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16. ABSTRACT

This report summarizes and evaluates information relevant to a preliminary interim assessment of adverse health effects associated with specific chemicals or compounds. The Office of Emergency and Remedial Response (Superfund) uses these documents in preparing cost-benefit analyses under Executive Order 12991 for decision-making under CERCLA. All estimates of acceptable intakes and carcinogenic potency presented in this document should be considered as preliminary and reflect limited resources allocated to this project. The intent in these assessments is to suggest acceptable exposure levels whenever sufficient data are available. The interim values presented reflect the relative degree of hazard associated with exposure or risk to the chemical(s) addressed. Whenever possible, two categories of values have been estimated for systemic toxicants (toxicants for which cancer is not the endpoint of concern). The first, RfD_S or subchronic reference dose, is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs during a limited time interval. The RfD is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs for a significant portion of the lifespan. For compounds for which there is sufficient evidence of carcinogenicity, q_1^*s have been computed, if appropriate, based on oral and inhalation data if available.

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HEALTH EFFECTS ASSESSMENT FOR PARATHION

ENVIRONMENTAL CRITERIA AND ASSESSMENT OFFICE
OFFICE OF HEALTH AND ENVIRONMENTAL ASSESSMENT
OFFICE OF RESEARCH AND DEVELOPMENT
U.S. ENVIRONMENTAL PROTECTION AGENCY
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This document has been reviewed in accordance with the U.S. Environmental Protection Agency's peer and administrative review policies and approved for publication. Mention of trade names or commercial products does not constitute endorsement or recommendation for use.

PREFACE

This report summarizes and evaluates information relevant to a preliminary interim assessment of adverse health effects associated with parathion. All estimates of acceptable intakes and carcinogenic potency presented in this document should be considered as preliminary and reflect limited resources allocated to this project. Pertinent toxicologic and environmental data were located through on-line literature searches of the TOXLINE and the CHEMFATE/DATALOG data bases. The basic literature searched supporting this document is current up to May, 1986. Secondary sources of information have also been relied upon in the preparation of this report and represent large-scale health assessment efforts that entail extensive peer and Agency review. The following Office of Health and Environmental Assessment (OHEA) sources have been extensively utilized:

U.S. EPA. 1984b. Reportable Quantity Document for Parathion. Prepared by the Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Emergency and Remedial Response, Washington, DC.

U.S. EPA. 1986a. Reference Doses (RfDs) for Oral Exposure. Parathion CAS# 56-38-2. Prepared by the Environmental Criteria and Assessment Office, Cincinnati, OH.

The intent in these assessments is to suggest acceptable exposure levels for noncarcinogens and risk cancer potency estimates for carcinogens whenever sufficient data were available. Values were not derived or larger uncertainty factors were employed when the variable data were limited in scope tending to generate conservative (i.e., protective) estimates. Nevertheless, the interim values presented reflect the relative degree of hazard or risk associated with exposure to the chemical(s) addressed.

Whenever possible, two categories of values have been estimated for systemic toxicants (toxicants for which cancer is not the endpoint of concern). The first, RfD_S (formerly AIS) or subchronic reference dose, is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs during a limited time interval (i.e., for an interval that does not constitute a significant portion of the lifespan). This type of exposure estimate has not been extensively used, or rigorously defined, as previous risk assessment efforts have been primarily directed towards exposures from toxicants in ambient air or water where lifetime exposure is assumed. Animal data used for RFD_S estimates generally include exposures with durations of 30-90 days. Subchronic human data are rarely available. Reported exposures are usually from chronic occupational exposure situations or from reports of acute accidental exposure. These values are developed for both inhalation (RfD_{SI}) and oral (RfD_{SO}) exposures.

The RfD (formerly AIC) is similar in concept and addresses chronic exposure. It is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs for a significant portion of the lifespan [see U.S. EPA (1980) for a discussion of this concept]. The RfD is route-specific and estimates acceptable exposure for either oral (RfD_O) or inhalation (RfD_I) with the implicit assumption that exposure by other routes is insignificant.

Composite scores (CSs) for noncarcinogens have also been calculated where data permitted. These values are used for identifying reportable quantities and the methodology for their development is explained in U.S. EPA (1984a).

For compounds for which there is sufficient evidence of carcinogenicity RfD_S and RfD values are not derived. For a discussion of risk assessment methodology for carcinogens refer to U.S. EPA (1980). Since cancer is a process that is not characterized by a threshold, <u>any</u> exposure contributes an increment of risk. For carcinogens, q_1^*s have been computed, if appropriate, based on oral and inhalation data if available.

ABSTRACT

In order to place the risk assessment evaluation in proper context, refer to the preface of this document. The preface outlines limitations applicable to all documents of this series as well as the appropriate interpretation and use of the quantitative estimates presented.

Inhalation data were not available for parathion; therefore, inhalation risk assessment values could not be calculated. RfD_0 and RfD_{SO} values of 0.006 mg/kg/day or 0.4 mg/day for a 70 kg human were derived based on a human study in the CBI files showing a NOAEL for erythrocyte cholinesterase inhibition. Whether this value is protective against the reproductive and carcinogenic effects of parathion is uncertain. A CS of 36, based on reduced survival at weaning at 30 ppm in the diet of rats in a 3-generation study located in the CBI files (U.S. EPA, 1986b), was the highest CS calculated for parathion.

