August, 1987

METHYL PARATHION

DRAFT

Health Advisory
Office of Drinking Water
U.S. Environmental Protection Agency

I. INTRODUCTION

The Health Advisory (HA) Program, sponsored by the Office of Drinking Water (ODW), provides information on the health effects, analytical methodology and treatment technology that would be useful in dealing with the contamination of drinking water. Health Advisories describe nonregulatory concentrations of drinking water contaminants at which adverse health effects would not be anticipated to occur over specific exposure durations. Health Advisories contain a margin of safety to protect sensitive members of the population.

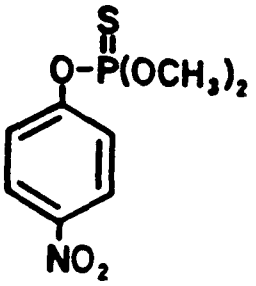
Health Advisories serve as informal technical guidance to assist Federal, State and local officials responsible for protecting public health when emergency spills or contamination situations occur. They are not to be construed as legally enforceable Federal standards. The HAs are subject to change as new information becomes available.

Health Advisories are developed for one-day, ten-day, longer-term (approximately 7 years, or 10% of an individual's lifetime) and lifetime exposures based on data describing noncarcinogenic end points of toxicity. Health Advisories do not quantitatively incorporate any potential carcinogenic risk from such exposure. For those substances that are known or probable human carcinogens, according to the Agency classification scheme (Group A or B), Lifetime HAs are not recommended. The chemical concentration values for Group A or B carcinogens are correlated with carcinogenic risk estimates by employing a cancer potency (unit risk) value together with assumptions for lifetime exposure and the consumption of drinking water. The cancer unit risk is usually derived from the linear multistage model with 95% upper confidence limits. This provides a low-dose estimate of cancer risk to humans that is considered unlikely to pose a carcinogenic risk in excess of the stated values. Excess cancer risk estimates may also be calculated using the One-hit, Weibull, Logit or Probit models. There is no current understanding of the biological mechanisms involved in cancer to suggest that any one of these models is able to predict risk more accurately than another. Because each model is based on differing assumptions, the estimates that are derived can differ by several orders of magnitude.

II. GENERAL INFORMATION AND PROPERTIES

CAS No. 298-00-0

Structural Formula



0,0-Dimethyl-0-(4-nitrophenyl) phosphorothioic acid

Synonyms

- Metron; Meptox; Metaphos; Dimethyl parathion; Nitrox; Azofos; Nitrox 80; BAY 11405; Metacide; Folidol M; Azophos; Methyl-E 605; Dalf; Meticide; Methylthiophos; Pencap M; Penncap M; Sinafid M-48; Wofotox; Vofatox; Thiophenit; Wofatox (Meister, 1983).

Uses

- A restricted-use pesticide for control of various insects of economic importance; especially effective for boll weevil control (Meister, 1983).

Properties (Hawley, 1981; Meister, 1983; CHEMLAB, 1985; TDB, 1985)

Chemical Formula	$C_8H_{10}O_5NSP$
Molecular Weight	263.23
Physical State (25°C)	White crystalline solid
Boiling Point	--
Melting Point	35 to 36°C
Density	--
Vapor Pressure (20°C)	0.97×10^{-5} mm Hg
Specific Gravity	--
Water Solubility (25°C)	55 to 60 mg/L
Log Octanol/Water Partition Coefficient	3.11 (calculated)
Taste Threshold	--
Odor Threshold	--
Conversion Factor	--

Occurrence

- Methyl parathion has been found in 1,402 of 29,002 surface water samples analyzed and in 25 of 2,878 ground water samples (STORET, 1987). Samples were collected at 3,676 surface water locations and 2,026 ground water locations, and methyl parathion was found in 22 states. The 85th percentile of all nonzero samples was 1.18 ug/L in surface water and 1 ug/L in ground water sources. The maximum concentration found was 13 ug/L in surface water and 1.6 ug/L in ground water.

Environmental Fate

- Methyl parathion (99% pure) at 10 ppm was added to sea water and exposed to sunlight; some samples were also kept in the dark (controls). After 6 days, 57% of the parent compound had degraded but the degradates were not identified. Since only 27% of the parent compound had degraded in the dark controls, this indicates that methyl parathion is subject to photodegradation in sea water (U.S. EPA, 1981).

- The degradation rate of two formulations (EC and MCAP) of methyl parathion, applied at 0.04 ppm, was compared in a sediment/water system. Degradates were not identified; however, the parent compound had a half-life of 1 to 3 days in water. In the hydrosoil plus sediment, methyl parathion applied as an emulsifiable concentrate formulation had a half-life of 1 to 3 days, whereas for the micro-encapsulated formulation, the half-life was 3 to 7 days (Agchem, 1983).

- Methyl parathion was relatively immobile in 30-cm soil columns of sandy loam, silty clay loam and silt loam soils leached with 15.7 inches of water, with no parent compound found below 10 cm or in the column leachate, which was the case for the column of sand (Pennwalt Corporation, 1977).

- Methyl parathion (MCAP or EC formulation) at 5 lb ai/A (active ingredient/acre) was detected in runoff water from field plots irrigated 4 to 5 days posttreatment. Levels found in soil and turf plots ranged from 0.13 to 21 ppm and 0.17 to 0.20 ppm, respectively (Pennwalt Corporation, 1972).

- A field dissipation study with methyl parathion (4 lb/gal EC) at 3 lb ai/A, applied alone or in combinaton with Curacron, dissipated to nondetectable levels (<0.05 ppm) within 30 days in silt loam and loamy sand soils (Ciba-Geigy Corporation, 1978).

III. PHARMACOKINETICS

Absorption

- Braeckman et al. (1983) administered a single oral dose of ^{35}S-methyl parathion (20 mg/kg) by stomach tube to four mongrel dogs. Peak concentrations in plasma ranged from 0.13 to 0.96 ug/mL, with peak levels occurring 2 to 9 hours after dosing. In two dogs given single oral doses of ^{35}S-methyl parathion (3 mg/kg) in this study, absorption was estimated to be 77 and 79%, based on urinary excretion of label. The authors concluded that methyl parathion was well absorbed from the gastrointestinal tract.

- Hollingworth et al. (1967) gave a single oral dose of ^{32}P-labeled methyl parathion by gavage (3 or 17 mg/kg, dissolved in olive oil) to male Swiss mice. Recovery of label in the urine reached a maximum of about 85%, most of this occurring within 18 hours of dosing. The amount of label in the feces was low, never exceeding 10% of the dose. This indicated that absorption was at least 90% complete.

