be applied to these crops by commercially certified aerial applicators and treated crops may not be harvested by hand.

Animal Studies

Literature pertaining to the toxicity of parathion in animals was summarized in a 1991 review.[1] Studies submitted in 1998 to the U.S. EPA to support re-registration were summarized and made public in 1999.[6] An addition review of these toxicity studies may be found on the EPA Integrated Risk Information System Integrated Risk Information System (IRIS) website.[7]

Acute

Parathion is a highly toxic organophosphate. Oral LD_{50} values in rats ranged from 3 to 6 mg/kg for females and from 7 to 30 mg/kg for males.[8,9] Thus, female rats were more sensitive to acute parathion toxicity than males. Oral LD_{50} values in male and female mice and guinea pigs ranged from 14 to 32 mg/kg, with no gender difference in sensitivity.[1,10]

When rats were given single oral doses of 0, 0.025, 2.5, or 10.0 mg/kg/day (males) or 0, 0.025, 0.5, or 2.5 mg/kg/day (females),[6] the males given 10 mg/kg exhibited mortality, cholinergic toxicity, and significantly decreased plasma, RBC, and brain cholinesterase activity; males given 2.5 mg/kg had significantly decreased plasma and RBC cholinesterase and RBC cholinesterase activity only. Females in the 2.5-mg/kg showed lethality or cholinergic effects and significant inhibition of plasma, RBC, and brain cholinesterase. The peak effect occurred at four hours with partial to full recovery noted by 14 days.

A single-dose oral exposure at 6 mg/kg parathion caused deficits in passive avoidance learning in mice and 50% depression in brain and RBC acetylcholinesterase activity after 0.5 hour, while subcutaneous exposures at 1, 2, or 4 mg/kg/day for 6 days had no effect on this type of behavior, despite a 76% decrease in brain and RBC acetylcholinesterase activity.[11] Similarly, among rats administered 1.5, 2.5, or 4.5 mg/kg/day every other day on days 1 to 5, 7 to 13, and 15 to 21, respectively, no sign of cholinergic over-stimulation was reported, despite a 69% inhibition of plasma and 84% to 91% inhibition of brain cholinesterase.[12]

Rats administered single oral doses of 2, 3.5, or 5 mg/kg parathion showed significantly altered conditioned taste aversion behavior even though plasma or brain cholinesterase activities were significantly inhibited at 3.5 and 5 mg/kg only.[13] A single oral dose of 2.0 mg/kg in monkeys led to clinical signs of toxicity, but 1.5, 1.0, or 0.5 mg/kg did not.[14] Performance on a visual discrimination task, however, was disrupted at 1 mg/kg and was associated with about a 40% inhibition of blood acetylcholinesterase activity.[14]

Parathion is highly toxic via dermal exposure. Dermal LD_{50} values were 21 and 7 mg/kg for male and female rats, respectively, when parathion was applied to their shaved backs.[8,9] The dermal LD_{50} was 400 mg/kg for mice whose feet were dipped in parathion.[15] Approximate 6-hour lethal dermal doses to the rabbit ranged from 150 to 2800 mg/kg, depending on the formulation.[16]

Intraperitoneal LD_{50} values were 3 to 7 mg/kg in adult rats and mice but was 1 mg/kg in neonates.[17] Subcutaneous maximum tolerated doses of 2 and 18 mg/kg were reported in neonate and adult mice, respectively.[18]

The acute toxicity of parathion is apparently enhanced by a low protein diet. The intraperitoneal LD_{50} was 1.2 mg/kg in rats fed a 5% casein diet, but it was 2.0 mg/kg among rats fed 20% casein and 1.6 mg/kg among rats fed a 20% casein diet and pair-fed to the 5% casein diet group.[19]

A 4-hour LC_{50} of 32 to 84 mg/m^3 was reported in rats.[20] Two-hour exposures at 3 to 4 mg/m^3 of a spray of commercial parathion were lethal in the female rat.[16] Depending on the primary route of exposure, lethal doses were first associated with either local contractions, diarrhea, and urination or increased respiration, respiratory congestion, and contraction of the pupils. With dermal exposure, death is often delayed. In rabbits, an intermediate-type syndrome occurred, characterized by paralysis affecting the muscles of the neck and the extensor muscles of the forelegs.[16] Initial symptoms were followed by unsteadiness, lack of coordination, generalized muscular twitches, and increased defecation, urination, lacrimation, and salivation. Severity of symptoms rapidly increased to prostration with generalized muscular fibrillations, body twitches, and tonic and clonic convulsions, followed by death due to respiratory failure.[1,21,22]

