Australian Pesticides & Veterinary Medicines Authority

The reconsideration of approvals of the active constituent fenthion, registrations of products containing fenthion and their associated labels

Part 1: Uses of fenthion in non-food-producing situations

Preliminary Review Findings

Volume 2: Technical Reports

DECEMBER 2005

Australian Pesticides & Veterinary Medicines Authority

Canberra Australia

This review report for products containing fenthion is published by the Australian Pesticides and Veterinary Medicines Authority. For further information about this review or the Pesticides Review Program, contact:

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FOREWORD

The Australian Pesticides & Veterinary Medicines Authority (APVMA) is an independent statutory authority with responsibility for the regulation of agricultural and veterinary chemicals in Australia. Its statutory powers are provided in the Agvet Codes scheduled to the *Agricultural and Veterinary Chemicals Code Act 1994*.

The APVMA can reconsider the approval of an active constituent, the registration of a chemical product or the approval of a label for a container for a chemical product at any time. This is outlined in Part 2, Division 4 of the Agvet Codes.

The basis for the current reconsideration is whether the APVMA is satisfied that continued use of the active constituent fenthion and products containing fenthion in accordance with the instructions for their use:

- would not be an undue hazard to the safety of people exposed to it during its handling; and
- would not be likely to have an effect that is harmful to human beings; and
- would not be likely to have an unintended effect that is harmful to animals, plants or things or to the environment.

The APVMA also considered whether product labels carry adequate instructions and warning statements.

A reconsideration may be initiated when new research or evidence has raised concerns about the use or safety of a particular chemical, a product or its label.

The reconsideration process includes a call for information from a variety of sources, a review of that information and, following public consultation, a decision about the future use of the chemical or product.

In undertaking reconsiderations (hereafter referred to as reviews), the APVMA works in close cooperation with advisory agencies including the Office of Chemical Safety, the Department of the Environment and Heritage, and state departments of agriculture as well as other expert advisers as appropriate.

The APVMA has a policy of encouraging openness and transparency in its activities and community involvement in decision-making. The publication of review reports is a part of that process.

The APVMA also makes these reports available to the regulatory agencies of other countries as part of bilateral agreements. The APVMA recommends that countries receiving these reports will not utilise them for registration purposes unless they are also provided with the raw data from the relevant applicant.

This document sets out the preliminary review findings relating to all products containing fenthion used in non-food-producing situations that have been nominated for review by the APVMA. The assessment of data for the review of fenthion products used in food-producing situations is still to be complete. It will form Part 2 of the fenthion review. The preliminary review findings and proposed recommendations are based on information collected from a variety of sources. The information and technical data required by the APVMA to review the safety of both new and existing chemical products must be derived according to accepted scientific principles, as must the methods of assessment undertaken.

ACRONYMS AND ABBREVIATIONS

Time

d	Day
h	Hour
min	Minute
mo	Month
wk	Week
s	Second
yr	Year

Weight

bw	Body weight
g	Gram
kg	Kilogram
µg	Microgram
mg	Milligram
ng	Nanogram
wt	Weight

Length

cm	Centimetre
m	Metre
µm	Micrometre
mm	Millimetre
nm	Nanometre

Dosing

id	Intradermal
im	Intramuscular
inh	Inhalation
ip	Intraperitoneal
iv	Intravenous
po	Oral
sc	Subcutaneous
mg/kg bw/d	mg/kg bodyweight/day

Volume

L	Litre
mL	Millilitre
µL	Microlitre

Concentration

M	Molar
ppb	Parts per billion
ppm	Parts per million

Clinical chemistry, haematology, urinalysis

A/G	Albumin/globulin ratio
ALT	Alanine Aminotransferase (SGPT)
AP	Alkaline Phosphatase
AST	Aspartate Aminotransferase (SGOT)
BUN	Blood Urea Nitrogen
ChE	ChE
CPK	Creatine Phosphatase (phosphokinase)
GGT	Gamma-Glutamyl Transferase
Hb	Haemoglobin
Hct	Haematocrit (packed cell volume)
LDH	Lactate Dehydrogenase
MCH	Mean Corpuscular Haemoglobin
MCHC	Mean Corpuscular Haemoglobin Concentration
MCV	Mean Corpuscular Volume
NTE	Neurotoxicity/neuropathy Target Esterase
PT	Prothrombin Time
RBC	Red Blood Cell (RBC)
WBC	White Blood Cell/leucocyte
WBC-DC	White Blood Cell – Differential Count

Anatomy

CNS	Central Nervous System
GIT	Gastro-Intestinal Tract

Chemistry

BH6	Obidoxime chloride
CMC	Carboxymethyl Cellulose
CO_2	Carbon Dioxide
DMSO	Dimethyl Sulfoxide
2-PAM	Pyridine-2-aldoxime methiodide
P-2-S	2-Pyridine-aldoxime methyl methanesulfonate
TMB-4	(1, 1-trimethylene-bis(4-formyl-pyridinium bromide) dioxime)
TOCP	Tri-Ortho Cresyl Phosphate

Terminology

ADI	Acceptable Daily Intake
ARfD	Acute Reference Dose
ECG	Electrocardiogram
FOB	Functional Observation Battery
gd	Gestational day
GLP	Good Laboratory Practice
HPLC	High Performance Liquid Chromatography
ld	Lactational day
LOEL	Lowest Observed Effect Level
MRL	Maximum Residue Limit or Level
NOEC	No Observed Effect Concentration
NOEL	No Observed Effect Level
NZW	New Zealand White
OP	Organophosphorus pesticide
OPIDN	Organophosphate Induced Delayed Neuropathy
PCO	Pest Control Operator
SCE	Sister Chromatid Exchange
SD	Sprague-Dawley (rats)
UDS	Unscheduled DNA Synthesis

Organisations & publications

ACPH	Advisory Committee on Pesticides and Health
APVMA	Australian Pesticides and Veterinary Medicines Authority
CRP	Chemical Review Program
FAO	Food and Agriculture Organisation of the United Nations
FAISD	First Aid Instructions & Safety Directions
IPCS	International Programme on Chemical Safety
JMPR	Joint FAO/WHO Meeting on Pesticide Residues
NCI	National Cancer Institute
NDPSC	National Drugs and Poisons Schedule Committee
NHMRC	National Health and Medical Research Council

NOHSC	National Occupational Health & Safety Commission
SUSDP	Standard for the Uniform Scheduling of Drugs and Poisons
US EPA	United States Environmental Protection Agency
WHO	World Health Organisation

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9. TOXICOLOGY ASSESSMENT

9.1 Summary Toxicology Report

9.1.1 Introduction

Fenthion was nominated for review as part of the Australian Pesticides and Veterinary Medicines Authority's (APVMA) Chemical Review Program (CRP) because of its high acute toxicity, its ocular toxicity potential and the age of the toxicological database. A number of additional data submissions on the toxicology of fenthion were received from industry and the public following the CRP data call-in process, and these data, together with all previously submitted data, have been assessed in detail. The detailed report is summarised below.

9.1.2 Metabolism and Toxicokinetics

Patterns of absorption, distribution, metabolism and elimination of administered fenthion are broadly comparable between rats, pigs, cows and goats. Absorption is rapid after any route of exposure, distribution is extensive particularly into lipid stores, metabolism is extensive and can generate active anti-ChE intermediates, and elimination is almost complete. Tissue residues were low in all species.

Metabolism of fenthion generally commences with desulphuration of thiophosphoric ester portion of fenthion (PS) to yield the phosphooxone oxygen analog (fenthoxone; POS). Both fenthion and fenthoxone can be oxidised to the corresponding sulphoxides (PSSO, POSO) and sulphones ($PSSO_2$, $POSO_2$) by oxidation of the ring $–SCH_3$ group. Further metabolites can be formed by demethylation of one of the two oxymethyl groups. Hydrolysis of the ring P-O bond leads to loss of the OP moiety and gives rise to a fenthion "phenol" (PhS) which can also be oxidised to the corresponding sulphoxide (PhSO) and sulphone ($PhSO_2$) forms. The oxygen analogue of fenthion and its sulphoxide and sulphone derivatives are generally regarded as principal active metabolites, rather than fenthion itself.

Rats

In a pre-GLP study, male rats were treated with single oral (100 mg/kg bw) or multiple intraperitoneal (10 mg/kg bw for 10 days) doses of [^{32}P]-labelled fenthion. For each route of administration metabolism was almost complete, excretion of the metabolites (hydrolysis products) was rapid (urine and faeces), and tissue residues were low. ChE activity in whole blood and brain rapidly declined in the intraperitoneal-dosed animals, reaching its lowest levels on day 10 and recovering slowly after dosing ceased. (Brady & Arthur 1961)

Rats were dosed with a single dose of ring-labelled fenthion, either intravenously at 2 mg/kg bw or orally at 10 or 100 mg/kg bw. A fourth group was given 14 daily doses of unlabelled fenthion at 10 mg/kg bw before receiving a single oral dose of labelled fenthion at 10 mg/kg bw. The orally administered fenthion was readily and almost completely absorbed (96-100% at 72 h) at both 10 and 100 mg/kg. The level of fenthion in plasma peaked at 20–45 min following single oral doses of 10 or 100 mg/kg bw. In those animals pretreated for 14 days with unlabelled fenthion, peak plasma levels were reached 2–3 h after a single oral dose of labelled fenthion. Fenthion was rapidly and nearly completely (>90%) excreted within 48 h mainly via the kidneys (>93%). The major metabolite group (ca. 60%) was composed of the three phenols and their sulphate and glucuronide conjugates. Four desmethyl metabolites totalled ca. 30% of the radiolabel. There were low levels of residues in tissues. (Puhl & Hurley 1982)

Fenthion was administered as a single dose by gavage, dermal application or subcutaneous injection to male rats at 0, 1, 5 or 25 mg/kg bw. There were no mortalities or clinical signs and necropsy findings did not significantly differ from the control groups for any dose or route of administration. There was variable depression of plasma and RBC ChE activity depending on assay time and dosage route. Oral treatment with 5 or 25 mg/kg bw induced plasma and RBC ChE inhibition on day 1 with rapid recovery of plasma followed by RBC activity; brain activity was reduced at both doses on day 14. Onset of inhibition was slower for the dermal and subcutaneous routes but lasted longer. Brain ChE, measured only at day 14, was depressed in all groups at 25 mg/kg bw, but at 5 mg/kg bw it was depressed in the oral treatment group only. (Christenson 1990c)

Rats were dosed with a single dose of ring-labelled fenthion, either intravenously at 0.125 mg/kg bw or orally at 0.3 or 1.5 mg/kg bw. A fourth group was given 14 daily doses of unlabelled fenthion at 0.3 mg/kg bw before receiving a single oral dose of labelled fenthion at 0.3 mg/kg bw. A further group was given a single oral dose of 0.3 mg/kg bw labelled fenthion for measurement of expired carbon dioxide (CO_2). Fenthion was rapidly and nearly completely (75-104%) excreted within 48 h mainly via the kidneys (>88%); only minor amounts (1-10% of the dose) were excreted in the faeces, and no label was found in expired CO_2. The excretion and metabolite profiles were generally similar, regardless of the route of administration, dose, sex of the rats, or pretreatment with unlabelled fenthion. Tissue retention of radiolabel was very low and the tissue residue levels were generally <1 ppb. (Doolittle & Bates 1993)

Rabbits

Rabbits were dosed with fenthion at 20 mg/kg bw via the oral, subcutaneous or intravenous routes (3/group). Fenthion reached peak plasma concentration at 10 h, 4 h and 1 h after oral, subcutanous and intravenous administration respectively. No fenthion was detected in any samples at 48 h. The half-life of fenthion in the blood was 11-12 h, regardless of the route of administration. (Emteres et al 1985)

Daily oral administration of fenthion to rabbits at 0, 5, 10 or 20 mg/kg bw/d produced a cumulative toxic effect, with death of all animals within 15 days at 20 mg/kg bw/d and within 35 days at 5 mg/kg bw/d. (Emteres et al 1986)

Pigs, cows and goats

Lactating Jersey cows were dosed with labelled fenthion as a single dermal dose of approximately 13 mg/kg bw or a single intramuscular dose of approximately 8.6 mg/kg bw. Radioactivity peaked in the milk 18 h and 8 h after dermal and intramuscular treatment respectively, but only 1.1% and 2.2% of the dermal and intramuscular doses respectively were eliminated in the milk within 2-3 weeks after dosing. (Knowles & Arthur 1966)

Lactating dairy cows consumed fenthion in the diet at 0.43, 0.70 or 1.29 mg/kg bw/d for 28 days. The peak total residues in the high-dose animals over the treatment period were: <0.1

mg/kg in milk; <0.31 mg/kg in faeces; and <1.1 mg/kg in urine. Seven days after the end of treatment, no residues were detected in milk, faeces or urine. (Johnson & Bowman 1972)

Lactating dairy cows were treated with a single dermal dose of radiolabelled fenthion at 9 mg/kg bw. The concentration of radiolabel in blood, milk, urine and faeces peaked between the first and second days after treatment. Urine was the main route of elimination of the predominantly hydrolytic products of fenthion. The cumulative percentage of radioactivity found in milk was <2% of the applied dose. (Avrahami & White 1975)

One male and one female pig were given a single oral gavage dose of ring-labelled fenthion at 5 mg/kg bw and seven days laterk, two or three consecutive daily doses of unlabelled fenthion at 10 mg/kg bw. Elimination of label was rapid; total excretion over the first 30 h being >84% of the administered dose. Urine was the main route of elimination, accounting for >80% of the dose within 24 h; only minor amounts (<10% of the single dose) were excreted in the faeces. The main urinary metabolites were conjugated phenols (phenol fenthion, phenol sulfoxide and phenol sulfone). Tissue residue levels declined rapidly indicating rapid elimination from tissues. (Pither 1979)

A male pig was given a single dermal dose of ring-labelled fenthion at 14 mg/kg bw, applied as a pour-on formulation along the spine. The pig was sacrificed 18 h after treatment, and skin and selected tissues were removed and analysed for residues. The tissue residues were mainly unchanged fenthion and were low except at the site of application, where significantly higher levels were measured in hair, skin and subcutaneous fat. Fenthion sulphoxide and fenthion sulphone were minor residue components. (Crosby *et al* 1990)

A lactating dairy cow was given a single dermal dose of ring-labelled fenthion at 5.1 mg/kg bw, applied as a pour-on formulation along the spine. The cow was sacrificed 18 h after treatment, and urine, milk, skin and selected tissues removed and analysed for residues. Residue levels were high in urine (4 ppm) but low in milk (<0.05 ppm). Tissue residues were mainly unchanged fenthion and were low in sampled tissues except at the site of application, where significantly higher levels were measured in hair, skin, and subcutaneous fat. Fenthion sulphoxide was a minor residue component. (Krautter 1990a)

A study was conducted to characterise the unknown polar metabolite(s) found in liver and kidney tissues after cows and pigs were treated dermally with a radiolabelled fenthion formulation and sacrificed 18 h later (see Krautter 1990a; Crosby et al 1990). For both cows and pigs, at 18 h after dosing parent fenthion accounted for 50-96% of total residues in tissue (liver, kidney, muscle, fat), except for pig kidney where parent fenthion was 23% of total residues. Two or more unknown polar metabolites found in the liver and kidney represented 22-57% of the total residues for these tissues. These were identified as glucuronide conjugates of fenthion phenol sulfoxide and fenthion phenol sulfone. (Krautter 1990b; Waggoner 1991)

A lactating goat was dosed orally with ring-labelled fenthion at 20 mg/kg bw daily for three days. The goat was sacrificed 3.5 h after the last dose, and the level and nature of the residues were determined in urine, milk and edible tissues. Absorption was rapid and a peal plasma level was reached approximately 3 h after the first dose with a half-life of ca. 3.3 h during the next 20 h. Milk residue levels were 2.8 and 3.4 μg/g at 8 h after the first and second doses, respectively, while tissue residues 3.5 h after the last dose were found in kidney (24.1 μg/g), liver (3.32 μg/g), fat (1.04-2.73 μg/g) and muscle (0.62 μg/g). Phenol fenthion, phenol sulfoxide, and phenol sulfone were the three major metabolites in all tissues examined. At sacrifice (3.5 h after last dose) the total excretion of radiolabel was 50.6% (44.1% was excreted in urine, 6.3% in faeces, 0.2% in milk). Residue in edible tissue and organs was 0.9%. (Weber & Ecker 1992)

Comparative studies

Fenthion (96.5%) and some oxidative metabolites were administered to mice, rats, guinea pigs, rabbits and hens by oral and dermal routes in order to establish LD_{50} values and levels of ChE inhibition. Oral LD_{50} values (mg/kg bw) established in mice (150 male, 190 female), rats (215 male, 615 female) and rabbits (150-175 male) were generally similar, while hens were very sensitive (30-40 female) and guinea pigs resistant (>1000 male) to single dose oral toxicity. The acute toxicity manifested as a variety of signs including fasciculations appearing 40-90 min after an oral dose, salivation, tremors, gross weakness, spasticity and chromodacryorrhoea. Time of death after a lethal dose varied between species, being from 6-72 h in rats, 1.5-48 h in mice, and 24-48 h in rabbits and hens. Repeated oral dosing in rats indicated that recovery from dosing was slow and that brain ChE inhibition was sustained. The authors suggest that the prolonged effect of fenthion after a single dose is because a large part of the administered doses is stored and only slowly released for metabolism. Experiments with metabolites indicated an order of dermal toxicity of fenthion>fenthion sulphone>fenthion sulphoxide. (Francis & Barnes 1963)

Radiolabelled fenthion was administered orally or subcutaneously to lean, fasting rats and rabbits or to well-fed corpulent animals. The peak concentration of radiolabel appeared in the plasma one hour after treatment for the lean animals and 6-9 hours after treatment for the well-fed animals. Excretion of radiolabel was primarily urinary in both groups and for each species. It appears that there is a more rapid breakdown and elimination of the administered compound from the system of lean animals rather than well-fed ones. (Begum 1967)

9.1.3 Acute Toxicity

Active constituent

In general, signs of acute fenthion intoxication in animals were consistent with ChE inhibition, and included inactivity, salivation, muscle fasciculations, dyspnoea, flaccid paralysis, vomiting, piloerection, exophthalmia and diarrhoea.

Fenthion was moderately toxic by the oral route; the ranges for oral LD_{50} values were 140-615 mg/kg bw for rats and 200-290 mg/kg bw for mice. Males were slightly more sensitive than females in some tests in rats and mice. The acute dermal toxicity of fenthion is also moderate, ranging from 271->5000 mg/kg bw in rats and 500-2000 mg/kg bw in mice. Fenthion has a low to moderate acute toxicity when administered inhalationally as a mist; LD_{50} values ranged from 454->1878 mg/m^3 in rats (4 h exposure) and 2000-2400 mg/m^3 in mice (1 h exposure). Fenthion did not irritate rabbit skin (Pauluhn 1985; Eigenberg 1987c). There was evidence of slight eye irritation after one but not 24 hours in rabbits (Eigenberg 1987d; Pauluhn 1985). It did not sensitise guinea pig skin in the Magnusson and Kligman maximisation test (Flucke 1987).

The acute oral and intraperitoneal toxicity of the oxygen analogue of fenthion and its sulphoxide and sulphone derivatives, thought to be the principal active metabolites, were 5-10-fold that of fenthion.

Female rats were dosed intraperitoneally with single equitoxic doses of fenthion and one of 16 other anti-ChE insecticides. Potentiation of approximately 2- to 3- fold was seen in combination with either malathion, diaxathion or coumaphos. (Dubois & Kinoshita 1964)
Male and female dogs were fed diets containing low levels of fenthion in combination with one of malathion, dioxathion or coumaphos for 6-weeks. Potentiation, measured as significant serum or RBC ChE inhibition, was seen with coumaphos and malathion but not dioxathion. (Doull et al 1962)

Antidote studies in rats using subcutaneous doses of pyridine-2-aldoxime methane sulphonate (P2S) found that that a single oral dose of fenthion is metabolised slowly enough to require the antidote being administered regularly until clinical signs have abated completely. (Francis & Barnes 1963)

Another study in rats found that single intraperitoneal doses of the antidotes Pyridine-2-aldoxime methiodide methiodide (2-PAM) or (1, 1-trimethylene-bis(4-formyl-pyridinium bromide) dioxime) (TMB-4) did not have any antidote effect on the acute toxicity of intraperitoneal-administered fenthion. (DuBois 1960)

The antidote effects of obidoxime chloride (BH6) in the presence and absence of atropine sulphate were measured by changes in the acute toxicity of orally administered fenthion in male rats. BH6 had an antidote effect when given at 30 minutes, 6 hours or 24 hours after fenthion, an effect which was improved by simultaneous administration of atropine sulphate. The antidote effect of BH6 was greater if more than one dose was given. (Kimmerle 1963)

Dogs were given sublethal or lethal oral doses (stomach tube) of 7 insecticide products including a 50% fenthion formulation. With the exception of parathion, the reactivation of RBC ChE by obidoxime was transient and varied considerable between the test chemicals. Fenthion was the only tested substance which recorded significant reactivation of plasma as well as RBC ChE. (Han & Henschler 1968)

Products

The acute toxicity of fenthion formulations was closely correlated with the concentration of the active constituent in the end-use products. The signs associated with intoxication were similar to those seen with the active.

9.1.4 Short-Term Repeat-Dose Studies

In three pilot studies, mice were fed fenthion in the diet at doses between 0-12 mg/kg bw for 2-3 weeks. There were no clinical signs or mortalities. Plasma ChE activity was inhibited in a dose-related manner. RBC ChE activity was reduced in females more than in males. Brain ChE activity in both sexes were reduced by up to 47% at 12 mg/kg bw fenthion. (Suberg 1988)

Mice were dosed with fenthion in the diet for 5 weeks at 0, 25, 40 or 55 mg/kg bw/d. There were no clinical signs and no mortalities. Plasma, RBC and brain ChE activities were inhibited across all doses (96-98%, 88-100% and 57-69%, respectively). (Leser 1989)

Mice were dosed with fenthion in the diet for 4 weeks at 0, 85, 115 or 145 mg/kg bw/d. There were some clinical signs and mortalities in males during the study and reduced liver weights in 145 mg/kg bw/d females. Plasma, RBC and brain ChE activities were inhibited across all doses (>98%, 80-98% and 68-80%, respectively). (Leser 1990).

Rabbits were dosed with fenthion dermally 5 days/week at 0, 5 or 25 mg/kg bw/d for three weeks. There were no clinical signs and no mortalities. Plasma and RBC ChE activities were reduced by 50% at 25 mg/kg bw/d. Brain ChE activity was unaffected by treatment. (Mihail & Schilde 1979)

Rabbits were dosed with fenthion dermally at 0, 5, 50 or 100 mg/kg bw/d, 5 days/week for three weeks. There were no clinical signs and no mortalities. Plasma, brain and RBC ChE activity were slightly reduced at the high dose, with males generally more sensitive than females. (Bailey 1987)

Rabbits were dosed with fenthion dermally at 0, 150, 200 or 400 mg/kg bw/d, 5 days/week for three weeks. There were early deaths and clinical signs at the two highest doses and these treatments were discontinued. At 150 mg/kg bw/d there were clinical signs in the males. Plasma, brain and RBC ChE activities were reduced in both sexes, with males more sensitive than females. (Bailey 1988)

In an inhalation study, rats were exposed to fenthion aerosol at 0, 1, 3 or 16 mg/m^3, 5 days/week for 3 weeks. Clinical signs occurred only in the females and there were no mortalities. Plasma, RBC, and brain ChE activities were inhibited in a dose dependent manner in both sexes. (Thyssen 1979)

9.1.5 Subchronic Studies

An oil-based spray containing 2.9% fenthion was applied daily for 12 successive days to the shaven backs of female rats (5 rats/dose) giving doses equivalent to 2.9, 7.25 or 14.5 mg/kg bw fenthion. Blood ChE activity was markedly reduced by 3 days at all doses (43, 60 and 78% reductions at 2.9, 7.25 and 14.5 mg/kg bw, respectively). In a similar experiment using daily application for 60 days to the shaven backs of female rats (5 rats/dose), the dose levels were equivalent to 14.5 and 25 mg/kg bw fenthion. No deaths were seen at 14.5 mg/kg bw, whilst 2 out of 5 rats in the 25 mg/kg bw group died. There were marked tremors during the first 30 days of treatment at 25 mg/kg bw, an effect which decreased during the second 30 days. (Dubois & Puchala 1960; Dubois 1961)

Fenthion was administered intraperitoneally once per day for 60 days to young adult female rats (5/group) at 0, 10, 20, 40, 50 or 100 mg/kg bw/d. The animals receiving 100 mg/kg bw/d died within five days, the 40 and 50 mg/kg bw/d groups within 5-10 days and the 20 mg/kg bw/d group within 10-30 days. Only the control and 10 mg/kg bw/d groups survived to day 60 without any mortalities (DuBois & Raymund 1960).

Female rats were dosed intraperitoneally with 200 mg/kg bw fenthion or its sulphone or sulphoxide derivatives and sacrificed at intervals over the next 28 days. ChE activity was markedly inhibited (>85% inhibition) in brain, serum and submaxillary gland with rapid onset (1-2 days) and slow recovery (>4-weeks). The S-methyl fenthion derivative produced similar results. The oxygen analog of fenthion (16 mg/kg bw), and its sulphoxide (14 mg/kg bw) and sulphone (5.5 mg/kg bw) produced significant inhibition of ChE activity in brain, serum and submaxillary gland with rapid recovery (12 h). (DuBois & Kinoshita 1964)

In a 16-week rat dietary study (0, 2, 3, 5, 25 or 100 ppm fenthion), early toxic signs including diarrhoea, salivation and lacrimation were observed and there were dose-dependent reductions in serum, RBC, submaxillary gland and brain ChE at and above 5 ppm. The NOELs for serum, RBC and brain ChE activities were 0.33 and 0.41 mg/kg bw/d for males and females, respectively. (Doull et al 1961a)

In a 12-week dog dietary study (0, 2, 5 or 50 ppm fenthion) the only treatment-related effects were significant inhibition of serum ChE activity at 5 and 50 ppm and of RBC ChE activity at 50 ppm. The respective NOELs for serum and RBC ChE inhibition were 2 ppm and 5 ppm, (equivalent to 0.04 and 0.09 mg/kg bw/d, respectively). (Doull et al 1961b)

Hens were given fenthion in the diet at 0 or 4 mg/kg bw/d for 90 days. There were no deaths and no significant clinical signs during the study. Blood and tissue ChE activities were depressed by treatment. Treatment also induced mild oesophageal thickening due to hyperplasia/hypertrophy of the smooth muscle. (Hayes 1989)

9.1.6 Chronic Studies

Mice were exposed to fenthion in the diet at nominal levels of 0, 0.1, 1, 5 or 25 ppm for two years, with an interim (1 year) sacrifice group. The dietary levels of 0, 0.1, 1, 5 and 25 ppm equate to a daily dietary exposure of 0, 0.03, 0.4, 1.95 and 9.42 mg/kg bw/d for males, and 0, 0.03, 0.47, 2.25 and 10.63 mg/kg bw/d for females, respectively. Mortality during the study was unaffected by exposure to fenthion. Dietary intake of fenthion was tolerated without clinical signs, at doses up to and including 25 ppm. There were bodyweight increases in both sexes at the 25 ppm level associated with larger liver and kidney weights. There was some evidence of metabolic adaption to the dietary intake, especially in females. The NOEL for plasma ChE inhibition was 0.1 ppm (0.03 mg/kg bw/d) based on significant inhibition in both sexes at 1.0 ppm (0.4 mg/kg bw/d, male; 0.047 mg/kg bw/d, female). The NOEL for RBC ChE inhibition was 5 ppm (1.95 mg/kg bw/d, male; 2.25 mg/kg bw/d, female) based on significant inhibition in both sexes at 25 ppm (9.4 mg/kg bw/d, male; 10.6 mg/kg bw/d, female). The NOEL for inhibition of brain ChE activity was considered to be 0.1 ppm (0.03 mg/kg bw/d) based on the toxicologically and statistically significant inhibition seen in females at and above 1 ppm (0.47 mg/kg bw/d) at the interim sacrifice. The gross pathology and histopathology findings recorded no indication of a treatment-related effect of dietary intake of fenthion. There was no significant increase in the incidence of benign or neoplastic tumours in the study at any dose. (Leser & Suberg 1990 & 1992; Van Goethem & Leser 1993)

Rats were exposed to fenthion in the diet at 0, 5, 20 or 100 ppm (equivalent to 0, 0.2, 0.8, 5.2 mg/kg bw/d in males, 0, 0.3, 1.3, 7.3 mg/kg bw/d in females, respectively) for two years. A satellite group at 0 and 100 ppm were sacrificed at one year. Mortality during the study was unaffected by exposure to fenthion and there was no evidence of any treatment-related oncogenic effect. Clinical signs were recorded predominantly in the 100 ppm animals and included an increased incidence of urine staining, enlarged preputial glands, alopecia, hunched back, loose stool, rough coat, eye opacity zones and increased incidence of irritation of the penis, as well as lower bodyweights at termination. Several clinical chemistry, haematology and urinalysis parameters recorded statistically significant differences between controls and treated groups, however many of these statistically flagged results were not considered biologically significant. The NOEL for clinical chemistry results other than ChE activity was considered to be 100 ppm in both sexes. Haematology findings were minor and/or transient and the NOEL for haematology parameters was considered to be 100 ppm for both sexes. Pathology findings in the 100 ppm group included an increased incidence of raised zones on the stomach and on the skin of tail and feet, as well as vacuolar degeneration of the epididymis and the nasolacrimal duct which was evident in 20 ppm females also. Ophthalmological findings included significantly increased incidence of corneal scars in 100 ppm males and females, retinal degeneration in 100 ppm females, and suppressed or absent electroretinograms in 20 and 100 ppm females. There was a dose-related and mostly statistically and/or toxicologically significant inhibition of brain, plasma and RBC ChE activities in both sexes at all dose levels. There was no NOEL demonstrated for ChE inhibition in this study. The lowest dose tested (5 ppm; 0.2 and 0.3 mg/kg bw/d for males and females, respectively) is considered a LOEL for plasma, RBC and brain ChE inhibition. (Christenson 1990a & 1993b)

Dogs were dosed with fenthion via the diet at 0, 2, 10 or 50 ppm for one year. This equated to 0, 0.06, 0.26 and 1.23 mg/kg bw/d for males, and 0, 0.06, 0.26 and 1.18 mg/kg bw/d for females, respectively. There were no mortalities, bodyweight changes or treatment-related clinical signs. Gross pathology examination revealed only incidental, non-treatment-related findings. The ophthalmological investigations revealed no significant findings in either sex at any dose level. Clinical pathology findings did not reveal any consistent dose-related differences between the groups for blood biochemistry, haematology or urinalysis except for ChE measurements. There was a dose-related inhibition of plasma ChE in both sexes which was of borderline significance at 2 ppm but clearly significant at 10 and 50 ppm, with females slightly more sensitive than males. RBC and brain ChE activities were generally reduced at 10 and 50 ppm in both sexes but this inhibition only achieved statistical significance at 50 ppm. The NOEL for plasma ChE inhibition in this study was 2 ppm (0.06 mg/kg bw/d). The NOEL for both RBC and brain ChE was 10 ppm (0.26 mg/kg bw/d). (Christenson 1990b; Christenson 1993a)

In a poorly documented pre-GLP study, four groups of mongrel dogs (2/sex/group) were fed diets containing technical-grade fenthion (92.1% purity) at 0, 2, 5, or 50 ppm (equivalent to 0, 0.05, 0.125 and 1.25 mg/kg bw/d, respectively) for one year. A slight increase in spleen weight with splenic congestion, extramedullary haematopoiesis, and haemosiderosis, was observed in all treated animals; the effect was not dose-related and not considered adverse. The NOEL for serum ChE was 0.05 mg/kg bw/d based on significant inhibition at higher doses. The NOEL for RBC and brain ChE activity was 0.125 mg/kg bw/d based on significant inhibition at the next higher dose of 1.25 mg/kg bw/d. (Doull *et al* 1963b)

In a well documented but non-GLP study, groups of beagle dogs were fed for 2 years with diets containing 0, 3, 10 or 30/50/60 ppm fenthion (30 ppm from week 1-64; 50 ppm from week 65-67; 60 ppm from week 68-104) (equivalent to 0, 0.09, 0.32, and 1.28 mg/kg bw/d, respectively). There were no changes in appearance, behaviour, food or water intake or bodyweight gain due to fenthion. There were no deaths during the study. Ophthalmoscopic examination showed no changes in either the outer or inner eye parts. Haematology and urinalysis parameters were not altered and most clinical chemistry values were normal, except for slightly lower plasma protein in males of the 30-60 ppm group from week 39 onwards considered treatment-related. Elevated levels of the liver specific enzyme, glutamate-pyruvate transaminase (SGPT) observed transiently in 1 dog from each of the 10 and 30-60 ppm groups during the study did not appear to be treatment-related. Moreover, the finding that histopathological examination showed no morphological alterations in the livers of these dogs suggested that fenthion administration did not adversely affect the liver. There were no changes in organ weights of treated dogs. Macroscopic and microscopic examination showed no treatment-related adverse effects in the organs. The main treatment-related effects were reduced plasma ChE activities at 10 and 30-60 ppm (NOEL 3 ppm, 0.09 mg/kg bw/d) in both sexes. RBC ChE was inhibited from 10 ppm upwards in males (NOEL 3 ppm, 0.09 mg/kg bw/d) and at 30-60 ppm in females (NOEL 10 ppm, 0.32 mg/kg bw/d). Brain (bulbus olfactorius) ChE activity was significantly reduced at the end of the study in males and females receiving 30 ppm and above (NOEL 10 ppm, 0.32 mg/kg bw/d) in both sexes. The lowest NOEL based on plasma ChE inhibition was 3 ppm, corresponding to an average daily intake of 0.09 mg/kg bw/d. (Hoffmann & Weischer 1975)

Four groups of rhesus monkeys were given daily doses of technical-grade fenthion in corn oil by oral gavage at 0, 0.02, 0.07, or 0.20 mg/kg bw/d for two years. There were no treatment-related clinical signs. Gross examination revealed abnormally small testes and ovaries in animals at 0.20 mg/kg bw/d; however, in the absence of historical organ weights and histopathological data, the toxicological significance of this finding could not be fully assessed. No other treatment-related adverse effect was recorded. This pre-GLP study has adequate reporting of limited clinical laboratory testing and plasma and RBC ChE measurements. The study is deficient as it lacked detailed reporting of clinical signs, necropsies were carried out on only four animals, statistical analyses were not provided, and ophthalmological testing results were not provided. The NOEL for brain ChE inhibition could not be established as there was insufficient data. The NOEL for RBC ChE inhibition was 0.2 mg/kg bw/d, based on a lack of significant inhibition at any time point. The NOEL for plasma ChE inhibition was 0.02 mg/kg bw/d based on biologically significant inhibition seen at 0.07 and 0.2 mg/kg bw/d at several time points but peaking at the 4-month assay time. (Rosenblum 1980)

9.1.7 Reproduction Studies

Rats were utilised in a two generation, one litter per generation reproduction study. The F0 generation were exposed by diet to fenthion at 0, 0.08, 0.16, 1.16 or 8.3 mg/kg bw/d from 10 weeks of age for 70 days prior to pairing, and treatment continued through to the end of lactation and sacrifice. F1 litters were exposed to the test diets for 77 days prior to pairing through to the end of the lactation period when the F2 pups were sacrificed. There were no treatment-related effects on mortality, clinical signs, food consumption or gross pathology in F0 and F1 adult animals, other than increase in absolute and/or relative epididymal weights in 2/30 rats at 1.16 mg/kg bw/d and all rats at 8.3 mg/kg bw/d for both F0 and F1 males. Histopathology described cytoplasmic vacuolation in the lining ductal epithelial cells of the corpus epididymis of some 1.16 and all 8.3 mg/kg bw/d F0 and F1 males. Reproductive parameters of the F0 and F1 parents and foetal parameters were adversely affected at the high dose only. ChE activity was depressed in a complex manner. Brain ChE activity was significantly depressed in neonates only at the highest dose, in most adults at 1.16 and 8.3 mg/kg bw/d and also at 0.16 mg/kg bw/d in F0 adults. Hence significant inhibition of plasma and RBC ChE was recorded for all parental adults (F0 and F1) and all pups (F1 and F2) at the 14 and 100 ppm levels, while brain ChE was inhibited at 14 ppm and above in adults, but only at 100 ppm in pups. The NOEL for maternal toxicity was 2 ppm (0.16 mg/kg bw/d) based on plasma ChE inhibition at 14 ppm and above. The NOEL for paternal toxicity was 0.16 mg/kg bw/d based on epididymal changes, while the NOEL for foetotoxicity was 14 ppm (1.16

mg/kg bw/d) based on increased neonatal deaths and decreased bodyweight gain. The NOEL for reproductive parameters was 14 ppm (1.16 mg/kg bw/d) based on decreased fertility and litter size at the next dose of 100 ppm. (Kowalski et al 1989 & 1993)

9.1.8 Developmental Studies

Groups of mated female rats were gavaged with fenthion daily between days 6-15 of pregnancy at doses of 0, 1, 4.2 or 18 mg/kg bw. Five animals/group were sacrificed on day 16 (24 h after dosing), and the remaining 28 dams/group were sacrificed on gd 20, 5 days after the last dosing. There were no treatment-related deaths but there were overt clinical signs of toxicity including salivation, lacrimation, tremors and urine stained ventral surface at 18 mg/kg bw/d, and lower food consumption and bodyweight gain at 4.2 and 18.0 mg/kg bw/d at some intervals. There were no remarkable maternal macroscopical findings at sacrifice, and reproduction parameters were not affected by treatment. Foetal weight measures and external, visceral and skeletal examination revealed no compound-related malformations at any dose level. There was a non-statistically significant increase in the mean number of resorptions as well as a slight delay in skeletal maturation at the 18 mg/kg bw/d level only. There was significant and dose-related inhibition of maternal brain, plasma and RBC ChE activities at most dose levels on both gd 16 and 20. Foetal brain ChE activity was not significantly affected by treatment. No NOEL for maternotoxicity was established, based on plasma and RBC ChE inhibition at all doses, and the NOEL for embryo and foetotoxicity was 4.2 mg/kg bw/d based on increased resorptions and delayed skeletal maturation at the next dose of 18 mg/kg bw/d. (Kowalski et al 1987)

Groups of pregnant rabbits were given daily oral doses of fenthion by gavage at 0, 1.0, 2.75 or 7.5 mg/kg bw/d during gestation days (gd) 6-18. The animals were sacrificed on gd 28 and the dams and foetuses examined for toxic effects including ChE inhibition. There were no treatment-related deaths or signs of toxicity other than a slight increase in occurrence of soft stool at the mid- and high-dose levels. Maternotoxicity was evidenced by slight lowering of food consumption, bodyweight gain and final mean bodyweight at 7.5 mg/kg bw/d compared to controls. There were no remarkable maternal gross pathology findings at sacrifice. Reproduction and foetal parameters were not affected by treatment other than a slight increase in the mean number of resorptions in the 7.5 mg/kg bw/d group, and this was regarded as a LOEL for foetotoxicity. Foetal external, visceral and skeletal examinations did not reveal any statistically significant increases in compound-related malformations or variations at any dose. ChE activity in dams was biologically or statistically significantly inhibited at gd 19 in plasma and RBCs at 2.75 and 7.5 mg/kg bw/d, and at gd 28 in brain at the mid- and high-dose but in RBC at the high-dose only. The NOEL for maternotoxicity was 1 mg/kg bw/d based on significant inhibition of maternal brain, RBC and plasma ChE activities at higher dose levels. The NOEL for foetotoxicity was 2.75 mg/kg bw/d based on the slight increase in the mean number of resorptions in the 7.5 mg/kg bw/d group. (Clemens et al 1987)

9.1.9 Genotoxicity Studies

Fenthion showed no evidence of mutagenicity in 7 reverse-mutation studies in S. *typhimurium* (Herbold 1980a, 1987, 1990a & 1994; Inukai & Iyatomi 1976; Waters et al 1982), although in an eighth study it was weakly mutagenic in strain TA 1535 at 5000 µg/plate in the presence of exogenous metabolic activation (Shirasu et al 1979). However, this effect was not concentration-dependent and it is doubtful whether it is of toxicological significance. Fenthion was not mutagenic in mammalian cells (Lehn 1990a).

In DNA damage and repair assays, fenthion showed little evidence of genotoxicity (Herbold 1983; Waters et al 1982; Bai et al 1990), except for a weakly positive result in an Unscheduled DNA synthesis (UDS) assay in rat hepatocytes (Lehn 1990b). Fenthion produced negative results in a number of *in vitro* chromosomal effects assays (Inukai & Iyatomi 1976; Shirasu et ak 1979; Kajiwara 1989; Putman & Morris 1989; Sobti et al 1982). It caused Sister Chromatid Exchanges (SCE) in Chinese Hamster lung cells (Chen et al 1982a & b) and human lymphocytes (Rani & Rao 1991).

When tested in *in vivo* systems, fenthion showed no evidence of mutagenicity in two dominant lethal assays in male mice (Herbold 1997; Machemer 1978). It did cause SCE in rat bone marrow (Bai et al 1990). A weakly positive result was obtained in one of two micronucleus tests in mice (Herbold 1980b & 1990b).

9.1.10 Neurotoxicity Studies

Hens

Hens were dosed with weekly dermal applications of fenthion at 0, 1 or 4 mg/kg bw for 24 weeks. Sixteen hens were treated identically with Tri-Ortho Cresyl Phosphate (TOCP) (15 mg/kg bw) as a positive control. Clinical signs were seen at 4 mg/kg bw and included a 10% inhibition of egg production and 8% reduced body weight during the second half of the study. Four of 24 hens at the high dose exhibited transitory loss of proprioception, perching ability, and righting reflex after 8 to 16-weeks of exposure. All hens receiving the high dose lost the ability or desire to escape from a box (by jumping) during the latter half of the exposure period. Muscle electrical activity in the peroneus longus muscle was recorded electromyographically via telemetry. Fibrillation (denervation) potentials were absent, but motor unit potentials were generally higher in the high-dose hens, suggesting a mild neuropathy. Ultrastructural examinations of the sciatic nerve revealed evidence of distal axonopathy in the TOCP-treated hens but not in fenthion-treated hens, although mild neuropathy was present (large variation in cross-sections of nerve fibres). Fenthion treatment induced a dose-related increase in swollen and/or atrophic muscle fibres as compared to controls. Inhibition of serum and brain ChE by fenthion was dose-related but brain NTE was not inhibited. Behavioural changes were not correlated with changes in brain concentrations of enzymes or neurotransmitters or their metabolites. (Tuler & Bowen 1999)

In a dose-ranging study, 5 groups of 8 hens were exposed to fenthion via the diet at 0, 300, 1000, 3000 or 10,000 ppm for 30 days and then observed for a 4-week recovery period for signs of neurotoxicity. All treated hens showed cholinergic signs within a few days of dosing, and all but 2 hens (1 each from the 300 and 1000 ppm groups) died by the third week. No neurotoxic signs were observed in the surviving hens. In the principal study, 5 groups of 8 hens were exposed to fenthion in the diet at 0, 10, 25, 50 or 100 ppm for 30 days and then observed for a 4-week recovery period. There were no toxic signs in hens receiving 10 or 25 ppm, whilst cholinergic signs were apparent in the 50 and 100 ppm groups, with 1 death at 100 ppm. Decreased bodyweight and food intake were observed in the 100 ppm group and there were significant dose-dependent reductions in blood ChE activity in the 25, 50 and 100 ppm groups. No signs of neurotoxicity were observed during the trial or the recovery period. No hens showed any signs of either gangliocyte and axon degeneration or demyelination. (Kimmerle 1965; Dieckmann 1971)

Atropine-protected hens five, were dosed with fenthion, three weeks apart, via oral (40 mg/kg bw) or dermal (200 mg/kg bw) routes. A positive control group of five hens was given TOCP orally as a single dose of 375 mg/kg bw. Six hens given vehicle only and six hens remaining untreated served as negative controls. All animals were observed for 21 days after the second dose, with the exception of the TOCP-treated hens that were sacrificed in moribund condition on day 22 after their single dose. The TOCP hens exhibited no signs of acute toxicity, but showed signs of delayed neurotoxicity from day 7 post-dose, progressing to ataxia or paresis in all animals at sacrifice as well as marked fibre degenerations in the sciatic nerve and the cervical segments of the spinal cord. The oral and dermal fenthion dosage groups displayed signs of acute intoxication with a variable recovery period, but no clinical symptoms or neurohistopathological lesions characteristic of delayed neuropathy. (Flucke & Kaliner 1986).

Groups of nine atropine-protected hens were given a single oral dose of fenthion by intubation at 0 or 40 mg/kg bw. Additional groups of nine atropine-protected adult hens were given a single dermal dose (applied to the comb) of 200 or 400 mg/kg bw. Nine positive controls received TOCP as a single oral dose of 100 mg/kg bw. The 400 mg/kg bw dose was highly acutely toxic. Sequential sacrifice over 7 days showed minimal inhibition (0-14%) of NTE activity in brain and spinal cord in the orally dosed fenthion animals, slight inhibition (11-20%) in the dermally dosed animals but severe inhibition (52-95%) in the TOCP animals at all assay times. (Flucke & Eben 1988a & b)

Adult hens were gavaged with fenthion at 0, 1, 2 or 4 mg/kg bw/d for 14 weeks. Two additional groups were treated with 0 or 10-60 mg/kg bw/d TOCP as a second negative control and the positive control. There was increased mortality, decreased food consumption and decreased bodyweight at 4 mg/kg bw/d. All hens treated with TOCP died or were sacrificed *in extremis* between days 61-78. Transient clinical signs were seen at 4 mg/kg bw/d in the first hours after dosing, whereas TOCP-treated hens exhibited decreased activity at week 5 and both ataxia and decreased activity from weeks 6 and 7 onwards. Forced activity tests recorded generally normal locomotor activity for the controls and fenthion-treated groups while signs typical of delayed neurotoxicity were evident in the TOCP treated hens from week 7 onwards. Muscle hypertrophy was present in the digestive organs of all fenthion-treated hens. The lowest dose tested (1 mg/kg/ bw/d) was considered a LOEL for whole blood ChE inhibition and histopathological changes. The highest dose tested (4 mg/kg bw/d) was considered a NOEL for neurotoxicity. (Hayes & Ramm 1988)

Rats

Pigmented Long-Evans and albino Wistar rats were dosed with 50 mg/kg bw fenthion subcutaneously twice weekly for 1 year. In pigmented rats, the amplitude of the ERG gradually declined, disappearing by the 12^{th} month. In albino rats, the ERG amplitude disappeared by the 6^{th} month in 7/15 animals. Fundoscopy revealed retinal degeneration in all rats when ERG responses had disappeared. Histopathology demonstrated degeneration of the sensory retina and abnormalities in the pigment epithelium cells. Pigmented rats also had reduced rhodopsin concentration in the retina by the 3^{rd} month but photoreceptors were structurally normal. Plasma vitamin A levels were normal with liver vitamin A levels increasing. Liver and plasma ChE activities were markedly reduced after 3 months fenthion treatment. Decreases were 11% and 38% of the controls in plasma and liver respectively. (Imai et al 1983)

A dose-ranging study in rats established that for clinical signs, the time range for peak effect was 5 h to 7 h following dosing. In the main study, rats were dosed once with fenthion at 0, 1, 50 or 125 mg/kg bw for males and 0, 1, 75 or 225 mg/kg bw for females, and then observed for 15 days. At 50 mg/kg bw for males and 75 mg/kg bw for females, typical signs of acute cholinergic toxicity were observed including decreased motor activity, presence of muscle fasciculation, uncoordinated gait, decreased body temperature, diarrhoea, and decreased reactivity. At 125 mg/kg bw in males the same symptoms increased and in addition there were convulsions and several other treatment-related reactions. At 225 mg/kg bw in females there were 4 deaths as well as increased incidence and severity of the symptoms. The decrease in motor activity reversed slowly with some symptoms remaining at day 14 in high-dose males and females and mid dose females. ChE activity in plasma, RBC and brain was inhibited (>76%) at 50 mg/kg bw for males and 75 mg/kg for females. At 1 mg/kg bw plasma ChE (-23%, not significant), RBC ChE (-22%, $p<0.05$) and brain ChE (-9%, $p<0.01$) were inhibited in females. Males showed decreases but they did not reach statistical significance. The NOEL and LOEL for inhibition of ChE/AChE is <1 mg/kg bw (females more affected than males). The NOEL for the neurotoxicity observations was 1 mg/kg bw; the LOEL was 50 mg/kg bw in males and 75 mg/kg bw in females based mainly on muscle fasciculation and related clinical signs. (Driest and Popp 1997a)

Wistar rats were fed diet containing 0, 2, 25 or 125 ppm fenthion for 13 weeks. Measured mean concentrations were 0, 2, 24 and 112 ppm, respectively. The achieved dose based on these dietary levels was calculated to be 0, 0.13, 1.63 and 8.50 mg/kg bw/d for males and 0, 0.17, 2.19 and 12.62 mg/kg bw/d for females, respectively. Treatment reduced bodyweight gain in both sexes at the high dose, despite higher food consumption in these groups. Body weights were significantly reduced in high-dose males throughout the study; body weight reduction was significant but less severe in mid- and high dose females. There were no treatment-related deaths. There was a low frequency of mild cholinergic signs in high-dose males. These signs became less frequent as the study progressed and only palmospasms were present throughout the study. Motor activity and locomotor activity were reduced in high dose animals of both sexes. There were no treatment-related histopathological lesions reported. For neurotoxicity, the LOEL was 25 ppm (1.63 mg/kg bw/d for males and 2.19 mg/kg bw/d for females) based mainly on body weight reduction and fasciculations seen at the LOEL of 125 ppm (8.5 mg/kg bw/d for males and 12.6 mg/kg bw/d for females). There were indications of a dose response for plasma and RBC ChE activity in both sexes, but 2 ppm was considered a borderline NOEL. At 25 and 125 ppm, plasma, RBC and brain ChE activity were significantly inhibited. The NOEL for ChE inhibition in all compartments (plasma, RBC and brain) was 2 ppm (0.13 mg/kg bw/d for males and 0.17 mg/kg bw/d for females). The LOEL was 25 ppm. There were no treatment-related effects seen at the 2 ppm dose level and this can be considered as the overall NOEL for this study. (Driest & Popp 1997b

Dogs

Female dogs received a weekly dermal application of 44 mg/kg bw fenthion for 10 weeks, then the dosage was decreased to 22 mg/kg bw for an additional 13 treatments. Cholinergic signs were slow to develop but by 10 weeks there were severe cholinergic signs in all dogs including ataxia, muscle fasciculations, proprioceptive deficits, hyper-reflexia and paralysis in one dog; there was partial recovery of neuromuscular function at the end of the study. Electromyography recordings showed changes from one month onwards. There was progressive muscle fibre necrosis, ultrastructural changes in nerve axons and alterations in some central nervous system (CNS) neurotransmitters. Brain neurotoxicity target esterase

(NTE) activity was inhibited 52% at 6 months, and there was no evidence of changes typically associated with delayed neurotoxicity (flaccid paralysis or dying-back neuropathy). (Tuler et al 1988)

Male dogs received dermal applications of 0, 8 (twice, 14d apart) or 33 mg/kg bw/d (4-times, once/week) fenthion. There were no clinical signs. Plasma ChE was significantly inhibited at both doses while RBC ChE activity was only significantly inhibited at 33 mg/kg bw. ChE depression was slow to develop. The fenthion-treated dogs gave a slightly smaller response to atropine sulfate challenge compared to controls suggesting induction of a tolerance mechanism involving down-regulation of the muscarinic cholinergic receptors or their affinity. (Dellinger & Mostrom 1988)

9.1.11 Human Studies

Adult male volunteers were given fenthion (in corn oil) in capsules at doses of 0, 0.02 or 0.07 mg/kg bw/d for 4 weeks. Aspects of the study design and conduct mitigated against detecting adverse effects from fenthion administration, a compound for which the time of peak effect is 5-7 h after oral intake (in rats). There was no evidence of RBC ChE inhibition but clear evidence of a dose response for inhibition of plasma ChE, with statistically significant inhibition at both doses. The possibility that clinical signs were present at the high dose, even in the absence of significant RBC ChE inhibition, cannot be discounted. The LOEL for plasma ChE inhibition was considered to be 0.02 mg/kg bw/d. The NOEL for RBC ChE inhibition was 0.07 mg/kg bw/d (Coulston et al 1979).

A number of case reports of human exposure to fenthion, generally via intentional ingestion, have been published. A common feature was that fenthion poisoning often involved lengthy periods of critical care after the initial acute cholinergic crisis had passed.

9.2 Hazard Assessment

The toxicological database for fenthion is adequate. It consists of unpublished reports generated by industry and a range of published studies.

9.2.1 Mechanism of Mammalian Toxicity

In common with all organophosphate compounds, the primary mode of action of fenthion is via the inhibition acetylcholinesterase activity, which causes over-stimulation of those parts of the nervous system that use acetylcholine to transmit nerve impulses. Signs of intoxication are consistent with acetylcholinesterase inhibition and include inactivity, salivation, dyspnoea, flaccid paralysis, vomiting, piloerection, exophthalmia and diarrhoea. If intoxication is severe, muscle twitching, loss of reflexes, convulsions and death can eventuate.

9.2.2 Metabolism and Toxicokinetics

Fenthion is almost completely absorbed and oxidised or hydrolysed to generate anticholinesterase metabolites. The oxygen analogue of fenthion and its sulphoxide and sulphone derivatives and the oxygen analogues of the sulphoxide and sulphone are generally regarded as principal active metabolites, rather than fenthion itself.

The administration of fenthion by the oral, dermal, subcutaneous or intraperitoneal routes to various species (rat, pig, cow, goat and rabbits) resulted in a comparable pattern of absorption and metabolism in all animals. Single doses are readily absorbed after all routes of administration and rapidly excreted in urine (approx. 90%) and faeces. For example, in several studies using rats treated with ^{14}C-labelled fenthion orally or intravenously, no major differences were seen in metabolite profiles with route of administration, dose, sex, or pretreatment with unlabelled fenthion for 14 days. No unchanged parent compound was detected in the urine and very little (< 2%) in the faeces. Fourteen urinary metabolites were identified which represented 93-96% of the total recovered label. The major group of metabolites (about 60% of the total label) was composed of the three phenol thioethers resulting from hydrolysis of the OP moity (phenol fenthion, phenol sulfoxide, and phenol sulfone) and their glucuronide, sulfoxide, and sulfone conjugates. Four desmethyl metabolites were also identified, accounting for about 30% of the label, while the oxygen analogue sulfoxide constituted only 1-4%. Mean tissue-residue levels of fenthion or metabolites were generally low except at the actual site of dermal or subcutaneous administration, suggesting that there is no tendency for fenthion to bioaccumulate in the rat or domestic animals.

Oral dosing results in an earlier onset of ChE inhibition and more rapid recovery compared to dermal and subcutaneous administration, which have a later onset and more prolonged effect (Emteres et al 1985; Christenson 1990c).

9.2.3 Acute toxicity

Fenthion is moderately toxic by the oral route; the ranges for oral LD_{50} values were 140-615 mg/kg bw for rats and 200-290 mg/kg bw for mice. Males were slightly more sensitive than females in some tests in rats and mice. The acute dermal toxicity of fenthion is also moderate, ranging from 271->5000 mg/kg bw in rats and 500-2000 mg/kg bw in mice. Fenthion has a low to moderate acute toxicity when administered inhalationally as a mist; LD_{50} values ranged from 454->1878 mg/m^3 in rats (4 h exposure) and 2000-2400 mg/m^3 in mice (1 h exposure). Fenthion did not irritate rabbit skin (Pauluhn 1985; Eigenberg 1987c). There was evidence of slight eye irritation after one but not 24 hours in rabbits (Eigenberg 1987d; Pauluhn 1985). It did not sensitise guinea pig skin in the Magnusson and Kligman maximisation test (Flucke 1987).

The acute oral and intraperitoneal toxicity of the oxygen analogue of fenthion and its sulphoxide and sulphone derivatives, thought to be the principal active metabolites were 5-10 times that of fenthion.

Fenthion potentiated the acute toxicity of malathion, dioxathion and coumaphos in the rat, whereas in the dog fenthion potentiated malathion and coumaphos but not dioxathion (Dubois Kinoshita, 1964; Doull et al 1962).

9.2.4 Repeat-dose toxicity

Dose-related inhibition of plasma, RBC and brain ChE activities was the most common manifestation of fenthion toxicity in short-term, subchronic and chronic studies in mice, rats, dogs and monkeys. Cholinergic signs and occasional mortalities occurred in rats and dogs at the same doses as the inhibition of brain ChE activity. The rat inhalational study confirmed the bioavailability of fenthion by this exposure route with clinical signs apparent at low doses. The study in hens described morphological changes in the oesophagus presumably due to a cholinergic mechanism ie. the overstimulation of the muscles due to ChE inhibition, although given the extreme sensitivity of avians to ChE inhibitors, this anatomical finding may not be of general applicability.

There was little indication that repeated oral or inhalational exposure had any effect on haematology, clinical chemistry or urinary parameters, or on organ weights or pathology.

9.2.5 Carcinogenicity

Chronic dietary studies in mice and rats showed no evidence of oncogenicity and therefore, fenthion is not considered to pose a carcinogenic risk to humans.

9.2.6 Genotoxicity

Results from a range of *in vitro* and *in vivo* genotoxicity assays indicated that fenthion is not genotoxic.

9.2.7 Reproductive and developmental toxicity

Fenthion did not induce major malformations or significant effects on most reproductive parameters in experimental animals. The single reproduction study in rats reported epididymal changes in parental males, and RBC and plasma ChE inhibition in both parental sexes at high doses. However, the study demonstrated a clear NOEL of 1.16 mg/kg bw/d for reproductive parameters and foetotoxicity. Developmental studies with fenthion in rats and rabbits revealed no teratogenic effects and foetotoxicity only at maternotoxic levels; there was inhibition of maternal but not foetal brain ChE activity.

9.2.8 Neurotoxicity

There was no evidence that fenthion causes delayed neuropathy (REF) or significant NTE inhibition in the studies using single oral or dermal doses at or above the LD_{50}. As expected, dose-related, reversible inhibition of ChE activity was observed, but this effect was not accompanied by any microscopic changes in nerve tissues, even in those animals that displayed gross clinical signs. On occasion, some impairment of motor activity was reported at higher doses, but this effect was transient and reversible (Flucke & Kalner 1986; Flucke & Eben, 1988a, b).

Similarly, a 14-week study in hens revealed no signs of delayed neurotoxicity consequent to fenthion administration by gavage, but did show hypertrophy in muscle layers of the oesophagus, crop, proventriculus, gizzard and intestine (Hayes & Ramm, 1988). A subsequent study established that the hypertrophy was probably induced by localised ChE inhibition, with subsequent overstimulation of the oesophageal smooth muscle layers (Hayes 1989).