Distribution

- Ackermann and Engst (1970) administered methyl parathion to pregnant albino rats and examined the dams and fetuses for the distribution of the pesticide. The pregnant rats (weighing about 270 g each) were given 3 mg (11.1 mg/kg) of methyl parathion orally on days 1 to 3 of gestation and sacrificed 30 minutes after the last dose. Methyl parathion was detected in the maternal liver (25 ng/g), placenta (80 ng/g), and in fetal brain (35 ng/g), liver (40 ng/g) and back musculature (60 ng/g).

Metabolism

- Hollingworth et al. (1967) gave ^{32}P-labeled methyl parathion by gavage (3 or 17 mg/kg, dissolved in olive oil) to male Swiss mice. About 85% of the label appeared in the urine within 72 hours. Urinary metabolites identified 24 hours after the low dose were: dimethyl phosphoric acid (53.1%); dimethyl phosphorothioic acid (14.9%); desmethyl phosphate (14.1%); desmethyl phosphorothioate (11.7%); phosphoric acid (2.0%); methyl phosphoric acid (1.7%); and phosphate (0.6%). The radioactivity in the urine was fully accounted for by hydrolysis products and P=O activation products. No evidence was found for reduction of the nitro group to an amine, oxidation of the ring methyl group, or hydroxylation of the ring. A generally similar pattern was observed at the high dose, except for a lower percentage of dimethyl phosphoric acid (31.9%) and higher percentages of desmethyl phosphate (23.1%) and desmethylphosphorothionate (18.8%). Based on this, the authors proposed a metabolic scheme involving oxidative desulfuration, oxidative cleavage of the phospho group from the ring and hydrolysis of the phosphomethyl esters.

- Neal and DuBois (1965) investigated the in vitro detoxification of methyl parathion and other phosphorothioates using liver microsomes prepared from adult male Sprague-Dawley rats. Metabolism was found to involve oxidative desulfuration followed by hydrolysis to yield p-nitrophenol. Extracts from livers of adult male rats exhibited higher metabolic activity than that of adult females (3.2 versus 1.9 units, where one unit equals 1 ug p-nitrophenol/50 mg liver extract) ($p < 0.01$). The activity of weanling rat liver (2.7 units) was intermediate between these two. In the case of adult CF-1 mice, the activity of female liver (3.2 units) was significantly greater ($p < 0.05$) than that of the males (2.3 units). The activity of young adult male guinea pig liver extracts was 5.6 units. The authors noted that these differences in metabolic detoxification rates correlated with the sex and species differences in susceptibility to the acute oral toxic effects of this family of compounds.

- Nakatsugawa et al. (1968) investigated the degradation of methyl parathion using liver microsomes from adult male rats and rabbits (strains not specified). Metabolism occurred by two oxidative pathways: activation of the phosphorus-sulfur bond to the phosphorus-oxygen analog, and cleavage at the aryl phosphothioate bond to yield p-nitrophenol. These reactions occurred only in the presence of oxygen and

$NADPH_2$. The amounts of phenol and oxygen analog formed were 3.8 and 3.7 uM in the rabbit liver extract and 2.5 and 5.4 uM in the rat liver extract, respectively.

Excretion

- Braeckman et al. (1983) administered individual doses of 3 mg/kg of ^{35}S-methyl parathion to two mongrel dogs. In each dog, the agent was given once intravenously and, 1 week later, once orally via stomach tube. This dosing pattern was repeated once in one dog. Urine was collected every 24 hours for 6 days after each treatment. Urinary excretion 6 days after oral dosing was 63% in the animal without repeated dosing and 70% and 78% in the other. Urinary excretion 6 days after intravenous dosing was 80% in the animal without repeated dosing and 95 to 96% in the other. Most of the label appeared in urine within two days. Other excretory routes were not monitored.

- Hollingworth et al. (1967) gave ^{32}P-labeled methyl parathion (3 or 17 mg/kg, dissolved in olive oil) by gavage to male Swiss mice. Recovery of label in the urine reached a maximum of about 85%, most of this occurring within 18 hours of dosing. The amount of label in the feces was low, never exceeding 10% of the dose. This indicated that absorption was at least 90% complete.

IV. HEALTH EFFECTS

Humans

Short-term Exposure

- Nemec et al. (1968) monitored cholinesterase (ChE) levels in two workers (entomologists) who examined plants in a cotton field after it had been sprayed with an ultra-low-volume (nonaqueous) preparation of methyl parathion (1.5 to 2 lb/acre). The men entered a cotton field to examine the plants on 3 different days over a 2-week period; two of these occasions were within 2 hours after the ultra-low-volume spraying, and the third occasion was 24 hours after a spraying. After each field trip their arms were washed with acetone and the adhering methyl parathion determined. It was found that contact with the plants 2 hours after spraying resulted in 2 to 10 mg of methyl parathion residue on the arms; exposure 24 hours after spraying resulted in a residue on the arms of 0.16 to 0.35 mg. The amount of pesticide absorbed was not estimated. No toxic symptoms were experienced by either man, but measurement of red blood cell ChE activity immediately after the third of these exposures showed a decrease in activity to 60 to 65% of preexposure levels. These values did not increase significantly over the next 24 hours. It was concluded that workers should not enter such a field until more than 24 hours, and preferably 48 hours, have elapsed after spraying with ultra-low-volume insecticide sprays. Water emulsion sprays were not tested, but the authors cautioned that it cannot be assumed that they are less hazardous than the ultra-low-volume spray residues.

° Rider et al. (1969, 1970, 1971) studied the toxicity of technical methyl parathion (purity not specified) in human volunteers. Each phase of the study was done with different groups of seven male subjects, five of whom were test subjects and two were vehicle controls (Rider et al., 1969). Each study phase was divided into a 30-day pre-test period for establishing cholinesterase baselines, a 30-day test period when a specific dose of methyl parathion was given, and a post-test period.