The available data on carcinogenicity places parathion in EPA Group C. This category is for the agents with limited evidence of carcinogenicity in animals, and no or inadequate data on humans (U.S. EPA, 1986c).

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LIST OF ABBREVIATIONS

ATP	Adenosine triphosphate
AUC	Area under the curve
BCF	Bioconcentration factor
bw	Body weight
CBI	Confidential business information
CHO	Chinese hamster ovary
CNS	Central nervous system
CS	Composite score
DDC	Diethyldithiocarbamate
DNA	Deoxyribonucleic acid
EEG	Electroencephalogram
HA	Health advisory
LD_{50}	Median lethal dose
MED	Minimum effective dose
MFO	Mixed function oxidase
MTD	Maximum tolerated dose
NOAEL	No-observed-adverse-effect level
NOEL	No-observed-effect level
PEL	Permissible exposure limit
ppm	Parts per million
RBC	Red blood cell
RfD	Reference dose
RfD_I	Inhalation reference dose
RfD_O	Oral reference dose
RfD_S	Subchronic reference dose
RfD_{SI}	Subchronic inhalation reference dose
RfD_{SO}	Subchronic oral reference dose
RQ	Reportable quantity
SCE	Sister chromatid exchange
TLV	Threshold limit value
TWA	Time-weighted average

1. ENVIRONMENTAL CHEMISTRY AND FATE

Selected chemical and physical properties and environmental fate of parathion are presented in Table 1-1. Synonyms for parathion are: phosphorothioic acid; 0,0-diethyl-0-(4-nitrophenyl)ester; 0,0-diethyl-0-p-nitrophenyl phosphorothioate; diethyl-p-nitrophenyl monothiophosphate and DNTP. Trade names are: S.N.P.; E605; AC3422; ENT 15108; Alkron; Alleron; Aphamite; Etilon; Folidol; Fosferno; Niran; Paraphos; Rhodiatox and Thiophos.

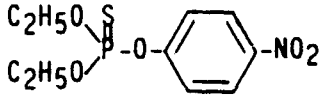
The half-life of parathion in the atmosphere could not be located in the available literature. Monitoring data indicate that parathion and its initial transformation product, paraoxon, may exist in the atmosphere in vapor form and adsorbed onto airborne particulate matter (Sanborn et al., 1977).

The persistence and fate of parathion residues in environmental media depend on such factors as temperature, humidity, light, pH, the presence of organic matter, and micro- and macroflora and fauna prevailing in a given environment. These parameters influence activation or chemical/biological degradation of the parent molecule to nontoxic products (Felsot and Dahm, 1979).

In water and soil, parathion is decomposed primarily by biologically mediated hydrolysis. Mechanisms of decomposition also include other biological processes, oxidation and sunlight. Laboratory and field studies of the persistence of parathion show half-lives of the parent compound, resulting from normal usage concentrations, to be on the order of days in ambient waters. In soils, the half-life of parathion ranges from a few weeks to a few months, depending on soil characteristics and the climate.

TABLE 1-1

Selected Chemical and Physical Properties
and Environmental Fate of Parathion

Property	Value	Reference
CAS number:	56-38-2	
Chemical class:	organophosphorus pesticide	
Molecular weight:	291.27	
Chemical formula:		
Melting point:	6°C	
Boiling point: (760 mm Hg)	375°C	
Vapor pressure:	3.78×10^{-5} mm Hg at 20°C	Sanborn et al., 1977
Water solubility:	24 mg/ℓ at 25°C	Sanborn et al., 1977
Log octanol/water partition coefficient:	3.83	Hansch and Leo, 1985
Bioconcentration factor:	103-480 (estimated)	Lyman et al., 1982
Soil adsorption coefficient:	1038-1388 965-1724	Felsot and Dahm, 1979 Sharon et al., 1984
Half-lives:		
Air	NA	
Water	days	
Soil	a few weeks to a few months	

NA = Not available

2. ABSORPTION FACTORS IN HUMANS AND EXPERIMENTAL ANIMALS

2.1. ORAL

Parathion is readily absorbed from the gastrointestinal tract. This is indicated in a study by Morgan et al. (1977) where volunteers were given 2 mg parathion orally. Within 48 hours, 30-40% of the administered dose of parathion was excreted in the urine as metabolites (paranitrophenol, alkyl phosphates and thiophosphates). Braeckman et al. (1983) studied the absorption of parathion in ethanol-propylene glycol following gavage administration to mongrel dogs of either sex. They found that radiolabeled parathion appeared to be well absorbed since urinary excretion of radioactivity following oral dosing at 5 mg/kg was nearly as complete and as rapid as following intravenous dosing with a dose of the same size. Orally administered parathion appeared to have very low bioavailability (<30%), compared with intravenous dosing, evaluated by comparing the AUCs for serum concentration, as a result of first-pass extraction in the liver. Additional quantitative data regarding the absorption of parathion following oral administration could not be located in the available literature.