Toxic signs following single, sub-lethal exposure reflected less severe cholinergic stimulation. Among male rats given 0, 2, 4, or 7 mg/kg parathion via oral gavage in corn oil, tremors, ataxia, and 10%

mortality were observed in the 7-mg/kg group, while only decreased tail-pinch responsivity was observed in the 2-mg/kg group.[23]

Subchronic

For Sherman female rats given feed containing parathion for 90 days and observed until death, a 90-dose LD_{50} was calculated as 3.1 to 3.5 mg/kg/day.[24] Using the 90-dose LD_{50} and the single-dose LD_{50} of 3 to 4 mg/kg previously observed,[7] a "chronicity factor" (single-dose LD_{50}/90-dose LD_{50}) of about 1 was calculated, indicating that parathion is not expected to exhibit a cumulative toxic effect.

In a subchronic neurotoxicity study, both sexes of rats given feed delivering 0.05, 1.25, or 2.5 mg/kg/day (females) or 0.05, 2.5, or 5.0 mg/kg/day (males) showed a statistically significant decrease in RBC cholinesterase activity at the lowest dose.[6]

A diet containing 125 ppm parathion (15.4 mg/kg/day) for 15 weeks caused severe illness, growth suppression, and death in rats as well as severe RBC, brain, and plasma cholinesterase inhibition (4%, 9%, and 10% of control, respectively).[25] A diet containing 25 ppm (2.4 mg/kg/d) was without overt toxic effects, but RBC, brain and plasma cholinesterase activities were 8%, 44%, and 89%, respectively, of control.[25] No adverse symptoms were observed among female rats fed diets containing 0.05, 0.5, or 5.0 ppm parathion (about 0.005, 0.05, or 0.5 mg/kg/day) for 84 days; however, RBC cholinesterase activity was depressed in the 0.05- and 0.5-mg/kg/day groups.[26] Plasma cholinesterase activity was slightly inhibited at 0.5 mg/kg/day, but brain cholinesterase activity was unaffected at any exposure level.

Groups of five rats and five mice of each sex were given diets containing 5, 10, 20, 40, 80, 160, or 320 ppm for 6 weeks, while only the mice continued with 640 or 1280 ppm parathion for the same period.[27] All exposure groups were then observed for an additional 2 weeks. In rats, 5 to 40 ppm parathion was without effect, but diets of 80 ppm or more in females, 160 ppm or more in males, and 320 ppm or more in mice were associated with decreased body weight and increased mortality.

Ocular toxicity was assessed in dogs exposed 7 days/week for 6 month at 0.02, 0.08, or 8 mg/kg/day parathion via gelatin capsule.[28] At 8 mg/kg/day, plasma cholinesterase activities were 21% to 25% of control levels from week 1 and continued until week 26; RBC cholinesterase activities were 78% to 87% of control levels from week 6 to week 26, while retinal cholinesterase was 45% to 63% of control levels at week 26. However, no ocular toxicity or cholinergic signs were detected at any dose.

Chronic/Carcinogenicity

Four groups of beagle dogs were given feed delivering parathion doses of 0, 0.01, 0.03, or 0.10 mg/kg/day for 12 months.[6] Cholinergic toxicity was not observed. Plasma and RBC cholinesterase activity was sporadically, but significantly depressed at all dose levels at 2 and 12 months, but not at 4 months. Brain cholinesterase was only statistically decreased in dogs given 0.03 mg/kg/day.

Beagle dogs (5/sex/dose) were orally dosed by capsule with parathion at 0, 0.0024, 0.079, or 0.7937 mg/kg/day for 6 months.[6] Dogs given 0.7937 had significantly decreased plasma, RBC, and brain (males only) cholinesterase activity; female dogs given 0.079 mg/kg/day had reduced plasma cholinesterase activity only.