° Thirty-two different dosages were evaluated by Rider et al. (1969), ranging from 1 to 19 mg/day. Early in the study, several of the groups were given more than one dose level during a single phase. The initial amount was 1.0 mg with an increase of 0.5 mg during each succeeding test period up to 15.0 mg/day. At this point, the dose was increased by 1.0 mg/day to a total dose of 19.0 mg/day. Pesticide in corn oil was given orally in capsules, once per day for each test period of 30 days. At no time during any of the studies were there any significant changes in blood counts, urinalyses, or prothrombin times, or was there any evidence of toxic side effects. Cholinesterase activity of the plasma and red blood cells (RBCs) was measured twice weekly prior to, during and after the dosing period. The authors considered a mean depression of 20 to 25% or greater in ChE activity below control levels to be indicative of the toxic threshold. At 11.0 mg/day, a depression of 15% in plasma ChE occurred, but doses up to and including 19 mg/day did not produce any significant ChE depression.

° Rider et al. (1970) studied the effects of 22, 24 and 26 mg/day technical methyl parathion. There were no effects observed at 22 mg/day. At 24 mg/day, plasma and RBC ChE depression was produced in two subjects, the maximum decreases being 24 and 23% for plasma, and 27 and 55% for RBC. The mean maximal decreases (in all five subjects) were 17% for plasma and 22% for RBC. With 26 mg/day RBC ChE depression was again produced in only two of the subjects, with maximum decreases of 25 and 37%. The mean maximum decrease was 18%. Plasma cholinesterase was not significantly altered.

° Rider et al. (1971) assessed the effects of 28 and 30 mg/day technical methyl parathion. At 28 mg/day, a significant decrease in RBC ChE was produced in three subjects (data not given), with a maximum mean decrease of 19%. With a dose of 30 mg/day, a mean maximum depression of 37% occurred. Based on their criteria of 20 to 25% average depression of ChE activity, the authors concluded that this was the level of minimal incipient toxicity. Body weights of the test subjects were not reported, but assuming an average body weight of 70 kg, a dose of 22 mg/day corresponds to a No-Observed-Adverse-Effect-Level (NOAEL) of 0.31 mg/kg/day, and the 30 mg/day dose corresponds to 0.43 mg/kg/day. The NOAEL is considered to be 22 mg/day herein because of the apparent sensitivity of some individual subjects at higher doses to have met the 20 to 25% criteria for ChE depression as an effect.

Long-term Exposure

° No information was found in the available literature on the health effects of methyl parathion in humans.

Animals

Short-term Exposure

- Reported oral LD_{50} values for methyl parathion include 14 and 24 mg/kg in male and female Sherman rats, respectively (Gaines, 1969); 14.5 and 19.5 mg/kg in male and female CD-1 mice, respectively (Haley et al., 1975); 30 mg/kg in male ddY mice (Isshiki et al., 1983); 18.0 and 8.9 mg/kg in male and female Sprague-Dawley rats, respectively (Sabol, 1985); and 9.2 mg/kg in rats of unreported strain (Galal et al., 1977).

- Galal et al. (1977) determined the subchronic median lethal dose (C-LD_{50}) of methyl parathion (purity not specified) in adult albino rats. Groups of 10 animals received an initial daily oral dose (by gavage) of 0.37 mg/kg (4% of the acute oral LD_{50}). Every 4th day the dose was increased by a factor of 1.5 (dose based on the body weight of the animals as recorded at 4-day intervals). Treatment was continued until death or termination at 36 days. Hematological and blood chemistry analyses were performed initially and on the 21st and 36th days of the study. Histopathological studies of the liver, kidneys and heart were also carried out on the 21st and 36th days of treatment. The C-LD_{50} obtained was 13 mg/kg. The authors concluded that the most predominant hazards of subchronic exposure to methyl parathion were weight loss, hyperglycemia and macrocytic anemia, all probably secondary to hepatic toxicity. Since an increasing dose protocol was used, this study does not identify a NOAEL or a Lowest-Observed-Adverse-Effect-Level (LOAEL).

- Daly et al. (1979) administered methyl parathion (technical, 93.65% active ingredient) to Charles River CD-1 mice for 4 weeks at levels of 0, 25 or 50 ppm in the diet. Assuming that 1 ppm in the diet of mice corresponds to 0.15 mg/kg/day (Lehman, 1959), this is equivalent to doses of about 0, 3.75 or 7.5 mg/kg/day. Five animals of each sex were used at each dose level. Mean body weights were lower ($p < 0.05$) than control for all treated animals throughout the test period. Mean food consumption was lower ($p < 0.05$) throughout for all test animals except females at the 25-ppm level. Mortality, physical observations, and gross postmortem examinations did not reveal any treatment-related effects. Cholinesterase measurements were not performed. Based on body weight gain, the LOAEL for this study was identified as 25 ppm (3.75 mg/kg/day).

- Tegeris and Underwood (1977) examined the effects of feeding methyl parathion (94.32% pure) to beagle dogs (4 to 6 months of age, weighing 5 to 10 kg) for 14 days. Two animals of each sex were given doses of 0, 2.5, 5 or 10 mg/kg/day. All animals survived the 14-day test period. Mean feed consumption and weight gain were significantly ($p < 0.05$) depressed for both sexes at the 5 and 10 mg/kg/day dose levels. After the 3rd day, animals in the high-dose group began vomiting after all meals. Vomiting was observed sporadically at the lower dose levels, particularly during the 2nd week. The authors attributed this to acetylcholinesterase inhibition, but no measurements were reported. No other symptomatology was described. Based

on weight loss and vomiting, this study identified a LOAEL of 2.5 mg/kg/day in the dog.

- Fan et al. (1978) investigated the immunosuppressive effects of methyl parathion administered orally to Swiss (ICR) mice. The pesticide (purity not specified) was fed in the diet at dose levels corresponding to 0, 0.08, 0.7 or 3.0 mg/kg/day for 4 weeks. Active immunity was induced by weekly injection of vaccine (acetone-killed Salmonella typhimurium) during the period of diet treatment. Defense against microbial infection was tested by intraperitoneal injection of a single LD_{50} dose of active S. typhimurium cells. Protection by immunization was stated to be decreased in methyl parathion-treated animals, but no dose-response data were provided. The authors stated that pesticide treatment extending beyond 2 weeks was required to obtain significant increases in mortality. Increased mortality was associated with an increased number of viable bacteria in blood, decreased total gamma-globulins and specific immunoglobins in serum, and reduced splenic blast transformation in response to mitogens.