2.2. INHALATION

Parathion is absorbed during inhalation exposure (Simpson and Beck, 1960; Wolfe et al., 1967). To prevent dermal exposure, Durham et al. (1972) exposed an individual completely covered with rubber and plastic clothing to mist from an airblast spray machine during parathion application in orchards, and collected tissue for several days. p-Nitrophenol, a major metabolite of parathion, was excreted in urine collected within 24 hours after exposure. More quantitative data regarding the inhalation absorption of parathion could not be located in the available literature. Absorbtion from dermal exposure may exceed respiratory intake (Cohen et al., 1977; Maibach et al., 1971).

3. TOXICITY IN HUMANS AND EXPERIMENTAL ANIMALS

3.1. SUBCHRONIC

3.1.1. Oral. Moeller and Rider (1961) gave parathion in corn oil in gelatin capsules at doses of 3-4.5 mg/day for 28 days and 6.0 mg/day for 43 days to volunteers. Plasma and RBC cholinesterase activities were depressed by 10-15% at 6 mg/day, but not at lower doses.

In a study by Rider et al. (1969), groups of volunteers (five test subjects and two controls/dose level) were given capsules containing 3.0, 4.5, 6.0 or 7.5 mg parathion/day. Controls received capsules containing corn oil. Before treatment, baseline measurements of plasma and RBC cholinesterase activities were made. Depression of plasma or RBC cholinesterase activity was not observed at doses <6.0 mg/day. At 6.0 mg/day, there was a slight but not significant depression of plasma cholinesterase activity. In subjects receiving 7.5 mg/day, average plasma cholinesterase activity was depressed by ~15% from days 4-35 as compared with baseline values. Individual variability was fairly large, with three subjects at 7.5 mg/day showing a decreased plasma cholinesterase activity of 50-55%. At 7.5 mg/day, a 7-10% depression in baseline RBC cholinesterase activity was also observed.

Edson et al. (1964) exposed humans orally to parathion at 0 or 0.6 mg/day, which was increased to 4.8 mg/day during weeks 4-13 (TWA = 4.0 mg/day) or to 1.2 or 2.4 mg/day for ≤70 days. Four females received 7.2 mg parathion/day, 5 days/week for 6 weeks. RBC and plasma cholinesterase activity levels were 84 and 63% of control levels, respectively, in females treated at 7.2 mg/day. No changes in cholinesterase activities were observed at lower dose levels.

Edson et al. (1964) also studied the effects of parathion in female rats (20/dose level) and female pigs (2/dose level). The rats received parathion in the diet at 0, 0.05, 0.5 and 5 ppm for 84 days. The pigs were fed diets containing parathion at 0, 0.2, 1.0 and 5 ppm for ~89 days. The 0.2 and 1.0 ppm levels in pigs were increased to 25 and 100 ppm on days 33-72 and 73-114, respectively. No effects on general health, growth, food consumption and gross organ appearance were observed in either rats or pigs. In rats fed diets containing parathion at 0.5 and 5 ppm, RBC cholinesterase activity was 46 and 20% of levels in controls after 12 weeks. In rats, RBC cholinesterase activity appeared to be inhibited more than plasma cholinesterase activity. In pigs fed 100 ppm, RBC cholinesterase activity was 20% of controls after 7 weeks of treatment.

Edson and Noakes (1960) fed female Wistar rats diets containing parathion at 1, 5, 25 and 125 ppm for 16 weeks. The high-dose group showed reduced weight gain, cardiac fibrillations, nervousness and mortality of 7/10 rats. In rats fed 25 ppm, slight fibrillations were observed. At 5, 25 and 125 ppm, dose-related depressions of RBC, plasma and brain cholinesterase activities were observed. RBC cholinesterase activity was 28, 8 and 4% of control levels at 5, 25 and 125 ppm, respectively. Plasma cholinesterase activities were 44 and 10% of control levels at 25 and 125 ppm, and brain cholinesterase activities were 89 and 9% of control levels at 25 and 125 ppm, respectively.

In a 90-day study by Dikshith et al. (1978), a group of 12 adult male white rats were treated by gavage with parathion in peanut oil at 2.6 mg/kg/day. Controls received peanut oil. Four of the treated rats died, but no gross abnormalities were observed in any organ. A significant decrease in activity of succinic dehydrogenase in the liver ($p<0.0011$) and

kidney ($p<0.001$) was observed. There was also a significant decrease in ATPase activity of the liver and kidney ($p<0.0011$). In the testes, the activities of most enzymes remained unchanged except for increased ($p<0.011$) ATPase activity. A significant ($p<0.001$) inhibition of acetylcholinesterase activity in the blood and brain was observed.

Frawley and Fuyat (1957) fed groups of one male and one female mixed breed dogs diets containing parathion at 1, 2 and 5 ppm (0.021, 0.047 and 0.117 mg/kg/day) for 24 weeks. Controls received parathion-free diets. In dogs fed 0.047 and 0.117 mg/kg/day, plasma cholinesterase was reduced by 30-50% compared with controls. At 0.021 mg/kg/day, plasma cholinesterase was reduced 20%. RBC cholinesterase was reduced 20-40% in dogs treated at the highest dose. Dogs recovered from these effects 6-8 weeks posttreatment.