Groups of ten male rats were given feed containing 10 or 25 ppm parathion for 88 weeks or 50 ppm (3 mg/kg/day) or 100 ppm (6 mg/kg/day) parathion for 104 weeks. Additional groups of female rats were given feed containing 10 or 50 ppm for 64 weeks, and some female rats were given feed containing 100 ppm for an unstated period of time.[29,30] Rats fed the 100-ppm diet occasionally showed peripheral tremors and irritability during the first few weeks but were later normal. Females were more seriously affected than males. At 50 ppm, the rats were normal throughout the experiment. No tumors were observed in either sex at any exposure level.[29]

Groups of 36 female and male rats were given food containing 10, 20, 50, 75, or 100 ppm parathion once a day for 1 year.[31] At the 75 or 100 ppm levels, rats experienced serious effects so that exposures were discontinued on days 19 and 27, respectively. Rats fed diets containing 50 ppm parathion exhibited much less severe poisoning and were maintained on the diet for 365 days. Sizable mortality occurred in the 50-, 75-, and 100-ppm groups. No signs of poisoning occurred in either the 10- or 20-ppm groups. (The 20- and 50-ppm diets resulted in exposures of about 1 and 3 mg/kg/day.)

The U.S. National Cancer Institute (NCI) conducted a bioassay of parathion in male and female B6C3F1 mice and Osborne–Mendel rats.[27] Mice were fed diets containing 80 or 160 ppm parathion (equivalent to about 12 and 23 mg/kg/day) for 62 to 80 weeks and were observed for an additional 9 to 28 weeks. Tremors, alopecia, abdominal distension, diarrhea, and hyperexcitability were noted in mice of both sexes at both exposure levels. Male rats were fed diets averaging 32 and 63 ppm for 13 or 67 weeks, while the female rats were fed diets averaging 23 or 45 ppm for 13, 21, or 46 weeks (equivalent to approximately 1.3 or 2.6 mg/kg/day). All rats were observed for an additional 32 weeks. Generalized body tremors and diarrhea occurred, especially at the higher dose. Male and female rats had an increase in adrenal cortical adenomas and carcinomas in the high-dose group. Most of these tumors were adenomas, as carcinomas occurred only in two rats of each sex and treatment group. Based on these results, the NCI concluded that parathion was not carcinogenic to B6C3F1 mice but that the evidence for carcinogenicity was equivocal in rats.[26] Noting that

exposure duration was less-than-lifetime, that adrenal cortical adenomas sometimes spontaneously arise in aged rats, and that most tumors were carcinomas rather than adenomas, the International Agency for Research on Cancer (IARC)[32] concluded that these data provided inadequate evidence to evaluate the carcinogenicity of parathion in animals.

In another study, 60 male and 60 female Sprague–Dawley rates per exposure group were maintained on diets containing 0, 0.5, 5.0, or 50 ppm parathion for 100 (males) or 120 (females) weeks. The mortality in the 5-ppm males was increased between months 7 and 23, but mortality in all groups was comparable to controls at termination. The maximum tolerated dose was slightly exceeded at the high dose in this study, but no compound-induced oncogenic response was observed.[7]

Genotoxicity

The genotoxicity of parathion was reviewed in 1983 by IARC.[32] The following discussion is based on that review.

Parathion was negative in the *rec*$^-$ assay (differential killing assay utilizing H17 *rec*$^+$ and M45 *rec*$^-$ strains of *Bacillus subtilis*) and the *Escherichia coli* Pol-assay without metabolic activation. In a large number of tests, it did not induce gene mutations in *E. coli, Salmonella typhimurium, Serratia marcescens, Saccharomyces cerevisiae*, or *Schizosaccharomyces pombe*, with or without metabolic activation.

No excess of sex-linked recessive lethal mutations was induced in *Drosophila melanogaster* by parathion. Negative results have also been reported for the induction of unscheduled DNA synthesis by parathion in WI38 human fibroblasts, with or without uninduced mouse liver microsomal fractions. No dominant lethal mutation was induced in mice fed parathion for 7 weeks at 62.5, 125, or 250 mg/kg of diet or following a single intraperitoneal injection.

Reproductive/Developmental Toxicity

When groups of pregnant New Zealand white rabbits were gavaged with parathion at doses of 0, 1, 4, or 16 mg/kg on gestational days 7 through 19, mortality occurred and body weight gain was decreased in the 16-mg/kg dosed dams.[6] A nonstatistically significant decrease in litter size occurred at the 16-mg/kg level, including the dams given 1 or 4 mg/kg.

When groups of pregnant Sprague–Dawley rats were gavaged with parathion at doses of 0, 0.25, 1.0, or 1.5 mg/kg on gestational days 6 through 19, mortality occurred and body weight gain was decreased in the 1.5-mg/kg dosed dams.[6] No fetotoxic effects were observed at any dose.