- Shtenberg and Dzhunusova (1968) studied the effect of oral exposure to methyl parathion (purity not specified) on immunity in albino rats vaccinated with NIISI polyvaccine. Three tests (six animals each) were conducted in which: (a) the vaccination was done after the animals had been on a diet supplying 1.25 mg/kg/day metaphos (methyl parathion) for 2 weeks; (b) the diet and vaccinations were initiated simultaneously; and (c) the diet was initiated 2 weeks after vaccination. The titer of agglutins in immunized control rats was 1:1,200. This titer was decreased in all exposed groups as follows: 1:46 in series (a), 1:75 in series (b) and 1:33.3 in series (c). The authors judged this to be clear evidence of inhibition of immunobiological reactivity in the exposed animals. Changes in blood protein fractions and in serum concentration of albumins were not statistically significant. Based on immune suppression, a LOAEL of 1.25 mg/kg/day was identified.

Dermal/Ocular Effects

- Gaines (1969) reported a dermal LD_{50} of 67 mg/kg for methyl parathion in male and female Sherman rats.

- Galloway (1984a,b) studied the skin and eye irritation properties of methyl parathion (technical; purity not specified) using albino New Zealand White rabbits. In the skin irritation test, 0.5 mL undiluted pesticide was applied and the treated area occluded for 4 hours. This treatment resulted in dermal edema that persisted for 24 hours, and in erythema that lasted for 6 days. After a total observation period of 9 days, a score of 2.0 was derived, and technical methyl parathion was rated as a weak irritant. In the eye irritation test, 0.1 mL of the undiluted pesticide was applied to nine eyes. Three were washed after exposure, and six were left unwashed. Conjunctival irritation was observed starting at 1 hour and lasting up to 48 hours postexposure. Maximum average irritation scores of 11 and 10.7 were assigned for nonwashed and washed eyes, respectively, and technical methyl parathion was considered a weak irritant.

- Galloway (1985) used guinea pigs to examine the sensitizing potential of methyl parathion (technical; purity not stated). Ten doses of 0.5 mL of a 10% solution (w/v in methanol) were applied to the clipped intact skin of 10 male guinea pigs (albino Hartley strain) over a 36-day period. This corresponds to an average dose of 13.9 mg/kg/day. Another group was treated with 2,4-dinitrochlorobenzene as a positive control. No skin sensitization reaction was observed in methyl parathion-treated animals.

- Skinner and Kilgore (1982) studied the acute dermal toxicity of methyl parathion in male Swiss-Webster mice, and simultaneously determined ED_{50} values for cholinesterase and acetylcholinesterase inhibition. Methyl parathion (analytical grade, 99% pure) was administered in acetone solution to the hind feet of the mice; the animals were muzzled to prevent oral ingestion through grooming. The dermal LD_{50} was 1,200 mg/kg. The ED_{50} was 950 mg/kg for cholinesterase inhibition and 550 mg/kg for acetylcholinesterase inhibition.

Long-term Exposure

- Daly and Rinehart (1980) conducted a 90-day feeding study of methyl parathion (93.65% pure) using Charles River CD-1 mice. Groups of 15 mice of each sex were given diets containing the pesticide at levels of 0, 10, 30 or 60 ppm. Assuming that 1 ppm in the diet of mice corresponds to 0.15 mg/kg/day (Lehman, 1959), this is equivalent to doses of about 0, 1.5, 4.5 or 9.0 mg/kg/day. All mice survived the test. Mean body weights were significantly ($p < 0.05$) depressed for both sexes at 60 ppm throughout the study and for males during the first 5 weeks at 30 ppm. Animals of both sexes had a slight but not significant ($p > 0.05$) increase in the mean absolute and relative brain weights at 60 ppm. There were dose-related decreases ($p < 0.05$) in the mean absolute and relative testes weights of all treated males and in the ovary weights of the females at 30 and 60 ppm. Gross and microscopic examination revealed no dose-related effects. Histological examination revealed no findings in the brain, testes or ovary to account for the observed changes in the weights of these organs. Measurements on ChE were not performed. Based on decreased testes weight, the LOAEL for this study was 10 ppm (1.5 mg/kg/day).

- Tegeris and Underwood (1978) investigated the toxicity of methyl parathion (94.32% active ingredient) in beagle dogs fed the pesticide for 90 days at dose levels of 0, 0.3, 1.0 or 3.0 mg/kg/day. Four dogs (4-months old, 4.5 to 8.0 kg) of both sexes were used at each dose level. Soft stools were observed in all treatment groups throughout, and there was also occasional spontaneous vomiting. There were no persistent significant ($p > 0.05$) effects on body weight gain, feed intake, fasting blood sugar, BUN, SGPT, SGOT, hematological, or urological indices. Organ weights were within normal limits, with the exception of pituitary weights of females at 3.0 mg/kg, which were significantly ($p < 0.05$) higher than the control values. Gross and microscopic examination revealed no compound-related abnormalities. Plasma ChE was significantly ($p < 0.05$) depressed in both sexes at 6 and 13 weeks at 3 mg/kg/day, and in the males only at 1.0 mg/kg/day

at 13 weeks; erythrocyte ChE was also significantly ($p < 0.05$) depressed in all animals at 6 and 13 weeks at 3 mg/kg/day, and in both sexes at 13 weeks at 1.0 mg/kg/day; brain ChE was significantly ($p < 0.05$) depressed in both sexes at 3.0 mg/kg/day. Based on ChE depression, the NOAEL and LOAEL for this study were identified as 0.3 mg/kg/day and 1.0 mg/kg/day, respectively.

- Ahmed et al. (1981) conducted a 1-year feeding study in beagle dogs. Methyl parathion (93.6% pure) was administered in the diet at ingested dose levels of 0, 0.03, 0.1 or 0.3 mg/kg/day. Eight animals of each sex were included at each dose level, with no overt signs of toxicity noted at any dose. There were no treatment-related changes in food consumption or body weight. Cholinesterase determinations in plasma, red blood cells and brain revealed marginal variations, but the changes were not consistent and were judged by the authors to be unrelated to dosing. Organ weight determinations showed changes in both males and females at 0.1 and 0.3 mg/kg/day, but the changes were neither dose-related nor consistent. It was concluded that there was no demonstrable toxicity of methyl parathion fed to the dogs at these levels. The NOAEL for this study was 0.3 mg/kg/day.