In a study by Hassan and Cueto (1970), two groups of New Zealand white rabbits were dosed by gavage with parathion in peanut oil at 0.5 or 1.0 mg/kg/day for 222 days. After 100 days of treatment, urinary excretion of 4-hydroxy-3-methoxymandelic acid (vanillylmandelic acid) and 5-hydroxy-3-indoleacetic acid was higher in treated rabbits than in controls. These increases were considered by the investigators to be a result of the increased metabolism rates of catecholamines and serotonin, respectively. Analysis of blood and urine levels of amino acids showed no significant differences between control and treated groups.

In a study by Barnes and Denz (1951), groups of 36 male and 36 female albino rats were fed diets containing parathion (76.8% pure) at 10, 20, 50, 75 or 100 ppm, 6 days/week for 1 year; 30 rats/sex fed diets without parathion served as controls. Treatment of rats fed 100 ppm was terminated after 19 days as a result of excessive mortality; 58/72 rats died and most only consumed 5 g of food/day. Treatment of rats fed 75 ppm was terminated

after 27 days; 53/72 rats died. Pathological changes in the submaxillary gland, pancreas, spleen and thymus were observed in these two high-dose groups. Survivors of these groups recovered after treatment termination and showed no permanent effects when examined after 1 year. In rats fed diets containing 50 ppm, mortality was ~61% with most deaths occurring before week 4. Body weight gains were reduced in both males and females at 50 ppm; this effect was not attributed to decreased food consumption. Moribund animals showed changes in the submaxillary gland, pancreas, spleen or thymus with no histological changes noted in survivors. Rats fed 10 or 20 ppm gained weight comparably with controls, and chemical-induced mortality was not indicated. No treatment-related pathological changes in rats fed 10 or 20 ppm were observed. Cholinesterase activities apparently were not monitored.

3.1.2. Inhalation. Kay et al. (1982) studied the effects of exposure to parathion spray on blood cholinesterase activities of apple growers. Sprayers were exposed for ~2 days at 10-day intervals for 2 months; airborne concentrations in the breathing zone ranged from 2-15 mg/m^3. Depression of RBC cholinesterase activity averaged 21% for all sprayers. No significant difference in RBC cholinesterase activity levels were noted between sprayers reporting symptoms and those apparently symptom-free; symptoms included nausea and headaches. The relative importance of inhalation exposure versus dermal exposure was not determined.

3.2. CHRONIC

3.2.1. Oral. In an NCI (1979) bioassay, groups of 50 Osborne-Mendel rats/sex and 50 B6C3F1 mice/sex were fed diets containing parathion. Low-dose male rats were fed at 40 ppm for 13 weeks then at 30 ppm for 67 weeks for a TWA of 32 ppm. High-dose males received diets containing 80 ppm for 13 weeks then 60 ppm for 67 weeks for a TWA of 63 ppm. TWA doses for female rats were 23 and 45 ppm for low- and high-dose rats, respectively.

Low-dose females received diets containing 20 ppm for 13 weeks, 30 ppm for 21 weeks and 20 ppm for 46 weeks, high-dose females received diets containing 40 ppm for 13 weeks, 60 ppm for 21 weeks and 40 ppm for 46 weeks. All rats were treated for a total of 80 weeks followed by a 32-week observation period. Matched controls from the parathion bioassay were pooled with controls from other bioassays for a total of 90 male and 90 female rats, which were observed for 112 weeks. Low-dose male mice were fed parathion in the diet at 80 ppm for 71 weeks with an 18-week observation period. High-dose male mice received 160 ppm in the diet for 62 weeks with a 28-week observation period. Low- and high-dose female mice received 80 or 160 ppm, respectively for 80 weeks followed by a 9-week observation period for low-dose mice and 10 weeks for high-dose female mice. Matched controls were pooled with controls from other bioassays for a total of 140 males and 130 females, which were observed for 90 weeks.

Rats showed lower mean body weights in the high-dose groups during the treatment period as compared with controls. This effect was particularly pronounced in females from weeks 14-35. Body tremors and diarrhea were observed in all treated rats; these effects were particularly pronounced in the high-dose females. No significant positive dose-related trend in mortality was observed in either sex. Histopathological examination showed no effect on the incidence of nonneoplastic lesions.

Mortality was not affected in female mice, but a positive dose-related trend was observed in males. Reduced mean body weight, body tremors and diarrhea were observed in all treated groups. Histopathological examination indicated that nonneoplastic lesions were not affected by parathion treatment.

3.2.2. Inhalation. Pertinent data regarding the effects of parathion following chronic inhalation exposure could not be located in the available literature.