An unusual or unique neurotoxic effect was attributed to fenthion in a series of published studies. In two initial studies (Farage-Elawar & Francis 1987; Francis & Farage-Elawar, 1987) and a repeat study (Farage-Elawar & Francis, 1988a), the effects of fenthion, debromoleptophos (which induces organophosphate-induced delayed neurotoxicity), and fenitrothion (which does not) were compared in very young chicks. In a fourth study (Farage-Elawar & Francis, 1988b), chicks were exposed to the same chemicals *in ovo* by injection into eggs. The authors reported that fenthion significantly altered the gait of treated chicks, whereas fenitrothion did not. The authors concluded that this neurotoxic effect was not due to either NTE or AChE inhibition, and that fenthion-induced functional deficits can be distinguished from classical OPIDN. However, as noted by Flucke (1990), the three organophosphates were not administered in equitoxic doses, thus rendering direct comparison of their toxic effects inappropriate. Flucke further noted that the test animals were malnourished and hence likely to have limited ability to compensate for metabolic insults. It is also clear that the dosing regimen was not consistent between the studies. While neither fenitrothion nor fenthion inhibited NTE, fenthion but not fenitrothion induced prolonged inhibition of ChE activity and hence probably prolonged acute cholinergic intoxication. This may have led to an extensive period of muscle fasciculations in fenthion-treated animals and subsequent permanent muscular impairments such as altered gait. Hence the neurotoxic effects seen with both debromoleptophos and fenthion seem more likely, in the case of fenthion, to be attributable to primary effects of severe acute cholinergic intoxication and not to a particular (unknown) neurotoxic potential of fenthion, as postulated by Farage-Elawar & Francis.

Dermal treatment of dogs at one or 2-week intervals resulted in inhibition of plasma and RBC ChE but no clinical signs. Measurements of vagal nerve tone in treated animals showed a smaller response to atropine challenge reflecting down-regulation of muscarinic receptors, interpreted as an adaptive response rather than irreversible impairment of the neuromuscular junction (Dellinger Mostrom 1988).

Prolonged weekly dermal application of fenthion to dogs resulted in progressive muscle fibre necrosis, ultrastructural changes in nerve axons and alterations in some CNS neurotransmitters. There was no evidence of changes typically associated with delayed neurotoxicity (flaccid paralysis or dying-back neuropathy). While the changes seen were consistent with sensory nerve fibre damage, and the authors argued that chronic exposure to fenthion may have a primary effect on small motor axons as well as muscle fibres, it is clear that the most severe of the clinical signs exhibited by the dogs were likely to be the result of neuromuscular overstimulation due to severe acetylChE inhibition resulting in a depolarising paralysis and eventual necrosis of innervated fibres. Reversibility or recovery was seen in most of the dogs when the dose of fenthion was reduced from 44 to 22 mg/kg bw or stopped for one week, suggesting the neuropathy was reversible (Tuler et al 1988).

9.2.9 Human toxicity

Like other mammals, the inhibition of plasma ChE activity is the most sensitive toxicological endpoint in humans following repeated exposure. For acute or short-term exposures, the inhibition of RBC ChE activity is the most sensitive toxicological endpoint.

There is no compelling evidence that fenthion exposure can induce delayed neuropathy in humans. The study by Senanayake and Sanmuganathan (1995) found that symptoms of intermediate syndrome occurred only in patients who had been admitted for acute fenthion poisoning and not following admission due to poisoning by other OPs. They attribute this to the high lipid solubility of fenthion giving it access to the CNS. In the patients who survived, the symptoms resolved spontaneously in 1 to 4 weeks.

In two human studies, clinical and biochemical changes, nerve conduction velocity and neuromuscular synapse functions in 22-24 workers (mean age: 31-32) chronically exposed to fenthion were investigated. The results revealed no clinical signs of a peripheral neuropathy or myopathy and no pathophysiological findings indicative of any irreversible neurological deficits in applicators exposed regularly and repeatedly to fenthion for a mean of 8.2-8.5 years. The workers showed symptoms typical of acute cholinergic intoxication and inhibition of serum ChE. It was concluded that there was no evidence of a particular/delayed neurotoxic potential of fenthion in the workers examined (Misra et al 1985 & 1988).

A peripheral neuropathy was reported in three workers at a veterinary hospital where a 20% solution of fenthion was routinely applied topically to dogs. Plasma and red cell ChE activities were within normal range for all workers tested. Some gradual improvement was seen following discontinuation of exposure (Metcalf et al 1985).

A clinical and neurophysiological study was performed on 31 workers engaged in spraying fenthion. The mean age and duration of exposure were 32 years and 10.5 years respectively. While there was no clinical evidence suggestive of excessive cholinergic activity, the plasma acetylChE level was 27% less in the exposed *versus* the control group. Additionally, clinical pyschometry revealed significant changes in tests of long and short-term memory. The same authors who concluded there was no delayed neurotoxicity with chronic fenthion exposure (see Misra et al 1985 & 1988 above), now concluded that there are subtle subclinical effects of chronic fenthion exposure on cognitive functions and event related potentials (Misra et al 1994).

Overall, the toxicity databases from both the published and unpublished literature provide no conclusive evidence of a particular or delayed neurotoxic potential of fenthion. It is however possible that fenthion might induce idiosyncratic neurotoxic reactions in some human individuals. A case report from Australia described long-lasting and severe physical and psychological symptoms following use of a Lebaycid product in the home garden (CRP submission).

9.2.10 Ocular toxicity

In the 1960's and 70's, people living in a number of agricultural areas in Japan experienced a high incidence of visual disorders and a variety of ocular lesions. It appeared that these disorders were connected to exposure to OP insecticides, particularly from aerial spraying. The effects noted were sufficiently common and widespread for it to be named 'Saku Disease'. The effects include myopia, astigmatism, narrowing of the visual field, reduced vision and histopathological evidence of degeneration of extraocular muscle, ciliary muscle, retina and other ocular tissues (Ishikawa 1971; Ishikawa 1973; Ishikawa & Miyata 1980).

Fenthion was one of the OPs being used near cases of Saku disease. The Japanese conducted animal studies which included reports with ethylthiometon, fenthion, disulfoton, fenitrothion and fenthion, in which electroretinographic (ERG) changes were noted (Ishikawa & Miyata 1980; Dementi 1994). Data submitted to the US EPA indicate that parathion, methyl parathion, tribufos and fenthion have ocular toxicity (Boyes et al 1994). A study in rats using fenthion found long lasting inhibition of muscarinic receptor function in the retina and frontal cortex. Additionally the second messenger release system in the retina (measured as carbachol-induced inositolphosphate release) was still inhibited at 56 days, the longest assay time after treatment. The authors concluded that this long lasting depression in the retinal cholinergic second messenger system induced by fenthion may occur independently of depressed ChE activity and down regulation of the muscarinic receptor (Tandon et al 1994).

A review by Dementi (1994) summarised the Japanese literature which reported experiments with fenthion administered to rats and concluded that ERG changes occurred progressively after fenthion exposure across the dose range of 0.005-50 mg/kg bw following single dose administration, and no NOEL was identified. These changes were not accompanied by measurable decreases in ChE activity in the retina and cerebellum at doses below 0.5 mg/kg bw. Additionally there were strain differences, with Wistar rats being more resistant than the Long-Evans strain to induced retinal degeneration. Dementi concluded that the retinal effects of fenthion may be progressive, from early measurable changes in the ERG to the extinction of the ERG, accompanied by progressive, ultimately severe, retinal degeneration at high doses. However this effect appears to be species specific as it was not evident in long-term studies in mice (Leser & Suberg 1990 & 1992), dogs (Christenson 1990b) and Rhesus monkeys (Rosenblum, 1980) Other than the Japanese literature, case reports of human poisoning by fenthion provide no evidence of ocular toxicity to humans.

9.2.11 DOSE Levels Relevant For Risk Assessment

To identify the lowest NOELs for the establishment of public health standards, a summary of the NOELs determined in those studies considered adequate for regulatory purposes are shown in the following Table 18.

Table 18: Studies relevant for the establishment of an ADI

Species	NOEL (mg/kg bw/d)	LOEL (mg/kg bw/d)	Toxicological Endpoint	Reference
Chronic studies				
Mouse 2-y	0.03	0.5	Plasma and brain ChE inhibition	Leser & Suberg (1990 & 1992)
Rat 2-y	No NOEL	0.3	Plasma, RBC and brain ChE inhibition	Christenson (1990a)
Dog 1-y	0.06	0.26	Plasma ChE inhibition	Christenson (1990b)
Dog 2-y	0.09	0.32	Plasma and RBC ChE inhibition	Hoffmann & Weischer (1975)
Monkey 2-y	0.02	0.07	Plasma ChE inhibition	Rosenblum (1980)
Human studies				
28-d		0.02*	Plasma ChE inhibition	Coulston et al (1979)

* Based on a similar magnitude observed in long-term animals studies, the ACPH considered this value to be the NOEL (see Appendix IX)

9.3 Main toxicology report

9.3.1. Introduction

Fenthion (*O*,*O*-dimethyl *O*-4-methylthio-*m*-tolyl phosphorothioate) is an OP insecticide, and like other OPs, its insecticidal activity is due to its ability to inhibit nerve conductance. A similar mechanism of toxicity occurs in mammals involving the inhibition of acetylChE at nerve terminals, which causes accumulation of acetyl choline that in turn over stimulates nicotinic and muscarinic receptors in the central and peripheral nervous system.

Fenthion has been available in Australia for many years. Its main food use is for the control of fruit fly and codling and lightbrown apple moth on tree and vine crops (apples, pears, quinces, citrus, stone fruit, tropical and subtropical fruit, figs, grapes, loquats, pepinos, pawpaws, persimmons). It is also used to treat other insect pests on non-tree and vine crops (eg. tomatoes, capsicums, eggplant, ornamentals and chillies). It is used as an ectoparasiticide for beef and dairy cattle. Non-food uses cover outdoor or subfloor treatments for flies, mosquitoes, spiders, ants and fleas, and as a bird eradication agent. Homegarden uses include treatment for fruit fly, aphids, caterpillars, bugs and other insects on fruit, vegetables and ornamentals, for general outdoor and subfloor insect control around the home and for the treatment of ornamental ponds and septic tanks. Home veterinary products include spot-on treatments for flea control on dogs.

9.3.1.1 History of Public Health Considerations of Fenthion in Australia

A detailed history of the public health considerations of fenthion by Australian regulatory committees is detailed in Appendix VI.

ADI and ARfD

The current acceptable daily intake (ADI) for fenthion is 0.002 mg/kg bw/d. This ADI was derived from an NOEL of 0.02 mg/kg bw/d for plasma ChE inhibition seen in a human volunteer 28-day study, and using a 10-fold safety factor.

There is currently no Australian ARfD for fenthion.

Poisons Schedule

Fenthion is in Schedule 7 of the SUSDP except when in Schedules 5 or 6. Fenthion is in Schedule 5 when: (a) present in preparations containing 10% or less fenthion or (b) used in preparations containing 25% or less and packed in single use containers having a capacity of 2 mL or less. Fenthion is in Schedule 6 when present in preparations containing 60% or less, except when included in Schedule 5.

Drinking Water Quality Guidelines

The Australian Drinking Water Guidelines (ADWG) are a joint publication of the National NHMRC and the Agricultural and Resource Management Council of Australia and New Zealand (see *Australian Drinking Water Guidelines* - 1996; ISBN 0 642 24462 6 or http://www.nhmrc.gov.au/publications/pdf/eh19.pdf). The ADGW are not legally enforceable but rather provide a standard for water authorities and State health authorities to ensure the quality and safety of Australia's drinking water.

The *Guideline Value* (mg/L) is analogous to an MRL in food and is generally based on the analytical limit of determination. It is set at a level consistent with good water management practice and that would not result in any significant risk to the consumer over a lifetime of consumption. If a pesticide is detected at or above this value then the source should be identified and action taken to prevent further contamination.

The *Health Value* (also expressed as mg/L) is intended for use by health authorities in managing the health risks associated with inadvertent exposure such as a spill or misuse of a pesticide. The health values are derived so as to limit intake *from water alone* to approximately 10% of the ADI, on the assumption that (based on current knowledge) there will be no significant risk to health for an adult weighing 70 kg having a daily water consumption of 2 L over a lifetime.

Fenthion does not have a *Guideline Value* or *Health Value* in Australian drinking water.

9.3.2. Metabolism And Toxicokinetics

9.3.2.1 Metabolic pathway for fenthion

In several studies of rats treated with ^{14}C-labelled fenthion (purity, >98%) orally or intravenously, no major differences were seen in metabolite profiles with route of administration, dose, sex, or pretreatment with unlabelled fenthion for 14 days. No unchanged parent compound was detected in the urine and very little (<2%) in the faeces. Fourteen urinary metabolites were identified which represented 93-96% of the total recovered label. The major group of metabolites (approximately 60% of the total label) was composed of the three phenols (phenol fenthion, phenol sulfoxide, and phenol sulfone) and their glucuronide, sulfoxide, and sulfone conjugates. Four desmethyl metabolites were also identified, accounting for approximately 30% of the label, while the oxygen analogue sulfoxide constituted only 1-4%.

<u>Key to molecules</u>

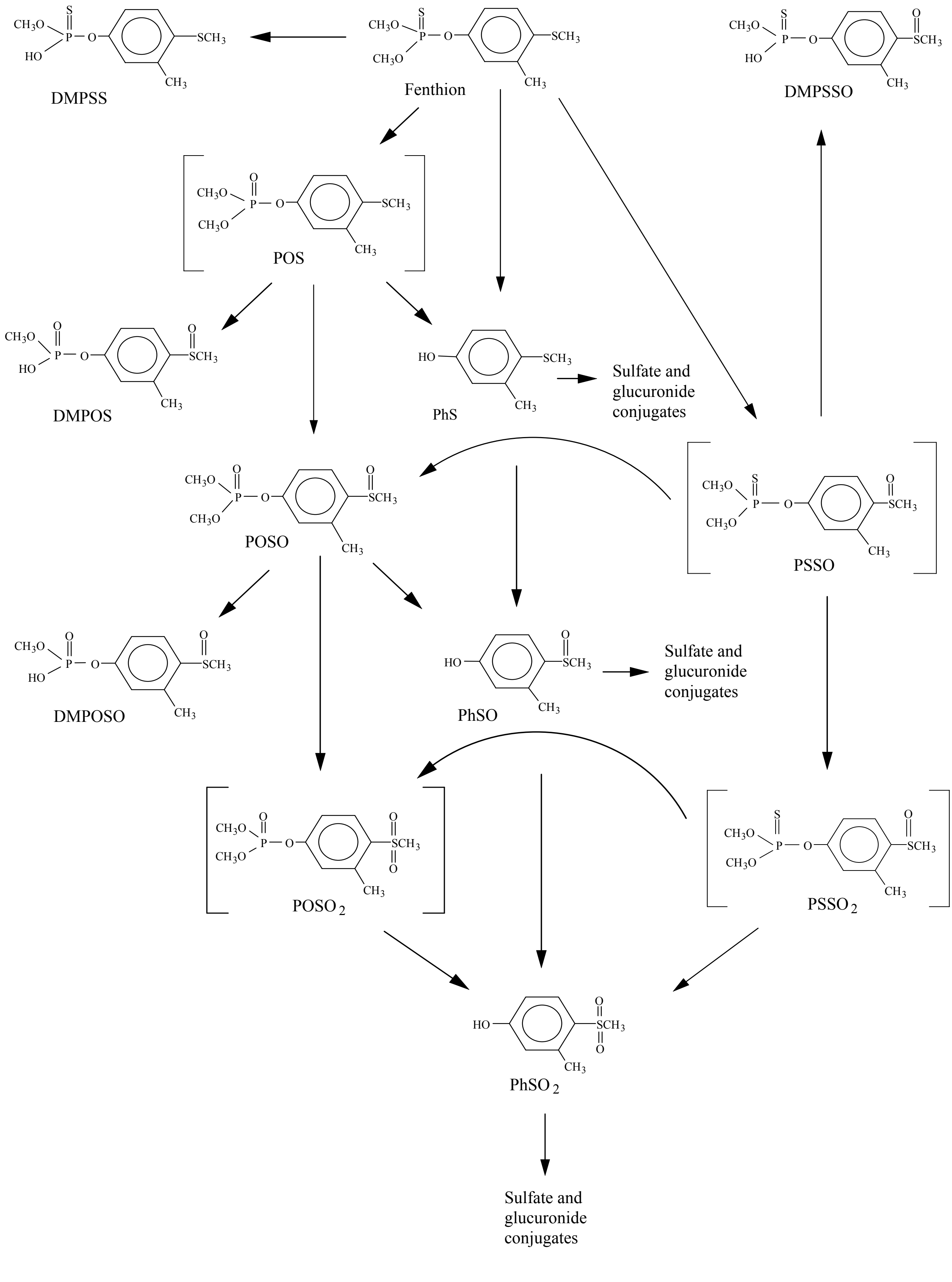
Table 19: Oxidative Metabolites

Molecule	Oxidative/sulphuration	Code	Desmethyl form
Fenthion:	P=S, S	PSS	DMPSS
Sulphoxide of fenthion:	P=S, SO	PSSO	DMPSSO
Sulphone of fenthion:	P=S, SO_2	$PSSO_2$	
Oxygen analog of fenthion:	P=O, S	POS	DMPOS
Sulphoxide of fenthion oxygen analog:	P=O, SO	POSO	DMPOSO
Sulphone of fenthion oxygen analog:	P=O, SO_2;	$POSO_2$	

Hydrolytic products

Phenol thioether: PhS
Sulphoxide of phenol thioether: PhSO
Sulphone of thioether: $PhSO_2$

Metabolic Pathway of Fenthion in Rats



Brady UE Jr & Arthur BW (1961) Metabolism of O,O-dimethyl-O-[4-(methylthio)-m-tolyl] phosphorothioate by white rats. J Econ Entomol 54, 1232-1236

This study reports the results of metabolism studies on white rats following single oral administrations or multiple intraperitoneal injections of [^{32}P]-labelled fenthion. Male rats (Group A) were treated intraperitoneally at 10 mg/kg bw for 10 consecutive days while maintained in metabolism cages, then sacrificed (3/time) at 1, 3, 7, 10, 13 and 20 days. Various tissues were extracted for measurement of total radioactivity. Tissue residues were quantified on the assumption that fenthion and its oxidative metabolites were present in the acetonitrile extract. Urine and faecal samples were extracted with chloroform to separate fenthion and its oxidative metabolites from the presumed hydrolytic products remaining in the aqueous phase; recoveries were >85%. ChE activity was measured in blood and brain at sacrifice. A second group of males (2 animals - Group B) were treated intraperitoneally with 200 mg/kg bw of fenthion and sacrificed at the onset of clinical signs (approximately 1.5 hours after treatment) and processed as for Group A. A third group of males (4 animals - Group C) were treated orally (stomach tube) with fenthion at 100 mg/kg bw in corn oil and treated as for group A with sacrifice (2/time) on days 3 and 7 after treatment.

ChE activity in whole blood and brain rapidly declined in Group A, reaching its lowest levels on day 10 (blood ca. 98% & brain ca. 75% inhibited) and recovering slowly thereafter to day 20 (blood ca. 80% & brain ca. 50% inhibited). In Group B, ChE activities of blood and brain were inhibited by 98% and 69%, respectively, at 1.5 h after treatment.

Tissue retention of [^{32}P]-labelled residues of fenthion or its oxidative products remained low in (Group A) rats that received 10 daily doses of fenthion at 10 mg/kg bw intraperitoneally. However, the total extraction procedure revealed significant [^{32}P] materials in the liver and bone, indicating rapid degradation of the parent fenthion compound. After this series of 10 intraperitoneal injections, approximately 80% of the administered radioactivity was recovered in the excreta (ca. 60% in urine and 20% in faeces) by 10 days after the last injection. The urine extracts contained predominantly (>90%) hydrolytic products, identified as dimethyl phosphoric and thioc acids. There was some evidence that the rate of hydrolysis decreased as the number of doses increased, and the authors postulated an inhibition/inactivation of the hydrolytic enzymes as an explanatory mechanism.

Three days after administration of a single oral dose of 100 mg/kg bw (Group C); there were no detectable acetonitrile-soluble residues except in the liver (0.2 mg/kg bw), while other tissues were all less than 0.01 mg/kg bw. Seven days after the single oral dose, 86% of the orally administered [^{32}P] radiolabel had been eliminated in the excreta (46% in urine and 40% in faeces), the majority being excreted within the first three days. Only 1% - 4% of this excreted radiolabel was fenthion or its oxidative products. The authors stated that blood, brain and fat contained no acetonitrile-soluble residues, but no data were presented.

Knowles CO & Arthur BW (1966) Metabolism of and residues associated with dermal and intramuscular application of radiolabelled fenthion to dairy cows. J Econ Entomol, 59: 1346-1352.

Two lactating cows (Jersey) received [^{32}P]-labelled fenthion as a single dermal dose of approximately 13 mg/kg bw and another two received a single intramuscular dose of approximately 8.6 mg/kg bw.

The peak concentration of radioactivity appeared in the milk 18 and 8 h after dermal and intramuscular treatment respectively. The elimination of radiolabel through the milk was low: ca. 1.1% and 2.2% of the dermal and intramuscular doses respectively were eliminated in the milk within 2-3 weeks. Unchanged fenthion, the sulphone of fenthion and the sulphone and sulphoxide of the oxygen analog of fenthion comprised 60%-90% of the nonionic residues in the milk. In urine, >95% of the radiolabel excreted was in the form of hydrolytic products; the parent compound accounted for only a small percentage of the chloroform-soluble residues. In faeces, unchanged fenthion constituted >50% of the acetonitrile-soluble residues. The animals were slaughtered 14 days after the dermal and 21 days after the intramuscular treatment; >50% of the tissue residues appeared as unchanged fenthion, but oxidation products were also present.

Begum A (1967) Effect of diet on metabolism of fenthion in animals (Doctoral Thesis, Auburn university, Al, USA) Unpublished. [BA; sub: 734, A3162, Box 104, Vol 1, attachment 4-3]

Radiolabelled [^{35}S]-fenthion was administered orally or subcutaneously to lean, fasting rats and rabbits or to well-fed corpulent animals.

The peak concentration of radiolabel appeared in the plasma one hour after treatment for the lean animals and 6-9 h after treatment for the well-fed animals. Excretion of radiolabel was primarily urinary in both groups and for each species. The author concluded that there is a more rapid breakdown and elimination of the administered compound from the system of lean animals rather than well-fed ones.

Johnson JC Jr & Bowman MC (1972) Responses from cows fed diets containing fenthion or fenitrothion. J Dairy Sci 55(6): 777-782

Fenthion was given to lactating dairy cows (2/group) at dietary levels of 25, 50 or 100 ppm for 28 days; the ingested amount was 0.43, 0.70 or 1.29 mg/kg bw/d of fenthion, respectively.

The peak total concentrations of residues of fenthion, its sulfoxide and sulfone, and the sulfoxide and sulfone of the oxygen analogue in the milk over the treatment period were 0.016, 0.049, and 0.099 mg/kg milk, respectively. The peak total residues of fenthion and its sulfoxide in faeces were 0.042-0.308 mg/kg, and the peak total residues of the sulfoxide and sulfone of fenthion and its oxygen analogue in urine were 0.43-1.05 mg/kg. Seven days after the end of treatment, no residues were detected in milk, faeces, or urine. A weekly blood sample was used to assess whole-blood ChE activity of cows fed 25, 50 or 100 ppm. Activity was depressed 39%, 70% and 81%, respectively, when compared to controls.

Avrahami M & White DA (1975) Residues in milk of cows after spot-treatment with [^{32}P]-fenthion. New Zealand Exp Agric 3: 309-311

Two lactating dairy cows (Friesan-Jersey cross) were treated with a single dermal dose of [^{32}P]-labelled fenthion at 9 mg/kg bw. The total [^{32}P]-radiolabel in blood, milk, urine, and faeces peaked between the first and second days after treatment. During the 4-week period after administration, 45-55% of the administered dose was recovered in the urine, 2-2.5% in the faeces, and 1.2-2% in the milk. The residues were predominantly water-soluble hydrolysis products of fenthion. The highest level of fenthion and its organo-soluble metabolites in the milk was 0.1 mg/mL, found on the first day after treatment. The cumulative percentage of radioactivity found in milk was <2% of the applied dose.

Pither KM (1979) Metabolism of Baytex in male and female pigs. Report No. 68475 from Mobay Corporation, Corporate Toxicology Department, Kansas, USA. Unpublished. [BA; sub: 734, A3162, Box 104, Vol 1, attachment 4-6]

One male and one female Duroc pig were given a single dose of radiolabelled fenthion at 5 mg/kg bw ([^{14}C]fenthion, purity, 99%) by oral gavage and seven days later two or three consecutive daily doses of 10 mg/kg bw [^{14}C]-fenthion.

Elimination of label was rapid; total excretion over the first 30 h being >84% of the administered dose, rising to >91% recovery for both sexes by 54 h. Urine was the main route of elimination, accounting for >80% of the dose within 24 h; only minor amounts (<10% of the single dose) were excreted in the faeces. Tissue residue levels declined rapidly, from 2.4 ppm (male brain) - 8.6 ppm (male liver) at 6 h after the third daily dose, to <0.2 ppm (female, multiple tissues) - 1.15 ppm (female fat) at 30 h after the second daily dose, indicating rapid elimination from tissues.

The main urinary metabolites were conjugated phenols (phenol fenthion, phenol sulfoxide and phenol sulfone). It was proposed that the primary route of metabolism in the pig is oxidation of the thiomethyl and thiophosphate moieties to form fenthion sulfoxide and sulfone and oxygen analogue metabolites, which are then hydrolysed at the P-O-phenyl bond to yield the corresponding phenols. The phenols are conjugated before elimination in urine.

Puhl RJ & Hurley JB (1982) The absorption, excretion and metabolism of Baytex-ring-1-[^{14}C] by rats. Report No. 82227 from Mobay Corporation, Corporate Toxicology Department, Kansas, USA. Unpublished. [BA; sub: 734, A3162, Box 104, Vol 1, attachment 4-2]

Wistar rats (5/sex/group) were fasted for 16-24 h and then given: a single dose of ring-labelled [^{14}C]-fenthion (98-99% purity), either intravenously at 2 mg/kg bw (Group A) or by gavage at 10 (Group B) or 100 mg/kg bw (Group D). A fourth group of animals (Group C) was given 14 daily doses of unlabelled fenthion at 10 mg/kg bw (97.2% purity) before receiving a single oral dose of [^{14}C]-fenthion at 10 mg/kg bw. Animals were sacrificed at 72 h after dosing with radiolabel, and collected excreta and tissues were extracted for analysis.

Orally administered labelled fenthion was readily absorbed from the gastrointestinal tract; absorption (GIT) (96-100% at 72 h) was not dose-dependent over the dose range tested. Plasma peak levels were reached in 20-45 min at the single oral doses of 10 and 100 mg/kg bw (groups A and D), but the peak levels were not reached until 2–3 h after the single oral dosing in the animals which received 14 doses as a pretreatment (group C). Fenthion was rapidly eliminated, >90% of the administered radiolabel being excreted within 48 h. Urine was the major route of elimination, accounting for 93-97% of the total label recovered 72 h after treatment. Only 2-6% was recovered in faeces, and none was found in expired gases. The excretion profiles were generally similar, regardless of the route of administration, dose, sex of the rats, or pretreatment with unlabelled fenthion for 14 days.

Fourteen metabolites were identified and the metabolite profile was similar for male and female animals and for each group. The major metabolite group (ca. 60%) was composed of the three phenols and their sulphate and glucuronide conjugates. Four desmethyl metabolites totalled ca. 30% of the radiolabel. There were only minor fractions of the organosoluble unchanged parent fenthion (<2%) and its oxygen analog sulphoxide (1–4%). The inferred major metabolic transformations were thus hydrolysis (followed by conjugation), S-oxidation, *O*-demethylation, and P=S to P=O conversion. Tissue retention of radiolabel was low; 72 h after treatment, a range of 0.1–1.4% of the administered dose was retained. The highest tissue concentrations were found in fat, gonads, and liver.

Emteres R, Abdelghani A & Anderson AC (1985) Determination of the half life of fenthion in New Zealand white rabbits using three routes of administration. J Environ Sci Health B20(5): 577-591

Fenthion (94%) was administered to NZW rabbits (sex unknown) at 20 mg/kg bw via the oral, subcutaneous or intravenous routes (3/group). The concentration of fenthion was determined in blood sampled at 2-4 h and up to 48 h after dosing.

Fenthion appeared at trace levels in the blood at 0.5 h after oral dosing, reaching high levels at 2-20 h after dosing, with a peak at 10 h (50 ppm). The subcutaneous and intravenous routes yielded maximum concentrations at 4 h (55 ppm) and 1 h (67 ppm) respectively, after dosing. No fenthion was detected in any samples at 48 hours. The half-life of fenthion in the blood was 11-12 h, regardless of the route of administration.

Crosby J, Hoglen N & Krautter G (1990) Nature of residues in skin and tissues of swine after dermal treatment with [^{14}C]fenthion. Mobay report No. 73984 from Pharmacology and Toxicology Research Laboratory, Kentucky, USA. [BA; sub: 11793, Vol 18] GLP

A single male pig (Yorkshire cross-breed) was given a single dermal dose of [^{14}C]fenthion (purity, 97.6%) at 14.4 mg/kg bw, prepared as a formulation for treatment of lice in pigs (Tiguvon Swine Pour-on) and applied uniformly along the animal's backbone. The pig was sacrificed 18 h after treatment, and skin and selected tissues were removed and analysed for residues

The tissue residue levels were generally low (0.1-0.8 ppm [^{14}C]-fenthion equivalents in muscle, liver, kidney, and fat), except at the site of application, where significantly higher levels were measured in hair (1398 ppm), skin (134 ppm), and subcutaneous fat (3.9 ppm). Analysis of tissue residues showed that unchanged fenthion was the major component, accounting for >96% of the residue in all samples (hair, skin, and subcutaneous fat) collected from the application site, 69-88% in liver, peritoneal fat, and muscle, and 26% in kidney. Other minor residue components were fenthion sulfoxide (in peritoneal fat and muscle; 11-12% of residue) and fenthion sulfone (in kidney; 7% of residue). A number of unknown polar metabolites were also found in the liver and kidney, representing respectively 30 and 67% of the total residues in these tissues. Two of these compounds were identified by high-performance liquid chromatography (HPLC) in a later study (Krautter 1990b) as glucuronide conjugates of phenol sulfoxide and phenol sulfone, the primary metabolites of fenthion.

Krautter G (1990a) Nature of residues in milk, skin and tissues of a lactating cow after dermal treatment with [^{14}C]-fenthion. Mobay report No. 74012 from Pharmacology and Toxicology Research Laboratory, Kentucky, USA. [BA; sub: 11793, Vol 18] Guideline: USEPA 171-4 part 3. GLP

One lactating dairy cow (Jersey) was given a single dermal dose of [^{14}C]-fenthion (purity, 98.2%) at 5.08 mg/kg bw, prepared as a formulation (Lysoff Pour-on) for treatment of lice in cattle and applied uniformly along the animal's backbone. The cow was sacrificed 18 h after treatment, and urine, milk, skin, and selected tissues were analysed for residues.

The mean residue level in milk 6, 12, or 18 h after treatment was <0.05 ppm [^{14}C]-fenthion equivalents. The mean urinary concentration 0-18 h after treatment was 3.9 ppm. The tissue residues were generally low: 0.1-0.3 ppm in skin, liver, kidney, muscle, and peritoneal fat; 1.8 ppm in subcutaneous fat; and 2.3 ppm in hair. At the site of application, significantly higher levels were measured: 16 215 ppm in hair, 106 ppm in skin, and 6.1 ppm in subcutaneous fat. Analysis of tissue residues showed that unchanged fenthion was the major component, accounting for >95% of the residue in all samples (hair, skin, and subcutaneous fat) collected from the application site, 71-95% in liver, peritoneal fat, and muscle, and 51% in kidney. A minor residue component was fenthion sulfoxide (muscle; 5% of residue). An unidentified polar metabolite (see Krautter 1990b for identification) was found in the liver and kidney, representing respectively 21 and 44% of the total residues in these tissues.

Krautter G (1990b) Characterization of polar metabolites in river and kidney tissues from a cow and pig treated dermally with [^{14}C]fenthion. Mobay report No. 74124 from Pharmacology and Toxicology Research Laboratory, Kentucky, USA [BA; sub: 11793, Vol 18] Guideline: USEPA 171-4 part 3. GLP

Waggoner TB (1991) Fenthion - Nature of the residue (metabolism) Swine and Bovine Mobay report No. 74130 from Animal Health division, Kansas, USA, dated Jan 7, 1991. [BA; sub: 11793, Vol 18]

This study (Krautter 1990b, summarised by Waggoner 1991) was conducted to characterise the unknown polar metabolite(s), found in cow and pig liver and kidney tissues after these animals were treated dermally with a [^{14}C]-fenthion labelled formulation (Tiguvon Pour-on) and sacrificed 18 h later (see Krautter 1990a; Crosby et al 1990). Liver and kidney samples were extracted with non-polar solvents followed by partitioning with water. The aqueous phases were subjected to hydrolysis catalysed with enzymes and acid.

For both cows and pigs, at 18 h after dosing, parent fenthion accounted for 50-96% of total residues in tissue (liver, kidney, muscle and fat) except for pig kidney where parent fenthion was 23% of total residues. Other intact OP metabolites (fenthion oxygen analog, fenthion phenol sulfoxide and fenthion phenol sulfone) were detected in tissues and accounted for 3-13% of total residues. Two or more unknown metabolites readily extractable with acetonitrile and characterised as water soluble residues were found in the liver and kidney. These residues represented 22-57% of the total residues for these tissues. The major polar unknowns (up to 50% of this fraction) were identified by enzyme hydrolysis HPLC as glucuronide conjugates of fenthion phenol sulfoxide and fenthion phenol sulfone, the primary metabolites of fenthion.

Christenson, WR (1990c) Technical grade fenthion (Baytex): A special study to examine the effect of the route of acute administration of technical grade fenthion (Baytex) on ChE activity in the rat. Mobay Corporation, Kansas, USA. Study no. 89-992-DJ, report no. 5360. GLP [BA; sub:11793, vol. 3, ref. 9]

Fenthion (97.5%) was administered in corn oil by gavage, dermal application (6-h occlusion) or subcutaneously to 12-week old male Fisher 344 [CDF(F-344)/Crl/Br] rats (10/group) at 0, 1, 5 or 25 mg/kg bw and the animals observed for 14 days prior to sacrifice and necropsy, which included assay of brain tissue for ChE activity. Animals were bled 7 days prior to administration of fenthion, then at days 1, 4 and 14 post-dose for assay of plasma and RBC ChE.

There were no clinical signs or mortalities during the course of the study. The body weights, food consumption and necropsy findings did not significantly differ from the control groups for any dose or route of administration. The oral treatment group at 1 mg/kg bw recorded no ChE depression at any assay time in any sample. At 5 mg/kg bw, significant depression of ChE activity was recorded for plasma (32%) and RBC (8%) ChE at day 1, RBC ChE at day 4 (9%) and RBC ChE (7%) and brain ChE (8.5%) at day 14. At 25 mg/kg bw there was significant depression of plasma and RBC ChE at day 1 (66% and 36.5%) and day-4 (18.5% and 24.7%), and RBC ChE (17%) and brain ChE (19.3%) at day 14. The oral route recorded maximum inhibition for plasma and RBC ChE at day 1after dosing .

The dermal treatment group at 1 and 5 mg/kg bw recorded significant plasma ChE depression at days 4 and 14. At 25 mg/kg bw there was significant depression of plasma ChE and RBC ChE at days 1 and 4, and RBC ChE and brain ChE at day 14.

The subcutaneous treatment group at 1 mg/kg bw recorded significant RBC ChE depression at day 4. At 5 mg/kg bw, significant depression of activity was recorded for plasma ChE and RBC ChE at day 4. At 25 mg/kg bw there was significant depression of plasma ChE and RBC ChE at day 4, and RBC ChE, plasma ChE and brain ChE at day 14.

Brain ChE, measured only at day 14, was depressed in all groups at 25 mg/kg bw, but at 5 mg/kg bw it was depressed in the oral treatment group only. There were no observable effects on ChE activity of 1 mg/kg bw fenthion administration at 24 hours, but some depression at 4 and 14 days in the dermal and subcutaneous groups; however these values tended towards control values by day 14 (Table 20).

Table 20: Percentage brain ChE inhibition at day 14

Dose route	Oral	Dermal	Subcutaneous
Dose (mg/kg bw/d)			
0	0	0	0
1	1.1	1.3	0
5	8.5*	+2.6	0.6
25	19.3*	9.6*	25.1*

*significantly different from control p<0.05

Weber H & Ecker W (1992) [phenyl-1-^{14}C]Fenthion: Absorption, distribution, excretion and metabolism in a lactating goat. Bayer Laboratories, Germany. Miles Report No. 105012. Guideline: USEPA 171-4b; GLP [BA; sub: 11793, Vol 11]

A single lactating goat was given [phenyl-1-^{14}C]-fenthion (chemical and radiopurity, >99%) by gavage in gelatine capsules at 20 mg/kg bw/d for three days. The goat was sacrificed 3.5 h after the last dose, and the level and nature of the residues were determined in urine, milk, and edible tissues.

At sacrifice, the total excretion of radiolabel was 50.6% (44.1% was excreted in urine, 6.3% in faeces, 0.2% in milk). Residue in edible tissue and organs was 0.9%. The rate of gastrointestinal absorption was rapid: the elapsed time for plasma concentration of radiolabel to increase from 25% to 75% of maximum value was 0.96 h, and a plasma peak level of 7.74 µg/mL was reached approximately 3 h after the first dose. The radiolabel was eliminated from the plasma with a half-life of ca. 3.3 h during the last 20 h before the second dose. The maximal residue level in milk was 2.8 and 3.4 µg/g 8 h after the first and second doses, respectively. Tissue residue concentrations 3.5 h after the last dose were judged to be low, the highest being found in kidney (24.1 µg/g), liver (3.32 µg/g), fat (1.04-2.73 µg/g), and muscle (0.62 µg/g).

Phenol fenthion, phenol sulfoxide, and phenol sulfone were the three major metabolites in all tissues examined. Various intermediate metabolites in the biodegradation from parent fenthion to the phenols (demethylated phosphorus-containing compounds with varying oxidation at the methylsulfur moiety and/or at the phosphoric acid moiety of the molecule) were also identified. Demethyl fenoxon sulfoxide and sulfone were especially predominant in muscle, while the sulfoxide and sulfone of fenthion constituted approximately 30% of the residues in fat. Unchanged fenthion was not detected in any tissue sample. The metabolites excreted in urine were similar to those in the liver, except for the higher percentage of phenol sulfide in the urine.

Doolittle KD & Bates NL (1993) Absorption, distribution and elimination of ^{14}C-fenthion in rats following a single oral, repeated oral and single intravenous administration. Miles report No. 74395 from Southwest Bio-Labs, Inc., New Mexico, USA. Guideline USEPA 171-4. GLP. Unpublished [BA; sub:11793, vol. 3, ref. 15]

Five groups of five or six Wistar rats of each sex were fasted for approximately 2 h and then given a single dose of [^{14}C] fenthion (purity, 98%), either intravenously at 0.125 mg/kg bw or by gavage at 0.3 or 1.5 mg/kg bw. One group was given 14 consecutive daily doses of 0.3 mg/kg bw unlabelled fenthion (purity, 96.5%) before receiving a single oral dose of 0.3 mg/kg bw [^{14}C]fenthion ; a further group of two male and two female rats was given a single oral dose of 0.3 mg/kg bw [^{14}C] fenthion for measurement of expired CO_2, and one of three male and three female rats served as untreated controls.

Table 21: Dose regimens and termination times

Group No.	Dose (mg/kg bw)	Route	No. of doses	Sacrifice time (h post [^{14}C]-dose	No. of rats (M,F)	Assays
I	0.30	oral	1	72	2, 2	CO_2 and residues
II	0.30	oral	1	168	5, 5	residues
III	1.50	oral	1	168	5, 5	residues
IV	0.125	iv	1	24, 72, 168[b]	5, 5	residues
V	0.30	oral	15[a]	168	5, 5	residues
VI	1.51	oral	1	NA	6, 6	ChE assay
VII					3, 3	controls

[a] unlabelled fenthion for 14-d followed by a single dose of [^{14}C]-fenthion
[b] unlabelled fenthion only

Excretion of the radiolabel was rapid, 75-104% of the dose being eliminated within 48 h; the mean total excretion over 168 h was 80-107%. The excretion profiles were similar, regardless of sex, dose, route of administration, or pretreatment with unlabelled fenthion. Urine was the main route of excretion, accounting for 88-98% of the total radiolabel excreted; only minor amounts (1-10% of the dose) were excreted in the faeces, and no label was found in expired CO_2. The main metabolites in the urine were phenol sulphoxide, phenol sulphoxone and phenol fenthion indicating that the major metabolic route in the rat is via oxidation of the thiomethyl and thiophosphate groups, with hydroxylation at the P-O-phenyl sites to phenols and formation of glucuronide or sulphate conjugates to form the major urinary metabolites.

Serum ChE activity, used as a measure of exposure to fenthion, was inhibited to 36-50% of the control value 24 h after a single oral dose of 1.5 mg/kg bw [^{14}C]-fenthion. By 72 h, serum ChE activity appeared to return to control levels, and it was unchanged at 168 h. These results reflect the excretion profile of fenthion in the rats. Tissue retention of radiolabel was very low; the mean total label recovered in the tissues and carcass at termination was <0.5%, and the amount recovered in the tissues alone was either below the detection limit or <0.01% in all treated groups. The tissue residue levels were generally <1 ppb.

9.3.3. Acute Studies

9.3.3.1 Active Constituent

Acute oral toxicity

Summaries of submitted and published findings of acute median lethal dose studies with fenthion are shown in Table 22 below. In general, the signs of acute fenthion intoxication are consistent with that of the OPs as a class.

Table 22: Acute oral toxicity

Species [strain]	Sex	Group Size	Vehicle	Purity (%)	Doses Tested (mg/kg bw)	LD_{50} (mg/kg bw)	Reference
Mouse [Kunming]	M/F	NS	W & Tween-80	96	NS	200 (M) 233 (F)	Bai et al (1990)
Mouse [Carworth]	M/F		E & G	NS	NS	226.9 M 224.7 F	DuBois (1968)
Mouse [Swiss, TO]	M/F	NS	Arachis oil	96.5	NS	150 (M) 190 (F)	Francis & Barnes (1963)
Mouse [NS]	M/F	NS	Emulsifier	94.7	NS	272 (M) 273 (F)	Iyatomi (1978)
Mouse [NS]	M/F	NS	CEL	95	NS	290 (M) 280 (F)	Iyatomi (1980)
Rat [NS]	M	5	W & EM	NS	62.3, 124.6, 186.9, 249.2, 311.5 or 373.8	311.5	Bayer Ag (1960)
Rat [NS]	M	NS	E & G	96.1	100, 200, 250, 350, 500 or 700	230	Bayer Ag (1967)
			W & CMC		100, 200, 300, 400 or 500	194	
Rat [NS]	M	NS	W & tragacanth	96.1	100, 150, 250, 350, 500 or 750	264	Bayer Ag (1967)
			W & CEL		100, 250, 350, 500 or 750	319	
			W & EM		100, 175, 250, 500 or 750	235	
Rat [Wistar]	M/F	NS	W & Tween-80	96	NS	171 (M) 287 (F)	Bai et al (1990)
Rat [SD]	M/F	ca.30	E & G	NS	NS	190 M 310 F	DuBois & Kinoshita (1964)

Species [strain]	Sex	Group Size	Vehicle	Purity (%)	Doses Tested (mg/kg bw)	LD_{50} (mg/kg bw)	Reference
Rat [SD]	M	NS	E & G	80	NS	140	DuBois & Kinoshita (1965)
Rat [Holtzman]	M/F	4 or 5	E & G	93	200, 250, 300 or 350 (M/F) or 400 (F) or 225 or 275	255.8 (M) 298.7 (F)	DuBois & Kinoshita (1970b)
				97	200, 250 or 300 (M/F) or 350 or 400 (F) or 225 or 275	250.2 (M) 295.6 (F)	
Rat [SD]	M/F	5/sex	Corn oil	96.9	100, 200, 300, 400 or 500 (M/F) or 600 or 700 (F)	405 (M) 566 (F)	Eigenberg (1987a) (GLP)
Rat [Wistar]	M/F	15/sex	Distilled W	81.5	10, 25, 50, 100, 250, 350 or 500 (M/F) or 450 (M) or 200 or 750 (F)	343 (M) 363 (F)	Flucke & Thyssen (1978a)
Rat [Wistar]	M/F	15/sex	Distilled W	82.5	10, 25, 50, 100, 250, 350 or 500 (M/F) or 200 (M) or 300 or 750 (F)	281 (M) 404 (F)	Flucke & Thyssen (1978b)
Rat [Albino, Porton]	M/F	NS	Arachis oil	96.5	NS	215 (M) 615 (F)	Francis & Barnes (1963)
Rat [Sherman]	M/F	NS	Peanut oil	NS	NS	215 (M) 245 (F)	Gaines (1969)
Rat [Wistar Bor: WISW]	M	5	W & CEL	NS	1, 10, 100, 250, 280, 355 or 500	344 (a.i. at 20°C))	Heimann (1987)
					1, 10, 100, 250, 355 or 500	340 (a.i at 54°C)	
Rat [NS]	M/F	NS	Emulsifier	94.7	NS	320 (M) 509 (F)	Iyatomi (1978)
Rat [NS]	M/F	NS	CEL	95	NS	390 (M) 500 (F)	Iyatomi (1980)
Rat [NS]	M	5	W & EM	NS	50, 100, 150, 200, 250 or 300	250	Kimmerle (1960)
Rat [Wistar CFN]	M	5 or 10	EM W233	99	140, 160, 180, 200, 225, 250, 300, 400, 450, 500, 550	315	Klimmer (1963)
		5		97.4	155, 175, 200, 225, 250, 275, 300, 360 or 400	241	
				97	155, 175, 200, 225, 250, 275, 300, 360, 400, 450	268	
Rat [Wistar]	M/F	15	W	NS	5, 100, 250, 500 or 1000 (M/F); 750 (M); 50, 150, 200 or 350 (F)	474 (M) 309 (F)	Mihail & Thyssen (1979)
Rat [Wistar]	F	2	W & EM W 233	NS	250, 500 or 1000	500–1000 (0/2-2/2 deaths)	Thyssen (1974)
Guinea-pig [NS]	M	25	E & G	NS	NS	260 M	DuBois & Kinoshita (1964)
Guinea-pig [NS]	M	NS	Arachis oil	96.5	NS	>1000 (M)	Francis & Barnes (1963)

Species [strain]	Sex	Group Size	Vehicle	Purity (%)	Doses Tested (mg/kg bw)	LD_{50} (mg/kg bw)	Reference
Guinea-pig [NS]	M	2	W & EM	NS	100, 250, 500 or 1000	375	Kimmerle (1963)
Rabbit [NS]	NS	NS	W & EM	NS	124.6 or 311.5	124.6	Bayer Ag (1960)
Rabbit [NZW]	F	3	Distilled W	81.5	50, 100 or 250	100	Flucke & Thyssen (1978a)
Rabbit [NZW]	F	3	Distilled W	82.5	50, 100 or 250	100	Flucke & Thyssen (1978b)
Rabbit [NS]	M	NS	Arachis oil	96.5	NS	150-175 (M)	Francis & Barnes (1963)
Cat	NS	2	None	NS	124.6 or 311.5	>311.5 (0/2 deaths)	Bayer Ag (1960)
Cat	NS	1	NS	NS	25 or 100	>100 (0/1 death)	Kimmerle (1960)

NS = Not stated; NZW = New Zealand White; W =Water; E & G = 20% ethanol & 80% propylene glycol; W & EM =W and emulsifiers; CEL = Cremaphor EL; E:L = 1:1, Ethanol: Lutrol

Francis JI & Barnes JM (1963) Studies on the mammalian toxicity of fenthion. Bull World Health Org 29: 205-212

Fenthion (96.5%) and some oxidative metabolites were administered to mice, rats, guinea-pigs, rabbits or hens by oral or dermal routes in order to establish LD_{50} values and levels of ChE inhibition.

The authors described the toxic reactions as being similar for rats and mice; ie. fasciculations appearing 40-90 min after an oral dose, salivation, tremors, gross weakness and chromodacryorrhoea. Guinea pigs appeared especially refractory to the toxicity of fenthion but displayed normal sensitivity to another OP, being sacrificed by 30 mg/kg bw parathion. Rabbits were not visibly affected until the dose approached the LD_{50} at which time a general restlessness followed by excessive salivation and rapid noisy breathing preceded weakness and muscle fasciculations. Hens were especially sensitive to orally administered fenthion, developing excessive salivation at approximately 2 hours after dosing, followed by diarrhoea and characteristic cholinergic spasticity. Time of death after a lethal dose varied between species, being from 6-72 h in rats, 1.5-48 h in mice, and 24-48 h in rabbits and hens.

Repeated oral dosing in male rats indicated that recovery from dosing was slow. Only one out of four rats survived five daily doses of 50 mg/kg bw. Similarly brain ChE inhibition was sustained in female rats given a single oral dose of 200 mg/kg bw fenthion; brain ChE activity expressed as percentage of control was 48%, 25%, 31%, 39%, 52% and 74% at days 1, 2, 3, 4, 8, and 14 after dosing respectively.

Four weeks of dietary intake of fenthion by rats at levels up to 114 mg/kg bw/d (males) and 153 mg/kg bw/d (females) recorded >80% inhibition of brain ChE in both sexes; brain ChE was still below control values after 4 weeks recovery.

For male and female rats the LD_{50} for a single dermal dose of fenthion was 500 mg/kg bw. For male rats given a single dermal dose, the sulphoxide of fenthion produced no signs of poisoning at doses of 800 mg/kg bw or below, fasciculations at 1600 and 2000 mg/kg bw and

1/4 deaths at 3000 mg/kg bw. Similarly dermal doses of fenthion sulphone produced fasciculations at 400 and 800 mg/kg bw and 4/4 deaths at 1600 mg/kg bw.

On the basis of experiments with fenthion metabolites (insufficient details provided and hence not reported here) the authors concluded that fenthion is not directly converted to the active oxon by a simple oxidation P=S → P=O, but that oxidation at the thioether linkage to give the sulphoxide and sulphone will take place first, and may be followed by other uncharacterised transformations. The authors also state that the prolonged effect of fenthion after a single dose suggests that a large part of administered doses is stored and only slowly released for metabolism.

Bayer Ag (1967) LEBAYCID a.i / solvent dependence of the acute oral toxicity in rats. Farbenfabriken Bayer Ag, Institute of Technology, Wuppertal-Elberfeld. Unpublished. [BA; sub: 734, A3162, Box 104, Vol 1, Attachment 2-1]

The solvent dependence of the oral LD_{50} value for 96.1% technical grade fenthion was investigated in an acute oral toxicity study using male rats (15/dose group). The results are tabulated in Table 23 below.

Table 23: Rat acute oral toxicity study

Solvent	Oral LD_{50}
Ethanol/propylene glycol (20/80)	230
Water 0.5%, carboxymethyl cellulose	194
Water 0.5%, tragacanth	264
Water, Cremophor EL	319
Water, Emulsifier W	235

Emteres R, Abdelghani A & Anderson AC (1986) Subacute toxicity of fenthion to New Zealand White Rabbits (Orcyctalagus cuniculus). Environmental Technology Lett. (1986) 7: 27-30

Mortality was measured in groups of NZW (female, 5/group) rabbits dosed orally with fenthion (94%) in vegetable oil at 0, 5, 10 or 20 mg/kg bw/d. Cumulative percent mortality was a function of both dose and exposure time as shown in Table 24 below.

Table 24: Percent mortality in rabbits

Dose (mg/kg bw/d)	Time intervals (days)						
	0-5	5-10	10-15	15-20	20-25	25-30	30-35
0	0	0	0	0	0	0	0
5	0	0	0	20	40	80	100
10	20	40	60	80	100	100	100
20	40	80	100	100	100	100	100

Cholinergic signs were observed at all doses, with their onset as early as 24 h post-dose at 20 mg/kg bw/d. These results are in contrast to those of Francis & Barnes (1963) who reported that rabbits were asymptomatic until receiving doses approaching the LD_{50}.

9.3.3.2 Acute dermal toxicity

The toxicological database contains many studies describing the acute dermal toxicity of fenthion and these are tabulated below with only a few illustrative studies presented in greater detail. There is a very large range of dermal LD_{50} values even within the same strain of test species, and females generally appear to be less sensitive than males.

There are substantial species differences in the observed acute dermal toxicity values with avians being particularly sensitive. A GLP study testing undiluted fenthion on Wistar rats recorded acute oral LD_{50} values of 586 mg/kg bw for males and 800 mg/kg bw for females, while another in rabbits recorded an LD_{50} of 963 mg/kg bw for both sexes. In terms of relative toxicity, in rats fenthion appears to be approximately two times more toxic by the oral route compared to the dermal route. The differential may be larger in other species such as rabbits.

Klimmer OR (1963) Toxicological testing of "Bayer 29493". Farbenfabriken Bayer Ag, Leverkusen. 25 March 1963. Unpublished. [BA; sub 734, A3162, Box 104, Vol 1, attachment 2-2; sub: 11793, Vol 9]

One of two batches of undiluted technical grade fenthion (97.4 and 97.0% purity) was applied to the shaven dorsal non-irritated skin of male Wistar rats (5 rats per dose) and rubbed in with a glass rod. The fenthion was not removed and the rats were observed for 2 weeks. The acute dermal LD_{50} values were 410 and 345 mg/kg bw for batches 1 and 2 of fenthion, respectively. Toxic signs and time to develop toxicity were typical of those seen after acute oral administration of fenthion.

Dubois KP & Kinoshita F (1964) Acute toxicity and anti-ChE action of O,O-dimethyl-O-4-(methylthio)-m-tolyl) phosphorothioate (DMTP; Baytex) and related compounds. Toxicol Appl Pharmacol, 6: 86-95 [BA; sub:734, A3162, Box 104, Vol 1, Attach 2-5]

Undiluted fenthion was applied to the shaven backs of male and female SD rats. The approximate dermal LD_{50} for both males and females was 500 mg/kg bw.

Gaines TB (1969) Acute toxicity of pesticides. Toxicol Appl Pharmacol, 14: 515-534

Fenthion dissolved in xylene was applied to the shaven dorsal skin of male and female Sherman rats at a constant rate of 0.0016 mL/g bw. The fenthion was not removed. The dermal LD_{50} for both males and females was 330 mg/kg bw. The oral LD_{50} of fenthion suspended in peanut oil and administered at 0.005 mL/g bw was 215 and 245 mg/kg bw for males and females respectively.

Mihail F (1978) S 1752 (Lebaycid active ingredient): Determination of percutaneous toxicity. Bayer AG, Institut für Toxikologie, Wuppertal, Germany. Report No. 7604. Unpublished. [BA; sub: 734, A3162, Box 104, Vol 1, attachment 2-13]

Technical grade fenthion (98.2% purity) was applied either undiluted (doses up to 1500 mg/kg bw) or as a cellulose powder paste (2500 mg/kg bw and above) to the shaven dorsal skin of male and female Wistar rats. Exposure time was 24 hours. The dermal LD_{50} values were 1680 and 2830 mg/kg bw for males and females, respectively. Toxic signs were typical of those seen with organophosphate compounds.

Table 25: Acute dermal toxicity

Species [strain]	Sex	Group Size	Vehicle	Purity (%)	Doses Tested (mg/kg bw)	LD_{50} (mg/kg bw)	Reference
Mouse [NS]	F	4	Acetone	NS	150, 250, 500, 1000, 2000 or 4000	500	Crawford et al (1970)
Mouse [NS]	M/F	NS	Acetone	94.7	NS	2000 (M/F)	Iyatomi (1978)
Mouse [NS]	M/F	NS	Acetone	95	NS	>2000 (M/F)	Iyatomi (1980)
Rat [NS]	M	2	None	NS	124.6	>124.6 (0/2 deaths)	Bayer Ag (1960)
Rat [Wistar]	M	5	None	98.2	25, 100, 500 or 1000 (24 h, with occlusion and washoff)	586	Bomann (1991a) [GLP]
	F				10, 25, 100, 250, 300, 355, 500 or 710 (24 h, with occlusion and washoff)	800	
Rat [SD]	M	NS	None	80	NS	325	DuBois & Kinoshita (1965)
Rat [Wistar]	M/F	5 or 10/sex	NS	81.5	1000, 2500 or 3500 (M/F) or 4500 or 5000 (M) or 1250, 1750, 2000 or 3000 (F)	3461 (M) 2062 (F)	Flucke & Thyssen (1978a)
Rat [Wistar]	M/F	5 or 10/sex	NS	82.5	1000, 1750,2500, 3500 or 5000 (M/F) or 500 (F) (24 h with occlusion and wash off)	2565 (M) 1922 (F)	Flucke & Thyssen (1978b)
Rat [Sherman]	M/F	NS	Xylene	NS	NS (72 h, no occlusion, with wash-off)	330 (M/F)	Gaines (1969)
Rat [NS]	M/F	NS	Acetone	94.7	NS	2000 (M/F)	Iyatomi (1978)
Rat [NS]	M/F	NS	Acetone	95	NS	>2000 (M/F) (deaths not stated)	Iyatomi (1980)
Rat [Wistar CFN]	M	5	None	99	200, 250, 300, 350, 400, 450, 500 or 600 (no occlusion or wash-off)	410	Klimmer (1963)
				99	200, 250, 300, 350, 400, 450, 500, 550 or 600 (no occlusion or wash-off)	345	
Rat [NS] 2 h & 4 h)	M	2	None	NS	1000	>1000 (0/2 deaths)	Kimmerle (1960)
Rat [Wistar]	M	5 or 10/sex	None	98.2	500, 750, 1000, 1500, 2500 or 3000 (24 h, with occlusion and wash-off)	1680	Mihail (1978)
	F				1500, 2500, 3000, 3500 or 5000 (24 h, with occlusion and wash-off)	2830	

Species [strain]	Sex	Group Size	Vehicle	Purity (%)	Doses Tested (mg/kg bw)	LD_{50} (mg/kg bw)	Reference
Rat [Wistar]	M/F	5 or 10	cellulose	NS	500, 1000 or 5000 (M/F) or 1500, 2000 or 2500 (F) (24 h, with occlusion and wash-off)	>5000 (M: 0/5 deaths) 5000 (F)	Mihail & Thyssen (1979)
Rabbit [NS]	NS	1, 2 or 5/group	None	NS	100, 150, 200, 300 or 500 (no occlusion or wash-off)	<150 (3/5 deaths)	Crawford & Anderson (1971)
Rabbit [NS]	M	2	None	93 97	200 or 500	200	Dubois & Kinoshita (1970b)
Rabbit [NZW]	M/F	5/sex	None	96.9	100, 300, 400, 800, 1000 or 1200 (24 h, with occlusion and wash-off)	963 (M/F)	Eigenberg (1987b) [GLP]
Rabbit [NZW]	M/F	4/sex	None	NS	100, 150 or 225 (M/F) or 338 (M) or 67 (F) (abraded; 24 h, no occlusion, with wash-off)	150 (M) 131 (F)	Lamb & Anderson (1974)

Abbreviations: NS = Not stated; NZW = New Zealand White; W =Water; E & G = 20% ethanol & 80% propylene glycol; W & EM =W and emulsifiers; CEL = Cremaphor EL; E:L = 1:1, Ethanol: Lutrol

9.3.3.3 Acute inhalational toxicity

The toxicological database contains many studies describing the acute inhalational toxicity of fenthion and these are tabulated below. The range of recorded inhalational LD_{50} values is fairly broad even within strains, and females exhibit either comparable or more sensitivity than males.