- NCI (1978) conducted a 2-year feeding study of methyl parathion (purity not specified) in F344 rats (50/sex/dose) at dose levels of 0, 20 or 40 ppm in the diet. Assuming that 1 ppm in the diet of rats corresponds to 0.05 mg/kg/day (Lehman, 1959), this is equivalent to dose levels of about 0, 1 or 2 mg/kg/day. Cholinesterase levels were not measured, but no remarkable clinical signs were noted, and no significant ($p < 0.05$) changes were observed in mortality, body weight, gross pathology or histopathology. Based on this, a NOAEL of 40 ppm (2 mg/kg/day) was identified in rats.

- NCI (1978) conducted a chronic (105-week) feeding study in $B6C3F_1$ mice (50/sex/dose). Animals were initially fed methyl parathion (94.6% pure) at dose levels of 62.5 or 125 ppm. Assuming that 1 ppm in the diet of mice corresponds to 0.15 mg/kg/day (Lehman, 1959), this is equivalent to doses of about 9.4 or 18.8 mg/kg/day. Because of severely depressed body weight gain in males, their doses were reduced at 37 weeks to 20 or 50 ppm, and the time-weighted averages were calculated to be 35 or 77 ppm. This corresponds to doses of about 5.2 or 11.5 mg/kg/day, respectively. Females were fed at the original levels throughout. Mortality was significantly ($p < 0.05$) increased only in female mice at 125 ppm. Body weights were lower ($p < 0.05$) for both sexes throughout the test period and decreases were dose-related. No gross or histopathologic changes were noted, and ChE activity was not measured. Based on body weight, this study identified a LOAEL of 35 ppm (5.2 mg/kg/day) in male mice.

- Daly et al. (1984) conducted a chronic feeding study of methyl parathion (93.65% active ingredient) in Sprague-Dawley (CD) rats (60/sex/dose) at dose levels of 0, 0.5, 5 or 50 ppm in the diet. Using food intake/body weight data given in the study report, these levels approximate doses of about 0, 0.025, 0.25 or 2.5 mg/kg/day. At 24 months, five animals of each sex were sacrificed for qualitative

and quantitative tests for neurotoxicity. Ophthalmoscopic examinations were conducted on females at 3, 12 and 24 months and terminally. Hematology, urinalysis and clinical chemistry analyses were performed at 6, 12, 18 and 24 months. Mean body weights were reduced ($p < 0.05$) throughout the study for both sexes at 50 ppm. At this dose level, food consumption was elevated ($p < 0.05$) for males during weeks 2 to 13, but reduced for females for most of the study. Hemoglobin, hematocrit and RBC count were significantly ($p < 0.05$) reduced for females at 50 ppm at 6, 12, 18 and 24 months. For males at 5 and 50 ppm at 24 months, hematocrit and RBC count were significantly ($p < 0.05$) reduced and hemoglobin was reduced, but not significantly ($p > 0.05$). At 50 ppm, plasma and erythrocyte ChE were significantly ($p < 0.05$) depressed for both sexes during the test, and brain ChE was significantly ($p < 0.05$) decreased at termination. Slight decreases in ChE activity were also observed in animals at 5 ppm, but these changes were not statistically significant ($p > 0.05$). For males, the absolute weight and the ratio to brain weight of the testes, kidneys and the liver were reduced by 10 to 16% (not significant, $p > 0.05$) in both the 5- and 50-ppm groups, while for females absolute and organ/body weights for the brain and heart (also heart/brain weight) were found to be elevated significantly ($p < 0.05$) at the same dose levels. Overt signs of cholinergic toxicity (such as alopecia, abnormal gait and tremors) were observed in the 50-ppm animals and in one female at 5 ppm. At 24 months, 15 females were observed to have retinal degeneration. There was also a dose-related occurrence of retinal posterior subcapsular cataracts, possibly related or secondary to the retinal degeneration, since 5 of the 10 cataracts occurred in rats with retinal atrophy. The incidence of retinal atrophy was 20/55 at 50 ppm, 1/60 at 5 ppm, 3/60 at 0.5 ppm and 3/59 in the control group. Examination of the sciatic nerve and other nervous tissue from five rats per sex killed at week 106 gave evidence of peripheral neuropathy (abnormal fibers, myelin corrugation, myelin ovoids) in both sexes at 50 ppm ($p < 0.05$). Too few fibers were examined at the lower doses to perform statistical analyses, but the authors stated that nerves from both sexes in low- and mid-dose groups could not be distinguished qualitatively from controls. Slightly greater severity of nerve changes found in two males was not clearly related to treatment. No other lesions were observed that appeared to be related to ingestion of methyl parathion. Based on hematology, body weight, organ weights, clinical chemistry, retinal degeneration and cholinergic signs, a NOAEL of 0.5 ppm (0.025 mg/kg/day) was identified in this study.

Reproductive Effects

- Lobdel and Johnston (1964) conducted a three-generation study in Charles River rats. Each parental dose group included 10 males and 20 females. The investigators incorporated methyl parathion (99% pure) in the diet of males and females at dose levels of 0, 10 or 30 ppm, except for reduction of each dose by 50% during the initial 3 weeks of treatment, to produce dose equivalents of 0, 1.0 and 3.0 mg/kg/day, respectively. There was no pattern with respect to stillbirths, although the 30-ppm groups had a higher total number of stillborn. Survival was reduced in weanlings of the F_{1a}, F_{1b} and F_{2a} groups at

30 ppm, and in weanlings of the F_{3a} group at 10 ppm. At 30 ppm, there was also a reduction in fertility of the F_{2b} dams at the second mating; the first mating resulted in 100% of the animals having litters, while at the second mating, only 41% had litters. Animals exposed to 10 ppm methyl parathion did not demonstrate significant deviations from the controls. A NOAEL of 10 ppm (1.0 mg/kg/day) was identified in this study.

° Daly and Hogan (1982) conducted a two-generation study of methyl parathion (93.65% pure) toxicity in Sprague-Dawley rats. Each parental dose group consisted of 15 males and 30 females. The compound was added to the diet at levels of 0, 0.5, 5.0 or 25 ppm. Using compound intake data from the study report, equivalent dose levels are about 0, 0.05, 0.5 or 2.5 mg/kg/day. Feeding of the diet was initiated 14 weeks prior to the first mating and then continued for the remainder of the study. Reduced body weight ($p < 0.05$) was observed in F_0 and F_1 dams at the 25-ppm dose level. A slight decrease in body weight was noted in F_{1a} and F_{2a} pups in the 25-ppm group, but this was not significant ($p > 0.05$). Overall, the authors concluded that there was no significant ($p > 0.05$) effect attributable to methyl parathion in the diet. Based on maternal weight gain, the NOAEL for this study was 5.0 ppm (0.5 mg/kg/day).