3.3. TERATOGENICITY AND OTHER REPRODUCTIVE EFFECTS

3.3.1. Oral. In a study by Deskin et al. (1979), pregnant CD mice were treated by gavage with parathion in peanut oil at 0.01, 0.10 and 1.00 mg/kg/day from day 2 of gestation to day 15 of lactation. Control mice received peanut oil. Ten offspring at each dose were observed for toxic effects on day 24 postpartum. Male offspring showed no significant change ($p \leq 0.05$) in RBC and plasma cholinesterase. Female offspring from dams dosed at ≥ 0.01 mg/kg/day showed significant reduction of plasma cholinesterase activity, but not RBC cholinesterase activity. Electrocardiographs of male and female offspring showed significant changes, but these are difficult to evaluate without histopathological examinations of the heart.

In a study by Barnes and Denz (1951), rats were fed diets containing 50, 20 or 10 mg/parathion/kg diet (50, 20 or 10 ppm, 76.8% pure) before mating through to parturition. Litter sizes of the 50 ppm diet rats were decreased. Survival of neonates was inversely dose-related; there were no survivors at 50 ppm, 43% survived at 20 ppm and 100% survived in the 10 ppm group and controls. Offspring of the group treated at 10 ppm were fed a similar diet and mated after 178 days. Five of six mated females produced litters, but only 7/37 neonates born survived more than a few days. Cross mating of six exposed females with control males resulted in only 2 litters. The number of offspring was normal in these litters, but only 38% survived. Mating an exposed F_1 male with control dams resulted in fertility and survival of young that were comparable with control matings.

Studies in the CBI files (U.S. EPA, 1986b) conflict with the findings of Barnes and Denz (1951). In a 3-generation study in rats, effects on pups were observed at a higher dietary concentration but not at 10 ppm.

3.4. TOXICANT INTERACTIONS

The ability of many agents to alter the toxicity of parathion has been investigated. One of the most significant ways to alter the toxicity of parathion is by the induction or inhibition of drug-metabolizing enzymes. Male rats have been found to be less susceptible to the toxicity of parathion than female rats, perhaps as a result of the inducing effects of testosterone (Newell and Dilley, 1978).

Rats pretreated with ethylestrenol gained some protection from the toxic effects of parathion (Robinson et al., 1976). Norbolethan and spironolactone, two other steroids, also provided some protection.

In a study with rats, carbon monoxide exposure prolonged time until death caused by an intraperitoneal injection of parathion (Baeza et al., 1972). Pretreatment with turpentine (Omirov and Aberkulov, 1972), ovex (Black et al., 1975), halogenated benzenes (Townsend and Carlson, 1981) and tri-o-tolyl phosphate (Lynch and Coon, 1972) also provided some protection against parathion toxicity. In a study by Murphy (1980), phenobarbital pretreatment was found to protect against the anticholinesterase activity of parathion in an unspecified species. Pretreatment with di-2-ethylhexyl phthalate also reduced the degree of cholinesterase inhibition in rats caused by parathion (Srivastava et al., 1976).

Homann et al. (1985) studied the effect of DDC, a known inhibitor of mixed-function oxidase activity, on the toxicity of parathion to male rats. DDC, when injected into rats 45 minutes before or 10 minutes after parathion intoxication, had no effect on the survival rate. DDC administered simultaneously with parathion resulted in the rate of survival rising 53%.

Mirer et al. (1977) studied the effects of piperonyl butoxide pretreatment on parathion toxicity in mice. An injection of piperonyl butoxide 1 hour before parathion treatment resulted in a 2-fold potentiation of parathion toxicity.

A study by Vukovich et al. (1971) examined the effects of intraperitoneal injections of chlorpromazine on the oral toxicity of parathion to mice. Chlorpromazine injected 1 or 6 hours before parathion treatment increased the oral toxicity of parathion. The toxicity was decreased when chlorpromazine was administered 1 day before parathion treatment. Weiss and Orzel (1967) found that an intraperitoneal injection of reserpine, chlordiazepoxide-HCl, hexobarbital sodium or phenobarbital sodium enhanced the toxicity of rats to intraperitoneally injected parathion at 2 and 4 mg/kg. Chlorpromazine-HCl and meprobamate only increased the toxic effect of parathion at 4 mg/kg.

To determine if parathion alters hepatic microsomal drug metabolism, the effect of the pesticide on hexobarbital sleeping times in mice was studied (Hart and Fouts, 1963). An intraperitoneal injection of parathion (2.5 mg/kg) was administered to CF No. 1 white mice. Significant prolongation of sleeping times was observed 1 and 3 days following parathion injection.

A number of studies have investigated the interaction of parathion with other pesticides. Schein and Thomas (1975) found that oral doses of parathion and dieldrin caused a greater disturbance in testosterone dynamics in male mice than either compound alone. The acute toxicity was found to be greater than additive when parathion was administered with chlorbufam (Niedner and von Oettingen, 1976), fenitrotion (Kawai et al., 1973) and chlordane plus malathion (Keplinger and Deichmann, 1967).

Triolo and Coon (1966) studied the effects of orally administered aldrin on the toxic effects of oral parathion in mice. They found that 1 hour after aldrin administration parathion toxicity was increased. Aldrin administered 16 hours to 12 days before parathion resulted in protection from parathion toxicity. This protection reached a maximum when parathion was given 4 days after aldrin administration.