In a two-generation study, four groups of Sprague–Dawley rats were given feed containing 0, 1, 10, or 20 ppm parathion (equivalent to 0, 0.05, 0.5, or 1.0 mg/kg/day).[6] In the F_0 generation, plasma, RBC, and brain cholinesterase activity were decreased in females given the 10- or 20-ppm diet and in males given the 20-ppm diet. In the F_1 generation, reduced body weight and body weight gain occurred in pups fed the 20-ppm diet, and reduced RBC and brain cholinesterase activity occurred in the female adults fed the 20-ppm diet. No effects were observed in the F_2 generation, nor were any reproductive effects seen throughout the study.

A two-generation study with rats fed 10 ppm parathion in the diet for 93 days showed that parathion interfered with both reproductive process and developmental viability.[31] The 24-day old progeny of spontaneously hypertensive rats given 0.01, 0.1 or 1.0 mg/kg/day parathion orally from day 2 of pregnancy through day 15 of lactation had reduced plasma cholinesterase and/or decreased heart ratio.[33]

Conception and litter size were not affected in wild rabbits given two oral 8 mg/kg doses of parathion 30 days apart, although brain acetylcholinesterase activity was reduced by 30% and dosed animals had lower perirenal and kidney fat weights.[34]

Intraperitoneal injection of pregnant Swiss–Webster mice with 4, 8, 10, 11, or 12 mg/kg parathion in corn oil on gestational days 12, 13, and 14 caused increased resorptions and a significant reduction in fetal weight at doses of 8 mg/kg and above. The highest dose was associated with 90% fetal mortality. With the lowest dose, fetal body weight was reduced, although the incidence of resorptions was normal.[35] Intraperitoneal injection of 10 mg/kg on gestational days 8, 9, and 10 had no impact on fetal weight. Intraperitoneal injection of pregnant rats with 3 or 3.5 mg/kg parathion on gestational day 11 produced increases in resorptions, decreased fetuses/litter, reductions in fetal and placental weight, and maternal toxicity.[20] Subcutaneous injection of pregnant rats for 4 days during the first, second, or third trimester of gestation resulted in inhibition of brain acetylcholinesterase in dams, but not in pups, which however, had delays in development of the righting reflex.[36]

Dose-related decreases in acetylcholinesterase activity and muscarinic agonist binding occurred in cerebral cortex of 21- and 28-day-old rat pups treated subcutaneously with either 1.3 or 1.9 mg/kg/day parathion on postnatal days 5 to 20 compared with controls.[37] Rat pups given 0.882 mg/kg/day parathion subcutaneously on postnatal days 5 to 20 showed reduced acetylcholinesterase activity and muscarinic agonist binding at 12 days and cellular disruption and necrosis of the hippocampus at 21 days.[38] Neonatal rats were given subcutaneous injections of 0.5, 1.0, 1.5, or 2.0 mg/kg parathion on postnatal days 8 to 20, and developmental effects were assessed at various days of age from postnatal day 10 to day 36.[39] A

dose of 0.5 mg/kg had no effect on neonatal rats; doses of 1.0, 1.5, and 2.0 mg/kg caused mild tremors, brain acetylcholinesterase inhibition, decreases in body weight gain and muscarinic receptor density, and mortality.[39]

Absorption, Distribution, Metabolism, and Excretion

Absorption/Distribution/Elimination

Few studies were available quantifying pharmacokinetics following inhalation exposure. However, absorption, distribution, metabolism, and elimination were presumably rapid and complete as evidenced by the results of studies where parathion was administered intravenously, a route of exposure with distribution and excretion characteristics similar to inhalation since it allows parathion to bypass the extensive "first pass" metabolic effect of the liver. In humans, 46% of an intravenous dose (amount not specified) was excreted in urine by 120 hours, and an elimination half-life of 8 hours was observed.[40] Intravenous administration of 5 mg/kg parathion to dogs demonstrated high serum protein binding, a very high liver extraction ratio (82%–97%), rapidly decreasing serum levels, and rapid excretion with 85% to 92% of the dose excreted in urine by 14 hours.[41] A plasma half-life of 8.5 to 11.2 hours was determined in another experiment.[42] In atropinized rats, parathion was rapidly distributed to tissues (brain, fat, liver) and eliminated from blood following intravenous administration of 3 mg/kg; the elimination half-life was 3.4 hours.[42] Absorption, distribution and elimination were also rapid in rabbits given intravenous doses of 1.5 mg/kg parathion.[43]