A GLP study testing fenthion nose-only exposure in SD rats recorded acute inhalational 4-h LC_{50}(mg/m^3) values of 507 (male) and 454 (female) and for 1 h exposure 1838 (male) and 1637 (female)

Table 26: Acute inhalational toxicity

Species [strain]	Sex	Group Size	Vehicle/ mode	Purity (%)	Dose Tested (mg/m^3)	LC_{50} (mg/m^3)	Reference
Mouse [Carworth] (1 h)	F	10	Xylene/ whole body	92.1	1100, 1570, 1660, 1690, 1970, 2200, 2320, 2340, 2520 or 3110 (50% droplets ≤3 μm)	2000	Dilley & Doull (1961)
Mouse [Carworth] (1 h)	M/F	5	Xylene/ whole body	NS	1430 (droplets ca. ≤2 μm), (0/5 deaths/sex)	>1430	Doull (1960)
Mouse [Carworth] (1 h)	M	6	Xylene/ whole body	93	1528, 1834, 2110, 2500, 2866 or 3275 (nominal) (50% droplets ≤3 μm)	2400	DuBois (1970)
Rat [Holtzman]	M/F	5/sex	Xylene/ whole body	93	2000, 2500 or 3000 (50% droplets ≤3 μm)	3000	DuBois & Wong (1970b)
Rat [SD] (1 h)	F	10	Xylene/ whole body	92.1	1100, 1570, 1660, 1690, 1970, 2200, 2320, 2340, 2520 or 3110 (50% droplets ≤3 μm)	2400	Dilley & Doull (1961)

Species [strain]	Sex	Group Size	Vehicle/ mode	Purity (%)	Dose Tested (mg/m^3)	LC_{50} (mg/m^3)	Reference
Rat [Holtzman] (1 h)	M	10	Xylene/ whole body	93	1658, 2105, 3053, 3286, 3528, 3932 or 4520 (nominal) (50% droplets ≤3 µm)	3450	DuBois (1970)
Rat [Wistar] (1 h)	M/F	10/sex	E:L/ Head only	81.5	257, 748 or 1474 (droplet sizes not given)	>1474 (M/F)	Flucke & Thyssen (1978a)
Rat [Wistar] (4 h)					73, 238, 804 or 985 (droplet sizes not given)	>985 (M)) 804 - 985 (F))	
Rat [Wistar] (1 h)	M/F	10/sex	E:L/ Head only	82.5	272, 668 or 1293 (droplet sizes not given)	>1293 (M) >1293 (F))	Flucke & Thyssen (1978b)
Rat [Wistar] (4 h)	M/F	10/sex	E:L/ Head only	82.5	155, 294, 434, 708, 1271 or 1878 (droplet sizes not given)	1500 (M) >1878 (F))	Flucke & Thyssen (1978b)
Rat [NS] (4 h)	M	20	E:L	96.5	1000, 2500 or 5000 (droplet sizes not given)	1800	Kimmerle (1966)
Rat [Wistar] (4 h)	M/F	10/sex	NS/ Head only	NS	72, 211, 457 or 1102 (droplet sizes not given)	>1102 (M) >1102 (F))	Mihail & Thyssen (1979)
Rat [SD] (4 h)	M/F	10/sex	NS/ Head only	96.9	209, 293, 461, 476 or 862 (100% droplets ≤2µm)	507 (M) 454 (F)	Shiotsuka (1987a) [GLP]
Rat SD] (1 h)	M/F	10/sex	NS/ Head only	96.9	1619, 1872, 2353 or 3235 (M/F) or 723 (F) (100% droplets ≤2.1µm)	1838 (M) 1637 (F)	Shiotsuka (1987b) [GLP]
Rat [Wistar] (1 h)	M/F	10/sex	E:L/ Head only	98.2	272, 834 or 1197 (droplet sizes not given)	>1197 (M/F)	Thyssen (1978)
Rat [Wistar] (4hr)	M	10	E:L/ Head only	98.2	53, 291, 331, 369, 567, 813, 844, 1149, 2208 or 2472 (droplet sizes not given)	Ca. ≥1200	Thyssen (1978)
Rat [Wistar] (4hr)	F	10	E:L/ Head only	98.2	53, 291, 331, 567, 813, 844, 1149 or 2472 (droplet sizes not given)	Ca. 800	Thyssen (1978)

NS = Not stated; NZW = New Zealand White; W =Water; E & G = 20% ethanol & 80% propylene glycol; W & EM =W and emulsifiers; CEL = Cremaphor EL; E:L = 1:1, Ethanol: Lutrol; SD=Sprague-Dawley

9.3.3.4 Skin Irritation

Pauluhn, J. (1985) E 1752 Technical (c.n. fenthion): Study for irritant/corrosive effect on skin and eye (rabbit). Unpublished report No. 13446 from Bayer AG, Institute für Toxikologie, Wuppertal, Germany. Unpublished. [BA; sub: 734, A3162, Box 104, Vol 1, attachment 2.16]

Guideline OECD 404

Skin irritation tests were carried out with 3 NZW rabbits (2 females, 1 male). Fenthion (500 µL of technical grade, 98.5% purity) was applied to cellulose squares, approximately 2.5 x 2.5 cm. Further squares were moistened with water. The squares were taped to opposite sides of the shaven flank skin of the rabbits for 4 hours. After removal of the squares the skin areas were washed with water and observed at 24, 48, and 72 hours after the beginning of the test using the Draize scoring criteria. Total scores were zero at all time points. Fenthion did not cause any irritation to the skin.

Eigenberg DA (1987c) Primary dermal irritation of Baytex technical in albino rabbits. Mobay Corporation, Corporate Toxicology Department, Kansas. Report No. 896. [BA; sub: 11793, Vol 7, tab 34]

Guideline USEPA 81-5. GLP

Baytex technical (0.5 mL, purity 96.9%) was applied under occlusive dressing to the shaved backs of 6 NZW rabbits (3/sex) for 4 hours before dressings were removed and the application sites wiped with damp paper towels. Test areas were scored for erythema and oedema within 1 h and at 24, 48 and 72 hours after patch removal.

There was no oedema observed in any rabbits at any time and very slight erythema (score of 1) was observed in two rabbits within one hour of patch removal but was absent at 24 h. The primary irritation index is 0.0. Fenthion did not cause any irritation to the skin.

9.3.3.5 Eye irritation

Pauluhn J (1985) E 1752 Technical (c.n. fenthion): Study for irritant/corrosive effect on skin and eye (rabbit). Unpublished report No. 13446 from Bayer AG, Institute für Toxikologie, Wuppertal, Germany. Unpublished. [BA; sub: 734, A3162, Box 104, Vol 1, attachment 2.16]

Guideline OECD 405

Eye irritation studies were carried out with 3 NZW Albino rabbits (2 males, 1 female). Fenthion (98.5%, 100 µL) was applied to the conjunctival sac of one eyelid of 3 rabbits, and rinsed with saline after 24 h. The untreated contralateral eyelid served as a control. Draize scores were recorded after 1, 24, 48, 72 and 168 h. All scores were zero at 24 h and later. Fenthion was not an irritant to the rabbit eye.

Eigenberg DA (1987d) Primary eye irritation of Baytex technical in albino rabbits. Mobay Corporation, Corporate Toxicology Department, Kansas, USA. Report No. 817 [BA; sub: 11793, Vol 7, tab 35]

Guideline USEPA 81-5. GLP

Baytex technical (0.1 mL, purity 96.9%) was applied to the left conjunctiva of 6 NZW rabbits (3 F, 3 M) without rinsing. Eyes were scored for lesions of the cornea, iris and conjunctiva at 1, 24, 48 and 72 h after dosing.

The cornea and iris were not affected by treatment. Conjunctival discharge (grade 1-3) was present in all rabbits at 1 h of dosing but was absent at 24 hours. Redness of the conjunctiva (grade 1) was present in all rabbits 1 h after dosing but was absent by 48 hours. Chemosis was observed in three 3-rabbits 1 h after dosing but was absent by 48 hours. Fenthion is a slight eye irritant

9.3.3.6 Skin sensitisation

Flucke W (1987) E 1753 Technical (c.n fenthion): Study for skin sensitising effect on guinea pigs (Magnusson and Kligman's maximization test). Unpublished report No. 15428 from Bayer AG, Institut für Toxikologie, Wuppertal, Germany. GLP [BA; sub: 734, A3162, Box 104, Vol 1, attachment 2.18]

The skin sensitisation potential of fenthion was assessed by the maximization test of Magnusson and Kligman using guinea pigs (DHPW), 20 animals for test and two control groups of 10 animals. Intradermal induction was performed with 0.2% fenthion (98.5% purity) emulsified in either Cremophor EL, 2% in physiological saline or in equal parts of a mixture of Cremophor EL, 2% in saline and Freund's adjuvant. One week after intra-dermal induction, topical induction was carried out with 50% fenthion in Cremophor EL, 2% in physiological saline. Three weeks after intra dermal induction a topical challenge was made with 12.5% fenthion in Cremophor EL, 2% in physiological saline for 24 hours. The treated skin areas were scored for irritation at 24 and 48 hours after dressings were removed. There were no positive reactions on any animals. Fenthion did not have any skin sensitising effect in guinea pigs.

9.3.3.7 Potentiation studies

Dubois KP & Kinoshita F (1964) Acute toxicity and anti-ChE action of O,O-dimethyl-O-4-(methylthio)-m-tolyl) phosphorothioate (DMTP; Baytex) and related compounds. Toxicol Appl Pharmacol 6: 86-95 [BA; sub:734, A3162, Box 104, Vol 1, Attach 2-5]

The acute toxicity of fenthion in female SD rats (20/group) was measured in combination with 16 other anti-ChE insecticides. Potentiation tests were performed by intraperitoneal administration of half of the LD_{50} of fenthion (dissolved in 20% ethanol, 80% propylene gylcol) in combination with half the LD_{50} of each of the other compounds (dissolved in the same vehicle as fenthion). Potentiation was indicated by the occurrence of more than 50% mortality from administration of combinations of the compounds.

Fenthion given in combination with either malathion, diaxathion (Delnav) or coumaphos (Co-Ral) resulted in 100% mortality, thus indicating potentiation. Additional experiments measuring the LD_{50} of equitoxic mixtures showed that the potentiation was approximately 2- to 3- fold (1.7-2.8).

Doull J, Root M & Cowan J (1962) Effect of adding Bayer 29493 in combination with other cholinergic insecticides to the diet of male and female dogs. Unpublished Bayer report from Department of Pharmacology, University of Chicago, Illinois, USA. [BA; sub:734, A3162, Box 104, Vol 1, Attach 2-17]

Groups of 2 male and 2 female beagle dogs were fed for 6 weeks with diets containing fenthion in combination with malathion, dioxathion or coumaphos. Feeding of a diet containing "safe levels" of fenthion (2 ppm) plus coumaphos (2 ppm) caused a marked (75%) inhibition of serum ChE activity and a moderate (30%) inhibition of RBC ChE activity, indicating potentiation of fenthion by coumaphos. Potentiation also occurred when this combination was fed to dogs at one-half of the safe levels of each insecticide. Feeding of a diet containing 2 ppm fenthion and 100 ppm malathion resulted in more than additive effects on serum and RBC ChE activities. Potentiation of the ChE inhibiting effects of fenthion (2 ppm) and dioxathion (3 ppm) did not occur when these were fed in combination for 6 weeks.

9.3.3.8 Antidote studies

Francis JI & Barnes JM (1963) Studies on the mammalian toxicity of fenthion. Bull. World Health Org., 29, 205-212.

Male rats were given a single dose of fenthion (645 mg/kg bw) equivalent to 3 x LD_{50}. Pyridine-2-aldoxime methane sulphonate (P_2S) was given subcutaneously in saline (50 mg/kg bw) with or without atropine (17.4 mg/kg bw). A single dose of P_sS with or without atropine given an hour after atropine reduced the fasciculations temporarily but had no effect on mortality. When P_2S and atropine were given hourly (7 doses) on the first and second day after fenthion, 3/6 animals survived although displaying signs of toxicity for 7 days. In other experiments, P_2S was given as the fasciculations reappeared at any time during the 2 or 4 days following treatment. Two out of four animals survived when P_2S was given for two days, and 4/6 survived when P_2S was given for four days. It is suggested that a single dose of fenthion is metabolised slowly enough to require the antidote being administered regularly until clinical signs have abated completely.

Dubois KP (1960) The absence of antidotal activity by pyridine-2-aldoxime methiodide (2-PAM) and TMB-4 against acute poisoning by Bayer 29493. Unpublished report from Department of Pharmacology, University of Chicago, Illinois, USA. [BA; sub:734, A3162, Box 104, Vol 1, Attachment 2-19]

The antidote effects of 2-PAM methiodide and TMB-4 were tested in female Sprague-Dawley rats (5 per group) given either 300 or 400 mg/kg bw fenthion (LD_{50} is 325 mg/kg bw) as an intraperitoneal injection. A single intraperitoneal injection of 2-PAM (100 mg/kg bw) or TMB-4 (75 mg/kg bw) was given immediately before fenthion. Mortality of rats given 300 or 400 mg/kg bw fenthion was 40% and 80% respectively for each antidote. Single injections of 2-PAM or TMB-4 did not have any antidote effect on the acute toxicity of fenthion.

Kimmerle G (1963) Product BH 6 and S 1752 poisoning. Unpublished letter from Bayer AG, Institut für Toxikologie, Wuppertal, Germany. [BA; sub: 734, A3162, Box 104, Vol 1, attachment 2.20]

The antidote effects of BH 6 (obidoxime chloride, toxogonin) in the presence and absence of atropine sulphate on the acute toxicity of fenthion were tested in male rats (10 per group). The rats were dosed with fenthion orally as an aqueous emulsion in Emulsifier W and BH 6 (20 mg/kg bw) in the presence and absence of atropine sulphate (50 mg/kg bw) was given intraperitoneally at intervals after fenthion. The rats were observed for 7 days after fenthion administration.

BH 6 had an antidote effect when given at either 30 minutes, 6 hours or 24 hours after fenthion, an effect which was improved by simultaneous administration of atropine sulphate. The antidote effect of BH 6 was greater if more than one dose of it was given after fenthion. The LD_{50} for fenthion was increased almost two-fold (from 250 to 440 mg/kg bw) when BH 6 and atropine sulphate were given 30 minutes, 17 hours and 24 hours after fenthion administration.

Hahn HL & Henschler (1968) Reactivation of phosphorylated ChEs by obidoxime (toxogonin) in vivo. Arch Toxikol 24: 147-163 [BA; sub: 734, A3162, Box 104, Vol 1, Attachment 2.21]

Non-anaesthetised, slightly atropinised mongrel dogs of both sexes weighing between 7.5 and 24 kg were given sublethal or lethal oral doses (stomach tube) of commercial preparations of 7 insecticides: parathion, malathion, dimethoate, fenthion (Lebaycid, 50% a.i.), demeton-O-methyl sulphoxide, mevinphos and triamphos. The experimenters monitored inhibition of the blood ChEs (manometric method), which in the dog mimic closely the esterase spectrum of humans. Obidoxime chloride (5 mg/kg, iv) was used because it is a superior reactivating agent to pralidoxime and is able to penetrate the CNS to some extent. Mild atropinisation (0.2 mg/kg bw) of the animals prior to treatment with the test substances prevented vomiting in most cases.

The data from the *in vivo* experiments is summarised in the table below. The authors note that with the exception of parathion, the reactivation of RBC ChE by obidoxime was transient and varied considerable between the test chemicals. Fenthion was the only tested substance which recorded significant reactivation of plasma as well as RBC ChE.

Table 27: % reactivation of blood esterases by obidoxime injection at 3 hours post oral dose of test substance

Substance	Dose (mg/kg bw)	% RBC AChE reactivation	% Plasma BuChE reactivation
Parathion	10	83	5
Malathion	2000-7000	36	-18
Dimethoate	80-200	45	-33
Fenthion	300-500	30	35
Demeton-O-methylsulphoxide	15-25	13	0
Mevinphos	1-3	47	-5
Triamphos	8-15	1	4

In a series of *in vitro* experiments, obidoxime was added (immediately and at 24 h) to blood samples from the treated dogs and the percentage reactivation of plasma and RBC esterases was recorded. By contrast to the *in vivo* results, there was a marked reactivation of the RBC esterase for most test substances (not triamphos). The plasma esterase exhibited a variable response to in vitro reactivation, with slight reactivation seen after malathion treatment, but additional inhibition seen with the other test substances after obidoxime addition. The authors conclude that *in vitro* experiments with reactivating agents do not accurately predict the outcome of *in vivo* treatments. They further conclude that the lack of *in vivo* reactivation of RBC ChE by obidoxime after treatment with most of the test substances indicates the presence and ongoing formation of metabolites refractory to reactivation or possibly the presence of impurities of a similar nature.

9.3.2 Metabolites/degradation products

Table 28: Metabolites/degradation products

Acute oral toxicity				
Metabolite	**Descriptor**	**Number of rats tested**	**Approx LD_{50} (mg/kg bw)**	**Reference**
S-methyl isomer		35	55	DuBois & Kinoshita (1964)
Sulphoxide	PSSO	36	250	
Suphone	$PSSO_2$	34	250	
Oxygen analog	POS	36	26	
Oxygen analog sulphoxide	POSO	36	22	
Oxygen analog sulphone	$POSO_2$	36	9	
Oxygen analog	POS	NS	125 (male) 110 (female)	DuBois & Perry (1959)
Acute intraperitoneal toxicity				
Metabolite	**Descriptor**	**Number of rats tested**	**Approx LD_{50} (mg/kg bw)**	**Reference**
S-methyl isomer		20	175	DuBois & Raymund (1962)
Sulphoxide	PSSO	20	140	
Suphone	$PSSO_2$	20	150	
Oxygen analog	POS	20	15	
Oxygen analog sulphone	$POSO_2$	20	15	
Oxygen analog	POS	NS	20 (male) 21 (female)	DuBois & Perry (1959)

9.3.3 Products/Formulations

9.3.3.1 Eye irritation

There were no eye irritation studies performed on any of the currently registered Australian fenthion products.

9.3.3.2 Skin irritation

There were no skin irritation studies performed on any of the currently registered Australian fenthion products.

9.3.3.3 Skin sensitisation

There were no skin sensitisation studies performed on any of the currently registered Australian fenthion products.

9.3.4 Short-Term Repeat-Dose Studies

9.3.4.1 Oral dosing

Mice

Suberg H (1988) E 1752: Orientative subacute toxicity studies in mice (up to three-week dietary administration), Bayer Report 16809, Study Nos. T5019979, T 3020344, T 5020887, not GLP. [BA; sub 11009, Vol 2]

Fenthion (98.5%, batch EG 191284) was administered via the diet to 4-6 week mice (5/sex/group) in three pilot studies. NRMI mice (Bor:NMRI (SPF-Cpb) received 0, 0.2, 1 or 5 ppm (male 0, 0.080, 0.481, 1.955; female 0, 0.107, 0.502, 2.740 mg/kg bw, measured) for 21 days (T 5019979); NRMI (Bor:NMRI (SPF-Cpb) mice received 0 or 25 ppm (male 0, 9.9; F 0, 12.1 mg/kg bw, measured) for 17 days (T 3020344); and B6C3F1 mice received 0, 0.1, 1.5 or 25 ppm (male 0, 0.094, 0.662, 10.775; female 0, 0.117, 0.773, 12.95 mg/kg bw, measured) (T 5020887) for 21 days. Clinical signs were noted daily, bodyweights and food consumption weekly. Plasma and RBC ChE activities were generally determined weekly in all mice, and brain ChE was determined at study determination after sacrifice and necropsy. The Ellmann et al (1961) assay was used for ChE determinations.

There were no clinical signs in any dose group. Food and water consumption and bodyweights were unaffected by treatment. There were no treatment-related mortalities or necropsy findings. Relative and absolute brainweights were comparable to controls in all groups. Brain ChE activity in both sexes were significantly reduced at the 25 ppm dose level (range 24%-47% inhibition), but not at the 5 ppm level (males 12% and females 3% inhibition). Non-significant dose responses were seen for brain ChE inhibition in male NMRI mice (5%, 7% and 12% inhibition at 0.2, 1 and 5 ppm respectively) and in male B6C3F1 mice (5%, 10% and 36% inhibition at 0.1, 1.5 and 25 ppm respectively). RBC ChE activity in males was generally insensitive to treatment with mostly statistically non-significant reductions of up to 25% seen at 5 and 25 ppm only. Females were more sensitive and 10% RBC ChE inhibition was recorded at 0.1 ppm (week 2, B6C2F1) rising to 31% inhibition at 25 ppm (NRMI, week2), although these reductions were mostly not statistically significant. Plasma ChE activity was inhibited in a dose-related and generally statistically significant manner in both sexes at all assay times, the maximum inhibition being 96% (NRMI females, week 1, 25 ppm).

Leser KH (1989) E 1752 (cn fenthion): Range finding study to determine the maximum tolerated dose (MTD) of B6C3F1 mice (administration in the feed for up to 5 weeks) Bayer Report 17950, Study No. T 8029430, not GLP. [BA; sub 11009, Vol 2]

Fenthion (98.5%) was administered via the diet to mice (10/sex/group) in a pilot study. B6C3F1 mice received 0, 50, 75 or 100 ppm (0, 25, 40, 55 mg/kg bw/d, measured food intake) for 5 weeks. Clinical signs were noted daily, bodyweights and food consumption weekly. Plasma, RBC and brain ChE activities were determined in all mice at study termination when mice were sacrificed and necropsied for examination of gross pathology.

There were no clinical signs and no mortalities during the study. While water consumption, food consumption and hence fenthion intake was unaffected by treatment, bodyweight gain was lower in males of the 50 and 100 ppm groups in weeks two and three, but bodyweights in all treatment groups were comparable to controls by study end. ChE activities were inhibited in all compartments in a dose-related manner. Plasma, RBC and brain ChE was almost completely inhibited in all dose groups (96-98%, 88-100% and 57-69% inhibition for plasma, RBC and brain respectively). Gross pathology examination and organ weight measurements revealed no treatment-related differences.

Leser KH (1990) E 1752 (cn fenthion): Study for ChE inhibition following high doses of E1752. (Administration to B6C3F1 mice in the diet over a period of about four weeks) Bayer Report 19088, Study No. T 9030349, not GLP. [BA; sub 11009, Vol 2]

Fenthion (98.5%) was administered via the diet to mice (10/sex/group) in a pilot study. B6C3F1 mice received 0, 150, 200 or 250 ppm (0, 85, 115, 145 mg/kg bw/d, measured food intake) for 4 weeks. Clinical signs were noted daily, bodyweights and food consumption weekly. Plasma, RBC and brain ChE activities were determined in all mice at study termination when mice were sacrificed and necropsied for examination of gross pathology.

There were clinical signs of ChE inhibition (tremor) in all treated males during weeks one and two, but these were absent by week three. Transient (first week only) and marked apathy was seen in 2 of the 200ppm and 3 of the 250 ppm males. Two males in each of the 200 and 250 ppm groups were sacrificed in a moribund condition, while one 250 ppm male died after one week. At study termination, the stress of blood withdrawal lead to the deaths of 75% of all treated males and 14% of treated females. While water consumption was lower than controls in all treated groups, food consumption and hence fenthion intake was unaffected by treatment. Bodyweights were lower than commencement weight in all treated groups after one week, but bodyweight gains were recorded after weeks two and three although all treatment groups had lower bodyweights than controls at study end.

ChE activities were inhibited in all compartments at all doses. Plasma, RBC and brain ChE was almost completely inhibited in all dose groups (>98%, 80-98% and 68-80% inhibition for plasma, RBC and brain respectively). Gross pathology examination and organ weight measurements revealed few treatment-related differences other than lower spleen weights in all males and 250 ppm females; these findings may be to due to the rapid death of the mice after bleeding was performed. Liver weights in 250 ppm females were also reduced, both absolute (25%) and relative (15%), and this may reflect some liver toxicity. Serum insulin levels were markedly higher in all treated females and the 150 ppm and 200 ppm males, but not the 250 ppm males; this finding probably reflects a disturbance of carbohydrate metabolism.

9.3.4.2 Dermal administration

Rabbits

Mihail F & Schilde B (1979) E 1752 (fenthion, the active ingredient of Lebaycid and Baytex): Subacute dermal cumulative toxicity study on rabbits. Bayer Report 8624, Study # S 1752/004, not GLP. [BA; sub 11009, Vol 1]

Fenthion (98.2% pure, aqueous suspension with 1.5% Cremophor EL) was applied and left uncovered to either the clipped (weekly) intact or abraded dorsal skin of NZW rabbits (3/sex/group) for 7 hours on 5 days/week for three weeks at 0, 5 and 25 mg/kg bw. The treated areas were washed with soap and water at the end of each exposure period when skin reactions were scored based on the Draize guidelines. Clinical signs were noted daily, bodyweights and food consumption weekly. Blood (ear vein) and urine samples were taken for simple clinical chemistry and haematology analysis at the start and finish of the treatment period. At study termination all rabbits were sacrificed and necropsied for examination of gross pathology, organ weights and histopathology.

There were no clinical signs and no mortalities during the study. Bodyweights, skinfold thickness, haematological parameters and urinalysis were unaffected by treatment. Plasma and RBC ChE activity, measured at treatment days 0, 10 and 15, was reduced (max. 50%

inhibition) at 25, but not at 5 mg/kg bw, with abraded skin generally recording the most rapid onset of inhibition. Brain ChE activity was unaffected by treatment in males, but trended downwards with dose in females. Gross pathology was similar in all groups as were organ weights, histopathology findings and skin thickness measurements.

Table 29: Intact skin: percentage ChE inhibition at day-15 (M, F)

Dose (mg/kg bw/d)	Plasma	RBC	Brain
0	0, 0	0, 0	0, 0
5	6, 22	11, 19	+1, 10
25	19, 45	25, 50	+11, 31

Bailey DE (1987) 21-day dermal toxicity study in rabbits with Baytex technical Hazelton Laboratories Report 938, HLA study No. 339-118, GLP, EPA 82-2. [BA; sub 11009, Vol 1]

Rabbits (NZW) in groups of 5/sex/dose were dermally exposed to fenthion (96.9% pure) by occlusive dressing on intact shaved back-skin for 6 hours/day, 5days/week for 3 weeks. The nominal doses were 0, 5, 50 or 100 mg/kg bw. Animals were observed for clinical signs each day. Signs of local skin irritation were investigated daily. Body weights and food consumption were determined weekly. Laboratory investigations which included blood ChE, haematology and blood chemistry were determined at the beginning and end of treatment. All animals were necropsied at the end of the treatment period, selected organs weighed, brain ChE activity were assayed and a number of organs and tissues including skin examined histopathologically.

There were no compound-related clinical signs, one treatment unrelated mortality and no body weight changes. In all groups, the treatment had no effect on the haematological and blood chemistry parameters, on organ weights, and on macro or microscopic pathology. There was some scattered dermal irritation, scaling and skin thickening but no other significant histopathological changes of the skin.

Table 30: Percentage ChE inhibition at week-3 (M, F)

Dose (mg/kg bw/d)	Plasma	RBC	Brain
0	0, 0	0, 0	0, 0
5	8, 0	+3, 13	2, 12
50	19*, 3	+13, 9	15, 13
100	19*, 14	11, 3	13, 14*

***** significantly different from control $p<0.05$

The plasma ChE values were depressed (max 19%) in both sexes at the high dose for weeks 1-3. RBC ChE values were slightly depressed (11-13%) in high dose males only. Brain ChE values were depressed (24%) in high dose females only.

Bailey DE (1988) 21-day dermal toxicity study in rabbits with Baytex technical (Addendum to 938) Hazelton Laboratories Report 1031, HLA study No. 339-118, GLP, EPA 82-2 [BA; sub 11009, Vol 1]

Rabbits (NZW) in groups of 5/sex/dose were dermally exposed to fenthion (96.9% pure) by occlusive dressing on intact shaved back-skin for 6 hours/day, 5days/week for 3-weeks. The nominal doses were 0, 200 and 400 mg/kg bw. The animals in both dose levels commenced dying after one and two weeks and the study was terminated. New animals were initiated into the study at 0 and 150 mg/kg bw/d and the study continued for three weeks of exposure. Animals were observed for clinical signs each day. Signs of local skin irritation were recorded daily. Body weights and food consumption were determined weekly. Laboratory investigations which included blood ChE, haematology and blood chemistry were determined at the beginning and end of treatment. All animals were necropsied at the end of the treatment period, selected organs weighed, brain ChE activity were assayed and a number of organs and tissues including skin examined histopathologically.

There were definite compound-related clinical signs in 1-2 males including soft faeces, emaciation, listlessness, polyuria and a hunched appearance. There were no treatment-related mortalities and at study termination no body weight differences between treatment groups. In all groups, the treatment had no effect on the haematological and blood chemistry parameters, on organ weights apart from an increase in relative liver weights, nor on macro or microscopic pathology. There was some scattered dermal irritation and skin thickening as well as scaling in all treated animals, which histopathology described as inflammation, hyperkeratosis and acanthosis.

Table 31: Percentage ChE inhibition at week-3 (male, female)

Dose (mg/kg bw/d)	Plasma	RBC	Brain
0	0, 0	0, 0	0, 0
150	53*, 32*	57*, 24*	65*, 33*

- significantly different from control $p<0.05$

The plasma ChE values were depressed in both sexes from weeks 1-3 (max 53% males, max. 32% females). RBC ChE values were slower to respond and were depressed in males from weeks 2-3 (max. 57%) and from week 3 in females (24%). Brain ChE values were depressed 65% in males and 33% in females.

9.3.4.3 Inhalational administration

Thyssen, J. (1979) Fenthion (S 1752, the active ingredient of Lebaycid and Baytex): Subacute inhalation toxicity study on rats. Unpublished report No. 8383 from Bayer AG Institut für Toxikologie, Wuppertal, Germany not GLP. [BA; sub 11009, Vol 1]

Rats (Wistar TNO/W 74, 10/sex/group) were exposed nose/head only in exposure tubes to fenthion (98.2%) aerosol at 0, 1, 3 or 16 mg/m^3 air (nominally 0, 3, 15, 75 mg/m^3) for 6 hours/day, 5 days/week for 3 weeks. Clinical signs were noted daily and bodyweights weekly. At the end of the exposure period 5 animals of each sex from each group were subjected to clinical examination of haematological, urine and clinical chemistry parameters. At study termination 5 animals of each sex from each group were sacrificed and necropsied for examination of gross pathology and tissues prepared for histopathology. Plasma, RBC and brain ChE activities were determined in all rats at the beginning and end of the exposure period.

There were no clinical signs in the male rats, but the females exhibited apathy and lack of preening during weeks 2 and 3 (16 mg/m^3) and week 3 at 3 mg/m^3. There were no mortalities. Bodyweights were not statistically different from controls by study end, however in females at 16 mg/m^3 bodyweights were decreased by treatment in week 2 and had not returned to control values by study end. Thrombocyte and neutrophil counts were slightly increased in females at the two highest doses, although not in a statistically significant manner. Clinical chemistry determinations showed no significant treatment-related effects although urea levels were slightly increased in both sexes at 16 mg/m^3. There were no treatment-related effects detected by gross pathology examination, and both absolute and relative organ weights were comparable to controls in all groups, however no values were reported for brain weights. Histopathology findings were unremarkable except for severe inflammatory changes to the respiratory tract in high dose females.

Table 32: Percentage ChE inhibition at day-15 (M, F)

Dose (mg/m^3)	Plasma	RBC	Brain
0	0, 0	0, 0	0, 0
1	13, 8	5, 4	3, 22
3	27, 53	13, +1	12, 16
16	62, 89	31, 31	49, 53

Plasma ChE activity in control males was ca. one third of that in females, whereas absolute activity of RBC and brain ChE was comparable between the sexes. Plasma ChE was inhibited from day 5 in a dose dependent manner in both sexes at all doses, with the females being more sensitive. Similarly, RBC ChE activity showed less dose-dependence but inhibition was evident from day 5 onwards in males at 3 mg/m^3 and in both sexes at 16 mg/m^3. Brain ChE activity showed dose dependent inhibition at all doses in both sexes.

9.3.5 Subchronic Studies

Rats

Dubois KP & Puchala E (1960) Influence of Bayer 29493 applied dermally on the ChE activity of the blood of rats. Unpublished report from Department of Pharmacology, University of Chicago, Illinois, USA. . [BA; sub:734, A3162, Box 104, Vol 1, Attachment 2-28]

Dubois KP (1961) Effects of repeated dermal application of Bayer 29493 on rats. Unpublished report from Department of Pharmacology, University of Chicago, Illinois, USA. . [BA; sub:734, A3162, Box 104, Vol 1, Attachment 2-27]

An oil-based spray containing 2.9% fenthion was applied daily for 12 successive days to the shaven backs of female rats (5 rats per dose). The three doses applied were equivalent to 2.9, 7.25 and 14.5 mg/kg bw fenthion. Blood ChE activity was markedly reduced by 3 days at all doses (43, 60 and 78% reductions at 2.9, 7.25 and 14.5 mg/kg bw, respectively).

The same oil-based spray containing 2.9% fenthion as used in the 12 day study, was applied daily for 60 days to the shaven backs of female rats (5 rats per dose). The two dose levels were equivalent to 14.5 and 25 mg/kg bw fenthion. No deaths were seen in the 14.5 mg/kg bw group, whilst 2 out of 5 rats in the 25 mg/kg bw group died during the test. There were marked tremors during the first 30 days of treatment in the 25 mg/kg bw group, an effect which decreased during the second 30 days.

DuBois KP & Raymund AB (1960) The subacute toxicity of Bayer 29493 to rats. Department of Pharmacology, University of Chicago, Chicago, Illinois, USA. Report No. 5242, 5 May 1960. Unpublished. [BA; sub: 11793, Vol 7]

Fenthion dissolved in carrier (20% ethanol:80% ethylene glycol) was administered intraperitoneally once per day for 60 days to young adult female SD rats (5/group) at 0, 10, 20, 40 ,50 and 100 mg/kg bw/d. Only the control and 10 mg/kg bw/d groups survived to day 60 without mortality; the results are tabulated below.

Table 33: Cumulative mortality in rats given fenthion intraperitoneally

Dose (mg/kg bw/d)	Days after 1st injection				Mortality in 60 d (%)
	0-5	5-10	10-30	30-60	
	Mortality				
0	0	0	0	0	0/5 (0)
10	0	0	0	0	0/5 (0)
20	0	0	4	0	4/5 (80)
40	0	5			5/5 (100)
50	0	5			5/5 (100)
100	5				5/5 (100)

Fenthion has a marked tendency to cause a cumulative toxic action.

Dubois KP & Kinoshita F (1964) Acute toxicity and anti-ChE action of O,O-dimethyl-O-4-(methylthio)-m-tolyl) phosphorothioate (DMTP; Baytex) and related compounds. Toxicol Appl Pharmacol 6: 86-95 [BA; sub:734, A3162, Box 104, Vol 1, Attach 2-5]

This study reports measurements of subacute toxicity of fenthion (purity unknown) administered intraperitoneally to 5 female SD rats/group as a solution in 20% ethanol and 80% propylene glycol for 60 days.

Table 34: Subacute parenteral toxicity of fenthion in female rats

Dose (mg/kg bw/d)	Mortality at various days after commencement				Mortality in 60 days	% Mortality in 60 days
	0-5 d	5-10 d	10-30 d	30-60 d		
0	0	0	0	0	0/5	0
10	0	0	0	0	0/5	0
20	0	0	4	0	4/5	80
40	0	5	-	-	5/5	100
50	0	5	-	-	5/5	100
100	5	-	-	-	5/5	100

The authors concluded that rats are unable to tolerate daily doses of fenthion in excess of 1/30th of the acute LD_{50}.

Another series of female rats were dosed intraperitoneally with fenthion at 200 mg/kg bw and sacrificed at intervals, in groups of three, during the next 28 days for assay of ChE activity in brain, serum and submaxillary gland. ChE was markedly inhibited (>85% inhibition) in all three tissues, with onset of effect at one day for serum and two days for brain and submaxillary gland. ChE activities were slow to recover and had still not reached control values 4-weeks after injection. Similar experiments with the sulphone and sulphoxide derivatives of fenthion at doses around 5/8 of the LD_{50} produced similar results in terms of severe inhibition of ChE in all three tissues and slow recovery of activity. By contrast, the S-methyl fenthion derivative produced differential inhibition in the samples, with inhibition of ChE activity in the order serum>submaxilliary gland>brain; recovery in these samples was relatively slow. Experiments (in female rats) with the oxygen analog of fenthion (16 mg/kg bw), and its sulphoxide (14 mg/kg bw) and sulphone (5.5 mg/kg bw) demonstrated significant inhibition (>60% for the analog) of ChE activity in brain, serum and submaxillary gland; recovery was rapid in two tissues and achieved 70-80% of control values in brain and submaxillary gland within 12 hours of dosing.

Possibly the first set of results tabled above is from DuBois & Raymund (1960)

Doull J, Vesselinovitch D, Fitch F, Cowan J, Root M & Meskauskas J (1961a) The effects of feeding diets containing Bayer 29493 to rats for a period of 16 weeks. Bayer, Department of Pharmacology, University of Chicago, Illinois, USA. Unpublished. [BA; sub:734, A3162, Box 104, Vol 1, Attachment 2-22]

Groups of 12 male and female Sprague-Dawley rats were fed for 16 weeks with diets containing 0, 2, 3, 5, 25 or 100 ppm fenthion (technical grade, 92.1% active ingredient) (ca. male 0, 0.13, 0.20, 0.33, 1.65 and 6.6 mg/kg bw/d; female 0, 0.16, 0.25, 0.41, 2.0 and 8.2 mg/kg bw/d). Food consumption was measured twice weekly, and clinical signs and body weights recorded weekly. At 16 weeks the animals were sacrificed and the tissues from 5 animals /sex/group were weighed and prepared for histology. ChE measurements were made on blood and tissues from 5 animals/sex/group.

Food intake was not altered in rats receiving fenthion. There was no change in growth rate in female rats and a slight reduction in males during the first few weeks of fenthion administration. During the first 2 weeks of the study, rats receiving 100 ppm showed diarrhoea, salivation and lacrimation. There were clear dose-dependent reductions in ChE activities in serum, RBC, submaxillary gland and brain of rats receiving doses of 5 ppm fenthion and higher.

Table 35: ChE inhibition in rats dosed with fenthion in the diet

Dietary fenthion (ppm)	Sex	ChE activity (% of control)			
		Serum	RBC	Submaxillary Glands	Brain
2	M	95	100	96	99
	F	91	103	88	103
3	M	112	96	92	95
	F	88	85	69	100
5	M	100	96	93	94
	F	85	95	94	94
25	M	55	58	72	69
	F	38	56	79	74
100	M	38	39	54	49
	F	19	19	50	45

The percentage reductions in serum and RBC ChE were greater in females than in males. There were no significant histopathological findings in fenthion-treated rats compared with controls. The NOELs for serum, RBC and brain ChE activities were 0.33 and 0.41 mg/kg bw/d for males and females respectively.

Dogs

Doull J, Root M & Cowan J (1961b) Determination of the safe dietary level for Bayer 29493 for dogs. Unpublished Bayer report No. 8342 from Department of Pharmacology, University of Chicago, Illinois, USA. BA; sub:734, A3162, Box 104, Vol 1, Attachment 2-24]

Groups of 2 male and 2 female beagle dogs were fed for 12 weeks with diets containing 0, 2, 5 or 50 ppm fenthion (ca. 0, 0.04, 0.09 & 0.9 mg/kg bw/d)(technical grade, 92.1%). Blood was sampled weekly for ChE measurements, body weights were recorded weekly, and clinical signs were recorded daily.

Growth rate was unaffected by fenthion administration and there were no significant clinical signs. There was significant inhibition of serum ChE activity in dogs fed either 5 or 50 ppm fenthion (approximately 40 and 50% reductions at 5 and 50 ppm, respectively, 12 week level) when feeding continued for more than 6 weeks. Dietary levels of greater than 5 ppm fenthion were required to significantly reduce RBC ChE activity within the 12 week period of the test (approximately 30% reduction at 50 ppm, 12 weeks).

The NOELs for inhibition of serum and RBC ChE activities were 2 and 5 ppm fenthion, respectively, in the diet for 12 weeks, equivalent to daily intakes of 0.04 and 0.09 mg/kg bw.

Hens

Hayes RH (1989) Subchronic feeding study with technical grade fenthion (Baytex) in hens with specific emphasis on gastrointestinal tract effects, Mobay Report 1132, Study No. 87-978-01, mainly GLP. [BA; sub 11009, Vol 1]

Two groups of 10 adult white Leghorn hens (Gallus gallus domesticus) were given technical-grade fenthion (purity, 96.9%) at dietary concentrations of 0 or 52 ppm (equivalent to 4 mg/kg bw/d) for 90 days. Clinical signs were recorded daily, bodyweight and feed consumption weekly. Blood ChE was measured at study initiation, weeks 5 and 9, and study end. Tissue samples were taken from 2 control and 4 fenthion hens for ChE determination. At necropsy, general pathology was recorded and the distal oesophagus was processed for histopathology.

There were no deaths and no significant clinical signs during the study. Treated hens ate 18% less than controls and lost 9% of their bodyweight compared to nil loss in the controls. Minimal to moderate muscular hypertrophy or hyperplasia was seen in the distal oesophagus (between the crop and the proventriculus) of all treated hens, which accounted for 98-99% of the increased thickness (+ 55%, in comparison with controls) in the oesophageal wall. Hypertrophy or hyperplasia of the oesophageal glandular components was also seen in four birds. In addition, treated hens had a statistically significant ($p<0.05$) depression of ChE activity in whole blood (>50% in comparison with controls) and tissue from all three regions of the upper GIT (oesophagus, crop, and proventriculus: approximately 70% in comparison with controls). It was concluded that the muscular hypertrophy and hyperplasia observed in the fenthion-treated hens was probably due to localised acetylChE inhibition with subsequent overstimulation of the oesophageal smooth muscle layers.

9.3.6. Chronic Studies

Mice

Leser KG & Suberg H (1990) E 1752: Oncogenicity study on B6C3F1 mice (feeding study for periods up to 24 months), Bayer Report 19624, Study # T 0020495 [BA; sub: 11009 Vol 10-12] OECD 451, GLP

Leser KG & Suberg H (1992) E 1752: Study for oncogenicity in B6C3F1 mice (administration in diet for over 24 months). Addendum to Bayer Report 19624 of 25.10.90, Bayer Report 21807. [BA; sub: 11009 Vol 13]

Van Goethem DL & Leser KH (1993) E 1752 (fenthion): Study for oncogenicity in B6C3FI mice (administration in diet for over 24 months) Addendum to Bayer Report 19624 of 25.10.90 Bayer Report 5406. [BA; sub: 11009 Vol 13]

Groups of SPF-bred B6C3F1 mice (CRL) (60/sex/dose) were dosed with fenthion (94.8%) in the diet at nominal levels of 0, 0.1, 1, 5 and 25 ppm (measured as 0, 0.09, 0.9, 4.6 and 23 ppm) for two years. Additional satellite groups of 20/sex/dose received the same doses in the diet and were sacrificed at one year. These doses equated to a daily dietary intake of 0, 0.03, 0.4, 1.95 and 9.42 mg/kg bw for males, and 0, 0.03, 0.47, 2.25 and 10.63 mg/kg bw for females.

The mice were observed daily and examined in detail weekly for clinical signs; body weights and food and test-substance consumption were recorded weekly. Some observations not required by this OECD guideline were performed; these included supplemental clinical laboratory tests (ChE activity measurements) and expanded histological examinations. Clinical pathology assessment was performed on blood samples from 10 mice/sex/dose at 6, 12, and 24 months as detailed below.

> Haematology parameters: RBC count, Hct, blood Hb, leucocyte differential count, leucocyte total count, platelet count, reticulocyte count, MCH, MCHC, MCV.
> Clinical chemistry parameters: AP, SGPT, SGOT, bilirubin, cholesterol, total protein, urea, creatinine, glucose. Plasma, RBC and brain ChE activities were determined by the modified Ellmann (1961) technique.

At 12 months, the satellite group of 20 animals/dose/sex were sacrificed and necropsied, and at 24 months all surviving mice were necropsied. Macroscopic and microscopic examination was conducted on all the protocol-specified organs and tissues (see below) from these groups. Mice found dead or removed from the study prior to scheduled necropsy were subjected to full necropsy. Appropriate statistical methods were applied to all data collected.

> Organs weighed: brain, testes, kidneys, liver, lung, heart, spleen and kidneys.
> Histopathological examinations: adrenals, aorta, bone marrow, brain, caecum, colon, duodenum, epididymis, eyes, eyes (optic nerve), femur, gall bladder, Harderian glands, head, heart, ileum, jejunum, kidneys, lacrimal gland, larynx, liver, lungs, lymph nodes, mammary gland, muscle (skeletal), nerve (sciatic), oesophagus, ovaries, pancreas, pituitary, prostate, rectum, salivary gland, seminal vesicle, skin, spinal cord (cervical, thoracic, lumbar), spleen, sternum, stomach, testes, thymus, thyroid, tongue, trachea, ureter, urethra, urinary bladder, uterus, vagina, gross lesions.

Results

All data were well presented as individual and summary data tables and graphs, with appropriate statistical analysis. Mortality in both the main and satellite groups during the study was unaffected by exposure to fenthion; the table below shows that the accumulated unscheduled deaths in the main groups at intake levels of 0, 0.1, 1, 5 and 25 ppm were respectively 25.0%, 6.7%, 16.7%, 16.7%, 15.0% (males) and 20.0%, 13.3%, 18.3%, 18.3% and 25.0% (females).

Table 36: Deaths (cumulative) in main study group over 2 years

Dose (ppm):-	Male					Female				
	0	**0.1**	**1**	**5**	**25**	**0**	**0.1**	**1**	**5**	**25**
start	**60**	**60**	**60**	**60**	**60**	**60**	**60**	**60**	**60**	**60**
6-months	3	0	0	1	3	0	0	1	0	1
12-months	3	0	0	1	3	0	0	1	0	1
18-months	6	2	3	2	5	5	3	3	4	3
24-months	15	4	10	10	9	12	8	11	11	15

Food and test substance consumption were not significantly affected by treatment. The following table shows these intakes for the first 102 weeks of the study. The food rations for the 0.1 ppm animals were replaced three times weekly due to the low stability of the test substance at this concentration. Other dose groups were fed once/week. This procedure resulted in the 0.1 ppm group achieving lower than expected dietary intake. The 5 ppm and 25 ppm animals recorded higher body weights and hence lower relative food and test substance consumption than other groups.

Table 37: Food and test substance intake

	Dose (ppm)	Food intake		Test substance intake	
		g/animal/d	**g/kg bw/d**	**mg/animal/d**	**mg/kg bw/d**
Males	0	13.6	433		
	0.1	8.8	272	0.001	0.03
	1	12.9	402	0.01	0.40
	5	12.7	390	0.06	1.95
	25	13.1	377	0.33	9.42
Females	0	13.7	479		
	0.1	9.3	318	0.001	0.03
	1	13.3	467	0.01	0.47
	5	13.3	449	0.07	2.25
	25	13.3	425	0.33	10.63

Body weight development in the 0.1 and 1 ppm groups was comparable to controls in both sexes at most time points. From 12 weeks onwards there were consistent and statistically significant higher body weights in the 5 and 25 ppm dose groups in both sexes when compared to controls. At 5 ppm these increases were generally less than 5%; at 25 ppm the increases were generally more than 10% and were regarded as related to treatment.

Haematology and clinical chemistry findings at 6, 12 and 24 months were unremarkable. Occasional statistically significant deviations from control values for some parameters were either within the range of historical control values or were not dose- or time related.

ChE activity: Plasma ChE activity was unaffected at the lowest dose of 0.1 ppm, but inhibition was clearly dose-related at dietary levels of 1 ppm and above; additionally, the mice showed slow adaptation to the dose, recording inhibition of plasma ChE of >20% in both sexes at 1 ppm at 28 weeks, but <10% inhibition at the same dose level by 104 weeks. The NOEL for plasma ChE is considered to be 0.1 ppm in the diet (0.03 mg/kg bw/d) based on significant inhibition in both sexes at 1.0 ppm (0.4 mg/kg bw/d, M; 0.047 mg/kg bw/d, F).

RBC ChE activity was consistently inhibited only in the 25 ppm group. This inhibition was slow to develop, and peaked at 54 weeks. Adaptation was evident by 104 weeks, especially in females. The NOEL for inhibition of RBC ChE activity was 5 ppm in the diet (1.95 mg/kg bw/d, M; 2.25 mg/kg bw/d, F) based on significant inhibition in both sexes at 25 ppm (9.4 mg/kg bw/d, M; 10.6 mg/kg bw/d, F).

Brain ChE activity recorded significant and dose-related inhibition, especially at the interim sacrifice. However at 104 weeks, toxicologically significant inhibition was seen only in males and only at the 25 ppm dose level. The NOEL for inhibition of brain ChE activity was considered to be 0.1 ppm in the diet (0.03 mg/kg bw/d) based on the toxicologically and statistically significant inhibition seen in females at 1 ppm (0.47 mg/kg bw/d) and above at the interim sacrifice. This result is consistent with the pattern of inhibition seen in the RBC compartment, and may be explained if the mice, especially females, possess an efficient adaptive response to dietary intake of fenthion.

Table 38: ChE activity in brain, RBCs and plasma (% depression cf. Controls)

Week	Dose (ppm)	Tissue					
		plasma		RBC		brain	
		M	F	M	F	M	F
28	0.1	13*	3	-	-	nd	nd
	1	39*	28*	-	-	nd	nd
	5	78*	69*	-	-	nd	nd
	25	93*	93*	15*	3	nd	nd
54	0.1	7	-	1	1	-	1
	1	28*	11	2	2	4	13*
	5	69*	72*	6	3	10*	15*
	25	93*	92*	24*	13*	29*	26*
79	0.1	1	2	-	-	nd	nd
	1	26*	26*	-	-	nd	nd
	5	62*	65*	-	5	nd	nd
	25	92*	94*	12*	13*	nd	nd
104	0.1	-	-	-	-	17*	4
	1	6	9	-	-	14*	2
	5	37*	7	2	-	14	5
	25	59*	41*	13*	1	32*	4

*statistically significant at p<0.05 or <0.01; - not inhibited relative to control; nd = not done at this time point

Organ weights: There were frequent observations of higher absolute kidney and liver weights in males from the 5 ppm and/or 25 ppm groups when compared to controls. However, when corrected for the higher body weights in these groups the relative organ weights were generally not affected by treatment. Gross pathology recorded no significant dose related findings at interim or final sacrifice.

Histopathology - non-neoplastic findings: The pathology results were presented as individual animal results and summary tables in a separate study. There were no non-neoplastic lesions in any animals found dead/sacrificed during the study or at scheduled sacrifice which were considered treatment-related; similar degenerative and inflammatory lesions were recorded in the control and treatment groups at similar frequencies.

Histopathology - neoplastic findings: There were no gross pathological findings or histopathology findings in either sex which indicated an increase in neoplastic lesions at any treatment level. The observations in the animals from the interim kill (1 year) are consistent with the findings in the 2-year kill group. The incidence of neoplasms and the chronology of their appearance in the animals sacrificed as moribund or found dead also did not indicate a relationship to treatment. Hepatocellular tumours were common in the main study group, especially in males and lymphomas were more common in females. These incidences were within historical control range and none of the benign or malignant tumours observed in the males or females exhibited a dose relationship or an absolute incidence differing significantly (Cochrane-Armitage trend test with continuity correction) from the concurrent controls.

Table 39: Summary of neoplasms recorded at terminal sacrifice

Sex	**Male**					**Female**				
Dose (ppm)	**0**	**0.1**	**1**	**5**	**25**	**0**	**0.1**	**1**	**5**	**25**
mice examined at term	**45**	**56**	**50**	**50**	**51**	**48**	**52**	**49**	**49**	**45**
total animals with neoplasms	13	26	25	27	21	27	29	28	33	27
total animals with benign tumours only	9	19	15	15	14	11	12	9	10	6
total animals with malignant tumours only	2	4	6	8	5	11	8	12	8	12
total animals with malignant and benign tumours	2	3	4	4	2	5	9	7	15	9
total animals with metastasising tumours			1							1
total neoplasms	19	32	37	37	27	37	46	37	59	43

Table 40: Total incidence of selected neoplasms in the main study groups

Sex	**Male**					**Female**				
Dose (ppm)	**0**	**0.1**	**1**	**5**	**25**	**0**	**0.1**	**1**	**5**	**25**
mice examined	**59**	**60**	**60**	**60**	**60**	**60**	**60**	**60**	**60**	**60**
pulmonary adenoma	7	7	12	3	3	-	3	-	1	1
pituitary adenoma	-	-	-	-	-	11	13	7	11	7
hepatocellular adenoma	7	12	9	14	11	2	2	4	7	5
hepatocellular carcinoma	4	4	10	7	8	2	1	2	2	2
malignant lymphoma	3	3	6	11	3	17	17	19	24	23
histiocytic sarcoma	-	2	-	1	-	-	3	2	3	1

Rats

Christenson WR (1990a) Combined chronic toxicity/oncogenicity study of technical grade fenthion (Baytex) with rats, Mobay Study No.87-271-01 USEPA 83-5, GLP. [BA; sub: 11009 Vol 3-5]

Christenson WR (1993b) Combined chronic toxicity/oncogenicity study of fenthion technical (Baytex) with rats. Supplemental report to Study 87-271-01, Miles Study 87-271-01 (Addendum), GLP. [BA; sub: 11009 Vol 6-8]

This was a combined chronic toxicity and oncogenicity study, which included ophthalmological observations designed to assess the potential of fenthion to induce ocular toxicity, and detailed brain histopathology to investigate the potential for CNS histopathology (gliosis, swollen and necrotic neurons in the hippocampus) which was reported after dermal exposure to fenthion in Long-Evans rats at 25 mg/kg bw (Veronesi et al 1990).

Fischer 344 rats (CRL/Br, 50/sex/group) were exposed to fenthion (94.8% purity) in the diet at nominal doses of 0, 5, 20, 100 ppm (measured as 0, 4.8, 17.9 and 92.5 ppm) for two years. A satellite group of rats (20/sex/group) were exposed daily to 0 and 100 ppm in the diet prior to sacrifice at one year. All animals were observed twice daily for morbidity and mortality and examined in detail weekly for clinical signs and palpable masses; body weights and food consumption were recorded weekly.

Prior to study commencement and at study end, all rats were subjected to ophthalmoscopic examination. The pupil reflex, conjunctiva, cornea and iris were initially examined prior to dilation with a mydriatic, after which the lens, vitreous humor and retina were examined. Additionally, electroretinograms were performed on 10 rats/sex/dose during week 75 and prior to study termination. Clinical pathology consisting of a complete biochemical, haematological and urinalysis assessment was performed on 20 rats/sex/dose at 3, 6, 12, 18 and 24 months; where possible the same rats were used at each sampling time. At 24 months, all surviving rats were necropsied with macroscopic and microscopic examination of organs and tissues. Rats found dead or removed from the study prior to scheduled necropsy were subjected to full necropsy. Results were presented as summary tables and as individual animal data; appropriate statistical methods were applied to all data collected.

<u>Haematology parameters</u>: RBC count, Hct (packed cell volume), Hb, leucocyte differential count, leucocyte total count, platelet count, reticulocyte count, MCH, MCHC, MCV.
<u>Clinical chemistry parameters</u>: albumin, AP, SGPT, SGOT, bilirubin, cholesterol, total protein, BUN, calcium, chloride, creatinine, creatine phosphokinase, GGT, globulin, glucose, LDH, phosphorus, potassium, sodium, triglycerides, uric acid. Plasma, RBC and brain ChE activities were determined using a modified Ellmann technique as described by Hackathorn et al (1983).
<u>Urinalysis parameters</u>: appearance, specific gravity, glucose, ketones, sediment (microscopic), occult blood, pH, protein, volume, bilirubin, urobilinogen.
Organs weighed: brain, testes, kidneys, liver, lung, heart, spleen, ovaries, adrenals
<u>Histopathological examinations</u>: adrenals, aorta, bone marrow, brain (three sections), cecum, cervix, colon, duodenum, epididymes, eyes, femur, gall bladder, Harderian glands, heart, ileum, jejunum, joint (fem/tib), kidneys, larynx, liver, lungs, lymph nodes (cervical, mesenteric), mammary gland, muscle (skeletal), nerve (optic, sciatic), oesophagus,

ovaries, pancreas, parathyroids, pituitary, prostate, rectum, rib, salivary gland, seminal vesicle, skin, skull, spinal cord (cervical, thoracic, lumbar), spleen, sternum, stomach, testes, thymus, thyroid, trachea, urinary bladder, uterus, gross lesions.

Results

The diets, prepared weekly, gave satisfactory results for analysis of homogeneity and storage stability. Calculated over the entire study period, the male rats consumed on average approx 130 g/week of diet and females 100 g/week, with average final body weights of 300-400 g for the males and 200-250 g for the females. This equates to a daily dietary exposure of 0, 0.2, 0.8, and 5.2 mg/kg bw for males, and 0, 0.3, 1.3 and 7.3 mg/kg bw for females. Mortality during the study was not significantly affected by exposure to fenthion, as shown in the table below.

Table 41: Summary of mortality data for rats fed fenthion for two years

		Males		
Dose (ppm)	**0**	**5**	**20**	**100**
No. of rats/group	**50**	**50**	**50**	**50**
Total found dead	4	2	4	4
Total unscheduled sacrificed	17	19	21	15
Total scheduled sacrificed	29	29	25	31
Mean time of death (days)	689	696	677	706
		Females		
Dose (ppm)	**0**	**5**	**20**	**100**
No. of rats	**50**	**50**	**50**	**50**
Total found dead	6	5	1	8
Total unscheduled sacrificed	9	9	16	13
Total scheduled sacrificed	35	36	33	29
Mean time of death (days)	697	704	701	644

Food consumption was unaffected by treatment. Body weight gains were lower in both sexes at the high dose, especially after weeks 30 and 50 in males and females respectively. This ensured that bodyweights throughout the study and at terminal sacrifice were significantly lower in the 100 ppm animals of both sexes, but the effect was slightly more marked in females, such that at terminal sacrifice bodyweights in the 100 ppm group were 7.8% lower in males and 9.5% lower in females when compared to controls.

Table 42: Mean bodyweights (g) of the main study group at six monthly intervals

	Week 26	**Week 52**	**Week 78**	**Week 104**
		Males		
Controls	350	401	409	368
5 ppm	352	402	403	366
20 ppm	353	395	413	366
100 ppm	341*	380*	376*	339*
		Females		
	Week 26	Week 52	Week 78	Week 104
Controls	193	223	257	275
5 ppm	195	229	269*	281
20 ppm	198*	226	269*	279
100 ppm	186*	211*	230*	239*

Bodyweights rounded to three significant figures; * significantly different from control values (p<0.05)

Relative organ weights were not affected by treatment. Clinical signs were recorded predominantly in the 100 ppm group and included an increased incidence of urine staining, enlarged preputial gland, alopecia, hunched back, loose stool, rough coat, eye opacity zones and increased incidence of irritation of the penis. The NOEL for gross effects is considered to be 20 ppm, based on decreased bodyweight and increased clinical signs at 100 ppm in both sexes.

Clinical signs: Clinical signs were recorded predominantly in the 100 ppm animals, and were of a nature and frequency consistent with the general signs of mild overt toxicity seen in the high-dose groups. The incidence of a selection of such signs in the main study group is shown in Table 43 below.