Malathion, when administered with parathion subcutaneously into male mice, has been shown to have a less than additive effect (Kawai et al., 1973). Pretreatment with carbaryl in the diet (Neskovic, 1979) or lindane (Chadwick et al., 1984) has also been shown to reduce parathion toxicity in rats.

The state of the animal has also been shown to affect parathion toxicity. Parathion is more toxic to rats under 35 days of age (Harbison, 1973; Benke and Murphy, 1975) and more toxic to pregnant than nonpregnant mice (Weitman et al., 1983). Food restriction (Villeneuve et al., 1978) and low protein diets (Casterline and Williams, 1971; Boyd, 1969; Bulusu and Chakravarty, 1986) have also been shown to increase parathion toxicity in rats.

4. CARCINOGENICITY

4.1. HUMAN DATA

Pertinent data regarding the carcinogenic potential of parathion in humans following oral or inhalation exposure could not be located in the available literature.

4.2. BIOASSAYS

4.2.1. Oral. Hazelton and Holland (1950) conducted a cancer bioassay using groups of 8-20 male and female albino rats (strain unspecified). Males were fed diets containing parathion at 50 or 100 ppm for 100 weeks or 10 or 25 ppm for 88 weeks. Females were fed diets containing parathion at 10 or 50 ppm for 64 weeks. Another group of females was fed 100 ppm in the diet for an unspecified length of time. Ten males observed for 104 weeks, 20 males observed for 88 weeks and 6 females observed for 64 weeks served as controls. No dose-related effect on mortality was noted. Histological examination of a limited number of tissues from high-dose group survivors showed no tumors.

In the NCI (1979) bioassay, groups of 50 male and 50 female Osborne-Mendel rats and B6C3F1 Charles River mice were fed parathion in the diet (see Section 3.2.1.). Male rats received TWA doses of 32 or 63 ppm, female rats 23 or 45 ppm. Rats were treated for 80 weeks and observed for 32 weeks. Male mice were fed diets containing 80 or 160 ppm for 71 or 62 weeks, respectively, and female mice were fed at 80 or 160 ppm for 80 weeks. Mice were observed for 9-28 weeks.

In rats, the incidence of adrenal cortical adenomas and carcinomas was increased; the incidence in low-dose males was 7/49, in high-dose males was 11/46, in low-dose females was 6/47 and in high-dose females was 13/42.

Incidences in controls were 0/9 in matched control males, 3/80 in pooled control males, 1/10 in matched control females and 4/78 in pooled control females. Using pooled controls, these results are significant by the Cochran-Armitage test for positive trend ($p \leq 0.001$), and high-dose results in both sexes are significant in the Fisher Exact test ($p \leq 0.002$). The biological significance of these results is uncertain. IARC (1983) states that "the significance of adrenal cortical adenomas in aged rats is not well understood, and that adrenal cortical carcinomas occurred only in two rats of each sex and treatment group." NCI (1979) reported that under the conditions of the bioassay, parathion appears to be carcinogenic in Osborne-Mendel rats.

In mice, no increased incidences of neoplastic lesions were observed. NCI (1979) reported that parathion was noncarcinogenic in mice.

Weisburger (1982) reviewed the NCI (1979) study and concluded that parathion was not carcinogenic in mice, but was suggestive of neoplasia in rats. After review of one mouse and three rat studies, IARC judged the rat adenomas to be of uncertain significance, and overall evaluated the data base to be inadequate for evaluation of human carcinogenic potential.

4.2.2. Inhalation. Pertinent data regarding the carcinogenic potential of parathion following inhalation exposure could not be located in the available literature.

4.3. OTHER RELEVANT DATA

IARC (1983) has reviewed mutagenicity and other short-term studies of parathion. Portions of that review are reproduced as follows:

> "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 exogenous metabolic activation (Simmon et al., 1977). In a large number of tests it did not induce gene mutations in *E. coli*, *Salmonella*

typhimurium, Serratia marcescens, Saccharomyces cervisiae or Schizosaccharomyces pombe, with or without exogenous metabolic activation (Mohn, 1973; Fahrig, 1974; Simmon et al., 1977; Bartsch et al., 1980; Degraeve et al., 1980)."

"No excess of sex-linked recessive lethal mutations was induced in Drosophila melanogaster by parathion (99% pure) (Valencia, 1977; Waters et al., 1982). Negative results have also been reported for the induction of unscheduled DNA synthesis by parathion (99% pure) in W138 human fibroblasts, with or without uninduced mouse liver microsomal fractions (Jones et al., 1982; Waters et al., 1982). No dominant lethal mutation was induced in mice fed parathion (99% pure) for seven weeks at dose levels of 62.5, 125 or 250 mg/kg of diet (Simmon et al., 1977) or following a single intraperitoneal injection (Degraeve et al., 1980)."

In a study not reviewed by IARC (1983), parathion was found to induce statistically significant increases in SCE in CHO cells (Nishio and Uyeki, 1981).