Developmental Effects

° Gupta et al. (1985) dosed pregnant Wistar-Furth rats (10 to 12 weeks of age) with methyl parathion (purity not specified) on days 6 to 20 of gestation. Two doses were used: 1.0 mg/kg (fed in peanut butter) or 1.5 mg/kg (administered by gavage in peanut oil). The low dose produced no effects on maternal weight gain, caused no visible signs of cholinergic toxicity and did not result in increased fetal resorptions. The high dose caused a slight but significant ($p < 0.05$) reduction in maternal weight gain (11% in exposed versus 16% in controls, by day 15) and an increase in late resorptions (25% versus 0%). The high dose also resulted in cholinergic signs (muscle fasiculation and tremors) in some dams. Acetylcholesterase (AChE) activity, choline acetyltransferase (CAT) activity, and quinuclidinyl benzilate (QNB) binding to muscarinic receptors were determined in several brain regions of fetuses at 1, 7, 14, 21 and 28 days postnatal age, and in maternal brain at day 19 of gestation. Exposure to 1.5 mg/kg reduced ($p < 0.05$) the AChE and increased CAT activity in all fetal brain regions at each developmental period and in the maternal brain. Exposure to 1.0 mg/kg caused a significant ($p < 0.05$) but smaller and less persistent reduction of AChE activity in offspring, but no change in brain CAT activity. Both doses reduced QNB binding in maternal frontal cortex ($p < 0.05$), but did not alter the postnatal pattern of binding in fetuses. In parallel studies, effects on behavior (cage emergence, accommodated locomotor activity, operant behavior) were observed to be impaired in rats exposed prenatally to 1.0 mg/kg, but not to the 1.5-mg/kg dose. No morphological changes were observed in hippocampus or cerebellum. It was concluded that subchronic prenatal exposure to methyl parathion altered postnatal development of cholinergic neurons and caused subtle alterations in selected

behaviors of the offspring. The fetotoxic LOAEL for this study was 1.0 mg/kg.

° Gupta et al. (1984) administered oral doses of 1.0 or 1.5 mg/kg/day of methyl parathion (purity not specified) to female Wistar-Furth rats on days 6 through 15 or on days 6 through 19 of gestation. Protein synthesis in brain and other tissues was measured on day 15 or day 19 by subcutaneous injection of radioactive valine. The specific activity of this valine in the free amino acid pool and protein-bound pool (measured 0.5, 1.0 and 2.0 hours after injection) was significantly ($p < 0.05$) reduced in various regions of the maternal brain and in maternal viscera, placenta and whole embryos (day 15), and in fetal brain and viscera (day 19). The inhibitory effect of methyl parathion on protein synthesis was dose dependent, greater on day 19 than on day 15 of gestation and more pronounced in fetal than in maternal tissues. With respect to protein synthesis in both maternal and fetal tissues, the LOAEL of this study was 1.0 mg/kg.

Mutagenicity

° Van Bao et al. (1974) examined the lymphocytes from 31 patients exposed to various organophosphate pesticides for indications of chromosome aberrations. Five of the examined patients had been exposed to methyl parathion. Blood samples were taken 3 to 6 days after exposure and again at 30 and 180 days. A temporary, but significant ($p < 0.05$) increase was found in the frequency of chromatid breaks and stable chromosome-type aberrations in acutely intoxicated persons. Two of the methyl parathion-exposed persons were in this category, having taken large doses orally in suicide attempts. The authors concluded that the results of this study strongly suggest that the organic phosphoric acid esters exert direct mutagenic effects on chromosomes.

° Shigaeva and Savitskaya (1981) reported that metophos (methyl parathion) induced visible morphological mutations and biochemical mutations in Pseudomonas aeruginosa at concentrations between 100 and 1,000 ug/mL, and significantly ($p < 0.05$) increased the reversion rate in Salmonella typhimurium at concentrations between 5 and 500 ug/mL.

° Grover and Malhi (1985) examined the induction of micronuclei in bone marrow cells of Wistar male rats that had been injected with methyl parathion at doses between one-third and one-twelfth of the LD_{50}. The increase in micronuclei formation led the authors to conclude that methyl parathion has high mutagenic potential.

° Mohn (1973) concluded that methyl parathion was a probable mutagen, based on the ability to induce 5-methyltryptophan resistance in Escherichia coli. Similar results were obtained using the streptomycin-resistant system of E. coli and the trp-conversion system of Saccharomyces cerevisiae.

° Rashid and Mumma (1984) found methyl parathion to be mutagenic to S. typhimurium strain TA100 after activation with rat liver microsomal and cytosolic enzymes.

- Chen et al. (1981) investigated sister-chromatid exchanges (SCE) and cell-cycle delay in Chinese hamster cells (line V79) and two human cell lines (Burkitt lymphoma B35M and normal human lymphoid cell Jeff), and found methyl parathion to be the most active pesticide of eight tested with respect to its induction potential.

- Riccio et al. (1981) found methyl parathion to be negative in two yeast assay systems (diploid strains D3 and D7 of Saccharomyces cerevisiae), based on mitotic recombination (in D3), and mitotic crossing over, mitotic gene conversion, and reverse mutation (in D7).

Carcinogenicity

- NCI (1978) conducted chronic (105-week) feeding studies of methyl parathion in F344 rats and B6C3F_1 mice (50/sex/dose). Rats were fed methyl parathion (94.6% pure) at dose levels of 0, 20 or 40 ppm (equivalent to doses of 0, 1 or 2 mg/kg/day). Mice were initially fed dose levels of 62.5 or 125 ppm, but because of severely depressed body weight gain in males, their doses were reduced at 37 weeks to 20 or 50 ppm, respectively. Time-weighted averages for males were calculated to be 35 or 77 ppm (about 5.2 or 11.5 mg/kg/day). Females received the original dose level throughout. Based on gross and histological examinations, no tumors were observed to occur at an incidence significantly higher than that of the control value in either the mice or rats. The authors concluded that methyl parathion was not carcinogenic in either species under the conditions of the test.

- Daly et al. (1984) fed Sprague-Dawley rats (60/sex/dose) methyl parathion (93.65%) in the diet for 2 years. Doses tested were 0, 0.5, 5 or 50 ppm, estimated as equivalent to doses of 0, 0.025, 0.25 or 2.5 mg/kg/day. There were no significant ($p > 0.05$) increases in neoplastic lesions between treated and control groups.