Table 43: Summary of selected clinical signs for all main study group

	Male				Female			
Dose (ppm):-	**0**	**5**	**20**	**100**	**0**	**5**	**20**	**100**
Observations								
Urine stain	3	3	1	19	16	17	26	44
Alopecia	3	4	7	11	13	17	26	26
Loose stool	0	2	7	8	0	0	1	7
Opacity zone both eyes	0	1	0	0	2	3	5	24
Preputial gland enlarged	9	9	15	13	3	2	6	7
Penis irritation	1	1	0	6				
Hunched back	1	1	0	4	2	0	3	11
Rough coat	2	11	10	23	13	9	14	29
Tail lesions	26	22	24	47	5	0	0	38
Posterior paw lesions (both)	1	1	4	21	0	0	0	8

Ophthalmology: These investigations revealed significant findings in males and females at termination, as shown in the table below. Compound-related bilateral diffuse retinal atrophy was seen in most of the 100 ppm females and in one 20 ppm female; the incidence in the rest of the females and the males was unilateral. The peripheral retinal degeneration occurred in both treated and control animals and was not considered treatment-related; this finding is a common age related finding in rats. In the 100 ppm female group, these lesions were obscured by the diffuse retinal atrophy. Microscopic lesions indicative of corneal scars (corneal neovascularization and/or mineralisation) were significantly elevated for 100 ppm males and females and this lesion is considered treatment-related. A statistically significant increase in optic nerve atrophy, possibly arising from the retro-orbital bleeding techniques or the compound-related diffuse retinal atrophy, was recorded in both males and females at 100 ppm; however the incidence of this lesion bilaterally was statistically significant only for the 100 ppm females with incidences of 0, 0, 0, and 5 for the 0, 5, 20 and 100 ppm groups respectively. Hence treatment at 100 ppm induced several eye lesions affecting the cornea, retina and optic nerve, with females more sensitive than males. The NOEL for ophthalmological morphology was considered to be 20 ppm for males and 5 ppm for females.

Table 44: Ophthalmascopic findings from all eyes of males and females at termination.

Lesion	0 ppm	5 ppm	20 ppm	100 ppm
Males				
Diffuse retinal atrophy	5/50	6/50	5/50	7/50

Peripheral retinal degeneration	34/50	32/50	25/50	37/50
Corneal neovascularisation	4/50	2/50	4/50	13/50*
Optic nerve atrophy	3/46	3/48	6/49	11/46*#
Females				
Diffuse retinal atrophy	5/50	3/50	5/50[1]	40/50*
Peripheral retinal degeneration	34/50	34/50	43/50	1/50
Corneal neovascularisation	4/50	3/50	7/50	29/50*
Optic nerve atrophy	6/47	6/48	3/47	15/46*

* statistically significant ; # unilateral lesions due to orbital bleeding techniques; [1] one animal with bilateral atrophy.

Electroretinography: Electroretinography of selected rats at week 75 and at termination revealed a sex-specific effect on retinal function. All males, control females and 5 ppm females recorded normal electroretinograms. The 20 ppm and 100 ppm females recorded either suppressed or absent electroretinograms. The NOEL for electroretinography was considered to be 100 ppm for males and 5 ppm for females.

Clinical pathology: Several clinical chemistry, haematology and urinalysis parameters recorded statistically significant differences between controls and treated groups. Many of these statistically flagged results were not considered biologically significant and hence were not considered treatment-related because of one or more of the following characteristics: 1) there was no dose relationship; 2) the instances were sporadic in time and scattered between the dose levels; and 3) the values fell within historical control values.
Clinical chemistry: These results included sporadic statistically significant differences from controls for many measures. Among these differences, reduced serum glucose levels were recorded in 20 ppm and 100 ppm females at weeks 14 and 79, and reduced serum protein, albumin and globulin levels were recorded in 100 ppm males and females also at weeks 14 and 79. These statistically significant findings were transient and were not regarded as biologically significant. The NOEL for clinical chemistry results other than ChE activity was considered to be 100 ppm in both sexes.

Haematology: there were slight decreases in RBC count, Hb, HCT, MCV, MCH and/or MCHC primarily in 20 ppm and 100 ppm males and females at weeks 27, 53 and 79. These changes were generally small, transient and within historical control values and were not considered biologically significant. The NOEL for haematology parameters was considered to be 100 ppm for both sexes.

ChE activity: These enzyme activities at the various sample times are shown in the table below. Plasma and RBC ChE activities when compared to controls were depressed in a dose-related manner, and females showed greater depression than males. The plasma ChE activity also generally declined with time as the experiment continued, and by week 105 there was >20% inhibition at all dose levels in both sexes. The RBC ChE activity also showed dose-related inhibition when compared to controls. The inhibition was less marked than for plasma activity and recorded some recovery with time presumably due to metabolic adaptation. Biologically significant inhibition (>20%) of RBC ChE was not evident at the 5 ppm dose level in either sex at any sample time. However, at 20 ppm and 100 ppm there was significant inhibition in both sexes at most time points. Brain ChE activity recorded dose-related, statistically ($p<0.05$) and toxicologically significant (>10%) inhibition in both sexes at all dose levels. The satellite animals sacrificed at 52 weeks gave results consistent with the main study groups.

There was no NOEL demonstrated for ChE inhibition in this study, based on the toxicologically significant inhibition of plasma, RBC and brain ChE activities at all doses. The lowest dose tested (5 ppm; 0.2 and 0.3 mg/kg bw/d for males and females, respectively) is considered a LOEL for plasma, RBC and brain ChE inhibition.

Table 45: ChE activity in brain, RBC and plasma (expressed as % of controls)

	Plasma					
	Week 14	**Week 27**	**Week 53**	**Week 79**	**Week 105**	**Week 52^s**
Males						
Controls	100	100	100	100	100	100
5 ppm	88*	84*	93*	81*	72*	
20 ppm	72*	65*	70*	52*	42*	
100 ppm	58*	51*	54*	36*	31*	54*
Females						
Controls	100	100	100	100	100	100
5 ppm	59*	62*	65*	63*	69*	
20 ppm	32*	31*	34*	34*	33*	
100 ppm	22*	21*	21*	21*	22*	20*
	RBC					
	Week 14	**Week 27**	**Week 53**	**Week 79**	**Week 105**	**Week 52^s**
Males						
Controls	100	100	100	100	100	100
5 ppm	89*	92*	99	84*	97	
20 ppm	69*	67*	72*	64*	84*	
100 ppm	50*	50*	47*	42*	62*	47*
Females						
Controls	100	100	100	100	100	100
5 ppm	88*	92*	91*	82*	93*	
20 ppm	65*	66*	65*	60*	72*	
100 ppm	55*	52*	47*	45*	59*	47*

	Brain	
	Week 106	**Week 52^s**
Males		
Controls	100	100
5 ppm	87*	
20 ppm	61*	
100 ppm	24*	26*
Females		
Controls	100	100
5 ppm	86*	
20 ppm	57*	
100 ppm	22*	21*

* statistically significant ($p<0.05$); ^{s} satellite groups

<u>Body and organ weights</u>: At termination there was a statistically significant decrease in bodyweight at the 100 ppm dose level in both sexes in the satellite (6% in males, 5% in females) and main groups (7% in males, 13% in females). There were statistically significant increases in relative organ weights at 100 ppm in the satellite group (brain, heart and lung weights in males; brain and kidney in females). Similarly, statistically significant increases in relative organ weights were recorded in the main study group (males - brain and lungs at 20 ppm and 100 ppm, liver at 100 ppm; females - kidneys and liver at 100 ppm). As no clear dose response was recorded, the NOEL for bodyweight or organ-weight changes is considered to be 20 ppm.

Gross and micro-pathology findings: Those findings considered treatment-related are summarised in the table below. Observations included an increased incidence of raised zones on the stomach of 100 ppm males and females (60% and 44% of males and females respectively *versus* 0% for controls), due to mineralisation in the outermost muscular layer. Similarly, there was an increased incidence of raised zones on the skin of tail and feet in 100 ppm males and females, due to thickening of the squamous epithelium. Males in the 100 ppm group recorded an increased incidence of the normal age-related vacuolar degeneration of the epididymis; this arose due to vacuolated cytoplasm of the epithelium of the epididymal body and head. There was vacuolar degeneration of the naso-lacrimal duct in 100 ppm males and females and in 20 ppm females, and an increase incidence of granulomatous pneumonia in the lungs of 20 and 100 ppm males and 100 ppm females. The NOEL for gross and micropathology findings was considered to be 5 ppm in both sexes.

Table 46: Incidence of pathology findings in males and females at the 2-year sacrifice

Dose (ppm)	0	5	20	100
No. of animals examined	50	50	50	50
Lesion				
Males				
vacuolar degeneration of nasolacrimal ducts	3	2	5	37*
granulomatous pneumonia, lungs	8	14	16*	22*
mineralisation in stomach muscle layers or serosa	1	2	5	32*
vacuolar degeneration in body of epididymis[a]	0	0	0	35*
vacuolar degeneration in head of epididymis[a]	0	0	4	43*
Females				
vacuolar degeneration of nasolacrimal ducts	3	7	26*	44*
granulomatous pneumonia, lungs	2	0	3	18*
mineralisation in stomach muscle layers or serosa	2	2	1	27

*statistically significant ($p<0.05$); [a] abnormality seen in epithelial cells; [b] bilateral lesion in 39/40

Neoplastic findings: There were no macro- or micropathology findings which indicated an increase in neoplastic lesions at any treatment level. The table below shows the incidence of some neoplasias common in this strain of rat; in neither sex was there a dose relationship for these or any of the other neoplasias documented in this study. The observations in the animals from the interim kill (1-year) are consistent with the findings in the 2-year kill group.

Table 47: Total incidence of selected neoplasms in the main study group

Sex	Male				Female			
Dose(ppm)	**0**	**5**	**20**	**100**	**0**	**5**	**20**	**100**
rats examined	50	50	50	50	50	50	50	50
C-cell adenoma	8	4	9	6	2	2	3	2
pituitary adenoma	18	17	22	25	23	36	28	26
hepatocellular adenoma	6	3	0	3	3	2	2	1
hepatocellular carcinoma	1	2	1	0	0	0	0	1
malignant lymphoma	2	1	2	1	2	2	2	0
leukaemia	22	18	14	10	11	11	9	6
fibrosarcoma	3	2	0	1	0	3	0	0
endometrial polyp					19	18	13	13
Leydig cell tumour	46	47	46	46				

There was no NOEL in this study, based on the significant inhibition of brain ChE activity at all doses.

Dogs

Christenson WR (1990b) Chronic feeding toxicity study of fenthion technical (Baytex) with dogs. Mobay Report 5272, Study No. 87-274-01, [BA; sub:11009, Vol 9; sub: 11793,Vol 2] USEPA 83-1, OECD 452, GLP

Christenson WR (1993a) Chronic feeding toxicity study of fenthion technical (Baytex) with dogs (Supplemental submission to report 5272 of 31.7.90), Mobay Report 5272A. [BA; sub: 11009, Vol 9; sub: 11793, Vol 2]

Groups of Beagle dogs (4/sex/dose) were dosed with fenthion (94.8% purity, corn oil vehicle) in the diet at 0, 2, 10, 50 ppm (measured as 0, 1.9, 9.0 and 45.6 ppm) for one year. This equates to a daily dietary exposure of 0, 0.06, 0.26, and 1.23 mg/kg bw/d for males, and 0, 0.06, 0.26 and 1.18 mg/kg bw/d for females. The dogs were observed daily and examined in detail weekly for clinical signs; body weights and food consumption were recorded weekly and daily respectively.

Cage-side observations were recorded on a daily basis and detailed physical examination weekly. Prior to study commencement and at study end, all dogs were subjected to ophthalmic examination. The pupil reflex, conjunctiva, cornea and iris were examined pre-mydriasis and the lens, vitreous humour and retina were examined post-mydriasis.

Clinical pathology consisting of complete biochemical, haematological and urinalysis assessment was performed on all animals at 3, 6, 9 and 12 months. At 12 months all animals were necropsied with macroscopic and microscopic examination of organs and tissues. Results were presented as summary tables and as individual animal data; appropriate statistical methods were applied to all data collected.

Haematology parameters: RBC count and morphology, Hct (packed cell volume), Hb, leucocyte differential count, leucocyte total count, platelet count, reticulocyte count, MCH, MCHC, MCV.
Clinical chemistry parameters: albumin, AP, SGPT, SGOT, bilirubin, cholesterol, total protein, BUN, calcium, chloride, creatinine, creatine phosphokinase, GGT, globulin, glucose, LDH, phosphorus, potassium, sodium, triglycerides, uric acid. Plasma, RBC and brain ChE activities were determined using a modified Ellmann technique as described by Hackathorn et al (1983).
Urinalysis parameters: appearance, specific gravity, glucose, ketones, sediment (microscopic), occult blood, pH, protein, volume, bilirubin, urobilinogen.
Organs weighed: *a*drenals, brain, ovaries, pituitary, testes, kidneys, liver, lung, heart, spleen, thyroid with parathyroids.
Histopathological examinations: adrenals, aorta, bone (femur, rib, sternum), bone marrow, brain sections (cerebellum-midbrain, cerebellum, medulla-pons), caecum, cervix, colon, duodenum, epididymis, eyes, gall bladder, Harderian glands, heart, ileum, jejunum, joint (fem/tib), kidneys, larynx, liver, lungs, lymph nodes (cervical, mesenteric), mammary gland, muscle (skeletal), nerve (optic, sciatic), oesophagus, ovaries, pancreas, parathyroids, pituitary, prostate, rectum, salivary gland, seminal vesicle, skin, skull, spinal

cord (cervical, thoracic, lumbar), spleen, stomach, testes, thymus, thyroid, trachea, urinary bladder, uterus, gross lesions.

Results

The test diet exhibited satisfactory results for tests of homogeneity, stability and concentration (90-95% of nominal). All animals survived to scheduled termination. Clinical signs (alopecia, eye discharge, skin lesions on paws or limbs, loose stools, salivation, vomiting) were sporadic and not regarded as treatment-related. Feed consumption was unaffected by treatment. Body weight gains during the study were statistically comparable to controls for all dose levels; while the mean bodyweight of 50 ppm males was consistently higher than controls (10%, 11%, 18% and 16% at weeks 13, 26, 39 and 52 respectively), this increase could be attributed to the increase in bodyweight of just one male evident from week 13 onwards and is not regarded as treatment-related. Relative organ weights were not affected by treatment.

Gross pathology examination revealed only incidental, non-treatment-related findings including: brain dilatation, kidney discolouration, cervical and mesenteric lymph node discolouration, raised zones in the spleen, enlarged uterus and ovary. Histopathology observations were minimal to slight in nature and none were considered biologically significant. The NOEL for morphological effects is considered to be 50 ppm. The ophthalmological investigations revealed no significant findings in males or females at any dose level. Clinical pathology findings did not reveal any consistent dose-related differences between the groups for blood biochemistry, haematology or urinalysis, except for ChE measurements.

ChE activity: There was a dose-related inhibition of plasma ChE in both sexes which was of borderline significance at 2 ppm but clearly significant at 10 and 50 ppm, with females slightly more sensitive than males. RBC and brain levels were generally reduced at 10 and 50 ppm in both sexes but this inhibition only achieved statistical significance at 50 ppm. The NOEL for plasma ChE inhibition in this study was considered to be 2 ppm (0.06 mg/kg bw/d). The NOEL for both RBC and brain ChE was considered to be 10 ppm (0.26 mg/kg bw/d) in both sexes.

Table 48: ChE activity at various times (absolute value and % of concurrent control)

	Plasma (IU/mL)					Plasma (% of control)				
	Pre-test	Week 14	Week 27	Week 40	Week 53	Pre-test	Week 14	Week 27	Week 40	Week 53
Males										
Controls	1.21	1.37	1.29	1.27	1.32	100	100	100	100	100
2 ppm	1.24	1.27	1.25	1.25	1.16	102	92	97	98	88
10 ppm	1.34	0.94*	0.84*	0.93*	0.81*	111	68*	65*	74*	61*
50 ppm	1.60	0.56*	0.64*	0.61*	0.61*	132	41*	50*	48*	46*
Females										
Controls	1.39	1.55	1.60	1.49	1.52	100	100	100	100	100
2 ppm	1.40	1.53	1.20*	1.38	1.29	101	98	75*	92	85
10 ppm	1.42	1.03*	0.95*	0.88*	0.93*	102	67*	60*	59*	62*
50 ppm	1.44	0.35*	0.62*	0.70*	0.57*	104	22*	39*	47*	38*
	RBC (IU/mL)					**RBC (% of controls)**				
	Pre-test	**Week 14**	**Week 27**	**Week 40**	**Week 53**	**Pre-test**	**Week 14**	**Week 27**	**Week 40**	**Week 53**
Males										

Controls	2.29	2.23	2.33	2.41	2.34	100	100	100	100	100
2 ppm	2.68	2.81	2.66	2.90	2.73	117	126	114	120	116
10 ppm	2.29	2.00	2.09	2.18	2.00*	100	90	90	90	86
50 ppm	2.38	0.98*	1.10*	1.16*	1.05*	104	44*	47*	48*	45*
Females										
Controls	2.20	2.25	2.36	2.46	2.59	100	100	100	100	100
2 ppm	2.17	2.12	2.46	2.47	2.38	98	94	104	100	95
10 ppm	2.61	2.41	2.52	2.68	2.43	119	107	107	109	97
50 ppm	2.44	1.10*	1.12*	1.18*	1.10*	111	49*	47*	48*	44*

	Brain (IU/g) (week 53)		Brain (% of control)	
	Males	Females	Males	Females
Controls	5.83	6.08	100	100
2 ppm	5.83	5.93	100	98
10 ppm	5.05	5.08	87	84
50 ppm	4.08	3.43*	70*	56*

***** statistically significantly lower than concurrent control (p<0.05)

Doull J, Root M, Cowan J & Vesselinovitch D (1963b) Chronic oral toxicity of Bayer 29493 to male and female dogs. Unpublished Bayer report No. 10853 from Department of Pharmacology, University of Chicago, Illinois, USA. [BA; sub:734, A3162, Box 104, Vol 5, Attachment 2-33]

Groups of Beagle dogs (2/sex/dose) were exposed to fenthion (92.1% purity, vehicle not stated) in the diet at 0, 2, 10, 50 ppm (equivalent to 0, 0.05, 0.125, and 1.25 mg/kg bw/d) for one year. The dogs were observed daily for cholinergic signs or other toxic effects. Body weights were reported monthly. Blood samples were taken fortnightly for ChE determinations; pre-test ChE activity (the mean of five duplicate samples) was also recorded for each dog.

At 12 months, all animals were necropsied, with macroscopic and microscopic examination of the following organs and tissues: liver; kidneys; adrenals; spleen; gonads; heart; lung; thymus; and brain. Samples of liver, brain and blood were taken at necropsy for ChE determinations using the manometric method of Dubois and Mangun (1947).

Results

Results from this old (1963) study were presented as summary tables or graphs; no statistical analysis was reported. Diets were prepared at least weekly but no dietary analyses were provided. Body weights were presented graphically and could not be evaluated; the authors stated that the growth rates of the animals were not decreased by treatment at any dose level. The authors further stated that there was no treatment effect on either average daily food consumption or the presence of cholinergic or other toxic signs; however, no data were provided for these parameters.

<u>ChE activity</u>: The raw data for the ChE determinations during the study were not provided. The data were represented graphically only and were not interpretable. The authors stated that: there was no effect on serum or RBC ChE activity at the 2 ppm dose level; at 5 ppm there was approximately 40% inhibition of serum ChE only; and that at 50 ppm there was significant inhibition of serum ChE (50%) and RBC ChE (25% inhibition).

Data were provided for the ChE determinations from the necropsy samples (see table below). There was a dose response in all tissues; serum ChE activity was significantly inhibited at 5 and 10 ppm, while RBC and liver only record biologically significant inhibition at 50 ppm. The dose response seen in all tissues indicates that the brain inhibition of 16% seen at 50 ppm was probably also biologically significant.

Table 49: ChE activity in tissues obtained at terminal sacrifice (1 year)

Dose (ppm)	ChE activity[1] (% inhibition cf. concurrent control)			
	Serum	**RBC**	**Liver**	**Brain**
0	9.8 ± 1.0[2]	13.3 ± 1.1	49.9 ± 3.7	50.2 ± 3.3
2	10.2 ± 1.1	14.7 ± 0.8	48.2 ± 1.3 (3%)	50.0 ± 4.2
5	7.1 ± 1.8 (28%)	13.1 ± 0.5 (2%)	47.1 ± 2.2 (6%)	49.4 ± 5.2 (2%)
50	3.4 ± 1.6 (65%)	9.6 ± 0.8 (28%)	23.1 ± 2.9 (54%)	42.4 ± 2.7 (16%)

[1] µL of CO_2 produced /10 min/50mg tissue (wet weight)
[2] mean ± SD from duplicate samples from 4 dogs (2M, 2F)

Necropsy and histopathology: Interpretation of the organ weight data is difficult because there was no interpretable data on terminal body weights and neither relative organ weights nor historical control data were provided. The authors noted that most of the animals receiving the test substance exhibited moderate enlargement of the spleen, with dark red swollen areas in the red pulp. Histopathology of the spleens of animals receiving fenthion in the diet revealed a decreased cellularity (mild to moderate) and decreased extramedullary haematopoiesis, neither of which was dose-related in severity. Mild to moderate haemosiderosis was present in both control and treated groups.

Table 50: Organ weights (g) at terminal sacrifice (1 year)

Organs	Dietary level of fenthion							
	0 ppm		2 ppm		5 ppm		50 ppm	
	Male	Female	Male	Female	Male	Female	Male	Female
Brain	72	67	71	61	69	68	77	70
Liver	226	201	244	218	315	213	353	255
Kidneys	45	32	48	31	48	35	58	39
Spleen	18	16	43	26	24	59	47	23
Heart	75	60	75	58	81	69	79	79
Lung	71	62	67	59	79	55	83	66
Thymus	4.0	5.1	4.0	5.0	4.0	5.5	6.0	4.0
Adrenals	1.8	1.0	1.5	2.0	1.2	1.0	1.2	1.5
Gonads	21		15		19		23	

[1] mean value for paired animals (2 males and 2 females) in each group

This pre-GLP and non-guideline study has inadequate documentation of most test procedures and results. Some results presented only as graphs were uninterpretable. The study is also deficient insofar as it lacks detailed reporting of clinical signs and statistical analyses were not provided. Utilising only the ChE data reported at terminal sacrifice (which is presented as an average for grouped male and female animals), the NOEL for serum ChE was considered to be 2 ppm (0.05 mg/kg bw/d) based on biologically significant inhibition at higher doses. The NOEL for RBC and brain ChE activity was considered to be 5 ppm (0.125 mg/kg bw/d) based on biologically significant inhibition at the next higher dose of 50 ppm (1.25 mg/kg bw/d).

Hoffmann K & Weischer CH (1975) Fenthion chronic study on dogs (two-year feeding experiment). Unpublished report No. 5737 from Bayer AG, Institut für Toxikologie, Wuppertal, Germany [BA; sub: 734, A3162, Box 104, Vol 5, attachment 2.34]

Beagle dogs (4/sex/group) were fed for 2 years with diets containing 0, 3, 10 or 30/50/60 ppm fenthion (30 ppm from week 1-64; 50 ppm from week 65-67; 60 ppm from week 68-104) ppm (equivalent to 0, 0.09, 0.32, and 1.28 mg/kg bw/d in animals of each sex). At study commencement, the animals were 19-21 weeks old and weighed between 5.5-7.9 kg. All animals were inspected daily for appearance and behaviour and food and water intake were measured daily.

Clinical observations: Once pre-test and at 13-week intervals thereafter the animals were examined in detail. This consisted of testing the pupillary, patellar and flexor reflex and the extensor thrust, measuring of body temperature, and conducting direct ophthalmoscopic examination of the eyes of each dog, and ECG recordings.

Clinical pathology investigations: Once pre-test and at 13 week intervals thereafter the following parameters were measured.

Haematology parameters: RBC count and morphology, Hct, Hb, leucocyte differential count, leucocyte total count, platelet count, reticulocyte count, thromboplastin time, MCH.
Clinical chemistry parameters: AP, SGPT, SGOT, bilirubin, cholesterol, total protein, BUN, creatinine, glucose.
Urinalysis parameters: appearance, specific gravity, glucose, sediment (microscopic), occult blood, pH, protein, volume.

ChE activities: Plasma and RBC ChE activities were measured pre-test and at weeks 3, 5, 7, 9, 11, 13, 26, 39, 48, 52, 65, 78, 92 and 104. Plasma and RBC ChE activities were determined by the hydroxamate method described by Pilz and Eben (1967). Brain ChE was measured in the Bulbus olfactorius of each dog at terminal sacrifice using a modified Ellmann technique (Voss and Sachsse 1970)

Terminal sacrifice: At terminal sacrifice the dogs were necropsied with recording of organ weights and histopathology examinations.

Organs weighed: Adrenals, brain, ovaries, pituitary, testes, kidneys, liver, lung, heart, spleen, thyroid, prostate and pancreas.
Histopathological examinations: ovaries, pituitary, testes, kidneys, spleen, thyroid, prostate, pancreas, adrenals, bone (Os femoris), bone marrow (sternum), colon, duodenum, epididymes, brain, eyes, gall bladder, heart, ileum, jejunum, kidneys, liver, lungs, lymph nodes (mesenteric), oesophagus, stomach, urinary bladder, aorta, muscle (skeletal), N. optici, N. ischiadicus, Glandula parotis, uterus.

Results

Clinical observations: There were no effects of treatment on physical appearance, behaviour patterns, body temperature or reflex tests. Water intake was unaffected by treatment. Food consumption was unaffected by treatment in most groups; however, 3 of the 4 females in the high dose group frequently left some ration uneaten. The dietary intake of test substance averaged 1.03, 3.45 and 13.62 mg/dog/d in the 3, 10, and 30/50/60 ppm groups. Differences in body weights between the dose groups at various times and total body weight gains were not statistically significant (see table below). No data for ophthalmoscopic findings were presented; the authors stated that there was no effect of treatment on the transparent media of the eye (cornea, lens and vitreous humor) or in the Fundus oculi, nor any effects on conjunctivae or the outer parts of the eye. ECG data were presented and analysis showed no effect of treatment on heart rates or cardiac rhythm in any group at any sampling time.

Table 51: Mean body weight (kg) and body weight gain (kg) over the two year feeding study

Dose (ppm)	Mean body weight at various times					Mean bw gain
	Week 0	Week 26	Week 52	Week 78	Week 104	Weeks 0 - 104
0	6.7	10.6	10.9	11.1	11.6	4.9
3	7.0	10.5	10.6	11.2	11.6	4.6
10	7.2	10.6	10.9	11.4	11.9	4.7
30 - 60	6.9	10.7	11.0	11.4	11.8	4.9

Clinical pathology investigations: The data from the haematological tests at 13-week intervals were presented in full; there was no effect of treatment on any of the measured parameters. The data from the clinical chemistry tests at 13-week intervals were presented in full; there was no effect of treatment on any of the measured parameters apart from a transient increases in GPT activity in one mid-dose female and one high-dose male, and a consistent decrease (10-17% compared to controls) from week 39 onwards in plasma protein values for high-dose males only. The data from the urinalysis tests at 13-week intervals were presented in full; there was no effect of treatment on any of the measured parameters.

ChE activities: No statistical analysis was provided. Blood samples obtained at terminal sacrifice (104 weeks) recorded clear and marked dose related inhibited of plasma ChE activity in both sexes. This inhibition was considered biologically significant at doses of 10 ppm (0.32 mg/kg bw/d) and above. Samples at earlier times recorded consistent significant inhibition at the high dose (30-60 ppm), occasional significant inhibition at the mid dose (10 ppm) and borderline values at the low dose of 3 ppm (0.09 mg/kg bw/d), which was considered the NOEL for plasma ChE inhibition in both sexes.

Inhibition of RBC ChE in males demonstrated a NOEL of 3 ppm (0.09 mg/kg bw/d). The inhibition of RBC ChE activity in females was not dose related as the mid-dose group recorded unusually high RBC ChE values throughout the study; the NOEL for RBC ChE inhibition in females was 10 ppm (0.32 mg/kg bw/d).

Brain ChE activity was clearly significantly inhibited at the high dose in both sexes, while at 10 ppm brain activity in males was unaffected but inhibition in females was of borderline significance. The NOEL for brain ChE inhibition was considered to be 10 ppm (0.32 mg/kg bw/d) in both sexes.

Table 52: ChE activity at various times (absolute value and percentage of control)

	Plasma (μM/mL)					Plasma (% of control)				
	Pre-test	Week 26	Week 52	Week 78	Week 104	Pre-test	Week 26	Week 52	Week 78	Week 104
Males										
Controls	9.15	8.52	7.72	7.47	7.12	100	100	100	100	100
3 ppm	10.5	7.45	7.35	6.52	6.07	115	87	95	87	85
10 ppm	9.65	6.62	7.10	6.65	4.55	105	78	92	89	64
30-60 ppm	10.1	5.15	3.77	3.10	2.92	110	60	49	41	41

Females										
Controls	10.4	7.70	8.47	7.37	8.47	100	100	100	100	100
3 ppm	10.5	7.07	7.45	6.97	6.87	101	92	88	95	81
10 ppm	10.4	6.17	5.25	6.75	5.70	100	80	62	92	67
30-60 ppm	9.65	3.30	2.85	2.12	3.42	93	43	34	29	40

	RBC (μM/mL)					**RBC (% of controls)**				
	Pre-test	**Week 26**	**Week 52**	**Week 78**	**Week 104**	**Pre-test**	**Week 26**	**Week 52**	**Week 78**	**Week 104**
Males										
Controls	6.80	5.75	5.95	7.00	7.45	100	100	100	100	100
3 ppm	7.15	6.20	7.57	7.42	7.10	105	118	127	106	95
10 ppm	5.52	4.60	4.95	5.37	5.32	81	80	83	77	71
30-60 ppm	5.42	3.05	3.27	1.46	1.55	80	53	55	21	21
Females										
Controls	6.17	5.97	6.20	6.40	6.50	100	100	100	100	100
3 ppm	6.77	6.45	5.82	6.35	6.15	110	108	94	99	95
10 ppm	7.10	6.85	6.92	7.30	8.25	115	115	112	114	127
30-60 ppm	7.15	4.87	3.90	1.55	2.52	116	82	63	24	39

	Brain* (week 104)		**Brain (% of control)**	
	Males	**Females**	**Males**	**Females**
Controls	26.8	25.6	100	100
3 ppm	27.9	27.8	104	109
10 ppm	26.3	20.6	98	80
30-60 ppm	16.1	18.1	60	71

* (μM/mg)

Terminal sacrifice: Macroscopic pathology was conducted on all animals and there were no effects reported which were considered treatment-related; some parasitic infections (worms) were reported. Absolute and relative organ weights were reported in full; there was considered no treatment-related effect. Histopathological examination of the protocol-specified tissues showed the normal findings expected in these animals; there was no effect of treatment.

This non GLP study was well documented apart from the lack of ophthalmological testing data; these test results were stated to be normal. The lowest NOEL in this study was based on plasma ChE inhibition seen at the dose of 3 ppm in the diet for 2 years, corresponding to an average daily intake of 0.09 mg/kg bw for males and females.

Monkeys

Rosenblum I (1980) A safety evaluation of fenthion (S 1752) in rhesus monkeys (Macaca mulatta). Unpublished Mobay report No. 68789 from Albany Medical College, New York, USA. [BA; sub: 734, A3162, Box 104, Vol 4, attachment 2-35]

Rhesus monkeys (5/sex/group) were given daily doses of technical-grade fenthion (purity, 98.1%) in corn oil by gavage at concentrations of 0, 0.02, 0.07, or 0.20 mg/kg bw/d for two years. Animals were observed daily for general appearance and clinical signs; body weight and ophthalmological parameters were recorded monthly, and clinical chemistry, haematology, and urinalyses were performed at 0, 1, 3, 6, 12, 18, and 23 months. Plasma and RBC ChE activities were measured (Michel 1949) weekly for the first four weeks and monthly thereafter. One animal of each sex at 0 and 0.20 mg/kg bw/d was sacrificed seven months and three weeks after the beginning of treatment for measurement of brain acetylChE and gross and histopathology. All monkeys underwent necropsy after 23 months, but no histopathology was performed. Clinical observations and laboratory tests (serum chemistry, haematology, urinalysis) were stated to have been performed twice prior to commencement of treatment and weekly thereafter. Routine clinical biochemical, haematological, and urine parameters were determined from the collected blood and urine.

Clinical signs: daily observation for general appearance, signs of miosis, salivation, tremors and consistency of stools.
Haematology parameters: RBC count, Hct, Hb, leucocyte differential count, leucocyte total count.
Clinical chemistry parameters: creatinine phosphokinase, SGPT, BUN, calcium, creatinine, ornithine carbamyl transferase, potassium, sodium, chloride.
Urinalysis parameters: appearance, specific gravity, glucose, sediment (microscopic), pH, protein.
Organ weights: liver, kidneys, adrenals, spleen, testes, ovaries, vagina, uterus, heart, thyroids, pituitary, brain

Results

Clinical signs: Data were not provided. The author states that all monkeys presented the appearance of good health throughout the study and that there was no evidence of miosis, salivation or tremors.

Ophthalmic examination: Data were not provided. The author states that the eyes of individual monkeys appeared normal throughout, and there was no evidence of opacification of the lens.
Body weights: Treatment had no significant effect on body weights.

Table 53: Group mean body weights (kg) at 6 monthly intervals

Dose (mg/kg bw/d)	Sex	Body weight				
		Initial	6 months	12 months	18 months	23 months
0	M	3.03	4.22	4.95	6.28	7.43
0.02	M	3.03	3.94	4.74	6.4	7.18
0.07	M	3.04	4.02	4.99	6.62	7.36
0.2	M	3.06	4.22	5.27	6.93	8.03
0	F	2.79	3.38	3.2	4.48	4.65
0.02	F	2.73	3.72	4.05	4.02	5.64
0.07	F	2.68	3.49	4.04	4.70	4.88
0.2	F	2.66	3.58	4.15	5.08	5.63

ChE values: Plasma but not RBC ChE declined significantly during the last 5 months of the testing period. Plasma ChE activity was significantly inhibited in a dose-related and time related manner in both sexes. Peak inhibition occurred at 4 months and was considered biologically significant at the 0.07 and 0.2 mg/kg bw/d levels in both sexes. Plasma activity slowly recovered, presumably because the animals became physiologically adapted, until significant inhibition was seen only at the high dose at 18 and 23 months in both sexes. RBC ChE was not effected by treatment at any sample time; the slightly lower values reported in the mid- and high-dose males and high-dose female groups were consistent with differences in the pretreatment values. Brain ChE was measured in one animal/sex at 0 and 0.20 mg/kg bw/d at 32-weeks after the beginning of treatment; values of 9% and 2% inhibition were recorded for the female and male pairs respectively. The NOEL for brain ChE inhibition could not be established as there was insufficient data. The NOEL for RBC ChE was considered to be 0.2 mg/kg bw/d, based on a lack of significant inhibition at any time point. The NOEL for plasma ChE was considered to be 0.02 mg/kg bw/d in both sexes, based on biologically significant inhibition seen at 0.07 and 0.2 mg/kg bw/d at several time points but peaking at the 4 month assay time.

Table 54: Group mean plasma ChE at 1 monthly intervals*

Dose mg/kg bw/d	Sex	Initial		1 month		2 months		3 months		4 months		5 months	
Plasma ChE													
0.00	M	7.7		9.2		7.5		7.5		7.4		6.8	
0.02	M	7.5	**3%**[1]	8.8	**4%**	6.9	**8%**	6.9	**8%**	5.7	**23%**	6.6	**3%**
0.07	M	7.1	**8%**	7.0	**24%**	6.2	**17%**	6.2	**17%**	5.6	**24%**	6.4	**6%**
0.20	M	8.6		5.7	**38%**	4.3	**57%**	4.8	**36%**	4.0	**46%**	5.2	**24%**
0.00	F	8.3		9.1		8.6		7.5		7.0		7.5	
0.02	F	10.1		9.5		8.0	**7%**	7.7		6.7	**4%**	8.3	
0.07	F	8.4		7.6	**16%**	6.4	**26%**	6.7	**11%**	4.4	**37%**	5.7	**24%**
0.20	F	8.7		7.5	**18%**	6.4	**26%**	4.6	**39%**	4.8	**31%**	5.8	**23%**

* units are µM acetic acid liberated/min/mL; [1] % inhibition compared to control

Table 55: Group mean RBC and plasma ChE at 6 monthly intervals*

Dose mg/kg bw/d	Sex	Initial		6 months		12 months		18 months		23 months	
Plasma ChE											
0.00	M	7.7		8.4		9.5		8.8		4.9	
0.02	M	7.5	**3%**[1]	8.2	**2%**	10.4		9.4		5.3	
0.07	M	7.1	**8%**	6.5	**33%**	8.5	**11%**	8.7	**1%**	4.8	**2%**
0.20	M	8.6		5.5	**35%**	6.1	**36%**	6.2	**30%**	4.1	**16%**
0.00	F	8.3		8.3		11.5		9.1		5.3	
0.02	F	10.1		8.9		11.9		9.9		5.9	
0.07	F	8.4		7.6	**8%**	7.5	**35%**	10.4		5.7	
0.20	F	8.7		5.5	**34%**	7.0	**39%**	6.9	**24%**	4.6	**13%**
RBC ChE											
0.00	M	12.6		12.6		14.9		14.6		11.9	
0.02	M	11.7	**7%**	10.3	**18%**	13.8	**7%**	14.8		11.5	**3%**
0.07	M	10.8	**14%**	9.9	**21%**	12.7	**15%**	12.3	**16%**	9.9	**17%**
0.20	M	11.2	**11%**	10.7	**15%**	12.0	**19%**	11.8	**19%**	9.8	**18%**
0.00	F	11.7		11.7		13.5		13.3		10.5	
0.02	F	12.2		12.4		15.1		14.6		11.9	
0.07	F	12.2		14.2		15.1		13.7		11.2	
0.20	F	10.7	**9%**	9.7	**17%**	13.2	**2%**	11.1	**17%**	10.2	**3%**

* units are µM acetic acid liberated/min/mL; [1] % inhibition compared to control

Clinical tests: Treatment had no significant effect on any of the haematological, clinical biochemistry or urinalysis parameters reported.

Organ weights: Necropsy findings were limited to the four animals sacrificed at approximately 8 months; there were large differences in absolute and relative organ weights of testes (14 *versus* 4 g/kg for control *versus* treated) and liver (43 *versus* 24 g/kg for control *versus* treated) ovaries (10 *versus* 2 g/kg for control *versus* treated) and heart (7 *versus* 4 g/kg for control *versus* treated) in the females. The significance of these differences is unknown as the relative ages of the animals was not reported and historical control data were provided. The author states that the absolute and relative weights of organs did not indicate any marked deviation from the norm. There were no significant histopathological findings in these animals.

This pre-GLP study has adequate reporting of limited clinical laboratory testing and plasma and RBC ChE measurements. The study is deficient in so far as it lacks detailed reporting of clinical signs, necropsies were limited to four animals, statistical analyses were not provided, and ophthalmological testing results were not provided. The ChE data thus provide the only means of establishing regulatory endpoints in this study. The NOEL for brain ChE inhibition could not be established as there was insufficient data. The NOEL for RBC ChE was considered to be 0.2 mg/kg bw/d based on a lack of significant inhibition at any time point. The NOEL for plasma ChE was considered to be 0.02 mg/kg bw/d in both sexes based on biologically significant inhibition seen at several time points but peaking at the 4 month assay time.

9.3.7. Reproduction Studies

Kowalski RL, Clemens GR, Jasty v, Troup CM & Hartnagel RE Jr. (1989) A two-generation reproduction study with fenthion (Baytex) in the rat. Study No. 1166. Miles Laboratories. Report No. MTD0133, Tox. Report No. 1166, 22 December 1989. [BA; sub: 11009, A3162, Box 22, Vol 13-14]

Kowalski RL, Clemens GR, Jasty v, Troup CM & Hartnagel RE Jr. (1993) A two-generation reproduction study with fenthion (Baytex) in the rat, Addendum to Miles Report 1166, 25.5.93, Miles Laboratories Report 5026, [BA; sub: 11009, A3162, Box 22, Vol 13-14]

Charles River (Crl:CD BR) male and female rats (30/sex/group) were utilised in a two generation, one litter per generation reproduction study. The animals were exposed by diet to fenthion (97.0%) at levels of 0, 1, 2, 14 or 100 ppm (0, 0.08, 0.16, 1.16 and 8.3 mg/kg bw/d, based on pre-mating food intake) from 10 weeks of age. The F0 animals were exposed to the test diets for 70 days prior to pairing, and treatment continued through to the end of lactation on day 21 post-partum (ld 21), when they were sacrificed. Litters were culled to 8 pups/litter on LD4. At the end of the lactation period, 30 males and 30 females from each group were exposed to the test diets for 77 days prior to pairing to produce the F2 generation, and again treatment continued through to the end of the 21-day post-delivery lactation period when they were sacrificed. F1 males were necropsied following delivery of the last F2 litter. F2 litters were culled to 8 pups/litter on LD4, and these pups were sacrificed at 21 days of age.

Pairing in both generations allowed for one period of 21 days cohabitation on a one-to-one basis, and if insemination did not occur during this period females were paired with a different proven male for a further 7 days. Care was taken to avoid sibling pairings. Females were removed from pairing when vaginal lavage showed sperm, this day being gd 0.

All pups that were culled, died spontaneously, or were stillborn were necropsied. Neonates were weighed on days 0, 4, 7, 14 and 21 postpartum and observed daily. Clinical observations were performed daily on all animals. Litter data were recorded and included litter size at birth, incidence of live and dead pups on days 0, 1, 4, 7, 14 and 21 post partum, and sex and weight of pups on ld 1, 4, 7, 14 and 21. Body weights and food consumption were recorded twice weekly during pre- and post-breeding. Body weights of dams were recorded on gd 0, 7, 14 and 20 and on ld 1, 4, 7, 14 and 21.

Plasma and RBC ChE activities were measured in parental animals (10/sex/group) at 10-14 days prior to mating, and including brain ChE were recorded again at necropsy following LD21. Plasma, RBC and brain ChE were measured in neonates at necropsy following culling (LD4) and weaning (LD21). Reproductive organs from all control and high dose animals, plus testes and epididymides from all low- and mid-dose males were examined microscopically.

There were no treatment-related effects on mortality, clinical signs, food consumption or gross pathology in F0 and F1 adult animals. Male reproductive performance measured as "number of days to inseminate" was not affected by treatment in the F0 or F1 breeding cycles. High dose F0 and F1 females but not males showed significantly (p<0.01) higher body weights and body weight gain than controls during premating. During gestation, high dose F0 females showed significantly (p<0.01) lower bodyweight gain (88.2g) than did the other groups (108.1 g for controls), but food consumption was unaffected; high dose F1 females showed a similar response (89.6 g *versus* 104.7 g for controls), albeit not statistically significant

There was a treatment-related increase in absolute and/or relative epididymal weight in 100 ppm F0 and F1 males. Histopathology described cytoplasmic vacuolation in the lining ductal epithelial cells of the corpus epididymis of 2/30 14 ppm and all 100 ppm F0 and F1 males. Reproductive parameters of the F0 and F1 parents were affected at the high dose only and these changes included: decreased fertility, birth, viability and weaning indices; decreased number of litters, total implants and litter size as well as increased total and mean number of dead pups. Foetal parameters adversely affected by treatment at 100 ppm included increased percentage of F0 and F1 stillborn pups and increased neonatal deaths. F1 pups at the high dose recorded a significantly (p<0.01) lower body weight gain than the other groups on LD14 and LD21; F2 pups at the high dose showed a similar response, albeit not statistically significant. Sex ratio in the high dose F2 pups was outside the historical control range (median % males = 42.9-53.8). The overall pattern is one of diminished reproductive performance of the F0 females at 100 ppm, with some indication of effect on the pups at 14 ppm (Mean viability index). These effects are amplified in the F2 generation where the fertility index is considerably reduced at 100 ppm compared to controls. Similarly, the mean weaning and birth indices are both reduced in the high dose F2 pups. In the F2 generation the mean birth index is below the historical control range (89.8-93.1) at all doses including controls, indicating an unusually low breeding performance for all of this generation and hence some caution in interpreting the data.

Table 56: F0 dam reproductive data & F1 neonate data

	Control	1 ppm	2 ppm	14 ppm	100 ppm
Sex distribution at birth (median % males)	53.7	42.9	53.8	48.3	50.0
Fertility index[a]	96.7	90.0	69.0*[e]	93.3	73.3*[e]
Gestation index	96.6	100	100	96.4	100
Gestation length (mean days)	22.0	22.1	22.1	22.2	22.2

No. of litters		28	27	20	27	22
Total pups born		354	336	251	354	232
Mean litter size		12.6	12.4	12.6	13.1	10.5
Total no. dead pups (Stillbirths and deaths)		15	3	7	24	28**
Pup deaths after birth (LDs 0-4)		9	2	7	20	17
Mean Viability index[b]		97.5	99.5	97.3	91.3	85.0
Pup deaths after birth (LDs 5-21)		0	0	0	1	4
MeanWeaning index[c]		100	100	100	99.5	97.6
Total implantations (Mean)		375 (13.4)	367 (13.6)	272 (13.6)	368 (13.6)	256 (11.6)
Mean birth index[d]		90.1	90.3	90.6	92.2	84.3[e]
Median Weight (g) of viable pups	Birth	6.2	6.4	6.1	6.2	6.4
	LD14	33.6	33.9	34.6	33.5	30.5**
	LD21	54.8	55.4	56.8	54.2	50.6**
	Gain	48.5	49.3	50.4	48.3	44.2**

Table 57: F1 dam reproductive data & F2 neonate data

		Control	1 ppm	2 ppm	14 ppm	100 ppm
Sex distribution at birth (median % males)		48.5	53.3	44.5	55.6	39.2[e]
Fertility index[a]		86.7	81.5	81.5	86.7	38.5*[e]
Gestation index		100	100	90.9	96.2	100
Gestation length (mean days)		21.8	22.0	22.0	21.8	22.1
No. of litters		26	22	20	25	10[e]
Total pups born		325	265	248	320	111
Mean litter size		12.5	12.0	12.4	12.8	11.1[e]
Total no. dead pups (Stillbirths and deaths)		19	12	15	23	24
Pup deaths after birth (LDs 0-4)		7	6	7	15	17
Mean Viability index[b]		98.1	97.8	97.1	94.8	73.9[e]
Pup deaths after birth (LDs 5-21)		1	0	0	1	1
MeanWeaning index[c]		99.5	100	100	99.5	87.5[e]
Total implantations (Mean)		352	287	275	352	124
Mean birth index[d]		88.9[e]	89.1[e]	79.4[e]	85.9[e]	81.2[e]
Median Weight (g) of viable pups	Birth	6.0	6.0	6.3	6.1	6.0
	LD14	31.8	32.1	32.6	31.7	26.4[e]
	LD21	50.8	49.4	52.4	50.6	43.2[e]
	Gain	44.6	43.2	46.4	44.9	37.6

[a] No. pregnant animals/No. of animals with successful copulation x 100; [b] No. of viable neonates on LD4/No. of viable neonates at birth x 100; [c] No. of viable neonates on LD21/No. viable neonates on LD4 following culling x 100; [d] No. of liveborn/No. of implantations x 100; [e] Outside historical control range; * and ** Significantly different from control (p<0.05 and 0.01 repectively)

Plasma, RBC and brain ChE were inhibited in a dose-related manner in adult F0 and F1 males and females, with 2 ppm being at or below the NOEL value for these measures. A similar pattern was recorded in the F1 and F2 pups, except that brain ChE was significantly depressed in neonates only at 100 ppm. Hence significant inhibition of plasma and RBC ChE was recorded for all parental adults (F0 and F1) and all pups (F1 and F2) at the 14 and 100 ppm level, while brain ChE was inhibited at 14 ppm and above in adults, but only at 100 ppm in pups.

Table 58: % inhibition (cf control) of ChE activity in adults (1, 2, 14, 100 ppm)

		Plasma	RBC	Brain
F0 males	Pre-mating	0, 0, 27, 60	6, 0, 81, 94	
F0 females	Pre-mating	0, 0, 69, 92	6, 34, 33, 94	

F0 males	Termination	6, 0, 27, 62	NI	0, 4, 19, 64
F0 females	Termination	0, 42, 67, 88	NI	22, 17, 51, 78
F1 males	Pre-mating	2, 12, 33, 63	0, 0, 30, 64	
F1 females	Pre-mating	2, 0, 62, 88	17, 14, 53, 60	
F1 males	Termination	2, 0, 39, 70	10, 0, 4, 64	14, 7, 28, 56
F1 females	Termination	0, 1, 67, 90	19, 13, 42, 70	1, 0, 18, 56

NI = Not Interpretable

Table 59: % inhibition (cf control) of ChE activity in pups (1, 2, 14, 100 ppm)

		Plasma	RBC	Brain
F1 males	Day 4 Day 21	4, 0, 15, 37 0, 2, 38, 81	1, 0, 6, 30 0, 0, 10, 89	8, 0, 2, 4 1, 0, 6, 53
F1 females	Day 4 Day 21	1, 6, 4, 31 1, 4, 38, 82	1, 7, 14, 34 15, 0, 3, 81	0, 0, 2, 2 1, 0, 5, 51
F2 males	Day 4 Day 21	0, 0, 13, 40 4, 0, 33, 58	0, 0, 8, 45 10, 7, 14, 45	0, 3, 0, 12 0, 0, 6, 37
F2 females	Day 4 Day 21	0, 0, 12, 38 12, 0, 34, 73	0, 9, 5, 35 10, 0, 21, 55	0, 0, 0, 6 0, 5, 14, 37

The NOEL for maternal toxicity was 2 ppm (0.16 mg/kg bw/d) based on plasma, brain and RBC ChE inhibition at 14 ppm and 100 ppm. The NOEL for reproductive parameters was 14 ppm (1.16 mg/kg bw/d) based on amongst other changes, decreased fertility, litter size and neonatal survival and bodyweight gain at the next dose of 100 ppm.

Loser E (1969) Bay 29493 generation study with rats, Bayer AG report 1400, 2.5.69 [BA sub 734 attachment 2-38; sub: 11793, Vol 10]

This is a poorly documented pre-GLP study of the reproductive toxicity of fenthion. FB30 rats were fed fenthion (96.1%) in the diet (Silkasil S solvent) at doses of 0, 3, 15, or 75 ppm (10 males, 20 females per dose level; the F0 generation). Reproductive effects were studied in a four generation, 2-litters per generation study. The rats were treated with fenthion during the entire study period, including mating, gestation and pup lactation. Each generation was fed the fenthion diet for an average of 100 days before being bred to produce two litters. Rats were weighed weekly; pup-weights were recorded at birth, d5, d7 and then weekly thereafter. Litters were culled to ten pups at d5 after birth. Pups form the first matings were reared for 4 weeks before sacrifice (F1a, F2a, F3a). Pups from the second mating were reared for eight weeks before selection of 10 males and twenty females for the next parental generation; these animals were mated at 100 d after birth at which stage their parental generation was sacrificed (F0, F1b, F2b). The mean values of various parameters of the treated groups were compared to control values using Wilcoxon's non-parametric rank sum test.

Tests of acute oral toxicity made at the beginning, during and at the end of the study were consistently normal during a 7 day observation period.

Bodyweight gains in the 3 and 15 ppm groups were not different from controls. Males and females in the F0 generation receiving 75 ppm had significantly lower bodyweight gains than controls, but otherwise showed normal behaviour. This effect on growth was apparent only in the F0 generation, suggesting that the rats adapted to consumption of fenthion in the diet.

At the three dose levels tested, fenthion had no effect on fertility, litter size, pups' mean weight at birth or at 4 weeks or lactation performance. Fenthion at doses up to 75 ppm in the diet therefore did not affect reproduction in rats over 4 generations. None of the young rats showed malformations at autopsy.

This study contains no detailed reporting of most parameters of importance including malformations observed. It is considered not of regulatory standard.

9.3.8. Developmental Studies

Rats

Kowalski RL, Clemens GR, Bare JJ & Hartnagel Jr. RE (1987) A teratology study with fenthion (Baytex technical) in the rat. Aug 26, 1987, Miles Laboratories Report 935, Report # MTD0029, GLP [BA; sub: 11009, A3162, Box 22, Vol 15]

Groups of mated female rats (Crl:CD BR), 33/group, were given technical fenthion (Batch 85R-01-46I, 96.5% pure, in 5% aqueous Emulphor solution) daily by gavage between days 6-15 of pregnancy at doses of 0, 1, 4.2 or 18 mg/kg bw. Five animals/group were sacrificed on day 16 (24 h after dosing), and the remaining 28 dams/group were sacrificed on gd, 5 days after the last dosing. Clinical signs, food consumption and body weights were recorded every 2-3 days. Macroscopic changes in the main organs, numbers of corpora lutea in each ovary, as well as number and location of foetuses, resorptions and abortion sites were recorded at necropsy. Foetuses were sexed, weighed, subjected to external examination and processed either for visceral or skeletal examination. ChE activity in the brain, RBC and plasma compartments was measured in twenty dams and foetuses from each dose group.

Results

Analysis revealed satisfactory (<5% variation) concentration, homogeneity and storage-stability of the solutions used for dosing. There were no treatment-related deaths. At 18 mg/kg bw but not at the lower doses, there were overt clinical signs of toxicity in many animals including salivation, lacrimation, tremors and urine stained ventral surface. Additionally there was a clear negative dose response for food consumption, bodyweight gain and final mean bodyweight compared to controls, reaching statistical significance at 4.2 and 18.0 mg/kg bw/d at some intervals.

Table 60: Body weights and food consumption of pregnant dams during gestation[a]

	Control	1.0 mg/kg bw/d	4.2 mg/kg bw/d	18.0 mg/kg bw/d
Bodyweight d 15	351.4 (5.3)	341.1 (5.3)	334.3* (4.1)	335.2 (5.3)
Bodyweight d 20	421.3 (6.8)	408.7 (6.4)	399.0* (4.7)	391.7** (6.6)
Gain: days 0-20	128.4 (4.5)	123.9 (4.3)	119.0 (4.0)	101.1** (6.1)
Consumption d 15	23.0 (0.5)	23.5 (0.6)	22.0 (0.6)	19.9* (1.2)
Consumption d 20	27.0 (0.6)	26.3 (0.5)	25.3 (0.6)	24.8 (0.9)

[a]22-26 animals/group; weights in g (SE); * <control (P<0.05) or ** <control (P<0.01, Dunnett's test)

There were no remarkable maternal macroscopical findings at sacrifice. Reproduction parameters including pre- and postimplantation loss, number of foetuses per litter, abortions, or foetus death were not affected by treatment. Mean foetal weights were comparable to the control group.

Table 61: Reproductive efficiency and foetal data

	Control	1.0 mg/kg bw/d	4.2 mg/kg bw/d	18.0 mg/kg bw/d
No. of pregnant dams/total	31/33	28/33	28/33	28/33
No. of litters[a]	26	23	23	25
No. of dams aborting	0	0	0	
Mean No. of Corpora Lutea	15.3	15.4	14.7	15.1
Mean No. of implantations	14.4	13.6	13.1	14.0
Mean litter size	13.5	12.7	12.3	12.6
Median percent male foetuses	48.3	50.0	50.0	50.0
Median Wt. Viable foetuses (g)	3.8	3.8	3.9	3.8
Mean No. of resorption sites	0.9	1.0	0.8	1.5
Mean % preimplantation loss	8.2	12.3	13.0	8.3
Mean % postimplantation loss	6.5	6.6	5.5	10.5

[a] includes dams from day 20 sacrifice only

However there was a slight and not statistically significant increase in the mean number of resorptions in the 18 mg/kg bw/d group; the number also lay outside the historical control range (1.5 *versus* 0.3-1.4).

Table 62: Distribution of resorptions in dams

	Number of dams with resorptions			
No. of resorptions	Control	1.0 mg/kg bw/d	4.2 mg/kg bw/d	18.0 mg/kg bw/d
0	12	9	11	6
1	6	7	8	8
2	6	6	3	8
3	2	1	0	1
4	0	0	1	1
6	0	0	0	1
Total resorptions	24	22	18	37
No. of dams with more than 1 resorption	8	7	4	11
Mean No. of resorption sites	0.9	1.0	0.8	1.5
Percent with resorptions	53.8	60.9	52.2	76.0

Foetal external, visceral and skeletal examination revealed no compound-related malformations at any dose level. There was a slight increase in foetal skeletal variations (increased incidence of incomplete ossification of the cervical arches, skull bones, sternebrae, metacarpals and metatarsals) indicating a delay in skeletal maturation at the 18 mg/kg bw level only.

Table 63: Summary of foetal malformations and variations

	Malformations			
	Control	1.0 mg/kg bw/d	4.2 mg/kg bw/d	18.0 mg/kg bw/d
No. of litters	26	23	23	25
Litter incidence	4	2	1	0
No. of foetuses[a]	350	292	284	314

Foetal incidence	4	2	2	0
	Variations			
No. of litters	26	23	23	25
No. of foetuses[a]	182	151	149	161
Foetuses with extra ribs	12	6	11	11
Foetuses with abnormal vertebrae[b]	2	1	2	2
Foetuses with abnormal ribs[c]	1	1	5	3

[a] malformations include both visceral and skeletal foetuses, variations include skeletal foetuses; [b] additional pre-sacral vertebrae or sacral shift; [c] wavy, curved or bulbous ribs

There was significant and dose-related inhibition of maternal brain (>10%) and RBC (>20%) ChE activities at all dose levels on both gd 16 and 20. Plasma ChE was also depressed at the 1 mg/kg bw level or higher on day 16, and at 18 mg/kg bw/d on day 20. Foetal brain ChE activity was not significantly affected by treatment.

Table 64: % ChE inhibition inhibition relative to controls

Gestation day	Dose (mg/kg bw)	N	Plasma	RBC	Dam Brain	Foetal Brain
16	0	5	0	0	0	-
16	1.0	5	49.1*	32.5	19.5	-
16	4.2	5	67.8*	36.9	47.7*	-
16	18.0	3[a]	93.9*	93.4*	78.1*	-
20	0	20	0	0	0	0
20	1.0	20	14.1*	20.5*	11.7*	5.9
20	4.2	20	5.6	26.7*	35.8*	2.9
20	18.0	20	26.0*	52.3*	56.0*	8.7*

[a] data from 2 non-pregnant dams not included; * Significantly different from control (P<0.05, Dunnett's test)

There was no NOEL for maternotoxicity based on inhibition of maternal brain and RBC ChE activities at all dose levels. The NOEL for foetotoxicity was 4.2 mg/kg bw/d based on an increase in the mean number of resorptions in the 18 mg/kg bw/day group.

Rabbits

Clemens GR, Bare JJ & Hartnagel Jr. RE (1987) A teratology study in the rabbit with fenthion (Baytex technical) G R Clemens et al 7.12.87, Miles Report 970, Study # MTD0039. GLP [BA; sub: 11009, A3162, Box 22, Vol 15]

Groups of artificially inseminated American Dutch rabbits, 17/group, were given technical fenthion (96.5% pure, in 5% aqueous Emulphor solution) daily by gavage between days 6-18 of pregnancy at doses of 0, 1, 2.75 and 7.5 mg/kg bw. The animals were sacrificed on gd 28. Clinical signs were noted daily, food consumption and body weights were recorded every 3-7 days. Macroscopic changes in the main organs, numbers of corpora lutea in each ovary, as well as number and location of foetuses, resorptions and abortion sites were recorded at necropsy. Foetuses were sexed, weighed, subjected to external examination and processed first for visceral then for skeletal examination. ChE activity in the brain, RBC and plasma compartments was measured in the does at gd 18 (not brain) and at termination.

There were no treatment-related deaths. There were few overt clinical signs of toxicity in any animals other than an increase in occurrence in soft stool at the mid-and high-dose levels. The animals at 7.5 mg/kg bw/d recorded slight lowering of food consumption, bodyweight gain and final mean bodyweight compared to controls.