The plasma concentration time curve followed a three-compartment kinetic model, with two very rapid distribution phases (elimination rate constants of about 30 and 3 hr^{-1}, respectively) followed by a final slower disposition phase (elimination rate constant of 0.2 hr^{-1}), with a β elimination half-life of 5.3 hours. Maximal cholinergic effects, including one death, occurred 10 to 20 minutes after injection. These results were consistent with observations in 8-week-old pigs given a nontoxic intravenous dose of 0.5 mg/kg ^{14}C-parathion.[44] In this case, plasma concentration time curves were consistent with both a two- and three-compartment model, and a model-independent elimination rate constant of 0.0771 min^{-1} was determined. By 3 hours after dosing, parathion was generally distributed, and about 82% of the dose had been eliminated in urine. Elimination rate constants and urinary excretion of metabolites were much lower in newborn (1 to 2 days old) and neonatal (1 week old) pigs administered the same dose, and parathion tended to accumulate in newborn and neonatal tissues to a much greater extent than in the 8-week-old pigs, providing a basis for the apparent sensitivity of developing mammals to parathion.[17,18]

Absorption was also rapid following oral exposure, but because of extensive hepatic metabolism, the volume of distribution was smaller, elimination rate constants were greater, and the β elimination half-life was smaller compared to intravenous exposure. The plasma concentration time curve in rabbits given 3 mg/kg parathion orally was consistent with a two-compartment model and was characterized by α and β elimination rate constants of about 5.2 and 0.7 and 0.1 hr^{-1}, respectively, and a β elimination half-life of about 0.3 hour.[43] Urinary excretion was rapid, accounting for 46% and 85% of the administered dose 3 and 6 hours after exposure, respectively, and was directly correlated with levels of parathion in plasma.[45] Maximum cholinergic effects were slightly delayed compared to intravenous administration, occurring 30 to 90 minutes after oral dosing. Similar results were observed in dogs given 10 mg/kg and in mice given 1 mg/kg parathion orally.[46,47]

Rapid absorption, metabolism, and elimination of parathion following oral exposure were confirmed in human volunteers given single oral doses of 1 to 2 mg parathion for 5 consecutive days.[48] Metabolites detected in urine 24 hours after dosing included para-nitrophenol, diethylphosphate, and diethyl thiophosphate. Excretion of the primary metabolite, p-nitrophenol, was 60% complete in 4 hours and 86% complete in 8 hours and was directly correlated with exposure. Urinary excretion of diethyl phosphate was more prolonged, reaching maximum rates 4 to 8 hours after ingestion.

Dermal absorption of parathion is extensive and has been the major cause of occupational poisonings (*see* the Human Studies section below). Humans absorbed about 20% to 30% of a dermally applied emulsion of parathion (approximately 2.5 mg) after 300 minutes,[49] from 0.1% to 2.8% of parathion dermally applied using an absorbent pad,[50] and 10% of an applied dose of 4 $\mu g/cm^2$ in acetone.[40] In another study, 5 grams of 2% parathion dust was placed on the right hand and forearm of a volunteer for 2 hours, after which the hand and arm were thoroughly washed, and urinary p-nitrophenol was monitored for 40 hours.[51] Dermal absorption was indicated by increases in urinary p-nitrophenol which peaked after 5 to 6 hours and decreased to very low levels within 40 hours. Marked differences in dermal absorption, depending on the anatomic site of exposure, were observed among six men who were dosed with 4 $\mu g/cm^2$ ^{14}C-parathion on 13 different locations and requested not to wash the site of application for 24 hours.[52] After 5 days, the following percentages of applied dose had been absorbed from each anatomic site tested: forearm, 9%; palm, 12%; ball of the foot, 14%; abdomen, 18%; back of the hand, 21%; jaw angle, 34%; post-auricular area, 34%; forehead, 36%; axilla, 64%; and scrotum, 102%. Maximum rates of absorption occurred 1 to 2 days after exposure, but were still significant 5 days after exposure.

Location-specific absorption rates were

observed in pigs:[53] 30% to 50% for occluded skin and 8% to 25% for nonoccluded skin, depending on site of application. Times of maximum excretion were 8 to 13 hours for occluded skin and 12 to 17 hours for nonoccluded skin. Rats treated dermally with 1.7 to 2.0 mg/kg (44–48 μg/cm^2) ^{14}C-parathion reached steady-state and absorbed 1.4% of the applied dose within 1 hour and 57% to 59% of the applied dose over a period of 168 hours.[54] The skin absorption rates were 0.33 and 0.49 μg/hour/cm^2 and the permeability constants were 7.5×10^{-3} and 1.0×10^{-2} cm/hour for males and females, respectively. Absorbed parathion was rapidly distributed to heart, liver, and kidneys. Plasma concentration time curves indicated elimination half-times of 39.5 and 28.6 hours for males and females, respectively. Mice absorbed nearly 100% of a 1 mg/kg dose of parathion to a 1 cm^2 area on their shaved backs by 2 days after treatment.[55] Eight hours after treatment, nearly 50% of the absorbed dose was excreted in urine and the rest was generally distributed.