V. QUANTIFICATION OF TOXICOLOGICAL EFFECTS

Health Advisories (HAs) are generally determined for one-day, ten-day, longer-term (approximately 7 years) and lifetime exposures if adequate data are available that identify a sensitive noncarcinogenic end point of toxicity. The HAs for noncarcinogenic toxicants are derived using the following formula:

$$HA = \frac{(NOAEL \text{ or } LOAEL) \times (BW)}{(UF) \times (\_\_\_ \text{ L/day})} = \_\_\_ \text{ mg/L } (\_\_\_ \text{ ug/L})$$

where:

NOAEL or LOAEL = No- or Lowest-Observed-Adverse-Effect-Level in mg/kg bw/day.

BW = assumed body weight of a child (10 kg) or an adult (70 kg).

UF = uncertainty factor (10, 100 or 1,000), in accordance with NAS/ODW guidelines.

___ L/day = assumed daily water consumption of a child (1 L/day) or an adult (2 L/day).

One-day Health Advisory

No data were located in the available literature that were suitable for deriving a One-day HA value. It is recommended that the Ten-day HA value for the 10-kg child (0.31 mg/L calculated below) be used at this time as a conservative estimate of the One-day HA value.

Ten-day Health Advisory

The studies by Rider (1969, 1970, 1971) have been selected to serve as the basis for calculation of the Ten-day HA for methyl parathion. In these studies, human volunteers ingested methyl parathion for 30 days at doses ranging from 1 to 30 mg/day. The most sensitive indicator of effects was inhibition of plasma ChE. No effects in any subject were observed at a dose of 22 mg/day (about 0.31 mg/kg/day with assumed 70-kg body weight), and this was identified as the NOAEL. Doses of 24 mg/day inhibited ChE activity in plasma and red blood cells in two of five subjects, maximum decreases being 23 and 24% in plasma and 27 and 55% in red blood cells. Higher doses (26 to 30 mg/day) caused greater inhibition. On this basis, 24 mg/day (0.34 mg/kg/day) was identified as the LOAEL. Short-term toxicity or teratogenicity studies in animals identified LOAEL values of 1.0 to 2.5 mg/kg/day (Gupta et al., 1984, 1985; Shtenberg and Dzhunusova, 1968; Tegeris and Underwood, 1977), but did not identify a NOAEL value.

Using a NOAEL of 0.31 mg/kg/day, the Ten-day HA for a 10-kg child is calculated as follows:

$$\text{Ten-day HA} = \frac{(0.31 \text{ mg/kg/day})\ (10 \text{ kg})}{(10)\ (1 \text{ L/day})} = 0.31 \text{ mg/L } (310.0 \text{ ug/L})$$

where:

0.31 mg/kg/day = NOAEL, based on absence of toxic effects or inhibition of ChE in humans exposed orally for 30 days.

10 kg = assumed body weight of a child.

10 = uncertainty factor, chosen in accordance with NAS/ODW guidelines for use with a NOAEL from a study in humans.

1 L/day = assumed daily water consumption of a child.

Longer-term Health Advisory

The 90-day feeding study in dogs by Tegeris and Underwood (1978) has been selected to serve as the basis for calculation of the Longer-term HA for methyl parathion. In this study, a NOAEL of 0.3 mg/kg/day was identified,

based on absence of effects on body weight, food consumption, clinical chemistry, hematology, urinalysis, organ weights, gross pathology, histopathology and ChE activity. The LOAEL, based on ChE inhibition, was 1.0 mg/kg/day. These values are supported by the results of Ahmed et al. (1981), who identified a NOAEL of 0.3 mg/kg/day in a 1-year feeding study in dogs, and by the study of Daly and Rinehart (1980), which identified a LOAEL of 1.5 mg/kg/day (based on decreased testes weight) in a 90-day feeding study in mice.

Using a NOAEL of 0.3 mg/kg/day, the Longer-term HA for a 10-kg child is calculated as follows:

$$\text{Longer-term HA} = \frac{(0.3 \text{ mg/kg/day})\ (10 \text{ kg})}{(100)\ (1 \text{ L/day})} = 0.03 \text{ mg/L } (30 \text{ ug/L})$$

where:

0.3 mg/kg/day = NOAEL, based on absence of effects on body weight, food consumption, clinical chemistry, hematology, urinalysis, organ weights, gross pathology, histopathology and ChE activity in dogs fed methyl parathion for 90 days.

10 kg = assumed body weight of a child.

100 = uncertainty factor, chosen in accordance with NAS/ODW guidelines for use with a NOAEL from an animal study.

1 L/day = assumed daily water consumption of a child.

Using a NOAEL of 0.3 mg/kg/day, the Longer-term HA for a 70-kg adult is calculated as follows:

$$\text{Longer-term HA} = \frac{(0.3 \text{ mg/kg/day})\ (70 \text{ kg})}{(100)\ (2 \text{ L/day})} = 0.10 \text{ mg/L } (100 \text{ ug/L})$$

where:

0.3 mg/kg/day = NOAEL, based on absence of effects on body weight, food consumption, clinical chemistry, hematology, urinalysis, organ weights, gross pathology, histopathology and ChE activity in dogs fed methyl parathion for 90 days.

70 kg = assumed body weight of an adult.

100 = uncertainty factor, chosen in accordance with NAS/ODW guidelines for use with a NOAEL from an animal study.

2 L/day = assumed daily water consumption by an adult.

Lifetime Health Advisory

The Lifetime HA represents that portion of an individual's total exposure that is attributed to drinking water and is considered protective of noncarcinogenic adverse health effects over a lifetime exposure. The Lifetime HA is derived in a three-step process. Step 1 determines the Reference Dose (RfD), formerly called the Acceptable Daily Intake (ADI). The RfD is an estimate of a daily exposure to the human population that is likely to be without appreciable risk of deleterious effects over a lifetime, and is derived from the NOAEL (or LOAEL), identified from a chronic (or subchronic) study, divided by an uncertainty factor(s). From the RfD, a Drinking Water Equivalent Level (DWEL) can be determined (Step 2). A DWEL is a medium-specific (i.e., drinking water) lifetime exposure level, assuming 100% exposure from that medium, at which adverse, noncarcinogenic health effects would not be expected to occur. The DWEL is derived from the multiplication of the RfD by the assumed body weight of an adult and divided by the assumed daily water consumption of an adult. The Lifetime HA is determined in Step 3 by factoring in other sources of exposure, the relative source contribution (RSC). The RSC from drinking water is based on actual exposure data or, if data are not available, a value of 20% is assumed for synthetic organic chemicals and a value of 10% is assumed for inorganic chemicals. If the contaminant is classified as a Group A or B carcinogen, according to the Agency's classification scheme of carcinogenic potential (U.S. EPA, 1986a), then caution should be exercised in assessing the risks associated with lifetime exposure to this chemical.