Table 65: Body weights and food consumption of pregnant dams during gestation[a]

	Control	1.0 mg/kg bw/d	2.75 mg/kg bw/d	7.5 mg/kg bw/d
Bodyweight d 19	3.34 (0.07)	3.31 (0.07)	3.33 (0.06)	3.22 (0.08)
Bodyweight d 28	3.45 (0.080	4.31 (0.06)	3.38 (0.06)	3.26 (0.08)
Gain: days 0-28	0.25 (0.03)	0.25 (0.02)	0.21 (0.04)	0.18 (0.06)
% gain GD 0-28	7.90	7.84	6.49	5.94
Consumption d 19	101.9 (7.9)	102.4 (8.3)	109.9 (6.3)	96.6 (8.6)
Consumption d 28	83.2 (7.9)	79.8 (7.9)	80.9 (10.3)	71.0 (9.4)

[a]14-16 animals/group; weights in kg (SE)

There were no remarkable maternal gross pathology findings at sacrifice. Reproduction parameters including pre- and postimplantation loss, number of foetuses per litter, abortions, or foetus death were not affected by treatment. Mean foetal and placental weights were slightly but not significantly less than concurrent and historical control values at the mid- and high-dose levels, but this was probably related to increased median litter size for both groups.

Table 66: Reproductive efficiency and foetal data

	control	1.0 mg/kg bw/d	2.75 mg/kg bw/d	7.5 mg/kg bw/d
No. of pregnant dams/total	16/17	16/17	16/17	14/17
No. of litters[a]	16	16	16	14
No. of dams aborting	0	0	0	
Mean No. of Corpora Lutea	8.6	7.4	9.0	10.1
Mean No. of implantations	7.6	7.2	7.1	9.4
Total no. of foetuses	116	106	107	116
Mean litter size	7.3	6.6	6.7	8.3
Median litter size	6.5	6.0	7.0	8.0
Median percent male foetuses	50.0	50.0	50.0	52.8
Median Wt. Viable foetuses (g)	34.1	35.8	33.8	32.4
Median Wt. Of placentas (g)	5.2	5.8	4.9	4.8
Mean No. of resorption sites	0.4	0.6	0.4	1.1
Mean % preimplantation loss	17.3	10.1	24.5	10.4
Mean % postimplantation loss	5.8	10.3	8.7	12.0

However there was a slight and not statistically significant increase in the mean number of resorptions in the 7.5 mg/kg bw/d group; the number was also equal to or outside the historical control range.

Table 67: Distribution of resorptions in dams[a]

No. of resorptions	Number of dams with resorptions			
	control	1.0 mg/kg bw/d	2.75 mg/kg bw/d	7.5 mg/kg bw/d
0	10	10	11	8
1	6	4	4	1
2	0	1	1	2
3	0	1	0	1
4	0	0	0	2

Total resorptions	6 (3-16)	9	6	16
No. of does with more than 1 resorption	0 (0-4)	2	1	5
Mean No. of resorption sites	0.4 (0.2-1.0)	0.6	0.4	1.1
Percent with resorptions	37.5 (19-50)	37.5	31.2	42.9

[a] numbers in parentheses are historical control values (the range seen in 11 studies of 17 does)

Foetal external, visceral and skeletal examination revealed no statistically significant increases in compound-related malformations or variations at any dose level.

Table 68: Summary of foetal malformations and selected variations

	Malformations			
	control	**1.0 mg/kg bw/d**	**2.75 mg/kg bw/d**	**7.5 mg/kg bw/d**
No. of litters	16	16	16	14
Litter incidence	7	5	4	5
No. of foetuses[a]	116	106	107	116
Foetal incidence (%)	9 (7.8)	6 (5.7)	4 (3.7)	5 (4.3)
	Variations			
No. of litters	16	16	16	14
No. of foetuses[a]	116	106	107	116
Foetuses with extra ribs	24	7**	22	21
Foetuses with abnormal vertebrae[b]	6	4	7	6

[a] malformations and variations both include visceral and skeletal foetuses; [b] additional pre-sacral vertebrae or sacral shift; ** Significantly different from control (P<0.01, Chi-squared and Fisher's exact test)

There was biologically (>20%) and generally statistically significant dose-related inhibition of maternal brain (day 28) and RBC (days 19 and 28) ChE activities at the mid- and high-dose levels, with some recovery of RBC levels at the mid-dose on GD28. Plasma ChE was also depressed at the mid- and high-dose levels on day 19, but had effectively recovered at both doses by GD 28.

Table 69: Pregnant Does: % ChE inhibition inhibition relative to controls

Gestation day	Dose (mg/kg bw)	N	Plasma	RBC	Brain
19	0	16	0	0	
19	1.0	16	4.8	9.6	
19	2.75	16	15.6*	21.7	
19	7.5	13	45.6*	82.9*	
28	0	16	0	0	0
28	1.0	16	0	0	6.5
28	2.75	15	0	14.0	20.3*
28	7.5	14	6.5	47.5*	40.2*

* Significantly different from control (P<0.05, Dunnett's test)

The NOEL for maternotoxicity was 1 mg/kg bw/d based on significant inhibition of maternal brain, RBC and plasma ChE activities at higher dose levels. The NOEL for foetotoxicity was 2.75 mg/kg bw/d based on the slight increase in the mean number of resorptions in the 7.5 mg/kg bw/d group.

9.3.9. Genotoxicity

The following Tables summarise the findings of *in vitro* and *in vivo* genotoxicity studies submitted and evaluated as part of the current fenthion review.

Table 70: Summary of Mutagenicity Testing with Fenthion

Assay	Bacterial strain or Cell type	Concentration (or Dose)	Metabolic activation	Results	Reference
Gene Mutation					
S. typhimurium	TA 100 TA 1535	375-1562.5 µg/plate	+, - +, -	-, - -, -	Herbold (1980a)
	TA 98 TA 100 TA 1535 TA 1537	20-2500 µg/plate	+, - +, - +, - +, -	-, - -, - -, - -, -	Herbold (1987) [GLP]
	TA 98 TA 100 TA 1535 TA 1537	8-1000 µg/plate	+, - +, - +, - +, -	-, - -, - -, - -, -	Herbold (1990a) [GLP]
	TA 98 TA 100 TA 1535 TA 1537	16-5000 µg/plate	+, - +, - +, - +, -	-, - -, - -, - -, -	Herbold (1994) [GLP]
	TA 98 TA 100 TA 1535 TA 1537	1000 µg/plate 0.1-1000 µg/plate (with activation)	+, - +, - +, - +, -	-, - -, - -, - -, -	Inukai & Iyatomi (1976)
	TA 98 TA 100 TA 1535 TA 1537 TA 1538	10-5000 µg/plate	+, - +, - +, - +, - +, -	-, - -, - + (weak), - -,- -,-	Shirasu et al (1979)
	TA 98 TA 100 TA 1535 TA 1537 TA 1538	NS	-	-	Waters et al (1982)
E. coli	WP2 *uvrA*	NS	+, -	-, -	
E. coli	*hcr* WP2	10-5000 µg/plate	+, -	-, -	Shirasu et al (1979)
		NS	-	-	Nagy et al (1975)
Mammalian cells (in vitro)	Chinese hamster ovary cells (CHO-K1-BH4)	12.5-100 µg/mL	+, -	-, -	Lehn (1990a) [GLP]
DNA Damage and Repair					
Pol test	*E. coli* K12 W3110	625-10000 µg/plate	+, -	-, -	Herbold (1983)
Rec	*S. cerevisiae* D3	NS	-	-	Waters et al (1982)
Unscheduled DNA synthesis	Human lymphoid cells	1-1000 µg/mL	-	-	Bai et al (1990)
Unscheduled DNA synthesis	Rat Hepatocytes	5-100 µg/mL DMSO vehicle	-	+ (weak)	Lehn (1990b) [GLP]

Unscheduled DNA synthesis	Human lung fibroblasts WI-38	NS	+, -	-, -	Waters et al (1982)
Chromosomal Effect Assays *(in vitro)*					
Rec-	*B. subtilis* NIG17 NIG45	0.3-300 µg/disc	-	-	Inukai & Iyatomi (1976)
	B. subtilis H-17 M-45	1-100 % v/v	+, -	-, -	Shirasu et al (1979)
Chromosomal Aberration	Chinese hamster lung fibroblasts	11.7-94 µg/mL	+, -	-, -	Kajiwara (1989) [GLP]
	Chinese hamster ovary cells (K1)	0.02-0.15 µL/mL	+, -	-, -	Putman & Morris (1989) [GLP]
Sister Chromatid Exchange	Chinese hamster lung cells (V79)	10-80 µg/mL	+, -	+, +	Chen et al (1982a)
		10-80 µg/mL	-	+ (weak)	Chen et al (1982b)
	Human lymphocytes	0.5-5.0 µg/mL	-	+	Rani & Rao (1991)
		0.02-20 µg/mL	+, -	-, -	Sobti et al (1982)

Results (+, positive; -, negative) are expressed relative to the presence (+) or absence (-) of metabolic activation.

Assay	Species	Dose	Result	Reference
Chromosomal Effect Assays *(in vivo)*				
Micronucleus (marrow cells)	Mouse (NMRI/ W 77)	2x50, 2x100 mg/kg bw, po	-	Herbold (1980b)
	Mouse (Bor: NMRI)	150 mg/kg bw, ip	+ (weak)	Herbold (1990b) [GLP]
Sister Chromatid Exchange (lymphoid cells of bone marrow)	Rat [Wistar]	10–100 mg/kg, unspecified dose route	-	Bai et al (1990)
Dominant lethal	Mouse (HSD/WIN: NMRI)	30 or 60mg/kg, po	-	Herbold (1997) [GLP]
	Mouse (NMRI)	10 or 25 mg/kg bw ,po	-	Machemer (1978)

9.3.10 Neurotoxicity studies

Hens

Tuler SM & Bowen JM Chronic fenthion toxicity in laying hens (1999) Veterinary and human toxicology 41: 302-307

White leghorn laying hens were exposed to weekly dermal applications of fenthion (20% (w/v) in dipropylene glycol monomethyl ether) at 0, 1 or 4 mg/kg bw for 24 weeks. Sixteen hens were treated identically with TOCP (15 mg/kg bw) as a positive control. The test substances were applied to the underside of the wing once weekly. Throughout the study, hens were evaluated for clinical signs (proprioceptive and limb positioning deficits, ability to perch, to right themselves, to jump out of a box), food consumption and egg production. Electromyographic (EMG) recordings consisting of individual motor unit potentials (MUPs) were recorded weekly from the left peroneus longus muscle of 4 hens/group, and the mean values (for the 4 hens) were presented as averages to give a mean for the six 4-weekly intervals. Every four weeks 4 hens/group were sacrificed for brain-NTE activity, concentrations of brain neurotransmitters and their metabolites, blood and brain ChE determinations, and histopathological examination of the right sciatic nerve and right peroneus longus muscle.

Results

Food intake did not differ significantly between the groups. The low dose initially produced 8% stimulation of egg production while the high dose inhibited egg production 10% during the latter 16 w of the study and reduced body weight 8% during this period. Four of 24 hens at the high dose exhibited transitory loss of proprioception, perching ability, and righting reflex after 8 to 16-weeks of exposure. All hens receiving the high dose lost the ability or desire to escape from a box by jumping during the latter half of the exposure period.

Muscle electrical activity was recorded electromyographically via telemetry. Fibrillation (denervation) potentials were absent, but amplitude times duration values for motor unit potentials of the peroneus longus muscle for 5 of the 6 4-week evaluation intervals were higher in the high-dose hens. This EMG response suggested the presence of a mild neuropathy. Ultrastructural examinations of the sciatic nerve revealed no evidence of nerve degeneration but mild neuropathy was present (large variation in cross-sections of nerve fibres); evidence of distal axonopathy was present in the TOCP-treated hens. Fenthion treatment induced a dose-related increase in swollen and/or atrophic muscle fibres as compared to controls. Inhibition of serum ChE and brain acetylChE was greater in the high-dose hens. Brain neuropathy target esterase was not inhibited in hens treated with fenthion but was inhibited 47%-56% in TOCP-treated hens. Behavioural changes were not correlated with changes in brain concentrations of enzymes or neurotransmitters or their metabolites. It would appear that muscle fibre abnormalities were of greater magnitude than nerve fibre abnormalities and were not the result of a neuropathy that included denervation.

Table 71: Effects of fenthion on muscle histopathology and ChE activity

Week	Histopathology (muscle)		ChE activity	
	Swollen fibres	Atrophic fibres	Serum	Brain
Dose = 1 mg/kg bw				
	% of control	% of control	% of control	% of control
4	33	100	113	87*
8	200	100	102	91
12	235*	160*	82	93
16	450*	130	93	95
20	73	114	97	95
24	120	194*	79*	98
Dose = 4 mg/kg bw				
4	92	312*	98	76*
8	200	169*	81	56*
12	300*	168*	60*	70*
16	550*	370*	76*	78*
20	118	114	62*	83*
24	197*	197*	53*	84*

*statistically significant cf controls

Kimmerle G (1965) Neurotoxic investigation using S1752 active ingredient. Farbenfabriken Bayer Ag, Institute of Technology, Wuppertal-Elberfeld, Germany [BA; sub: 734, A3162, Box 104, Vol 1, attachment 2-25]

Dieckmann W (1971) Bay 29 493 (S1752) Neurotoxicity studies on hens – Histopathology. Unpublished report No. 2735 from Bayer AG, Institut für Pathol. Histologie, Wuppertal, [BA; sub: 734, A3162, Box 104, Vol 1, attachment 2-26]

In a preliminary study, 5 groups of 8 hens (HNL strain) were dosed with fenthion in the diet at 0, 300, 1000, 3000 and 10,000 ppm for 30 days. They were then observed for a 4-week recovery period for signs of neurotoxicity. Two hens/group were sacrificed at the end of the feeding experiment and the others after the 4-week recovery period. Parts of the spinal cord and the sciatic nerve from these animals were prepared for histological examination.

All of the treated hens showed strong signs of organophosphate poisoning a few days after the start of the trial, and all but 2 hens (1 each from the 300 and 1000 ppm groups) died by the third week. In the surviving hens, blood ChE activity was reduced to 21% (300 ppm) and 8% (1000 ppm) after 30 days. No neurotoxic signs were observed.

In the principal study, 5 groups of 8 hens were exposed to fenthion in the diet at 0, 10, 25, 50 and 100 ppm for 30 days. They were then observed for a 4-week recovery period for signs of neurotoxicity. Two hens/group were sacrificed at the end of the feeding experiment, and the others after the 4-week recovery period. Parts of the spinal cord and the sciatic nerve from these animals were prepared for histological examination. There were no toxic signs in hens receiving 10 or 25 ppm, whilst typical symptoms of organophosphate poisoning were apparent in the 50 and 100 ppm groups, with 1 death at 100 ppm during the study. Decreased bodyweight and food intake were observed in the 100 ppm group and there were significant dose-dependent reductions in blood ChE activity in the 25, 50 and 100 ppm groups. No signs of neurotoxicity were observed during the trial or the recovery period. The histopathologist reported that no hens showed signs of either gangliocyte and axon degeneration or demyelination.

Flucke W & Kaliner G (1986) E 1752 (cn fenthion, the active ingredient of Baytex): Acute neurotoxicity studies on hens following oral and dermal administration, W Flucke, G Kaliner 22.9.86, Study # T 8021654, Bayer Report 15088. [BA; sub: 11009, A3162, Box 22, Vol 15]

Guideline: stated to have been performed in accordance with USEPA guidelines, Nov 1984.

Adult (5-7 months) white leghorn hens (Gallus gallus; 15/group), were twice dosed with fenthion technical (purity 98.5%) either orally at 40 mg/kg bw (in 2% v/v Cremophor EL in water) or dermally (undiluted) at 200 mg/kg bw; the doses were administered at an interval of three weeks along with atropine protection. Three other groups of 6 animals each comprised: the positive control group (a single dose of TOCP at 375 mg/kg bw); vehicle-only; and untreated control groups. All animals were observed for 21 days after the second dose (at day 21) except for TOCP animals that were seen to be moribund and thus were sacrificed at day 22 after the single dose. At necropsy, peripheral and central nervous tissues were removed for histopathology.

The control groups exhibited no anomalies with respect to walking and motor coordination at any time. Compared to the control animals, TOCP hens exhibited no signs of acute toxicity, but showed signs of delayed neurotoxicity including abnormal gait from day 7 post-dose, progressing to ataxia or paresis in all animals at sacrifice. The oral and dermal dosage groups displayed signs of acute intoxication (staggering gait and ruffled feathers on the first day, tachypnea beginning on day 2, sternal and lateral recumbency on days 3 and 4) with recovery beginning on day 5. The second dose caused similar signs in both groups with recovery starting later and taking longer (up to 18 days in the dermal dose group). There were no clinical symptoms nor neurohistopathological lesions characteristic of delayed neuropathy in these two dose groups. TOCP hens however displayed marked fibre degenerations in the sciatic nerve and the cervical segments of the spinal cord; these are typical signs of delayed neuropathy.

Flucke W & Eben A (1988a) E 1752 technical (cn fenthion): Study of the effect on the neurotoxic esterase (NTE) following oral administration to hens, Bayer Report 17307, Study # T 3021893 [BA; sub: 11009, A3162, Box 22, Vol 15] GLP

Flucke W & Eben A (1988b) E 1752 technical (cn fenthion): Study of the effect on the neurotoxic esterase (NTE) following dermal administration to hens, Bayer Report 17308, Study #'s T 3021893 / T 8022798, [BA; sub: 11009, A3162, Box 22, Vol 15] GLP

Study # T3021893: A group of 9 adult hens (Lohman Selected Leghorn, 9-10 months) received a single oral dose (by intubation in 2% Cremophor EL and water) of fenthion (98.5% purity) at 40 mg/kg bw under atropine protection. Two other groups of 9 hens each, comprised a positive control group (a single oral dose of TOCP at 100 mg/kg bw) and vehicle-only as the negative control. Three animals from each group were sacrificed at 24 hours, 48 hours and 7 days post-treatment to determine NTE activity in brain and spinal cord. When compared to controls, inhibition of brain and spinal cord NTE was minimal in the orally dosed fenthion animals (0-14%).

Study # T8022798: Another two groups of 9 adult hens (Lohman Selected Leghorn, 8 or 10 months old) were dermally dosed with fenthion (98.5% purity in 2% Cremophor EL and water) at 200 and 400 mg/kg bw (200 mg/kg bw twice, 24 h apart), under atropine protection. Doses were applied as 50 mg/kg bw aliquots to one side of the comb; consecutive aliquots were applied 1.5 h apart. Three animals from each group were sacrificed at 24 hours, 48 hours and 7 days after the last treatment to determine NTE activity in brain and spinal cord. The 400 mg/kg bw group was markedly affected and only three animals at 48 hours and two at 72 hours were sacrificed and results recorded. When compared to controls (Study # T3021893), inhibition of brain and spinal cord NTE was minimal in the dermally dosed fenthion animals (11-20% up to 7 days post-dose).

TOCP treated animals exhibited depressed (52-95%) NTE activity in brain and spinal cord at all sample times.

Hayes RH & Ramm WW (1988) Subchronic delayed neurotoxicity study of fenthion technical (Baytex) with hens, Mobay Report 1062, Study #'s 8641801 and 8649801 [BA; sub: 11009, A3162, Box 22, Vol 15] GLP

Guideline: US-EPA-FIFRA, F 82-5

Adult white Leghorn hens (Gallus gallus), 10 hens/group), were dosed with fenthion technical (purity 96.5%) orally (by gavage, in clear corn oil solution) at dose levels of 0, 1, 2, or 4 mg/kg bw/d for 14 weeks. TOCP (10-60 mg/kg bw/d with another 0 mg/kg bw/d control group) was used as the positive control substance. Hens were weighed weekly and doses calculated accordingly. Food consumption was recorded weekly. Hens were subjected to weekly tests of forced motor activity (ladder climbing from week 1onwards, and "shooing" around an open turfed area from week 5 onwards). ChE activity was determined in blood samples taken 24 h after the previous dose at weeks –3, -2, -1, 1, 2, 5, 9 and 14 for the main study groups, and in weeks –3, -2, –1, 1, 3, 5 and 9 for the TOCP-treated animals. All hens were necprosied and the following tissues collected in formalin for histopathology: brain, upper and lower cervical spinal cord, thoracic and lumbosacral spinal cord, right and left sciatic, tibial, peroneal nerves.

Results

Measured doses were within 80% of nominal. There was increased mortality at 4 mg/kg bw/d with three hens found dead on days 7, 27 and 48. All hens treated with TOCP died or were sacrificed *in extremis* between days 61-78. Food consumption was slightly decreased at 2 mg/kg bw/d and significantly decreased at 4 mg/kg bw/d from week 1. Bodyweight was significantly decreased (up to 25%) at 4 mg/kg bw/d from week 2.

At 4 mg/kg bw/d, clinical signs of decreased activity and ataxia were noted, but the effects were seen predominantly in the first hours after dosing and were no longer observed prior to the next dose, suggesting that these findings were likely to be caused by repetitive, severe acute cholinergic intoxication and not related to delayed neurotoxicity. Concurrent positive TOCP-treated controls exhibited decreased activity at week 5 and both ataxia and decreased activity from weeks 6 and 7 onwards. Forced activity tests recorded normal locomotor activity for the controls and fenthion-treated groups; the 4 mg/kg bw/d group showed decreased activity during weeks 6 and 7 only. Signs typical of delayed neurotoxicity were evident in the TOCP-treated hens from week 7 onwards; by week 8 these signs were moderate to severe and by week 11 these hens were frequently immobile.

Mean blood ChE was statistically significantly inhibited at all fenthion doses from week 2 onwards, and in TOCP-treated hens from week 1 onwards.

Table 72: Mean whole blood ChE values

Week	Control-1	1 mg/kg bw	2 mg/kg bw	4 mg/kg bw	Week	Control-2	TOCP
-3	0.91	0.87	0.95	0.97	-3	0.97	1.09
-2	1.00	1.00	0.92	0.89	-2	0.88	1.01
-1	0.96	0.94	0.98	0.90	-1	0.97	0.98
1	0.99	1.00	0.92	0.88	1	0.96	0.72*
2	0.92	0.48*	0.43*	0.43*	3	1.08	0.63*
5	1.04	0.45*	0.408	0.44*	5	0.91	0.65*
9	1.13	0.51*	0.41*	0.42*	9	1.05	0.63*
14	1.02	0.50*	0.43*	0.43*	12	1.16	

* statistically significant (p<0.05)

Histopathological examination revealed a dose-related increase in incidence of muscular hypertrophy/hyperplasia (in all muscle layers) of the oesophagus, crop, proventriculus, gizzard and intestine of all fenthion-treated hens (1, 2 and 4 mg/kg bw/d), and glandular and/or non-glandular epithelial hyperplasia in the oesophagus, crop and proventriculus of some mid- and most high-dose hens. These lesions were likely to be caused by localised ChE inhibition with subsequent overstimulated muscle hypertrophy.

There was no NOEL for whole blood ChE inhibition in this study with statistically significant inhibition evident at the LOEL of 1 mg/kg bw/d. The lowest dose tested (1 mg/kg bw/d) was considered a LOEL for histopathological changes in this study as muscle hypertrophy was present in the digestive organs of all fenthion-treated hens. The highest dose tested (4 mg/kg bw/d) was considered a NOEL for neurotoxicity; no treatment-related clinical symptoms nor increases (incidence and/or severity) in histopathological lesions of nervous tissue characteristic of organophosphate-induced delayed neurotoxicity (OPIDN) were evident in adult hens when administered fenthion orally at daily doses of up to 4 mg/kg bw/d for a period of 14 weeks.

Rats

Imai H, Miyata M, Uga S & Ishikawa S (1983) Retinal Degeneration in Rats Exposed to an Organophosphate Pesticide (Fenthion) Environ Res 30: 453-65

Forty male pigmented Long-Evans and twenty male albino Wistar rats were dosed with 50 mg/kg bw fenthion subcutaneously twice weekly for 1 year. Twenty pigmented and fifteen albino rats were used as controls. Electroretinograms (ERG), histopathology, vitamin A and ChE activities were measured.

In pigmented rats, the amplitude of the ERG gradually declined, disappearing by the 12th month. In albino rats, the ERG amplitude disappeared by the 6th month in 7/15 animals. Fundoscopy revealed retinal degeneration in all rats when ERG responses had disappeared. Histopathology demonstrated degeneration of the sensory retina and abnormalities in the pigment epithelium cells. Pigmented rats also had reduced rhodopsin concentration in the retina by the 3rd month but photoreceptors were structurally normal. Plasma vitamin A levels were normal with liver vitamin A levels increasing. Liver and plasma ChE activities were markedly reduced after 3 months fenthion treatment. Decreases were 11% and 38% of the controls in plasma and liver respectively.

Driest M & Popp A (1997a) E1752 (fenthion) Acute oral neurotoxicity screening study in Wistar rats. Bayer AG, Toxicology, Wuppertal Study No. T 1059124 Report No. 26113, dated 20.3.97 [BA; sub: 11793, vol 5] GLP

Guidelines: US-EPA-FIFRA

The authors reported that a dose-ranging study had established that: for clinical signs, the time range for peak effect was 5h to 7h following dosing; these signs could persist for longer than 14 days; and 5 mg/kg bw was a NOEL for clinical signs in both sexes, but there was significant inhibition of plasma and RBC ChE at this dose, 6h after treatment. A dose of 1 mg/kg bw was expected to be a NOEL for ChE effects.

This study was designed to evaluate the acute neurotoxicity of fenthion when administered as a single dose via the oral route (gavage) to rats. In the main study, groups (12/sex/dose) of SPF-bred Wistar rats (Hsd Cpb:WU) were fasted overnight and then administered a single dose of fenthion (batch 230402031; purity 94.6%) in corn oil (5 mL/kg) at doses of 0, 1, 50 and 125 mg/kg bw (males) or 0, 1, 75, and 225 mg/kg bw (females). Four satellite groups (6/sex/dose) were treated at the same doses as the main groups; these animals were exclusively used for clinical pathology (ChE) investigations. The dosing was staggered over 4 days to accommodate the schedule for behavioural testing. All animals from the main study groups were used for neurobehavioural examination and then half were subjected to neuropathology.

Cage-side observations were conducted twice daily. Detailed physical examinations for clinical signs of toxicity were conducted once daily. Body weights were recorded weekly at the time of the behavioural testing. A comprehensive FOB was performed one week prior to dosing, 5h (minimum) after dosing and at 7 and 14 days after treatment. The FOB (Moser, 1989) was conducted blind and comprised home cage/handheld, open field and response observations, as follows:

> Home cage/hand held observations: posture; piloerection; gait abnormalities; involuntary motor movements, both clonic and tonic; vocalisation; stains (colour and location); reaction to handling; ease of removal; body tone; lacrimation; pupil size and response; salivation; palbebral closure; other signs.
> Open field observations: arousal; posture; piloerection; gait abnormalities; posture; vocalisation; stereotypy; involuntary motor movements, both clonic and tonic; numbers of rears; urine pools and faecal boli; other signs.
> Response observation (open field): approach response, touch response, auditory response, tail pinch response.
> Performance indicators: forelimb and hindlimb grip strength; landing foot splay; righting reflex; colonic body temperature; body weight.

Motor activity was measured by automated testing of individual animals for 70 minutes in one of ten figure eight mazes; this testing took place after the FOB. Motor activity was measured as the number of beam interruptions that occurred during a session, locomotor activity was measured by eliminating consecutive counts for a given beam and hence measuring only those events involving movement around the maze. Results were presented as counts for ten-minute intervals as well as total counts for the entire session (summary session). Habituation was evaluated as a decrement in activity during the session.

Clinical pathology testing was limited to measurement of plasma, RBC and brain ChE activity in all satellite group animals ca. 5.5h after treatment. A complete gross necropsy was conducted on all main group animals. In addition, 6 males and 6 females from each dose group were selected for perfusion and collection of tissues on day 15.

Tissues were processed for histopathology from the control and high-dose groups and all tissues with macroscopic findings from perfused and non-perfused animals. An extensive range of nervous tissues were processed for histopathology, and data were reported for: coronal sections of brain with brainstem; Gasserian ganglia; spinal cord (cervical, thoracic, lumbar); cervical and lumbar dorsal and ventral root fibres and ganglia. The proximal sciatic, sural and tibial nerves from the perfused control and high-dose animals were examined in cross sectional (sciatic) or longitudinal section.

Appropriate statistical analyses were performed on each dataset.

Results

The nominal doses of 0, 1, 50 and 125 mg/kg bw (males) or 0, 1, 75, and 225 mg/kg bw (females) were analytically confirmed as 0, 1.04, 49.05, and 125.6 mg/kg bw (males) and 0, 1.04, 74.8, and 222.3 mg/kg bw (females).

Clinical observations: Four females died within 72h of receiving 225 mg/kg bw. The table below shows that treatment- and dose-related clinical signs typical of acute cholinergic toxicity were evident in mid- and high-dose males and females, with onset generally by 7h post-dose. These signs persisted up to 5 days after treatment but then resolved. The NOEL for clinical observations is considered to be 1 mg/kg bw for both sexes.

Table 73: Group incidences of main clinical signs

Sign		Males			Females		
	Dose (mg/kg bw)	1	50	125	1	75	225
Piloerection	Number	-	-	5	-	2	6
	Duration	-	-	4	-	1	3
	Intensity	-	-	3	-	1	3
Decreased motility	Number	-	1	12	-	6	12
	Duration	-	1	4	-	1	3
	Intensity	-	1	3	-	2	3
Uncoordinated gait	Number	-	12	12	-	12	12
	Duration	-	1	5	-	1	3
	Intensity	-	3	3	-	2	3
Spastic gait	Number	-	8	12	-	11	12
	Duration	-	1	5	-	1	3
	Intensity	-	2	2	-	2	2
Palmospasm	Number	-	6	11	-	11	12
	Duration	-	1	<1	-	1	3
	Intensity	-	2	2	-	2	2
Temporary tremor	Number	-	-	9	-	8	10
	Duration	-	-	3	-	1	3
	Intensity	-	-	1	-	1	2
Labored breathing	Number	-	-	12	-	3	12
	Duration	-	-	3	-	1	3
	Intensity	-	-	2	-	1	3
Diarrhoea	Number	-	9	11	-	5	6
	Duration	-	1	1	-	1	2
	Intensity	-	-	-	-	-	-
Salivation clear	Number	-	-	5	-	-	5
	Duration	-	-	<1	-	-	1
	Intensity	-	-	3	-	-	1
Stains, oral, red	Number	-	4	9	-	1	3
	Duration	-	1	2	-	1	2
	Intensity	-	2	2	-	2	2
Decreased reactivity	Number	-	4	12	-	8	12
	Duration	-	1	5	-	1	3
	Intensity	-	1	3	-	2	3

- = no findings; Number = number of animals; Duration of sign in days; intensity (1 = weak, 3 = strong)

Bodyweights were unaffected by treatment at the low- and mid-doses in either sex. Compared to controls, statistically significant reductions in bodyweights were seen in high dose males (reduced 15% and 10% at days 7 and 14 respectively), while bodyweights in high dose females were reduced (5%) at day 7 only.

FOB: Historical control data were provided consisting of open field rearing incidence (control means for pretreatment and days 0, 7 and 14); grip strength and foot splay (% difference between highest and lowest pretreatment group means); motor activity and locomotor activity (control means for pretreatment and days 0, 7 and 14).

In this study findings were restricted to the day of treatment (day 0) in mid- and high-dose males and females. Findings included gait abnormalities, involuntary clonic motor movements, labored breathing, decreased activity in home cage and open field, flaccid muscle tone, autonomic signs, slightly impaired righting reflex, slightly increased touch response, decreased body temperature, decreased grip strength (see table and comments below), and decreased hind limb foot splay in high-dose males (-17%). The incidence and severity of these effects generally increased with dose, and males recorded slightly more effects than females. Persistent marginal hyperactivity (measured as rearing incidence and posture differences) persisted through to day 7 in both sexes and to day 14 in males. This is consistent with the long persistence of clinical signs seen in the range finding study. Fore- and hind limb grip strength was only slightly decreased at the high dose in both sexes on day 7. The NOEL for the FOB is considered to be 1 mg/kg bw for both sexes.

Table 74: Forelimb and hindlimb grip strength on Day 0 (% difference from control)

Dose group (mg/kg bw) Male/female	Forelimb grip strength		Hindlimb grip strength	
	Males	Females	Males	Females
1 / 1	+3	-2	+13*	-7
50 / 75	-30*	-20*	-22*	-16*
125 / 225	-81*	-42*	-71*	-29*

* statistically significant

Motor and locomotor activity: The summary session (70-minute) motor activity (MA) and locomotor activity (LMA) data are presented in the table below. The pretreatment values give some indication of the background variability that can be expected between the group measurements, and differences of less than 25% can be considered within the range of normal variability. For example, pretreatment MA measurements for the male dose groups were up to 23% less than controls, while values for the equivalent females varied from 2% less to 8% higher than controls. After treatment on day 0 both males and females from the mid- and high dose groups recorded significantly lower MA and LMA. Recovery was evident by day 7 when LMA and MA in the mid dose males but not the females had recovered to normal levels. The decreases in MA and LMA were persistent, and high dose males and females and mid dose females were still affected on day 14. Based on biologically significant deviations from control values, the NOEL for MA and LMA is considered to be 1 mg/kg bw for both sexes.

Table 75: Summary session MA and LMA (% difference from untreated controls)

Dose (mg/kg bw)	Day pre-treatment		Day 0		Day 7		Day 14	
	MA	LMA	MA	LMA	MA	LMA	MA	LMA
Males								
1	-1	+2	+12	+8	+3	+9	-11	-10
50	-23	-23	-62	-75	-16	-23	-25	-21
125	-20	-14	-76	-94	-34	-42	-33	-27
Females								

1	+8	-6	-15	-1	-5	+5	-12	-4
75	+8	-15	-41	-53	-26	-33	-26	-33
225	-2	+2	-64	-69	-27	-30	-29	-33

ChE activity: ChE activity measurements were limited to day 0 to the estimated time of peak effect for clinical signs at 5.5h after dosing. ChE activity was profoundly depressed in the plasma, RBC and brain compartments at the mid- and high doses in both sexes. Low dose females also recorded significant inhibition in all three compartments. The authors argue that the statistically significant 9% brain ChE inhibition seen in females is not biologically significant. Furthermore, they extrapolate a semi-log plot of the plasma and RBC values for females to arrive at a NOEL value of 0.7 mg/kg bw for 20% inhibition of either plasma or RBC ChE. There is a clear dose relationship for ChE inhibition in all three compartments in females. The lack of effect at the low dose in males may simply reflect more rapid metabolic activation of fenthion in females. While a NOEL of 1 mg/kg bw can be established for ChE inhibition in males, there is considered to be effects at 1 mg/kg bw in females and no NOEL can be determined. The absence of ChE measurements at the later assay times prevents any conclusions being drawn regarding recovery of enzyme activity.

Table 76: ChE inhibition (% inhibition compared to control at time of peak effect)

	Males			**Females**		
	Plasma	**RBC**	**Brain**	**Plasma**	**RBC**	**Brain**
Low	-10	-8	-4	-23	-22*	-9**
Mid	-90**	-89**	-80**	-95**	-89**	-76**
High	-90**	-92**	-86**	-96**	-90**	-81**

**** statistically different from control values (p<0.05); ** statistically different from control values (p<0.01)***

Pathology: The only treatment-related gross pathology finding was emaciation in the four high-dose females that died before terminal sacrifice. Terminal brain weights (absolute and relative) were unaffected by treatment. Terminal bodyweights were unaffected by treatment except for a slight decrease (7%) in high-dose males only.

Microscopic histopathology examinations were conducted on tissues from animals in the high dose and control groups. Examination was restricted to those tissues implicated in neurotoxicity and there were findings in only a few animals. These findings were regarded as spontaneous changes with no toxicological significance. The NOEL for histopathology findings is thus 125 mg/kg bw and 225 mg/kg bw for males and females respectively.

Driest M & Popp A (1997b) E1752 (fenthion) Subchronic neurotoxicity screening study in Wistar rats (Thirteen-week administration in the diet) Bayer AG, Toxicology, Wuppertal, Study No. T 4060125. Report No. 26392 [BA; sub: 11793, vol 6]

Guidelines: OECD GLP; US-EPA-FIFRA 82-5(b)

The authors reported that dose selection was based on NOELs recorded for ChE activity in previous studies, specifically: 5 ppm (males) and 3 ppm (females) in a 16-week dietary study; 3 ppm (both sexes) in the first three months of a chronic dietary study; 5 ppm (a LOEL) in the first three months of another chronic dietary study; and 2 ppm in a two-generation study (F0 and F1 parents). A dose of 2 ppm was chosen as the expected NOEL for ChE effects for this subchronic study.

This study was designed to evaluate the subchronic neurotoxicity of fenthion when administered in the diet to rats for 13 weeks. Groups (12/sex/dose) of SPF-bred Wistar rats (Hsd Cpb:WU) were fed diet containing 0, 2, 25 and 125 ppm fenthion (batch 230402031; 94.3%) for 13 weeks. Measured mean concentrations were 0, 2, 24 and 112 ppm. The achieved dose based on these dietary levels was calculated to be 0, 0.13, 1.63 and 8.50 mg/kg bw/d for males and 0, 0.17, 2.19 and 12.62 mg/kg bw/d for females.

All animals were used for neurobehavioural examination and then half were subjected to neuropathology and half to ChE determination. Cage-side observations were conducted twice daily. Detailed physical examinations for clinical signs of toxicity were conducted once daily. Body weights were recorded weekly at the time of the behavioural testing.

A comprehensive FOB was performed during the week prior to dosing and again during weeks 4, 8 and 13 of treatment. The FOB (Moser, 1989) was conducted blind and comprised home cage/handheld, open field and response observations, as follows:

> Home cage/hand held observations: posture; piloerection; gait abnormalities; involuntary motor movements, both clonic and tonic; vocalisation; stains (colour and location); reaction to handling; ease of removal; body tone; lacrimation; pupil size and response; salivation; palbebral closure; other signs.
>
> Open field observations: respiration; arousal; posture; piloerection; gait abnormalities; posture; vocalisation; stereotypy; involuntary motor movements, both clonic and tonic; numbers of rears; urine pools and faecal boli; other signs.
>
> Response observation (open field): approach response, touch response, auditory response, tail pinch response.
>
> Performance indicators: forelimb and hindlimb grip strength; landing foot splay; righting reflex; colonic body temperature; body weight.

Motor activity was measured by automated testing of individual animals for 70 minutes in one of eight figure eight mazes; this testing took place after the FOB. Motor activity was measured as the number of beam interruptions that occurred during a session, locomotor activity was measured by eliminating consecutive counts for a given beam and hence measuring only those events involving movement around the maze. Results were presented as counts for ten-minute intervals as well as total counts for the entire session (summary session). Habituation was evaluated as a decrement in activity during the session.

Ophthalmology studies of all animals consisted of pre-exposure and pre-terminal (week 13) examination of pupillary reflex, microscopic examination of the fundus and light-diffracting parts after mydriasis. The authors stated that corneal dystrophy was seen in almost all rats at both examination times and hence this condition was not recorded for individual animals.

Clinical pathology consisted of plasma and RBC ChE activity determinations during weeks 4 and 14 (orbital plexus blood sampling), whereas brain ChE activity was measured only at week 14. Gross necropsy data was recorded for all animals at termination.

After 13-weeks treatment, a whole body perfusion was performed on 6 animals/sex/group, but tissues were processed for histopathology from the control and high-dose groups only. An extensive range of nervous tissues were processed for histopathology including: brain with brainstem (8 sections); Gasserian ganglia; cervical, thoracic and lumbar spinal cord; cervical and lumbar dorsal and ventral root fibres and ganglia. The proximal sciatic, sural and tibial nerves from the perfused control and high-dose animals were examined in cross sectional (sciatic) and longitudinal (all) section.

Appropriate statistical analyses were applied to each data set.

Results

Dietary analysis indicated formulations were within 20% of target. Treatment reduced bodyweight gain in both sexes at the high dose despite higher food consumption in these groups. Body weights were significantly reduced in high-dose males throughout the study (8% lower cf controls at week 14); body weight reduction was significant but less severe in mid- and high dose females (respectively 6% and 4% lower cf controls at week 14). Treatment had no effect on food consumption in low- or mid dose males or females; however, total consumption in high-dose males and females was respectively around 6% and 20% higher than controls when expressed as gram per kilogram body weight. Thus, the high-dose animals appeared to try to compensate for treatment-related inhibition of body weight gain.

Table 77: Cumulative feed and test substance intake

Dose (ppm)	Sex	Days	Mean bw (week 14)		Feed intake	Fenthion intake	
			grams	g/kg bw total	g/kg bw per day	mg/kg bw total	mg/kg bw per day
0	M	91	412 ± 21	5846	64	0	0
2	M	91	434 ± 31	5769	63	11.5	0.13
25	M	91	407 ± 30	5947	65	148.7	1.63
125	M	91	378 ± 31	6188	68	773.5	8.50
0	F	91	220 ± 16	7654	84	0	0
2	F	91	217 ± 14	7790	86	15.6	0.17
25	F	91	206 ± 17	7954	87	198.9	2.19
125	F	91	211 ± 13	9191	101	1148.9	12.62

There were no treatment-related deaths. There was a low frequency of mild cholinergic signs in high dose males (uncoordinated and spastic gait, palmospasms, piloerection, decreased reactivity, diarrhoea) and these were slightly more common in females (spastic gait, palmospasm, tremors) (see table below). These signs became less frequent as the study progressed and only palmospasms were present throughout the study. The NOEL for clinical signs is considered to be 25 ppm in both sexes.

Table 78: Clinical signs (total no. of rats affected) recorded during the 13 week study

	Male				Female			
Dose (ppm)	**0**	**2**	**25**	**125**	**0**	**2**	**25**	**125**
Clinical sign								
Piloerection	-	-	-	1	-	-	-	-
Hair loss	-	-	-	1	1	2	1	-
Eye deposit	-	-	-		1	-	-	-
Decreased reactivity	-	-	-	1	-	-	-	-
Uncoordinated gait	-	-	-	1	-	-	-	-
Spastic gait	-	-	-	4	-	-	-	11
Palmus	-	-	-	12	-	-	-	12
Tremor	-	-	-		-	-	-	10
diarrhea	-	-	-	3	-	-	-	-

- = no signs present in any animals

Functional Observation Battery: Historical control data were provided consisting of: open field rearing incidence (control means for pretreatment and weeks 4, 8 and 13); grip strength and foot splay (% difference between highest and lowest pretreatment group means); motor activity and locomotor activity (control means for pretreatment and weeks 4, 8 and 13).

In this study, treatment- and dose-related effects clearly related to acute cholinergic toxicity were recorded at the week 4 and week 8 testing in mid- and high dose males and females. Findings included gait abnormalities, involuntary clonic motor movements, decreased activity in the open field, slightly impaired righting reflex and marginally decreased body temperature. These compound related effects were generally most evident during week 4 (males) or during weeks 4 and 8 (females). At week 13 the incidence of findings was decreased in both sexes indicating some adaption to the treatment as the rats matured.

Decreased grip strength (fore- and hind limb) and decreased hind limb foot splay were recorded in both sexes. Incidence and severity of these effects generally increased with dose, reaching statistically significant levels at the high dose only. Females recorded slightly more effects than males. The authors argued that the variability in the mean historical pretreatment data indicates that for males and females respectively, differences of less than 6% and 7% (forelimb grip strength), 9% and 7% (hind limb grip strength), and 10% and 9% (foot splay), can be considered to be within normal biological variability, and this is considered likely. It is possible that the decreased body weight seen at the high dose in males and females contributed to the decreased grip strength seen in these animals. It is noteworthy that the decrease in grip strength is more pronounced in the forelimbs, a result which contrasts with the axonopathy caused by agents such as acrylamide where hind limb grip strength is primarily affected. The severity of the effects did not increase with duration of exposure indicating that effects were not cumulative.

Table 79 : Forelimb and hind limb grip strength and foot splay (% difference from control)#

Dose (ppm)	**Pre-treatment**			**Week 4**			**Week 8**			**Week 13**		
	Grip strength		Foot splay	Grip strength		Foot splay	Grip strength		Foot splay	Grip strength		Foot splay
	front	hind		front	hind		front	hind		front	hind	
Males												
2	+4	+4	+1	+1	+8	-2	-3	-2	-1	-7	+1	-2
25	+1	+6	+3	-3	+5	+4	-9	-3	+6	-6	-2	+5
125	0	-6	-1	-26*	-14	-7	-23*	-16*	-8*	-21*	-13*	-1
Females												
2	+4	+4	+7	+3	-4	-5	+8	+3	+1	+5	-2	-4
25	-7	-4	+5	-6	-11	-9	0	-4	-6	-4	-2	-11
125	-1	-2	+13	-31*	-21*	-13	-37*	-22*	-12	-41*	-15*	-18*

percent greater (+) or less (-) than control; * statistically significant ($p<0.05$)

Motor and locomotor activity: The summary session (70-minute) motor activity (MA) and locomotor activity (LMA) data are presented in the table below. The pretreatment values give some indication of the background variability that can be expected between the group measurements, and differences of less than 25% can be considered to be within the range of normal variability. Additionally the authors presented comparisons of the summary session MA and LMA data of the present study with historical control data. This comparison indicates that male controls in this study recorded consistently low values when compared to historical values whereas female controls were unusually high mainly at week 13. On the basis of the inherent variability in these measures and unusual control group means recorded in this study, MA and LMA were considered affected in males at the high dose in weeks 4 and 8 only, and in high dose females in weeks 4, 8 and 13. The increased activities seen in low- and mid-dose males are biologically implausible and are related to the low control values. Examination of the data presented as 10 minute intervals rather than the 70 minute session revealed that habituation (recorded as decreased activity during the session) was not affected by treatment.

Table 80: Summary session MA and LMA (% difference from control)#

Dose (ppm)	Day pretreatment		Week 4		Week 8		Week 13	
	MA	LMA	MA	LMA	MA	LMA	MA	LMA
Males								
2	+20	+8	+12	+18	+15	+35	+31*	+41*
25	+12	-4	+19	+10	+20	+31	+27	+27
125	+6	+3	-13	-10	-19	-7	-4	+13
Females								
2	-4	+1	+1	-2	-9	-20	-10	-9
25	+2	+6	-18	-18	-17	-25	-26	-25
125	+13	+7	-18	-25	-21	-38	-38*	-46*

 # percent greater (+) or less (-) than control; * statistically significant (p<0.05)

ChE activity: fenthion treatment inhibited ChE activity (plasma, RBC and brain) in a dose-related manner in both sexes. Males in the 2 ppm group recorded statistically significant reductions in plasma ChE activity at 4 and 14 weeks; these reductions were not considered biologically significant because the group means for the 4 and 14 week samples (respectively -17% and -16% or 0.35 and 0.38 kU/L) lay within the 95% range for historical controls (0.31 - 0.64 kU/L). Similarly the RBC ChE activity recorded in males at 4 weeks (-27%, 0.79 kU/L) is neither statistically significant nor considered biologically significant, as it lies within the historical control range of 0.40-0.97 kU/L. The 21% reduction in plasma ChE seen in females from the 2 ppm group at the 4 week sample is not considered of biological significance; the group mean of 1.13 kU/L lies within the 95% range of the historical control (1.09-2.25 kU/L).

The 78% reduction seen in RBC ChE in the 25 ppm females at 4 weeks is considered biologically significant; the group mean of 0.21 kU/L lies outside the 95% range of the historical control. Overall the ChE inhibition was slightly more pronounced in females, but was no more severe at 14 weeks compared to 4 weeks. There did not appear to be metabolic adaption to continued dosing with fenthion in this study. The NOEL for ChE activity inhibition is considered to be 2 ppm in both sexes.

Table 81: ChE inhibition (% inhibition compared to control at time of peak effect)

Dose (ppm)	Males			Females		
	Plasma	RBC	Brain	Plasma	RBC	Brain
Week 4						
2	-17*[a]	-27[a]	ND	-21[a]	-16	ND
25	-57**	-57*	ND	-81**	-78[b]	ND
125	-83**	-96**	ND	-94**	-97*	ND
Week 14						
2	-16*[a]	+15	-3	-17	+8	-4
25	-56**	-65*	-48**	-86**	-78**	-58**
125	-80**	-96**	-83**	-95**	-97**	-85**

* statistically different from control values (p<0.05); ** statistically different from control values (p<0.01)

[a] not considered biologically significant; [b] considered biologically significant

Pathology: Gross pathology of the non-perfused and the perfused animals (including the nervous system) did not record any significant findings. Histopathology did not record any treatment-related findings; degenerated nerve fibres were recorded in both control and high-dose animals of both sexes. Ophthalmology did not record any treatment-related findings.

Table 82: Histopathology findings in 6 perfused/fixed rats from the control and high-dose groups

Preparation	Abnormality	Male		Female	
		control	125 ppm	control	125 ppm
Sciatic nerve, left	Degenerated nerve fibres	-	1/6	-	-
Tibial nerves	Vacuolated Schwann cell	-	1/6	-	1/6
	Degenerated nerve fibres	-	1/6	1/6	
Sural nerves	Vacuolated Schwann cell	-	1/6	-	-
	Degenerated nerve fibres	1/6	1/6	1/6	-
Spinal cord, cervical	Degenerated nerve fibres	1/6	2/6	-	-
Spinal cord, thoracic	Degenerated nerve fibres	2/6	2/6	1/6	1/6
Spinal cord, lumbar	Degenerated nerve fibres	-	-	1/6	-
Spinal ganglia, lumbar	Degenerated nerve fibres	-	-	1/6	1/6

- No findings in any animals

Mean absolute and relative brain weights (see table below) show variations which reflect the differences in body weight between the groups and do not display a dose response relationship.

Table 83: Mean absolute and relative terminal brain weights for perfused animals (6/group)

Dose (ppm)	Males			Females		
	Body weight (g)	Brain weight (mg)	Relative brain weight (mg/100g)	Body weight (g)	Brain weight (mg)	Relative brain weight (mg/100g)
0	416	1857	447	226	1619	723
2	451	1910	424	220	1689	768
25	419	1849	442	205	1668	817
125	392	1862	477	218	1722	790

In conclusion, there were clear cholinergic effects seen in treated animals, especially at the high dose. Treatment-related effects appearing at the mid-dose were: a reduction in female bodyweight; the occurrence of cholinergic clinical signs in both sexes; and significant inhibition of ChE activity in all three compartments. At the high-dose additional treatment-related effects were recorded for motor activity (decreased), locomotor activity (decreased), grip strength (decreased) and foot splay (decreased). There were no treatment effects recorded for gross or micro-pathology. There were no treatment-related effects seen at the 2 ppm dose level and this can be considered as the overall NOEL for this study.

Dogs

Tuler SM, Febles D & Bowen JM (1988) Neuromuscular effects of chronic exposure to fenthion in dogs and predictive value of electromyography. Fundam Appl Toxicol 11: 155-168.

A group of 7 female dogs (random-source) received a weekly dermal application of 44 mg/kg bw fenthion (20% w/v formulation, 4 cm^2 spot under the hair) for 10 weeks. The dosage was decreased to 22 mg/kg bw for an additional 13 treatments. Electromyograms (EMG) were used to monitor motor unit potential (MUP) activity in 4 different muscles. Fenthion at 44 mg/kg bw produced no acute toxic signs, although plasma ChE activity was reduced to 22% of control at 1 month. At 3 months clinical signs included ataxia, muscle fasciculations, proprioceptive deficits, hyper-reflexia (myotatic reflex) and paralysis (the latter in one dog). After reducing the fenthion dose to 22 mg/kg bw there was partial recovery of neuromuscular function at the end of the study. Significant EMG changes were seen in all muscles during the study, beginning as early as 1 month. Analysis of individual MUPS revealed a general increase in all parameters, due to an increase in the number of large (high amplitude, long duration) potentials, most likely reflecting a loss of smaller motor units. The EMG changes were most consistent in the gastrocnemius muscle and were detected prior to development of clinical signs.

Light microscopic analysis of biopsied muscles showed an increase in the number of degenerating and necrotic muscle fibres during the study. Ultrastructural analysis of the distal sciatic nerve showed evidence of nerve fibre degeneration and regeneration and half of the dogs had new myelin growth. Variable diameter axons and accumulation of mitochondria, particularly in the unmyelinated sensory nerves, was evident in treated dogs compared to controls. Brain neurotoxic esterase activity was inhibited 52% at 6 months in fenthion-treated dogs. Brain dopamine was significantly decreased and cerebrospinal fluid levels of noradrenaline were increased. Haematological analysis revealed a decrease in neutrophils and an increase in lymphocytes in fenthion-treated dogs.

In summary, prolonged weekly dermal application of fenthion to dogs resulted in progressive muscle fibre necrosis, ultrastructural changes in nerve axons and alterations in some CNS neurotransmitters. There was no evidence of changes typically associated with delayed neurotoxicity (flaccid paralysis or dying-back neuropathy). The changes seen were consistent with sensory nerve fibre damage and destruction of small motor units and were partly reversible.

Dellinger & Mostrom M (1988) Effects of topical fenthion on blood ChE and vagal tone in dogs. Vet Hum Toxicol Jun;30(3):229-34

Male dogs (mixed breeds, 5/group) were treated dermally (backline) with fenthion (20% formulation) at 8 mg/kg bw (2 treatments at 14-day intervals), and 33 mg/kg bw (4 treatments at 7-day intervals). Controls were treated with vehicle only (4 treatments at 7-day intervals). The dogs were observed for 2-weeks after dosing finished.

There were no clinical signs. Plasma ChE was significantly inhibited with maximum inhibition to 52% and 24% of pre-dose activity occurring 4 days after the final fenthion treatment of 8 and 33 mg/kg bw, respectively. RBC ChE activity was unaffected at 8 mg/kg bw but showed a downward trend to 32% of normal activity measured 9 days following the last treatment of fenthion at 33 mg/kg bw. Vagal tone was monitored via analysis of ECG recordings made throughout the study. There was no effect on vagal tone during the period of fenthion treatment. All dogs were challenged with atropine sulfate (0.02 mg/kg, sc) on the last day of the observation period, and the fenthion-treated dogs gave a slightly smaller response to the challenge (which induces a vagal block) compared to controls. The authors suggest that in the dog, the responses to subchronic fenthion exposure included a tolerance mechanism involving down-regulation of the muscarinic cholinergic receptors or their affinity.

9.3.11 Human Studies

9.3.11.1 Toxicity studies

Coulston F, Griffin T & Rosenblum I (1979) Safety evaluation of fenthion in human volunteers. Institute of Comparative and Human Toxicology, Albany, New York, USA and International Center of Environmental Safety, Holloman AFB, New Mexico, USA, June 1979 [BA; sub: 734, A3162, Box 104, Vol 8, attachment 2-55]

Dose selection in this study was based on interim results from a 12-month study in Rhesus monkeys which were treated with doses of 0, 0.02, 0.07 and 0.20 mg/kg bw/d. Twelve human adult male volunteers (4/group) were given fenthion (98.1% in corn oil) in capsules at doses of 0, 0.02 or 0.07 mg/kg bw/d for approximately 4 weeks. While all groups were given capsules daily for 6 weeks, treatment with fenthion was commenced at different times in the groups; the 0.02 mg/kg bw/d group commenced treatment on day 1 of the study, 14 days prior to the 0.07 mg/kg bw/d group who were dosed from days 15–40. This procedure was stated to allow an evaluation of the effects in the volunteers before initiating the higher-dose treatment. It is unclear whether the 0.07 mg/kg bw/d group received 25 or 26 doses.

Clinical observations (including self-reported symptoms) and laboratory tests (serum chemistry, haematology, urinalysis) were stated to have been performed twice prior to commencement of treatment and weekly thereafter. Routine clinical biochemical, haematological, and urine parameters were determined from the collected blood and urine.

- Clinical signs and symptoms: body weight, temperature, pulse rate, blood pressure; sweating, runny nose, tearing, light-headiness, dizziness, tight chest, abdominal cramps, chest pain, coughing mucous, cold, diarrhoea, headache, nervousness, ringing in ears, plugged sinuses.
- Haematology parameters: RBC count, Hct, Hb, leucocyte differential count, leucocyte total count.
- Clinical chemistry parameters: AP, SGPT, SGOT, bilirubin, cholesterol total protein, BUN, calcium, creatinine, glucose, LDH, phosphorus, potassium, sodium, uric acid.
- Urinalysis parameters: appearance, specific gravity, glucose, ketones, sediment (microscopic), occult blood, pH, protein, volume, bilirubin, urobilinogen.

Plasma and RBC ChE activities were determined on four non-consecutive days prior to treatment, 24h after the first dose and then twice weekly 24h after the previous dose. The authors discussed the results of detailed statistical analyses of the ChE results but only a portion of the full analysis was available.

Results

Dosing and sampling: Three different volunteers of four in the 0.02 mg/kg bw/d group missed the 7th, 14th and 28th dose respectively. One volunteer from the 0.07 mg/kg bw/d group missed the 21st dose. Another volunteer from the 0.07 mg/kg bw/d group was withdrawn from the study after 12 doses due to diagnosis of "middle ear infection". On a few occasions volunteers did not present for medical examination nor provide blood or urine samples; these instances were represented by blanks in the data tables. The authors state that these omissions were considered to have little significance.

Clinical observations: The results indicate that clinical examination was performed on days 4, 11, 22, 25, 32, 39, 43 and 46 of the study. There were no clinical signs attributable to treatment at any time possibly because so few parameters were investigated. On day 4 of the study (after 3 doses) none of the 0.02 mg/kg bw/d group reported any symptoms. However on day 11 (after 10 doses) two individuals reported "runny nose" and tearing but these symptoms were attributed to an URTI and an allergy respectively. These symptoms were described as a "cold" in both individuals on day 22, and this "cold" persisted through to day 25 in one individual.

In the 0.07 mg/kg bw/d group two individuals reported symptoms of "runny nose" before treatment commenced. These symptoms rapidly resolved in one individual but persisted as a "runny nose" or "cold" in the other. Another subject from the 0.07 mg/kg bw/d group reported tight chest, chest pain, and headache before his 8th dose, and sweating, headache and nervousness before his 11th dose; this subject was withdrawn from the study after 12 doses due to the aforementioned middle ear infection. On day 39 of the study, only one of the three remaining high dose individuals was examined for clinical signs or recording of symptoms.

While these inconsistent symptoms of "runny nose" and "cold" are not strongly indicative of cholinergic effects, they cannot be completely discounted in such small groups. Additionally the symptoms reported by the subject who was withdrawn from the 0.07 mg/kg bw/d group after 12 doses are consistent with a cholinergic response and the interpretation that they are sequelae of a middle ear infection is difficult to accept without reservation. The collection of symptoms 24 h after dosing is inappropriate as the peak time of action is expected to be 5-7h after dosing. Thus while the data are equivocal, it is possible that there were clinically significant cholinergic symptoms recorded at the high dose of 0.07 mg/kg bw/d.