Once absorbed, parathion is widely distributed, regardless of route of exposure. Distribution of parathion in blood, liver, adipose tissue, muscle, and brain was determined from 4 hours to 20 days after oral dosing of rats, and coefficients of distribution (blood concentration/tissue concentration) were derived for each organ.[56] Distribution coefficients were greatest in the liver (4.1–20.8) and adipose tissue (1.3–2.9), but it also exceeded 1.0 in the brain (1.0–1.4) and muscle (1.5–1.9), indicating retention of parathion by these tissues. Maximum concentrations in all tissues were reached 10 to 20 days after dosing. Extensive distribution of parathion to the liver was also demonstrated in mice following intraperitoneal, subcutaneous, oral, or dermal exposure[47,55,57,58] and in pigs following intravenous exposure,[44] consistent with its rapid hepatic metabolism and high affinity for hepatic esterase.[59,60] Distribution of parathion in fetuses has not been studied, although its placental transfer has been demonstrated *in vitro* using term perfused human placentas.[61]

Metabolism

Parathion is converted to paraoxon by cytochrome P-450 microsomal enzymes (primarily CYP3A4, but possibly also CYP1A2 and CYP2B6,[62,63] but binding to other cytochromes and their inactivation also occurs (e.g., CYP3A2, CYP2C11). Alternatively, parathion is dearylated to form diethyl phosphorothioic acid and para-nitrophenol in a reaction catalyzed by microsomal enzymes or hydrolyzed by paraoxonase (also termed A-esterase) to form O-ethyl-O-para-nitrophenyl thiophosphate.[59] p-Nitrophenol, the primary dearylation metabolic product formed from parathion, is eliminated in the urine, and its quantification provides an index of parathion exposure.[64] These metabolic conversions occur primarily in the liver but also occur in the lung and brain,[58,59,62,65] and a significant "first pass" metabolic effect in skin has been demonstrated.[66]

Differences in hepatic esterase binding and dearylation rates have been implicated as contributing to the greater sensitivity of female rats to parathion toxicity compared to male rats,[67–69] to the greater sensitivity of some tissues (e.g., brain) to parathion toxicity compared to other tissues,[70] and to the greater sensitivity of young animals to parathion toxicity compared to adults.[71] Differences in the relative rates of parathion desulfuration, dearylation, hydrolysis, and esterase binding probably also contribute to interspecies differences in sensitivity to parathion toxicity; however, the primary factor accounting for interspecies differences appears to be species-specific differences in the affinity of acetylcholinesterase for paraoxon.[72–75] In human plasma, lactate protected acetylcholinesterase from inhibition by paraoxon.[76]

Interindividual differences in paraoxonase activity may contribute to the differences in human sensitivity to parathion. Because this enzyme is polymorphic in the human population, its expression is determined by two co-dominant alleles, representing high and low activity.[72,77,78] The low activity phenotype is apparently more common than the high activity phenotype. In a Southeast Asian population, 4% to 18 % of individuals expressed the high activity form.[77] In another population, 6% were homozygous for high activity, 42% were homozygous for low activity, and 53% were heterozygous.[78] Differences in baseline levels of plasma cholinesterase activity may also contribute to inter-individual differences in sensitivity.[79]

Human Studies

Case Studies/Poisonings

Symptoms of parathion poisoning in humans are similar to what is observed in animals, are characteristic of other organophosphate anticholinesterase inhibitors, are secondary to massive acetylcholinesterase inhibition, and reflect a consistent spectrum of cholinergic signs, although the time until onset of poisoning and the sequence of occurrence of cholinergic signs vary according to primary route of exposure.[80] Upon oral exposure, initial symptoms of poisoning usually occur within 1 to 2 hours and include headache, dizziness, nausea, and abdominal pain. Miosis, contractions, excess secretions, hyperactive bowels, and possibly blurred vision and ocular pain may follow and constitute a classic presentation of organophosphate poisoning often referred to as a "cholinergic crisis." Loss of reflexes and sphincter control, convulsions, and coma precede death, which is ordinarily due to respiratory failure. Massive oral exposures can cause death within 5 minutes. Exposure to a vapor or aerosol may first produce miosis, headache, and conjunctival hyperemia along with respiratory congestion, tightness and occasionally wheezing within 2 hours, followed by systemic cholinergic effects, while dermal exposure may first

produce muscular contractions after a delay of several hours.[80]