Maronpot et al. (1983) tested parathion in the Strain A mouse pulmonary tumor-induction bioassay model. Groups of 20 or 30 Strain A mice of both sexes were injected intraperitoneally with parathion 3 times/week for 8 weeks. The doses used were the MTD, MTD/2, MTD/4 and MTD/5. The doses in mg were not specified. Vehicle, untreated and positive urethane controls were included as part of the experiment. The mice were killed 16 weeks after the last injection and grossly visible pulmonary tumors were counted. Parathion treatment resulted in a significant ($p<0.05$) increase in the number of mice with tumors and the multiplicity of tumors compared with negative controls. Positive controls responded appropriately.

4.4. WEIGHT OF EVIDENCE

IARC (1983) reviewed the weight of evidence of the carcinogenicity of parathion to humans and concluded that data are insufficient for evaluation.

The NCI (1979) study resulted in suggestive evidence for carcinogenicity in rats. Male and female rats treated with parathion had an increased incidence of combined adrenal cortical adenomas and carcinomas. The biological

significance of these tumors in aged rats is uncertain. Since the IARC (1983) evaluation, parathion has tested positive in the Strain A mouse pulmonary tumor bioassay model (Maronpot et al., 1983) and this evidence together with suggestive but uncertain response in rats is sufficient to place parathion in EPA Group C, a possible human carcinogen. This category is for the agents for which there is no evidence or no data on carcinogenicity in humans and only limited evidence in animals (U.S. EPA, 1986c).

NAS (1977) calculated 4.3 µg/kg/day as an RfD for parathion from the study by Rider et al. (1969). This value was obtained by applying an uncertainty factor of 10 to the dose of 3.0 mg/day that was the lower NOEL. From this level NAS (1977) calculated or suggested a NOAEL in drinking water of 0.03 mg/ℓ, assuming 70 kg as an average body weight and an average daily water intake of 2 ℓ, and that 20% of the total intake is from water.

An RfD of $5x10^{-3}$ mg/kg/day can be derived by applying an uncertainty factor of 10 to the NOEL of ~50 mg/kg/day in the Edson et al. (1964) study. This dosage appears to be calculated as the TWA of 0.6 mg/day for 4 weeks raised to 4.8 mg/day for an additional 9 weeks, assuming a human body weight of 70 kg. Using 2 ℓ as the average water intake for an average 70 kg human, and a fish intake of 0.0065 kg/day with a BCF of 347, 0.1 mg/ℓ can be recommended as the water criterion.

The most recent RfD calculated for parathion is 0.4 mg/day for a 70 kg man (U.S. EPA, 1986a). This value was based on a human NOEL of 4.5 mg/day located in the CBI files (U.S. EPA, 1986b). Higher doses were associated with blood cholinesterase inhibition.

The ACGIH (1986) TLV-TWA based on skin exposure is 0.1 mg/m³. The OSHA (1985) PEL based on skin exposure has also been set at 0.1 mg/m³. A tolerance of 1.0 ppm parathion has been established for most agricultural commodities (U.S. EPA, 1983).

6. RISK ASSESSMENT

6.1. SUBCHRONIC REFERENCE DOSE (RfD_S)

6.1.1. Oral (RfD_{SO}). Risk assessment of parathion is based on its action as a cholinesterase inhibitor. The threshold for cholinesterase inhibition varies between species, indicating that human data would be most appropriate for risk assessment.

A number of RfDs have been calculated from human data (see Chapter 5). The most recent RfD, 0.006 mg/kg/day (U.S. EPA, 1986a,d), was derived from a human study found in the CBI files, which identifies a human NOAEL for erythrocyte cholinesterase inhibition. The value calculated from this study, 0.006 mg/kg/day or 0.4 mg/day for a 70 kg human, will be recommended as the RfD_{SO} for the purpose of this document.

6.1.2. Inhalation (RfD_{SI}). Pertinent data regarding the toxicity of parathion following inhalation exposure could not be located in the available literature; therefore, an RfD_{SI} cannot be derived.

6.2. REFERENCE DOSE (RfD)

6.2.1. Oral (RfD_O). No chronic human oral studies of parathion are available. Subchronic studies have been used to calculate an RfD. The most recent RfD, derived from a human NOAEL for erythrocyte cholinesterase activity found in a CBI study, and an uncertainty factor of 10, is 0.006 mg/kg/day or 0.4 mg/day for a 70 kg human (U.S. EPA, 1986a,d). For the purpose of this document, these values will be recommended as the RfD_O for parathion. Whether this level will be protective against the carcinogenicity or reproductive effects of parathion is uncertain.

In deriving an RQ for parathion, CSs have been calculated (U.S. EPA, 1984b). The largest CS value in this document was derived from the study by Barnes and Denz (1951). This 3-generation study, however, used parathion

that was only 76.8% pure and only six rats were used. Because of these deficiencies and because better studies are available, CS values from the Barnes and Denz (1951) study will not be presented in this document.

Human MEDs derived in U.S. EPA (1984b) are higher than the values reported in this document because it appears that the cube root of the body weight ratio was not used to convert from animal exposure to the human MED. CSs for parathion from a number of studies are presented in Table 6-1.