Table 84: Dosing Regimen

Dose mg/kg bw/d	Subject Codes	Total Doses	Day of study						
			1 - 7	8 - 14	15 - 21	22 - 28	29 - 35	36 - 40	41 - 54
0	C, D, I, L	0	P	P	P	P	P	P	P
0.02	A, E, H, K	28	0.02[1]	0.02	0.02	0.02	P	P	P
0.07	B*, F, G, J	25	P	P	0.07	0.07	0.07	0.07	P

* received only 12 doses (last dose d 26); P = vehicle only; [1] shading indicates in-treatment phase

Table 85: Symptoms reported by subjects

Dose mg/kg bw/d	Subject Code	Day of examination and symptom report							
		Day 4	**Day 11**	**Day 22**	**Day 25**	**Day 32**	**Day 39**	**Day 43**	**Day 46**
0	**C**	A	B	I	Miss	None	Miss	None	None

0	**D**	None	C	None	None	None	J; *1*	None	None
0	**I**	None	D	Miss	None	None	None	None	None
0	**L**	None	None	B	B; K	M	B	None	B
0.02	**A**	None	None	None	None	B; N; E; *2*	None	None	None
0.02	**E**	None	B; C; K; G; F; *3*	J	J	Miss	None	None	B
0.02	**H**	None	B; C; *4*	F; I; J	None	None	L	None	None
0.02	**K**	None	None	None	None	None	L	None	Miss
0.07	**B***	None	None	F; H; L	L; A; M	K; *5*	None	E	L
0.07	**F**	None	B; *6*	K; *7*	None	**None**	**Miss**	None	J
0.07	**G**	None	B	J	B	**None**	**B**	None	None
0.07	**J**	None	None	None	None	**None**	**Miss**	None	O

shading indicates in-treatment phase

Codes for symptoms and notes

A = sweating	F = tight chest	K = diarrhoea
B = running nose	G = abdominal cramps	L = headache
C = tearing	H = chest pain	M = Nervousness
D = light-headedness	I = coughing mucous	O = plugged sinuses
E = dizziness	J = cold	
None = no symptoms	Miss = no examination	

1 Subject felt related to "springtime"	***2*** Ears contained wax plug
3 Related to URTI and reported stomach upset before study commencement	
4 Reported related to allergy	***5*** In family
6 When visiting "mountains"	***7*** Food related

Clinical pathology: No significant treatment-related alteration were seen in any of the haematological, clinical biochemistry or urinalysis parameters.

ChE activity

No significant depression in RBC ChE was seen at either dose. In general, plasma ChE activity was significantly depressed in those treated with 0.07 mg/kg bw/d, and these levels were slow to recover. Plasma ChE activity was less depressed in those treated with 0.02 mg/kg bw/d. The authors presented the results of detailed statistical analysis of the plasma and RBC ChE data. These tests indicated that RBC ChE was not statistically significantly different from controls at either dose level, but plasma ChE activity was statistically significantly inhibited at both dose levels when compared to controls. Further detailed analysis reported that plasma ChE activity in the subjects receiving 0.02 mg/kg bw/d was not significantly decreased compared to their own baseline values during treatment and recovery, but was significantly decreased when compared to control values on 3 of 9 occasions during the treatment period and 4 of 7 occasions during the 25 d recovery period. Plasma ChE activity at 0.07 mg/kg bw/d was significantly inhibited at all times during the treatment phase and most occasions during the recovery period of one week. Additionally there was a significant difference between the low and high dose mean plasma ChE activity during treatment, indicating a dose response relationship.

Table 86: Mean plasma ChE activity in volunteers as a percentage *of baseline values*

Volunteer	Controls[1]			Dose 0.02 mg/kg bw/d		
	Baseline IU/mL	During[2] treatment	During[2] recovery	*Baseline IU/mL*	During treatment	During recovery
1	*4.24*	97%	101%	*3.78*	94%	97%
2	*3.33*	108%	115%	*3.29*	90%	95%
3	*3.59*	101%	106%	*3.84*	93%	98%
4	*4.20*	95%	97%	*3.05*	95%	102%
Group Mean	***3.84***	**100%**	**105%**	***3.60***	**93%**	**98%**
Volunteer	**Controls**			**Dose 0.07 mg/kg bw/d**		
	Baseline IU/mL	During treatment	During recovery	*Baseline IU/mL*	During treatment	During recovery
1	*4.24*	95%	107%	*3.92*	84%	99%
2	*3.33*	116%	118%	*4.02*	72%	82%
3	*3.59*	104%	108%	*2.73*	61%	82%
4	*4.20*	94%	104%	*2.99*	74%	92%
Group Mean	***3.84***	**103%**	**109%**	***3.42***	**73%**	**89%**

Baseline values for all groups are the mean of at least three pretreatment measures; [1] Values for controls are for the same sample days as the paired dose-group; [2] During treatment and during recovery values are the mean activity for each individual during that phase expressed as a percentage of their own mean baseline value

Table 87: Mean plasma ChE activity in volunteers during treatment (% of control values)

Volunteer	Plasma ChE activity (*IU/mL*)			
	Controls[1]	**0.02 mg/kg bw/d**	**Controls**	**0.07 mg/kg bw/d**
1	4.13	3.56	4.05	3.30
2	3.16	2.96	3.71	2.88
3	3.62	3.56	3.73	1.66
4	4.00	2.91	3.96	2.21
Group Mean (% of control)	**3.73**	**3.25 (87%)**	**3.86**	**2.51 (65%)**

[1] Values for controls are for the same sample days as the paired dose-group

This 1979 study was considered to have serious flaws. Only male subjects were enrolled. Despite the possibility of cholinergic signs being induced by treatment, the physical examination of the subjects was cursory at best and occurred 24h after dosing. Insufficient information is provided to enable independent assessment of the significance of the withdrawal of one high dose subject from the study prematurely. The symptoms reported by the subjects and the occasional exculpatory note are insufficiently detailed to allow independent assessment of their significance.

The NOEL for RBC ChE inhibition was 0.07 mg/kg bw/d. No NOEL was established for the inhibition of plasma ChE activity based on reduction seen during the treatment period at the low dose level of 0.02 mg/kg bw/d. While the mean reduction in plasma ChE activity at this dose was only 13%, it persisted into the recovery period and was statistically significant. Additionally this value was obtained on samples taken 24 h after the previous dose when the time of peak effect is 4-6 h. The dose of 0.02 mg/kg bw/d may be considered a LOEL for inhibition of plasma ChE in humans.

9.3.11.2 Occupational Exposure Reports

Wolfe HR, Armstrong JF & Durham WF (1974) Exposure of mosquito control workers to fenthion. Mosquito News 34: 263-267

Values for potential dermal and respiratory exposure were determined for workers applying fenthion for mosquito control. Application was by hand gun power spray equipment, back-pack hand pressure sprayer and hand granular dispersal. Mean dermal and respiratory exposure values during operation of power sprayers were 3.6 and <0.016 mg/hr of work, respectively, and for hand pressure sprayer operators the values were 3.6 and <0.021 mg/hr, respectively. Mean dermal and respiratory exposure values for hand granular dispersal were 12.3 and 0.088 mg/hr of work. Thus potential dermal exposure was much greater than potential respiratory exposure and exposure was greatest during hand granular dispersal. Highest total dermal respiratory exposure for any individual was only 0.03% of a toxic dose per hour of work activity. Tests to determine hazard from cigarette smoking during fenthion application indicated greater contamination of cigarettes because of contact with unwashed hands following hand granular application than following spray application. There were no significant changes in RBC ChE activity, but plasma ChE activity was significantly decreased in some workers. There were no toxic signs in any of the workers.

Taylor A (1963) Observations on human exposure to the organophosphorus insecticide fenthion in Nigeria. Bull World Health Org 29: 213-218.

Inhabitants of 2 Nigerian villages were studied during a trial of fenthion used as a residual spray in malaria eradication. In one village spraying was performed with a 40% suspension of fenthion at a rate of 1.5 g/m^2 on one occasion only, while the other village served as a control. There was a significant reduction in plasma ChE activity in almost all inhabitants of the fenthion sprayed village one week after spraying, with a further smaller reduction 4 weeks later. Mean reductions of plasma ChE activities in relation to age were 39.9, 16.5, 16.3 and 23.8% in age groups <7, 7-14, 15-30 and >30 years, respectively. RBC ChE activity was not altered after fenthion spraying. There were no toxic signs of organophosphate poisoning. In an attempt to determine possible clinical effects of fenthion on bronchoconstriction, peak expiratory flow rate (PEF) measurements were made. There was a significant mean reduction in PEF one week after spraying. There was no correlation between the degree of plasma ChE inhibition and changes in PEF.

9.3.11.3 Case Reports

von Clarmann M & Geldmacher von Mallinckrodt M (1966) On the successful treatment of acute oral poisoning with fenthion and its detection in the stomach contents and urine. Arch Toxikol 22: 2-11

This report described the case of a young man attempting suicide by drinking Lebaycid and brandy. Toxic signs on admission to hospital included excess sweating, tremors and miosis. Antidote treatment included intravenous atropine and toxogonin. Serum ChE activity was almost zero before therapy began. TLC and spectrographic evidence demonstrated fenthion in the gastric contents and the aromatic hydrolysis product of fenthion, 3-methyl-4-methyl mercaptophenol, in urine.

Dean G, Coxon J & Brereton D (1967) Poisoning by an organophosphorus compound: A case report. S Afr Med J 41: 1017-1019

This report described the case of a young man attempting suicide by drinking Lebaycid. Very early toxic signs (within a few minutes) included blurred vision, unsteady walking, slurred speech and vomiting. After admission to hospital casualty, his stomach contents were pumped out to reduce absorption of the poison. Antidote treatments given regularly throughout the hospitalisation included atropine sulphate and 2-PAM. After 24 hours toxic signs included vomiting, diarrhoea and miosis. Due to respiratory difficulty resulting from paralysis of respiratory muscles, the patient was artificially ventilated at 72 hours and toxic signs at that time included sweating, salivation, miosis, fasciculation of facial muscles, violent movements of the limbs and high blood pressure. Serum electrolytes were normal except for hypokalaemia following severe diarrhoea, which was corrected by intravenous potassium. A chest infection developed on the fifth day. Toxogonin (1.5 g) was given intravenously on the third day of artificial ventilation. Spontaneous respiratory muscle activity and pupillary mydriasis returned after 7 days. Serum ChE activity was zero on day 5 and had recovered to normal levels 5 weeks later. It would appear that treatment with atropine sulphate enabled control of muscarinic effects of fenthion poisoning, but the nicotinic effect on respiratory muscles required artificial ventilation for some days before ChE reactivators became effective.

Wadia RS, Bhirud RH, Gulavani AV & Amin, RB (1977) Neurological manifestations of three organophosphate poisons. Indian J Med Res 66, 460-468

A prospective study was carried out on 150 cases of anti-ChE insecticide poisoning to observe clinical signs and prognosis. Of the 150 cases, 32 had consumed fenthion, 48 sumithion, 50 malathion and 20 either carbamates or unknown compounds.

Clinical signs which occurred after fenthion ingestion included miosis, fasciculations, toxic delirium, paralytic signs, bradycardia and occasionally impaired consciousness and convulsions. Paralytic signs occurring in 81% of fenthion-poisoned cases included neck weakness, inability to sit up with arms folded, slow or restricted eye movement, facial weakness, respiratory paralysis, limb weakness, areflexia, opthalmoplegia, swallowing problems and bilateral pyramidal signs. The mean time between ingestion to paralysis was 24 hours (range 4-72 hours) and the mean recovery time in survivors was 132 hours (range 24-456 hours in 15 cases). Occurrence and severity of late paralysis was not correlated with severity of early muscarinic signs such as vomiting, diarrhoea, sweating and diarrhoea. Toxicity of fenthion was not affected by early or late admission to hospital (treatment included repeated high doses of atropine, but no treatment with 2-PAM or other oximes, due to unavailability). Death occurred in 31% of fenthion-poisoned patients. In 18 of 27 cases serum ChE activity was essentially zero (or below the lowest measurable level, which was not stated; normal level 130-250 units). Depression of serum ChE was sometimes long-lasting, with two severe cases showing levels of essentially zero for 17 and 32 days, respectively.

Comparison of fenthion, sumithion and malathion poisoning showed that paralytic signs were more frequent with fenthion than with sumithion or malathion (81, 30 and 23% of cases, respectively) and that the signs occurred later with fenthion and lasted longer. Death occurred significantly more often with fenthion (mortality rates were 36, 2 and 4% for fenthion, sumithion and malathion, respectively). These differences were observed even when cases consuming equal doses were compared. Depression of serum ChE activity was most marked with fenthion.

Merrill DG, Mihm FG (1982) Prolonged toxicity of organophosphate poisoning. Crit Care Med 10(8):550-1

A case of poisoning of a 39 y old female with fenthion was reported in which the initial cholinergic crisis was delayed 5 days and recurred 24 days after ingestion. The patient had also ingested diazepam, coperamide and wine in a suicide attempt. Fenthion (ca. 0.16 ppm) was detected in a fat biopsy on day 23 but none was detected on day 31 after ingestion. The authors describe periods of psychosis in the patient as a persistent and "sometimes singular" manifestation of the intoxication.

Mahieu P, Hassoun A, Van Binst R, Lauwerys R & Deheneffe Y (1982) Severe and prolonged poisoning by fenthion. Significance of the determination of the anticholinetserase capacity of plasma. J Toxicol Clin Toxicol 1982 Jul 19(5):425-32

A case report of prolonged symptomatology due to ingestion of fenthion in a 43 yr old male, was presented. Intense cholinergic manifestations with convulsive crises were apparent at various times through the first 18 days of hospitalisation.

Bryant DH (1985) Asthma due to insecticide sensitivity Aust N Z J Med 15(1):66-8

This paper presents case reports of two patients in whom asthma was precipitated by exposure to fenthion (a 3% dust formulation) in one case and fenthion in the other. Investigation showed no evidence of systemic poisoning or ChE inhibition and indicated that the asthmatic reactions may have been due to a sensitivity response. The fenthion-exposed patient was a histamine-reactive asthmatic. In a bronchial provocation test where the patient inhaled ca. 0.12 mg of fenthion over 6 min, there was a delayed response of 2 h before asthmatic symptoms commenced and a maximal response at 6 h after exposure. Two asthmatic volunteers, with similar histamine reactivity to the patient, showed no response after an identical challenge with fenthion. The mechanism of this response is unknown but it was inhibited by corticosteroids in the patient exposed to fenthion.

Misra UK, Nag D, Misra, NK, Mehra MK & Ray PK (1985) Some Observations on the Macula of Pesticide Workers. Hum Toxicol 4: 135-45

Retinal changes in 79 subjects occupationally exposed to fenthion were studied. Fifteen workers (19%) had macular changes characterised by perifoveal irregularity of pigmentation and areas of hypopigmentation. Fluorescein angiography suggested pigment epithelium defects.

De Wilde V, Vogelaers D, Colardyn F, Vanderstraeten G, Van den Neucker K, De Bleecker J, De Reuck J & Van den Heede M (1991) Postsynaptic neuromuscular dysfunction in organophosphate induced intermediate syndrome. Klin Wochenschr 1991 Feb 26;69(4):177-83

A 65 y old female developed an intermediate syndrome (IMS) seven days after an acute cholinergic crisis, caused by the ingestion of fenthion. The patient's initial cholinergic crisis had resolved within 24 h of admission, but the patient underwent a recurrence of the cholinergic crisis 43 h after admission. ChE activity in the blood, plasma, and red cells underwent a cyclical decline and recovery, the activity peaking at days 4 and 9 still well below the normal range. By day 21 ChE activities were still below the normal range but evidently recovering. Fenthion levels in serum showed a slow decline measuring 27, 4.8, 1.75, 0.2 ng/mL on days 1, 3, 5 and 9 respectively. Electromyographic studies of the patient during the course of treatment showed various abnormalities (fibrillation at rest; reduced response (fade) to tetanic stimulation by surface electrodes) which slowly disappeared as the patient recovered. Limited nerve and muscle biopsies did not reveal gross abnormalities. The authors suggest that changes in the postsynaptic structures by a desensitisation process similar to those seen in myasthenia gravis may be contributing to the development of an IMS.

De Bleecker J, Van den Neucker K, Colardyn F (1993) Intermediate syndrome in organophosphorus poisoning: a prospective study. Crit Care Med 21(11):1706-11

A study of the prevalence of an intermediate syndrome (IMS) was conducted in a series of 19 patients hospitalised for OP poisoning; most patients had ingested the OP in a suicide attempt. An intermediate syndrome developed in 8 patients including one (65-y old female) who had ingested fenthion. Prolonged and severe ChE inhibition occurred during the intermediate syndrome in all patients. As the intermediate syndrome evolved, repetitive nerve stimulation initially demonstrated decrement, then increment, and finally, normal responses. Cholinergic symptoms appeared only gradually (several hours after ingestion) in the patient who had taken fenthion, but the patient progressed to severe poisoning, coma and a prolonged intermediate syndrome. In this patient, fenthion was detected in the blood until 9 days after ingestion. The IMS was present for 15 d and the patient was recovered by d 20. The authors concluded that: the IMS coincides with prolonged ChE inhibition, and is not due to muscle fibre necrosis; the clinical and electromyographic features are best explained by combined pre- and post-synaptic dysfunction of neuromuscular transmission; and that the IMS is not related to an incipient delayed neuropathy.

9.4 References

[Figures in square brackets are an Australian identification code and indicate the location of the submitted data.]

Avrahami M & White DA (1975) Residues in milk of cows after spot-treatment with 32P-fenthion. New Zealand Exp Agric **3:**309-311.

Bai CL, Qiao C, Zhang W, Chen Y & Qu S (1990) A study of the pesticide fenthion: Toxicity, mutagenicity and influence on tissue enzymes. Biomed Environ Sci **3:**262-275.

Bailey DE (1987) 21-day dermal toxicity study in rabbits with Baytex technical Hazelton Laboratories Report 938, HLA study No. 339-118, GLP, EPA 82-2. [BA; sub 11009, Vol 1]

Bailey DE (1988) 21-day dermal toxicity study in rabbits with Baytex technical (Addendum to 938) Hazelton Laboratories Report 1031, HLA study No. 339-118, GLP, EPA 82-2 [BA; sub 11009, Vol 1]

Bayer Ag (1960) Active substance S1752. Toxicological and Industrial Hygiene Laboratory, Bayer Ag. Unpublished. [BA; sub: 734, A3162, Box 104, Vol 1]

Bayer Ag (1967) LEBAYCID a.i / solvent dependence of the acute oral toxicity in rats. Farbenfabriken Bayer Ag, Institute of Technology, Wuppertal-Elberfeld. Unpublished. [BA; sub: 734, A3162, Box 104, Vol 1, Attachment 2-1]

Begum A (1967) Effect of diet on metabolism of fenthion in animals (Doctoral Thesis, Auburn university, Al, USA) Unpublished. [BA; sub: 734, A3162, Box 104, Vol 1, attachment 4-3]

Bomann W (1991) E 1752 (c.n.: fenthion) study for acute dermal toxicity in the rat. Bayer AG, Institut für Toxikologie, Wuppertal, Germany. Report No. 20221, 10 May 1991. Unpublished [BA; sub: 11009, A3162, Box 22, Vol 2]

Boyes WK, Tandon P, Barone S Jr & Padilla S (1994) Effects of organophosphates on the visual system of rats. J. Appl. Toxicol. **14**:135-143

Brady UE Jr & Arthur BW (1961) Metabolism of O,O-dimethyl-O-[4-(methylthio)-m-tolyl] phosphorothioate by white rats. J Econ Entomol **54:**1232-1236

Bryant DH (1985) Asthma due to insecticide sensitivity Aust N Z J Med **15**(1):66-8

Chen HH, Sirianni SR & Huang CC (1982a) Sister chromatid exchanges in Chinese hamster cells treated with seventeen organophosphorus compounds in the presence of a metabolic activation system. Environ Mutag **4:**621-624. [BA; sub: 11793, Vol 17]

Chen HH, Sirianni SR & Huang CC (1982b) Sister-chromatid exchanges and cell-cycle delay in Chinese hamster V79 cells treated with 9 organophosphorus compounds (8 pesticides and 1 defoliant). Mut Res **103:**307-313. [BA; sub: 11793, Vol 17]

Christenson WR (1990a) Combined chronic toxicity/oncogenicity study of technical grade fenthion (Baytex) with rats, Mobay Study No.87-271-01 USEPA 83-5, GLP. [BA; sub: 11009 Vol 3-5]

Christenson WR (1990b) Chronic feeding toxicity study of fenthion technical (Baytex) with dogs. Mobay Report 5272, Study No. 87-274-01, [BA; sub:11009, Vol 9; sub: 11793,Vol 2] USEPA 83-1, OECD 452, GLP

Christenson WR (1990c) Technical grade fenthion (Baytex): A special study to examine the effect of the route of acute administration of technical grade fenthion (Baytex) on ChE activity in the rat. Study no. 89-992-DJ. Mobay Corporation, Kansa, USA. [BA sub: 11793,Vol 2] Report No. 5360. GLP.

Christenson WR (1993a) Chronic feeding toxicity study of fenthion technical (Baytex) with dogs (Supplemental submission to report 5272 of 31.7.90), Mobay Report 5272A. [BA; sub: 11009, Vol 9; sub: 11793, Vol 2]

Christenson WR (1993b) Combined chronic toxicity/oncogenicity study of fenthion technical (Baytex) with rats. Supplemental report to Study 87-271-01, Miles Study 87-271-01 (Addendum), GLP. [BA; sub: 11009 Vol 6-8]

Clemens GR, Bare JJ & Hartnagel Jr. RE (1987) A teratology study in the rabbit with fenthion (Baytex technical) G R Clemens et al 7.12.87, Miles Report 970, Study # MTD0039. GLP [BA; sub: 11009, A3162, Box 22, Vol 15]

Coulston F, Griffin T & Rosenblum I (1979) Safety evaluation of fenthion in human volunteers. Institute of Comparative and Human Toxicology, Albany, New Year, USA and International Center of Environmental Safety, Holloman AFB, New Mexico, USA. June 1979. [BA; sub: 734, A3162, Box 104, Vol 8, attachment 2-55]

Crawford CR, Anderson RH & Nelson DL (1970) The acute dermal toxicity of Bay 29493 technical to adult female mice. Chemagro Corporation, Research Department. Report No. 28729, 2 March 1970. Unpublished. [BA; sub: 11793, Vol 3]

Crawford CR & Anderson RH (1971) The acute dermal toxicity of Bay 29493 technical and Bay 29493 4 lb/gal SC to rabbits. Chemagro Corporation, Research Department. Report No. 29679, 19 March 1971. Unpublished. [BA; sub: 11793, Vol 3]

Crosby J, Hoglen N & Krautter G (1990) Nature of residues in skin and tissues of swine after dermal treatment with [^{14}C]fenthion. Pharmacology and Toxicology Research Laboratory, Kentucky, USA. Report No. 73984. Unpublished [BA; sub: 11793, Vol 18]

De Bleecker J, Van den Neucker K, Colardyn F (1993) Intermediate syndrome in organophosphorus poisoning: a prospective study. Crit Care Med 21(11):1706-11

Dean G, Coxon J & Brereton D (1967) Poisoning by an organophosphorus compound: A case report. S Afr Med J **41:**1017-1019

Dellinger, J. & Mostrom, M. (1988) Effects of topical fenthion on blood ChE and vagal tone in dogs. Vet Hum Toxicol **30:**229-234

Dementi B (1994) Ocular effects of organophosphates: A historical perspective of Saku disease. J Appl Toxicol, **14:**119-129

De Wilde V, Vogelaers D, Colardyn F, Vanderstraeten G, Van den Neucker K, De Bleecker J, De Reuck J & Van den Heede M (1991) Postsynaptic neuromuscular dysfunction in organophosphate induced intermediate syndrome. Klin Wochenschr **69**(4):177-83

Dieckmann W (1971) Bay 29 493 (=S1752) Neurotoxicity studies on hens – Histopathology. Bayer AG, Institut für Pathol. Histologie, Wuppertal. Report No. 2735. Unpublished. [BA; sub: 734, A3162, Box 104, Vol 1, attachment 2-26]

Dilley J & Doull J (1961) Acute inhalation toxicity of Bayer 29493 to rats and mice. Dept of Pharmacology, University of Chicago, Chicago 37, Illinois, USA. Unpublished. [BA; sub: 734, A3162, Box 104, Vol 1]

Doolittle KD & Bates NL (1993) Absorption, distribution and elimination of ^{14}C-fenthion in rats following a single oral, repeated oral and single intravenous administration. Southwest Bio-Labs, Inc., New Mexico, USA. Report No. 74395 [BA; sub:11793, vol. 3, ref. 15].

Doull J (1960) Inhalation toxicity of Bayer 29493. Department of Pharmacology, University of Chicago, Illinois, USA. 16 November 1960. Unpublished. [BA; sub: 11793, Vol 4]

Doull J, Root M & Cowan J (1962) Effect of adding Bayer 29493 in combination with other cholinergic insecticides to the diet of male and female dogs. Bayer, Department of Pharmacology, University of Chicago, Illinois, USA. Unpublished. [BA; sub:734, A3162, Box 104, Vol 1, Attachment 2-17]

Doull J, Root M Cowan J & Vesselinovitch D (1963b) Chronic oral toxicity of Bayer 29493 to male and female dogs. Bayer, Department of Pharmacology, University of Chicago, Illinois, USA. Report No. 10853. Unpublished. [BA; sub:734, A3162, Box 104, Vol 5, Attachment 2-33]

Doull J, Vesselinovitch D, Fitch F, Cowan J, Root M & Meskauskas J (1961a) The effects of feeding diets containing Bayer 29493 to rats for a period of 16 weeks. Bayer, Department of Pharmacology, University of Chicago, Illinois, USA. Unpublished. [BA; sub:734, A3162, Box 104, Vol 1, Attachment 2-22]

Doull J, Root M & Cowan J (1961b) Determination of the safe dietary level for Bayer 29493 for dogs. Bayer, Department of Pharmacology, University of Chicago, Illinois, USA. Report No. 8342. Unpublished. [BA; sub:734, A3162, Box 104, Vol 1, Attachment 2-24]

Driest M & Popp A (1997a) E1752 (fenthion) Acute oral neurotoxicity screening study in Wistar rats. Bayer AG, Toxicology, Wuppertal. Study No. T 1059124. Report No. 26113, 20 March 1997. Unpublished. [BA; sub: 11793, vol 5].

Driest M & Popp A (1997b) E1752 (fenthion) Subchronic neurotoxicity screening study in Wistar rats (Thirteen-week administration in the diet) Bayer AG, Toxicology, Wuppertal. Study No. T 4060125. Report No. 26392, 24 June 1997. Unpublished. [BA; sub: 11793, vol 6]

Dubois KP & Kinoshita F (1964) Acute toxicity and anticholinesterase action of O,O-dimethyl-O-4- (methylthio)-m-tolyl) phosphorothioate (DMTP; Baytex) and related compounds. Toxicol Appl Pharmacol **6:**86-95 [BA; sub:734, A3162, Box 104, Vol 1, Attach 2-5]

DuBois KP & Kinoshita F (1965) The acute oral and dermal toxicity of some pesticide formulations to male rats. Department of Pharmacology, University of Chicago, Chicago, Illinois, USA. Report No. 16756, 18 August 1965. Unpublished. [BA; sub: 11793, Vol 7]

DuBois KP & Kinoshita FK (1970b) The acute oral and dermal toxicity of two samples of Bay 29493. Toxicity Laboratory, University of Chicago, Chicago, Illinois, USA. Report No. 28579, 2 November 1970 Unpublished. [BA; sub: 11793, Vol 7]

Dubois KP & Mangun G (1947) Proc Soc Exptl Biol Med **64:**137

DuBois KP & Perry M (1959) The acute toxicity of the oxygen analogue of Bayer 29493. Department of Pharmacology, University of Chicago, Chicago, Illinois, USA. Report No. 4392, 5 November 1959. Unpublished. [BA; sub: 11793, Vol 7]

Dubois KP & Puchala E (1960) Influence of Bayer 29493 applied dermally on the cholinesterqse activity of the blood of rats. Department of Pharmacology, University of Chicago, Illinois, USA. Unpublished. [BA; sub:734, A3162, Box 104, Vol 1, Attachment 2-28]

DuBois KP & Raymund AB (1960) The subacute toxicity of Bayer 29493 to rats. Department of Pharmacology, University of Chicago, Chicago, Illinois, USA. Report No. 5242, 5 May 1960. Unpublished. [BA; sub: 11793, Vol 7]

DuBois KP & Raymund AB (1962) Acute toxicity of some derivatives of Bayer 29493 to female rats. Department of Pharmacology, University of Chicago, Chicago, Illinois, USA. Report No. 9142, 23 April 1962. Unpublished. [BA; sub: 11793, Vol 7]

DuBois KP & Wong W (1970) Acute inhalation toxicity of two fenthion samples to rats. Toxicity Laboratory, Chicago, Illinois, USA. Report No. 27997, 1 September 1970. Unpublished. [BA; sub: 11793, Vol 7]

Dubois KP (1960) The absence of antidotal activity by pyridine-2-aldoxime methiodide (2-PAM) and TMB-4 against acute poisoning by Bayer 29493. Unpublished report from Department of Pharmacology, University of Chicago, Illinois, USA. [BA; sub:734, A3162, Box 104, Vol 1, Attachment 2-19]

Dubois KP (1961) Effects of repeated dermal application of Bayer 29493 on rats. Department of Pharmacology, University of Chicago, Illinois, USA. Unpublished. [BA; sub:734, A3162, Box 104, Vol 1, Attachment 2-27]

Dubois KP (1968) Comparison of the acute oral toxicity of Bayer 29493 and Sumithion to mice. Department of Pharmacology, University of Chicago, Illinois, USA. Report No. 22503. Unpublished. [BA; sub:734, A3162, Box 104, Vol 1]

DuBois KP (1970) Acute inhalation toxicity of two Baytex formulations to rats and mice. Toxicity Laboratory, University of Chicago, Chicago, Illinois, USA. Report No. 26639, 4 February 1970. Unpublished. [BA; sub: 11793, Vol 7]

Eigenberg DA (1987a) Acute oral toxicity of baytex technical in albino rats. Mobay Corporation, Health, Environment and Safety, Corporate Toxicology Department, Stilwell, Kansas, USA. Study no. 87-011-01. Report No. 839, 20 April 1987. Unpublished. [BA; sub: 11793, Vol 7]

Eigenberg DA (1987b) Acute dermal toxicity of (BAYTEX technical in albino rabbits. Mobay Corporation, Stilwell, Kansas, USA. Report No. 838. Unpublished. [BA; sub: 734, A3162, Box 104, Vol 1, attachment 2.12]

Eigenberg DA (1987c) Primary dermal irritation of Baytex technical in albino rabbits. Mobay Corporation, Corporate Toxicology Department, Kansas, USA. Report No. 896 [BA; sub: 11793, Vol 7, tab 34]

Eigenberg DA (1987d) Primary eye irritation of Baytex technical in albino rabbits. Mobay Corporation, Corporate Toxicology Department, Kansas, USA. Report No. 817 [BA; sub: 11793, Vol 7, tab 35]

Emteres R, Abdelghani A & Anderson AC (1985) Determination of the half life of fenthion in New Zealand white rabbits using three routes of administration J Environ Sci Health B20**(5):**577-591

Emteres R, Abdelghani A & Anderson AC (1986) Subacute toxicity of fenthion to New Zealand White Rabbits (Orcyctalagus cuniculus). Environmental Technology Lett **7**:27-30

Farage-Elawar M & Francis BM (1987) Acute and delayed effects of fenthion in young chicks. J Toxicol Environ Health 21(4):455-69

Farage-Elawar M & Francis BM (1988a) Effects of multiple dosing of fenthion, fenitrothion, and desbromoleptophos in young chicks. J Toxicol Environ Health 23(2):217-28

Farage-Elawar M & Francis BM (1988b) Effects of fenthion, fenitrothion and desbromoleptophos on gait, acetylChE, and neurotoxic esterase in young chicks after in ovo exposure. Toxicology 49(2-3):253-61

Flucke W & Eben A (1988a) E 1752 technical (cn fenthion): Study of the effect on the neurotoxic esterase (NTE) following oral administration to hens. Study No. T 3021893W., Bayer. Report No. 17307, 26 October 1988. Unpublished.

Flucke W & Eben A (1988b) E 1752 technical (cn fenthion): Study of the effect on the neurotoxic esterase (NTE) following dermal administration to hens. Study No. T 3021893 / T 8022798. Bayer. Report No. 17308. Unpublished.

Flucke W & Kaliner G (1986) E 1752 (cn fenthion, the active ingredient of Baytex): Acute neurotoxicity studies on hens following oral and dermal administration Bayer. Report No.15088, 22 September 1986. Unpublished. [BA; sub: 11009, A3162, Box 22, Vol 15]

Flucke W & Thyssen J (1978a) Lebaycid 1000 E.C. acute toxicity studies. Bayer Ag, Institut für Toxikologie, Wuppertal-Elberfeld. Report No. 7375, 10 March 1978. Unpublished. [BA; sub: 11793, Vol 7]

Flucke W & Thyssen J (1978b) Baytex 1000 E.C. (fenthion) acute toxicity studies. Bayer Ag, Institut für Toxikologie, Wuppertal-Elberfeld. Report No. 7376, 10 March 1978. Unpublished. [BA; sub: 11793, Vol 7]

Flucke W (1987) E 1753 Technical (c.n fenthion): Study for skin sensitising effect on guinea pigs (Magnusson and Kligman's maximization test). Bayer AG, Institut für Toxikologie, Wuppertal, Germany. Report No. 15428. Unpublished. [BA; sub: 734, A3162, Box 104, Vol 1, attachment 2.18]

Flucke W (1990) Position paper regarding the literature on neurotoxicity for the BGA [German Federal Health Agency]. Bayer AG, Institut für Toxikologie, Wuppertal, Germany. Report No. 18928. Unpublished. [BA; sub: 11793, Vol 7, tab 41]

Flucke, W. & Kaliner, G. (1987) E 1752 (c.n. fenthion, the active ingredient of Baytex): Acute neurotoxicity studies on hens following oral and dermal administration. Bayer AG, Institut für Toxikologie, Wuppertal, Germany. Report No. 91341. Unpublished.

Francis JI & Barnes JM (1963) Studies on the mammalian toxicity of fenthion. Bull. World Health Org **29:**205-212.

Gaines TB (1969) Acute toxicity of pesticides. Toxicol Appl Pharmacol **14:**515-534

Hackathorn DR, Brinkman WJ, Hathaway TR, Talbott TD & Thompson LR (1983) Validation of a whole blood method for ChE monitoring. Am Ind Hyg Assoc J **44(7):**547-51.

Hahn HL & Henschler (1968) Reactivation of phosphorylated ChEs by obidoxime (toxogonin) in vivo. Arch Toxikol **24:**147-163 (1969) [BA; sub: 734, A3162, Box 104, Vol 1, Attachment 2.21]

Hayes RH & Ramm WW (1988) Subchronic delayed neurotoxicity study of fenthion technical (Baytex) with hens, Mobay. Study No. 8641801 & 8649801. Report No. 1062.

Hayes RH (1989) Subchronic feeding study with technical grade fenthion (Baytex) in hens with specific emphasis on gastrointestinal tract effects, Mobay Report 1132, Study No. 87-978-01, mainly GLP. [BA; sub 11009, Vol 1]

Heimann KG (1987) Comparative study on acute oral toxicity in rats. Bayer Ag, Department of Toxicology, Wuppertal-Elberfeld. Report No. 15983, 6 August 1987. Unpublished. [BA; sub: 11793, Vol 8]

Herbold B (1980a) S 1752 Fenthion ®Lebaycid active ingredient, Salmonella/microsome test for detection of point-mutagenic effects. Bayer Ag, Institute of Toxicology, Wuppertal, Germany. Unpublished. [BA; sub: 734, A3162, Box ?, Vol 6]

Herbold B (1980b) S 1752 fenthion Lebaycid active ingredient micronucleus test on mouse to evaluate S 1752 for mutagenic potential. Bayer Ag, Institute for Toxicology, Wuppertal-Elberfeld, Germany. Unpublished. [BA; sub: 734, A3162, Box ?, Vol 6]

Herbold BA (1983) E 1752 Lebaycid active ingredient, Baytex active ingredient Pol test on E. coli to evaluate for potential DNA damage. Bayer Ag, Wuppertal-Elberfeld, Germany. Unpublished. [BA; sub: 734, A3162, Box ?, Vol 6]

Herbold BA (1987) E 1752 (cn fenthion): Salmonella/microsome test for point-mutagenic effect. Bayer Ag Institute of Toxicology, Wuppertal, Germany. Report No. 15485. Unpublished. [BA; sub: 11009, A3162, Box 26, Vol 15]

Herbold BA (1990a) E 1752: Salmonella/microsome test. Bayer Ag Institute of Toxicology, Wuppertal, Germany. Report No. 18713. Unpublished. [BA; sub: 11009, A3162, Box 26, Vol 15]

Herbold BA (1990b) E 1752: Micronucleus test on the mouse. Bayer Ag Institute of Toxicology, Wuppertal, Germany. Report No. 18714 & 100025. Unpublished. [BA; sub: 11009, A3162, Box 26, Vol 15]

Herbold BA (1994) Lebaycid EC 500. Salmonella/microsome test plate incorporation and preincubation method. Study No. T 4054032. Bayer Ag, Fachbereich Toxicology, Friedrich-Ebert-Straße, Wuppertal. Report No. 23344, 14 September 1994. Unpublished. [BA; sub: 11793, Vol 8]

Herbold BA (1997) Dominant lethal test on the male mouse. Study No. T 6061630. Bayer Ag Toxicology, Friedrich-Ebert- Straße, Wuppertal. Report No. 26620, 16 September 1997. Unpublished. [BA; sub: 11793, Vol 8]

Hoffmann K & Weischer CH (1975) Fenthion chronic study on dogs (two-year feeding experiment). Bayer AG, Institut für Toxikologie, Wuppertal, Germany. Report No. 5737. Unpublished [BA; sub: 734, A3162, Box 104, Vol 5, attachment 2.34]

Imai H, Miyata M, Uga S and Ishikawa S (1983) Retinal degeneration in rats exposed to an organophosphate pesticide (Fenthion). Environ Res **30:**453-65.

Inukai H & Iyatomi A (1976) Fenthion mutagenicity test on bacterial systems. Nitokuno Agricultural Chemicals Institute, Laboratory of Toxicology, Tokyo, Japan. Unpublished. [BA; sub: 734, A3162, Box ?, Vol 6]

Ishikawa S & Miyata M (1980) Development of myopia following chronic organophosphate pesticide intoxication: an epidemiological and experimental study. In 'Neurotoxicity of the Visual system", Eds Merigan WH and Weiss B. pp 233-254. Raven Press, NY.

Ishikawa S (1971) Eye injury by organic phosphorus insecticides (preliminary report). Jpn J Ophthalmol **15:**60-68.

Ishikawa S (1973) Chronic optico-neuropathy due to environmental exposure of organophosphate pesticides (Saku Disease) - Clinical and experimental Study. Nippon Ganka Gakkai Sasshi, **77:** 1835-1886.

Iyatomi A (1978) Report of acute toxicity - A. Nitokuno Agricultural Chemicals Institute, Tokyo, Japan. Report No. A-20, 8 December 1978. Unpublished. [BA; sub: 11793, Vol 9]

Iyatomi A (1980) Report of acute toxicity - A. Nitokuno Agricultural Chemicals Institute, Tokyo, Japan. Report No. A – 30, 30 July 1980. Unpublished. [BA; sub: 11793, Vol 9]

Johnson JC Jr & Bowman MC (1972) Responses from cows fed diets containing fenthion or fenitrothion. J Dairy Sci **55(6):**777-782

Kajiwara Y (1989) Chromosomal aberration test of fenthion using cultured mammalian CHL cells. Hita Research Laboratories, Japan. Submitted to WHO by Bayer AG, Wuppertal, Germany. Report No. T-1824E. Unpublished. [BA; sub: 11793, Vol 15]

Kimmerle G (1960) Active substance S 1752. Bayer Ag, USA. 8 November 1960. Unpublished. [BA; sub: 11793, Vol 9]

Kimmerle G (1963) Product BH 6 and S 1752 poisoning. Bayer AG, Institut für Toxikologie, Wuppertal, Germany. Unpublished letter. [BA; sub: 734, A3162, Box 104, Vol 1, attachment 2.20]

Kimmerle G (1963) Studies on mammalian toxicity of fenthion (S 1752) by J.I Francis and J.M Barnes. Farbenfabriken Bayer Ag, Toxicology Laboratory, Wuppertal-Elberfeld. 18 January 1963. Unpublished. [BA; sub: 11793, Vol 9]

Kimmerle G (1965) Neurotoxic investigation using S1752 active ingredient. Farbenfabriken Bayer Ag, Institute of Technology, Wuppertal-Elberfeld, Germany. Unpublished. [BA; sub: 734, A3162, Box 104, Vol 1, attachment 2-25]

Kimmerle G (1966) S 1752 (96.5%, Batch No. 3747). Farbenfabriken Bayer Ag, Wuppertal-Elberfeld. 3 June 1966. Unpublished. [BA; sub: 11793, Vol 9]

Klimmer OR (1963) Toxicological testing of “Bayer 29493”. Farbenfabriken Bayer Ag, Leverkusen. 25 March 1963. Unpublished. [BA; sub 734, A3162, Box 104, Vol 1, attachment 2-2; sub: 11793, Vol 9]

Knowle CO & Arthur BW (1966) Metabolism of and residues associated with dermal and intramuscular application of radiolabelled fenthion to dairy cows. J Econ Entomol **59:**1346-1352.

Kowalski RL, Clemens GR, Bare JJ & Hartnagel Jr. RE (1987) A teratology study with fenthion (Baytex technical) in the rat. Aug 26, 1987, Miles Laboratories Report 935, Report # MTD0029, GLP [BA; sub: 11009, A3162, Box 22, Vol 15]

Kowalski RL, Clemens GR, Jasty V, Troup CM & Hartnagel RE Jr. (1989) A two-generation reproduction study with fenthion (Baytex) in the rat. Study No. 1166. Miles Laboratories. Report No. MTD0133, Tox. Report No. 1166, 22 December 1989. [BA; sub: 11009, A3162, Box 22, Vol 13-14]

Kowalski RL, Clemens GR, Jasty V, Troup CM & Hartnagel RE Jr. (1993) A two-generation reproduction study with fenthion (Baytex) in the rat, Addendum to Miles Report 1166, 25.5.93, Miles Laboratories Report 5026, [BA; sub: 11009, A3162, Box 22, Vol 13-14]

Krautter G (1990a) Nature of residues in milk, skin and tissues of a lactating cow after dermal treatment with [^{14}C]fenthion. Mobay report from Pharmacology and Toxicology Research Laboratory, Kentucky, USA. Report No. 74012.

Krautter G (1990b) Characterization of polar metabolites in river and kidney tissues from a cow and pig treated dermally with [^{14}C]fenthion. Mobay report from Pharmacology and Toxicology Research Laboratory, Kentucky, USA. Report No. 74124.

Lamb DW & Anderson RH (1974) The acute dermal toxicity of Tiguvon technical to rabbits. Chemagro Division of Baychem Corporation, Research and Development. Report No. 41455, 22 August 1974. Unpublished. [BA; sub: 11793, Vol 10]

Lamb DW & Matzkanin CS (1975) The acute dermal and oral toxicity of Tiguvon 20% spotton. Chemagro Agricultural Division, Mobay Chemical Corporation, Research and Development. Report No. 43115, 20 January 1975. Unpublished. [BA; sub: 11793, Vol 10]

Lehn H (1990b) E 1752 (cn fenthion): Mutagenicity test on unscheduled DNA synthesis in rat liver primary cell cultures in vitro. Bayer Ag Institute of Toxicology, Wuppertal, Germany. Report No. 19604. Unpublished. [BA; sub: 11009, A3162, Box 26, Vol 15]

Lehn HE (1990a) 1752 (cn fenthion): Mutagenicity study for the detection of induced forward mutations in the CHO-HGPRT assay in vitro. Bayer Ag Institute of Toxicology, Wuppertal, Germany. Report No. 18740. Unpublished. [BA; sub: 11009, A3162, Box 26, Vol 15]

Leser KG & Suberg H (1990) E 1752: Oncogenicity study on B6C3F1 mice (feeding study for periods up to 24 months), Bayer Report 19624, Study # T 0020495 [BA; sub: 11009 Vol 10-12] OECD 451, GLP

Leser KG & Suberg H (1992) E 1752: Study for oncogenicity in B6C3F1 mice (administration in diet for over 24 months). Addendum to Bayer Report 19624 of 25.10.90, Bayer Report 21807. [BA; sub: 11009 Vol 13]

Leser KH (1989) E 1752 (cn fenthion): Range finding study to determine the maximum tolerated dose (MTD) of B6C3F1 mice (administration in the feed for up to 5 weeks) Bayer Report 17950, Study No. T 8029430, not GLP. [BA; sub 11009, Vol 2]

Leser KH (1990) E 1752 (cn fenthion): Study for ChE inhibition following high doses of E1752. (Administration to B6C3F1 mice in the diet over a period of approximately four weeks) Study No. T 9030349. Bayer AG, Institut für Toxikologie, Wuppertal, Germany. Report 19088. Unpublished. [BA; sub 11009, Vol 2]

Loser E (1969) Bay 29493 generation study with rats, Bayer AG report 1400, 2.5.69 [BA sub 734 attachment 2-38; sub: 11793, Vol 10]

Machemer L (1978) S 1752 (Fenthion, Lebaycid active ingredient): Dominant lethal study of male mice to test for mutagenic effects. Bayer AG, Institut für Toxikologie, Wuppertal, Germany. Report No. 7449. Unpublished. [BA; sub: 734, A3162, Box ?, Vol 6]

Mahieu P, Hassoun A, Van Binst R, Lauwerys R & Deheneffe Y (1982) Severe and prolonged poisoning by fenthion. Significance of the determination of the anticholinetserase capacity of plasma. J Toxicol Clin Toxicol **19**(5):425-32

Merrill NG & FG Mihm (1982) Prolonged Toxicity of Organophosphate Poisoning, Crit Care Med **10:**550-1.

Metcalf RL, Branch CE, Swift TR & Sikes RK (1985) Neurologic findings amoung workers exposed to fenthion in a veterinary hospital-Georgia. MMWR Morb Mortal Wkly Res **34:**402-3.

Michel OH (1949) J Lab Clin Med **34:**1564.

Mihail F & Schilde B (1979) E 1752 (fenthion, the active ingredient of Lebaycid and Baytex): Subacute dermal cumulative toxicity study on rabbits. Bayer Report 8624, Study # S 1752/004, not GLP. [BA; sub 11009, Vol 1]

Mihail F & Thyssen J (1979) E 1752 550 EC 558 Acute toxicity studies (occupational toxicology studies). Bayer Ag Institut für Toxikologie, Wuppertal-Elberfeld. Report No. 8331, 23 April 1979. Unpublished. [BA; sub: 11793, Vol 10]

Mihail F (1978) S 1752 (Lebaycid active ingredient): Determination of percutaneous toxicity. Bayer AG, Institut für Toxikologie, Wuppertal, Germany. Report No. 7604. Unpublished. [BA; sub: 734, A3162, Box 104, Vol 1, attachment 2-13]

Misra UK, Nag D, Bhushan V & Ray PK (1985) Clinical and biochemical changes in chronically exposed organophosphate workers. Toxicol Lett **24:**187-193.

Misra UK, Nag D, Khan WA & Ray PK (1988) A study of nerve conduction velocity, late responses and neuromuscular synapse functions in organophosphate workers in India. Arch Toxicol **61:**496-500.

Misra UK, Nag D, Misra, NK, Mehra MK & Ray PK (1985) Some observations on the macula of pesticide workers. Hum Toxicol **4:**135-45.

Misra UK, Prasad M & Pandey CM (1994) A study of cognitive functions and event related potentials following organophosphate exposure. Electromyogr Clin Neurophysiol **34(4):**197-203.

Nagy Z, Mile I & Antoni F (1975) The mutagenic effect of pesticides on Escherichia coli WP2 try$^-$. Acta microbiol Acad Sci hung **22:**309-314. [BA; sub: 11793, Vol 15]

Pauluhn J (1985) E 1752 Technical (c.n. fenthion): Study for irritant/corrosive effect on skin and eye (rabbit). Bayer AG, Institute für Toxikologie, Wuppertal, Germany. Report No. 13446. Unpublished. [BA; sub: 734, A3162, Box 104, Vol 1]

Pilz W & Eben A (1967) Archiv Toxikologie **23:**27.

Pither KM (1979) Metabolism of Baytex in male and female pigs. Mobay Corporation, Corporate Toxicology Department, Kansas, USA. Report No. 68475.

Puhl RJ & Hurley JB (1982) The absorption, excretion and metabolism of Baytex-ring-1-^{14}C by rats. Mobay Corporation, Corporate Toxicology Department, Kansas, USA. Report No. 82227. Unpublished. [BA; sub: 734, A3162, Box 104, Vol 1, attachment 4-2]

Putman D & Morris M (1989a) Chromosome aberrations in Chinese hamster ovary (CHO) cells. Microbiological Associates, Inc., Maryland, USA. Report 1144. Unpublished. [BA; sub: 11009, A3162, Box 26, Vol 15]

Putman DL & Morris MJ (1989b) Chromosome aberrations in Chinese hamster ovary (CHO) cells. Microbiological Associates Inc., Maryland, USA. Submitted to WHO by Bayer AG, Wuppertal, Germany. Report No. 99660. Unpublished.

Rani MVU & Rao MS (1991) In vitro effect of fenthion on human lymphocytes. Bull Environ Contam Toxicol **47:**316-320. [BA; sub: 11793, Vol 16]

Rosenblum I (1980) A safety evaluation of fenthion (S 1752) in rhesus monkeys (Macaca mulatta). Albany Medical College, New York, USA. Submitted to WHO by Bayer AG, Wuppertal, Germany. Report No. 68789. Unpublished.

Senanayake N and Sanmuganathan PS (1995) Extrapyramidal manifestations complicating organophosphorus insecticide poisoning. Hum Exp Tox 14:600-604.

Shiotsuka RN (1987a) Acute inhalation toxicity study with Baytex technical in rats. Study No. 86-041-26. Mobay Corporation, Health, Environment and Safety, Corporate Toxicology Department, Stilwell, Kansas. Report No. 820. 18.3.1987 Unpublished. [BA; sub: 11793, Vol 10]

Shiotsuka RN (1987b) Acute one-hour inhalation toxicity study with technical grade Baytex in rats. Mobay Corporation, Stilwell, Kansas, USA. Unpublished. [BA; sub: 11793, Vol 10]

Shirasu Y, Moriya M & Kaneda Y (1979) Report of the mutagenicity study of fenthion. Bayer Ag, Wuppertal-Elberfeld, Germany. Unpublished. [BA; sub: 734, A3162, Box ?, Vol 6]

Shmidl JA, Kohlenberg ML & Rainey LA (1980a) Oral LD_{50} evaluation for Tiguvon 3% pour-on. Bayvet Division of Cutter Laboratories, Inc, Pharmaceutical Research and Development Toxicology. Report No. 71665. 10.4.1980 Unpublished. [BA; sub: 11793, Vol 11]

Shmidl JA, Kohlenberg ML & Rainey LA (1980b) Dermal LD_{50} evaluation of Tiguvon 3% pour-on in rabbits. Bayvet Division of Cutter Laboratories, Inc, Pharmaceutical Research and Development Toxicology. Report No. 71712. 30.4.1980 Unpublished. [BA; sub: 11793, Vol 11]

Sobti RC, Krishan A & Pfaffenberger CD (1982) Cytokinetic and cytogenic effects of some agricultural chemicals on human lymphoid cells in vitro: organophosphates. Mut Res **102**:89-102. [BA; sub: 11793, Vol 16]

Suberg H (1988) E 1752: Orientative subacute toxicity studies in mice (up to three-week dietary administration), Bayer Report 16809, Study Nos. T5019979, T 3020344, T 5020887, not GLP. [BA; sub 11009, Vol 2]

Tandon P, Padilla S, Barone S Jr, Pope CN, Tilson HA (1994) Fenthion produces a persistent decrease in muscarinic receptor function in the adult rat retina; Toxicol Appl Pharmacol, **125**(2):271-280.

Taylor A (1963) Observations on human exposure to the organophosphorus insecticide fenthion in Nigeria. Bull World Health Org **29**:213-218.

Thyssen J (1974) 3-methyl-4-methyl-mercaptophenol [metabolite of Baytex] acute toxicity to rats. Bayer Institut fuer Toxikologie, Wuppertal-Elberfeld, Germany. 25.2.1974 Unpublished. [BA; sub: 11793, Vol 11]

Thyssen, J. (1978) S 1752 (Lebaycid-active ingredient): Acute inhalation toxicity studies. Unpublished report No. 7842 from Bayer AG, Institut für Toxikologie, Wuppertal, Germany. Unpublished. [BA; sub: 734, A3162, Box 104, Vol 1]

Thyssen, J. (1979) Fenthion (S 1752, the active ingredient of Lebaycid and Baytex): Subacute inhalation toxicity study on rats. Unpublished report No. 8383 from Bayer AG Institut für Toxikologie, Wuppertal, Germany not GLP. [BA; sub 11009, Vol 1]

Tuler SM & Bowen JM Chronic fenthion toxicity in laying hens (1999) Veterinary and human toxicology 41**:302-307**

Tuler SM, Febles D & Bowen JM (1988) Neuromuscular effects of chronic exposure to fenthion in dogs and predictive value of electromyography. Fundam Appl Toxicol **11**:155-168.

Van Goethem DL & Leser KH (1993) E 1752 (fenthion): Study for oncogenicity in B6C3FI mice (administration in diet for over 24 months). Addendum to Bayer Report 19624 of 25.10.90. Bayer Report 5406 [BA; sub: 11009 Vol 13]

Veronesi B, Jones K, Pope C (1990) The neurotoxicity of subchronic acetylChE (AChE) inhibition in rat hippocampus. Toxicol Appl Pharmacol, **104**(3): 440-456.

von Clarmann M & Geldmacher von Mallinckrodt M (1966) On the successful treatment of acute oral poisoning with fenthion and its detection in the stomach contents and urine. Arch Toxikol **22**:2-11.

Voss G & Sachsse K (1970) Toxicol Appl Pharmacol **16**:764-772.

Wadia RS, Bhirud RH, Gulavani AV & Amin, RB (1977) Neurological manifestations of three organophosphate poisons. Indian J Med Res **66**:460-468.

Waggoner TB (1991) Fenthion - Nature of the residue (metabolism) Swine and Bovine Mobay report No. 74130 from Animal Health division, Kansas, USA, dated Jan 7, 1991. [BA; sub: 11793, Vol 18]

Waters MD, Sandhu SS, Simmon VF, Mortelmans KE, Mitchell AD, Jorgenson TA, Jones DCL, Valencia R & Garrett NE (1982) Study of pesticide genotoxicity In: Genetic toxicology: An agricultural perspective. Fleck RA & Hollaender A eds. Plenum Press, New York & London. p 275-326. [BA; sub: 11793, Vol 16]

Weber H & Ecker W (1992) [phenyl-1-^{14}C]Fenthion: Absorption, distribution, excretion and metabolism in a lactating goat. Bayer Laboratories, Germany. Miles Report No. 105012. Guideline USEPA 171-4b; GLP [BA; sub: 11793, Vol 11]

Wolfe HR, Armstrong JF & Durham WF (1974) Exposure of mosquito control workers to fenthion. Mosquito News **34**:263-267

Appendix 1: History of public health considerations of fenthion in Australia

Australian public health standards for agricultural and veterinary chemicals include the Poisons Schedule, FAISDs, the ADI and ARfD. A further regulatory standard called the maximum residue level (MRL) is a limit on the residues present in unprocessed food (eg. grain, meat etc.) and reflects good agricultural practice.

From the mid 1950s until 1992, Australian public health standards were set by a committee process under the auspices of the National Health and Medical research Council (NHMRC). "Pesticide Tolerances" in food were first set in 1956 by the Food Additives Committee. Between 1962 and 1966, the Food Additives Committee maintained a Sub-Committee on Pesticides and Agricultural Chemical Residues In Or On Foods (later re-named the Pesticide Residues in Food Sub-Committee), which adopted the then Canadian scheme as a basis for establishing tolerances. From 1967 onwards, Australian MRLs and ADIs for pesticides were established by the Pesticide and Agricultural Chemicals Committee (PACC), until the Department of Health and Ageing (DoHA) became directly responsible for setting ADIs in November 1992. Responsibility for pesticide and veterinary chemical MRLs was transferred to the APVMA in June 1994, after which the PACC was removed from the control of the NHMRC and re-constituted as the Advisory Committee on Pesticides and Health (ACPH). The ACPH provides toxicological and public health advice to the DoHA on agricultural and veterinary chemicals as part of the National Registration Scheme, and as part of the APVMA's Chemical Review Program. The ACPH has also been available to the OCS and the APVMA for the provision of advice on technical policy issues where they have possible implications for public health and the proper use of chemicals in agriculture and elsewhere.

Poisons Schedules for agricultural and veterinary chemicals, drugs and some other hazardous substances are set by the National Drugs and Poisons Schedule Committee (NDPSC). Originally known as the Committee on Poisons Scheduling, the NDPSC was established in 1955 as a sub-committee of the NHMRC Public Health Committee. The NDPSC publishes its decisions in the SUSDP, which recommends controls on availability, labelling, packaging and advertising. These are incorporated into and enforced by the various Australian State and Territory legislative systems. In 1994, the NDPSC was transferred from the NHMRC to the Australian Health Ministers' Advisory Council, and was re-constituted again in 1999 as a Statutory Committee of the Therapeutic Goods Administration (TGA).

Date	Decision
November 1975	NDPSC: New entry: Fenthion in preparations containing 20% or less of fenthion when packed in single use containers having a capacity of 0.3ml or less Amend the entry under fenthion in S6 by adding: Except when included in Schedule 5
August 1982	NDPSC: Amend current Schedule 5 entry to read "… in preparations containing 20% or less of fenthion when packed in sealed single-use containers having a capacity of 1.0ml or less
August 1988	NDPSC: Amend Schedule 5 entry to read: Fenthion in preparations containing 25% or less of fenthion when packed in single use containers having a capacity of 2 mL or less.

Date	Decision
November 1989	NDPSC: Amend: • New Schedule 7 entry: Fenthion **except** when included in Schedule 6 • Amend Schedule 6 entry to read: • Fenthion in preparations containing 25% or less of fenthion when packed in single use containers having a capacity of 2ml or less • Delete Schedule 5 entry. Secretary to advise the company (including the Victorian Stock Medicines Board) of the foreshadowed recommendations and invite comment. Clearance to be deferred until scheduling proposal resolved.
November 1989	PACC: Noted the toxicology review presented by the client, and based on the human studies established an NEL of 0.02 mg/kg/day and an ADI of 0.002 mg/kg/day.
August 1990	NDPSC: The company is requested to provide information on the timetable and range of studies proposed for new 100g/L HG fenthion product and the range of studies considered suitable by DPSC to be advised to the Company. Previous Schedule 6/7 foreshadowed recommendations to remain as foreshadowed until above data is received and evaluated.
February 1993	NDPSC: Committee recommended the following entries in the SUSDP and requested that the AAVCC be advised that the registration of the Home Garden product should only be supported where the container is fitted with a child resistant closure (CRC). • New Schedule 7 entry: Fenthion except when included in Schedule 5 or 6 • Amend Schedule 6 entry to read: Fenthion in preparations containing 60% or less of fenthion **except** when included in Schedule 5 • Amend Schedule 5: FENTHION (a) in preparations containing 25% or less of fenthion when packed in single-use containers having a capacity of 2ml or less; or (b) in preparations containing 10% or less of fenthion. • New entry – Appendix H, Part 2 Fenthion HG EC 100g/L or less 129 133 210 211 219 223 279 283 290 312 340 342 350 360 361 366 • Appendix H, Part 2 – amendment: Delete entry: Fenthion EC All strengths 100ml pack
1996	CNPD recommends NOEL 0.03, ADI 0.0003 mg/kg bw/d based on plasma ChE inhibition in a chronic mouse study
November 1997	ACPH: The most sensitive biological effect was the most appropriate end-point to base the NOEL. NOEL of 0.02 based on plasma ChE inhibition at 0.07 mg/kg bw/d in a 4-week 1979 human study was acceptable. 10-fold safety factor on the NOEL was satisfactory. ADI amended to 0.002 mg/kg bw/d
October 2000	ACPH: NOEL of 0.02 for plasma ChE inhibition (LOEL 0.07 mg/kg bw/d) and clinical signs in a 4-week 1979 human study (Coulston), supported by 1980 monkey study (Rosenblum). 10-fold safety factor on the NOEL was satisfactory. ADI affirmed as 0.002 mg/kg bw/d. ACPH: ARfD of 0.007 mg/kg bw was derived by applying a tenfold SF to the NOEL for RBC ChE inhibition (0.07 mg/kg bw) in a 4-week 1979 human study (Coulston), supported by the NOEL of 1 mg/kg bw for neurotoxicity findings in an acute oral neurotoxicity study in rats (Driest and Popp, 1997a).