Estimates of lethal parathion exposures in adults range from 120 to 900 mg (about 2–13 mg/kg assuming 70 kg body weight) but are much lower in children, ranging from 0.1 to 1.3 mg/kg.[1] In cases where parathion-contaminated food was eaten by humans of different ages, death occurred mainly or exclusively among children.[1,81] The sensitivity of young animals to parathion is due, at least in part, to their relatively lower levels of detoxifying enzyme activity compared to adults.[71]

Plasma and RBC cholinesterase activities among 51 mild-to-moderately poisoned humans averaged 58% to 59% and 58% to 64% of normal levels, respectively, although some individuals showed essentially no cholinesterase inhibition.[71] Plasma and RBC cholinesterase activities among seven severe-to-fatal poisoning cases averaged 19% to 35% and 14% to 29% of normal levels, respectively, with all affected individuals exhibiting marked depression. Clinical symptoms in all moderately and severely poisoned individuals included gastrointestinal signs (abdominal pain, anorexia, diarrhea, nausea, vomiting), fatigue, malaise, miosis or visual disturbance, headache, diarrhea, and respiratory difficulty. Giddiness, ataxia, drowsiness, paresthesia, and loss of consciousness also occurred.

Some acutely poisoned individuals surviving a cholinergic crisis had symptoms consistent with an "intermediate syndrome" that began 2 days after recovery from an acute cholinergic crisis precipitated by ingestion of parathion[82–85] and included acute respiratory paresis, severe nystagmus, weakness in proximal limb muscles, and depressed tendon reflexes. These effects lasted for approximately 3 weeks and were not influenced by atropine.[81] Plasma and RBC cholinesterase activities ranged from 2% to 11% and 5% to 32% of normal values, respectively, for as long as this syndrome persisted. Five instances of "intermediate syndrome" were also reported in individuals ingesting or inhaling a combination of methyl parathion and parathion and were also accompanied by severe plasma (< 5% of mean control value) and RBC cholinesterase inhibition (< 15% of mean control value).[83,85] An intermediate syndrome was reported to be followed by axonal polyneuropathy in humans severely poisoned by ingestion of parathion.[86]

Observational Studies

Parathion levels in air during various operations in a manufacturing plant over a 6-month period ranged from 0.2 to 0.8 mg/m^3. RBC and plasma cholinesterase activities in 13 workers increased markedly 5 months after parathion manufacture ceased, suggesting that parathion exposure had depressed them in the first place.[87]

Field workers or pilots involved in spraying parathion on agricultural fields have had cholinesterase activities ranging from 60% to 70% of baseline and RBC activities ranging from 30% to 50% of baseline.[79,88,89]

Experimental Studies

Oral intake of 0.07 mg/kg produced no clinical signs of toxicity and 0.1 mg/kg produced uneasiness, warmth, tightness of the abdomen, and frequent urination with a 12% depression in whole-blood cholinesterase activity, while 0.4 mg/kg resulted in increased peristalsis, tightness of the chest and 47% cholinesterase activity inhibition in whole blood.[90]

Ten male volunteers given 0.003, 0.010, 0.025, and 0.050 mg/kg/day parathion in capsules sequentially for 3 days at each dose exhibited no signs or symptoms of toxicity at any dose. Plasma and RBC cholinesterase levels were monitored before, during, and after exposure and showed no effect except for a slight increase in plasma cholinesterase activity during treatment with 0.003 and 0.010 mg/kg.[91] Five men given 3.0, 4.5, 6.0, or 7.5 mg/day (0.04, 0.06, 0.08, or 0.10 mg/kg/day assuming a 70 kg body weight) for up to 30 days exhibited no clinical signs. Plasma cholinesterase activities in two individuals given 7.5 mg/day were 64% and 68% of pre-exposure levels by day 9 and had decreased to 50% and 52% of pre-exposure levels by day 15, at which time, exposure was discontinued. Plasma and RBC cholinesterase activity in all individuals recovered to pre-exposure levels by 37 days after cessation of exposure.[91,92] Women given 7.2 mg/day (0.1 mg/kg/day, assuming 60 kg body weight) orally, 5 days/week for 6 weeks exhibited no clinical signs but experienced a 16% decrease in RBC cholinesterase activity, a 27% decrease in plasma cholinesterase activity, and a 33% decrease in whole-blood cholinesterase activity,[26] while men given 1 or 2 mg/day orally for 5 days (0.01 or 0.03 mg/kg/day assuming 70 kg body weight) exhibited no clinical signs and no change in RBC or plasma cholinesterase activity,[48]