The 2-year feeding study in rats by Daly et al. (1984) has been selected to serve as the basis for calculation of the Lifetime HA for methyl parathion. In this study, a NOAEL of 0.025 mg/kg/day was identified, based on the absence of effects on body weight, organ weights, hematology, clinical chemistry, retinal degeneration and cholinergic signs. A LOAEL of 0.25 mg/kg/day was identified, based on decreased hemoglobin, red blood cell counts, and hematocrit (males), changes in organ-to-body weight ratios (males and females) and one case of visible cholinergic signs. There was increased retinal degeneration at 2.5 mg/kg/day, but this was not greater than control at 0.25 or 0.025 mg/kg/day. This LOAEL value (0.25 mg/kg/day) is lower than most other NOAEL or LOAEL values reported in other reports. For example, NOAEL values of 0.3 to 3.0 mg/kg/day have been reported in chronic studies by Ahmed et al. (1981), NCI (1978), Lobdell and Johnston (1964) and Daly and Hogan (1982).

Using a NOAEL of 0.025 mg/kg/day, the Lifetime HA for a 70-kg adult is calculated as follows:

Step 1: Determination of the Reference Dose (RfD)

$$RfD = \frac{(0.025 \text{ mg/kg/day})}{(100)} = 0.00025 \text{ mg/kg/day}$$

where:

0.025 mg/kg/day = NOAEL, based on absence of cholinergic signs or other adverse effects in rats exposed to methyl parathion in the diet for 2 years.

100 = uncertainty factor, chosen in accordance with NAS/ODW guidelines for use with a NOAEL from an animal study.

Step 2: Determination of the Drinking Water Equivalent Level (DWEL)

$$DWEL = \frac{(0.00025 \text{ mg/kg/day})\ (70 \text{ kg})}{(2 \text{ L/day})} = 0.009 \text{ mg/L } (9 \text{ ug/L})$$

where:

0.00025 mg/kg/day = RfD.

70 kg = assumed body weight of an adult.

2 L/day = assumed daily water consumption of an adult.

Step 3: Determination of the Lifetime Health Advisory

Lifetime HA = (0.009 mg/L) (20%) = 0.002 mg/L (2 ug/L)

where:

0.009 mg/L = DWEL.

20% = relative source contribution from water.

Evaluation of Carcinogenic Potential

- No evidence of carcinogenic activity was detected in either rats or mice in a 105-week feeding study (NCI, 1978).
- Statistically significant ($p < 0.05$) increases in neoplasm frequency were not found in a 2-year feeding study in rats (Daly et al., 1984).
- The International Agency for Research on Cancer (IARC) has not evaluated the carcinogenicity of methyl parathion.
- Applying the criteria described in EPA's guidelines for assessment of carcinogenic risk (U.S. EPA, 1986a), methyl parathion may be classified in Group D: not classified. This category is for substances with inadequate animal evidence of carcinogenicity.

VI. OTHER CRITERIA, GUIDANCE AND STANDARDS

- NAS (1977) concluded that data were inadequate for calculation of an ADI for methyl parathion. However, using data on parathion, NAS calculated an ADI for both parathion and methyl parathion of 0.0043 mg/kg/day, using a NOAEL of 0.043 mg/kg/day in humans (Rider et al., 1969) and an uncertainty factor of 10 (NAS, 1977). From this ADI, NAS calculated a chronic Suggested-No-Adverse-Response Level (SNARL) of 0.03 mg/L, based on water consumption of 2 L/day by a 70-kg adult, and assuming a 20% RSC.

- The U.S. EPA Office of Pesticide Program (EPA/OPP) previously calculated a provisional ADI (PADI) of 0.0015 mg/kg/day, based on a NOAEL of 0.3 mg/kg/day. This is based on the 90-day dog study by Tegeris and Underwood (1978) and a 200-fold uncertainty factor. This PADI has been updated to use a value of 0.0025 mg/kg/day based on a NOAEL of 0.0250 mg/kg/day in a 2-year rat chronic feeding study and a 100-fold uncertainty factor.

- ACGIH (1984) has proposed a time-weighted average threshold limit value of 0.2 mg/m^3.

- The National Institute for Occupational Safety and Health has recommended a standard for methyl parathion in air of 0.2 mg/m^3 (TDB, 1985).

- The U.S. EPA has established residue tolerances for parathion and methyl parathion in or on raw agricultural commodities that range from 0.1 to 0.5 ppm (CFR, 1985). A tolerance is a derived value based on residue levels, toxicity data, food consumption levels, hazard evaluation and scientific judgment; it is the legal maximum concentration of a pesticide in or on a raw agricultural commodity or other human or animal food (Paynter et al., undated).

- The World Health Organization established an ADI of 0.02 mg/kg/day (Vettorazi and van den Hurk, 1985).

VII. ANALYTICAL METHODS

- Analysis of methyl parathion is by a gas chromatographic (GC) method applicable to the determination of certain nitrogen-phosphorus containing pesticides in water samples (U.S. EPA, 1986b). In this method, approximately 1 liter of sample is extracted with methylene chloride. The extract is concentrated and the compounds are separated using capillary column LGC. Measurement is made using a nitrogen-phosphorus detector. The method detection limit has not been determined for methyl parathion, but it is estimated that the detection limits for analytes included in this method are in the range of 0.1 to 2 ug/L.

VIII. TREATMENT TECHNOLOGIES

- Available data indicate that granular-activated carbon (GAC) and reverse osmosis (RO) will effectively remove methyl parathion from water.

- Whittaker (1980) experimentally determined adsorption isotherms for methyl parathion and methyl parathion diazinion bi-solute solutions. As expected, the bi-solute solution showed a lesser overall carbon capacity than that achieved by the application of pure solute solution.

- Under laboratory conditions, GAC removed 99+% of methyl parathion (Whittaker et al., 1982).

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*Confidential Business Information submitted to the Office of Pesticide Programs.