Data in the CBI files indicate that the MED for blood cholinesterase inhibition in humans is 0.079 mg/kg/day or 5.53 mg/day, assuming a human reference body weight of 70 kg. This dose is associated with an RV_d of 4.4. Inhibition of blood cholinesterase activity is assigned an RV_e of 1. A CS of 4.4 results. The highest value, 36, was obtained from a 3-generation rat study found in the CBI file (U.S. EPA, 1986b).

6.2.2. Inhalation (RfD_I). Pertinent data regarding the toxic effects of parathion following inhalation exposure could not be located in the available literature; therefore, an RfD_I cannot be derived.

6.3. CARCINOGENIC POTENCY (q_1^*)

6.3.1. Oral. The NCI (1979) bioassay showed an increase in the combined incidences of adenomas and carcinomas of the adrenal cortex in rats of both sexes. Adenomas predominated in the study, and the significance of these tumors in aged rats is uncertain. Because of the weakness in the specific animal cancer data for parathion, a q_1^* value will not be calculated for this document.

In a report in the CBI files (U.S. EPA, 1986b), the OPP reinterpreted the results of the NCI (1979) bioassay. Using the incidence of adrenal cortical tumors in female rats, OPP estimated "virtually safe" exposures.

TABLE 6-1

Composite Scores for the Oral Toxicity of Parathion

Species/Strain	Sex	Exposure/Dose (mg/kg/day)	Human MED[a] (mg/day)	RV_d	Effect	RV_e	CS	Reference
Human/NA	NR	0.074 mg/kg/day, 5 days/week for several weeks or months	5.53[b]	4.4	Cholinesterase inhibition in blood	1	4.4	U.S. EPA, 1986b
Rat/Osborne-Mendel	M	TWA-63 ppm diet (3.15 mg/kg/day)[c]	41.9	3.1	Reduced body weight gain	4	12.4	NCI, 1979
	F	TWA-45 ppm diet (2.25 mg/kg/day)[c]	26.9	3.4	Reduced body weight gain, tremors, diarrhea	7	23.8	NCI, 1979
Mice/B6C3F1	M	80 ppm diet (10.4 mg/kg/day)[c]	56.0	2.9	Reduced body weight gain, diarrhea, tremors	7	20.3	NCI, 1979
Rats/NR	M&F	50 ppm diet (2.5 mg/kg/day)[c]	29.9	3.3	Reduced body weight gain, retinal atrophy (F), sciatic nerve atrophy (M)	7	23.1	U.S. EPA, 1986b
		30 ppm diet (1.5 mg/kg/day)[c]	18.0	3.6	(F_2) reduced survival at weaning, tremors, reduced pup weaning weights	10	36	U.S. EPA, 1986b

[a]Human MED = animal dose (mg/kg/day) x [(animal bw/70 kg (human bw)) x 70 kg]
animal bw: male rat = 0.48 kg (estimated from graphic data provided by investigators)
female rat = 0.35 kg (estimated from graphic data provided by investigators)
male mice = 0.032 kg (estimated from graphic data provided by investigators)
reference bw of 0.35 kg used for rats from the CBI studies

[b]*Although exposure was subchronic, an uncertainty factor was not applied in computation of MED because cholinesterase inhibition, once established, is not dependent on duration of exposure*

[c]Doses calculated using food conversion factors, 0.05 (rats) and 0.13 (mice)

NA = Not applicable; NR = not reported

Applying the linear extrapolation model, the dose corresponding to a risk of 10^{-5} is almost an order of magnitude smaller than the RfD_{SO} and RfD_0 value presented in this document. The less conservative log-probit model estimates a dose corresponding to a risk of 10^{-5} that is of the same order of magnitude as the RfD_{SO} and RfD_0 value. The U.S. EPA uses the multistage model of Crump (U.S. EPA, 1980) to estimate risk for carcinogens. At low risk levels, this model usually results in values closer to the linear model (Park and Snee, 1983). Therefore, if adrenal adenomas and carcinomas in rats are a biologically significant tumorigenic response to parathion exposure, the RfD_{SO}/RfD_0 value of 6.4×10^{-3} mg/kg/day may not be protective from the carcinogenic potential of parathion at the risk level of 10^{-5}.

6.3.2. Inhalation. Data regarding the carcinogenic potential of parathion following inhalation exposure could not be located in the available literature; therefore, an inhalation q_1^* cannot be calculated.

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APPENDIX

Summary Table for Parathion

	Species	Experimental Exposure/Dose (mg/kg/day)	Effect	Reference Dose (RfD_S or RfD)	Reference
Oral					
RfD_{SO} (formerly AIS)	human	0.064	NOAEL - erythrocyte cholinesterase inhibition	0.4 mg/day	U.S. EPA, 1986a
RfD_O (formerly AIC)	human	0.064	NOAEL - erythrocyte cholinesterase inhibition	0.4 mg/day	U.S. EPA, 1986a
Maximum					
CS	rats	30 ppm diet, 3-generation reproduction study (1.5 mg/kg/day) (RV_d=3.6)	reduced survival at weaning (RV_e=10)	CS=36	U.S. EPA, 1986b