RBC and plasma cholinesterase activity were measured and correlated with urinary p-nitrophenol excretion for 112 hours following dermal exposure in an individual covered with 2% parathion dust and placed in a rubberized suit for 7 to 7 2 hours.[93] No signs or symptoms of toxicity were observed. Maximum depression of plasma and RBC cholinesterase activity occurred 12 to 24 hours from the start but did not exceed 56% or 16% depression, respectively.[93] The authors[94] estimated that 18.2 mg parathion had been absorbed over a period of 103 hours, which is equivalent to about 0.06 mg/kg/day assuming a 70 kg body weight.

To assess parathion toxicity and cholinesterase inhibition following inhalation exposures, a single volunteer was exposed to vapors generated from technical parathion spread over a 36-square-inch area and heated to 105° to 115°F, 30 minutes/day for 4 days.[94] No signs of toxicity were observed by day 4 of exposure, although RBC and plasma cholinesterase activities were 70% and 71% of pre-

exposure baseline activities, respectively. The authors estimated that 2.5 mg parathion had been absorbed each day over the 4-day period, an amount equivalent to about 0.04 mg/kg/day, assuming a 70-kg body weight. This is consistent with the occupational study noted above in which RBC cholinesterase activities rebounded 4 months after cessation of exposure to about 0.03 mg/kg/day.[87]

TLV Recommendation

A TLV–TWA of 0.05 mg/m^3 (inhalable aerosol and vapor) is recommended for occupational exposure to parathion. This exposure limit is intended to prevent the occurrence of cholinergic symptoms and other adverse biologic effects in workers. It is derived from a no-observed-adverse-effect level (NOAEL) obtained in humans and corresponds to a dose that is not expected to result in any reductions in RBC acetylcholinesterase activity in a group of workers. This approach is consistent with the use of the Biological Exposure Index, which is used to ensure that significant RBC acetylcholinesterase inhibition does not occur in a single user. Because the estimated saturated vapor concentration may significantly contribute to the exposure at the TLV–TWA and evaporative losses of collected particulate may occur during sampling, both the particulate and vapor phase concentrations should be considered and summed to determine total airborne concentration.

As summarized above, NOAELs for RBC acetylcholinesterase inhibition were below 0.1 mg/kg/day. Exposures of a small number of humans to about 0.03 or 0.08 mg/kg/day did not significantly inhibit RBC cholinesterase;[48,92] whereas, exposures to the slightly higher 0.1 mg/kg/day did.[26,92]

Dermal exposure to parathion is especially hazardous since workers are most likely to be significantly exposed via this route. Dermal absorption in humans can be very extensive[52] and has been associated with considerable numbers of fatalities due to massive acetylcholinesterase inhibition.[1] Hence, parathion is assigned a Skin notation, and any dermal exposure should be minimized. There are no data to suggest a Sensitization (SEN) notation is warranted.

There is no evidence that parathion exposure causes cancer in humans. However, because of equivocal evidence that it causes cancer in male laboratory rats,[27] it is assigned to the A4, Not Classifiable as a Human Carcinogen, category.

There is no specific BEI for chlorpyrifos. However, the reader may refer to the current *BEI Documentation* covering Acetylcholinesterase Inhibiting Pesticides for further information on biological monitoring.

TLV Basis® — Critical Effects

Cholinergic

TLV Chronology

1953 *proposed*: TLV–TWA, 0.1 mg/m^3
1955–present: TLV–TWA, 0.1 mg/m^3
1961–present: Skin notation
1976–1985: TLV–-STEL, 0.3 mg/m^3
1984 *proposed*: withdraw TLV–STEL
1986: TLV–STEL withdrawn
2000 *proposed*: TLV–TWA, 0.05 mg/m^3, Inhalable aerosol and vapor; Skin; A4, Not Classifiable as a Human Carcinogen
2003: TLV–TWA, 0.05 mg/m^3, Inhalable aerosol and vapor; Skin; A4

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