10. OCCUPATIONAL HEALTH AND SAFETY ASSESSMENT

10.1 Hazard Overview

10.1.1 Acute toxicity

Fenthion is moderately toxic by the oral, dermal and intraperitoneal routes for both rats and mice, with males being slightly more sensitive than females in some tests. Fenthion has a low to moderate toxicity when administered inhalationally as a mist. Fenthion was not an irritant to rabbit eye and a very slight irritant to rabbit skin. It is not a skin sensitizer in guinea pigs. A summary of the acute toxicity of technical fenthion is provided below:

Table 88: Summary of the acute toxicity of technical fenthion

Species	Sex	LD_{50} range (mg/kg)
Oral		
Mice	M	200 - 290
	F	225 - 280
Rats	M	140 - 474
	F	150 - 566
Dermal		
Mice	M	2000
	F	500 - >2000
Rats	M	325 - >5000
	F	271 - 5000
Inhalation		**LC_{50} range (mg/m^3)**
Mice	M	2400
	F	2000
Rats	M	507 - 3450
	F	454 - 3000

10.1.2 Repeat dose toxicity

A number of repeat dose animal studies were considered suitable for regulatory purposes by OCS. In all studies, inhibition of cholinesterase in plasma, RBC and brain was the most critical effect. The OCS considers that a NOEL of 0.02 mg/kg bw/day in 4-week human study (Coulston, 1979) is appropriate for OHS risk assessment purposes, based on the following argument:

- the statistical significance of plasma ChE inhibition at 0.02 mg/kg bw/day in humans was equivocal;
- 0.02 mg/kg bw/day was also a NOEL for clinical signs in the human study; and
- a 2-year monkey study (Rosenblum, 1980) had recorded an identical NOEL of 0.02 mg/kg bw/day for plasma ChE inhibition.

10.1.3 Dermal absorption

No dermal absorption data are available. To determine a dermal absorption factor, a rabbit oral and a dermal toxicity study were considered. Based on the ratio of the LOELs for cholinesterase inhibition in the oral development toxicity study (2.75 mg/kg bw/day, Clemens et al, 1987), and the 21-day dermal toxicity study (100 mg/kg bw/day, Bailey, 1987), a dermal absorption factor of 3% was extrapolated, .ie dermal absorption factor = 2.75 mg/kg bw/day ÷ 100 mg/kg bw/day x 100 = 3%. This dermal absorption factor will be used in the risk assessment.

10.1.4 Health effects relating to occupational exposure

Workers exposed to aerial application of fenthion dust over 5 days complained of generalised chills, headache, vomiting, diarrhoea and irregular pulse. One of the workers needed hospitalisation, but had an uneventful recovery (Jung, 1963).

Workers exposed to a 20% solution of fenthion on a regular basis in a veterinary hospital developed neurological symptoms such as multiple shooting pains, muscle weakness, back pain, numbness and tingling of the hands and feet, ocular muscle weakness and paralysis. Results of tests of plasma and red blood cell cholinesterase activity were within the normal range for all workers (Metcalf et al, 1985).

A 21 year old abattoir-shed worker who was a known asthmatic developed an exacerbation of his symptoms following exposure to 3% fenthion in talc dust. His duties included supervising the long-term storage of animal skins, which were sprayed monthly with 3% fenthion in talc dust. Bronchial provocation tests with powder components of the insecticide did not demonstrate any response to the inhalation of talc or lactose dust for 10 minutes after use. There was a delayed response which began after 2 hours and was maximal at 6 hours when the patient inhaled 3% fenthion in lactose powder for 6 minutes. Plasma and red blood cell cholinesterase activity was measured before, at 30 minutes, two hours and five hours after exposure. No alterations in plasma and erythrocyte cholinesterase levels were noted (Bryant, 1985).

Workers exposed to fenthion presented with symptoms and signs of Intermediate Syndrome (IMS). The clinical signs of IMS were weakness of several motor cranial nerves (diplopia, dysphagia, and facial diplegia), sudden respiratory weakness, neck and proximal limb muscle weakness and depression of the deep tendon reflexes. Muscle fasciculations were also present in certain cases. The duration of symptoms varied from a few days to several weeks. Severe acetylcholinesterase inhibition was noted in all patients during the entire duration of IMS (De Bleecker, 1995).

Public health workers exposed to fenthion for one week complained of headache, sweating, eye problems such as pain and watering, impaired vision, muscle cramps, chest tightness, dermatitis, excess salivation, and excessive secretions as compared to workers who were not exposed. Estimated concentrations of fenthion used ranged from 0.03 to 0.78 gm/100 mLs. Analysis of blood cholinesterase concentrations of workers exposed to fenthion showed no depression during the working day over the period of the study (Jeyaratanam and Ponnambalam, 1980)

The health effects of 22 workers who regularly sprayed fenthion were investigated using clinical and biochemical parameters. The workers were subjected to detail history-taking, noting their working conditions, dietary history and addictions. In addition, symptoms associated with spraying were noted for each worker. The mean age of the workers was 31 years, and the mean duration of fenthion exposure was 8.2 years. Headache, giddiness, ocular symptoms and paraesthesia were the commonest symptoms. Serum acetylcholinesterase and butrylcholinesterase levels were significantly lower than in controls. After withdrawing the workers from organophosphate exposure for 3 weeks, the follow-up study revealed absence of transient symptoms. There was no change in their neurological status, but serum acetylcholinesterase and butrylcholinesterase levels returned to normal pre-exposure levels (Misra et al, 1985).

A clinical and neurophysiological examination was carried out on thirty one workers engaged in spraying fenthion for about 1-14 years. The workers reported mild transient symptoms after spraying. There was no clinical evidence suggestive of excessive cholinergic activity. Results of clinical psychometry suggested subclinical effect of chronic fenthion exposure on the cognitive functions of the workers (Misra et al, 1994).

A telephone survey of health symptoms of pet handlers with occupational exposure to fenthion was conducted in California following several reports of ill workers. Work practices, PPE used and details of products were documented. Symptoms associated with exposure to fenthion were convulsions, muscle twitching, unusual tiredness, asthma, burning sensation in eyes and headache. Spraying and dusting were associated with increased symptom frequency for more adverse acute health symptoms than dipping. Spraying was associated with increased frequency of skin and eye irritation symptoms, whereas dusting was associated with increased frequency of gastrointestinal and respiratory symptoms, headaches and joint swelling or pain (Ames et al, 1989).

Retinal changes in 79 workers occupationally exposed to fenthion were studied. Fifteen workers (19%) had macular changes characterised by perifoveal irregularity of pigmentation and areas of hypopigmentation. Fluorescein angiography suggested pigment epithelium defects (Misra et al, 1985)

Potential dermal and respiratory exposures to fenthion were determined for mosquito-control workers during application by hand gun power spray equipment, backpack hand pressure sprayer (0.06% spray), and hand granular dispersal (1% granular formulation). A total of 33 work periods were studied over 2 seasons. Exposure pad and hand rinse techniques were used to estimate exposure. The amount of pesticide entering the body via the respiratory route was estimated from the contamination of special filter pads in single-unit respirators worn by the subjects. Mean dermal and respiratory exposure values during operation of power sprayers were 3.6 and <0.016 mg/hr of work, respectively, and for hand pressure sprayer operators the values were 3.6 and <0.021 mg/hr, respectively. Mean dermal and respiratory exposure values for hand granular dispersal were 12.3 and 0.088 mg/hr of work, respectively. Thus, potential dermal exposure was greater than potential respiratory exposure, and exposure was greatest during hand granular dispersal. Highest total dermal-respiratory exposure for any individual was only 0.03% of a toxic dose /hour of work activity. Tests to determine hazard from smoking during application operations indicated greater contamination of cigarettes as a result of contact with unwashed hands following hand granular application than following spray application operations. There was no important change in erythrocyte cholinesterase activity; however, there was some decrease in plasma cholinesterase activity in certain workers. There were no toxic signs in any of the workers (Wolfe et al, 1974).

10.2 Occupational Exposure Assessment

Fenthion products are currently registered for agricultural and veterinary use in a range of crops/animals/use situations. To facilitate the exposure and risk assessment, exposure scenarios were developed and grouped where possible.

10.2.1 End use exposure

The main route of occupational exposure to fenthion is expected to be by skin contamination during mixing/loading/spraying. Inhalation of spray mist may occur during spray application, particularly when using hand-held equipment. Workers handling undiluted solvent-based product can be potentially exposed to solvent vapour during spraying. Dermal exposure to paint may occur during treatment of commercial and domestic buildings.

Occupational exposure for the following agricultural scenarios was assessed using the Predictive Operator Exposure Model (POEM). Scenario details and estimates are presented in Section 10.4.3.

Scenario (1) Mixing/loading and hand-held spraying of water and septic tanks

Scenario (2) Mixing/loading and hand-held spraying of commercial and domestic areas

A qualitative exposure assessment was conducted for the following agricultural scenarios:

Scenario (3) Mixing/loading and application to ornamentals by hand-held equipment

Scenario (4) Application of paint to roost areas

Scenario (5) Application of 1% Dust formulation by Pest Control Operators (PCOs)

The following assumptions are used in the agriculture exposure assessment:

- A normal work day of 8 hours, consisting of a 6 hour application period - an internationally accepted default value;

- exposure estimates represent the exposure of a worker after all protection provided by clothing, protective clothing or engineering controls specified on registered product labels;

- 100% absorption of inhaled dose (default) -Thongsinthusak et al. (1993); and,

- *average body weight - 70 kg, consistent with the World Health Organisation

10.2.2 Measured exposure studies

No measured exposure studies were submitted.

10.2.3 Predicted exposure

UK Model – Predictive Operative Exposure Model

In the absence of relevant worker exposure data, the UK Predictive Operator Exposure Model (POEM) was used to assess uses of fenthion wherever possible.

POEM is a descriptive model based on databases of operator exposure field studies, which provides surrogate exposure values. Exposure calculations are divided into two parts; contamination from handling the concentrated product and contamination during actual application of the dilute spray. The model assumes that the level and distribution of potential dermal contamination are mainly dependent on the handling techniques used during the preparation of the product for use, the type of application equipment employed and the work practices of the individual operator.

In this model, exposure during mixing/loading, is assumed to be confined to the hands only, and no respiratory exposure is assumed to occur during mixing/loading. Dermal (hands, trunk and legs) and inhalation exposure is assumed during spray application.

The use of exposure values derived from predictive models (such as POEM) involve the use of conservative assumptions for unknowns, and a range of values for a particular method of spraying. In using POEM, it is necessary to make assumptions in order to estimate the actual exposure from potential exposure. These assumptions may be based on laboratory or field data, in the absence of which conservative estimates are deemed necessary.

In this assessment, POEM was used to assess occupational exposure for workers using airblast/misters, boom sprayers or hand-held applications for agricultural purposes. In instances where measured exposure data were not available, and predictive modelling were not appropriate to estimate worker exposure, a qualitative assessment was conducted.

A suitable model does not exist within the UK POEM to estimate worker exposure during animal treatments. Therefore, a qualitative assessment was conducted for veterinary applications.

The following assumptions are used in the agriculture exposure assessment:

*Hand contamination - 0.2 mL per operation (for 5 L containers with unspecified design)
0.01 mL per operation (for 5 L container with wide necks)

*PPE worn by operators - One layer clothing during application plus gloves during mixing/loading/application

The various end use applications for fenthion are described under scenarios with designated numbers (Section 10.5.1). The use pattern parameters for each end use scenario considered in the agriculture exposure assessment, using POEM are presented in the following table.

Table 89: Use pattern parameters used in the agricultural exposure assessment

Crop/situation/Pest formulation	Scenario number and description	Dilution, product application rate/spray volume and concentration of ai in spray	Work rate
Water and septic tanks EC 100 g/L	**Scenario (1)** Mixing/loading and hand-held spraying	80 mL/L of water/8 m^2 7.02-8.25 g ai/L (adult mosquitoes) 16.5-23.4 g ai/1500-10,000m^2 (larva) 55mL/septic tank 4.68-5.5 g ai/septic tank	Varying work rates, would depend on the area to be sprayed
Commercial and domestic areas EC 100 g/L Spiders, ants, cockroaches Fleas Flies	**Scenario (2)** Mixing/loading and hand-held spraying	50-80 mL/L of water 7.02-8.25 g ai/L 50 mL/Lwater/3m^2 11-16.7 g ai/3L/10 m^2 11 g ai/L water/8m^2	Would vary according to the number of sites

Agricultural applications

Details of the agricultural exposure scenarios using POEM are described below. Estimates reflect the size of the container, the different neck designs of the container (unspecified and wide neck), the application and work rates used, the spray volume, and the concentration of the active ingredient in the product. The 5 L container was used as the standard container size for mixing/loading as per label directions, and the maximum area sprayed as 20 ha/day, based on information provided by the APVMA, the range being 15-20 ha/day for fruits and vegetables.

Scenario (1) Mixing/loading and hand-held spraying of water and septic tanks (Estimates 5a-5d)
using the *Hand Held Outdoors Hydraulic Nozzles (H-Nozzle)* model for knapsack spraying and *Hand held outdoor rotary disc atomisers: high level application (H-RDA-high) for high volume hand-held sprayers* Mixer/loader and applicator exposure was estimated for workers exposed to fenthion when used in treating the adult and larval stages of mosquitoes in water at the rates of 7.02 – 8.25 g ai/L, and 16.5 – 234 g ai/1500-10000 m^2, and treatment of septic tanks at the rate of 4.68-5.5 g ai/septic tank. According to the APVMA Report, major mosquito breeding grounds are usually relatively inaccessible, dependent on available means of access and treatment is mostly high volume hand-held sprayers attached to motorised pumps mounted on vehicles (usually four wheel drive or ATVs) or knapsack sprayers. Small pumps are used in some circumstances. Similar equipment mounted on aluminium dinghies and swamp boats are also used for this type of application where land-based vehicle access is limited. Information provided by the APVMA states that the product could be used from aircraft since per hectare rate was specified, OCS however, will not assess aerial application as it is not a label use.

Scenario (2) Mixing/loading and hand-held spraying of commercial and domestic areas using *Hand Held Outdoors Hydraulic Nozzles (H-Nozzle)* model for knapsack spraying and

Hand held outdoor rotary disc atomisers: high level application (H-RDA-high) for high volume hand-held sprayers (Estimates 6a-6h).

Spraying of commercial and domestic areas for the treatment of various pests is normally carried out by licensed PCOs with hand-held sprayers attached to motorised pumps, which are mounted on the backs of trucks or in vans. There are no relevant POEM scenarios for indoor spraying. OCS uses the above outdoor model to estimate exposure for workers applying fenthion indoors. For the treatment of spiders, ants and cockroaches fenthion is applied at the rate of 0.7-0.82%, whereas for the treatment of fleas in non-wetting soil a wetting agent and a rate of 0.4-0.6% is used. Exposure is expected to be seasonal and intermittent, and of short duration depending on the size of the buildings and outdoor areas that are to be sprayed. Pre-wetting the soil with a garden hose may be required on very dry soils. All infested areas, and pets present are treated with a suitable flea control product to avoid re-infestation. Fenthion is applied as a coarse spray on walls and other areas where flies alight or congregate.

Exposure scenarios, caveats, parameters and absorbed doses for airblast spraying of fruits and vegetables are outlined in Table 7.

Exposure scenarios, caveats, parameters and absorbed doses for mosquito treatment of water (hand-held spraying) are outlined below.

Table 90: Agricultural uses (mosquito treatment of water) of Fenthion (100 g/L), exposure scenarios, caveats, parameters and absorbed doses (H nozzle and H-RDA-high)

Exposure scenario	Application rate (L/ha) (1) Spray volume (L/ha(1) Work rate (ha/d) (1)	PPE/Clothing	Equipment	Estimate No.	Operation	Daily absorbed dermal dose (mg/kg bw/d) (2)	Daily absorbed inhalation dose (mg/kg bw/d)(3)	Daily total absorbed dermal & inhalation dose (mg/kg bw/d)(4)
Scenario (1) Mixing/loading/application, to support hand-held spraying, water (H nozzle) (EC 100 g/L)	0.23 L/ha 1250 L/ha 1 ha/day	M/L - gloves Appl.–overalls (or long pants and long sleeved shirt), gloves	5 L non-specific design container	Estimate 5a	M/L Appl	0.003 ND**	NM* ND	0.003 ND*
			5 L wide-neck container	Estimate 5b	M/L Appl	ND ND	ND ND	ND ND
Scenario (1) Mixing/loading/application, to support hand-held spraying, water (H-RDA-High) (EC 100 g/L)	100 L/ha 1250 L spray /ha 1 ha/day	M/L - gloves Appl.–overalls (or long pants and long sleeved shirt), gloves	5 L non-specific design container	Estimate 5c	M/L Appl	0.003 ND	NM ND	0.003 ND
			5 L wide-neck container	Estimate 5d	M/L Appl	ND ND	NM ND	ND ND

*NM – not measured
**ND – not detected
(1) Label and APVMA recommended application rate and spray volume, considered to be representative for boom spraying of most crops.
(2) Daily absorbed dermal dose (mg/kg bw/d) = surface contamination (mL/operation or mL/hour) x number of operations or duration of exposure (hours) x concentration of ai in spray (mg/mL) x penetration through clothing/protective clothing (%) x dermal penetration (%)÷ average body weight (kg)
(3) Daily absorbed inhalation dose (mg/kg bw/d) = inhalation exposure (mL/hour) x concentration of active ingredient in spray (mg/mL) x duration of spraying (hours) x inhalation absorption (%)÷ average body weight (kg)
(4) Daily total absorbed dose (mg/kg bw/d) = Daily absorbed dermal dose (mg/kg bw/d) + Daily absorbed inhalation dose (mg/kg bw/d)

Exposure scenarios, caveats, parameters and absorbed doses for hand-held spraying of commercial and domestic areas are outlined below.

Table 91: Agricultural uses (commercial and domestic areas) of Fenthion (100 g/L), exposure scenarios, caveats, parameters and absorbed doses (H nozzle)

Exposure scenario	Application rate (kg ai/ha[(1)] Spray volume (L/ha) [(1)] Work rate (ha/d) [(1)]	PPE/Clothing	Equipment	Estimate No.	Operation	Daily absorbed dermal dose (mg/kg bw/d)[(2)]	Daily absorbed inhalation dose (mg/kg bw/d)[(3)]	Daily total absorbed dermal & inhalation dose (mg/kg bw/d)[(4)]
Scenario (2) Mixing/loading to support hand-held spraying of fleas , commercial and domestic areas (H nozzle) (EC 100 g/L)	15 L product/ha 270 L/ha 0.1 ha/day	M/L - gloves Appl.–overalls (or long pants and long sleeved shirt), gloves	5 L non-specific design container	Estimate 6a	M/L Appl	0.001 0.118	NM* 0.010	0.001 0.128
			5 L wide-neck container	Estimate 6b	M/L Appl	ND** 0.118	NM 0.010	ND 0.128
Scenario (2) Mixing/loading to support hand-held spraying of fleas , commercial and domestic areas (H – RDA High) (EC 100 g/L)	15 L product/ha 270 L/ha 0.1 ha/day	M/L - gloves Appl.–overalls (or long pants and long sleeved shirt), gloves	5 L non-specific design container	Estimate 6c	M/L Appl	0.001 0.113	NM 0.005	0.001 0.118
			5 L wide-neck container	Estimate 6d	M/L Appl	ND 0.113	NM 0.005	ND 0.118
Scenario (2) Mixing/loading to support hand-held spraying of flies , commercial and domestic areas (H nozzle) (EC 100 g/L)	12.4 L product/ha 112.5 L/ha 0.1 ha/day	M/L - gloves Appl.–overalls (or long pants and long sleeved shirt), gloves	5 L non-specific design container	Estimate 6e	M/L Appl	0.001 0.234	NM 0.019	0.001 0.253
			5 L wide-neck container	Estimate 6f	M/L Appl	ND 0.234	NM 0.019	ND 0.253

Scenario (2) Mixing/loading to support hand-held spraying of flies, commercial and domestic areas (H – RDA High) (EC 100 g/L)	12.4 L product/ha 112.5 L/ha 0.1 ha/day	M/L - gloves Appl.–overalls (or long pants and long sleeved shirt), gloves	5 L non-specific design container	Estimate 6g	M/L Appl	0.001 0.223	NM 0.009	0.001 0.232
			5 L wide-neck container	Estimate 6h	M/L Appl	0.000 0.223	NM 0.009	ND 0.253

*NM not measured

**ND not detected

(1) Label and APVMA recommended application rate and spray volume, considered to be representative for mosquito treatment of water

(2) Daily absorbed dermal dose (mg/kg bw/d) = surface contamination (mL/operation or mL/hour) x number of operations or duration of exposure (hours) x concentration of ai in spray (mg/mL) x penetration through clothing/protective clothing (%) x dermal penetration (%)÷ average body weight (kg)

(3) Daily absorbed inhalation dose (mg/kg bw/d) = inhalation exposure (mL/hour) x concentration of active ingredient in spray (mg/mL) x duration of spraying (hours) x inhalation absorption (%)÷ average body weight (kg)

US-Canada model: Pesticide Handlers Exposure Database (US EPA, 1999)

The Pesticide Handler's Exposure Database (PHED) is based on the principle that most dermal and respiratory exposure relates more to the formulation type, conditions of use, environmental conditions and personal protective measures than the physical and chemical properties of the active ingredient. PHED contains measured exposure data collected from field workers and allocates these into four separate worker groups (mixer/loaders, applicators, mixer/loader/applicators and flaggers). In PHED exposure scenarios for mixing/loading did not have a good number of replicates (only 6-8 numbers of replicates were available), therefore this scenario is not used in this assessment. Exposure scenarios were identified for airblast applications in various fruits. Applying sprays using an airblast sprayer (same treatment scenarios as above). The worker is assumed to be wearing long pants, long sleeve shirt, but no gloves. Additional PPE included gloves. Two scenarios were looked at, applications with open cabs and with closed cabs. The following parameters and assumptions were made in the PHED modelling:

Inhalation absorption	100%
Dermal absorption	3%
Average body weight	70 kg
Formulation type	EC (55% ai)
Work rate	20 ha /day

Scenario (4) Application of paint to roost areas

Fenthion is used as paint for the control of unwanted birds in industrial and commercial premises. The product is to be used only by registered pest control operators authorized by the manufacturer/registrant of the product. Standard Operating Procedures should be observed during use of the product. It is applied as paint to 10% of favoured roost areas. Occupational exposure is unlikely if the product is applied according to label instructions, and safety directions observed.

Scenario (5) Application of 1% Dust Formulations

Fenthion 1% Dust Formulation is used by PCOs for the control of crawling insects in cracks and crevices, wall voids and crawl spaces for cockroaches, ants, silverfish and crickets, and in ceiling voids for spiders. As the product will be applied only by PCOs in limited quantities and the concentration of fenthion is quite low in the product, occupational exposure is unlikely if the product is applied according to the label instructions, and safety directions observed.

10.2.4 Post-application exposure

It is uncommon for pest control operators to re-enter commercial areas post-treatment, except in certain circumstances. Registered product labels do not include a restriction on re-entering enclosed areas after treatment with fenthion.

No post application occupational exposure is anticipated in waterways, septic tanks, and roost areas.

10.3. Occupational Risk Assessment

The occupational risk assessment takes into consideration the hazard of the chemical as determined by toxicology testing (Section 2), its use pattern in Australia (Section 3) and worker exposure for each exposure scenario (Section 4). In order to adequately determine the risk associated with the use of fenthion, margins of exposure (MOE) were calculated by comparing the most appropriate NOEL with exposure values obtained from predictive modeling. A qualitative risk assessment was conducted where a suitable model was not identified.

The main adverse health effect of fenthion exposure is ChE inhibition. The most appropriate NOEL to assess short and long-term occupational risk to workers was determined to be 0.02 mg/kg bw/d, established in a 4 week human dietary study (Section 10.2.2). A dermal absorption adjustment of 3% was used in the risk assessment (Section 10.2.3). No correction was made for inhalation absorption, as 100% absorption was assumed (Section 10.2).

Fenthion is a slight skin irritant in experimental animals. This topical effect may manifest in workers who come in contact with fenthion products. The potential for topical effects when in contact with the working strength solutions is likely to be governed by the concentration of the product in the spray/solution in each case. In estimating the risk to workers handling fenthion products, it is assumed that workers wear appropriate PPE, as specified on product labels.

10.3.1 Risk from end use exposure

Water and Septic tanks

Treatment of stagnant water with fenthion is carried out using high volume hand-held sprayers attached to motorised pumps mounted on either four wheel drives or ATVs and knapsack sprayers. Exposure is anticipated when workers open containers, measure the required quantity of product and mix it with the appropriate amount of water, often within the spray tank of the application equipment. For hand-held spraying it is assumed that fenthion will be mixed in a 400 L spray tank. Predictive modelling was used to estimate worker exposure.

For the treatment of septic tanks worker exposure is anticipated when the workers open the container, measure the required quantity (40 mL/tank) and dispense the product. No dilution is carried out. Predictive modelling was not used to estimate exposure as no model exists for direct ‘flushing’ into septic tanks.

The risk associated with mixing/loading and treatment of water using hand-held equipment (Scenario 1) is found the table below.

Table 92: Risk associated with mixing/loading and treatment of water by hand-held equipment (H-nozzle and H RDA-High)

Scenario and conc.of ai in the product	Estimates	Operation	Daily total absorbed dose (mg/kg/d)	MOE(1)
Scenario (1) Mixing/loading and treatment of water using H-nozzle (100 g/L)	**Estimate (5a)**	M/L Appl	0.003 ND(2)	7 -
	Estimate (5b)	M/L Appl	ND ND	- -
Mixing/loading and treatment of water using H RDA-High (100 g/L)	**Estimate (5c)**	M/L Appl	0.003 ND	7 -
	Estimate (5d)	M/L Appl	ND ND	- -

(1) MOE = NOEL (0.02 mg/kg/d) ÷ daily total absorbed dose (mg/kg/d)
(2) not detected

Unacceptable MOEs were obtained for mixer/loaders of fenthion when using non-specific design containers (5a & 5c) for treatment of mosquitoes. Exposure was not detected for mixer/loaders using the wide neck containers (5b & 5d), and those applying fenthion using the hand-held and H-RDA-high models (5a – 5d) at the rate of 1250 L/ha.

.Commercial and domestic areas

Workers treating various commercial and domestic areas for fleas and flies are likely to be exposed when opening containers, measuring the required amount, diluting the product and loading the spray tank. Treatment is carried out using hand-held equipment, which is usually, hand-held sprayers attached to motorised pumps mounted on the backs of trucks or vans.

The risk associated with mixing/loading and treatment of commercial and domestic areas using hand-held equipment (H-nozzle and H RDA-High) (Scenario 6) is found in the following table.

Table 93: Risk associated with mixing/loading and treatment of commercial and domestic areas by hand-held equipment (H-nozzle and H RDA-High)

Scenario and conc.of ai in the product	Estimates	Operation	Daily total absorbed dose (mg/kg/d)	MOE(1)
Scenario (2) Mixing/loading and treatment of fleas in commercial and domestic areas, using H-nozzle (100 g/L)	**Estimate (6a)**	M/L Appl	0.001 0.128	20 <1
	Estimate (6b)	M/L Appl	ND(2) 0.128	- <1

Mixing/loading and treatment of fleas in commercial and domestic areas, using H RDA-High (100 g/L)	**Estimate (6c)**	M/L Appl	0.001 0.118	20 <1
	Estimate (6d)	M/L Appl	ND 0.118	- <1
Mixing/loading and treatment of flies in commercial and domestic areas, using H-nozzle (100 g/L)	**Estimate (6e)**	M/L Appl	0.001 0.253	20 <1
	Estimate (6f)	M/L Appl	ND 0.253	 <1
Mixing/loading and treatment of flies in commercial and domestic areas, using H RDA-High (100 g/L)	**Estimate (6g)**	M/L Appl	0.001 0.232	20 <1
	Estimate (6h)	M/L Appl	ND 0.253	- <1

(1) MOE = NOEL (0.02 mg/kg/d) ÷ daily total absorbed dose (mg/kg/d)
(2) ND not detected

Acceptable MOEs were obtained for mixer/loaders when using non-specific design containers (6a, 6c, 6e and 6g). Exposure was not detected for mixer/loaders using the wide neck containers (6b, 6d, 6f and 6h). Unacceptable MOEs were obtained for workers applying fenthion at the rates of 270 L/ha and 112.5 L/ha for the treatment of fleas and flies using hand-held equipment (H-nozzle and H-RDA-High models). PHED model could not be used for these scenarios as required number of replicates, were not available.

10.4 References

Ames RG, Brown SK, Rosenberg J, Jackson RJ, Stratton JW, Quenon SG (1989), Health Symptoms and Occupational Exposure to Flea Control Products among California Pet Handlers, Am Ind Hyg Assoc J. 50 (9), 466-472.

Bryant DH, Asthma due to insecticide sensitivity (1985), Aust NZ J Med, 15, (1), 66-68.

Coulston F, Griffin T, Rosenblum I (1979) Safety Evaluation of Fenthion in Human Volunteers, Institute of Comparative and Human Toxicology, Albany Medical College, New York and International Center of Environmental Safety, Albany Medical College, New York.

De Bleecker JL (1995) The Intermediate Syndrome in 0rganophosphate Poisoning: an Overview of Experimental and Clinical Observations, Clinical Toxicology, 33(6), 683-686.

Department of Health and Aged Care (2001) Review of the Mammalian Toxicology and Metabolism/Toxicokinetics of Fenthion, Chemical Review and International Harmonisation Section, Chemicals and Non-Prescription Drugs Branch, Therapeutics Goods Administration, Canberra, Australia.

EU Annex of the EEC Council Directive 67/548/EEC (as updated by EC Council Directive 96/54/EC), 2001

Handbook of First Aid Instructions and Safety Directions (1998) Commonwealth Department of Health and Family Services and National Occupational Health and Safety Commission, Australian Government Publishing Service, Canberra.

Jeyaratnam J, Ponnamblam N (1980) Monitoring of Public Health Workers Exposed to Fenthion, Field Worker Exposure during Pesticide Application, Studies in Environmental Science No. 7, Tordoir, W.F., and Van Heemstra-Lequin, Editors; Elsevier Scientific Publishing Company, New York.

Jung HF (1963) Poisoning cases caused from aerial application of Baytex dust, NTHS Letter (15/10/63).

Metcalf RL, Swift TR, Sikes RK (1985) Neurologic Findings among Workers Exposed to Fenthion in a Veterinary Hospital, MMWR Morbidity Mortality Weekly Report (USA), July 5, 34 (26), 402-403.

Misra UK, Prasad M, Pandey CM (1994) A study of cognitive functions and event related potentials following organophosphate exposure, Electromyography and Clinical Neurophysiology, 34 (4), 197-203.

Misra UK, Nag D, Bhushan V, Ray PK (1985) Clinical and Biochemical Changes in Chronically Exposed Organophosphate Workers, Toxicology Letters, 24, 187-193.

Misra UK, Nag D, Misra NK, Mehra MK, Ray PK (1985) Some observations on the Macula of Pesticide Workers, Human Toxicology, 4, 135-145.

National Occupational Health and Safety Commission (1994a) *Control of Workplace Hazardous Substances* [NOHSC:1005(1994), 2007(1994)], Australian Government Publishing Service, Canberra.

National Occupational Health and Safety Commission (1994b) *National Code of Practice for the Labelling of Workplace Substances* [NOHSC:2012 (1994)], Australian Government Publishing Service, Canberra.

National Occupational Health and Safety Commission (1994c) *National Code of Practice for the Preparation of Material Safety Data Sheets* [NOHSC:2011(1994)], Australian Government Publishing Service, Canberra.

National Occupational Health and Safety Commission (1995) *Guidelines for Health Surveillance* [NOHSC:7039 (1995)], Australian Government Publishing Service, Canberra.

National Registration Authority for Agricultural and Veterinary Chemicals (1997..), *Guidelines for Registering Veterinary Chemicals,* Canberra, Australia

National Occupational Health and Safety Commission (1998) *Approved Criteria For Classifying Hazardous Substances Revised Edition* [NOHSC:1008(1999) Australian Government Publishing Service, Canberra.

National Occupational Health and Safety Commission (1999) *Draft List of Designated Hazardous Substances* [NOHSC:10005(2001)], Australian Government Publishing Service, Canberra.

Tomlin C (ed) (2003), The Pesticide Manual, Crop Protection Publications, British Crop Protection Council, Thirteeth Edition.

Wolfe HR, Armstrong JF, Durham WF (1974) Exposure of Mosquito Control Workers to Fenthion, Mosquito News, 263-267.

The following literature reviews (not specific for fenthion), letters/case reports were reviewed, but not included in the report, as they were not considered relevant for assessment of OHS exposure.

Coosemans M, Carnevale P (1995) Malaria vector control a critical review on chemical methods and insecticides, Annales se la Societe Belge de Medecine Tropicale (1), 13-31.

Costa LG (1997) Basic Toxicology of pesticides, Occupational Medicine (Phildelphia) 12 (2), 251-268.

Faul J (1992) Fenthion – internal company experience (includes Bormann letters), Bayer AC letter 29.10.92.

Gordon CJ (1996) Thermoregulatory aspects of environmental exposure to anticholinesterase agents, Reviews on environmental health, 11 (3), 101-117.

Schack W (1976) Fenthion=lebaycid active agent, Bayer AG letter, 22.1.76.

Wagner SL (1990) Pesticide illness surveillance review of the national pesticide hazard assessment program, Am J In Med, 18 (3), 307-312.

Brunetto MR, Burguera JL, Burguera M, Villegas F, Bastidas C (1992), Observation on a human intentional poisoning case by the organophosphorous insecticide fenthion, Invest Clin (Venzuela), 33, (3), 89-94.

De Bleecker J, Van Den Neucker K, Colardyn F (1993), Intermediate syndrome in organophosphate poisoning: a prospective study, Critical Care Medicine, 21 (11), 1706-1711.

De Wilde V, Voglaers D, Colardyn F, Vanderstraeten G, Van den Neucker K, De Bleecker J, De Reuck J, Van den Heede M (1991) Postsynaptic neuromuscular dysfunction in organophosphate induced intermediate syndrome, Klin Wochenschr (Germany), Feb 26, 69 (4) 177-183.

Dich J, Zahm SH, Hanberg A, Adami H-O (1997) Pesticides and Cancer, Cancer causes and control, 8 (3), 420-443.

Goswamy R, Chaudhuri A, Mahashur AA (1994) Study of respiratory failure in organophosphate and carbamate poisoning, Heart & Lung, 23 (6), 466-472.

Karademir M, Ertuk F, Kocak R (1990) Two cases of organophosphorous poisoning with development of intermediate syndrome, Hum Exp Toxicol, 9 (3), 187-190.

Karalliedde L, Senanayake N, Ariaratnam A (1998) Acute organophosphorous insecticide poisoning during pregnancy, Hum Toxicol (England), 7, (4), 363-364.

Raschke AM, Burger A (1997) Risk assessment as a management tool used to assess the effect of pesticide use in an irrigation system, situated in a semi-desert region, Archives of Environmental Contamination and Toxicology, 32 (1), 42-49.

Sedgwick EM, Senanayake N (1997) Pathophysiology of the intermediate syndrome of organophosphorous poisoning, J Neurosurg Psychiatry (England), 62 (2) 201-202.

Senanayake N, Sanmuganathan PS (1995) Extrapyramidal manifestations complicating organophosphorous insecticide poisoning, Hum Exp Toxicol (England) 14 (7) 600-604.

Simonsen L, Lund SP (1992) A strategy for delineating risks due to exposure to neurotoxic chemicals, Am J Ind Med, 21, (6), 773-792.

Steenland K (1996) Chronic neurological effects of organophosphate pesticides, British Medical Journal, 312 (7042), 1312-1313.

Van den Neucker K, Vanderstraeten G, De Muynck M, De Wilde V (1991) The neurophysiologic examination in organophosphate ester poisoning. Cases report and review of the literature, Electromyrogr Clin Neurophysiol (Belgium), 31, (8), 507-511.

Wilson BW, Sanborn JR, O'Malley MA, Henderson JD, Billitti JR (1997) Monitoring the pesticide-exposed worker, Occupational Medicine (Philadelphia)12 (2), 347-363.

Tsatsakis AM, Aguridakis P, Michalodimitrakis MN, Tsakalov AK, Alegakis AK, Koumantakis E, Troulakis G (1996) Experiences with Acute Organophosphate Poisonings in Crete, Vet Human Toxicol 38 (2), 101-107.

Beat VB, Morgan DP (1977) Evaluation of Hazards Involved in treating Cattle with Pour-On Organophosphate Insecticides, JAVMA, Vol 170, No. 8, 812-814.

11. ENVIRONMENTAL ASSESSMENT

11.1 Environmental Exposure

11.1.1 Environmental Release

Current uses

General Pest Control
Product 32999 is used in outdoor and subfloor areas of dairies, stables, meatworks (non-product areas), commercial and industrial buildings and homes, for control of spiders, ants, fleas, flies and mosquitoes. Non-mosquito uses typically involve spraying walls of buildings or surrounding soil. Mosquito uses include spraying of surfaces where adults congregate and dilution in water where mosquitoes are breeding as well as in septic tanks.

Product 51627 is used to control spiders, ants and fleas in domestic outdoor areas. The label also permits use in water bodies, ornamental ponds and septic tanks to control mosquitoes. Product is applied as a spray (as above) except where added to water bodies for mosquito control.

Product 41138 is applied as a dust (apparently used only by licensed pest control operators) to control cockroaches, ants, silverfish, crickets and spiders within building structures (wall and ceiling voids etc.).
Over 7 tonnes were used in 2000.

Companion Animal Pest Control
Fenthion products (46206, 46222, 40084 and 54065) are used as spot-on treatments for the control of fleas on dogs, with less than 200 kg used for this purpose per annum.

Bird Control
Fenthion products (42202, 50244 and 52075) are used to control pest birds such as pigeons, starlings, Indian mynahs and sparrows in and around industrial, commercial, educational and domestic buildings. Information available to DEH suggests that application is undertaken by licensed pest control operators only, with application by brush or roller to roosting/nesting areas. The products are registered in Victoria, Tasmania and Northern Territory only, however permits have been issued covering use of fenthion bird control products in other jurisdictions from time to time. Use is very minor (< 200 kg product per annum).

Packaging and Disposal

Emulsifiable Concentrates (general pest control)
Product 32999 is supplied in 250 mL, 500 mL and 5L containers, which are to be disposed of by burial in landfill or non-crop producing land.
Product 51627 is supplied in 200 mL containers, which are disposed of with domestic waste.

Powders or Dusts (general pest control)
Product 41138 is supplied in containers at up to 5 kg, which are to be disposed of by burial in landfill or non-crop producing land.

Spot-ons (companion animal treatments)
The spot-on formulations are supplied in single use 0.5 mL and 1 mL doses for dogs (over or under 10 kg respectively). Containers are disposed of with domestic waste.

Gels (avicides)
Products 52075 and 50244 are supplied in containers at up to 10 kg, which are to be disposed of by burial in landfill or non-crop producing land.

Product 42202 is supplied in 20 L containers. The label provides no instructions in respect of container disposal.

11.2 Environmental Fate

Any risks potentially associated with the products that are the subject of this review are likely to be due to acute exposures to treated areas. In all circumstances, treated areas are mad-made structures or the immediate surrounds of treated areas. The limited extent of environmental exposure from these uses has not necessitated an assessment of environmental fate (risk is assessed based on acute exposures only). However, assessment for food uses suggests an aquatic half-life of between 7 and 9 days. Environmental fate will be considered in detail with the review report covering food uses of fenthion.

11.3 Environmental Effects

Bayer submitted most of the following reports, several of which are old and do not meet current requirements.

The Department of the Environment and Heritage rated the regulatory type studies as being reliable, acceptable or for information only. The ratings can be described as:

- Reliable: There is a high level of confidence in the results. The study has been performed satisfactorily and while there are only minor problems, they do not affect the results.
- Acceptable: The results of the study are scientifically sound but there is a lower level of confidence in the results due to a significant problem or lack of critical information. Often the results are nominal only.
- For information: There are sufficient problems in the test that the results are not suitable for regulatory use.

11.3.1 Aquatic Toxicity

Regulatory Studies for Fish

The following aquatic toxicity results for fenthion and an emulsifiable concentrate formulation of fenthion were considered.

Table 94: Toxicity of Fenthion technical to fish.

Test	Test method	Species	Results LC50, mg ac/L	References
96 hour acute static	US EPA 72-1	Rainbow trout	0.83* (0.49-3.3) [a]	Swigert, 1986
96 hour acute flow-through	US EPA 72-1	Bluegill	1.7* (0.95-3.6) [a]	Swigert, 1987
96 hour acute static	US EPA 72-1	Bluegill	1.6** (1.3-1.9) [a]	Carlisle and Roney, 1984
96 hour acute static	OECD	Golden Orfe	2.36** (2.32-2.44) [a,c]	Dorgerloh, 1994a
96 hour acute static	OECD	Rainbow trout	1.26** (0.71-6.9) [a,c]	Dorgerloh, 1994b
96 hour acute static		Golden Orfe	2.7** (2.6-2.9) [a,c]	Hermann, 1979
96 hour acute static		Rainbow trout	0.87** (0.74-1.00) [a]	Hermann, 1978
96 hour acute flow-through	US EPA	Sheepshead minnow	1.2 (0.87-1.4) [a]	Surprenant 1988a
Early life stage, embryos and larvae, 88 days	US EPA 72-4	Rainbow trout	MATC 0.013-0.027 Geo. Mean 0.019	Surprenant, 1988b

* Results calculated using nonlinear interpolation between confidence limits
** Results are nominal.
[r] Result considered reliable, [a] result considered acceptable, [c] results converted from product to active constituent

The acute toxicity studies for bluegill (Swigert, 1987) and rainbow trout (Swigert, 1986) are acceptable. The results are based on mean measured concentrations with measurements taken at time 0, 48 and 96 hours after exposure. The highest concentrations tested, 8.0 and 5.0 mg/L nominal for bluegill and trout respectively, had an oily film present at all sampling, which was considered to have interfered with the 96 h sample for bluegill. This was not considered to affect the study, as there was 100% mortality in these treatments and the next lower treatment group. Measurements of temperature, dissolved oxygen and pH were all satisfactory during the tests. The data was not suitable for probit analysis and result in Table are from nonlinear interpolation. Using Trimmed-Spearman the LC50 is 1.76 (1.52-2.05) mg/L for bluegill and 0.81 (0.68-0.97) mg/L for rainbow trout.

The results for bluegill (Carlisle and Roney, 1984) were not conducted to any International Guidelines and the report is lacking some details on the conditions used and there is limited the raw data provided. However, the study was conducted under GLP and there are sufficient details on the methodology used to indicate that if additional data had been presented, the study could meet the 1984 US EPA Guidelines. The test solutions were not analysed and the LC50 was based on probit analysis. Despite the lack of raw data and analysis of the test solutions, the LC50 was considered acceptable.

Dorgerloh, 1994a
The report for golden orfe by Dorgerloh was a revised report from original study conducted in 1978/79, rewritten to meet OECD reporting requirements. The test substance used was Lebaycid 500 EC (550 g ac/L). The testing was conducted over a 4-month period with 6 concentrations tested, 3.4, 4.0, 4.2, 4.4, 4.6 and 4.8 mg/L of the test substance. The test solutions were not analysed for concentration of test material, although a stability control dosed at 1 mg/L of active ingredient was tested after 2, 48 and 96 hours with 67% of nominal after 2 hours increasing to 80% after 96 hours. This was taken as evidence that the solution was sufficiently stable during the testing.

Most of the tests were conducted on different dates, ranging from a week to 4 week between tests and only one test concentration tested at a time. For each test there was a control used with a total of 13 controls. In determining the LC50 all the data was pooled, with the same test concentrations considered as replicates, which is not statistically valid. However, while the study does not meet current requirements, the result is expected to be a true reflection of the actual LC50 for this species and is considered acceptable, noting that the result is nominal. The NOEC was <3.4 mg/L (1.87 mg ac/L), based on the irregular swimming behaviour of all fish at 3.4 mg/L.

Dorgerloh, 1994b
The report is similar to that above in that it is a revised report from original study rewritten to meet OECD reporting requirements and using the same test substance, Lebaycid 500 EC. The testing was conducted over a 2-month period, again with one test concentration tested at each date and 7 concentrations tested, 0.8, 1.0, 1.7, 2.0, 2.4, 2.8 and 4.0 mg/L of the test substance. The results in Table are as given in the report using probit analysis of the results. The NOEC was given as < 0.8 mg/L (0.44 mg ac/L) based on irregular behaviour of all fish at 0.8 mg/L.

Hermann, 1978 and 1979
The two results from Hermann were conducted before Guidelines for testing were introduced and used pure active ingredient. The test solutions were not analysed and the results are nominal. The water temperature used for the trout study was higher than current Guidelines indicate, 16° C, but as there were no mortalities or effects noted in the control, this does to appear to affect the results. The results are considered as acceptable.

Surprenant 1988a
The flow-through test using sheepshead minnow was performed using fenthion and according to US EPA Guidelines. Analysis of the test solution showed that the test concentrations were 62-69% of nominal and were consistent throughout the 96-hour test. As there was only one partial response, the LC50 was determined by binomial probability and the NOEC is 0.61 mg ac/L, based on irregular swimming behaviour of the fish at 0.87 mg ac/L. Using Trimmed Spearman, DEH calculated an LD50 of 1.23 (1.13-1.34) mg ac/L.

Surprenant, 1988b
As a substitute for a full life-cycle toxicity test, the toxicity of fenthion to the embryos and larvae of Sheepshead minnows was determined under flow through conditions according to US EPA Guideline 72-4. The rationale, as stated by the authors of this study, is based on the observation that these embryo/larvae studies are reasonably accurate short-term predictors of the chronic life cycle studies. The criteria used to determine the MATC (Maximum Acceptable Toxicant Concentration) was based on larval growth (length) at the termination of the test. Analysis of the test solutions showed that the mean test concentrations were 71-90% of nominal over the test period. While there was a significant deviation from the test protocol, in that 20 viable embryos were selected before hatching with surviving larvae released for the 60-day post-hatch exposures rather than 20 fry post-hatch as stated in the protocol, this is unlikely to affect the study and the deviation is acceptable. The study was well performed and it meets the current Guidelines. The results are considered reliable and would suggest a high acute to chronic ratio.

Regulatory Studies for Invertebrates
The following studies on the toxicity of fenthion to aquatic invertebrates were presented by the registrants and have been summarised in the table below.

Table 95. Toxicity of fenthion to aquatic invertebrates.

Test	Test method	Species	Results EC50, µg ac/L	References
48 h mortality flow-through	US EPA	*Daphnia magna*	LC50 5.2 (4.6-6.0) [r]	Forbis, 1987
48 h static	OECD	*Daphnia magna*	EC50 5.7 (4.1-7.8) [r]	Heimbach, 1985a
21 day chronic flow-through	US EPA	*Daphnia magna*	MATC 0.042-0.082 (Geo. Mean 0.059) [r]	Forbis, 1988
21 day chronic static renewal	OECD	*Daphnia magna*	MATC** 0.009- 0.016 [a,c]	Adema, Dalsum and Bommel, 1989
96 h mortality, flow through	US EPA	Mysid shrimp	LC50 0.22 (0.19-0.27) [a]	Surprenant, 1988c
28 day emergence static	Proposed BBA Guideline	*Chironomus riparius*	1.04** (0.56-1.8) [r]	Heimbach, 1995
96 h, flow through	US EPA	*Eastern Oysters*	370 (140-1000) [r]	Surprenant, 1988d

* Results calculated using nonlinear interpolation between confidence limits
** Results are nominal.
[r] Result considered reliable, a result considered acceptable, [c] results converted from product to active ingredient.

Forbis, 1987
The acute 48 hours daphnia test was conducted according to US EPA Guidelines under flow-through conditions. The mean measured test concentrations for 0 and 48 hours were similar and the overall mean concentrations used to determined the LC50. There were 10 daphnids, <24 hours old, used per replicate and 4 replicates per test concentration. The LC50 was determined using probit analysis. This was a well-conducted study and the results are considered as reliable.

Heimbach, 1985a
The 48 h mortality test was conducted according to OECD 202 Guidelines using fenthion. Nominal concentrations were 1.8, 3.2, 5.6, 10, 18, 32, 56 and 100 µg/L. The test solutions were not analysed. A positive control gave satisfactory results and physical parameters (temperature, dissolved oxygen and pH) of the test solutions were satisfactory. The results are considered acceptable.

Forbis, 1988
A 21 day reproduction study was performed according to US EPA Guideline 72-4 using ^{14}C-fenthion under flow-through conditions. The mean concentrations of the test solutions used were 0.013, 0.021, 0.042, 0.082 and 0.20 µg ac/L. Analysis was by extraction of the test water followed by radioanalyses of the extract. Spiked samples (4.19, 22.1 and 236 ng/L) showed a mean recovery of 95% with a range of 91-97%. The methodology is satisfactory.

There was 100% mortality in the highest concentration after 13 days and 12% mortality in the next lowest test concentration. Statistically significant effects on reproduction and mean adult length occurred at 0.082 µg/L, with no statistically significant effect on reproduction or growth (body length) at the lower concentrations. The MATC of 0.042-0.082 µg/L was determined (geometric mean of 0.059 µg/L). The result is considered reliable.

Adema, Dalsum and Bommel, 1989
A 21-day reproduction study was performed according to OECD Guideline 202 under semi-static conditions using Lebaycid EC 50 containing fenthion at 50.3%. The test solutions used

were 0.0056, 0.01, 0.018, 0.032, 0.056 and 0.1 μg/L nominal of test material. Solutions were renewed on Monday, Wednesday and Friday. Analysis of the test solutions showed all were below the limit of detection of 1.0 μg/L. There was only 20% mortality in the highest concentration 0.1 μg/L after 21 days with statistically significant effects on reproduction at 0.032 μg/L and approximately 50% reduction in repopulation at the highest test concentration. An EC50 was estimated to be 0.1 μg/L, based on reproduction. The MATC of 0.018-0.032 μg/L (0.009-0.0016 μg ac/L) was determined for reproduction. Effects on subjective parameters were noted at 0.1 (size), 0.056 (swimming behaviour) and 0.032 (colour) μg/L. The results are considered acceptable.

Surprenant, 1988c
The mysid shrimp study was performed according to US EPA Guidelines under flow through conditions using radiolabelled fenthion. The test concentrations were analysed at time 0, 48 and 96 hours by extraction and radioanalysis of the extracts. Preliminary studies showed that the method gave 93% recovery with a limit of reporting of 12 ng/L. The highest test concentration 500 ng/L was also analysed by HPLC, which gave consistent results but was at the reporting limit.

The concentration of all the test solutions decreased over the study period, with average measured concentrations of 89, 77 and 46% of nominal at time 0, 48 and 96 hours respectively. For 500 ng/L nominal, the mean measured concentrations were 435, 365 and 190 ng/L for 0, 48 and 96 hours respectively and the HPLC analysis showed similar results, 710, 560 (760 and 360) and 240 ng/L respectively. The quality assurance samples, prepared at each sampling interval, showed that the analysis gave results consistent with their nominal concentrations. The report indicates that the decrease in test concentrations was due to the behaviour of Fenthion.

The LC50 was calculated by probit analyses as 220 (190-270) ng/L using mean measured concentrations over the 96 hours. Due to the difficulties encountered in maintaining the test concentrations during the test exposures, the results are considered as acceptable.

Heimbach, 1995
The influence of fenthion on the development and emergence of larvae of *Chironomus riparius* was conducted according to a proposed BBA Guideline entitled "Effects of plant protection products in the development of sediment–dwelling larvae of *Chironomus riparius* in a water sediment system", dated June 1995.

To a sediment water system (2 cm sediment, 20 cm water, artificial sediment) containing larvae of the test organism was added fenthion (technical 95.3% ac). The test concentrations used were 0.1, 0.18, 0.32, 0.56, 1.0, 1.8, 3.2, 5.6 and 10 μg/L. Three times during the study, on days 0, 7 and 28, the overlying water and pore water of the sediment was analysed for fenthion in the treatments 0.32, 1.8 and 10 μg/L only, the other treatments were not tested. The physical characteristics (temperature, pH, dissolved O_2) of the test water for all concentrations remained relatively consistent during the testing period. The concentration of fenthion declined sharply from initial values of 9.43, 0.93 and 0.16 μg/L for nominal concentration of 10, 1.8 and 0.32 μg/L respectively to 0.2 and 0.88 μg/L in pore water and overlaying water 7 DAT for the highest concentration. The pore water was 3.8 μg/L for 1.8 μg/L but the overlaying water was below detection (<0.1 μg/L). All samples were below detection for the 28 DAT analysis.

The time for emergence and the number of adult midges that emerged were reported. The EC50 was given as 1.04 µg/L (probit) for emergence of midges but confidence limits could not be determined (only one partial result). The confidence limits of 0.56-1.8 µg/L in Table are the 0 and 100% effect levels.

Surprenant, 1988d
The acute toxicity of fenthion (96.9%) to eastern oysters (*Crassostrea virginica*) was determined under flow-though conditions according to US EPA Guidelines. Analysis of the test solutions showed that at time 0 all were above nominal and averaged 144% of nominal. The 48- and 96-hour samples showed that concentration slowly decreased to be close to nominal after 96 hours. The mean concentrations were averaged 119% of nominal and were used to determine the EC50 of 370 (140-1000) µg/L. The NOEC was 130 µg/L. The study is rated as reliable.

Regulatory Studies for Algae

The following studies on the toxicity of fenthion to algae were presented by the registrants and have been summarised in Table 96.

Table 96: Toxicity of fenthion to algae.

Test	Test method	Species	Results EC50, mg ac/L	References
Growth Inhibition, 96 hours	OECD	*Scenedesmus subspicatus*	E_bC50 0.55 [a], E_rC50 1.79 [a]	Heimbach, 1985b
Growth Inhibition, 96 hour	US EPA	*Selenastrum capricornutum*	1.1 (0.87-1.3) i	Forbis, 1986
Growth Inhibition, 96 hours	ISO and OECD	*Scenedesmus subspicatus*	E_bC50 0.75 [c]	Heimbach, 1989a
Growth Inhibition, 7 days	US EPA	*Anabaena flos-aquae*	10.7 (3.2-72) [i]	Hughes, 1987a
Growth Inhibition, 7 days	US EPA	*Navicula pelliculosa*	1.2 (0.67-2.1) [1, a]	Hughes, 1986a
Growth inhibition, 7 days	US EPA	*Skeletonema costatum*	0.33 [a]	Hughes, 1986b
Growth inhibition 14 days	US EPA	*Lemna gibba*	NOEC[*]>2.8 i	Hughes, 1987b

[*]The NOEC is for inhibition of duckweed.
[1] Results recalculated by DEH.
[r] Result considered reliable, [a] result considered acceptable, [c] result converted from product to active constituent,
[i] results for information only.

Heimbach, 1985b
The algae test was performed to meet OECD Guideline 201. The test solutions were not analysed and results are based on nominal concentrations. The physical measurements of the water quality showed that the pH rose from 8.5 at test initiation to 10.2 after 96 hours in controls and all test concentrations, except for the highest where pH remained relatively stable. Comments in the report indicate that this could be due to the high growth rates. For the reference standard (potassium dichromate) the EC50 values for biomass and growth both agree with known values, indicating that test conditions conform to standards for the test. The E_bC50 was determined as 0.55 mg/L, the E_rC50 as 1.79 mg/L using probit analysis and the 4 day NOECs were <0.10 and 0.56 mg/L for biomass and growth rates respectively. No

confidence limits were given. DEH recalculated the results (Toxcal, cell per field entered as 10^6 cells per mL) to give E_bC50 as 0.98 (0.745-1.65) mg/L using probit analysis.

Forbis, 1986
This algae test was conducted according to US EPA Guideline 112-2. Analysis of the test solution at time 0 showed that concentrations varied from 88 to 105% of nominal but on termination of the tests the samples varied between 46 and 82% of nominal. The EC50 in Table 96 was based on mean measured concentrations and calculated using quadratic regressions. The data was not suitable for probit analysis and the EC50 was calculated by DEH using trimmed Spearman-Karber as 1.06 (0.72-1.57) mg ac/L.

Heimbach, 1989a
The algae test was conducted according to ISO Guidelines and OECD Guideline 201 using Lebaycid EC 50 as the test material. The analysis of the test solutions ranged from 78 to 99% of nominal at time 0. The solutions were not analysed again in the test. The E_bC50 was 1.5 mg /L (0.75 mg ac/L). An ErC50 could not be determined and was given as >2.0 mg/L.

Hughes, 1987a
The algae test using the blue-green alga *Anabaena flos-aquae* was conducted to meet US EPA Guidelines using fenthion as the test substance. Analysis of the test solutions were 40 to 81% of nominal at initiation and at termination of the test were 17, 25 and 36% of nominal for test concentrations of 1.6, 3.2 and 6.4 mg/L nominal. The three lowest test concentrations were less than the detection limit of 0.014 mg/L. The authors note that after 7 days under the growing conditions degradation (mainly photolysis, study conducted under aseptic conditions) or adsorption of the active could have occurred, eg adsorption to alga cells, filters etc (note that the samples were filtered through a membrane to remove cells before extraction), resulting in the loss of active noted in the analysis. In addition, it is noted that the QA samples for day 7 were not acceptable, 0.11, 0.9 and 3.1 mg/L for nominal concentrations of 0.2, 1.5, and 5.0 mg/L, which could indicate a significant problem with the analysis. The mean measured concentration from day 0 and 7 were used to determined the end-points of the study.

There was 21 to 42% inhibition over the duration of the test. End-points were determined by inverse estimation linear regression with the EC25 as 0.19 (0.05-0.56) mg/L and the EC50 as 10.7 (3.2-72) mg/L. The EC50 is not considered acceptable as there were significant problems with the analysis and there was no test concentration with greater than 50% inhibition. The result is for information only.

Hughes, 1986a
The test was conducted similarly to the above but using the freshwater diatom *Navicula pelliculosa*. The analysis at initiation showed a range from 96 to 100% of nominal concentrations but again after 7 days there was significant loss of active, with only the two highest concentrations (3.2 and 6.4 mg/L nominal) having detectable levels of active (0.50 and 1.5 mg/L respectively). The QA samples were acceptable for day 0 and 7. There was a response of 7 to 99% inhibition across the test concentrations with an EC50 of 0.98 mg/L but confidence limits could not be determined (the results were unsuitable for analysis by probit). When recalculated by DEH, the EC50 was 1.2 (0.67-2.1) mg/L using Trimmed Spearman Karber.

Hughes, 1986b
The test was conducted similarly to the above but using the saltwater algae *Skeletonema costatum*. The analysis at initiation showed a range from 45 to 53% of nominal for nominal concentrations 0.2 to 1.6 mg/L but was 66% and 97% for nominal concentrations of 3.2 and 6.4 mg/L. After 7 days there was significant loss of active, with only the two highest concentrations having detectable levels of active (0.38 and 1.4 mg/L respectively). The QA samples were only 56-64% for day 0 and 65-78% for day 7. There was a response of –9.5% to 99% inhibition across the test concentrations with an EC50 of 0.33 mg/L using inverse estimation least squares linear regression but confidence limits could not be determined. When recalculated by DEH using ToxCalc 5.0, the EC50 was 0.30 (0.25-0.35) mg/L using probit.

Hughes, 1987b
This test using duckweed, *Lemna gibba*, was conducted to US EPA requirements. The nominal concentrations used were 0.2, 0.4, 0.8, 1.6, 3.2 and 6.4 mg/L with initial (time 0) mean measured concentrations (HPLC analysis) of 0.092, 0.19, 0.51, 1.2, 2.5 and 5.4 mg/L. There were problems with the day 14 samples with all test replicates having 'less than' results, *i.e.*, for 3.2 mg/L nominal the day 14 results were 0.32, <0.24 and <0.24 mg/L (the detection limit ranged from 0.012 for lowest test concentration to 0.60 for highest). This possible is due to adsorption/degradation during the study.

There was no inhibition in any test concentration, although there were problems of algae contamination of controls and some test replicates. While the test does have significant problems with regard to the analysis of the test solutions and contamination, it was clear that fenthion did not significantly affect the growth of duckweed at an overall mean concentration of 2.8 mg/L. As a limit test the result is acceptable.

Other Aquatic End-points
A database from the Ecological Fate and Effects Division of the Office of Pesticide Programs, US EPA, to which DEH has access, contains the presently known ecotoxicity endpoints for registered pesticides used in the US. The toxicity data put into the database is compiled from actual studies reviewed by EPA in conjunction with pesticide registration or re-registration. These have been reviewed by Ecological Effects Branch biologists, judged to meet US EPA Guidelines, and therefore acceptable for use in the ecological risk assessment process. The studies are ranked as either core or supplemental (equivalent to reliable and acceptable used in this report). It should be noted, however, that some of these studies use nominal results and some care is needed in using these for the risk assessment. The results from this database for fish are in Table 97; those for aquatic invertebrates are given in Table 98; and for saltwater aquatic invertebrates, Table 99

Table 97. Summary of fish studies reviewed by the US EPA and found acceptable by them.

Species	Study date	US EPA Test Guideline & (category)*	Type, duration, %ac	EC or LC 50, µg/L	NOEL
Black bullhead (*Ictalurus melas*)	1980	72-1 (S)	Static, 96 h, 46	1350	N.R.
Bluegill sunfish (*Lepomis macrochirus*)	1980	72-1 (S)	Static, 96 h, 47.5	1380	N.R.
	1987	72-1a (C)	Flow-though, 96 h, 96.9	1700	410
Brown trout (*Salmo trutta*)	1980	72-1 (C)	Static, 96 h, 46	1330	N.R.
Carp (*Cyprinus carpio*)	1980	72-1 (S)	Static, 96 h, 46	1160	N.R.
Channel catfish (*Ictalurus punctatus*)	1980	72-1 (C)	Static, 96 h, 46	1600	N.R.
	1986	72-1 (C)	Flow-through, 96 h, 46	650	N.R.
Coho salmon (*Oncorhynchus kisutch*)	1980	72-1 (C)	Static, 96 h, 46	1320	N.R.
Cutthroat trout (*Oncorhynchus clarki*)	1980	72-1 (C)	Static, 96 h, 97	1580	N.R.
	1986	72-1 (S)	Flow-through, 96 h, 97	1150	N.R.
	1986	72-1 (C)	Static, 96 h, 97	1020	N.R.
Fathead minnow (*Pimephales promelas*)	1968	72-1 (S)	Static, 96 h, 93	3200	N.R.
	1986	72-1 (C)	Static, 96 h, 46	1680	N.R.
Goldfish (*Carassius auratus*)	1986	72-1 (S)	Static, 96 h, 47.5	2780	N.R.
Green sunfish (*Lepomis cyanellus*)	1986	72-1 (C)	Static, 96 h, 46	1880	N.R.
Guppy (*Poecilia reticulata*)	1968	72-1 (S)	Static, 24 h, N.R.	5810	N.R.
Lake trout (*Salvelinus namaycush*)	1986	72-1 (C)	Static, 96 h, 97	1450	N.R.
Largemouth bass (*Micropterus salmoides*)	1980	72-1 (S)	Static, 96 h, 47.5	1540	N.R.
	1986	72-1 (C)	Flow-through, 96 h, 97	1220	N.R.
Rainbow trout (*Oncorhynchus mykiss*)	1977	72-1 (S)	Static, 96 h, 93	840	N.R.
	1980	72-1 (C)	Static, 96 h, 46	930	N.R.
	1986	72-1 (C)	Static, 96 h, 97	550	N.R.
	1986	72-1b (C)	Flow-through, 96 h, 96.9	830	N.R.
	1988	72-4a (C)	Flow-through, 88 d, 96.9	LOEC 15	N.R
Yellow perch (*Perca flavescens*)	1980	72-1 (C)	Static, 96 h, 46	1650	N.R.
Sheepshead minnow (*Cyprinodon variegatus*)	1988	72-3 (C)	Flow-through, 96 h, 97	1200	610
Sheepshead minnow (*Cyprinodon variegatus*)	1986	72-3 (S)	Static, 48 h, 93,	1900	N.R.
Inland silverside (*Menidia beryllina*)	1986	72-3 (S)	Static, 48 h, 93	2200	N.R.
Spot (*Leiostomus xanthurus*)	1986	72-3 (S)	Flow-through, 48 h, 93	1200	N.R.
Striped mullet (*Mugil cephalus*)	1986	72-3 (S)	Flow-through, 48 h, 93	1600	N.R.
Striped bass (*Morone saxatilis*)	1968	72-3 (S)	Static, 96 h, N.R.	453	N.R.

* C = core, S = satisfactory

Table 98: Summary of freshwater aquatic invertebrate studies reviewed and found acceptable by the US EPA.

Species	Study date	US EPA Test Guideline & (category)*	Type, duration, test material, %ac	EC or LC 50, µg/L	NOEL
Water flea (*Daphnia magna*)	1986	72-2 (S)	Static, 48 h, 93	5.7	0.1
	1988	72-4b (C)	Flow-through, 21 d, 97.9	LOEC 0.021	
Water flea (*Daphnia pulex*)	1980	72-2 (C)	Static, 48 h, 97	0.8	N.R.
Daphnid (*Simocephalus serrulatus*)	1980	72-2 (C)	Static, 48 h, 97	0.62	N.R.
Scud (*Gammarus lacustris*)	1980	72-2 (C)	Static, 96 h, 97	8.4	N.R.
Scud (*Gammarus fasciatus*)	1986	72-2 (C)	Static, 96 h, 97	110	N.R.
Sowbug (*Asellus brevicaudus*)	1980	72-2 (C)	Static, 96 h, 97	1800	N.R.
Crayfish (*Orconectes nais*)	1980	72-2 (S)	Static, 5 d 97	50	N.R.
	1986	72-2 (S)	Static, 24 h, 97	350	N.R.
Stonefly (*Pteronarcys californica*)	1980	72-2 (C)	Static, 96 h, 97	4.5	N.R.
Stonefly (*Pteronarcella badia*)	1986	72-2 (C)	Static, 96 h, 97	10.7	N.R.
Glass shrimp (*Palaemonetes kadiakensis*)	1980	72-2 (C)	Static, 96 h, 46	10	N.R.

C = core, S = satisfactory

Table 99: Summary of saltwater aquatic invertebrate studies reviewed by the US EPA and found acceptable by them.

Species	Study date	US EPA Test Guideline & (category)*	Type, duration, test material, %ac	EC or LC 50, µg/L	NOEL
Mysid (*Mysidopsis bahia*)	1988	72-3 (C)	Flow-through, 96 h, 97	0.222	0.067
	1986	72-3 (C)	Flow-through, 96 h, 93	0.15	N.R.
	1985	72-4b (S)	Static, 14 D, N.R.	LOEC 0.079	0.037
Seed shrimp (*Cypridopsis vidua*)	1980	72-3 (S)	Static, 48 h, 46	18.0	N.R.
Brown shrimp (*Penaeus aztecus*)	1986	72-3 (S)	Flow-through, 48 h, 93	0.024	N.R.
Pink shrimp (*Penaeus duorarum*)	1986	72-3 (C)	Flow-through, 96 h, 93	0.11	N.R.
	1986	72-3 (S)	NR, 24 h, Tech	0.066	N.A.
Grass shrimp (*Palaemonetes pugio*)	1986	72-3 (S)	Static, 48 h, 93	4.7	N.R.
Blue crab (*Callinectes sapidus*)	1986	72-3 (S)	Flow-through, 48 h, 93.0	2.3	N.R.
Eastern oyster (*Crassostrea virginica*)	1986	72-3b (S)	Flow-through, 96 h, 93	340	N.R.
Eastern oyster (*Crassostrea virginica*)	1988	72-3b (C)	Flow-through, 96 h, 96.9	321	130

* C = core, S = satisfactory

It is clear from Tables 97, 98 and 99 that daphnia species are the most freshwater sensitive aquatic organisms with an acute EC50 of around 1 µg/L and brown shrimp the most sensitive saltwater organisms with an EC50 of 0.024 µg/L but Table , for which DEH has reviewed the full reports, shows the most sensitive organism is the mysid shrimp with LC50 of 0.22 µg/L. The results for fish range from an LC50 of 0.55 mg/L for rainbow trout to LC50 of 5.8 mg/L for guppy. The early life stage studies on fish and invertebrates clearly show that the early life stages are very sensitive and there is a very large acute to chronic ratio for the effects of fenthion on rainbow trout, with a ratio of 37, and for *D. magna* the ratio is 270. The high acute to chronic ratio is in Table 94 and Table 95.

Field Studies

Graney, 1988.
Bayer presented a review of the results of field studies conducted by the company, these are summarised in Table 100 below. While this was presented to the US EPA and, from the low application rates, relates mainly to mosquito applications, it shows that invertebrates are the most susceptible under field situations.

Table 100: Summary of a table in Graney (1988) presented to the US EPA on field studies using fenthion.

Application rate g/ha and method	Exposure route	Max. Conc. µg/L after each application	Field mortality, % effect *		Comments	Study year
			fish	Invertebrate		
33; Aerial fog 33; Aerial fog	Drift Drift	1.19 4.27	- -	0% 0%	Rapid dissipation Rapid dissipation	1976 1976
33; Aerial fog	Drift	1.69 <0.01 0.16 0.16	- no effect no effect no effect	no effect [1] 59% no effect -	Oil from thermal fog influences fenthion fate	1985
Unknown; ground ULV	Drift	0.49	No effect	-	Low DO caused mortality	1986
11.2; ground ULV	Drift	0.28 0.41 0.31 0.37	0% 0% 0% 0%	0% 0% 0% 0%		1985, 1986
11.2; ground ULV	Drift	0.68 0.38	- -	No effect No effect	Effects on invertebrates community structure	1985
11.2; ground ULV	Drift	0.48	-	33%	Sublethal effects, slow dissipation	1985
33; Aerial fog	Drift	1.5 0.29 2.6 0.51	0% 0% 0% 0%	0% 0% 100% 50%	Shrimp mortality occurred at sites where limited mixing occurred	1986, 1987
112, ULV	Drift	Not measured	-	No effect		1968
33; Aerial fog	Direct	Not measured	-	100%		1976
56, larvacidal	Direct	15-42	-	100%		1985
112,	Direct	27-32	0%	100%		1986
224, granular	Direct	Not measured	No effect	Effects	Affected fiddler crabs and amphipods not fish or molluscs	1971, 1973
112	Direct	Not measured	No effect	Effects	Affected midges and cladocerans, not snails, clams or fish	1964

* Percent effect relative to control.
[1] Indicates that some mortality occurred but mortality at the reference site was greater or equal to test site.

Nohara and Iwakuma, 1996
Residual pesticides and their toxicity to freshwater shrimp (*Paratya compressa improvisa*) were studied in a river mouth in Lake Kasumigaura, Japan. The river is used for rice irrigation with water from the paddies returning to the river. Water samples were taken every

ten days from April to July and analysed for several pesticides, including fenthion, as well as the toxicity to the local shrimp. The toxicity test was a 96-hour test in the river/lake water with 4-week-old shrimps (8 per test) and total mortality determined. The maximum toxicity was 50% in mid to late May, corresponding with peak concentrations for the pesticides fenthion, diazinon and fenobucarb (1.9, 0.8 and 6.5 μg/L respectively). Based on the toxicity of the pesticides to the shrimp, fenthion was considered to be the most likely toxicant.

Conclusion—Aquatic Toxicity

Toxicity to aquatic organisms, especially invertebrates, is very high. The acute toxicity to fish from submitted studies (9 species) ranges from an LD50 of 0.83 mg/L for rainbow trout to 2.7 mg/L for Golden orfe. Life cycle studies have not been performed but the embryonic and larvae life stages of rainbow trout have been tested and the maximum acceptable tolerated dose was determined to be between 0.013 and 0.027 mg/L. The early life stages are considered to be normally the most sensitive. There is a high acute to chronic ratio of 43. In a database of regulatory-type studies that have been reviewed by US EPA, the toxicity to fish of fenthion ranges from LC50 of 0.55 mg/L for rainbow trout to LC50 of 5.8 mg/L for guppy.

Fenthion is extremely toxic to invertebrates, which is typical for an organophosphate, with acute toxicity figures for *Daphnia magna* (EC50) of between 5.2-5.7 μg/L and for mysid shrimp EC50 = 0.22 μg/L. (Note that mysid is normally a very sensitive test species.) The chronic toxicity to daphnia has been determined and the MATC found to be between 0.009 and 0.016 μg/L. Again the acute to chronic ratio is high, with a value of 270. The US EPA database on reviewed regulatory studies gives the most sensitive freshwater species as a daphnid (*Simocephalus* sp.) EC50 = 0.62 μg/L, and least sensitive invertebrate as the sowbug (*Asellus brevicaudus*), EC50 = 1800 μg/L. For salt water species the most sensitive is brown shrimp (*Penaeus aztecus*), EC50 = 0.024 μg/L and least sensitive the seed shrimp (*Cypridopsis vidua*), EC50 = 18.0 μg/L.

Fenthion is highly toxic to green algae, with EC50s of 0.55 and 1.1 mg/L for *Scenedesmus* and *Selenastrum* species respectively and to the saltwater algae *Skeletonema costatum*, EC50 of 0.33 mg/L. It is also moderately toxic to blue green algae (*Anabaena flos-aqua*) EC50 = 10.7 mg/L and the freshwater diatom *Navicula pelliculosa*, EC50 = 1.2 mg/L. The toxicity to the freshwater plant *Lemna gibba* was studied but the only information from the study is that the NOEC is > 2.8 mg/L.

No field studies were presented. A summary of field studies conducted presented to the US EPA clearly shows that under field conditions at rates associated with mosquito use the most sensitive aquatic organisms are invertebrates, with effects noted relative to control sites at 0.5 μg/L and above, particularly where there was slow dissipation of fenthion.

A literature report on fenthion residues in a river mouth/lake associated with irrigated rice cultivation in Japan showed mortalities to local shrimp occurring at 1.9 μg/L of fenthion. However, other organophosphate insecticides were present but not at concentrations considered to be significant.

11.3.2 Non-target Terrestrial Invertebrates

Bees

The contact of 12 pesticides under standard conditions to worker honeybees was reported (Kudamatsu, 1977). This report is a summary of results and there is limited information. The contact LD50 for fenthion was given as 0.16 µg/bee.

US EPA Database
The database from the Effects Division of the Office of Pesticide Programs, US EPA database (see above for further information on the database) has only one entry for bees, a contact test (1975) using fenthion with an LD50 of 0.31 µg/bee and is rated as core (=reliable).

Earthworms

Heimbach, 1989b
The toxicity of Lebaycid (50.3% fenthion) to earthworms (*Eisenia foetida*) was tested according to OECD Guideline 207 using artificial soil. Nominal concentrations of Lebaycid used were 10, 100, 178, 316, 562 and 1000 mg/kg soil. There was 100% mortality in the highest test concentration and no mortalities in the next lowest concentration. The LD50 was determined as between 562 and 1000 mg/kg of soil. The LOEC was 178 mg/kg based on the reduction in weight of the surviving worms compared to control.

Woodley, 1990
The toxicity of Baytex 550 (55% ac) to earthworms (*Eophila [Helodrilus] foetidus*) was determined in two tests. In the first test the worms were immersed for 1 minute in solutions at 0, 10, 100, 1000 or 5500 mg/L of Baytex 550, then place onto a medium of manure sludge (from effluent tanks at Bahrs Hill Research Station). The number of live worms was recorded 0, 2, 3, 7 and 11 DAT. In the second test worms were placed on manure sludge before the sludge was covered with turf, which was sprayed with Baytex a day later at either the recommended rate 3 L/10 m^2 (1.65 g/m^2, equivalent to 9 kg ac/ha) or 3 L/5 m^2 of Baytex.

Results for the first test show that there were no survivors at 5500 mg/L (recommended dilution rate) and at 1000 mg/L there was a slight increase in mortalities compared to controls and reduction in average weight of surviving worms. The author noted that due to the diurnal nature of earthworms they were unlikely to be directly exposed to the spray solution. In the second test there were no apparent dose related effects on mortality or bodyweight of the worms.

Other Invertebrates

König, 1989
The effect of Lebaycid on *Trichogramma cacoeciae* was carried out according to BBA Guidelines. The wasps (3 replicates, 241, 293 and 327 wasps per replicate) were exposed in a test chamber to glass plates that were sprayed with Lebaycid (535 g ac/L,) using a 0.1% solution (1.6 mg/cm^2 wet residues applied, equivalent to 850 g ac/ha) 3 hours earlier and allowed to dry. After 24 hours no wasps survived. For the protected life stage study, parasitised eggs were kept for 7 days before dipping in a solution of Lebaycid (0.1% solution). The emerged wasps were then allowed to parasitise host eggs. No hatching

occurred in treatment group, where as in controls there was an average of 22.8 parasitised eggs /wasp. Fenthion is rated as harmful to *Trichogramma cacoeciae.*

Kűhner, 1992
The effect of Lebaycid on the lacewing larvae (*Chrysoperla carnea*) was determined according to IOBC Guidelines. Glass plates were sprayed with Lebaycid (0.1% solution) at 1.16 mg/cm^2, air-dried for 2-3 hours before the larvae (2-3 days old, 15 per replicate, 3 replicates) were exposed to the residues until pupation. The larvae were fed until pupation, then hatched. No larvae survived to pupation in treatments while 43 out of 45 larvae survived in control and hatched.

Mead-Briggs, 1992
The effect of Lebaycid on the hover fly *Episyrphus balteatus* was carried out according to BBA Guidelines. Glass plates were sprayed with Lebaycid (equivalent to 1.5 L/ha) and allowed to dry (90 minutes) before 43 larvae of the fly were exposed to the residues. After 24 hours no larvae survived.

Conclusion—Non-Target Terrestrial Invertebrates

There were no regulatory studies presented but an old report gives a contact LD50 of 0.16 μg/bee and the US EPA database of studies that have been reviewed by them gives a contact LD50 of 0.31 μg/bee.

In 3 laboratory studies on the effect of fenthion on parasitic wasps (*Trichogramma cacoeciae*), lace wings (*Chrysoperla carnea*) and hover fly larvae (*Episyrphus balteatus*), fenthion caused 100% mortality and can be rated as harmful according to IOBC. It should be noted that insects may be resistant to fenthion, which occurs in populations of predatory mites used in IPM.

The toxicity of fenthion to earthworms was tested according to OECD Guidelines. The LD50 was calculated as between 562 and 1000 mg/kg of soil. In a trial the spray solution was toxic to earthworms with direct contact for one minute but in simulated turf, at rates equivalent to 9 kg ac/ha, and earthworms covered by turf, there were no adverse effects.

11.3.3 Avian Toxicity

The available results for avian toxicity of fenthion are summarised in Table 101 and discussed below.

Table 101: Toxicity of fenthion to avian species.

Study Type	Study Guideline	Species	Age	Results, LD50 or LC50 as ac	Rating	Reference
Acute, single dose	US EPA	Bobwhite quail	21 Weeks	7.2 (CI 5.2-9.9) mg/kg	R	Stubblefield 1987a
Acute dietary	US EPA	Bobwhite quail	10 days	60 (CI 44-82) ppm	A	Stubblefield 1987b
	US EPA	Mallard	9 days	1259 (CI 906-1985) ppm	A	Stubblefield 1987c

Ratings: R = result considered reliable, A = result considered acceptable, I = result for information only.

Acute

There was only one acute test presented which was considered reliable. 10 Bobwhite quails per treatment group (5 males and 5 female) were dosed with fenthion in corn oil by oral gavage. Dose levels were 0.75, 1.5, 3.0, 6.0, 12.0, 24.0, 48 and 96 mg ac/kg bw. The dosed oil solutions were not analysed. There was 100% mortality in treatment 12 mg/kg and above. Statistical analysis of body weights, growth and feed consumption showed statically significant effects for all parameters in the 6.0 mg/kg treatment group and for the 3.0 mg/kg group only for feed consumption only. The LD50 was determined by probit analysis and the NOEC was set at 1.5 mg/kg.

Acute Dietary

The two acute dietary tests were performed to meet US EPA requirements. The birds (10 per treatment) were fed treated feed for five days and then observed for 3 days; the total number of mortalities recorded. Chemical analyses of the treated feed were within 96% of nominal for both the quail and mallard studies. Stability tests (samples of feed stored at room temperature for 6 days) showed <6% degradation had occurred for quail and for mallard feed there was <20% degradation.

Toxic effects (ataxia, wing drop, hyporeactive, tremors, etc) were observed at in all treatment groups for quail with 7 birds affected in the lowest treatment group (31 ppm). For mallards toxic effects were only noted at 489 ppm and all birds were affected. There was severe food avoidance noted in all treatment groups for both the quail chicks and mallard ducklings during the testing period with corresponding differences in body weights. However, all survivors from the treatment groups increased feed consumption when returned to fenthion-free feed at day 5 of the study.

The NOEC for quail was <31 ppm, based on gross observable clinical signs and reduced feed consumption and NOEC for mallards was <65 ppm based on feed consumption and reduced body weights.

These studies are considered acceptable.

Conclusion—Acute

The above results for acute toxicity shows that fenthion can be rated (according to US EPA) as very highly toxic to quail by the acute oral route. The dietary route of exposure for birds is rated as highly toxic for quail and moderately toxic for mallards, based on reviewed studies.

Chronic
No chronic tests were available.

Literature Reports

Keith, Ngondi, Bruggers, Kimball and Elliott, 1994
Fenthion (Queletox 60% ac) was applied to two bird roosts in Kenya at 2.88 and 12.0 kg ac/ha for Njoro dam and Gicheha farm dam respectively. Measured fenthion deposits reached 1.1 kg ac/ha. Following these applications, 61 birds of 14 species at the Njoro site and 22 birds of 8 species at the farm site were found dead or severely debilitated. The carcass

searches at the Njoro site were limited to the edges of the dam as there was an impenetrable standing of cattails covering the roost site. Residues of fenthion on the carcasses (feathers) ranged from 12 to 750 µg per carcass with a mean of 330 µg. The authors note that a large raptor with bodyweight of approximately 1 kg was observed eating 4 dead birds, which could indicate that raptors may be exposed to lethal doses, based on the LD50 for American Kestrels of 1.3 mg/kg.

Hall and Kobe, 1980
Tadpoles were exposed to fenthion (and other OPs) in water before being fed to mallard ducklings (2 weeks old). In the first test, tadpoles were exposed to fenthion at 5 mg/L in flow-through conditions before being force fed to the ducklings (4 birds used). After 15 hours all ducklings died. In the second test, the tadpoles were exposed to logarithmically spaced concentrations in water for 96 hours before being fed to the ducklings. The concentration of fenthion in the water exposures as well as concentration in tadpole tissues was determined by gas chromatography. Four out of 6 ducklings (67%) fed tadpoles exposed at 2.2 mg/L died. Measurements of the birds' cholinesterase activity showed a strong dose response curve with relationship to the concentration of fenthion that the tadpoles were exposed to. The bioconcentration factor for fenthion in tadpoles was determined to be 62.

The authors note that a rough estimate for the LD50 of 4.9 mg/kg indicates that most of the toxicity was due to parent compound and that for 50% inhibition of the birds cholinesterase the level in water would be 0.78 mg/L.

Other Avian End-points
A database from the Ecological Fate and Effects Division of the Office of Pesticide Programs, US EPA, to which DEH has access, contains the presently known ecotoxicity endpoints for registered pesticides used in the US. The toxicity data put into the database is compiled from actual studies reviewed by EPA in conjunction with pesticide registration or re-registration. These have been reviewed by Ecological Effects Branch biologists, judged to meet US EPA Guidelines, and therefore acceptable for use in the ecological risk assessment process. The studies are ranked as either core or supplemental (equivalent to reliable and acceptable used in this report). It should be noted, however, that some of these studies use nominal results and some care is needed in using these for the risk assessment.

As can be seen in Table 102 the acute oral toxicity to birds ranges from 2.5 mg/kg for the mourning dove to 25.9 mg/kg for the chukar and the acute dietary ranges from 30 ppm for the common grackle to 231 ppm for mallard duck. These results are less than those in Table 101, indicating that over a large range of studies fenthion is more toxic. However, these studies have not be seen by DEH but do give a broader indicating that the results for bobwhite quail in Table 101 represent a sensitive bird species, although not the most sensitive.

Table 102: Summary of avian toxicity studies reviewed by the US EPA and found acceptable by them.

Species	Study date	US EPA Test Guideline & category*	Type, duration, test material, %ac	LD_{50} or LC_{50}
Mallard duck	1984	71-1a, S	Oral, 14 d, 90%	5.94 mg/kg
Japanese quail	1984	71-1, S	Oral, 14 d, 99%	10.6 mg/kg
Ring-necked pheasant	1984	71-1, S	Oral, 14 d, 99%	17.8 mg/kg
Chukar (*Alectoris chukar)*	1984	71-1, S	Oral, 14 d, 90%	25.9 mg/kg
Rock dove (*Columba livia)*	1984	71-1, S	Oral, 14 d, 99%	4.63 mg/kg

Canada goose	1984	71-1, S	Oral, 14 d, 99%	12 mg/kg
California quail	1984	71-1, S	Oral, 14 d, 99%	15 mg/kg
Mourning dove (*Zenaida macroura)*	1984	71-1, S	Oral, 14 d, 99%	2.5 mg/kg
House finch (*Carpodacus mexicanus)*	1984	71-1, S	Oral, 14 d, 99%	10 mg/kg
House sparrow	1984	71-1, S	Oral, 14 d, 99%	22.7 mg/kg
Bobwhite quail	1975	71-2a, C	Dietary, 8 d, Tech	30 ppm
Mallard duck	1975	71-2b, C	Dietary, 8 d, Tech	231 ppm
Japanese quail	1975	71-2a, S	Dietary, 8 d, Tech	86 ppm
Ring-necked pheasant	1975	71-2, C	Dietary, 8 d, Tech	202 ppm
Common grackle (*Quiscalus quiscula)*	1982	71-2, S	Dietary, 8 d, Tech	30 ppm

* C = core, S = satisfactory

Reports of Australian Incidents

Fenthion was involved in a reported intentional bird-poisoning incident in Australia in Bowen area, Queensland (Bowen Independent, Wednesday 11 August 1999). The species affected and the numbers were not given in these reports. Follow up information provided to DEH concerning this incident from Queensland Environmental Protection Agency indicates that birds of all description, including raptors, were affected and a local fruit grower was illegally using fenthion to prevent bird damage to his fruit.

McKenzie, Lanham, Taylor, Gibson and Pierce, 1996.
The Queensland Department of Primary Industries investigated six incidents of poisoning of native birds over a 13-month period in 1993-1994. In total, 350 birds were found dead, with the major incident at a grain depot, 200 dead. Examination of the carcases showed fenthion present in the alimentary tract contents. It could not be determined if these deaths were from normal use but due to the number and occurrence in areas not associated with use of fenthion, it was considered that a significant number were due to malicious poisoning using fenthion.

Media reports, November 2004.
In November 2004, articles appearing in various newspapers suggested a potential risk of fenthion being carried to outdoor dining areas via the claws of poisoned birds. The Victorian "Herald Sun" also ran articles on the deaths of a pair of peregrine falcons and their chicks that had lived in the Melbourne Central Business District with the suggestion that the deaths were caused as a result of the falcons' eating pigeons that had been poisoned by the use of fenthion containing avicide products.

Reports of Overseas Incidents

Most incident reports from overseas are from the USA and are available from the US EPA website (http://www.epa.gov/pesticides/op/fenthion.htm)

As part of its re-registration process, the US EPA lists a large number of reported incidents where 'Rid-A Bird Perches' had been used and subsequently raptors had died by feeding on the dead and dying target birds (normally starlings and pigeons in buildings). Analysis clearly indicates the presence of fenthion in the intestines of these raptors at high levels up to 55 ppm. Note that this product was cancelled in 1998.

Use to control adult mosquitoes has resulted in several incidents of avian mortalities in the USA, the most recent in the late nineties. The report states that:

> The FWS (US Fish and Wildlife Service) investigator reported that dead and/or sick birds were found on at least 12 occasions between October, 1998, and August, 1999. The incidents occurred after aerial (helicopter) ULV application of Baytex at a rate of 2/3 ounce of Baytex (0.05 lb ac) per acre [56 g ac/ha], which conforms to the label application rate for aerial spraying. The FWS investigator observed dead and sick birds after several sprays, and others were reported by concerned citizens. According to the documentation, sprays were made over the beach early in the morning, and sick and dead birds were observed on the beach within 8-10 hours.

The US EPA also indicate several incidents in California also due to use as mosquito/midge control.

These reports collectively highlight a concern with the use for fenthion, in particular due to the low rates used that resulted in these report avian mortalities.

Conclusion—Avian Toxicity

Fenthion can be rated (according to US EPA) as very highly toxic to quail by the acute oral route. The dietary route of exposure for birds is rated as highly toxic for quail and moderately toxic for mallards, based on reviewed studies. Results in a database of studies reviewed by the US EPA confirm the acute toxicity rating as very highly toxic (10 species) and the acute dietary as ranging from highly toxic to very highly toxic (5 species).

In a literature report, the effect of aerial application to bird roosts in Kenya was examined. Following these applications, 61 birds of 14 species at one site and 22 birds of 8 species at the other site were found dead or severely debilitated. The report is not considered applicable to Australia but it does highlight the high avian mortalities that can occur when used inappropriately.

Six incidents of poisoning of native birds over a 13-month period were investigated by the Queensland Department of Primary Industries, with a total of 350 bird deaths, with 200 dead in the major incident at a grain depot. It was considered that a significant number were due to malicious poisoning using fenthion.

Tadpoles were exposed to fenthion in water before being fed to mallard ducklings (2 weeks old). Tadpoles exposed to fenthion at 5 mg/L caused 100% mortality and at 2.2 mg/L 67% mortality. The bioconcentration factor for fenthion in tadpoles was determined as 62.

The US EPA has reported that a number of adverse effects on non-target birds have been noted when fenthion is used to control pest birds and for mosquito control. In the former reports, fenthion was used to kill pest birds in buildings and then raptors were found dead after eating the dead or dying pest birds. In the latter reports where fenthion was used for mosquito control at low rates (56 g ac/ha), dead and sick birds were noticed after several sprays. These sprays were made over a beach early in the morning, and sick and dead birds were observed within 8-10 hours.

11.3.4 Mammals

Fenthion is moderately toxic to mammals by the oral route, with LC50s for rats 566 mg/kg (females) and 405 mg/kg male and the multi-generation reproduction studies show a NOEC of 10 ppm and LOEC 14 ppm (US EPA 1998).

11.3.5 Summary of Ecotoxicity

Fenthion is a highly toxic organophosphate insecticide. It is toxic to most organisms and in particular birds and aquatic invertebrates.

Aquatic

The toxicity to aquatic organisms, especially invertebrates, is very high. The acute toxicity to fish from submitted studies (9 species) ranges from an LD50 of 0.83 mg/L for rainbow trout to 2.7 mg/L for Golden orfe. Life cycle studies have not been performed but the embryonic and larvae life stages of rainbow trout have been tested and the maximum acceptable tolerated dose was determined to be between 0.013 and 0.027 mg/L. The early life stages are considered to be normally the most sensitive. There is a high acute to chronic ratio of 43. In a database of regulatory-type studies that have been reviewed by US EPA, the toxicity to fish of fenthion ranges from LC50 of 0.55 mg/L for rainbow trout to LC50 of 5.8 mg/L for the guppy.

Fenthion is extremely toxic to invertebrates, which is typical for an organophosphate, with acute toxicity figures for *Daphnia magna* (EC50) of between 5.2-5.7 µg/L and for mysid shrimp EC50 = 0.22 µg/L (note that the mysid is normally a very sensitive test species.) The chronic toxicity to daphnia has been determined and the MATC found to be between 0.009 and 0.016 µg/L. Again the acute to chronic ratio is high, with a value of 270. The US EPA database on reviewed regulatory studies gives the most sensitive freshwater species as a daphnid (*Simocephalus* sp.) EC50 = 0.62 µg/L, and least sensitive invertebrate as the sowbug (*Asellus brevicaudus*) EC50 = 1800 µg/L. For salt water species the most sensitive is brown shrimp (*Penaeus aztecus*), EC50 = 0.024 µg/L and least sensitive the seed shrimp (*Cypridopsis vidua*), EC50 = 18.0 µg/L.

Fenthion is highly toxic to green algae, with EC50s of 0.55 and 1.1 mg/L for *Scenedesmus* and *Selenastrum* species respectively and to the saltwater algae *Skeletonema costatum*, EC50 of 0.33 mg/L. It is also moderately toxic to blue green algae (*Anabaena flos-aqua*) EC50 = 10.7 mg/L and the freshwater diatom *Navicula pelliculosa*, EC50 = 1.2 mg/L. The toxicity to the freshwater plant *Lemna gibba* was studied but the only information from the study is that the NOEC is > 2.8 mg/L.

No field studies were presented. A summary of field studies conducted presented to the US EPA clearly shows that under field conditions at rates associated with mosquito use the most sensitive aquatic organisms are invertebrates, with effects noted relative to control sites at 0.5 µg/L and above, particularly where there was slow dissipation of fenthion.

A literature report on fenthion residues in a river mouth/lake associated with irrigated rice cultivation in Japan showed mortalities to local shrimp occurring at 1.9 µg/L of fenthion. However, other organophosphate insecticides were present but not at concentrations considered to be significant.

Non-Target Invertebrates

There were no regulatory studies presented but an old report gives a contact LD50 of 0.16 μg/bee and the US EPA database of studies that have been reviewed by them gives a contact LD50 of 0.31 μg/bee.

In 3 laboratory studies on the effect of fenthion on parasitic wasps (*Trichogramma cacoeciae*), lace wings (*Chrysoperla carnea*) and hover fly larvae (*Episyrphus balteatus*), fenthion caused 100% mortality and can be rated as harmful according to IOBC. It should be noted that insects may be resistant to fenthion, which occurs in populations of predatory mites used in IPM.

The toxicity of fenthion to earthworms was tested according to OECD Guidelines. The LD50 was calculated as between 562 and 1000 mg/kg of soil. In a trial at rates used for turf, the spray solution was toxic to earthworms with direct contact for one minute but in simulated turf there were no adverse effects.

Avian

The results show that fenthion can be rated (according to US EPA) as very highly toxic to quail by the acute oral route. The dietary route of exposure for birds is rated as highly toxic for quail and moderately toxic for mallards, based on reviewed studies. No chronic data are available.

In a literature report, the effect of aerial application to bird roosts in Kenya was examined. Following these applications, 61 birds of 14 species at one site and 22 birds of 8 species at the other site were found dead or severely debilitated. The report is not considered applicable to Australia but it does highlight the high avian mortalities that can occur when used inappropriately.

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The US EPA has reported that a number of adverse effects on non-target birds have been noted when fenthion is used to control pest birds and for mosquito control. In the former reports, fenthion was used to kill pest birds in buildings and then raptors were found dead after eating the dead or dying pest birds. In the latter reports where fenthion was used for mosquito control at low rates (56 g ac/ha), dead and sick birds were noticed after several sprays. These sprays were made over a beach early in the morning, and sick and dead birds were observed within 8-10 hours.

Mammals

Fenthion is moderately toxic to mammals by the oral route, with LC50s for rats 566 mg/kg (females) and 405 mg/kg male and the multi-generation reproduction studies show a NOEC of 10 ppm and LOEC 14 ppm (US EPA 1998).

The risk characterisation for the environmental assessment follows the US EPA approach (Urban and Cook, 1986) to establish a Q-value (or risk quotient) from the ratio of the Predicted Environmental Concentration (PEC) and lowest effect concentration, such as an LC_{50}. DEH has no formal framework for assigning levels of hazard for a given Q, but considers that the following is an appropriate guide in this assessment.

For the estimation of risk from acute toxicological end points under the various scenarios; if:

- Q > 0.5 then hazard is unacceptable,
- 0.1 ≤ Q ≤ 0.5 hazard may be able to be mitigated by some form of risk management, such as label restraints for a specific use, and
- Q < 0.1, hazard is considered low (and may or may not require some form of risk management, such as general label restraints).

11.4 Risk Characterisation

The following risk characterisation follows the US EPA approach (Urban and Cook, 1986) to establish a Q-value (or risk quotient) from the ratio of the Predicted Environmental Concentration (PEC) and lowest effect concentration, such as an LC_{50}. DEH has no formal framework for assigning levels of hazard for a given Q, but considers that the following is an appropriate guide in this assessment.

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- 0.1 ≤ Q ≤ 0.5 hazard may be able to be mitigated by some form of risk management, such as label restraints for a specific use, and

Q < 0.1, hazard is considered low (and may or may not require some form of risk management, such as general label restraints).

11.4.1 Summary of Use Patterns

The fenthion products that are the subject of this review between them are used for general pest control, companion animal pest control and bird control.

The general pest control uses are: outdoors, subfloor and ceilings, in and around commercial buildings (including dairies and stables), industrial and domestic buildings for control of flies, mosquitoes, cockroaches, ants and fleas and other household pests. The mosquito use involves applications to waterbodies where mosquitoes are breeding in home garden situations only. The companion animal uses are limited to dogs. Bird control uses are for control of pigeons, starlings, Indian mynahs and sparrows in industrial and commercial premises.

11.4.2 General Pest Control

Labels provide instructions for use outside and in subfloors areas of homes, flats, hotels and commercial and industrial buildings (including dairies and stables). These are for control of cockroaches, spiders, ants, fleas and flies. Product is sprayed onto hard surfaces at a range of rates. Mosquito uses include treatment where adults congregate, water around man-made structures where mosquitoes are breading and in septic tanks.

Solid Surface Treatments

The environmental exposure from domestic uses is expected to be low. The maximum rate for fleas (16.5 g ac/10 m^2) is high, however, use is expected to be confined to urban areas or inside domestic or farm buildings, with application by hand sprays. Thus, spray drift is not expected to affect sensitive environments when used as instructed. Application to walls of buildings is not expected to result in environmental exposure. However, run-off from areas outside of treated buildings could represent a risk. If a band 5 metres wide is sprayed around a large building (dairy or stable, 50 × 20 metres) at 16.5 g ac/10 m^2, then 1.32 kg ac would be applied. With the assumption that 1% of the applied chemical runs off (13.2 g) and enters a pond of 1 ha in size 15 cm deep (1.5 ML), then the concentration in the pond is 13.2 g/1.5 ML = 8.8 µg/L. The risk to fish (Q = 0.01; LC50 = 0.83 mg/L for rainbow trout) and algae (Q = 0.02; E_bC50 = 0.55 mg/L for *Scenedesmus*) would be acceptable, however it would be high for aquatic invertebrates (Q = 8.5; EC50 for *Chironomus riparius* 1.04 µg/L. Q = 1.7; EC50 for *Daphnia magna* 5.2 µg/L). Therefore, those labels that include application to the outside of dairies and stables, should include appropriate instructions.

There would potentially be a risk to insects that either crawl over or alight onto treated surfaces. Although likely to be toxic to individual organisms, these exposures are not expected to be significant at population levels, as non-target insects would not be likely to frequent surfaces treated by the products under review in significant numbers. Indeed, there is no evidence available to suggest that target species are at population level risk.

Sub-floor soils are not considered to be significant habitats for soil organisms. Product 32999, however, can be used to treat soil around buildings. Thus, soil dwelling organisms could be exposed and probably killed. It is not considered that soil immediately surrounding such structures constitutes an environment requiring protection.

Mosquito Larvae Control

The rates for mosquitoes vary slightly between the two registered products. Each is discussed in turn within the following sections, as relevant.

Aquatic Invertebrates

Product 51627: A rate of 146 g ac/ha is used for water where mosquitoes are breeding. Assuming treated water were 15 cm deep, the concentration of fenthion would be 97 µg/L. The risk to non-target aquatic invertebrates would be very high (Q = 19; EC50 for *Daphnia magna* 5.2 µg/L).

Product 32999: A rate of 165 g ac/ha is used for water where mosquitoes are breeding. Assuming treated water were 15 cm deep, the concentration of fenthion would be 110 μg/L. The risk to non-target aquatic invertebrates would be very high (Q = 21; EC50 for *Daphnia magna* 5.2 μg/L).

In both cases, the risk to aquatic invertebrates is high. Noting that the aquatic half-life of approximately 7 days, this risk is unable to be mitigated. Product 51627 is used only in domestic situations, where aquatic environments are confined. Product 32999 is used in domestic situations, as well as commercial and industrial situations. While unlikely to adversely impact natural environments, use of the product could impact on urban environments. Users should be warned of this potential by a label warning statement.

Fish and Algae

Product 51627: A rate of 146 g ac/ha is used for water where mosquitoes are breeding. Assuming treated water were 15 cm deep, the concentration of fenthion would be 97 μg/L. The risk to fish and algae require mitigation (Q = 0.1; LC50 for Rainbow trout = 0.83 mg/L. Q = 0.2; E_bC50 = 0.55 mg/L for *Scenedesmus*).

Product 32999: A rate of 165 g ac/ha is used for water where mosquitoes are breeding. Assuming treated water were 15 cm deep, the concentration of fenthion would be 110 μg/L. The risk to fish and algae require mitigation (Q = 0.1; LC50 for Rainbow trout = 0.83 mg/L. Q = 0.2; E_bC50 = 0.55 mg/L for *Scenedesmus*).

These estimates indicate that mitigation is required (Q = 0.1 – 0.5). Table 97 presented in Volume 2 indicates a lower rainbow trout LC50 of 0.55 mg ac/L. DEH has not assessed this study, however it is a US EPA Core Study. Using this endpoint calculates Q = 0.2 for both products, requiring mitigation.

Current labels for both products warn of the danger to fish and instruct that fish tanks and ponds be covered before use. Clearly it is not possible to cover a pond prior to treating it for mosquito control. Instructions should be clarified to remove the ambiguity, however they should also make it clear that application should only be to water that does not contain fish, whether an ornamental pond or other body of water.

Birds

Overseas reports indicate that birds have adversely been affected when fenthion was used for mosquito control at a beach in Florida at low rates, 56 g ac/ha (US EPA 1998). It is unclear from the reports as to whether the exposure was from direct overspray, contamination of food sources or dermal contact. Whichever route of exposure was responsible for the birds' exposure and death, it is clear the low rate of application can result in significant avian mortalities.

Sources of water for animals include free (drinking) water, metabolic water derived from the breakdown of food, and water moisture in food, and the total contribution of water intake may be derived from one or more sources concurrently.

Most Australian wildlife drink water from surface water bodies when available, but intake rates vary within and among species depending on individual requirements and the species' physiological adaptation to climatic conditions. However, few data are available on drinking water intake rates of Australian wildlife. Daily water requirements of wildlife depend on their rate of loss of water to the environment due to evaporation and excretion, which may vary spatially and temporally for individual animals or species. Water evaporation and excretion rates depend on several factors including body size, ambient air temperature, and physiological and behavioural adaptations for conserving water. Many drier climate species have physiological adaptations to reduce drinking water requirements when conditions are harsh.

Taking into account dietary and metabolic water intake rates, Calder and Braun (1993) developed a general allometric equation for drinking water intake (Iwater) by birds that is based on body weight as follows:

Equation 1

Avian Water Intake Rate (Iwater; L/kg-bw/day) = (0.059 x bw$^{0.67}$)/bw
where: bw = body weight (kg wet weight).

Equation *1* is used in the US EPA Wildlife Exposure Factors Handbook (US EPA, 1993) and been used to estimate drinking water intake rates for avian species. These water intake rates are considered estimates only. Daily water intake by birds may be more or less than estimated by Calder and Braun (1993), particularly depending on environmental conditions (eg. temperature).

Table 103 shows drinking estimates, using the
Equation 1.

Table 103: Drinking estimates for birds of various masses

Mass of bird (g)	**10**	**100**	**1000**	**2000**
Iwater (mL/kg/day)	269	126	60	47
Water intake per bird per day (mL/bird/day)	2.7	12.6	60	94

With these values and the worst-case estimated fenthion concentration in treated water of 110 µg/L (highest of the two products), the risk to birds of varying weights can be estimated using the following equation:

Equation 2

Fenthion intake per bird (µg/bird) = (water intake per bird x 110 / 1000)

The estimates are shown in Table 104.

Table 104: Estimated exposure of birds to fenthion drinking solely from water treated for mosquito larvae.

Mass of bird (g)	**10**	**100**	**1000**	**2000**
Fenthion intake (µg/bird)	0.3	1.4	6.6	10
Fenthion intake (µg/kg)	30	14	6.6	5

Using the avian acute NOEC of 1.5 mg/kg, presented at Section 11.3.3 in Volume 2, it is clear that the risk to birds is acceptable (Q = 0.02 for a 10 g bird, such as a fairy wren). These calculations assume that a bird would drink its entire requirement of water from a treated body of water. As this is unlikely, the probable risk is even lower.

Mammals

Based on measured body weights and drinking water intake from Calder (1981) and Skadhauge (1975), Calder and Braun (1993) developed an allometric equation for drinking water intake rates for mammals as follows:

Equation 3

Mammal Water Intake Rate (Iwater; L/kg-bw/day) = (0.099 x $bw^{0.90}$*)/bw*
where: bw = body weight (kg wet weight).

Equation 3 is used in the US EPA Wildlife Exposure Factors Handbook (US EPA, 1993) and been used to estimate drinking water intake rates for mammalian species. These water intake rates are considered estimates only. Daily water intake by mammals may be more or less than estimated by Calder and Braun (1993), particularly depending on environmental conditions (eg. temperature).

NTP (1993) reported that rats (0.225 kg average weight) consumed ~ 24.6 mL of drinking water per day under laboratory test conditions. This approximates to the value estimated using Equation 3 (*i.e.* ~ 25.9 mL/day) for a mammal of the same body weight.

Table 105 shows drinking estimates, using Equation 3.

Table 105: Drinking estimates for mammals of various masses

Mass of mammal (g)	10	100	1000	2000
Iwater (mL/kg/day)	157	125	99	92
Water intake per mammal per day (mL/mammal/day)	1.8	12.5	99	184

With these values and the worst-case estimated fenthion concentration in treated water of 110 µg/L (highest of the two products), the risk to mammals of varying weights can be estimated using the following equation:

Equation 4

Fenthion intake per mammal (µg/mammal) = (water intake per mammal x 110 / 1000)

The estimates are shown in Table 106.

Table 106: Estimated exposure of mammals to fenthion drinking solely from water treated for mosquito larvae.

Mass of mammal (g)	10	100	1000	2000
Fenthion intake (µg/mammal)	0.2	1.4	10.9	20.2
Fenthion intake (µg/kg)	20	14	10.9	10.1

Using the rat LC50 of 405 mg/kg, presented at Section 11.3.4 in Volume 2, it is clear that the risk to mammals is low ($Q << 0.01$) for a mammal $\geq$ 10 g). These calculations assume that a mammal would drink its entire requirement of water from a treated body of water. As this is unlikely, the probable risk is even lower.

11.4.3 Companion Animal Pest Control

Companion animal usage is for the control of fleas on dogs, where fenthion is applied in one spot, to the back of the neck.

This use is not expected to cause significant environmental exposure. Once the correct dose is determined, a number of applicators (small squeeze tubes) are used to apply product to the neck of the dog, where the material will spread across the fur and slowly degrade. It is expected that any fenthion that is absorbed by a treated animal would be metabolised before excretion. Once used, there are only minor residues in the plastic tubes. Used and unused applicators are disposed of via the domestic garbage. In landfill, residues are expected to slowly degrade.

11.4.4 Bird Control

Fenthion is used as an avicide to control pest birds such as pigeons, starlings, Indian mynahs and sparrows in industrial/commercial premises, processing/manufacturing plants and educational facilities as well as roof space of domestic buildings (houses, units and townhouses). Application is by trained company staff or pest control operators only, with application to roosting/nesting areas using brushes or rollers. Labels do not indicate application rates in terms amount of fenthion applied, but do refer to Standard Operating Procedures. These provide applications rates from which rates of fenthion can be calculated (pigeons 55 g ac/m^2; starling and Indian mynahs 27.5 g ac/m^2; sparrows 11 to 22 g ac/m^2). The products are registered in Victoria, Tasmania and Northern Territory only, however permits have been issued covering use of fenthion bird control products in other jurisdictions from time to time. As use of these products has historically been by pesticide control operators only, environmental exposure during application should be low. The products would then be expected to degrade *in situ*. The range of situations in which these products can be used is broad: virtually any man-made structure, although probably mostly to ledges.

Although there are the specific bird species listed on approved labels, there is nothing that would prevent another species of bird alighting on treated surfaces and thus also being killed – clearly the application rate (11 to 55 g ac/m^2) is sufficient to kill birds. Information on the proportion of populations of native birds roosting on the types of surfaces to be treated is not known, but is expected to be low relative to the targeted urbanised exotic species. There are certain questions that would need to be answered to estimate exposures: how many non-target species alight on treated surfaces for the period during which the gel remains toxic; how much fenthion is actually absorbed by birds' feet; what species cohabit with target species; to what extent do non-target species move into areas treated with fenthion after target species have been removed but during the period the gel remains toxic?

Without answers to these questions, it is not possible to estimate risk to bird populations. It is clear that individual non-target birds that alight on treated surfaces may die, however, how this relates to populations is cannot be estimated based on currently available information.

Current labels for two bird control products contain the following instruction: “DO NOT use product in areas where native birds are likely to come into contact with product.” The effectiveness of this statement is not known, although DEH is not aware of significant poisonings of native birds from the use of these products. None-the-less, the statement accords with the high risk of these products to native birds and so should be standard across all registered products.

The other principal risk is likely to be to non-target organisms that predate or scavenge the dying or dead birds. The number of incidents from use of ‘Rid-A-Bird’ perches in the US indicates that there may be a significant avian risk due to secondary poisonings from using fenthion to control pest bird species (note that its registration was cancelled in 1998). There have been press reports of such incidents in Australia in respect of a family of Peregrine Falcons in the Melbourne CBD.

DEH has not been able to source rigorous data on the extent to which fenthion is absorbed by target birds that alight onto treated surfaces. Nor is information available that might allow an estimate of dietary intake via predation of poisoned birds. Again DEH is not able to estimate the risk of these products to predatory organisms. If a risk does exist, there is a potential to mitigate it by requiring that treated sites be monitored and that poisoned birds and remaining gel be removed. However, this measure will not be effective for poisoned birds taken on the wing.

Labels lend support to the intention to limit use to trained staff or pest control operators. Because of the nature of the products and the way in which they are used, further restriction for the use of the product should be made.

11.5 References

Adema D M M, DaIsum M B and Bommel J K (1989). Reproduction test with Lebaycid EC 50 and *Daphnia magna*. TNO Division of Technology for Society, 12.10.89. Unpublished.

Calder, W. A. (1981). Scaling of physiological processes in homeothermic animals. Ann. Rev. Physiol. 43: 301-322. (Cited in USEPA, 1993).

Calder, W. A. and Braun, E. J. (1983). Scaling of osmotic regulation in mammals and birds. Am. J. Physiol. 244: R601-R606 . (Cited in USEPA, 1993).

Carlisle J C and Roney D J (1984). Acute toxicity of fenthion to bluegill sunfish. Mobay Corp report 457, January 23, 1984. Unpublished.

Dorgerloh M (1994a). Lebaycid 500 EC - acute toxicity (96 hours) to golden orfe in a static test. Bayer AG report DOM 94002, 19 January 1994. Unpublished.

Dorgerloh M (1994b). Lebaycid 500 EC - acute toxicity (96 hours) to rainbow trout in a static test. Bayer AG report DOM 94003, 25 January 1994. Unpublished.

Forbis A D (1986). Acute toxicity of Baytex to *Selenastrum capricornutum*. Mobay Corp report 829, December 12,1986. Unpublished.

Forbis A D (1987). Acute flow through toxicity of Baytex to *Daphnia magna*. Mobay Corp report 864, March 13, 1987. Unpublished.

Forbis A D (1988). Chronic toxicity of ^{14}C-Baytex to *Daphnia magna* under flow-through conditions. Mobay Corp report 98326, January 13, 1988. Unpublished.

Graney R L (1988). Evaluation of the requirement for an aquatic mesocosm study to support fenthion mosquito control use in Florida. Mobay Corp report 98330, October 10, 1988. Unpublished.

Hall R J and Kolbe E (1980). Bioconcentration of organophosphorus pesticides to hazardous levels by amphibians. *J Toxic and Environ Heath* **6**: 853-860, 1980. Published.

Heimbach F (1985a). Acute toxicity of fenthion (techn) to water fleas. Bayer AG report HBF/DM 52 (Mobay report 90586), 23.9.85. Unpublished.

Heimibach F (1985b). Growth inhibition of green algae (*Scenedesmus subspicatus*) by fenthion (technical). Bayer AG report HBF/Al03 (Mobay report 89082), 21.1.85. Unpublished.

Heimbach F (1989a). Growth inhibition of green algae (*Scenedesmus subspicatus*) by Lebaycid EC 50. Bayer AG report HBF/A 68; 29.9.89. Unpublished.

Heimbach F (1989b). Toxicity of Lebaycid to earthworms. Bayer AG report HBF/RG 105, 11.10.89. Unpublished.

Heimbach F (1995). Influence of fenthion (techn.) on development and emergence of larvae of *Chironomus riparius*. Bayer AG report HBF/CH 06, 29.9.95. Unpublished.

Hermann G (1978). Fish toxicity trout. Bayer AG report FF-56, 26.6.78. Unpublished.

Hermann G (1979). Fenthion = S 1752, golden orfe. Bayer AG report FO-244, 28.3.79. Unpublished.

Hughes J S (1986a). The toxicity of Baytex technical to *Navicula pelliculosa*. Malcolm Pirnie Inc, report 834, December 15, 1986. Unpublished.

Hughes J S (1986b). The toxicity of Baytex technical to *Skeletonema costalum*. Malcolm Pirnie Inc, report 836, December 8, 1986. Unpublished.

Hughes J S (1987a). The toxicity of Baytex technical to *Anabaena flos-aquae*. Malcolm Pirnie Inc. report 833, January 19,1987. Unpublished.

Hughes J S (1987b). The toxicity of Baytex technical to *Lemma gibba*. Malcolm Pirnie Inc, report 835, January 12, 1987. Unpublished.

Keith, J O; Ngondi, J G; Bruggers, R L; Kimball, B A and Elliott, C C H (1994). Environmental Effects on Wetlands of Queletox Applied to Ploceid Roosts in Kenya. *Environmental Toxicology and Chemistry*, **13**, 333-341. Published.

Kudamatsu A (1977). Bee toxicity of pesticides - laboratory test. Bayer AG report B-77463, 30.9.77. Unpublished.

Kühner Ch (1992). Detection of side effects of Lebaycid on the green lacewing, *Chrysoperla carnea* Steph. in the laboratory. Bayer AG report 008/0 1 -CC. 5.2.92. Unpublished.

McKenzie, R A; Lanham, A E L; Taylor, J D; Gibson, J A and Pierce, R J (1996). Fenthion poisoning of Native Birds in Southern Queensland. *Aust. Vet J* **74**, 321-323. Published

Matthews, G A (1992). *Pesticide Application Methods*-Second Edition. Longman Scientific

Nohara S and lwakuma T (1996). Residual pesticides and their toxicity to freshwater shrimp in the littoral and pelargic zones of Lake Kasumigaura, Japan. *Chemosphere* Vol **33**, No. 7, 1417-1424, 1996. Published.

NTP (National Toxicology Program). (1993). Technical Report on Toxicity Studies of Sodium Cyanide (CAS No. 143-33-9) Administered in Drinking Water to F344/N Rats and B6C3F1 Mice. U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health. (Hebert, C. D. ed). Report Series No. 37. NIH Publication 94-3386, November 1993. 37 pp.

Skadhauge, R. (1975). Renal and cloacal transport of salt and water. Symp. Zool. Soc. London 35: 97-106. (Cited in USEPA, 1993).

Stubblefield W A (1987a). Baytex techn: Acute LD50 to Bobwhite quail. Mobay Corp, report 83 1, April 1, 1987

Stubblefield W A (1987b). Baytex techn: Subacute dietary LC50 to Bobwhite quail. Mobay Corp report 830, April 2, 1987. Unpublished.

Stubblefield W A (1987c). Baytex techn: Subacute dietary LC50 to mallard ducks. Mobay Corp report 832, April 2, 1987. Unpublished.

Surprenant D C. (1988a). Acute toxicity of technical grade fenthion (trade name Baytex) to sheepshead minnow (*Cyprinodon variegatusi*) under flow-through conditions. Mobay Corp report 87180, January 22,1988. Unpublished.

Surprenant D C (1988b). The toxicity of technical grade fenthion (trade name Baytex) to rainbow trout embryos and larvae. Mobay Corp report 95641 .. March 2, 1988. Unpublished.

Surprenant D C (1988c). Acute toxicity of fenthion (trade name Baytex) to mysid shrimp (*Mysidopsis bahiai*) under flow-through conditions. Mobay Corp report 98335. October 17, 1988. Unpublished.

Surprenant D C (1988d). Acute toxicity of technical grade fenthion(trade name Baytex) to eastern oysters (*Crassostrea virginiaca*) under flow- through conditions. Mobay Corp report 95642, March 3, 1988. Unpublished.

Swigert J P (1986). Acute flow-through toxicity of Baytex to rainbow trout (*Salmo gairdneri*). Mobay Corp report 85 1., December 23, 1986. Unpublished.

Swigert J P (1987). Acute flow-through toxicity of Baytex to bluegill sunfish (*Lepomis macrochirus*). Mobay Corp report 876, March 3, 1987. Unpublished.

Tomlin, C (1997, ed.) The Pesticide Manual, Eleventh Edition. British Crop Protection Council Publications, Bracknell, Berks, UK. Published.

Urban, D J and Cook, N J (1986). Hazard Evaluation Division: Standard Evaluation Procedure-Ecological Risk Assessment. US EPA, Office of Pesticide Programs. Dated June 1986. Published.

US EPA (1993). Wildlife Exposure Factors Handbook. Office of Research and Development. EPA/600/R-93/187. Dec. 1993. http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=2799

US EPA (1998). At US EPA web site: http://www.epa.gov/pesticides/op/fenthion.htm

Woodley, I (1990). Fenthion 55% W/V- Safety-Earthworms. Bahrs Hill Research Station, Australia, Report No. BH 095/90. Dated 26/11/90. Owner: Bayer Australia Ltd. Unpublished.